Technische Universität Dortmund

Max-Planck Institut für molekulare physiologie

Novel concepts and methodologies in pseudo natural product chemistry

Dissertation

For the achievement of the academic degree of the

Doctor in Natural Science

(Dr. rer. nat.)

Submitted to

The Faculty of Chemistry and Chemical Biology

Technical University of Dortmund

By

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Wuxi, China

Dortmund 2021

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回首向来萧瑟处，归去。也无风雨也无晴。

苏轼《定风波》

Declaration/Erklärung

Die vorliegende Arbeit Wurde in der Zeit von März 2018 bis Mai 2021 am Max-Planck-Institut für molekulare physiologie Dortmund und Technische Universität Dortmund unter der Anleitung von Prof. Dr. Dr. h.c. Herbert Waldmann durchgeführt. Hiermit versichere ich an Eides statt, dass ich die vorliegende Arbeit selbstständing und nur mit den angegebenen Hilfsmitteln angefertigt habe.	The work described in this dissertation was carried out from March 2018 to May 2021 at Max-Planck Institute of Molecular Physiology Dortmund and Technical University of Dortmund under the supervision of Prof. Dr. Dr. h.c. Herbert Waldmann. I hereby declare that I performed the work independently without any external assistances except those indicated.

Dortmund 2021

Jie Liu

Teile dieser Arbeit wurden bereits in folgenden Publikationen veröffentlichen:	The present work was partly published in the following papers:

[5]. N. E. Nwosu, Enantioselective synthesis of pseudo-natural product pyrroquinoline *via* 1,3-dipolar cycloaddition, Bachelor thesis (**2020**) under **J. Liu**'s supervision.

[4]. **J. Liu**, J. Flegel, F. Otte, A. Pahl, S. Sievers, C. Strohmann, H. Waldmann, Combination of pseudo-natural product design and formal natural product ring distortion yields stereochemically and biologically diverse pseudo-sesquiterpenoid alkaloids, *Angew. Chemie. Int. Ed.* **2021**, 10.1002/anie.202106654.

[3]. **J. Liu**, F. Otte, C. Strohmann, H. Waldmann, Enantioselective synthesis of pyrro[3,4-*c*]quinoline pseudo-natural products, *Tetrahedron Lett.* **2021**, *76*, 153228-153231.

[2]. **J. Liu**†, G. S. Cremosnik†, F. Otte, A. Pahl, S. Sievers, C. Strohmann, H. Waldmann, Design, synthesis and biological evaluation of chemically and biologically diverse pyrroquinoline pseudo natural products, *Angew. Chem. Int. Ed.* **2021**, *60*, 4648-4656.

[1]. G. S. Cremosnik†, **J. Liu**†, H. Waldmann, Guided by evolution: from biology oriented synthesis to pseudo natural products, *Nat. Prod. Rep.* **2020**, *37*, 1497-1510.

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Abstract

Natural products (NPs) are an inspiring source for chemical biology and drug discovery research, featuring complex and diverse structures. However, the chemical space explored by nature is limited by the biosynthetic precursors and machineries available in NP-producing organisms. To explore the vast chemical space of biological relevance, pseudo natural product design is proposed to unprecedentedly recombine NP fragments from different sources. This thesis aims to develop novel concepts and methodologies in pseudo natural product design to supply structurally complex and diverse compound collections for biological study.

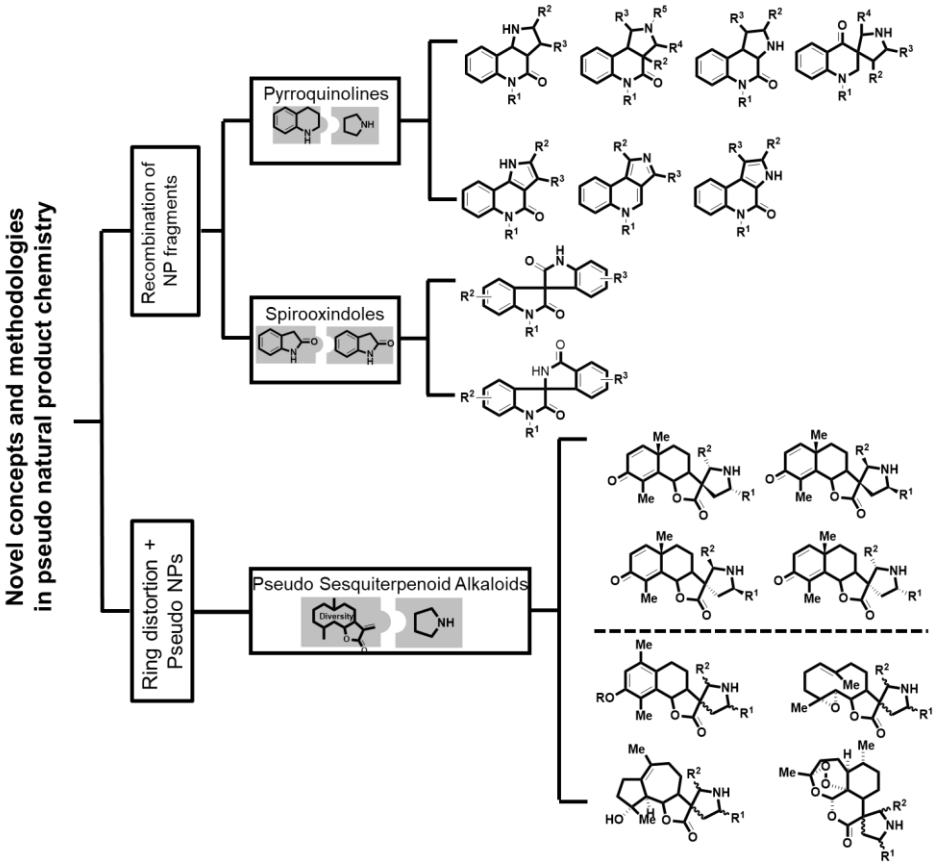


Figure 1. Overview of projects included in this thesis.

To answer the question whether varying connections between two fragments can lead to diverse biological performance, a systematic recombination of alkaloid-derived NP fragments pyrrolidine and tetrahydroquinoline is disclosed in Chapter 3. During the synthesis, 1,3-dipolar cycloaddition is applied strategically to access pyrrolidine fragments. Efficient and concise methodologies are developed to afford a library of 123 members and 7 scaffolds varying the connectivity patterns, positions and saturation states. Cheminformatic and cell

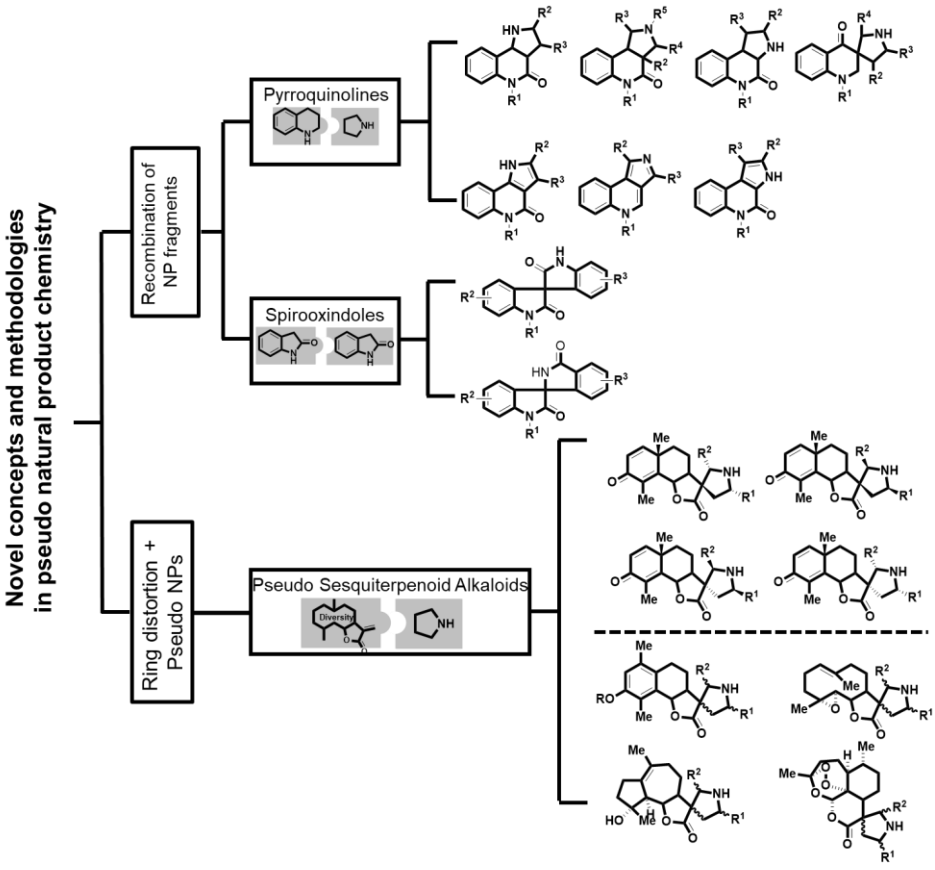
painting analyses of the resulting compound collections reveal that different connections between the same fragments can still afford novel chemical space and diverse biological performance. Cell-based biological screening of the library leads to the discovery of a novel inhibitor of the Hedgehog signaling pathway by binding the Smoothened protein.

To improve the synthetic efficiency, a previously neglected Rh(III)-catalyzed reaction between benzhydroxamate and diazooxindole is presented in Chapter 4. Variation of protecting groups on diazo oxindoles proves to be crucial to controlling the reaction selectivity. *N*-Bn diazo oxindole favors direct [4+1] annulation reaction pathway, while *N*-Ms favors C-H functionalization/carbene insertion/Lossen rearrangement cascade reaction. Mechanistic study suggests that a stereoelectronic effect dominates the reaction's selectivity. At last, a spirooxindole library is constructed in one step which illustrates the high efficiency of scaffold divergent synthesis in pseudo natural product chemistry.

Besides varying connections between two fragments, ring distortion can also lead to structural diversity. In Chapter 5, ring distortion and pseudo natural product design are conceptually combined where sesquiterpene lactones are converted to diverse scaffolds *via* ring distortion followed by incorporation of alkaloid-derived pyrrolidine fragments yielding pseudo sesquiterpenoid alkaloids. To increase the diversity of the compound collection, a stereodivergent 1,3-dipolar cycloaddition is developed to afford stereocomplementary pyrrolidines. During the synthesis, an unusual solvent-controlled *endo/exo* selectivity is discovered. Furthermore, enantiomeric ligands lead to the same products because of the substrate bias. The resulting 93-membered compound library is analyzed using cheminformatic tools and cell painting technology. The combination of ring distortion and pseudo natural product design yields a structurally complex and diverse compound collection with diversity in biological performance. Cell-based assays reveal a novel chemotype inhibiting Hedgehog-dependent osteoblast differentiation. This chapter emphasizes the significance and necessity of combining ring distortion, pseudo natural product design and stereodivergent synthesis approaches.

Zusammenfassung

Naturstoffe sind inspirierende Quellen sowohl für die chemische Biologie als auch für die Wirkstoffentwicklung und weisen komplexe und divergierende Strukturen auf. Jedoch ist der von der Natur explorierte chemische Raum durch Naturstoff-produzierende Organismen über biosynthetische Vorläufer und Mechanismen eingeschränkt. Um noch nicht definierte chemische Räume auf biologische Relevanz zu überprüfen, wird das Konzept von pseudo-Naturstoffen, die neue Kombinationen von Naturstoff-Fragmenten aus unterschiedlichen Quellen, aufweisen. Die vorliegende Dissertation strebt die Entwicklung von neuen Konzepten und Methoden hinsichtlich des Designs von pseudo Naturstoffen an, um strukturell komplexe Substanzklassen biologisch zu untersuchen.



Figur 1. Überblick der Projekte in der Thesis.

Bezüglich der Beantwortung der Frage, ob eine variierende Kombination von zwei Fragmenten zu unterschiedlichen biologischen Ergebnissen führt, wird eine systematische Rekombination der von Alkaloiden abgeleiteten Naturstofffragmente, Pyrrolidin und Tetrahydrochinolin, in Kapitel 3 thematisiert. Der Zugang zu den Pyrrolidin-Fragmenten erfolgt über eine 1,3-dipolare Cycloaddition. Effiziente und präzise Methoden werden

entwickelt, um eine 123-gliedrige Substanz-Bibliothek mit unterschiedlichen Verknüpfungsmustern und Positionen zu gewähren. Chemo-informatische Analysen der resultierenden Verbindungsklassen illustrierten, dass verschiedene Verknüpfungen von identischen Fragmenten in unterschiedlichen biologischen Ergebnissen und chemischen Räumen resultieren können. Zell-basierte biologische Untersuchung der Substanzbibliotheken führt zur Entdeckung von neuen Inhibitoren des Hedgehog Signalwegs.

Zur Entwicklung neuer Synthesemethoden, wird eine Rh(III)-katalysierte Reaktion von Benzhydroxamat und Diazo-oxindol in Kapitel 4 untersucht. Eine Schutzgruppe am Diazo-oxindol ist essentiell, um die Selektivität der Reaktion zu kontrollieren. N-*Bn* Diazo-oxindol begünstigt eine direkte [4+1] annulierung, während *N*-Ms eine Kaskaden-Reaktion aus C-H Funktionalisierung/Carben-Insertion/Lossen-Umlagerung begünstigt. Mechanistischen Untersuchungen zu Folge dominieren stereoelektronsiche Effekte die Selektivität der Reaktion. Schließlich wird eine Bibliothek von Spirooxindolen über effiziente Synthesemethoden hergestellt. Dieses Projekt illustriert die beispielhafte Anwendung der gerüst-divergierenden Synthese in der pseudo Naturstoffchemie.

Zusätzlich zur divergierenden Verknüpfung von zwei Fragmenten kann die Ringumwandlung ebenfalls zur strukturellen Diversität führen. In Kapitel 5 werden die Ringumwandlung und das pseudo Naturstoff-Design konzeptionell zusammengeführt, indem Sesquiterpen-Lactone zu diversen Gerüsten über eine Ringumwandlung und anschließender Einbettung von Alkaloid-Fragmenten zu pseudo Sesquiterpenoid-Fragmenten konvertiert werden. Um die Diversität der Verbindungen zu erweitern, wird eine stereodivergente 1,3-dipolare Cycloaddition zur Erhaltung von Stereokomplementären Pyrrolidin-Fragmenten durchgeführt. Während der Synthese wird eine ungewöhnliche, Lösungsmittel kontrollierte *endo/exo* Selektivität entdeckt. Enantiomere Liganden führen zum selben Produkt durch Substratkontrolle. Die resultierende 93-gliedrige Substanzbibliothek wird über Chemo-informatische Methoden analysiert. Die Kombination von Ringumwandlung und pseudo Naturstoff-Design resultiert in strukturell komplexen und diversen Verbindungen mit unterschiedlichen biologischen Eigenschaften. Zell-basierte Assays ergaben eine neue Klasse von Inhibitoren der Hedgehog-abhängigen Osteoblasten Differenzierung. Dieses Kapitel verdeutlicht die Bedeutung und Relevanz von Ringumwandlung, pseudo Naturstoffen und der stereodivergenten Synthese.

Chapter 1. Introduction

1. Introduction

Natural products (NPs) are a source of inspiration for the design of biologically active compounds, leading to the discovery of more than 50% of FDA approved small molecule drugs (Fig. 1.1a, b).[1] Therefore, NPs have already become attractive research agents in the field of chemical biology to modulate biological processes (Fig. 1.1c). In 1989, Schreiber and co-workers immobilized FK506, a potent immunosuppressive agent, on a matrix and identified a FK506 binding protein FKBP14, which functions as a *cis-trans* isomerase of proline residues.[2] Another binding protein FKBP12 can form a tertiary complex with rapamycin and FKBP-rapamycin-associated protein (FRAP),[3] wherein rapamycin is seen as a molecular glue.[4] These discoveries inspired the chemical biology research in natural products. Since then, more and more natural product-derived probes have been utilized to reveal the mechanism-of-actions (MoAs) of NPs. Biotin (an affinity tag), alkyne (a clickable tag) or diazirine (a photo-affinity tag) can be incorporated into NP structures (**I-4 – I-7**) to uncover the binding targets.[5]

Considering the great potential of natural products in drug discovery and chemical biology research, efficient access to NPs or NP-inspired compounds is in high demand. Harnessing the power of Nature's evolution, NPs display high structural diversity and complexity, which in turn hampers the sufficient supply of these molecules. Direct isolation of NPs from natural sources often offers limited quantities because of the low abundance and/or isolation efficiency. Even though it has come to an era of scalability for total synthesis of NPs, most cases are still time-consuming, lengthy and small scale, which limits the approach to pure products and their analogs.[6] The supply of taxol **I-1** (Fig. 1.1b) still relies on the semi-synthesis from 10-deacetylbaccatin.[7] Trabectedin **I-2** (Et-743; Fig. 1.1b) is a highly potent antitumor marine natural product used in clinic for the treatment of advanced soft tissue sarcoma.[8] However, the extremely complex structure poses a huge challenge to the synthesis community. Even though tremendous efforts have been devoted to the total synthesis of Et-743,[8a] few of them can supply this molecule in large scale.[9]

To supply structurally complex and diverse NP-inspired compound collections for biological study, biology-oriented synthesis (BIOS) and ring distortion and pseudo natural product design were proposed in the past two decades.

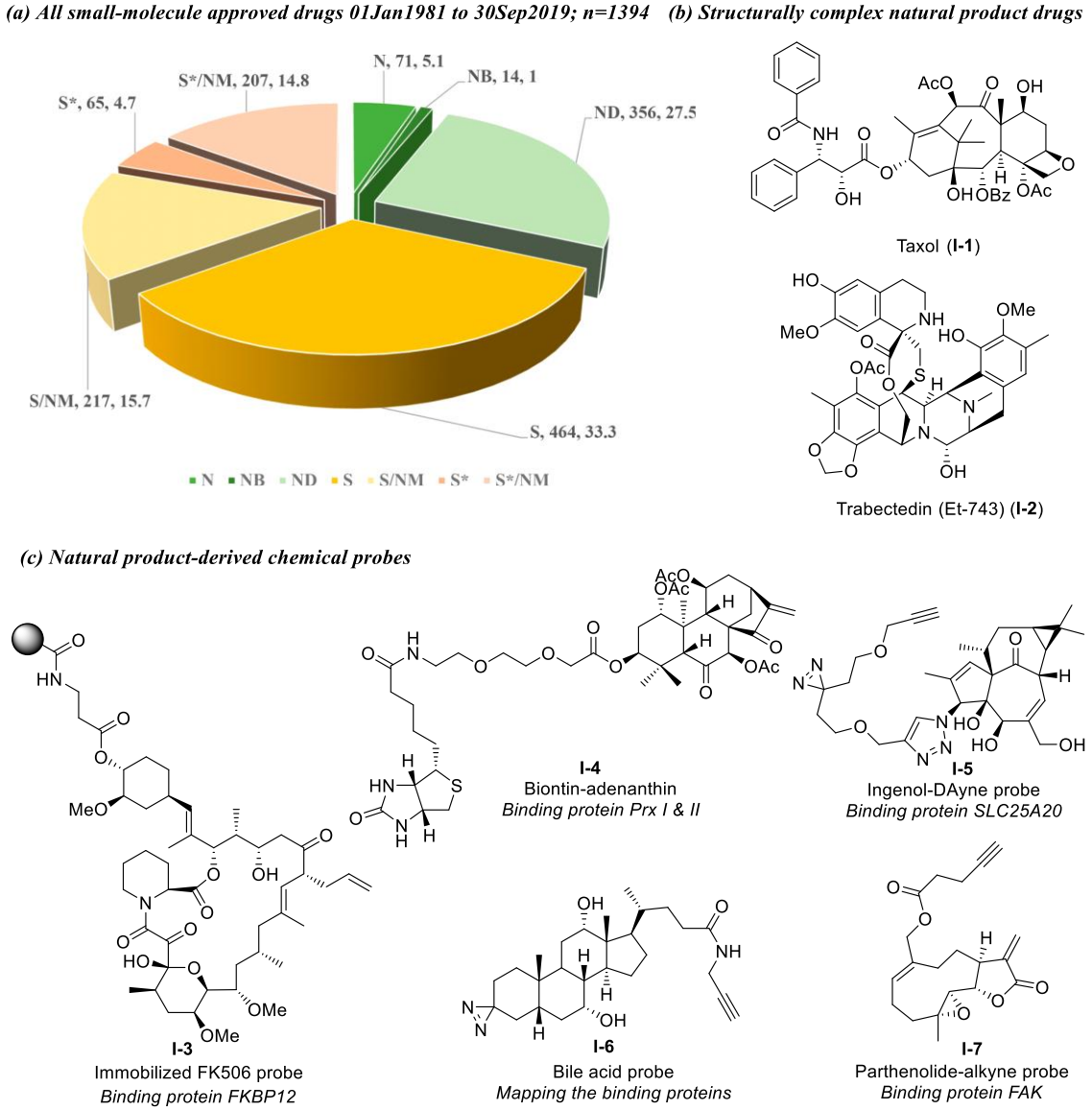


Figure 1.1. Natural products in drug discovery and chemical biology. (a) All small molecule drugs approved by FDA from 01 Jan. 1981 to 30 Sep. 2019. [1] "N": Natural product; "NB": Botanical natural product; "ND": Natural product derivative; "S": Totally synthetic drug; "S*": Made by total synthesis, but the pharmacophore is/was from a natural product. Reprinted from ref. [1] copyright (2020) American Chemical Society. (b) Taxol and Trabectedin are two structurally complex natural product drugs. (c) Classic chemical probes in disclosing the MoAs of NPs.

1.1 Biology-oriented synthesis

Natural products are synthesized by and have coevolved with proteins. Their molecular scaffolds are highly conserved but are decorated with different substituents. For example, more than 7,000 indole-containing natural products have already been isolated from nature, 17% of which are endowed with the same pyridoindole scaffold **I-8** (Fig. 1.2a). Analogously, only ca. 900 protein folding types and 1,300 ligand binding pockets are estimated to exist in spite of ca. 25,000 proteins encoded by the human genome.[10] NPs are biosynthesized by

proteins and display diverse biological activities, which can be seen as "native" ligands interacting with biological systems. The similar conservative and diversity of NPs and proteins are consistent with their reciprocally evolutional relationship (Fig. 1.2a). It is envisioned that same NP scaffolds with diverse substituents can bind with different protein targets of the similar folding types, which has been proved in the pioneering work of dysidiolide **I-10** (Fig. 1.2b).[11]

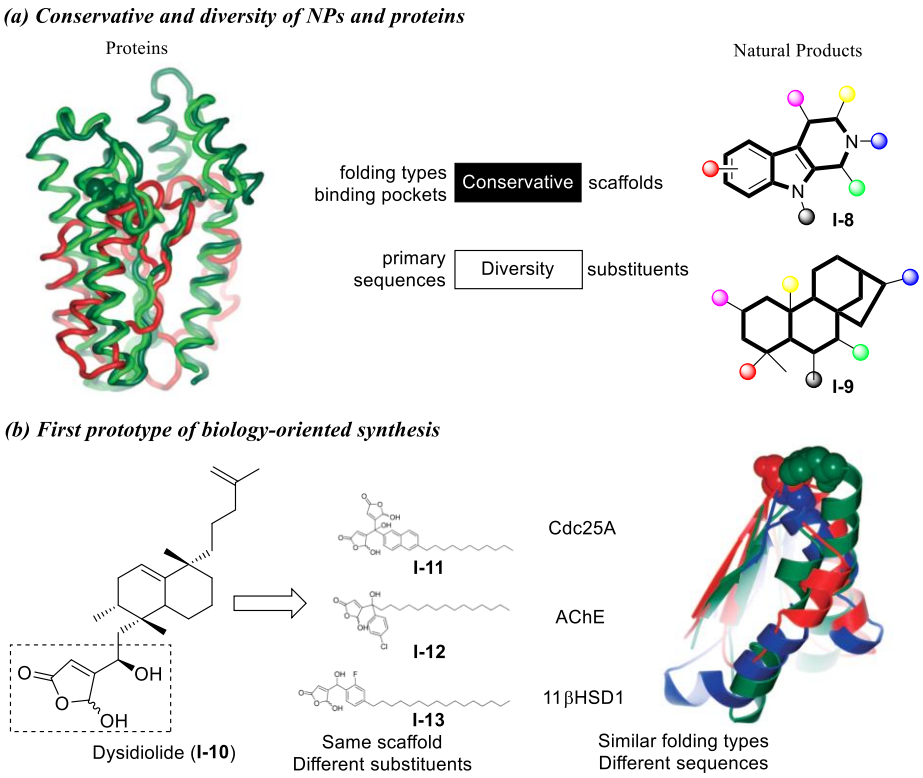


Figure 1.2. Conservative and diversity of natural products and protein structures. (a) Analogy between NPs and proteins in their structural conservative and diversity. (b) Same dysidiolide scaffold with different substituents bind with different proteins (Cdc25A:red; AChE:blue; 11βHSD1:green). A structural overlap of these three proteins is displayed. [11]

Dysidiolide (**I-10**) is a sesterterpene that inhibits protein phosphatase Cdc25A, featuring a γ-hydroxybutenolide scaffold.[12] Biological screening of the compound library derived from this scaffold revealed that by varying the substituents the compounds (**I-11 – I-13**) are able to selectively bind with diverse protein targets of similar folding types (Fig. 1.2b). This exciting discovery rationalizes the origins of diverse bioactivities of natural products and inspires the synthesis campaigns in library design and construction. Guided by coevolution of NPs and proteins, NP scaffolds can be seen as pre-validated and privileged structures to be synthesized, and diverse appendages on the scaffolds will bind with specific proteins. This can be seen as the prototype of biology-oriented synthesis (BIOS).[10, 13]

Biology-oriented synthesis (BIOS) aims to simplify the NP structures to their scaffolds, which are then decorated with diverse substituents.[13a] In the synthesis campaign, efficient synthetic routes or methodologies are developed to produce NP-inspired compound libraries wherein the synthetic challenges are relatively decreased, and the biological relevance is retained. Over the past two decades, the BIOS design has been employed to produce many fruitful results.

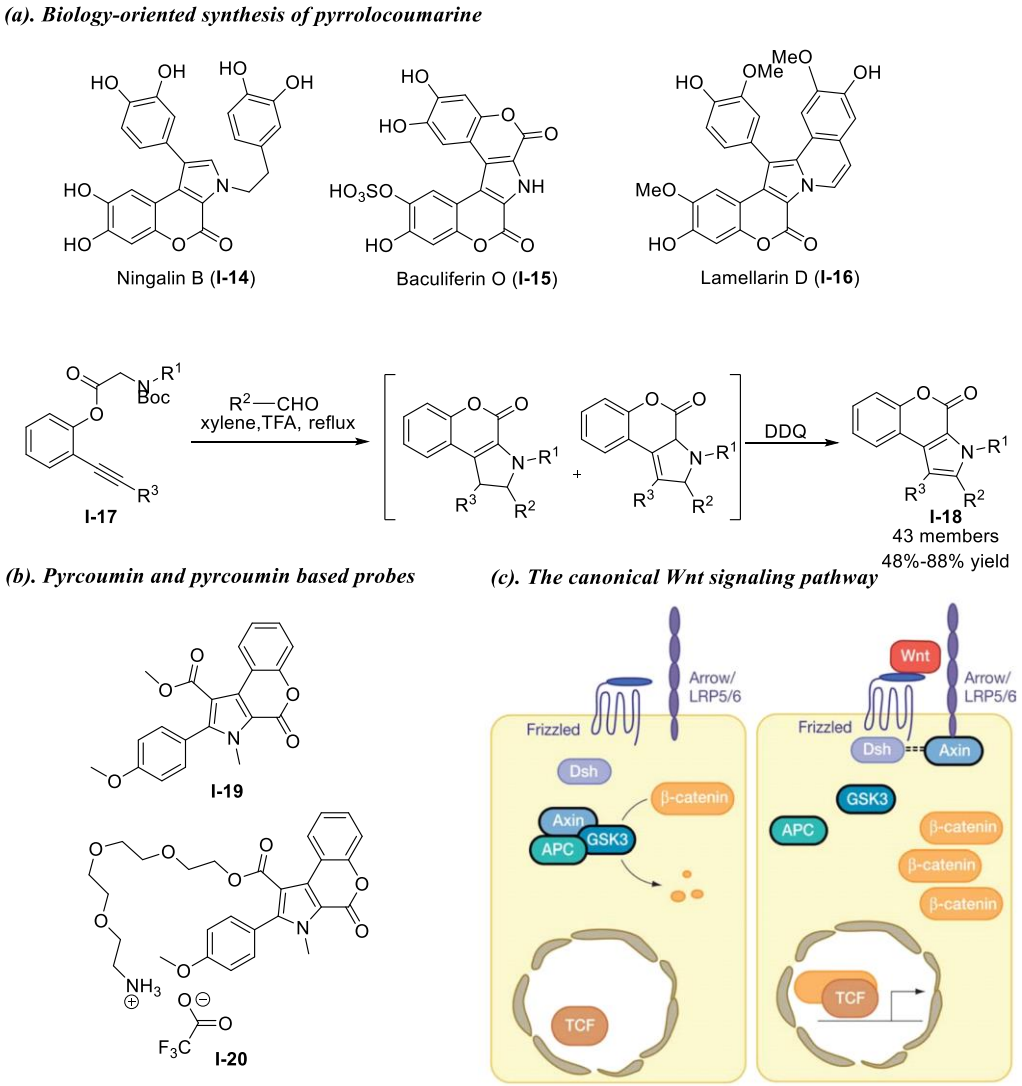


Figure 1.3. Biology-oriented synthesis of pyrrolocoumarine. (a) Representative pyrrolocoumarine-containing natural products. A one-pot synthesis was developed to synthesize the library of pyrrolocoumarine. (b) Molecular structures of active compound pyrcoumin and its affinity probe. (c) Outline of canonical Wnt signaling pathway. Reprinted from ref. [14] Copyright (2004) Annual Reviews.

Pyrrolocoumarine **I-18** is a common NP scaffold shown in many biologically active marine natural products, like Ningalin B (**I-14**)[15], Baculiferin O (**I-15**)[16] and Lamellarin D (**I-16**)[17]. The synthesis of this compound library featured an intramolecular 1,3-dipolar cycloaddition between azomethine ylides and alkynes followed by an oxidative aromatization

(Fig. 1.3a).[18] Biological evaluation of the synthesized compound collection revealed a novel chemotype pyrcoumin **I-19** (Fig. 1.3b) that inhibits canonical Wnt signaling pathway, with a half-maximal inhibitory concentration (IC_{50}) of 8.4 μM in reporter gene assay.[19]

Wnt signaling pathway exhibits an impact on the embryogenesis and homeostasis, and its deregulation is involved in carcinogenesis.[14] As depicted in Fig. 1.3c, when Wnt proteins are not present, Axin-APC-GSK3 mediates β-catenin degradation. Upon binding with Wnt proteins (Fig. 1.3c, right panel), the cellular receptors transduce the downstream signals, thus inhibiting the degradation of β-catenin. In β-catenin quantification experiment, no influence of the β-catenin abundance was observed when cells were treated with pyrcoumin **I-19**, which suggests a MoA regarding the downstream of β-catenin. Then, an affinity-based probe **I-20** based on pyrcoumin was designed and synthesized to identify the target using stable isotope labelling of amino acids in cell culture (SILAC). Immobilized on solid support, the probe was exposed to "light" (normal) cell lysate, while the control probe was incubated with "heavy" (^{13}C- and ^{15}N-labelled) lysate. Mass spectrometry-based proteomics identified the selective enrichment of deoxycytidine-triphosphate pyrophosphatase 1 (dCTPP1) with a high SILAC ratio. This target was confirmed by cellular thermal shift assay (CETSA) in cell lysates. Co-immunoprecipitation experiment of dCTPP1 identified its interacting partner, ubiquitin carboxyl-terminal hydrolase 7 (USP7).[20] Pyrcoumin **I-19** is capable of disrupting the interaction between dCTPP1 and USP7.

Ibogaine (**I-21**) is a naturally occurring psychedelic alkaloid produced by *Tabernanthe iboga*.[21] However, its toxicity and low accessibility hamper its development as therapeutic drugs.[22] In 2020, Olson et. al. reported the synthesis of ibogaine scaffold (**I-22** and **I-23**) and identified tabernanthalog (**I-24**) with better drug-like properties (Fig. 1.4a).[23] This example well-illustrates the power of biology-oriented synthesis in scaffold simplification of complex natural products. Because of the biological activities are retained, the example can also be viewed as function-oriented synthesis (FOS).[24] FOS is first proposed to simplify natural products to identify the essential pharmacophores. Under the design principle of FOS, phorbol ester (**I-25**), a PKC modulator, was simplified to 1,2-diacyl-*sn*-glycerol (DAG; **I-26**) and inspired the discovery of simplified molecule **I-27**, where the bioactivities were retained (Fig. 1.4c). This classic example shows the conceptual overlap and difference between BIOS and FOS (Fig. 1.4b). BIOS is a strategy with more emphasis on the molecular scaffold, so that the synthesized scaffolds resemble those of parent NPs. Diverse substituents will hopefully cover different biological activities. Different from FOS, BIOS has a wider

coverage of bioactivities. The mission of BIOS is to explore the diverse chemical and biological space inspired by natural products. While FOS aims to disclose the MoAs of selected natural products, and discover simple chemotypes with the same binding modes through structural simplification as shown in the case of phorbol esters (Fig. 1.4c).

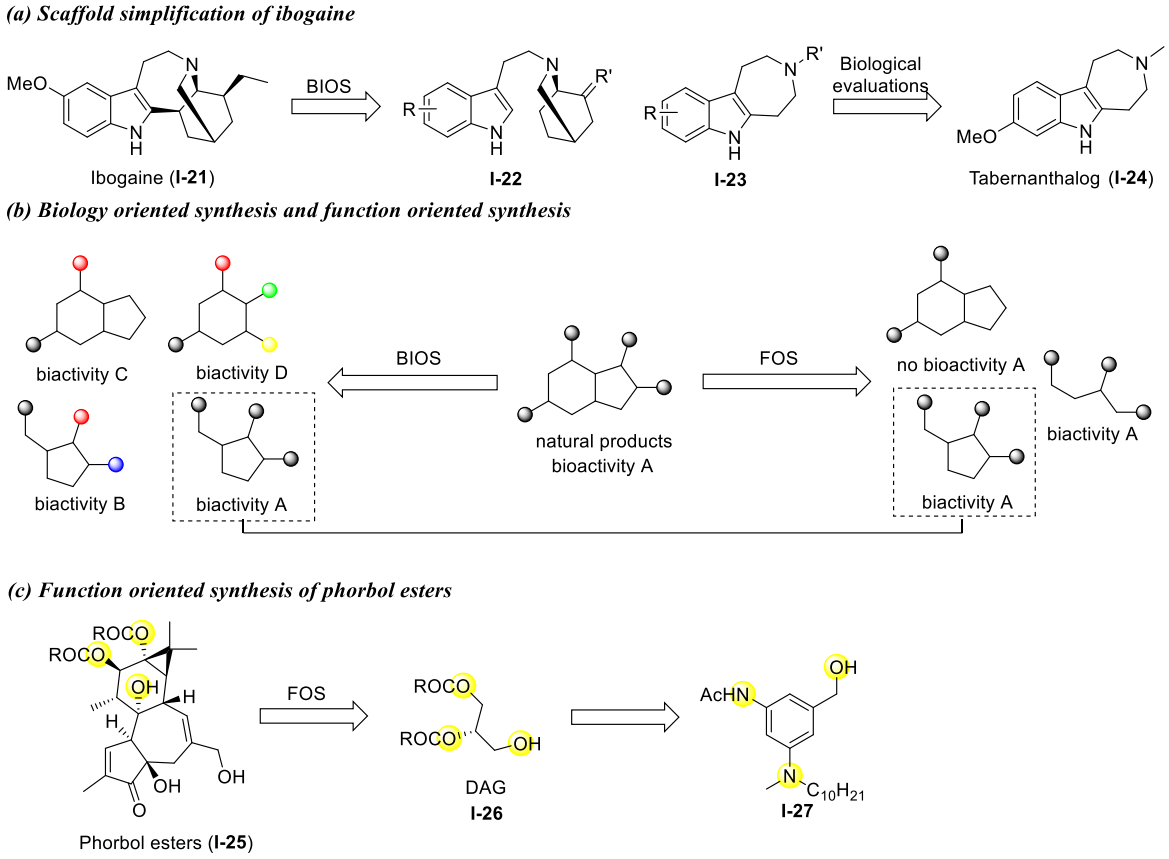


Figure 1.4. (a) Biology-oriented synthesis of ibogaine and discovery of a simplified analog tabernanthalog with better safety and drug-like properties. (b) Similarity and difference between biology-oriented synthesis (BIOS) and function-oriented synthesis (FOS). (c) FOS of phorbol esters.

1.2 Ring distortion

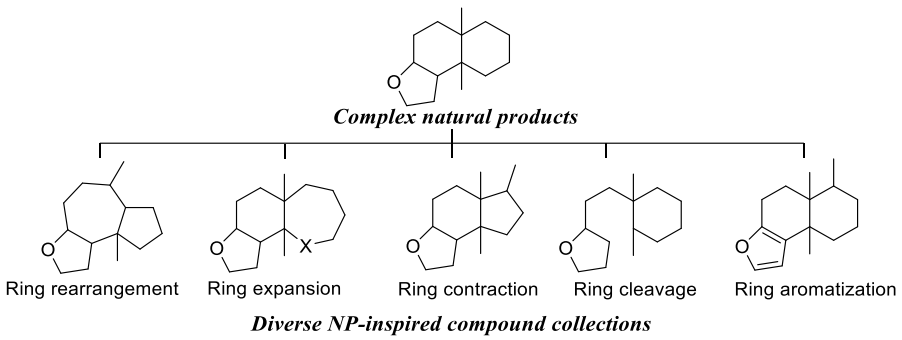


Figure 1.5. Ring distortion of natural products.

Different from *de novo* synthesis of NP-inspired compounds in BIOS, ring distortion utilizes natural products as starting points and conducts semi-synthesis of structurally complex and diverse NP-inspired compound collections.[25] In the synthesis campaigns, original ring systems are reorganized into cleaved/expanded/contracted/rearranged/aromatized rings. The molecular complexity is transformed to the compound diversity *via* multistep synthesis (Fig. 1.5).

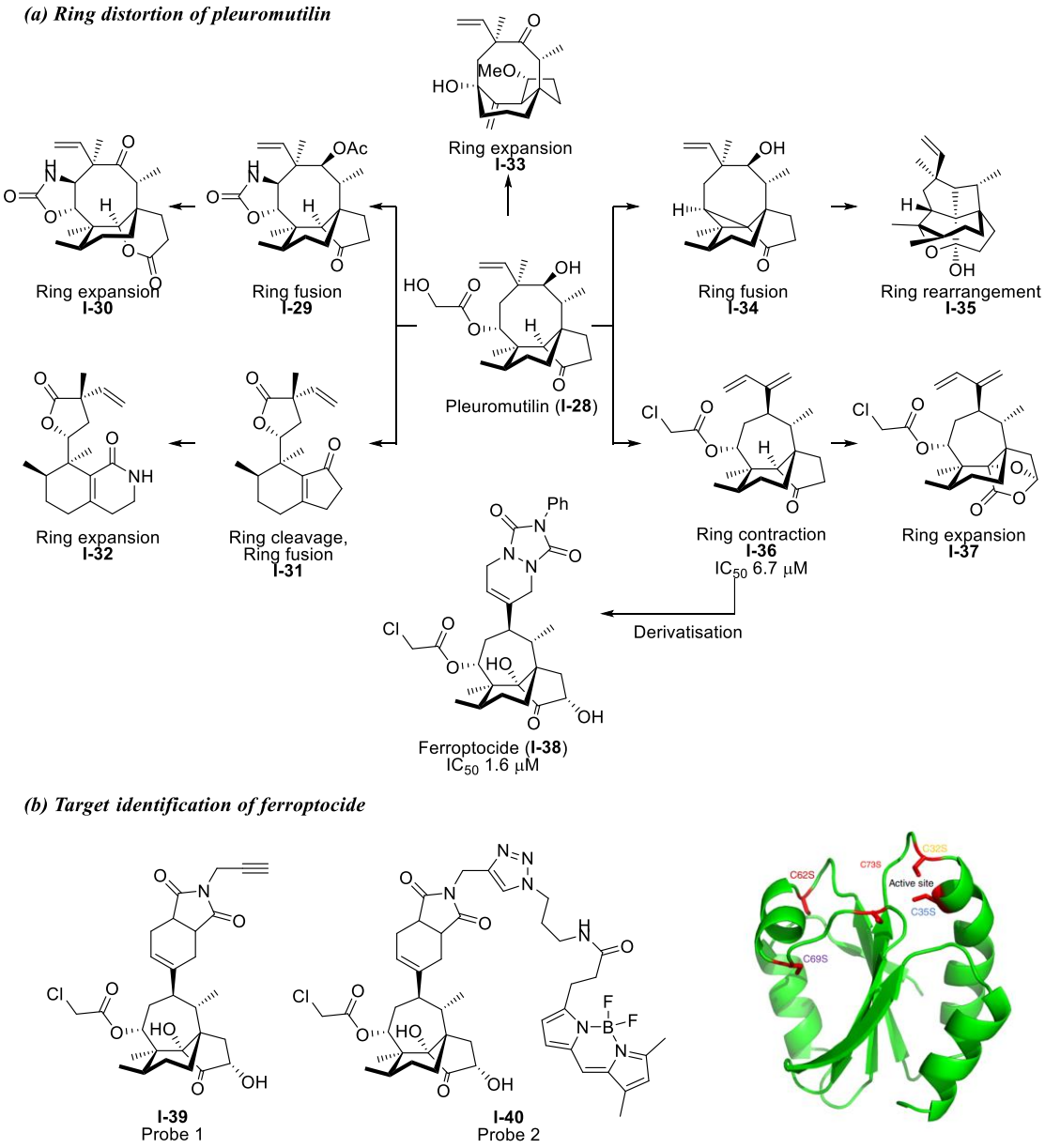


Figure 1.6. Ring distortion of pleuromutilin (**I-28**) led to the discovery of ferroptocide (**I-38**). (a) Diverse structures were derived from complex natural product pleuromutilin. (b) Chemical probes were used to identify the target of ferroptocide. X-ray structure of thioredoxin is shown, where C32S was believed to be its covalent binding site.

In 2019, Hergenrother et. al. reported the discovery of a novel inducer of ferroptosis by ring distortion of complex natural product pleuromutilin (**I-28**).[26] Pleuromutilin is a

commercially available diterpene antibiotic that inhibits the protein synthesis in bacteria by binding with the 50S ribosome. Under the guidance of ring distortion, more than 9 distinctly different scaffolds were derived from pleuromutilin (Fig. 1.6a). The reactions featured ring expansion/fusion/cleavage/rearrangement/contraction and yielded polycyclic structures.

In order to discover novel chemotypes inducing cell death, all the synthesized compound collections were evaluated in a cell-based assay for their ability to kill cancer cells. Interestingly, compound **I-36** was capable of inducing cell death in a half-maximal inhibitory concentration (IC_{50}) of 6.7 μM in ES-2 cell lines. SAR study of this compound led to the discovery of a more potent molecule ferroptocide **I-38**, and chemical probes **I-39** and **I-40** were synthesized accordingly. Structural truncation revealed that it is a covalent binder of a cysteine residue. When the α-chloro ester was replaced with acetyl acetate, the anticancer activity was totally abolished. Ferroptocide **I-38** induced cell death which can be rescued by iron chelator DFO and ferroptosis inhibitor ferrostatin. These results suggest that ferroptocide kills cancer cells through ferroptosis.[27] Pull down assay and chemical proteomics identified thioredoxin, a ubiquitous oxidoreductase, as its target.

Indole-containing natural products are of high therapeutic relevance, and some of them are commercially available. Ring distortion of these natural products will extremely increase the complexity and diversity of the resulting compound library.[28] Huigens and coworkers disclosed the divergent transformations based on indole-containing alkaloid yohimbine (**I-41**).[29] Ring cleavage and rearrangement yielded a compound library of around 70 members (Fig. 1.7a) that was endowed with novel biological activities. The synthesis campaigns resulted in the discovery of *P. falciparum* inhibitor **I-49**[30], antiproliferative agent **I-50**[29] and selective antagonist **I-51** against GPCRs[31] (Fig. 1.7b).

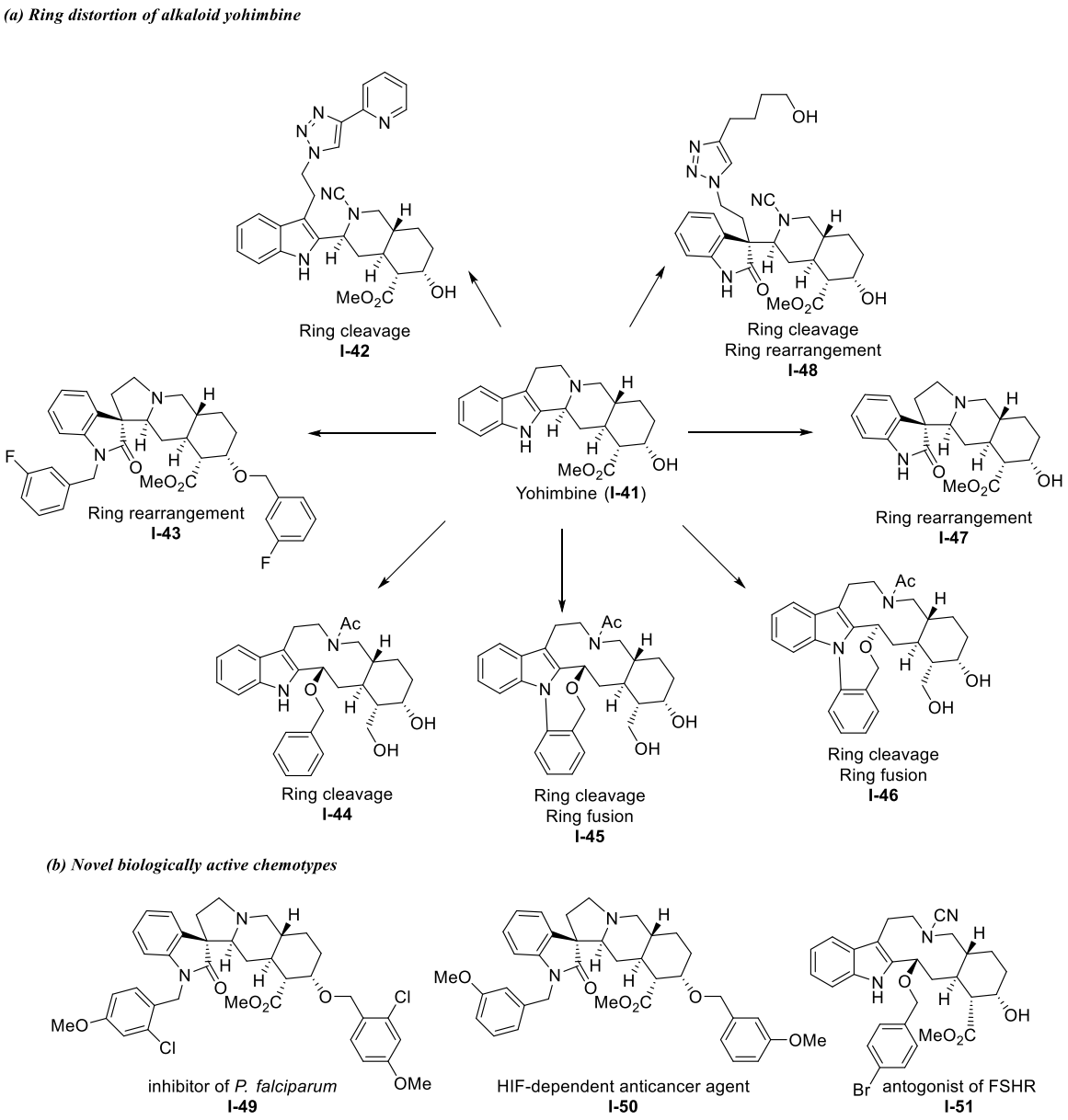


Figure 1.7. Ring distortion of indole-containing natural products. (a) Ring distortion of yohimbine. (b) Biological evaluation of synthesized compound collections.

1.3 Pseudo natural products

Biological relevance and molecular diversity are two key elements in library design and synthesis.[11] Biology-oriented synthesis and ring distortion harness the power of evolution and yield structurally complex and diverse molecules endowed with interesting biological activities. However, the chemical space explored by these two strategies is closely related with the guiding natural products, which limits the further exploration of novel biological space (Fig. 1.8). Therefore, a unified and NP-inspired synthetic strategy enabling broader coverage of NP-like chemical space is in high demand.

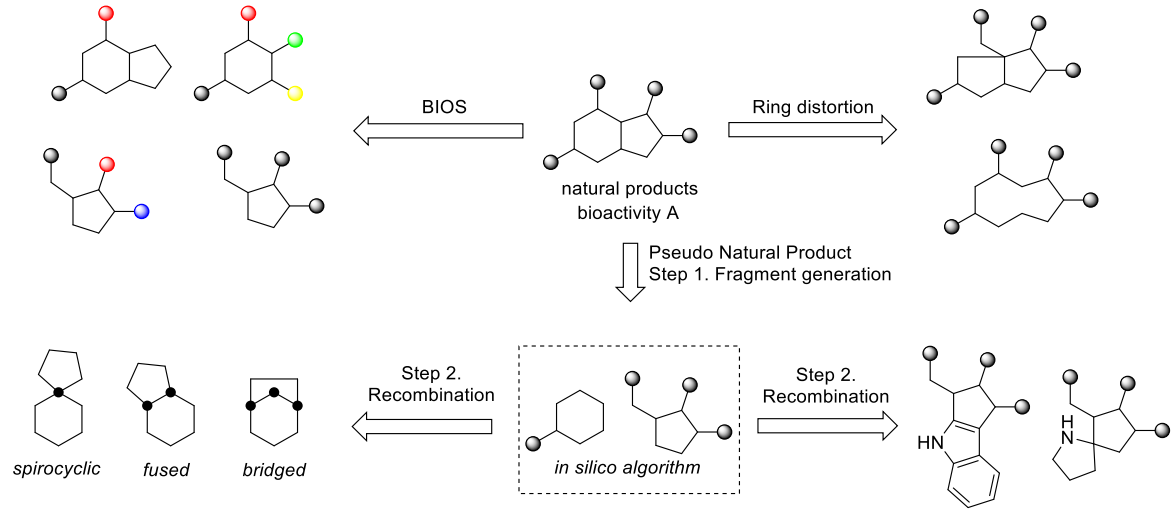


Figure 1.8. Comparison between BIOS, ring distortion and pseudo natural products.

Natural products can be viewed as the combination of NP fragments. In previous work, more than 180,000 NPs were disassembled into 2,000 clusters of natural-product-derived fragments (NP fragments) by *in silico* algorithm.[32] The resulting fragments are structurally diverse, sp^3 rich and biologically relevant. Protein X-ray crystallography aided ligand discovery based on NP fragments resulted in novel chemotypes inhibiting several phosphatases. Inspired by fragment-based drug discovery (FBDD),[33] fragments from different NP sources are recombined unprecedentedly enabling the exploration of novel chemical and biological space not accessible by BIOS, ring distortion and even Nature. Because these man-made molecules are derived from the artificial combination of different NP fragments, they are termed as "pseudo natural products" (Fig. 1.8). In the design principle of pseudo natural products, cyclic NP fragments (common NP fragments or NP-derived fragments) are recombined unprecedentedly. They can be classified based on the common atoms between these fragments, such as spirocyclic (1 atom), edge-on fused (2 atom) and bridged (3 atom) connections (Fig. 1.8). It is anticipated that different fragments and diverse connections and substituents can lead to the vast chemical and biological space.

Even though the first announced pseudo natural product chromopynone,[34] a potent glucose uptake inhibitor, was reported in 2018, we had unconsciously made pseudo natural products before. Indole and tropane are two common NP fragments shown in various natural products. Unprecedented recombination of these two fragments yielded myokinasib **I-56**, a novel inhibitor of myosin light chain kinase 1 (MLCK1) (Fig. 1.9).[35] Under the catalysis of Cu(I) and (*R*)-Fesulphos, the cyclic azomethine ylide **I-52** reacted with electron deficient nitroalkenes **I-53** in high stereo- and diastereo-selectivity. NP-likeness score is employed to quantify the frequency of structural moiety found in natural products.[36] The higher score

indicates a more NP-like structure. In the cheminformatic analysis of the synthesized compound collection, indotropane **I-54** displayed a NP-likeness score around 0 which overlaps with the space occupied by molecules from DrugBank (Fig. 1.9d). Even though both fragments are found in many NP structures, the unprecedented recombination leads to novel chemical space, and thus results in a relatively lower NP-likeness score resembling that of drug molecules. Biological evaluation of the synthesized compound collections led to the discovery of myokinasib **I-56**. The phenotypes of treated cells displayed impaired cytokinesis and multinucleation (Fig. 1.9c).[35a] Considering the significant roles of kinases in modulating cytokinesis, myokinasib was screened against a panel of kinases. It turned out to be an inhibitor of MLCK1 with a half-maximal inhibitory concentration (IC_{50}) of 7.3 ± 1.9 μM.

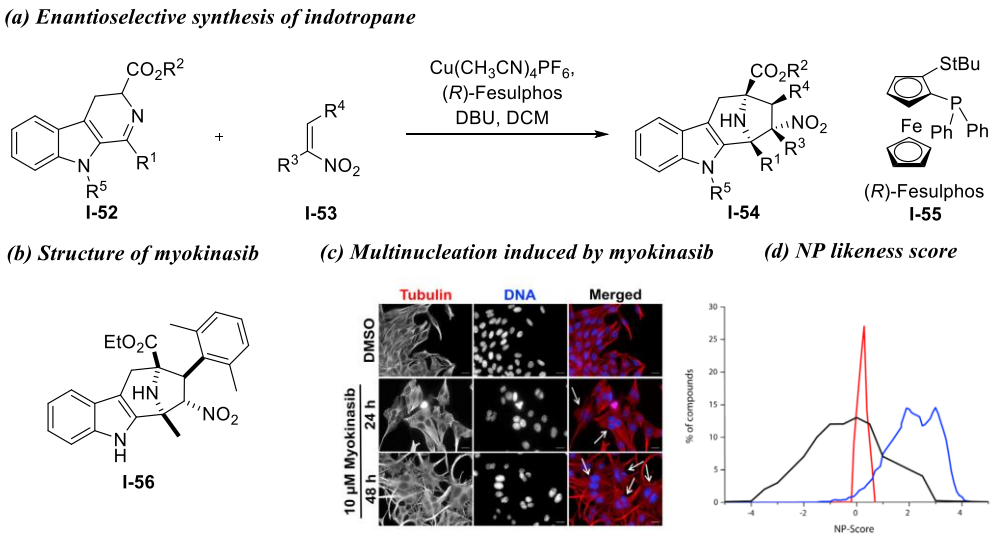


Figure 1.9. Pseudo natural product myokinasib. (a) Enantioselective synthesis of indotropane catalyzed by Cu(I) and (*R*)-Fesulphos. (b) Structure of myokinasib. (c) Myokinasib induced multinucleation. (d) NP-likeness score of synthesized myokinasib (red line) in comparison with ChEMBL natural products[37] (blue line) and molecules in DrugBank[38] (black line). Reprinted from ref.[35a] Copyright (2019) Elsevier.

Cinchona alkaloids are a type of antimalaria natural products. Commercial availability to these complex natural products enables late-stage modification of them. Indole fragment was incorporated into cinchona alkaloid derivatives to yield a novel class of pseudo natural product indocinchona alkaloids (Fig. 1.10).[39] The synthesis featured a Pd-catalyzed indole formation between cinchona derived ketones **I-57** and 2-iodoanilines. The resulting NP-inspired compound collections were then evaluated toward autophagy by monitoring autophagic flux. Phenotypic screening revealed that azaquindole-1 **I-59** inhibited rapamycin-induced autophagy with a half-maximal inhibitory concentration (IC_{50}) of 0.10 ± 0.02 μM, which indicated a downstream regulation of autophagy pathway. Cell painting suggest that it behaved similarly with kinase inhibitors. Considering the important roles of kinases in

modulating autophagy, azaquinole-1 was screened against a panel of kinases where PI3Ks stood out because of the high inhibitory potency. PIK3C3/VPS34 is an important target in autophagosome biogenesis, and therefore, this kinase might be responsible for the inhibitory activity. Cellular thermal shift assay (CETSA) was employed to evaluate the interaction between **I-59** and VPS34. A temperature shift of 5.03±1.8 ºC was observed, which indicated that azaquindole-1 directly binds VPS34.

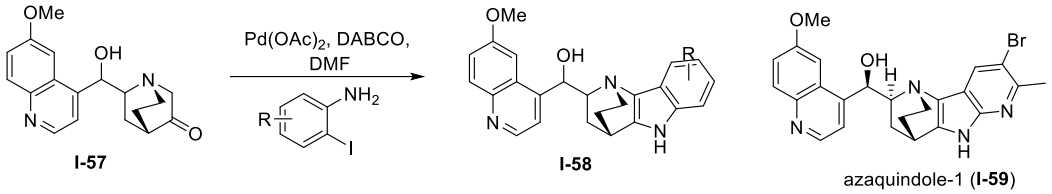


Figure 10. Pseudo natural product indocinchona alkaloids.

Natural products serve as a continuous source of inspiration for the development of drug discovery and chemical biology research. Biology-oriented synthesis and ring distortion strategies have already resulted in the discovery of many structurally complex and diverse NP-inspired compounds. Biological evaluation of them reveals some important targets of therapeutic relevance. However, owing to the limited chemical space explored by BIOS and ring distortion, a unified and NP-inspired synthetic strategy is in high demand. Inspired by fragment-based ligand discovery, NP fragments from different sources are unprecedently recombined to afford pseudo natural products that exhibit novel biological activities. With more efforts devoted to this field, more selective and potent chemotypes against interesting targets will be discovered.

Chapter 2. Design and aim of the thesis

2. Design and aim of the thesis

The aim of the thesis is to develop novel concepts and methodologies in pseudo natural product chemistry. Based on our previous studies, unprecedented recombinations of NP fragments yielded novel chemotypes and bioactivities, which proved the utility of the pseudo natural products concept.[34] Structural diversity and complexity are always the focus of pseudo natural product synthesis. In Chapter 3, a systematic study is presented to explore whether varying connections between two NP fragments is able to access highly diverse chemical space. Pyrrolidine and tetrahydroquinoline are two common NP fragments occurring in diverse natural products. Unprecedented combination of these two fragments will be enabled by strategic application of 1,3-dipolar cycloaddition. The resulting pseudo NP classes varying at connective positions, patterns and saturation states are compared using cheminformatic tools and the cell painting analysis. Asymmetric 1,3-dipolar cycloaddition will also be explored.

In Chapter 3, *de novo* synthesis of pseudo natural products from elaborate precursors is described. To improve the synthetic efficiency, a scaffold divergent synthesis of spirooxindoles will be presented in Chapter 4. Scaffold divergent synthesis is a strategy aiming to achieve the structural diversity *via* tuning the properties of the intermediates. With the development of the synthetic methodologies, more and more reaction processes are tunable through different ligands, catalysts and substituents. Herein, a previously neglected Rh(III)-catalyzed scaffold divergent synthesis of spirooxindoles will be disclosed.

The above two chapters are about the recombination of common fragments, like tetrahydroquinoline, pyrrolidine and oxindole. In Chapter 5, fragment-sized sesquiterpene lactones, whose structures are biologically relevant, are combined with alkaloid-derived fragment pyrrolidine. To increase the scaffold diversity of pseudo natural products, commercially available sesquiterpene lactones will be converted to diverse structures using a ring distortion strategy. Then, the electrophilic lactones will react with azomethine ylides *via* stereodivergent 1,3-dipolar cycloadditions. At last, a stereochemically and biologically diverse pseudo natural product library is expected to be constructed.

These three chapters aim to tackle a core question in chemical biology, that is how to identify structurally complex and diverse small molecules of therapeutic relevance? Inspired by NP structures, the pseudo natural product strategy is applied to all of the synthesis campaigns. Novel synthetic methodologies (1,3-dipolar cycloaddition; Rh(III)-catalyzed C-H

functionalization) and concepts (combination of ring distortion and pseudo NP) will be developed in this thesis. Coupled with unbiased morphological profiling technology, the synthesized compounds will be systematically evaluated. The efforts in these chapters will hopefully strengthen our understanding of pseudo natural products and lead to the discovery of novel chemotypes.

Chapter 3. Design, synthesis and biological evaluations of pyrroquinoline pseudo natural products

Part of the content has been published in
Angew. Chem. Int. Ed. **2021**, *60*, 4648-4656.
Tetrahedron Lett. **2021**, *76*, 153228-153231.

3. Design, synthesis and biological evaluations of pyrroquinoline pseudo natural products

3.1 Background

3.1.1 1,3-dipolar cycloaddition in the synthesis of bioactive molecules

1,3-dipolar cycloaddition has become a powerful approach to functionalized pyrrolidines through the development of catalysts, ligands, dipoles and dipolarophiles.[40] Among the diverse 1,3-dipoles, amino acid-derived azomethine ylides are of particular interest because of their synthetic versatility. Azomethine ylide (C-N-C) is usually represented in a zwitterionic form with the nitrogen atom positively charged, while the negative charge is distributed over the two terminal carbon atoms (Fig. 3.1a). The reactions with dipolarophiles (alkenes) involve six π electrons, and thus take place through a thermally allowed suprafacial process according to Woodward-Hoffmann rules (Fig. 3.1c). In most cases, the reaction proceeds in a concerted way in *endo* selectivity because of the secondary interaction between 1,3-dipoles and dipolarophiles to stabilize the transition states. However, azomethine ylides adopt a bent-type structure, so that the secondary interaction with the dipolarophiles is not strong enough compared with that of classic Diels-Alder reactions (Fig. 3.1d). Thus, tuning the properties of catalysts and ligands may be able to favor *exo* selectivity.

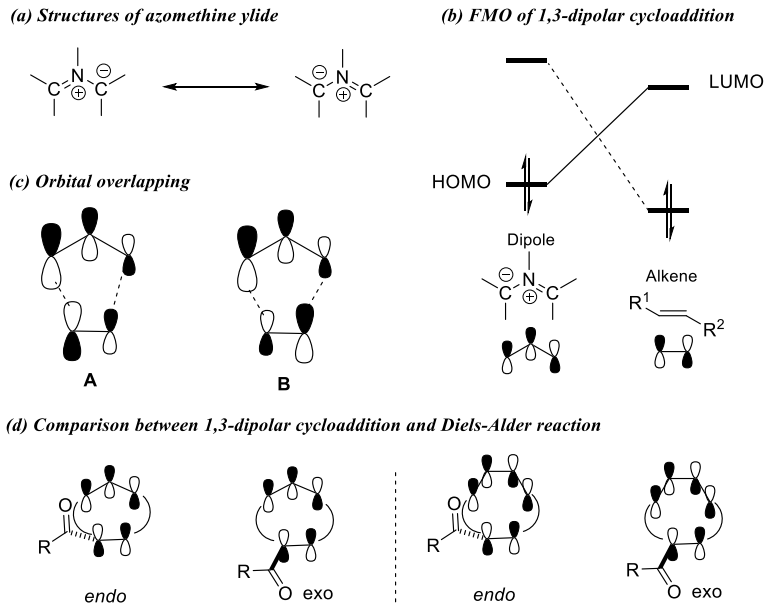


Figure 3.1. The structure, diastereoselectivity and regioselectivity of 1,3-dipolar cycloaddition. (a) Zwitterionic structure of azomethine ylide. (b) Frontier molecular orbitals of 1,3-dipolar cycloaddition. (c) Regioselectivity of 1,3-dipolar cycloaddition. (d) *Endo*/*exo* selectivity of 1,3-dipolar cycloaddition compared to Diels-Alder reaction.

The regioselectivity of the reaction is controlled by the frontier molecular orbitals (FMO). Azomethine ylides are electron-rich reactive species with high-energy HOMOs and LUMOs. In the reactions with electron deficient alkenes, the $HOMO_{dipole}$ preferentially overlaps with $LUMO_{dipolarophile}$ because of the smaller energy gap (Fig. 3.1b). The reaction proceeds in a way to maximize the highest overlap of the orbitals. As depicted in Fig. 3.1c, the transition state A is more stable than B because of more efficient orbital overlap. This property controls the regioselectivity of 1,3-dipolar cycloaddition.

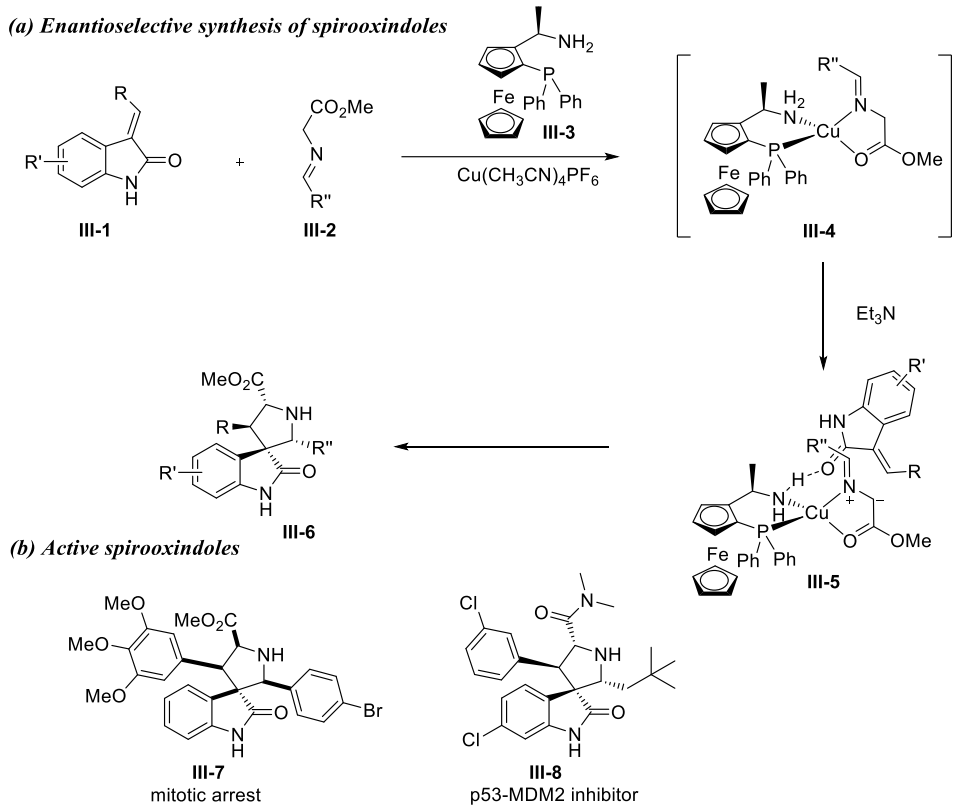


Figure 3.2. Hydrogen bond directed highly diastereo- and enantio-selective 1,3-dipolar cycloaddition. (a) Plausible reaction mechanism of hydrogen bond directed catalysis. (b) Spirooxindole **III-7** synthesized by reaction depicted in (a) induced mitotic arrest. Another reported spirooxindole **III-8** behaved differently inhibiting p53-MDM2 interaction.

Spirooxindole is a privileged scaffold with potent and diverse biological activities.[41] Under the guidance of BIOS, 3,3'-pyrrolidinyl-spirooxindole **III-6** was accessed *via* Cu(I) catalyzed highly diastereo- and enantio-selective 1,3-dipolar cycloaddition (Fig. 3.2a).[42] This catalytic reaction proceeds in a hydrogen bond directed transition state. Firstly, the complex **III-4** was deprotonated by base to give the azomethine ylide **III-5**, then the dipolarophile approached through a hydrogen bond with the ligand. All of the synthesized compounds were then screened using diverse biological assays, however, only compound **III-7** induced mitotic arrest. Different from Wang's report that 3,3'-pyrrolidinyl-spirooxindole is a hit scaffold

targeting p53-MDM2 interaction,[43] our results revealed that this scaffold could also interfere with microtube polymerization (Fig. 3.2b). This discovery again emphasizes the utility of biology-oriented synthesis in identifying novel chemotypes with new bioactivities by varying substituents on the scaffolds.

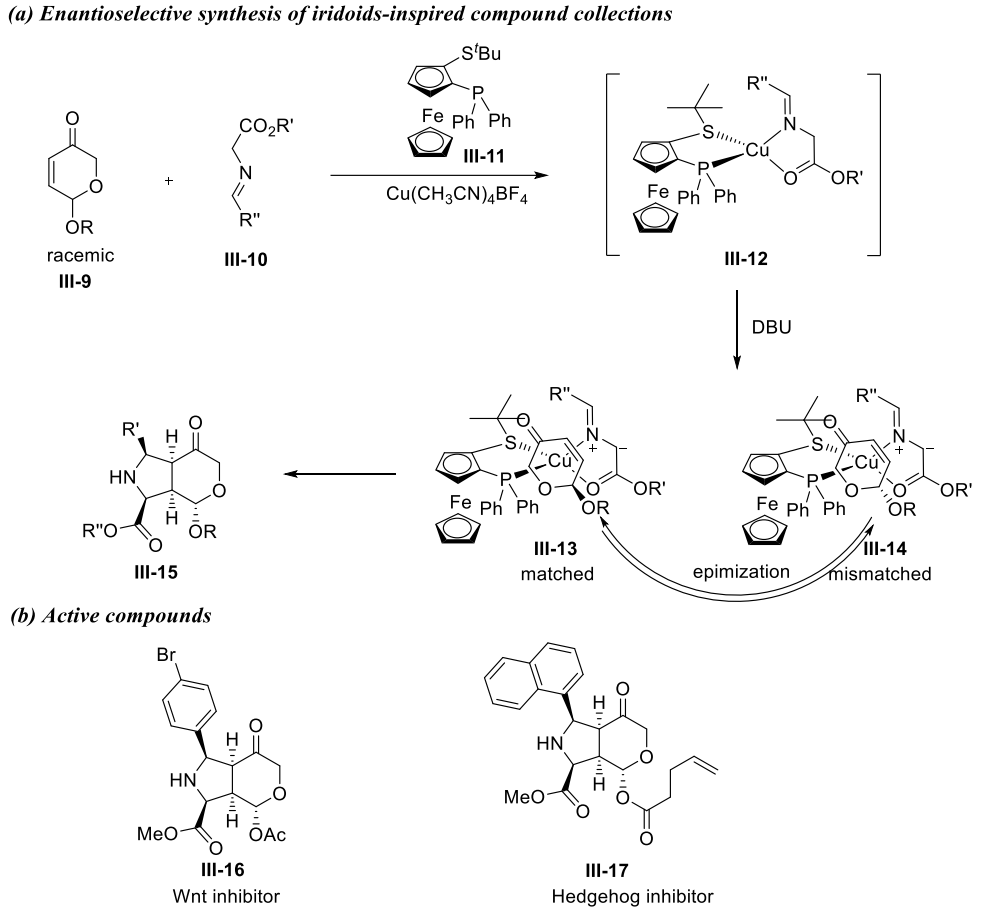


Figure 3.3. Dynamic kinetic resolution enabled by 1,3-dipolar cycloaddition. (a) Stereoconvergent 1,3-dipolar cycloaddition. (b) Biologically active compounds synthesized by the reaction depicted in (a).

In the synthesis of iridoid-inspired compound collections, Schiff base **III-10** reacted with the substrate **III-9** yielding highly potent inhibitors towards Wnt and Hedgehog signaling pathways (Fig. 3.3).[44] Notably, in the reaction with the racemic substrate **III-9**, only one cycloadduct **III-15** was formed. When the Cu(I) chelates with the azomethine ylide and Fesulphos, the steric hindrance confines the reaction to occur on the less hindered side. On another hand, the reaction favors *endo* selectivity. To avoid the repulsion between the OR group and azomethine ylide, only (*R*)-configured substrate matches with the chiral environment with its OR group oriented away from the azomethine ylide (**III-13**). However, there is a balance between the racemic substrates *via* epimerization. With the reaction

proceeding through dynamic kinetic resolution, the racemic substrates can be completely transformed to the solely chiral products.

3.1.2 Cell painting profiling

Unbiased biological evaluation of synthesized compound collections is highly crucial to the success of pseudo natural product design. Different from BIOS and ring distortion, pseudo-NPs have no guiding natural products, so that an unbiased and high-content profiling is in high demand. With the development of phenotypic screening and image-based analysis, cell painting has now emerged as a morphological profiling method to extract hundreds of biologically relevant parameters (Fig. 3.4).[45] U2OS cells are treated with testing compounds and then stained by six orthogonal fluorescent dyes to reveal the perturbations of seven cellular compartments and organelles, such as nucleus, mitochondria, endoplasmic reticulum, golgi/plasma membrane and F-actin.

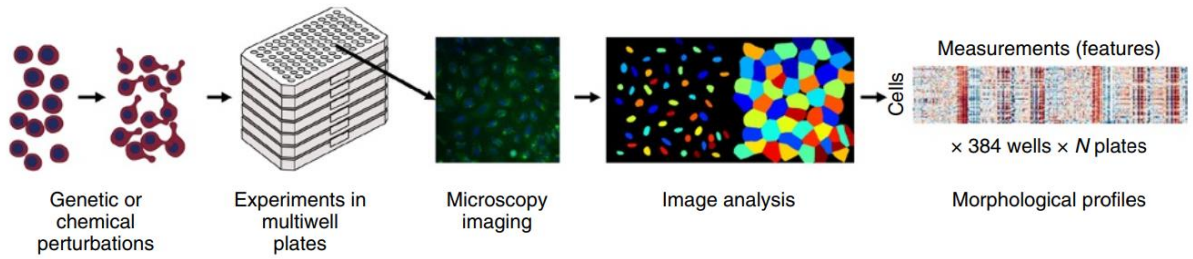


Figure 3.4. Cell painting workflow. Reprinted from ref.[45a] Copyright (2016) Nature.

In 2016, Schreiber et. al. utilized such a real-time biological profiling method to evaluate the synthesized compound collections.[46] All the tested compounds are isomeric triads and have similar molecular size. Cell painting profiles indicated that concentration, structural scaffolds and substituents exhibit an impact on the biological performance.

Besides evaluation of the library diversity, cell painting can also be used to predict possible MoAs of testing compounds. Biosimilarity is calculated according to the correlation distance between two profiles. High biosimilarity between tested compounds and reference compounds (those annotated with validated MoA) will suggest the possible bioactivity or targets. In our inhouse screening of the pseudo natural product pyrano-furo-pyridones (PFPs),[47] none of them exhibited significant inhibition towards Wnt- and hedgehog signaling pathways, autophagy, glucose transport, and histone deacetylase SIRT-1. After a careful comparison of cell painting profiles between PFPs and reference compounds,

researchers discovered that compound **III-18** displayed high cross biosimilarity with reference compound aumitin **III-20**[48], which is annotated as an inhibitor of mitochondrial respiration by targeting mitochondrial complex I (Fig. 3.6). Mito Stress Test assay was employed to validate the mitochondrial inhibition through the evaluation of oxygen consumption rate and extracellular acidification rate of treated cells. Compound **III-18** induced dose-dependent mitochondrial respiration with a half maximal effective concentration (EC_{50}) of 3.7 ± 0.9 μM. This is a strong support that cell painting can assist the discovery of biological activities unbiasedly.

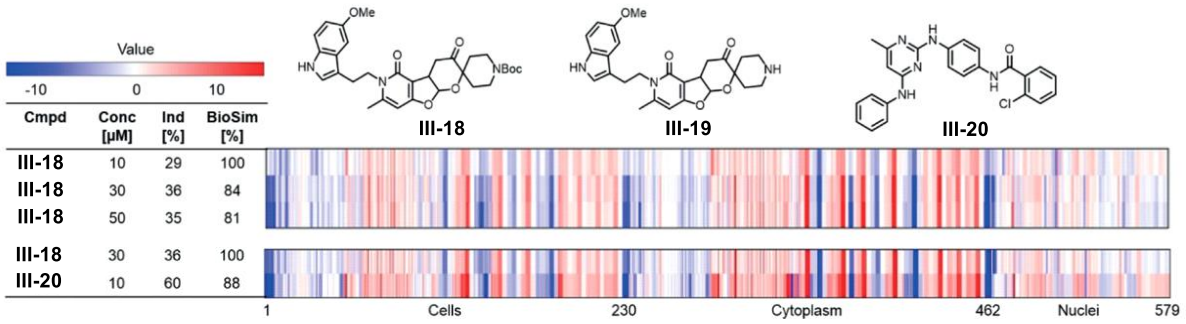


Figure 3.6. Cell painting assisted target hypothesis. [47]

3.2 Project design

In our previous work on pseudo natural products, two NP fragments were unprecedentedly recombined in one specific connective pattern, like indotropane[35b] and azaquindole[39]. Even though a structurally complex library was established, lack of diversity limited the development of pseudo natural product concept. Using different NP fragments for recombination is an approach to increasing the structural diversity of the compound library. In our recent work, different fragment-sized NP derivatives are recombined with indole or chromanone yielding a chemically and biologically diverse library (Fig. 3.7).[49]

Besides changing the recombined NP fragments, varying the connectivity patterns and positions would also lead to both structurally complex and diverse scaffolds that might display distinctly different biological performance. To validate this hypothesis, we aimed to design a systematic synthesis of the pseudo natural products, where the same two NP fragments are combined in different connectivity patterns, e. g. fused, spirocyclic or bridged combinations (Fig. 3.8, see structures **III-33**, **36**, and **37**), or fusion positions (Fig. 3.8, see structures **III-33**, **34**, and **35**).

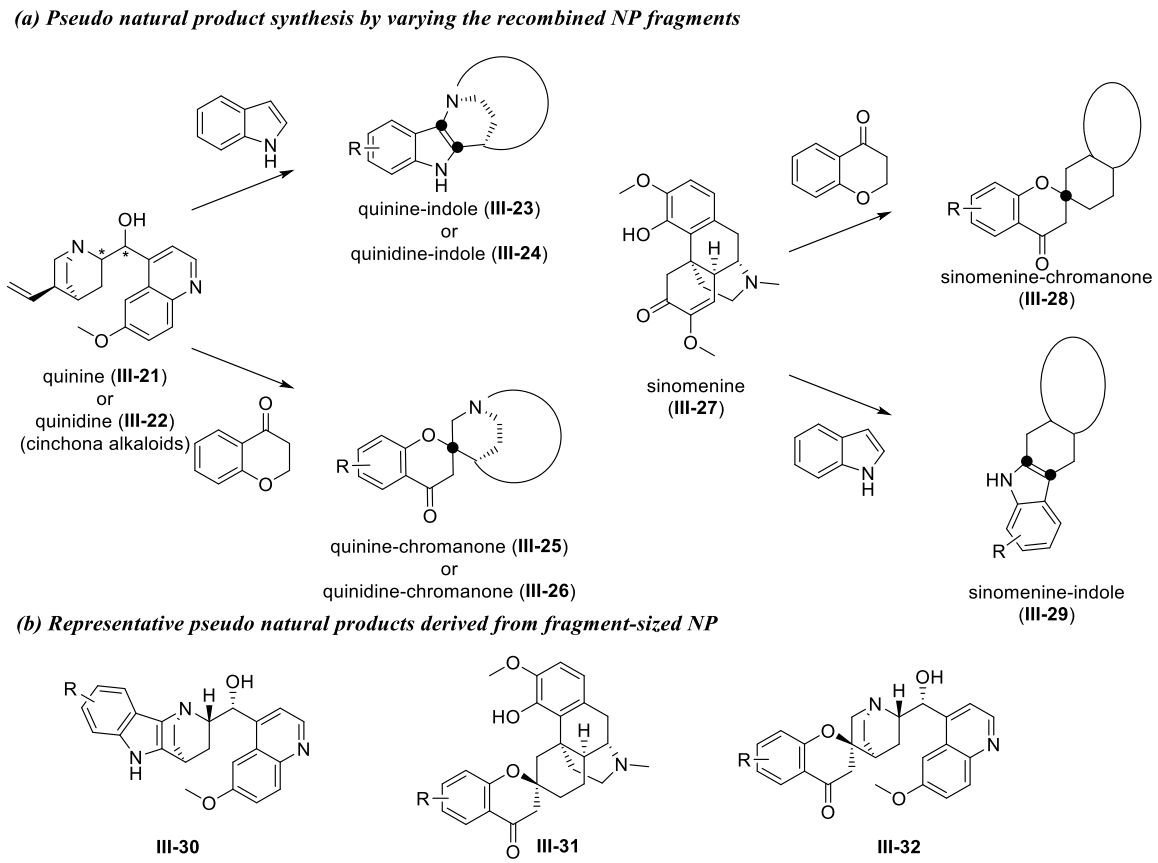


Figure 3.7. Representative pseudo natural products. (a) Pseudo natural products synthesis by varying the recombined NP fragments. (b) Representative pseudo natural products.

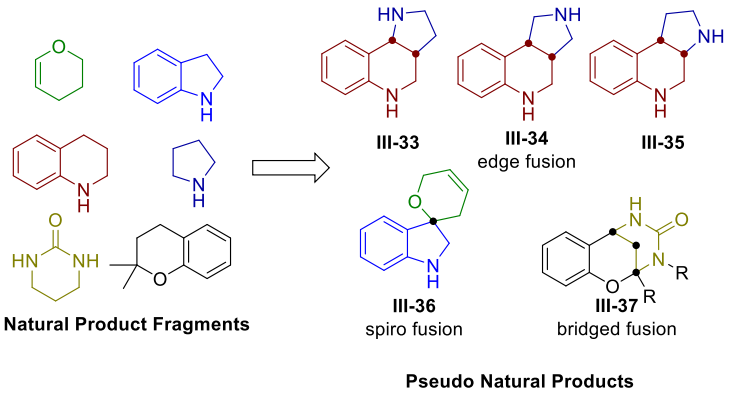


Figure 3.8. Systematic synthesis of pseudo natural products.

Pyrrolidine and tetrahydroquinoline are two common fragments rarely combined in natural products. Their broad occurrence in diverse biologically active natural products, such as kainic acid (**III-38**)[50], cocaine (**III-39**)[51], yaequinolone J1 (**III-41**)[52] and virantmycin (**III-42**)[53], inspired us that the unprecedented recombination of these two privileged fragments would lead to unexplored chemical and biological space (Fig. 3.9). To maximize the scaffold diversity, a systematic synthesis campaign was employed, where five pyrrolidine-

tetrahydroquinoline (pyrroquinoline) scaffolds were synthesized. These two fragments were fused in different arrangements to afford scaffold **III-43**, **44** and **45**. Different connectivity patterns, like spirocyclic and bridged combinations, yielded scaffolds **III-46** and **47** respectively. In order to obtain an overview of the relationship between sp^3 rich pseudo natural products and planar drug-like molecules, all the fused scaffolds (**III-43 – III-45**) were converted to their aromatized derivatives (**III-48 – III-50**) respectively. At last, a scaffold diverse NP-inspired pseudo natural product library was established by varying the connectivity patterns, positions and saturation states of the same NP fragments.

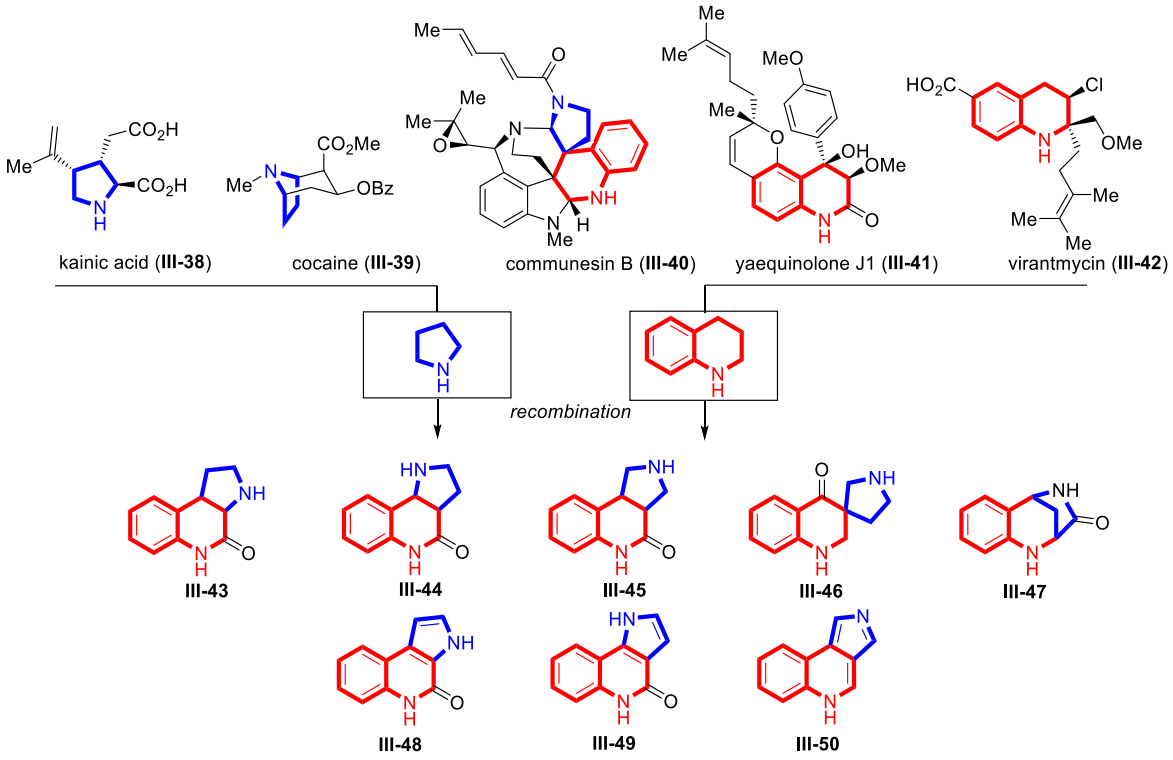


Figure 3.9. Design of pseudo natural product pyrroquinolines. Diverse connections (fused, spirocyclic and bridged combinations) and saturation states lead to eight pseudo-NP classes.

3.3 Results and discussion

3.3.1 Racemic synthesis of 7 classes of pyrroquinolines

1,3-Dipolar cycloaddition of azomethine ylide is a powerful and efficient synthetic methodology to incorporate pyrrolidine fragment into other scaffolds. All the scaffolds (except bridged **III-47**) were accessed using this unified methodology. Fused scaffold **III-43** was synthesized *via* intramolecular 1,3-dipolar cycloaddition according to our previous report

(Fig. 3.10).[54] It was then converted to the planar structure **III-48** using DDQ as the oxidant. Inspired by the success in the synthesis of **III-43** and **48**, a similar intramolecular Ag(I)-catalyzed cycloaddition was employed to give the scaffold **III-44** in excellent diastereoselectivity, which was then converted to its aromatized scaffold **III-49** in satisfying yield (Fig. 3.10).

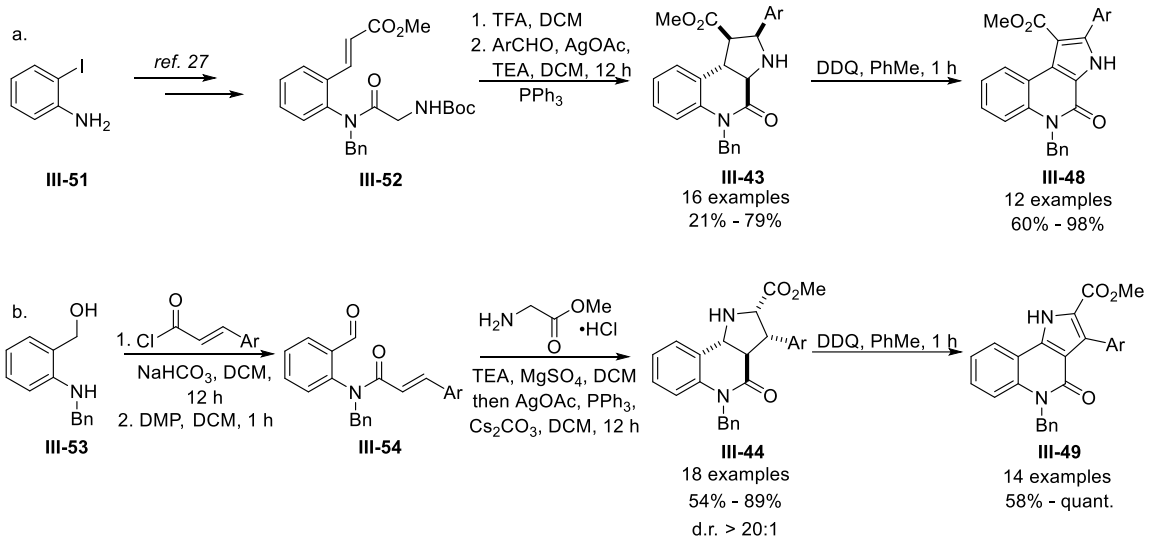


Figure 3.10. Synthesis of pseudo natural product pyrroquinoline **III-43**, **44**, **48** and **49**.

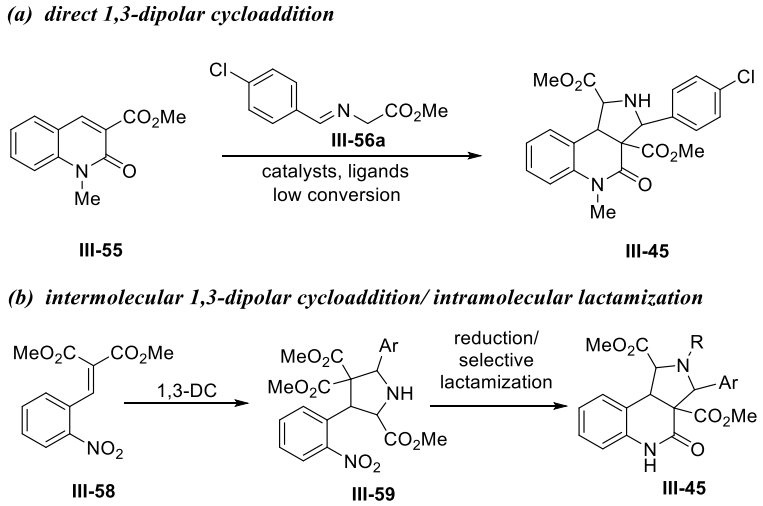


Figure 3.11. Synthetic strategy towards pseudo natural product pyrroquinoline **III-45**. (a) Low conversion was observed in 1,3-dipolar cycloaddition. (b) Intermolecular 1,3-dipolar cycloaddition followed by reduction/intramolecular lactamization cascade reaction.

We envisioned that the synthesis of fused scaffold **III-45** could be furnished by the 1,3-dipolar cycloaddition between Schiff base **III-56** and quinolinone **III-55** (Fig. 3.11a). However, only trace conversion was observed despite the screening of catalysts and ligands. The low reactivity was possibly attributed to the aromaticity of quinolinone. Then another strategy was proposed where 1,3-dipolar cycloaddition of linear dipolarophiles **III-58**

followed by reduction/intramolecular lactamization cascade reaction afforded the target scaffold **III-45** (Fig. 3.11b).

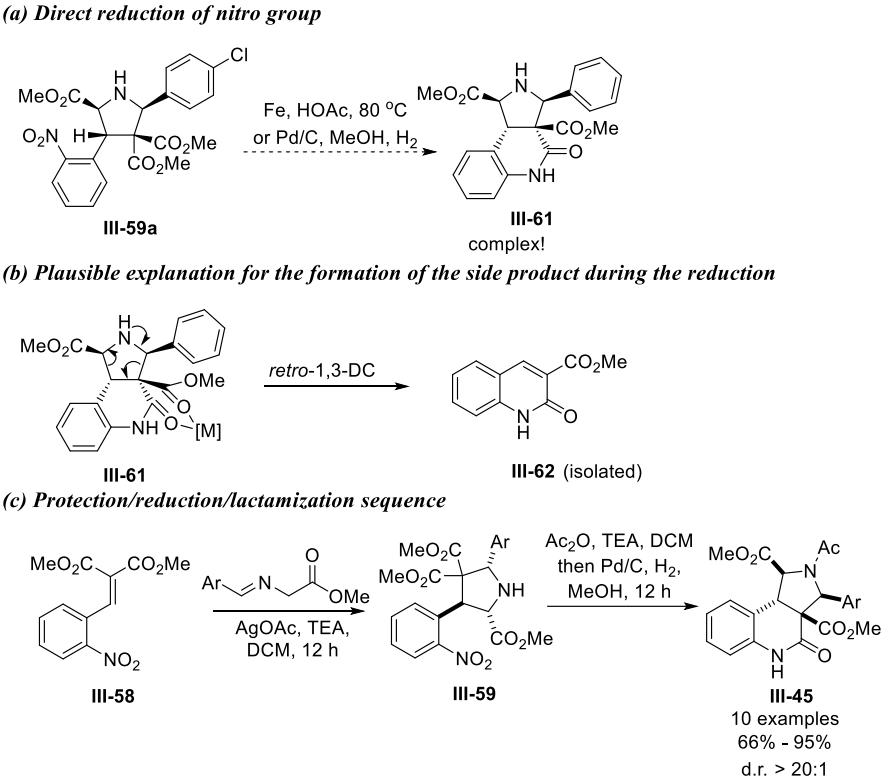


Figure 3.12. Synthesis of pyrroquinoline **III-45**. (a)(b) Unsuccessful reduction of pyrrolidine and proposed retro-1,3-dipolar cycloaddition. (c) Protection of pyrrolidine turned out to be crucial to stabilize the final product.

The cycloaddition between azomethine ylide and electron-deficient alkene **III-58** afforded functionalized pyrrolidine **III-59** in high yield and diastereoselectivity (Fig. 3.12c). However, the direct reduction of the product was problematic. Under the classic conditions for the reduction of nitro group, the reaction was really complex, and it was hard to isolate the desired product (Fig. 3.12a). When Pd/C was employed, one main product was isolated, which turned out to be the quinolinone fragment **III-62** (Fig. 3.12b). We postulated that the reduction of nitro group took place, however, the sequentially lactamized product **III-61** was not stable enough under the reduction conditions. Palladium would chelate with the 1,3-dicarbonyl moiety and activate the unusual retro-1,3-dipolar cycloaddition. To prevent such a process, protection of pyrrolidine was crucial. After the attachment of Ac group on the pyrrolidine, the following reduction and intramolecular lactamization took place to give single diastereomer **III-45** (Fig. 3.12c). To be noted, the reaction occurred in high diastereoselectivity and regioselectivity in spite of the presence of three ester groups.

However, the direct aromatization of scaffold **III-45** was not successful because of the quaternary center on the structure. Therefore, a *de novo* synthesis toward scaffold **III-50** should be developed. Based on the retrosynthetic analysis of this scaffold, direct cycloaddition between quinolinium salts **III-65** and azomethine ylides should be the most concise one (Fig. 3.13d). Many methodologies have already been developed for reactions with quinolinium salts. Under basic conditions, quinolinium salts can be converted to the ylides (1,3-dipoles), followed by the cycloaddition with dipolarophiles (Fig. 3.13a).[55] Owing to the electrophilic properties of quinolinium salts, they can also undergo the nucleophilic attack at C2 or C4 positions (Fig. 3.13b).[56] Recently, the Donohoe group reported the concise reductive C3-functionalizaiton of quinolinium salts through an interrupted transfer hydrogenation (Fig. 3.13c).[57] This reaction featured an Iridium-hydride (Ir-H) reduction, followed by the enamine trapping before a final C2-reductive quenching of the iminium **III-68**. Inspired by the cascade reaction on the quinolinium salts, we envisioned that dual-functional reagents can first undergo the C4-nucleophile attack and then intramolecular trapping of the electrophiles to fuse a new ring on C3/4 edge, which can be further quenched with oxidative conditions (Fig. 3.13d).

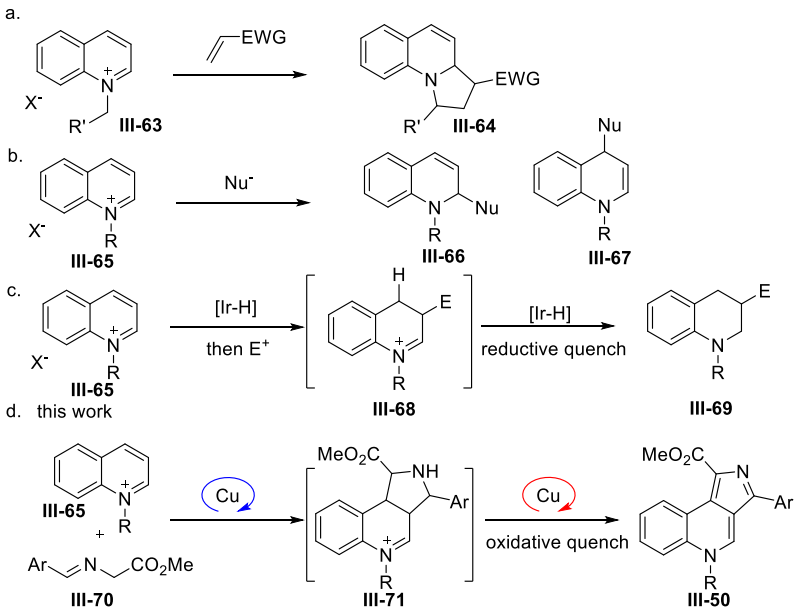
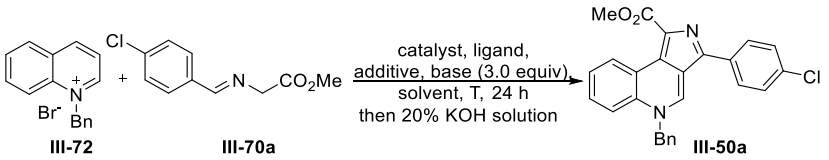


Figure 3.13. (a)-(c): Previous reports regarding the reactions of quinolinium salts. (d) Concepts of tandem dearomatization/oxidation cascade catalyzed by copper.

Azomethine ylides are such reagents that can possibly cyclize with the quinolinium salts *via* concerted or stepwise pathways. 1,3-Dipolar cycloaddition has emerged as a powerful method to synthesize the pyrrolidines from azomethine ylides and electron deficient alkenes, like linear or cyclic enones, or nearly neutral styrenes.[40a, 40b] However, there are almost no

reports about dearomative 1,3-dipolar cycloaddition of quinolinium salts. The challenges of this reaction come from two aspects: the driving force for the dearomatization and the efficiency of the oxidation step. Most pyrrolidines synthesized by 1,3-dipolar cycloaddition need additional oxidants to be converted into pyrroles. Considering the copper catalyzed aerobic oxidation,[58] is it possible to develop a tandem reaction to synthesize the pyrroquinoline **III-50** in one pot as shown in Fig. 3.13d.

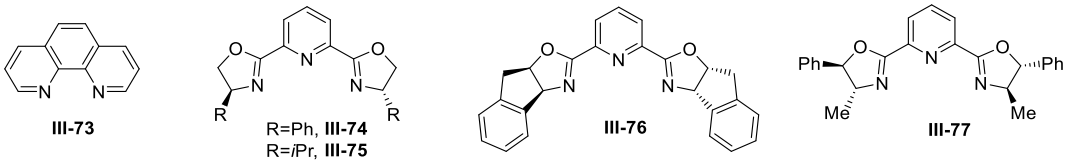
Table 3.1. Condition screening for 1,3-dipolar cycloaddition of quinolinium salts.



III-72 **III-70a** **III-50a**

Entry	Catalyst	Ligand	Additive	T [°C]	Yield[c]
1[a]	$CuPF_6(CH_3CN)_4$	-	-	r.t.	49%
2[a]	$CuPF_6(CH_3CN)_4$	-	O_2	40 °C	73%
3[a]	$CuPF_6(CH_3CN)_4$	-	Pd/C[d]	40 °C	79%
4[a]	$CuPF_6(CH_3CN)_4$	-	DDQ[e]	40 °C	76%
5[b]	$CuPF_6(CH_3CN)_4$	-	O_2	r.t.	71%
6[b]	$CuPF_6(CH_3CN)_4$	**III-73**	O_2	r.t.	77%
7[b]	$CuPF_6(CH_3CN)_4$	**III-74**	O_2	r.t.	84%
8[b]	$CuPF_6(CH_3CN)_4$	**III-75**	O_2	r.t.	81%
9[b]	$CuPF_6(CH_3CN)_4$	**III-76**	O_2	r.t.	80%
10[b]	$CuPF_6(CH_3CN)_4$	**III-77**	O_2	r.t.	87%
11[b]	-	-	O_2	r.t.	64%

(a) quinoline (1.0 equiv), iminoester (1.5 equiv), catalyst (15 mol%), reaction scale 0.20 mmol, CH_3CN 2.0 mL. (b) quinoline (1.0 equiv), iminoester (1.5 equiv), catalyst (5.0 mol%), ligand (6.0 mol%), reaction scale 0.10 mmol, CH_3CN 1.0 mL. (c) Isolated yield after column chromatography. (d) 25 mol%. (e) 3.0 equiv.



III-73 **III-76** **III-77**

Initial attempt began with the cycloaddition of *N*-benzyl quinolinium bromide **III-72** and Schiff base **III-70a**. Primary screening of the conditions revealed $Cu(CH_3CN)_4PF_6$, acetonitrile and triethylamine are the optimal catalyst, solvent and base, respectively, to give 49% yield of pyrroquinoline **III-50a** (Table 3.1, entry 1). Considering the second oxidation step, a series of oxidative additives was screened. Oxygen was more favored compared with

high loading quantities of Pd/C and DDQ (Table 3.1, entry 2-4). We further lowered the reaction temperature and the amount of copper catalyst to achieve only a small decrease in the yield (Table 3.1, entry 5). In the pioneering research of Cu-O_2 chemistry, ligands could assist the formation of peroxide complex, which was the active intermediate for the oxidation.[58] Inspired by these studies, an extensive screening of ligands revealed the ligand **III-77** as the best one yielding the cycloadduct **III-50a** in 87% yield (Table 1, entry 10). The catalyst and ligand were found to promote the reaction based on control experiments (Table 1, entry 5, 11).

With the optimal reaction conditions in hand, the scope of Schiff bases was first explored (Fig. 3.14). The substrates tolerated a series of electron-donating (R=Me, OMe) and -withdrawing groups (R=Cl, Br, F, CF_3) at the *para* position of the phenyl moiety. The corresponding products **III-50a – 50g** were isolated in 45-87% yield. The *meta*- or *ortho*-substituted Schiff bases reacted with **III-72** in satisfying yields. To be noted, this reaction could tolerate the sterically hindered *ortho*-bromo-substituted Schiff base to give **III-50m** in 62% yield. And only moderate yield was obtained when reacting with the *ortho*- oxygen-containing substitutions (**III-50o** and **50p**).

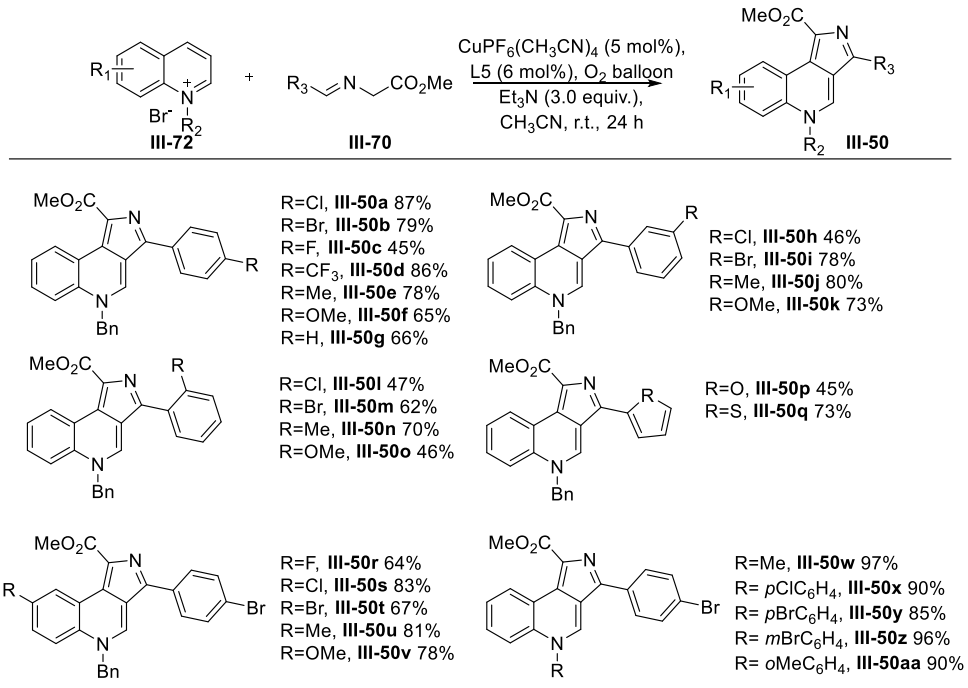


Figure 3.14. Substrate scope of azomethine ylides and quinolinium salts. Isolated yield after column chromatography.

Then the scope of quinolinium salts was investigated. Substitutions at C6 position of quinoliniums were tolerated, delivering products **III-50r – III-50v** in 64-83% yield.

Moreover, diverse substitutions at *N*-benzyl group also reacted in excellent yields. And the *N*-methyl quinolinium iodide afforded the product **III-50w** in 97% yield. However, the pyridinium salt failed to give the desired product, which was compatible with the higher aromatization energy of pyridines than that of quinolines.

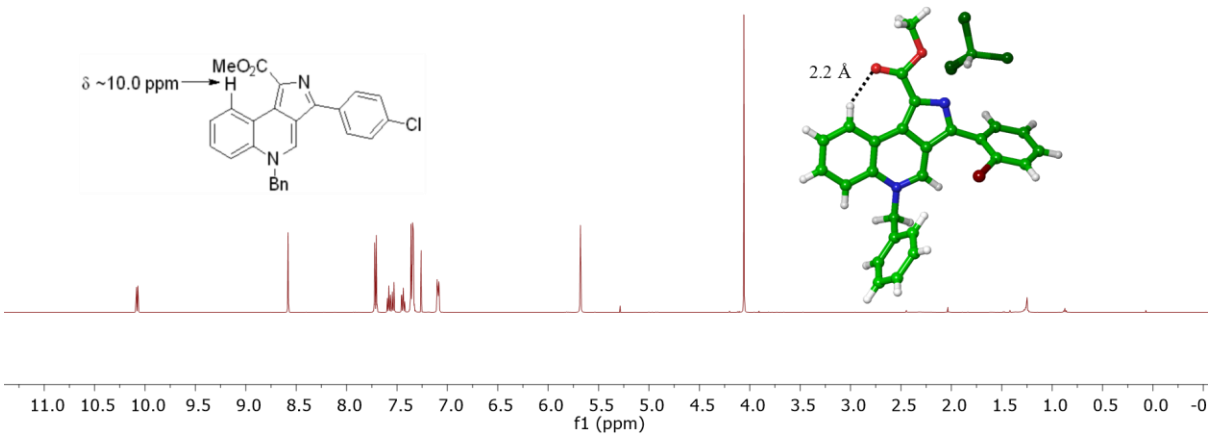


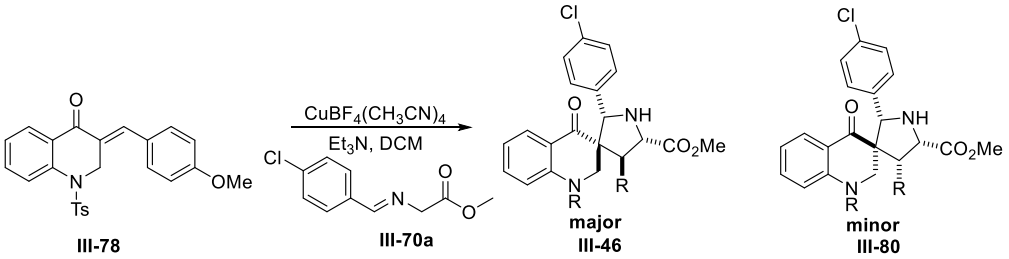
Figure 3.15. Structure and ^{1}H NMR of pyrroquinoline **H** in $CDCl_3$.

Notably, the ^{1}H NMR of the compound was really unusual, with a downfield shift of C5-H to ~10 ppm, which is rare in substituted quinolines. The structure of **III-50m** was confirmed by single crystal X-ray diffraction (Fig. 3.15). The downfield shift was possibly induced by the intramolecular hydrogen bond between ester oxygen atom and the proton at C-5 position. This hypothesis was validated based on its X-ray structure with a distance of 2.2 Å between these two atoms.

The spirocyclic scaffold **III-46** was then synthesized *via* an intermolecular 1,3-dipolar cycloaddition between enone **III-78** and azomethine ylides. Different from the intramolecular results, this reaction afforded a pair of inseparable diastereomers. After extensive screening of the catalysts, solvents and temperatures, the reaction could only yield the product in 4.6:1 selectivity (Table 3.2, entry 1). To gain the pure product for screening in biological assays, Boc-protected dihydroquinolinone was employed as the substrate. After the cycloaddition, deprotection of the Boc group enabled the isolation of pure *endo*-type product in acceptable yield (see experimental part 7.2.1.4).

In summary, 1,3-dipolar cycloaddition was applied strategically to yield the pyrroquinoline embedded with similar appendages. In addition to the scaffold **III-47** synthesized by Dr. Gregor Cremosnik (32 members), a structurally diverse library of eight scaffolds and 155 members was constructed.

Table 3.2. Screening table for intermolecular 1,3-dipolar cycloaddition towards spirocyclic scaffold **III-46**.



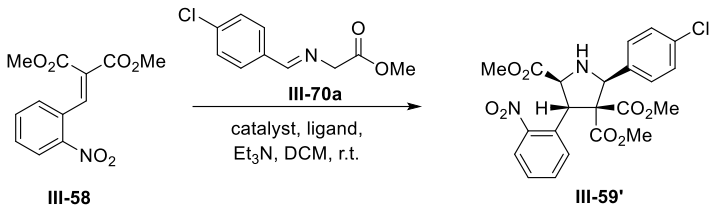
Entry	Catalyst	solvent	based	T [°C]	d.r. (**III-46**:**III-80**)
1	$CuBF_4(CH_3CN)_4$	DCM	Et_3N	r.t.	4.6:1
2	AgOAc	DCM	Et_3N	r.t.	2.9:1
3	AgTFA	DCM	Et_3N	r.t.	2.6:1
4	$CuPF_6(CH_3CN)_4$	DCM	Et_3N	r.t.	2.1:1
5	$CuBF_4(CH_3CN)_4$	DCM	Et_3N	0	4.3:1
6	$CuBF_4(CH_3CN)_4$	THF	Et_3N	r.t.	2.8:1
7	$CuBF_4(CH_3CN)_4$	DCE	Et_3N	r.t.	4.5:1
8	$CuBF_4(CH_3CN)_4$	DME	Et_3N	r.t.	3.2:1
9	$CuBF_4(CH_3CN)_4$	Et_2O	Et_3N	r.t.	2.3:1
10	$CuBF_4(CH_3CN)_4$	PhMe	Et_3N	r.t.	2.5:1
11	$CuBF_4(CH_3CN)_4$	MeOH	Et_3N	r.t.	3.1:1

Alkene **III-78** (0.10 mmol, 1.0 equiv.), Schiff base **III-70a** (0.15 mmol, 1.5 equiv.) and base (0.10 mmol, 1.0 equiv.) were reacted in solvent (0.10 M, 1 mL) with 10 mol% metal catalysts. d.r. was determined from the reaction mixture by means of ^{1}H NMR.

3.3.2 Asymmetric synthesis of pyrro[3,4-*c*]quinolines

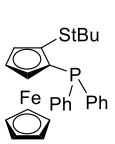
Encouraged by the excellent diastereoselectivity of the racemic synthesis of pyrroquinoline **III-45**, an enantioselective approach was developed. Initially, a series of ligands was screened for intermolecular 1,3-dipolar cycloaddition, among which (*R*)-Fesulphos[59] was the most optimal one to give excellent yield and enantioselectivity (Table 3.3, entry 1-5). In the presence of AgOAc, a decline of *ee* was observed (Table 3.3, entry 6). Increasing the amount of iminoester **III-70a** led to improved yield and excellent *ee* (Table 3.3, entry 7). However, no obvious enhancement was observed under higher catalyst and ligand loading (Table 3.3, entry 8).

Table 3.3. Condition screening of intermolecular 1,3-dipolar cycloaddition.

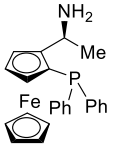


III-58 III-59'

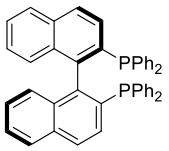
Entry	catalyst	ligand	Yield	*ee*
1	$CuBF_4(CH_3CN)_4$	**III-11**	74%	99%
2	$CuBF_4(CH_3CN)_4$	**III-3**	25%	26%
3	$CuBF_4(CH_3CN)_4$	**III-81**	20%	-64%
4	$CuBF_4(CH_3CN)_4$	**III-82**	12%	-81%
5	$CuBF_4(CH_3CN)_4$	**III-83**	trace	n.d.
6	AgOAc	**III-11**	33%	74%
7*	$CuBF_4(CH_3CN)_4$	**III-11**	94%	99%
8¶	$CuBF_4(CH_3CN)_4$	**III-11**	87%	98%



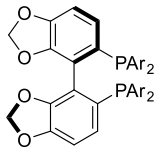
III-11



III-3

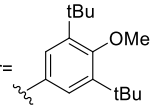


III-81



III-82 Ar=Ph

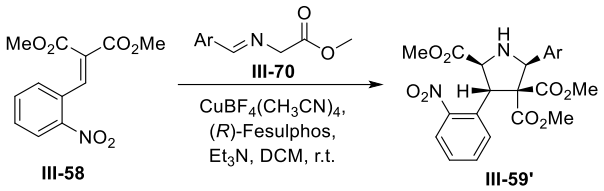
III-83 Ar=



Unless otherwise specified, all reactions were performed using dipolarophile **III-58** (0.10 mmol, 1.0 equiv.), Schiff base **III-70a** (0.15 mmol, 1.5 equiv.), Et_3N (0.02 mmol, 0.20 equiv.) in dry DCM (0.10 M, 1 mL) with 5 mol% catalyst and 6 mol% ligand for 24-48 hours. Isolated yield after column chromatography. The *ee* was determined by chiral HPLC. * Schiff base **III-70a** (0.20 mmol, 2.0 equiv.) was used. ¶ 10 mol% catalyst and 12 mol% ligand was used. N.d., not determined.

With optimal reaction conditions in hand (Table 3.3, entry 7), the substrate scope of the intermolecular 1,3-dipolar cycloaddition was explored (Table 3.4). Different substitutions on Schiff base **III-70a** were compatible with the reactions. Regardless of the electronic properties of substitutions on *para*- or *meta*- positions, high yield and more than 95% *ee* were obtained. The reaction could tolerate sterically hindered azomethine ylides with *ortho*-substitutions (Table 3.4, entry 12-15). However, a decline of yield and *ee* was observed when 2-thiophenyl azomethine ylide was employed (Table 3.4, entry 16).

Table 3.4. Scope of intermolecular 1,3-dipolar cycloaddition.

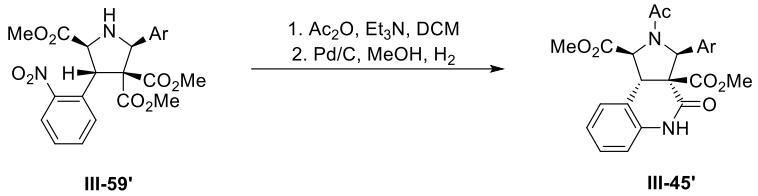


Entry	Product	Ar	Yield	ee
1	**III-59'a**	*p*-ClC_6H_4	89%	>99%
2	**III-59'b**	*p*-BrC_6H_4	88%	99%
3	**III-59'c**	*p*-FC_6H_4	73%	99%
4	**III-59'd**	*p*-$CF_3C_6H_4$	80%	98%
5	**III-59'e**	*p*-MeC_6H_4	78%	97%
6	**III-59'f**	*p*-$MeOC_6H_4$	80%	n.s.
7	**III-59'g**	*p*-CNC_6H_4	86%	96%
8	**III-59'h**	Ph	91%	n.s.
9	**III-59'i**	*m*-BrC_6H_4	99%	98%
10	**III-59'j**	*m*-MeC_6H_4	93%	99%
11	**III-59'k**	*m*-$MeOC_6H_4$	85%	95%
12	**III-59'l**	*o*-ClC_6H_4	75%	94%
13	**III-59'm**	*o*-BrC_6H_4	88%	95%
14	**III-59'n**	*o*-MeC_6H_4	83%	97%
15	**III-59'o**	*o*-$MeOC_6H_4$	60%	93%
16	**III-59'p**	2-thiophenyl	66%	91%

Unless otherwise specified, all reactions were performed on 0.3 mmol scale using optimal conditions.

After the asymmetric synthesis of pyrrolidines, the cycloadducts were converted to the target scaffolds **III-45'** sequentially (Table 3.5). The reduction/lactamization sequence took place in high efficiency and tolerated diverse substitutions on the phenyl group. The structures and absolute stereochemistry of pyrrolidine **III-59'b** and pyrroquinoline **III-45'c** were unambiguously confirmed by X-ray diffraction crystallography (Figure 3.16).

Table 3.5. Scope of lactamization.



III-59' **III-45'**

Entry	Product	R	Yield	*ee*
1	**III-45'a**	*p*-FC_6H_4	79%	99%
2	**III-45'b**	*p*-$CF_3C_6H_4$	66%	98%
3	**III-45'c**	*p*-MeC_6H_4	56%	n.s.
4	**III-45'd**	*p*-$MeOC_6H_4$	31%	99%
5	**III-45'e**	Ph	79%	95%
6	**III-45'f**	*m*-MeC_6H_4	93%	98%
7	**III-45'g**	*m*-$MeOC_6H_4$	85%	97%
8	**III-45'h**	*o*-$MeOC_6H_4$	47%	94%

Condition for step 1: pyrrolidine **III-59'** (0.1 mmol, 1.0 equiv.), Ac_2O (3.0 equiv.) and Et_3N (5.0 equiv.) were stirred until full consumption of the starting material. Step 2: the reaction mixture from step 1 underwent hydrogenation catalyzed by Pd/C (30 mg) in MeOH (3 mL).

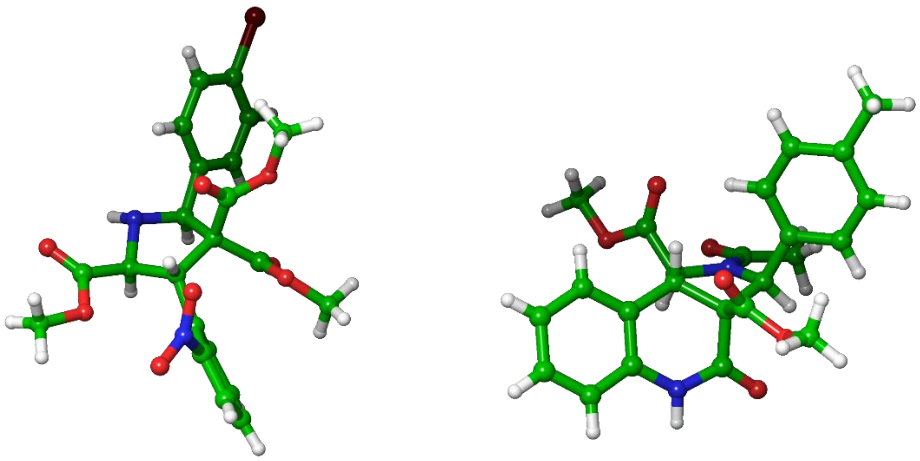


Figure 3.16. X-ray structure of pyrrolidine **III-59'b** (left) and pyrroquinoline **III-45'c** (right).

The proposed transition state for the asymmetric intermolecular 1,3-dipolar cycloaddition is shown in Fig. 3.17.[60] The azomethine ylide and (*R*)-Fesulphos are chelated by Cu(I) catalyst, and the chiral ligand confines the cycloaddition to take place on the front face. When the dipolarophile approaches the chelated complex in *endo*-selectivity, steric repulsion would disfavor such a pathway (**III-85**, Fig. 3.17). Therefore, the *exo*-product was formed in high yield and excellent *ee*.

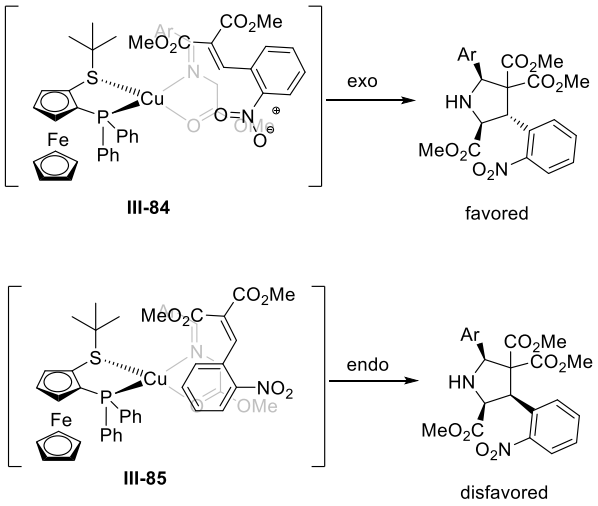


Figure 3.17. Proposed transition states for *exo*-selective 1,3-dipolar cycloaddition.

3.3.3 Asymmetric synthesis of pyrro[3,2-*c*]quinolines

Even though various intermolecular 1,3-dipolar cycloadditions have already been reported, the enantioselective intramolecular reactions are less explored,[54] mainly because of the higher rigidity of the substrate. To realize the asymmetric synthesis of pyrroquinoline **III-44**, diverse catalysts, ligands, solvents and temperatures were screened. Initially, all the reactions were conducted based on *N*-Me substrate. Aldehyde **III-86** reacted with the glycine methyl ester to give the Schiff base **III-87**, which was used sequentially for the asymmetric cycloaddition. The use of Cs_2CO_3 proved to be critical for the full conversion of the reaction compared with organic bases, like Et_3N and DBU. Under the catalysis of AgOAc and ligand **III-82**, the reaction afforded cycloadduct **III-88** in the highest yield and enantioselectivity (Fig. 3.18).

The low enantioselectivity might be attributed to the rigid substrate structure, and therefore, a mismatched substrate/catalyst pair was formed, although the screened ligands have been widely employed in other 1,3-dipolar cycloadditions. To reduce the rigidity of **III-86**, other substrates were explored. The benzylated derivative **III-54** showed higher reactivity and tunability relative to the *N*-Me substrate **III-86**.

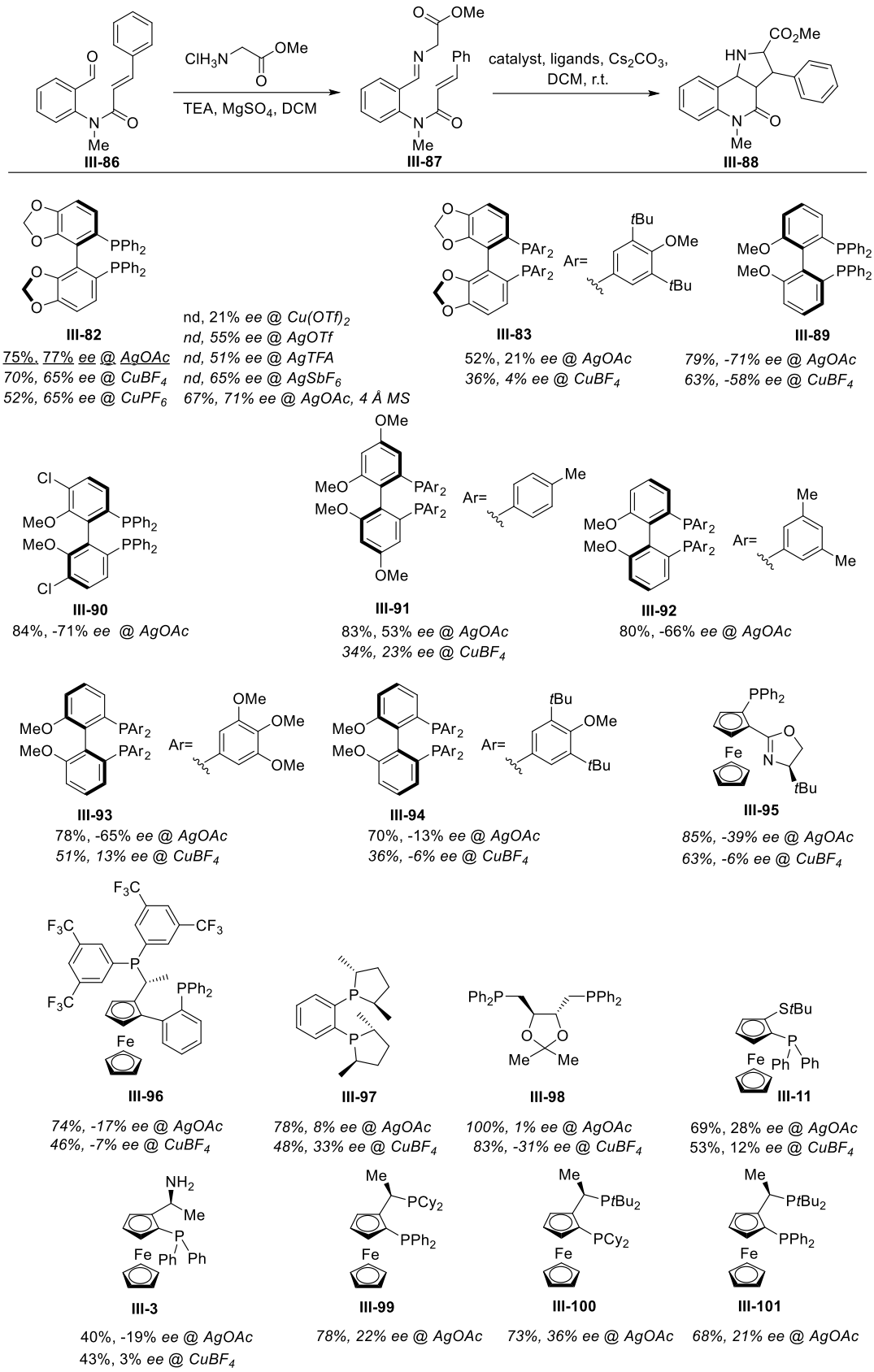
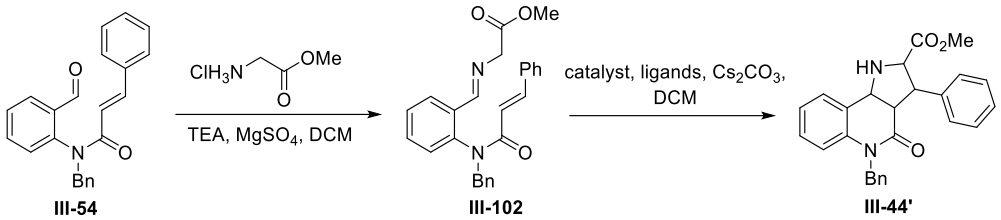


Figure 3.18. Condition screening for intramolecular 1,3-dipolar cycloaddition towards fused scaffold **III-88**. All the reactions were done based on aldehyde (0.1 mmol, 1.0 equiv.), catalyst (5% mol), ligand (6% mol) and Cs_2CO_3 (0.2 equiv.) in DCM (1.0 mL) at room temperature. $CuBF_4$ = $CuBF_4(CH_3CN)_4$.

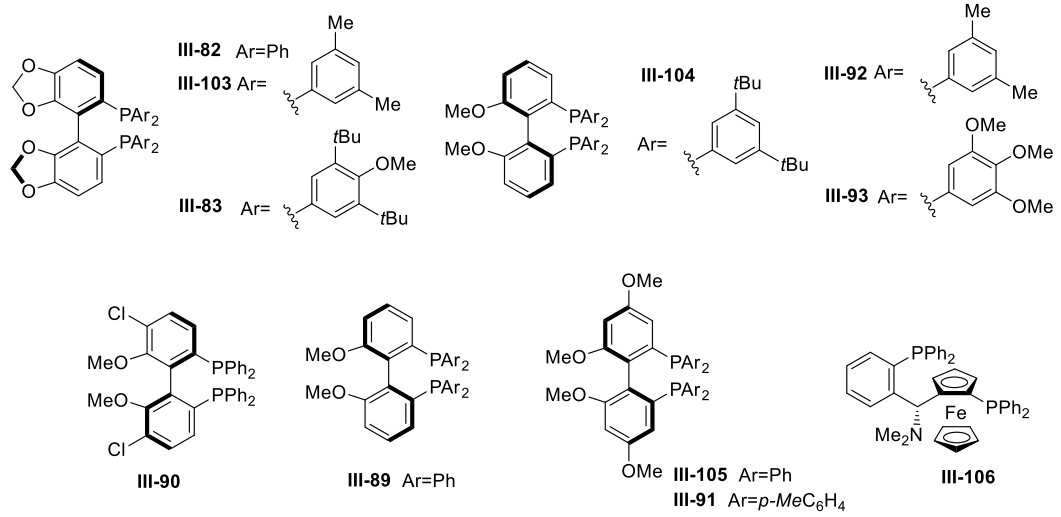
Table 3.7. Screening table for asymmetric intramolecular 1,3-dipolar cycloaddition



Entry	Catalyst	Ligand	solvent	T [°C]	Yield[c]	*ee*
1	AgOAc	**III-82**	CH_2Cl_2	r.t.	89%	75%
2	AgOAc	**III-82**	DCE	r.t.	55%	73%
3	AgOAc	**III-82**	THF	r.t.	90%	79%
4	AgOAc	**III-82**	Et_2O	r.t.	81%	77%
5	AgOAc	**III-82**	PhMe	r.t.	81%	73%
6	AgOAc	**III-82**	CH_3CN	r.t.	73%	69%
7	AgOAc	**III-103**	THF	r.t.	65%	74%
9	AgOAc	**III-83**	THF	r.t.	64%	5%
10	AgOAc	**III-104**	THF	r.t.	66%	17%
11	AgOAc	**III-92**	THF	r.t.	83%	79%
12	AgOAc	**III-93**	THF	r.t.	85%	6%
13	AgOAc	**III-90**	THF	r.t.	85%	26%
14	AgOAc	**III-89**	THF	r.t.	80%	73%
15	AgOAc	**III-105**	THF	r.t.	77%	71%
16	AgOAc	**III-91**	THF	r.t.	85%	67%
17	AgOAc	**III-106**	THF	r.t.	88%	1%
18	$CuBF_4$	**III-92**	THF	r.t.	70%	51%
19	$Cu(OAc)_2$	**III-92**	THF	r.t.	50%	56%
20*	AgOAc	**III-92**	THF	-10	67%	91%

Unless otherwise specified, all reactions were conducted on aldehyde (0.05 mmol, 1.0 equiv.), catalyst (10 mol%), ligand (12 mol%), base (20 mol%), solvent 1.0 mL. Isolated yield after column chromatography. The *ee* was determined by chiral HPLC. *The reaction was performed on 0.1 mmol scale.

Table 3.7. Screening table for asymmetric intramolecular 1,3-dipolar cycloaddition (continued).



Initially, solvent screening indicated that ether solvents (THF or Et_2O) afforded better selectivity (Table 3.7, entry 3, 4). Diverse ligands were then screened (Table 3.7, entry 7-17). When ligand **III-92** was employed, there was a slight increase of the enantioselectivity (Table 3.7, entry 11). The reaction was highly sensitive to the catalysts. Using Cu(I) or Cu(II) catalysts led to lower enantioselectivity (Table 3.7, entry 18, 19). To further improve the selectivity, the cycloaddition was conducted at -10 ^oC to yield 91% *ee* (Table 3.7, entry 20).

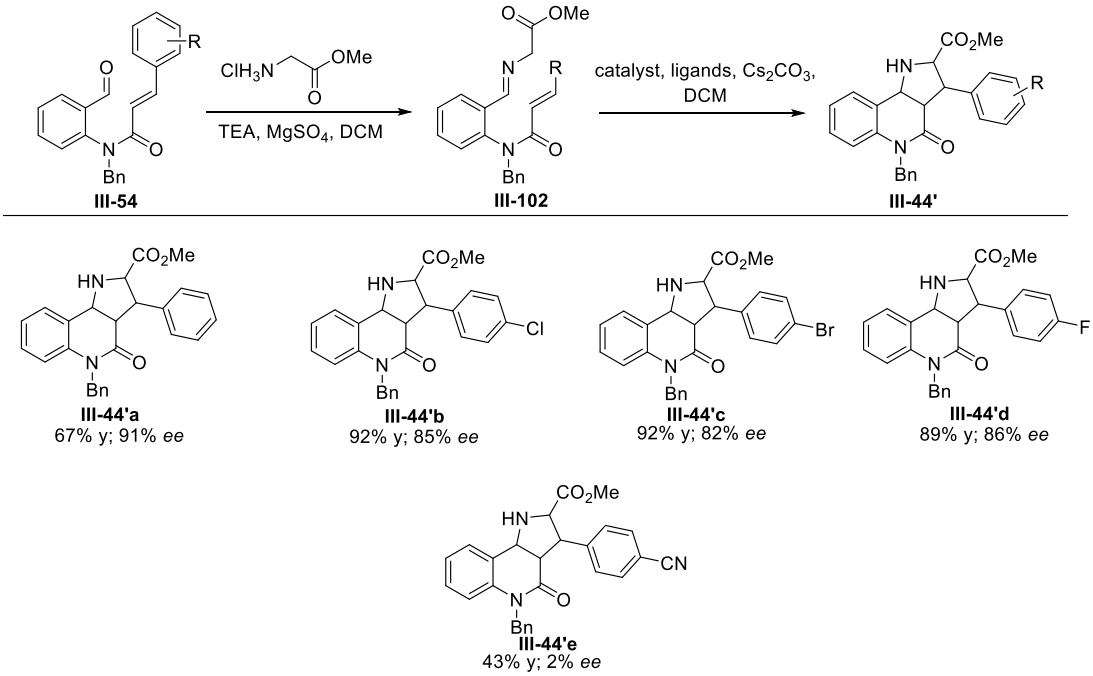


Figure 3.19. Substrate scope of *para*-substituted phenyl group.

With optimal conditions in hand, the substrate scope was then explored. It tolerated diverse substituents on the *para*-position of the phenyl group. However, electron deficient

substitution led to an extremely low enantioselectivity (**III-44'e**). This might be attributed to the Schiff base forming step, where the formation of racemic cycloadduct was observed. Furthermore, *meta*- or *ortho*-substituted substrates and different substituted benzyl group on amide were tolerated to give moderate enantioselectivity (Fig. 3.19). At last, a chiral compound collection was constructed and tested for biological activity.

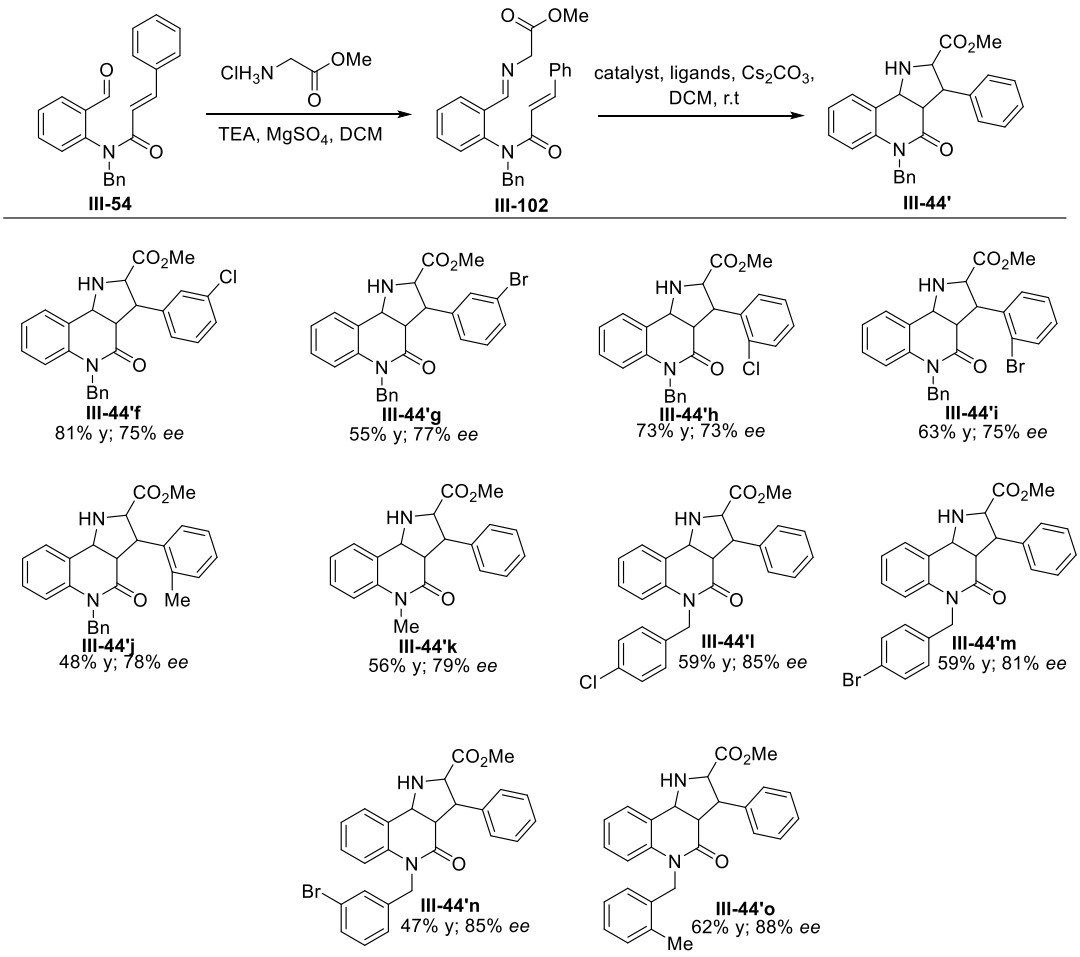


Figure 3.19. Substrate scope of *ortho/meta*-substituted phenyl group and different protections on amide.

3.3.4 Systematic analysis of pyrroquinolines

Data was produced by the compound management and screening center (COMAS) and analyzed by Jie Liu and Gregor Cremosnik.

The synthesized racemic compounds were first analyzed by a series of cheminformatic tools, like NP-likeness score and Tanimoto similarity. NP-likeness score, developed by Ertl et al.,[36] is calculated using the open-source software.[28, 61] It sums up the frequency of substructures found among natural products and man-made molecules in the range from -5 to +5. The

equation of NP-likeness score is given below where NP_i represents the number of NPs containing fragment i, while NP_{total} means the total number of NPs. "SM" represents synthesized or man-made molecules, SMi is the number of SMs containing fragment i, and SM_{total} is the total number of SMs. *fi*=0 indicates the substructure is found in NPs or SMs in the same frequency. *fi*>0 means the fragment occurs more frequently in NPs than SMs.

$$f_i = \log\left(\frac{NP_i / NP_{total}}{SM_i / SM_{total}}\right)$$

In the analysis of the pyrroquinoline library, the eight different scaffolds displayed distinctly different NP-likeness scores even though they contain almost the same NP fragments (Fig. 3.20). Only one scaffold **III-45** was found to display NP-likeness score higher than 0. This might be attributed to the common distribution of pyrrolidine and tetrahydroquinoline in SMs. Another plausible explanation to this score is that these two fragments are arranged in unprecedented ways not available in NPs.

Apparently, sp^3 rich scaffolds **III-43** – **47** exhibited higher NP-likeness scores than planar scaffolds **III-48** – **50**. Of the eight scaffolds, class **III-50** got lowest score. Notably, NP-likeness score seems to be independent on connection between two fragments. Scaffold **III-44** and its aromatized derivatives **III-49** displayed very similar scores, while scaffold **III-45** and **III-50** were highly different.

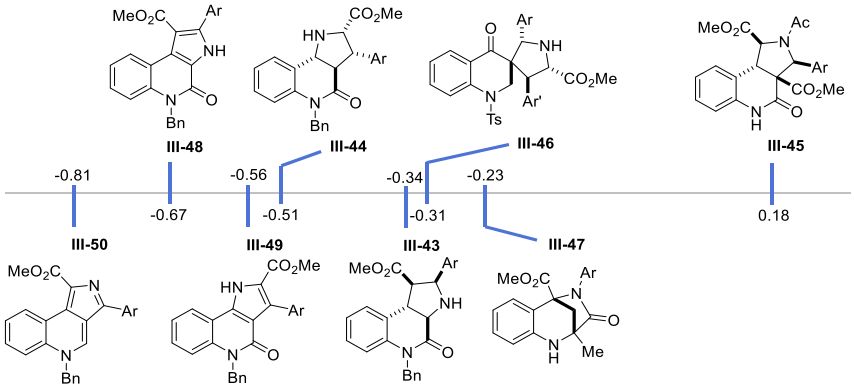


Figure 3.20. Average NP-likeness score of eight pyrroquinoline classes **III-43 – 50**.

We also compared the NP-likeness scores of all pyrroquinolines with the molecules from DrugBank[38] and NPs from ChEMBL database[37] (Fig. 3.21a). Although pyrrolidine and tetrahydroquinoline are two common NP fragments, the unprecedented combination of them led to novel chemical space resembling that of drug molecules. This tendency was also observed in pseudo natural product pyrano-furo-pyridones.[47]

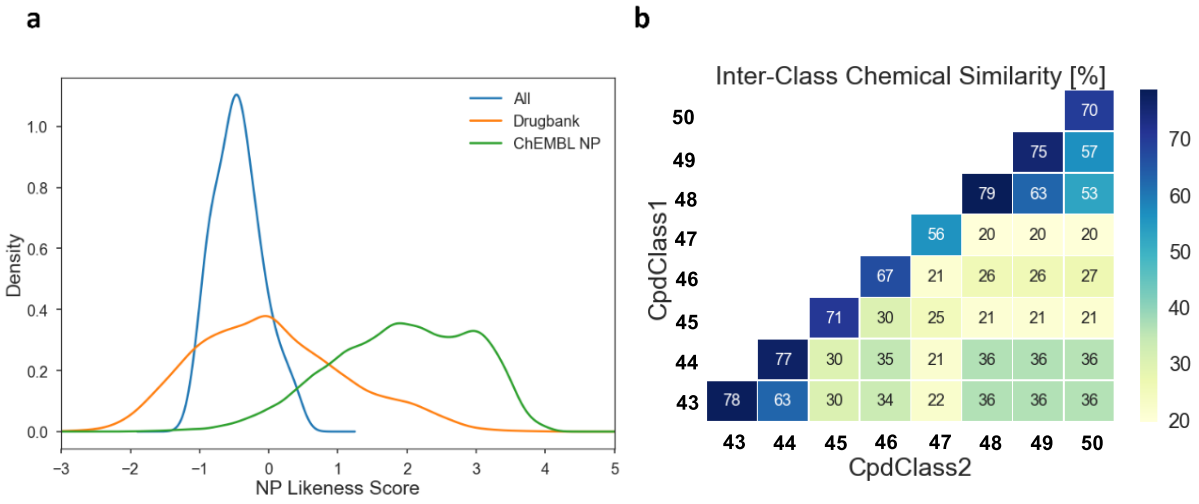


Figure 3.21. (a) NP-likeness scores of pyrroquinolines compared to compounds from DrugBank[38] and NPs from ChEMBL database[37]. (b) Chemical similarities of the different pyrroquinoline classes calculated based on the Tanimoto coefficients.

In addition to the NP-likeness score, chemical similarity of these eight scaffolds were calculated based on Tanimoto coefficients to evaluate the library diversity (Fig. 3.21b). Most of the scaffolds displayed high intra-class similarities above 70%. However, scaffold **III-47** only afforded 56% similarity because of the diverse substituents on the bridged scaffold. The inter-class similarities of these eight scaffolds were relatively low (<70%). Using the cheminformatic characterizations, like NP-likeness score and chemical similarity, we validated that varying the connectives and saturations can lead to structurally diverse compound collections that are distinctly different from known NPs.

Cell painting has now become a real-time and unbiased compound annotation assay, monitoring the morphological changes of treated cells. It has been employed to suggest possible targets/activities of testing compounds[47] and to evaluate the biological performance of a compound collection.[46] U2OS cells were treated with pyrroquinoline library at 10, 30 and 50 μM concentrations and then stained by six orthogonal fluorescent dyes to reveal the perturbations of seven cellular compartments and organelles, such as nucleus, mitochondria, endoplasmic reticulum, golgi/plasma membrane and F-actin. Then, 579 parameters were extracted for comparison using image analysis. Induction values were calculated based on the significantly changed phenotypic parameters compared with DMSO control. An obvious induction-dependent clustering was observed in principle component analysis (PCA) of these cell painting profiles (Fig. 3.22). Members of the same scaffold did not afford an aggregative cluster although they displayed high intra-class chemical similarity. And most of them

showed restricted space in the first component (Comp_1) ranging from -5-+5 (Fig. 3.22a). When plotted against different inductions (Fig. 3.22b), an induction-dependent Comp_1 was observed. Even though 579 parameters were extracted from the phenotypic features, the dominant effect of induction values misled the systematic analysis.

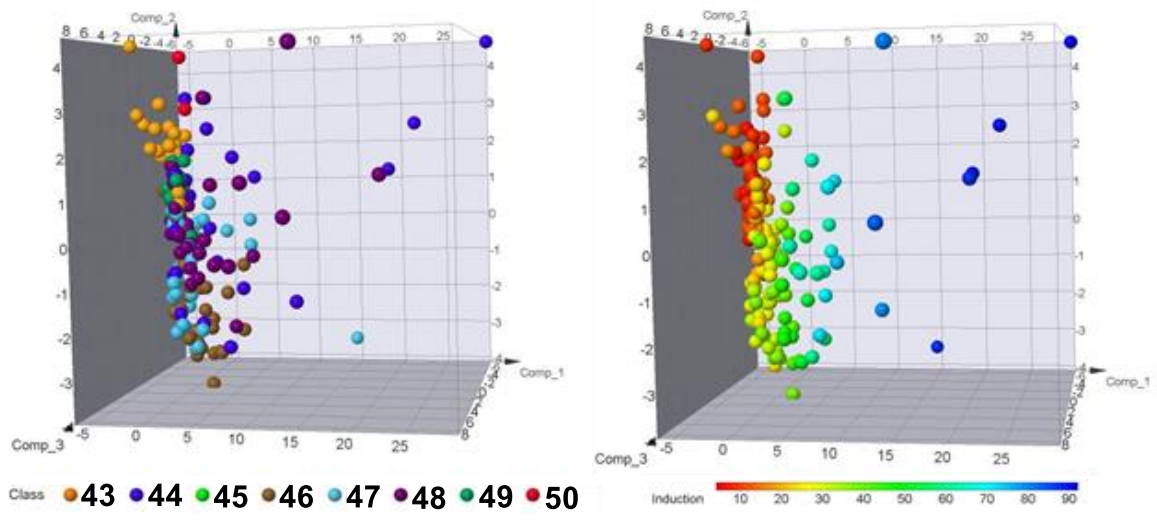


Figure 3.22. PCA of all active measurements with inductions more than 5%. Different scaffold classes (a) and different concentrations (b) were depicted.

To increase the comparability of the dataset, we found that low induction profiles (5-15% induction) at 10 µM became independent of the induction values. This induction window was then chosen for the further analysis. Of the eight classes, **III-45** did not induce any significant morphological changes, and therefore, they were not included in the analysis. Then we started the systematic biological evaluations of the pyrroquinoline library. Firstly, cross biological similarities of all compounds' cell painting fingerprints were computed based on the correlation distances between two profiles. As shown in Fig. 3.23a, profiles tested at 10 µM displayed a high intra-class similarity ranging from 72% to 91%. When class **III-44** was analyzed at higher concentrations, a decline of the intra-class biological similarity was noted (from 91% to 75%; Fig. 3.23b). The same tendency was also observed in other scaffolds (Figure 3.23c). Fused scaffold **III-43** and **44** displayed a high cross biosimilarity (85%), which might be attributed to their similar three-dimensional structures where pyrrolidine and tetrahydroquinoline were *trans*-fused. However, scaffold **III-48** and **49** of the same connection exhibited low cross similarity (45%) with each other.

Subsequently, cell painting profiles of different scaffolds were compared systematically using PCA data-processing. Scaffolds **III-43** – **III-44** and **III-48**– **III-49** formed by varying the fusion positions were analyzed first. As depicted in Fig. 3.24a, scaffold **III-43** and **III-44**

shared high cross biosimilarity. However, they differed largely when comparing cell painting profiles induced by higher concentrations. For the scaffold **III-48** – **III-49**, different connective positions led to distinctly different biological space (Fig. 3.24b). To investigate the influence of aromatization, scaffolds **III-43** – **III-44** were compared with its unsaturated derivatives **III-48** – **III-49** (Fig. 3.24c). Sp^3-rich saturated scaffolds mainly reside in the southwestern region of the PCA plot. The corresponding unsaturated scaffold **III-48** occupied the northwestern space, while scaffold **III-49** was distributed among the southeastern region. The vast distribution of unsaturated structures might be attributed to the promiscuous potential of planar structures to bind with diverse protein pockets. Different connections, like fused, spirocyclic and bridged arrangements, were then compared (Fig. 3.24d). Scaffold **III-46** occupied a narrow space in Comp_1 ranging from -5 to -4. Fused scaffolds (**III-43** – **III-44**) were condensed together, while bridged scaffold **III-47** had a wide distribution among the eastern region. When these diverse scaffolds were analyzed together by PCA, every class occupied a specific cluster in the biological space (Fig. 3.24e). These findings again validate our hypothesis that varying the connections can lead to chemically and biologically diverse space.

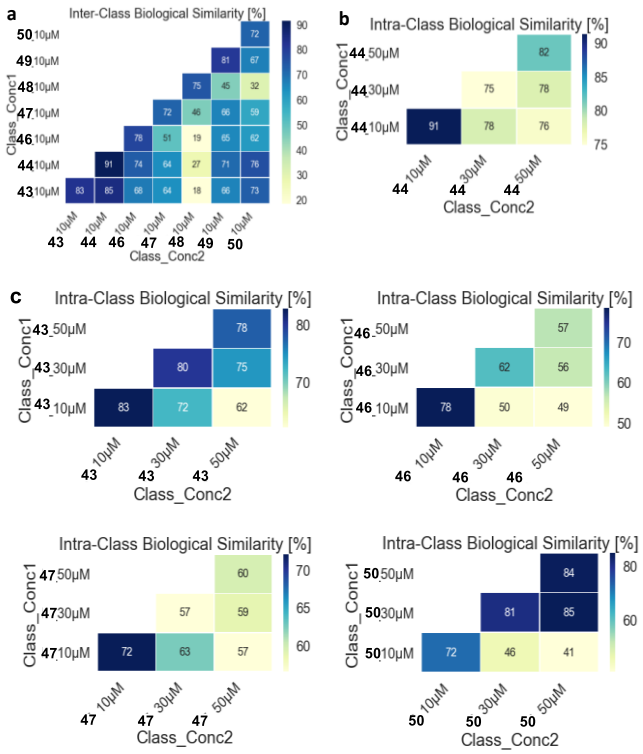


Figure 3.23. (a) Cross biosimilarity of all active compounds tested at 10 µM. (b) Intra-class biosimilarity table of class **III-44** at different concentrations. (c) Intra-class biosimilarity table of class **III-43**, **46**, **47**, and **50** at different concentrations.

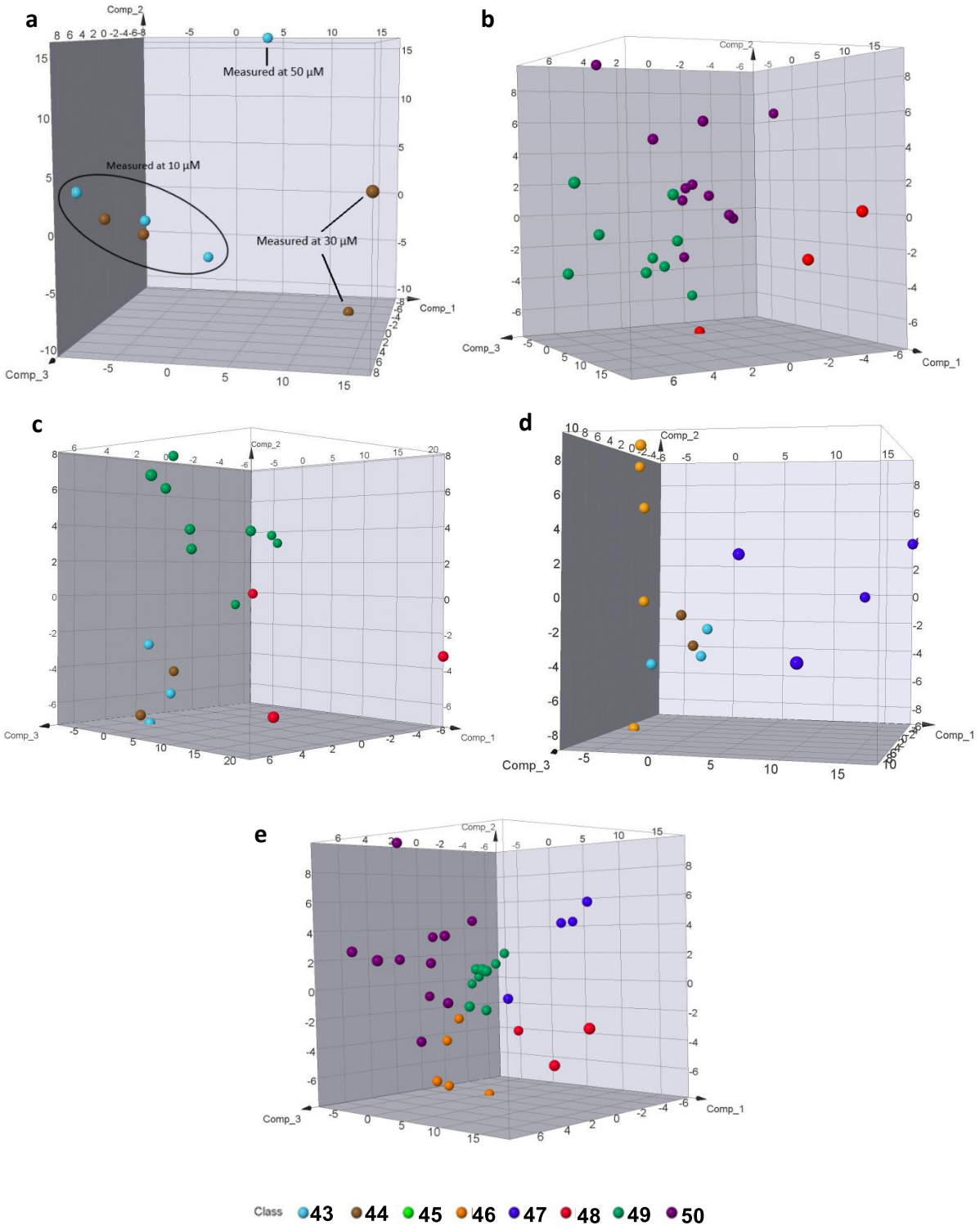


Figure 3.24. (a) PCA of saturated pyrroquinoline scaffolds **III-43** and **III-44** with induction 5-15% in different concentrations. Explained variance: 76%. (b) PCA of unsaturated pyrroquinoline scaffolds **III-48**, **III-49**, **III-50** with induction 5-15%. Explained variance: 52%. (c) PCA of the planar pyrroquinolines **III-43** and **III-44** with sp^3-rich scaffolds **III-48** and **III-49**. Explained variance: 64%. (c) PCA of sp^3-rich scaffolds with different connections. Explained variance: 51%. (d) PCA for the pyrroquinolines with induction 5-15%. Explained variance: 50%.

3.3.5 Hedgehog signaling pathway (Hh) inhibitory activity of pyrroquinolines (performed by Jana Flegel)

Hedgehog (Hh) signaling pathway is essential during vertebrate embryonic development, tissue homeostasis and regeneration.[62] Upregulation of Hh signaling in basal cell carcinoma and medulloblastoma was observed.[63] Therefore, discovering novel chemotypes for the inhibition of Hh signaling is highly significant.

Hh is a secreted protein that undergoes autoproteolytic cleavage and cholesterol modification.[62a] After palmitoylation mediated by SKI, dually lipid-modified Hh-N (amino-terminal peptide) is transported to the plasma membrane (Fig. 3.25a). Hh protein can bind with its receptor Patched (Ptc) and inhibit its suppression of Smoothened (Smo), which is a member of G protein-coupled receptor (GPCR) superfamily (Fig. 3.25b). Smo rests in its dimer state which is stabilized by electrostatic interactions between Arg and Asp. However, in the presence of Hh, Arg is neutralized by adjacent phosphorylation, leading to an open conformation of Smo, which can mediate the following transcription of GLI2,3 in vertebrates.

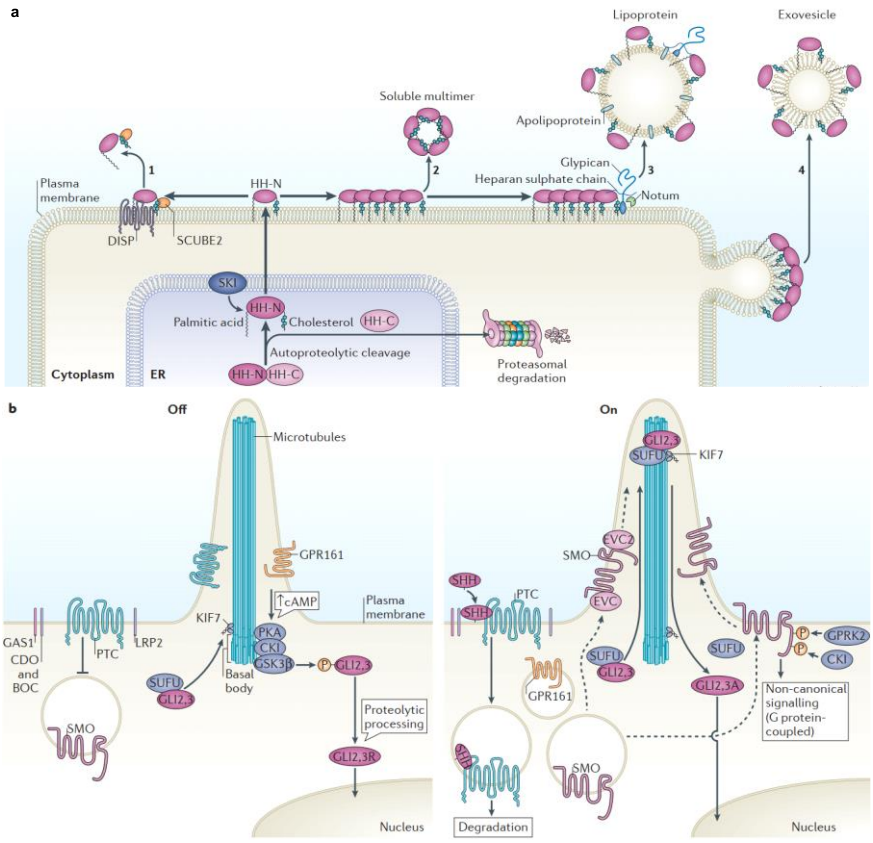
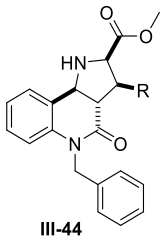


Figure 3.25. Hedgehog protein biogenesis and Hedgehog signaling pathway. Reprinted from ref. [62a] Copyright (2013) Springer Nature.

Table 3.8. ODA and RGA results of scaffolds **III-44**.



III-44

Entry	R	**ODA** IC_{50}	**RGA** IC_{50}
1	*p*-ClC_6H_4	4.0 ± 0.5 μM	8.8 ± 1.2 μM
2	*p*-BrC_6H_4	4.5 ± 0.1 μM	> 10 μM
3	*p*-FC_6H_4	0.3 ± 0.1 μM	3.3 ± 0.5 μM
4	*p*-$CF_3C_6H_4$	5.4 ± 0.8 μM	inactive
5	*p*-MeC_6H_4	inactive	inactive
6	*p*-$MeOC_6H_4$	2.5 ± 0.2 μM	7.6 ± 0.6 μM
7	*p*-CNC_6H_4	1.5 ± 0.2 μM	> 10 μM
8	*p*-$NO_2C_6H_4$	2.0 ± 0.9 μM	> 10 μM
9	Ph	0.4 ± 0.1 μM	6.4 ± 0.9 μM
10	*m*-ClC_6H_4	6.6 ± 2.0 μM	> 10 μM
11	*m*-BrC_6H_4	5.2 ± 3.0 μM	> 10 μM
12	*m*-MeC_6H_4	4.2 ± 2.0 μM	> 10 μM
13	*m*-$MeOC_6H_4$	inactive	inactive
14	*o*-ClC_6H_4	0.9 ± 0.3 μM	2.9 ± 0.4 μM
15	*o*-BrC_6H_4	0.3 ± 0.1 μM	3.0 ± 1.8 μM
16	*o*-MeC_6H_4	0.9 ± 0.2 μM	2.9 ± 0.1 μM
17	2-furanyl	5.8 ± 0.7 μM	> 10 μM
18	2-thiophenyl	2.7 ± 0.6 μM	> 10 μM

To investigate novel chemotypes that modulate the Hh signaling pathway, all pyrroquinolines were first tested in the Hh-dependent osteoblast differentiation assay (ODA) using C3H/10T1/2 cells stimulated by purmorphamine,[64] an agonist of Hh pathway. Once activated, the cells would differentiate into osteoblasts and express osteoblast - specific marker alkaline phosphatase. The activity of Hh inhibition was reflected by the reduced activity of this marker enzyme.[65] According to the data from the compound management and screening center (COMAS), scaffolds **III-44** stood out because of their high potency (Table

3.8). To validate that these compounds inhibited Hh signaling pathway, a *gli*-dependent reporter gene assay (RGA) was employed based on Shh-LIGHT2 cells. Cells were first activated with purmorphamine followed by the treatment with pyrroquinolines or DMSO as a control. Upon inhibition of Hh signaling pathway, the expression of firefly and *Renilla* luciferase will be decreased, whose activity can be detected by Dual-Luciferase Reporter Assay System. Even though some active compounds in ODA failed to exhibit inhibitory activity toward *gli* transcription, some pyrroquinolines still remained active in the reporter gene assay.

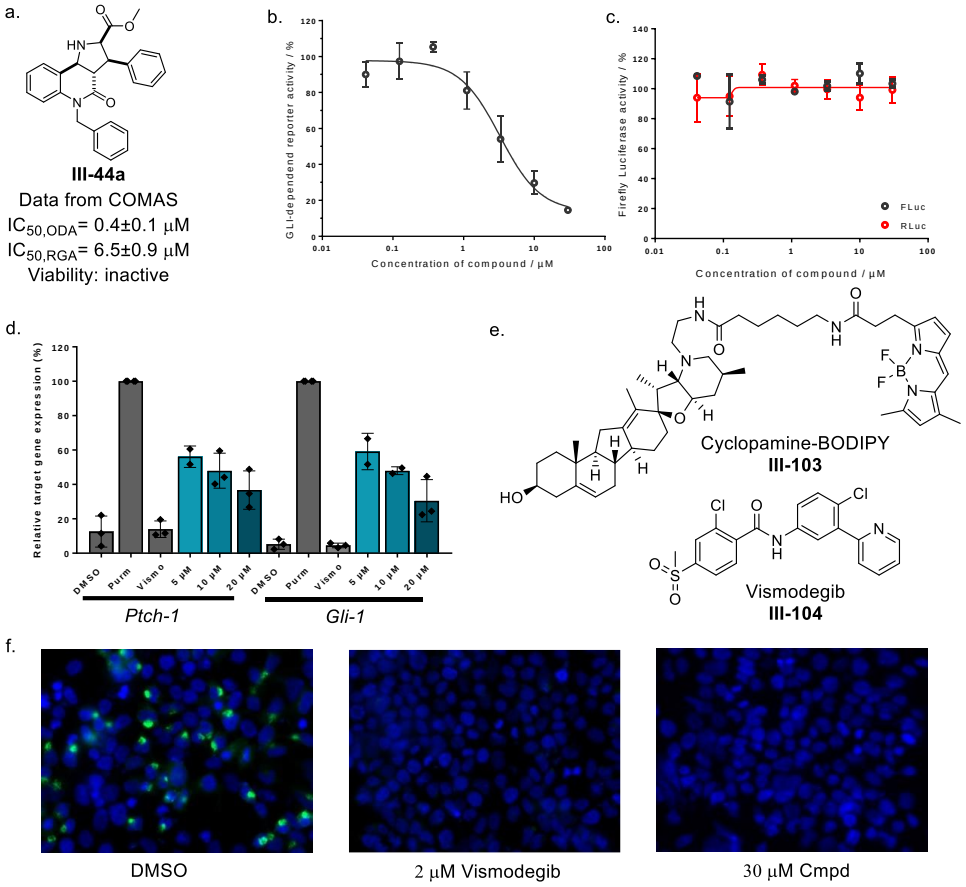


Figure 36. Compound **III-44a** inhibits Hh signaling pathway and proves to be a Smo binder.

Then a target identification and validation were conducted by Jana Flegel. To ensure that it is not a false positive hit caused by the inhibition of luciferase, a luciferase inhibition assay was performed, where compound **III-44a** was inactive (Fig. 3.26a,b,c). So, the activity of the compound was induced by the inhibition of Hh signaling pathway. Additionally, expression of *Patch-1* and *Gli-1* genes was monitored after the treatment with compound **III-44a**. This compound was able to dose-dependently downregulate the expression of these two genes, similar to vismodegib **III-104** (Fig. 3.26d), a Smo binder inhibiting Hedgehog signaling. To

investigate whether compound **III-44a** targets Smo, a competitive experiment was designed. BODIPY-cyclopamine **III-103** (Fig. 3.26e,f) is a reported fluorescent Smo binder.[66] Vismodegib could successfully compete with the fluorescent probe. The similar competition could be observed when the cells were treated with 30 μM **III-44a**, thus indicating that this compound was also a Smo binder.

3.4 Summary and outlook

In this project, pyrrolidine and tetrahydroquinoline fragments were recombined in unprecedented arrangements to give novel pseudo natural product collections. The resulting pyrroquinolines were designed by varying the connectivity positions, patterns and saturations, and 1,3-dipolar cycloaddition was strategically applied for the incorporation of pyrrolidine fragments. A highly asymmetric synthesis sequence was developed to afford scaffold **III-45'** in excellent yield and enantioselectivity. A mild and concise dearomative 1,3-dipolar cycloaddition was discovered for rapid preparation of scaffold **III-50**, where Cu(I)/Pybox promoted 1,3-dipolar cycloaddition and the following aerobic oxidation. An asymmetric intramolecular 1,3-dipolar cycloaddition was developed to afford scaffold **III-44'** in moderate enantioselectivity. Cheminformatic and cell painting analyses revealed that varying the fusion positions and connectivity patterns can increase the diversity of chemical and biological space. All of the synthesized compounds (7+1 classes) were submitted for biological evaluations using cell-based assays, which resulted in the discovery of novel inhibitors of Hh signaling pathway. All of these results illustrate the high value of pseudo natural product design to yield biologically active small molecules.

Another highlight of this project is the impact of systematic pseudo-NP synthesis on methodology development. In total, seven target scaffolds were elaborately designed and efficiently synthesized. The "target scaffolds"-oriented synthesis advances the development of synthetic methodologies. In this project, three methodologies were finally developed, which increased our understanding of 1,3-dipolar cycloaddition and the reactivity of azomethine ylides. In conclusion, systematic design and synthesis of pseudo natural products can not only provide structurally complex and diverse compound collections for biological studies, but also boost the development of synthetic methodologies.

Chapter 4. Rhodium(III)-catalyzed scaffold divergent synthesis of spirooxindoles

4. Rhodium(III)-catalyzed scaffold divergent synthesis of spirooxindoles

4.1 Background

4.1.1 Overview of C-H functionalization

Selective functionalization of inactivated C-H bonds was once considered the holy grail of organic chemistry.[67] Different from canonical transformative chemistry starting from preactivated C-X bonds, functionalization of C-H bonds can directly afford the target compounds enabling the late-stage modification of complex molecules. Considering the extremely high abundance of C-H bonds in most molecules, selective and efficient functionalization of C-H bonds can diversify molecular scaffolds, which will facilitate the study of structure-activity relationship of leads and natural products.[68] Even though we have witnessed great advances achieved in the past two decades, most of the reported C-H activation reactions suffer from low reactivity, hash conditions and/or high catalysts loading, which hampers its utility.[69]

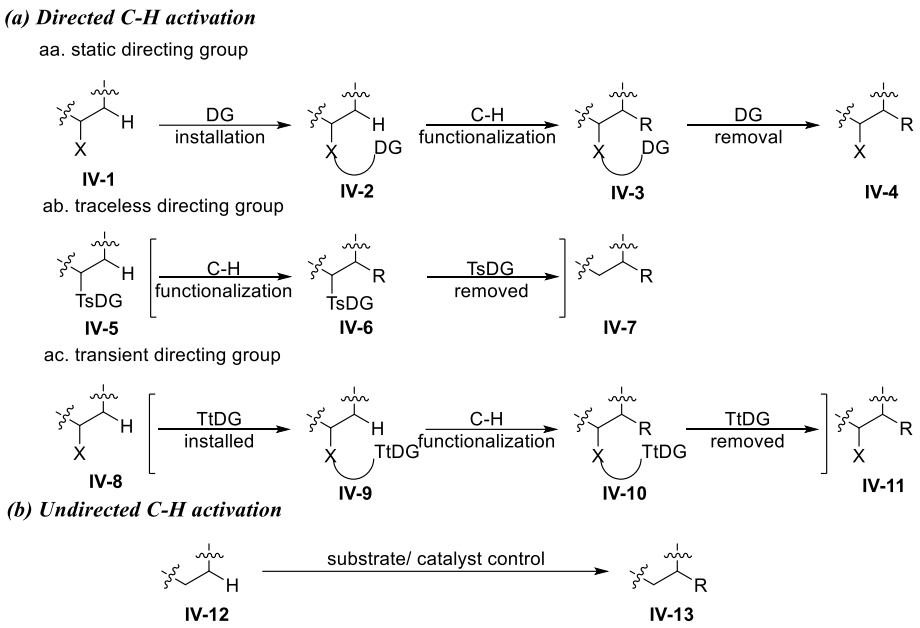


Figure 4.1. Strategies in C-H activation. (a) Directed C-H activation employing directing group. (b) Undirected C-H activation controlled by substrates and catalysts.

C-H functionalization reactions can be classified into two main categories depending on the usage of directing groups (Fig. 4.1). To increase the activity of C-H bonds, static directing groups can be incorporated into the molecules to trigger a proximity-induced C-H functionalization (Fig. 4.1aa). In 2014, Sanford and coworkers developed a Pd-catalyzed oxygenation of sp^3 C-H bonds in high regioselectivity using oxime directing group.[70] The

reaction can tolerate diverse substrates, for example, bridged camphor derivative **IV-14** can be converted to oxygenated product **IV-15** in 75% yield (Fig. 4.2a). Because of the high compatibility of this synthetic method, Sorensen and Li employed such a transformation in their total synthesis of jiadifenolide (**IV-18**)[71] and septedine (**IV-21**)[72], respectively (Fig. 4.2b,c). However, the installation and removal of directing groups need two additional steps.

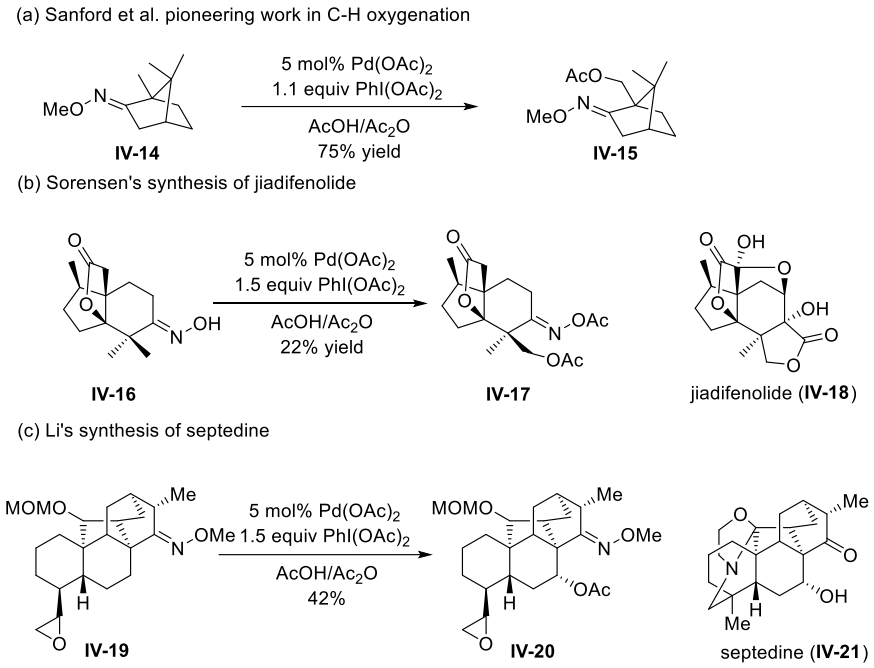


Figure 4.2. Sanford developed oxime-directed C-H oxygenation. (a) C-H oxygenation of camphor derivative. (b)(c) Sorensen[71] and Li[72] employed the methodology in the total synthesis of jiadifenolide and septedine respectively.

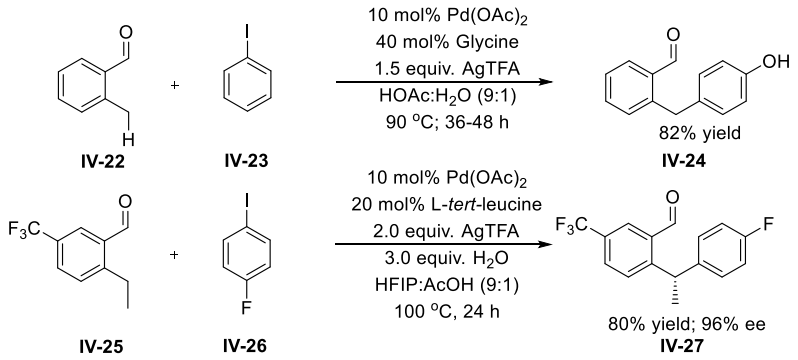


Figure 4.3. Transient directing group developed by Jinquan Yu et al.

To increase the pot-economy of the reaction, C-H activation using traceless directing group was developed. Carboxylic acids were employed in most cases where C-H activation and decarboxylation take place in one pot (Fig. 4.1ab). In 2016, Yu et al. developed a highly concise and efficient functionalization of sp^3 C-H bonds using a transient directing group (Fig. 4.1ac & 4.3).[73] In this method, amino acids can reversibly react with aldehydes or ketones.

The resulting imines served as transient directing groups to induce proximity-driven metalation of β or γ C-H bonds. Enantioselective synthesis was enabled by using chiral amino acids.

Another reaction class is undirected C-H activation, which is controlled by the substrates and catalysts (Fig. 4.1b). White and coworkers invented a non-heme catalyst **IV-30** enabling the selective C-H oxygenation of natural products (Fig. 4.4).[74] The selectivity of the reaction position is controlled by the steric and electronic effects or directing effect of the native functional groups among substrates (**IV-31**).

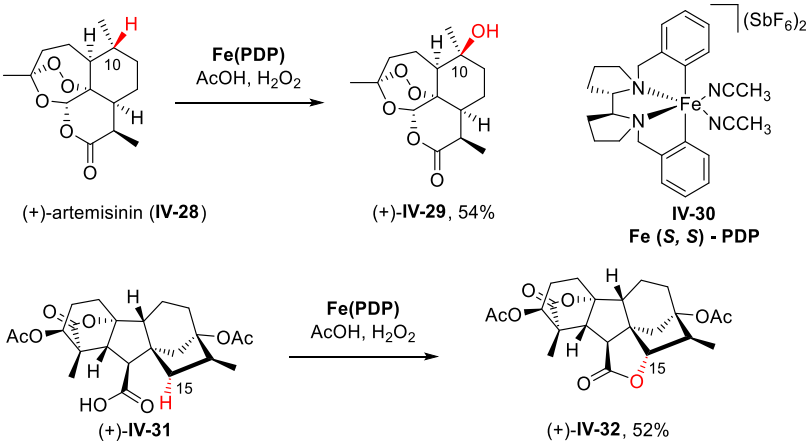


Figure 4.4. Undirected C-H functionalization developed by White and coworkers.

4.1.2 Lossen rearrangement in Rh(III)-catalyzed reactions

In previous reports of C-H functionalization, stoichiometric amounts of oxidants were essential to enable catalyst turnover. In 2010, Guimond and Fagnou reported the first case of Rh(III)-catalyzed redox neutral C-H functionalization using benzhydroxamate **IV-33** as the starting material.[75] The plausible mechanism is depicted in Fig. 4.5. Firstly, Rh(III) chelates benzhydroxamate affording a rhodacycle **IV-36**. Then, the alkyne is inserted into the C-Rh bond, yielding intermediate **IV-37**. N-O bond cleavage and C-N bond formation afford the final product **IV-35** and release the catalyst. The reaction features mild conditions, high efficiency, no external oxidant and is compatible to diverse substrates, which promotes the development and application of Rh(III)-catalyzed C-H functionalization.

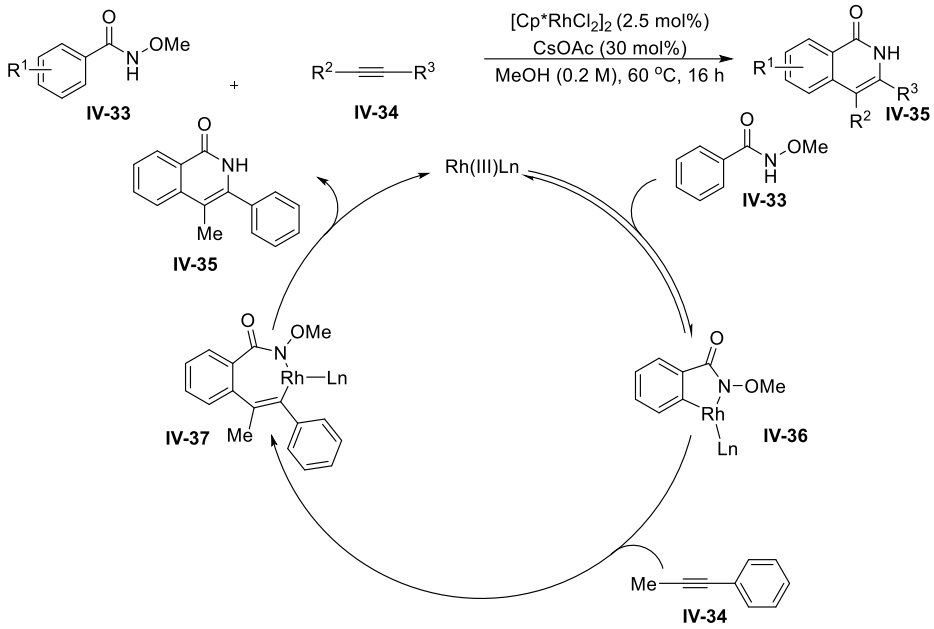


Figure 4.5. Redox neutral C-H functionalization catalyzed by Rh(III).

The Lossen rearrangement was first discovered by M. Lossen in 1872 (Fig. 4.6).[76] When the benzoyl benzhydroxamate **IV-38** underwent the thermolysis, carboxylic acid **IV-40** and isocyanate **IV-39** were obtained. In the past 150 years, more mild and useful conditions for the Lossen rearrangement have been developed.[77]

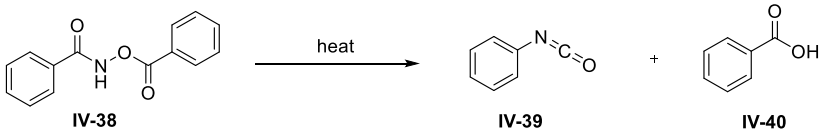


Figure 4.6. The discovery of Lossen rearrangement.

Because of the properties of hydroxamates, some Rh(III)-catalyzed C-H functionalizations involving benzhydroxamates also undergo tandem Lossen rearrangements. In 2015, Li and Wang reported a Lossen rearrangement as a side reaction in the annulation with 1-alkynylphosphine sulfide **IV-42** (Fig. 4.7a).[78] During the reaction condition screening, they identified a rearranged side product **IV-45** *via* a tandem Lossen rearrangement/alcohol addition to isocyanate **IV-48**/reductive elimination as shown in Fig. 4.7a. Two years later, Feng and coworkers reported a Lossen rearrangement when they incorporated *gem*-difluoromethylene alkyne **IV-51** into *N*-pivaloyloxy benzamide **IV-50** (Fig. 4.7b; right pathway).[79] Notably, the reaction delivered high yield and selectivity of the Lossen rearrangement. The resulting isocyanate **IV-56** was trapped by the acholic solvents followed by protonolysis to afford **IV-53**. Interestingly, *mono*-fluorine substituted alkyne or *gem*-dichloromethylene alkyne failed to yield the Lossen rearrangement product, which might be

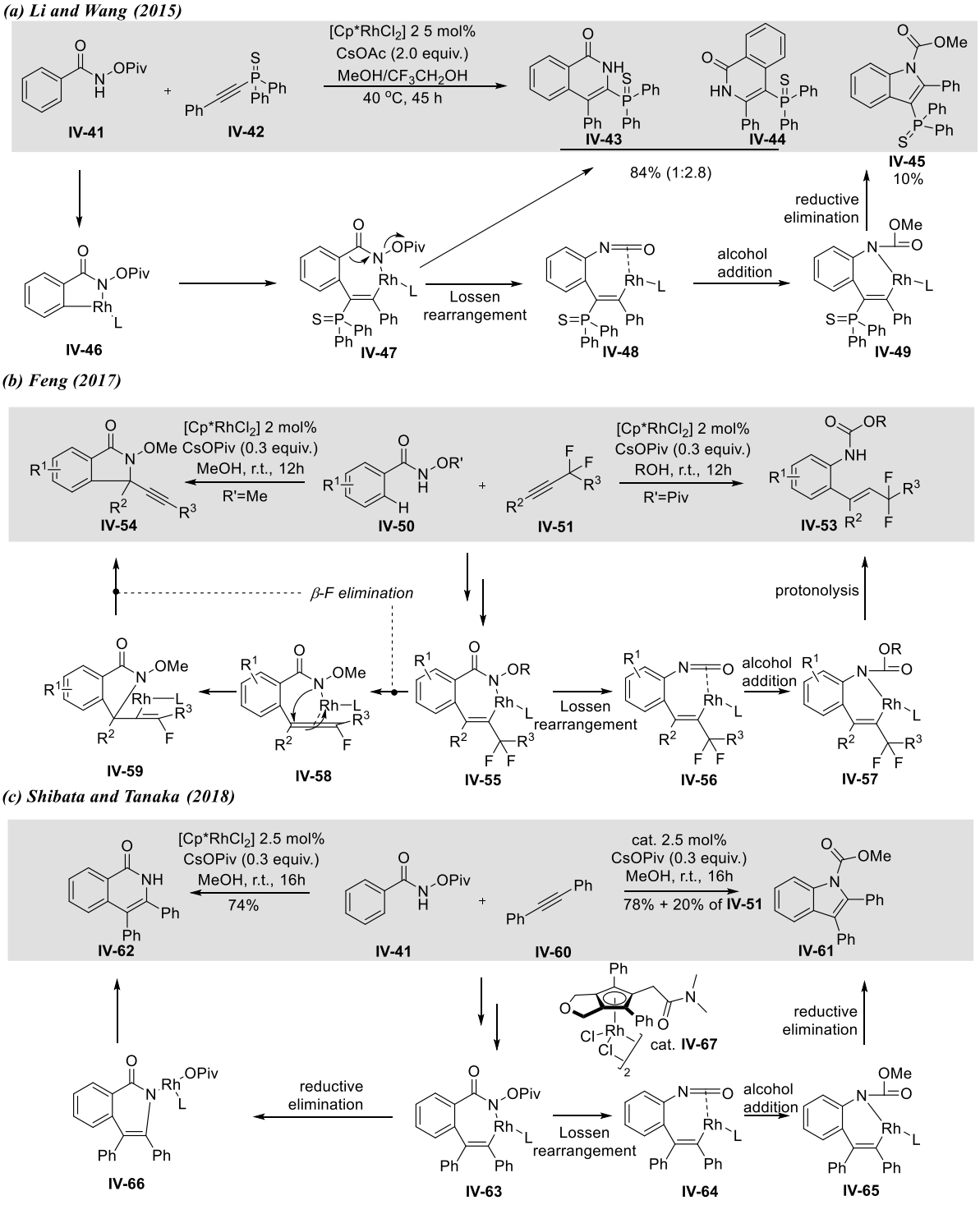


Figure 4.7. Reported Lossen rearrangement in Rh(III)-catalyzed C-H functionalization with alkynes.

attributed to the unique fluorine effects. Evidence indicated that protecting groups of hydroxamic acid were highly important. Methylated hydroxamic acid only afforded [4+1] product **IV-54** *via* fluorine elimination (Fig. 4.7b; left pathway).[80] In 2018, Shibata and Tanaka et al. reported ligand-controlled Lossen rearrangements in Rh(III)-catalyzed annulation reactions (Fig. 4.7c).[81] In the reaction with alkyne **IV-60**, they discovered that ligands played a significant role in controlling the reaction pathway. When $[Cp^*RhCl_2]_2$ was

used, the reaction only afforded formal [4+2] product **IV-62** (Fig. 4.7c; left pathway). However, formal [3+2] product **IV-61** was more favored when catalyst **IV-67** was employed (Fig. 4.7c; right pathway).

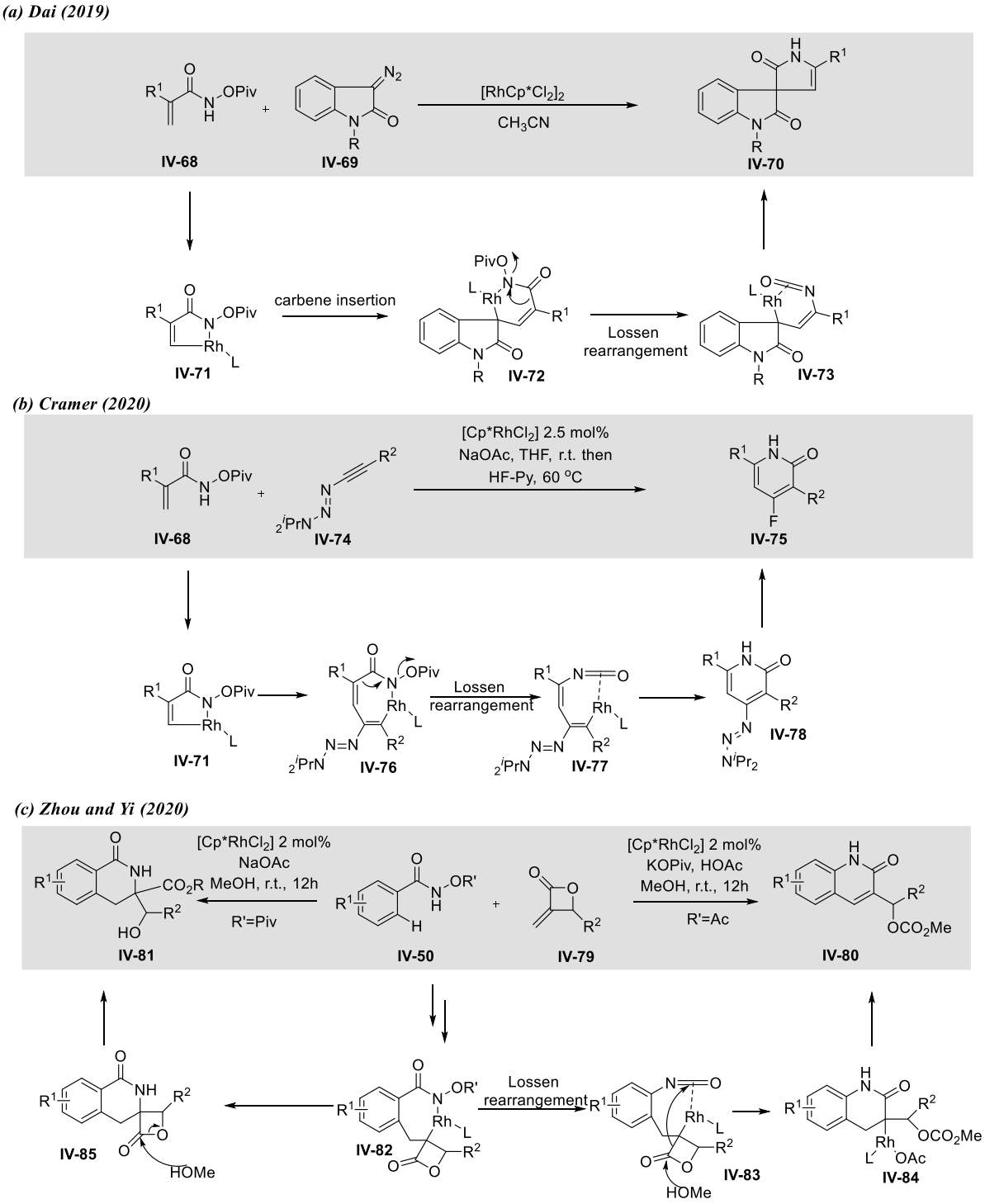


Figure 4.8. Reported Lossen rearrangement in Rh(III)-catalyzed C-H functionalization since 2019.

As indicated above, most of the Lossen rearrangements occurred in the reactions involving alkynes. In 2019, Dai et al. discovered that other substrates can also undergo Lossen

rearrangements (Fig. 4.8a).[82] When *N*-pivaloyloxy acrylamide **IV-68** reacted with diazooxindoles **IV-69**, the reaction yielded solely the rearranged product **IV-70**. C-H metalation of **IV-68** generated rhodacycle **IV-71**, which underwent carbene insertion/Lossen rearrangement to afford isocyanate **IV-73**. Subsequent intramolecular nucleophilic attack yielded spirooxindole **IV-70**. Inspired by their work, Cramer and coworkers combined *N*-pivaloyloxy acrylamide **IV-68** and alkynes **IV-74** together yielding fluorinated pyridines in one-pot manipulation (Fig. 4.8b).[83] Recently, Zhou and Yi et al. reported a scaffold divergent synthesis using Rh(III)-catalyzed C-H functionalization by varying the protecting groups of hydroxamic acids (Fig. 4.8c).[84] When *N*-pivaloyloxy benzamide was employed, the reaction underwent direct annulation to give **IV-85**, which was attacked by solvent alcohol to give isoquinolone **IV-81**. However, in the presence of *N*-acetoxy benzamide, the intermediate **IV-82** underwent a Lossen rearrangement (**IV-83**) followed by intramolecular nucleophilic attack (**IV-84**) and β-H elimination to afford quinolinone **IV-80**.

4.2 Project design

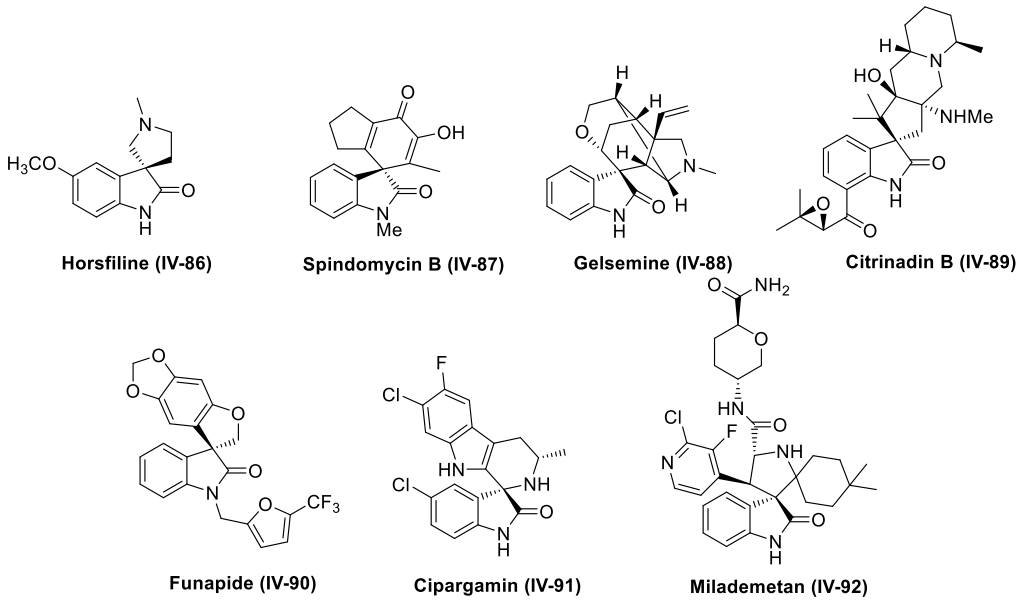


Figure 4.9. Spirooxindole-containing natural products and drugs.

Spirooxindole is a privileged NP fragment occurring in many biologically active natural products and drugs (Fig. 4.9).[41] Horsfiline (**IV-86**) is an analgesic oxindole alkaloid isolated from *Horsfieldia* superba.[85] Spindomycin B (**IV-87**) was found to possess inhibitory activity against tyrosine kinase.[86] Gelsemine (**IV-88**) is a highly toxic spirooxindole alkaloid isolated from the genus *Gelsemium*.[87] It is a potent agonist of glycine receptor perturbing chloride

ion influx and leads to muscle relaxation. Citrinadin B (**IV-89**) is isolated from *Penicillium citrinum* and exhibits cytotoxicity against L1210 cells.[88] Inspired by the promising bioactivity of spirooxindole natural products, many drugs or tool compounds, like funapide (**IV-90**), cipargamin (**IV-91**) and milademetan (**IV-92**), have been developed based on spirooxindole scaffolds.

Therefore, it was envisioned that pseudo natural product design based on spirooxindoles would lead to interesting compounds for biological study. In the previous work on pseudo natural product pyrroquinolines (Chapter 3), the synthetic route was linear and each compound needed to be synthesized *de novo*, which posed a huge challenge to the library construction. Herein, scaffold divergent synthesis was envisioned to afford diverse spirooxindole-containing scaffolds by tuning the properties of reaction intermediates.

Rh(III) catalysis attracted our attention because of its mild conditions, high yields, redox neutrality and compatibility with diverse functional groups. A Rh(III)-catalyzed [4+1] annulation reaction was first reported by Rovis and coworkers in 2013[89] where benzhydroxamate reacted with methylated diazooxindole in 64% yield without Lossen rearrangement (Fig. 4.10, right pathway), which is distinctly different from Dai's result (Fig. 4.8a; Fig. 4.10 left pathway). Notably, a small change of the substrates (**IV-68** vs **IV-41**) led to different reaction pathways.

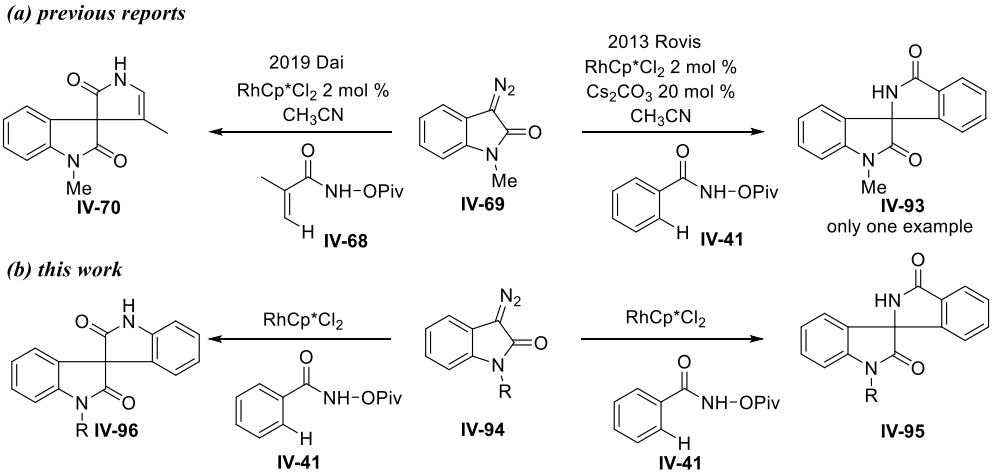


Figure 4.10. Rh(III)-catalyzed reactions with diazo spirooxindoles.

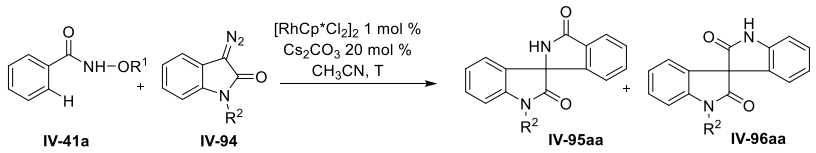
Inspired by Dai's and Rovis's reports, we planned to use protecting groups on diazooxindole **IV-94** to control the reaction pathway, thus, yielding diverse scaffolds (Fig.4.10b). After the condition screening, exploration of substrate scope will afford a focused compound collection.

An elaborate study of reaction mechanism was planned to uncover the factors triggering Lossen rearrangements in Rh(III)-catalyzed C-H functionalization.

4.3 Results and discussion

4.3.1 Condition screening

Table 4.1. Condition screening of Rh(III)-catalyzed [4+1] annulation



Entry	R^1	R^2	T[°C]	Yield[a] of **95**+**96** [%]	**95**/**96** [a]
1	Piv	H	50	99	1.3:1
2	Piv	Me	50	71	12:1
3	Piv	Boc	50	71	1:1.2
4	Piv	Bn	50	88	>20:1
5[b]	Piv	Bn	50	91 (91) †	>20:1
6	Piv	Ac	50	56%*	<1:20
7	Piv	Ms	50	70	<1:20
8[c]	Piv	Ms	50	74 (82) †	<1:20
9	Piv	Ms	r.t.	55	<1:20
10	Ac	Ms	50	42	n.d.

Unless otherwise specified, all reactions were conducted on benzhydroxamate **IV-41a** (0.10 mmol, 1.0 equiv.), diazole oxindole **IV-94** (0.10 mmol, 1.0 equiv.), $[RhCp^*Cl_2]_2$ (1 mol%) and Cs_2CO_3 (0.02 mmol, 0.20 equiv.) were reacted in CH_3CN (0.10 M, 1 mL). (a) Yield for all isomers and selectivity were determined from the reaction mixture by means of ^1H NMR with 1,3,5-trimethoxylbenzene as the internal standard. (b) THF was used as solvent. (c) 1.2 equiv. of diazooxindole was used. †The main isomer was purified by column chromatography; isolated yields are shown in brackets. * Deprotection of Lossen rearrangement product was observed in 20% yield.

Initially, the model reaction between benzhydroxamate **IV-41a** and diazooxindole **IV-94** was investigated. The reaction selectivity displayed a high reliance on the protecting group of diazooxindole. When diazooxindole was used directly without any protecting group, the reaction afforded the [4+1] product **IV-95aa** and **IV-96aa** in almost quantitative yield (Table 4.1, entry 1). However, the ratio between direct annulation (**IV-95aa**) and Lossen rearrangement (**IV-96aa**) was unsatisfying. In the presence of electron rich protecting groups (Me- and Bn-groups), the reaction selectivity was dramatically improved (Table 4.1, entry 2 and 4). Reaction with *N*-benzyl diazooxindole delivered the direct annulation product **IV-**

95aa as a single isomer (Table 4.1, entry 4). When THF was used as the solvent, a small increase of yield was observed (Table 4.1, entry 5). To be noted, even though methylated diazooxindole was employed by Rovis in direct annulation reaction,[89] Lossen rearrangement was still observed in low yield (Table 4.1, entry 2). Realizing the significant role of protecting group in controlling the reaction pathway, more electron deficient protecting groups were employed to switch the reaction selectivity (Table 4.1 entry 3, 6-7). Acetylated diazooxindole gave excellent selectivity for Lossen rearrangement, however, partial deprotection was observed (Table 4.1, entry 6). More stable electron deficient Ms- group was then used to afford the highest selectivity and good yield (Table 4.1, entry 7). In entry 7, isoindigo was isolated which indicated the dimerization of diazooxindole under the reaction conditions. To improve the reaction yield, 1.2 equivalents of diazooxindole was used and a slight increase of yield was observed (Table 4.1, entry 8). Lowering the temperature did not afford better results (Table 4.1, entry 9). Inspired by the previous reports that protecting groups of hydroxamic acid would affect the reaction pathway (Fig. 4.8c), benzyhydroxamic acetate was employed (Table 4.1, entry 10). However, this substrate failed to give an improved yield. In conclusion, *N*-Bn protected diazooxindole afforded direct annulation product **IV-95**, while *N*-Ms protected diazooxindole favored the Lossen rearrangement **IV-96**.

4.3.2 Substrate scope

With the optimal conditions in hand, the substrate scope of this reaction was explored. The reaction between substituted benzhydroxamate **IV-41** and *N*-Bn diazooxindole **IV-97a** was investigated (Fig. 4.11). Independent of the electronic properties, all *para*-substitutions delivered the direct annulation product in excellent yield (**IV-95a** – **h**). For the *meta*-substitutions, formation of regioisomers was observed. However, the *meta*-methyl substrate afforded the product **IV-95k** in excellent yield and selectivity, which might be attributed to the relatively higher steric effect of Me- group (**IV-95k**) compared with Cl, Br or OMe substitutions (**IV-95i**, **j** and **l**). All *ortho*-substitutions failed to give any isolatable products (**IV-95m**). The reaction also tolerated different electron rich heterocycles (**IV-95n** – **q**). The structure of **IV-95o** was unambiguously confirmed by single crystal X-ray analysis (see experimental part 7.3.3).

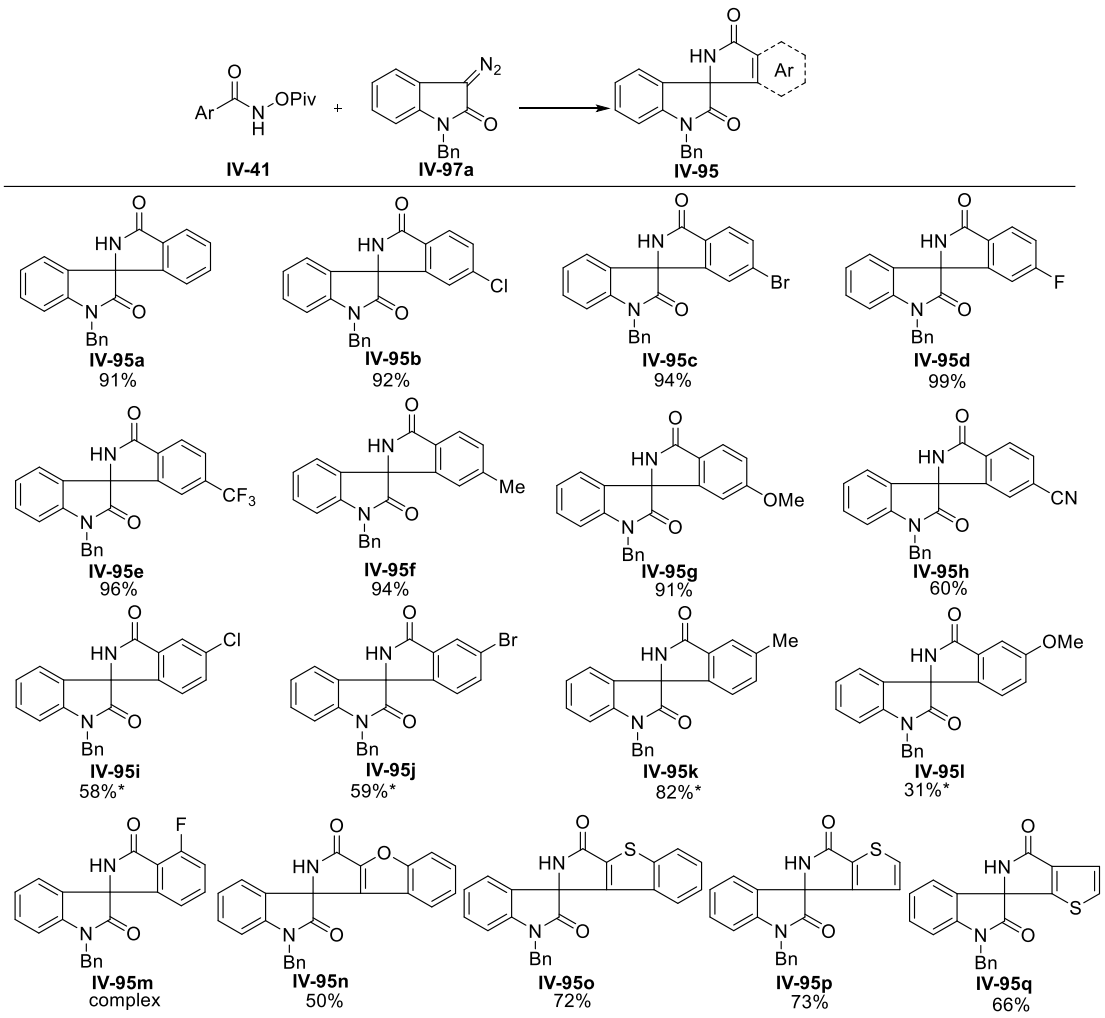


Figure 4.11. Substrate scope of benzhydroxamate reacting with *N*-Bn diazooxindole. *, other isomer were observed. Isolated yield for product was given.

Then the reaction between substituted benzhydroxamate **IV-41** and *N*-Ms diazooxindole **IV-98a** was explored (Fig. 4.12). In comparison to the reactions with *N*-Bn diazooxindole, the *N*-Ms group resulted in lower yield. For the *para*-substitutions, electron rich groups (Me-, MeO-) delivered the products **IV-96f** – **g** in higher yields compared with other substituents **IV-96b** – **h**. For *meta*-substitutions, similar tendency was observed in reactions with *N*-Bn diazooxindole. However, *ortho*-substitutions and electron-rich heterocycles were not tolerated in this reaction.

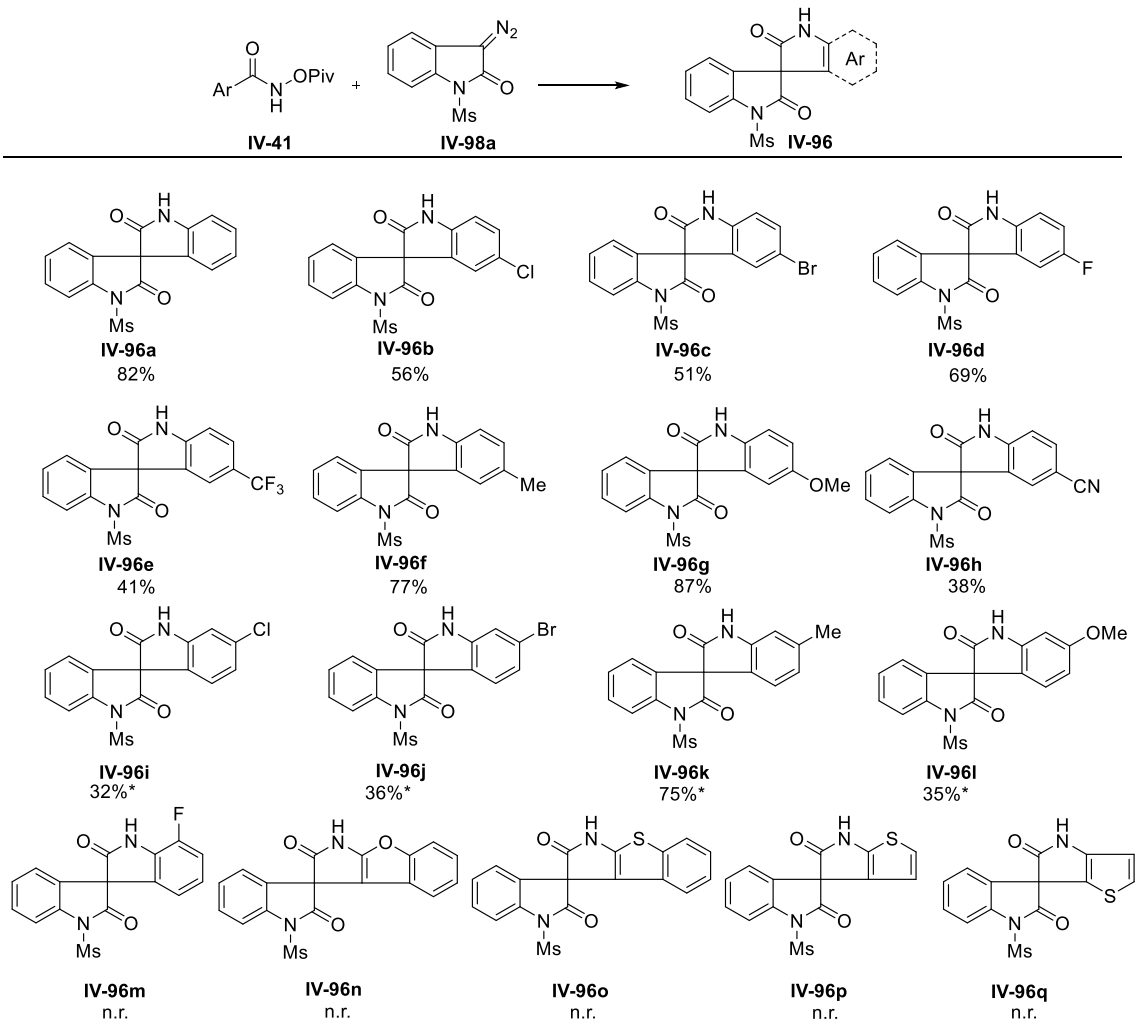


Figure 4.12. Substrate scope of benzhydroxamate reacting with *N*-Ms diazooxindole. *, other isomers were observed. Isolated yield for product was given.

Additionally, the scope of diazooxindoles was explored (Fig. 4.13). For the reaction between benzhydroxamate and *N*-Bn diazooxindole, most of them delivered the target products in excellent yields regardless of the properties or positions of substituents. However, electron deficient 5-NO_2 substitution afforded direct annulation product **IV-95x** in 50% yield alongside the Lossen rearrangement product. C4 substitution was not tolerated for the annulation reaction (**IV-95r**). For the reaction between benzhydroxamate and *N*-Ms diazooxindoles, the yields (**IV-96r** – **aa**) were relatively lower than those of *N*-Bn substrates.

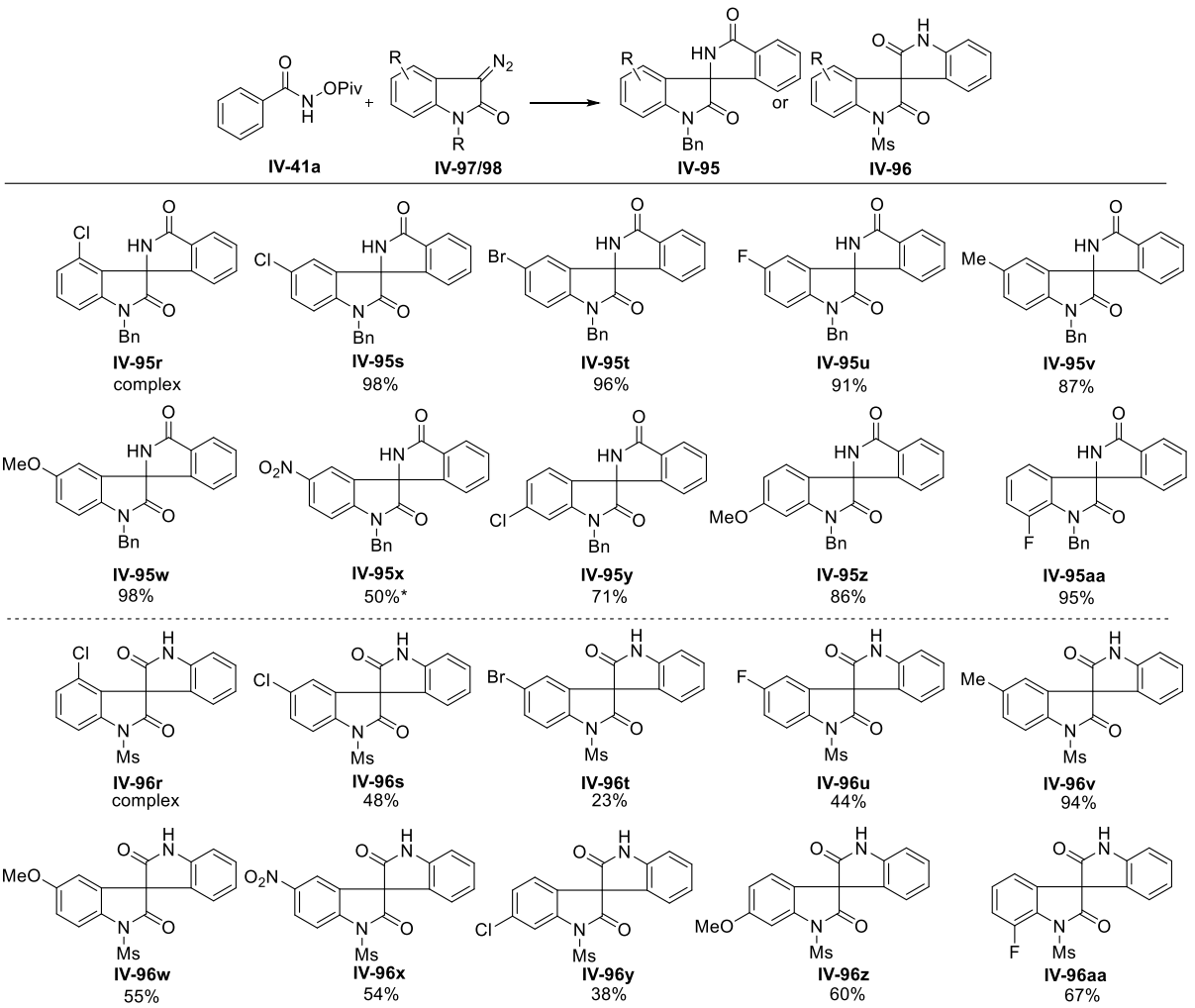


Figure 4.13. Substrate scope of diazooxindoles reacting with benzhydroxamate. *, other isomers were observed.

To explore the utility of this synthetic methodology, the natural product estrone was converted to the hydroxamate **IV-99** and underwent the reaction with diazooxindoles. The reaction afforded the products **IV-100** and **IV-101** in good yields (Fig. 4.14a) as an inseparable mixture of diastereomers. When the reactions were conducted on half gram scale, they still afforded good to excellent yields (Fig. 4.14b). The amide of the product was diversified by adding a propargyl or choloroacetyl motif. At last, a library of 52 members was efficiently synthesized using the developed synthetic methodology.

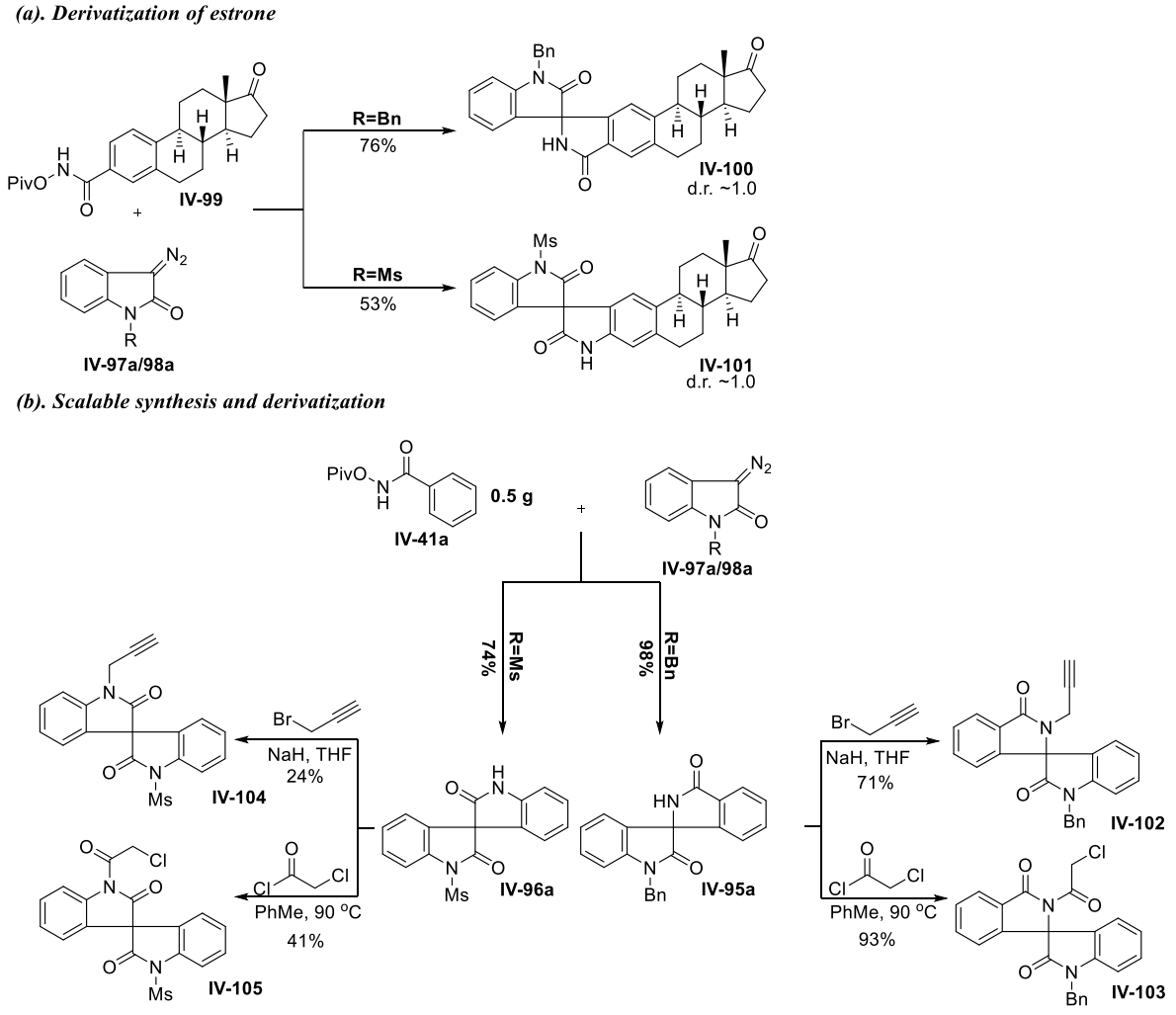


Figure 4.14. Reaction application. (a) Modification of estrone. (b) Scalable synthesis and derivatization of representative scaffolds.

4.3.3 Mechanistic investigation

To unravel the essentials of the protecting group-controlled Lossen rearrangement in Rh(III)-catalyzed C-H functionalization, mechanistic investigations were carried out. Firstly, competition reactions between different substituted benzhydroxamates were conducted (Fig. 4.15a). These two reactions turned out to favor electron deficient substitutions. Then, competition reaction between C5- Me/Cl substituted diazooxindoles was performed (Fig. 4.15b). The results indicated that these two reactions favored more electron rich oxindoles.

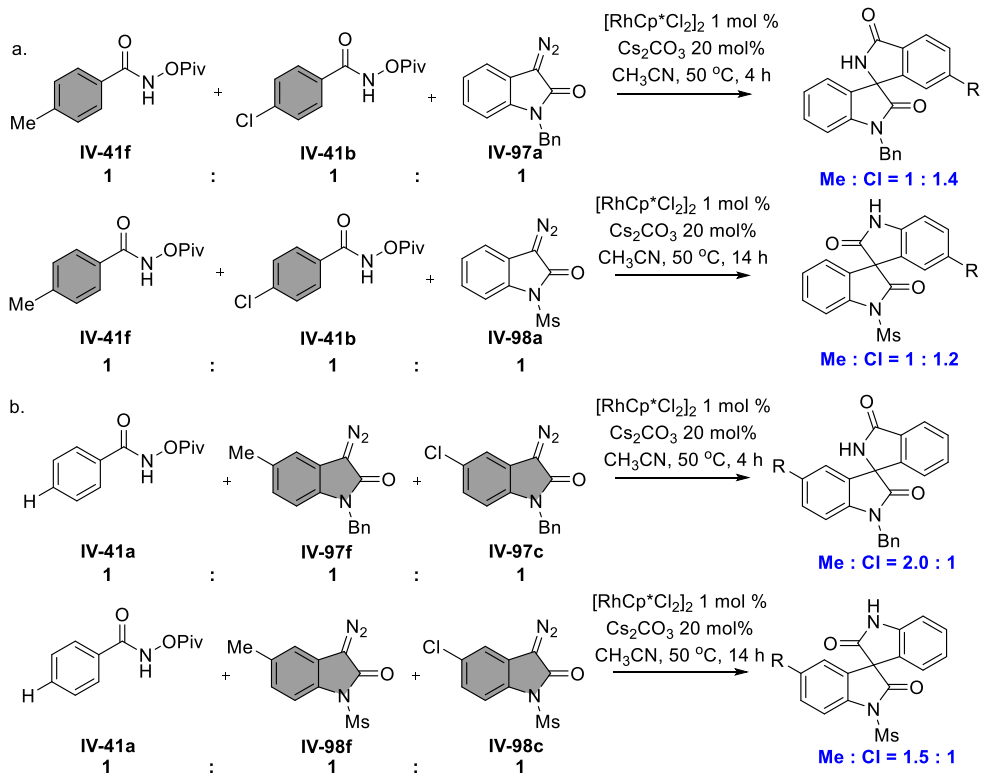


Figure 4.15. (a) Competition reaction between *para*- Me/Cl substituted benzhydroxamates. (b) Competition reaction between C5- Me/Cl substituted diazooxindoles.

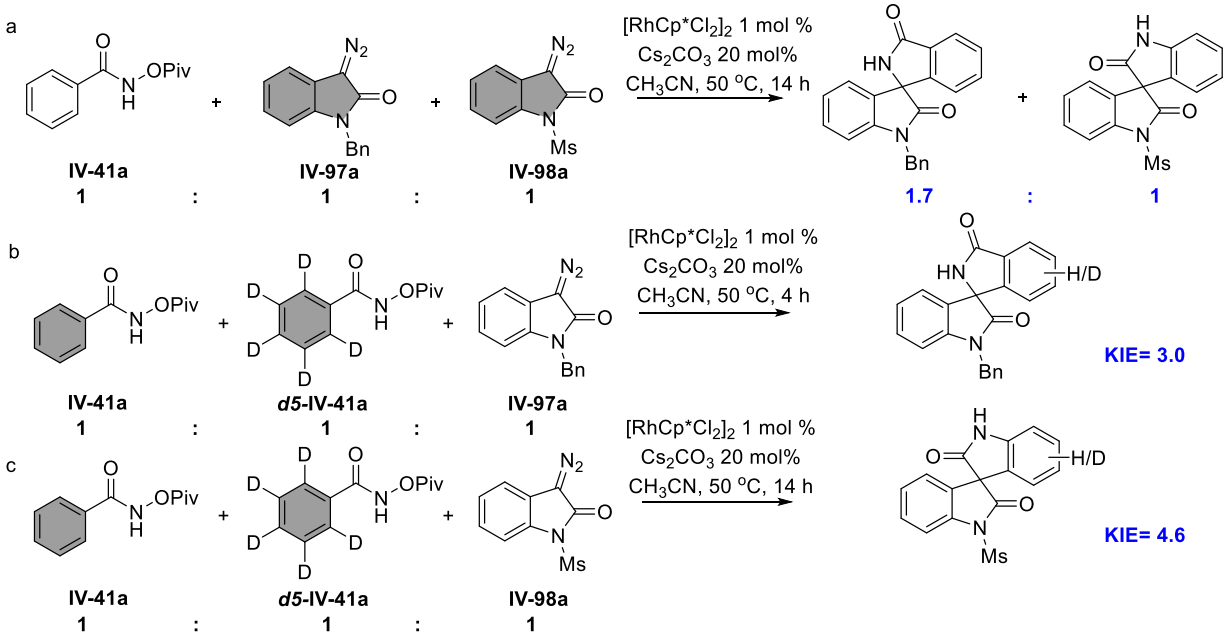


Figure 4.16. Preliminary KIE experiment.

To determine the rate-limiting step of the reaction, the kinetic isotope effect (KIE) was determined. Both benzhydroxamate **IV-41a** and its deuterated derivative ***d5*-IV-41a** were subjected to the standard conditions (Fig.4.16b,c). Their KIE values were above 3 which suggest C-H metalation is the rate-limiting step. This was also observed in Dai's[82] and

Rovis's[89] reports. A competition experiment between *N*-Bn and *N*-Ms diazooxindoles indicated that the former reacts faster (Fig. 4.16a).

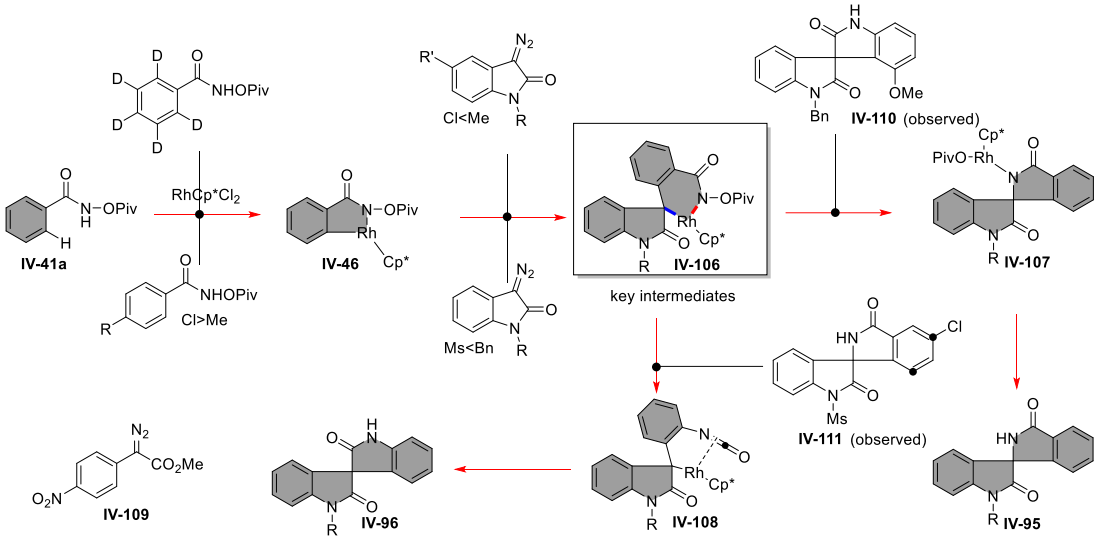


Figure 4.17. Plausible reaction pathways.

With all data in hand, a plausible explanation for the reaction mechanism was proposed (Fig. 4.17). C-H metalation of benzhydroxamate is the rate-limiting step for both pathways. Additionally, it favors electron deficient hydroxamates, whose pKa of C-H bond is lower. This is consistent with the previous mechanistic study that C-H metalation step proceeds *via* deprotonation.[90] The more acidic C-H bond will be deprotonated more easily. Then the rhodacycle **IV-46** undergoes carbene insertion to give an intermediate **IV-106**. Electron rich carbene reacts faster than electron deficient analogs. When R is Bn group, C-Rh bond is electron rich enough to undergo the direct reductive elimination to afford direct annulation product **IV-95**. However, when R is Ms group, C-Rh bond is electron deficient, and thus the direct elimination is not favored. In contrast, the benzhydroxamate undergoes Lossen rearrangement to generate isocyanate **IV-108** which can be attacked by C-Rh species to give rearranged scaffold **IV-96**. However, this reaction is not completely controlled by electronic properties. When linear diazo **IV-109** was subjected to the standard condition, only the direct annulation product was obtained.

In the exploration of substrate scope, the *para*-substituted benzhydroxamates delivered almost single isomers, while the *meta*-substituted benzhydroxamates delivered mixtures (**IV-110**, **IV-111**) in spite of the electronic properties of the substitutions, which suggest this reaction is controlled by stereoelectronic effects. In the Lossen rearrangement, the migratory groups and leaving groups should be arranged in antiperiplanar orientation to maximize the

orbital overlap. *Meta*-substituted benzhydroxamates will generate a congested reaction center, and thus affect the orbital interaction and lead to lower selectivity.

4.4 Summary and outlook

In this work, oxindole and oxoisoindole were unprecedentedly recombined in a spirocyclic connection featuring a Rh(III)-catalyzed C-H functionalization. Because of the mild conditions, the reaction can be applied to incorporate spirooxindoles into natural products. A mechanistic study of the reaction revealed that stereoelectronic effects dominate the reaction selectivity.

This project also highlights the importance of developing methodologies to modularly incorporate NP fragments into diverse scaffolds. There are dozens of reports of spirooxindole syntheses,[91] however, many of them start from complex and elaborate substrates and few of them are capable of NP modifications. Because of the abundant occurrence of carboxylic acid in bulk chemicals and natural products, benzhydroxamate derivatives can be easily obtained. Therefore, this concise and efficient methodology will broaden the chemical space explored before, and enable the exploration of novel biological activities.

Chapter 5. Design, synthesis and biological evaluations of pseudo sesquiterpenoid alkaloids

Part of the content has already been accepted for publication in *Angew. Chemie. Int. Ed.* **2021**, 10.1002/anie.202106654.

5. Design, synthesis and biological evaluations of pseudo sesquiterpenoid alkaloids

5.1 Background

5.1.1 Chemistry and biology of sesquiterpene lactones

Terpenes are a structurally diverse and ubiquitous class of natural products displaying many biological activities, some of which have been used as therapeutics. They are biosynthesized from prenyl precursors and classified based on the carbon atoms of scaffolds, like monoterpenes (10C), sesquiterpenes (15C) and diterpenes (20C). More than 8000 sesquiterpene lactones have been isolated from Nature, mainly distributed among *Asteraceae* plants.[92] These molecules feature a lactone moiety fused at C6/C8-C7 position, named with an "olide" suffix. According to the scaffold structures, they are categorized into four groups: germacranolides, guaianolides, pseudoguaianolides and eudesmanolides (Fig. 5.1).

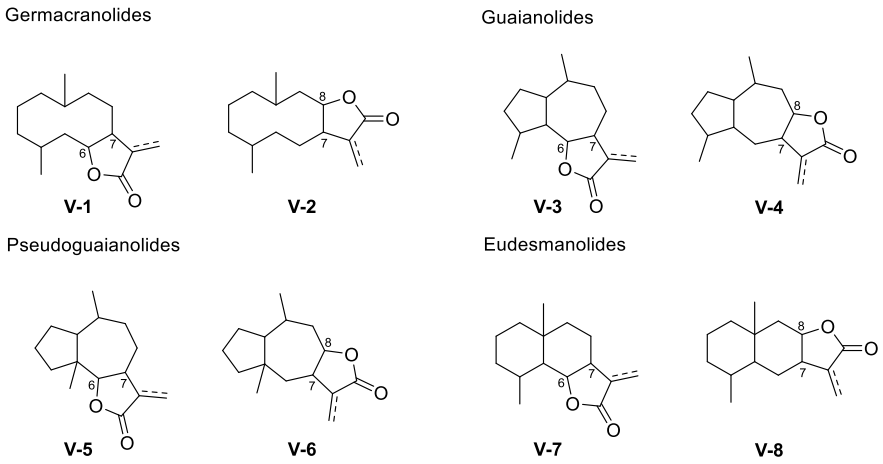


Figure 5.1. Sesquiterpene lactone classes.

Most of the sesquiterpene lactones are embedded with an α-methylene-γ-lactone moiety, which is believed to be a warhead covalently binding with biological nucleophiles. Due to the reactivity of α,β-unsaturated Michael acceptors, sesquiterpene lactones commonly adopt Diels-Alder reaction to afford dimeric molecules.[93] Sesquiterpene lactones exhibit diverse biological activities, such as antitumor, anti-inflammatory, antioxidant, antifeedant and cytotoxicity.[94] Dozens of synthetic routes have been developed in the past three decades, however, MoAs of many sesquiterpene lactones are waiting to be disclosed.

Ainsliadimer A (**V-12**) was first isolated by Zhang et al. from traditional Chinese medicine *Ainsliaea macrocephala*.[95] According to the plausible biogenesis, this molecule was derived from a hetero Diels-Alder cycloadduct **V-10** followed by acid-induced ring open and aldol reaction (Fig. 5.2a). This molecule has two covalent warheads with potent anti-inflammatory

activity. In 2010, Lei and coworkers reported the first biomimetic synthesis of ainsliadimer A from commercially available santonin **V-13** (Fig. 5.2b).[96] The synthesis features a light-induced scaffold rearrangement, a BINOL-catalyzed hetero Diels-Alder reaction and a biomimetic rearrangement. In their biological studies, this compound inhibits the NF-κB signaling pathway.[97] To shed light on the unknown biological process, probes (**V-15**) were then synthesized and subjected to pull down assays (Fig. 5.2c). Two proteins IKKα and IKKβ were found to be the binding targets of ainsliadimer A. This example well-illustrates how organic synthesis can assist biological study.

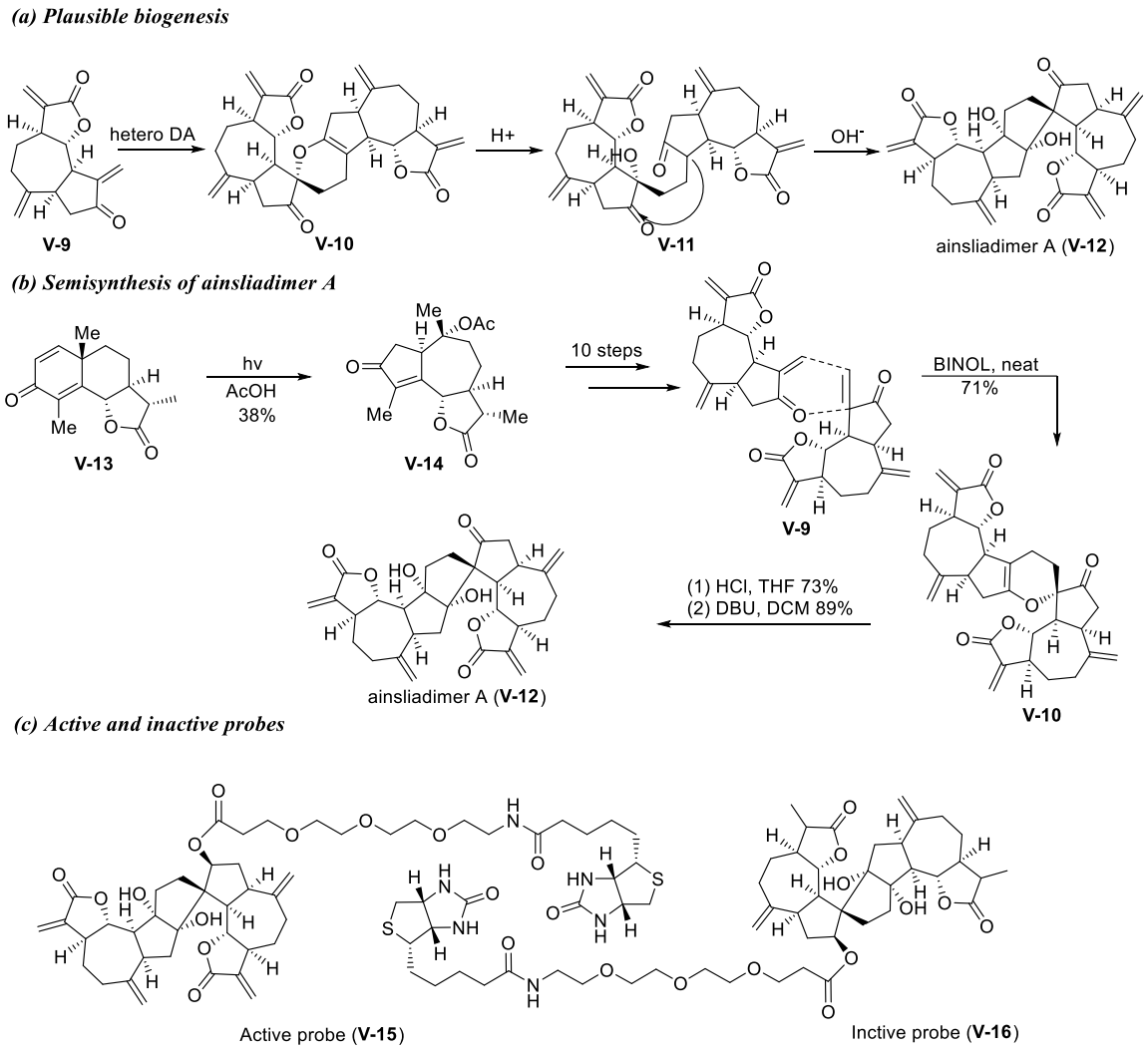


Figure 5.2. Chemistry and biology of ainsliadimer A. (a) Plausible biogenesis. (b) Semisynthetic routes from santonin. (c) Probe structures.

Different from semisynthesis, total synthesis is able to overcome the limits of chiral pools[98] and explore the vast chemical and biological space. In 2016, Winssinger and coworkers reported a concise and divergent route toward deoxyelephantopins (Fig. 5.3).[99] Realizing the

covalent binding activity of α-methylene-γ-lactone moiety, they designed a synthesis yielding not only target compound **V-26**, but also analogs equipped with the active warhead.

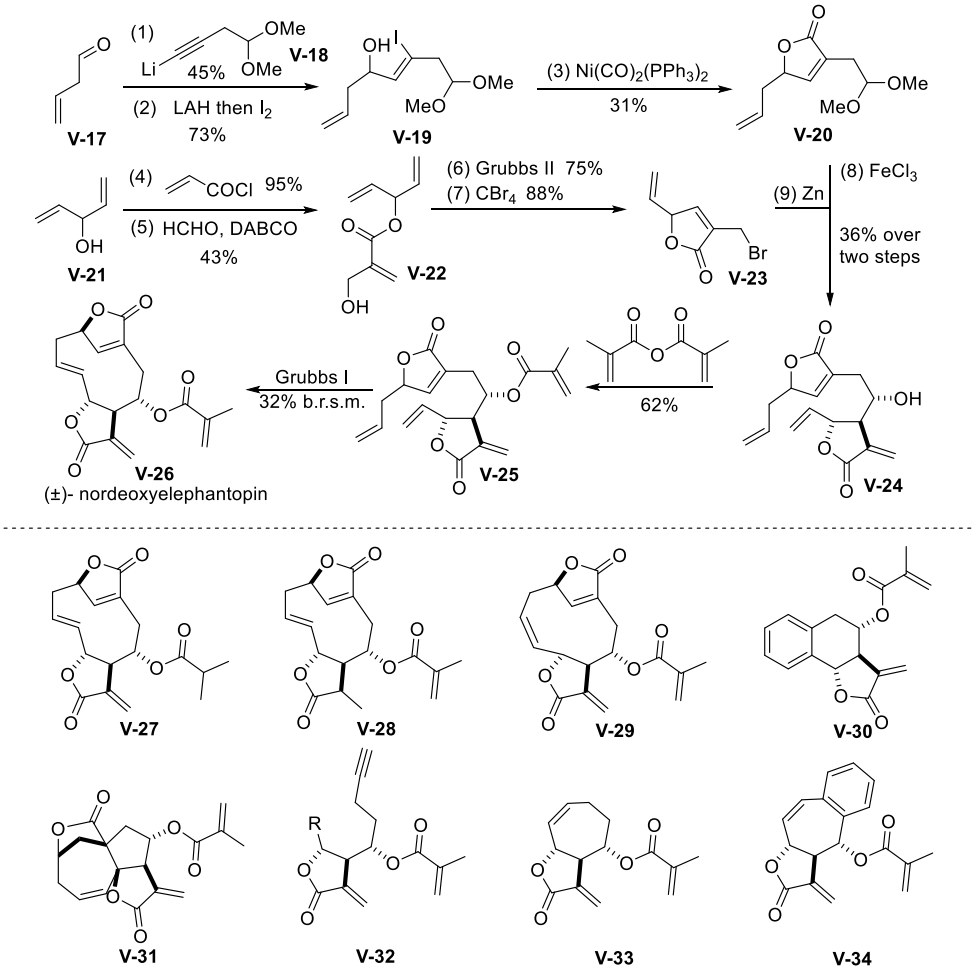


Figure 5.3. Chemistry and biology of deoxyelephantopins. (a) Synthetic route. (b) Analogs enabled by the same route.

Alkynylation of aldehyde **V-17** afforded alcohol in 45% yield followed by hydroxyl-directed alkyne reduction mediated by LAH. The resulting C-Al bond was trapped with iodine to yield solely the "*Z*" configured alkene **V-19**, which was sequentially converted to lactone **V-20** *via* a Ni-catalyzed carbonylation reaction. On the other hand, symmetric allylic alcohol **V-21** underwent esterification and Baylis-Hillman reaction to afford polyene structure **V-22**. Ring closing metathesis and bromination of the hydroxyl group yielded the second fragment **V-23**. Dimethyl acetal **V-20** was deprotected using iron trichloride. The resulting aldehyde underwent the Barbier reaction with the *in situ* generated zinc allylic reagent from **V-23**. To be noted, the reaction proceeded in high diastereoselectivity. After installation of the appendages, the intermediate was transformed to the racemic nordeoxyelephantopin (**V-26**)

through a RCM reaction. Interestingly, only one epimer afforded the final cyclization product. More analogs were enabled based on this synthetic route (Fig. 5.3).

Using probe design and chemical proteomics, they revealed the possible target of deoxyelephantopins. Furthermore, the whole synthesized library was screened against PPARγ using gel-based competitive experiment. At last (*Z*)-analog **V-29** proved to be the most effective covalent binder of PPARγ. The research highlights the workflow of chemical biology of natural products: total synthesis → library construction → probe design → chemical proteomics → screening.

5.1.2 Divergent 1,3-dipolar cycloaddition

As stated in Chapter 3, 1,3-dipolar cycloaddition is a powerful and versatile synthetic methodology to incorporate the alkaloid-derived NP fragment pyrrolidine into diverse scaffolds.[100] Because of the geometry of the 1,3-dipoles, the secondary interaction between dipoles and dipolarophiles is not strong enough. This property inspires the development of cycloaddition in unusual *endo*/*exo* or regio-selectivity.

The first enantioselective stereodivergent 1,3-dipolar cycloaddition of azomethine ylides with nitroalkenes **V-36** was reported by Hou et al. in 2006 (Fig. 5.4a).[101] The selectivity was controlled by electronic properties of the chiral P,N-ferrocene ligands. Electron deficient aryl groups will switch the selectivity from *exo* to *endo*. According to the computational calculation, the electrostatic interactions between nitro group and electron deficient aryl (**V-40**) will stabilize the transition state and yield *endo* product **V-38**.

Besides the electronic properties of the ligands, steric effects can also influence the reaction selectivity. In 2010, Adrio and Carretero et al. reported the stereodivergent 1,3-dipolar cycloaddition between azomethine ylides and phenylsulfonyl enones **V-42** (Fig. 5.4b).[102] When Segphos (**V-45**) was used, the reaction mainly delivered *endo* product **V-43**. However, in the presence of DTBM-Segphos (**V-46**), *exo* product **V-44** was more favored.

Stereodivergent 1,3-dipolar cycloaddition can also take place between azomethine ylides and 1,3-dienes (Fig. 5.4c). Inspired by previous work in stereodivergent catalysis, Carretero and coworkers discovered DTBM-Segphos (**V-46**) and BRFM-garphos (**V-50**) could lead to *exo* and *endo* selectivity, respectively.[103] In the presence of bulky phosphines, the reaction favored *exo* product, which is consistent with their discovery in cycloaddition with

phenylsulfonyl enones **V-42** (Fig. 5.4b). While electronic deficient aryl group on ligand **V-50** will stabilize the intermediate *via* electrostatic interactions, thus, yielding *endo* product **V-49**. To be noted, this reaction also displayed extremely high regioselectivity at γ,δ-double bond.

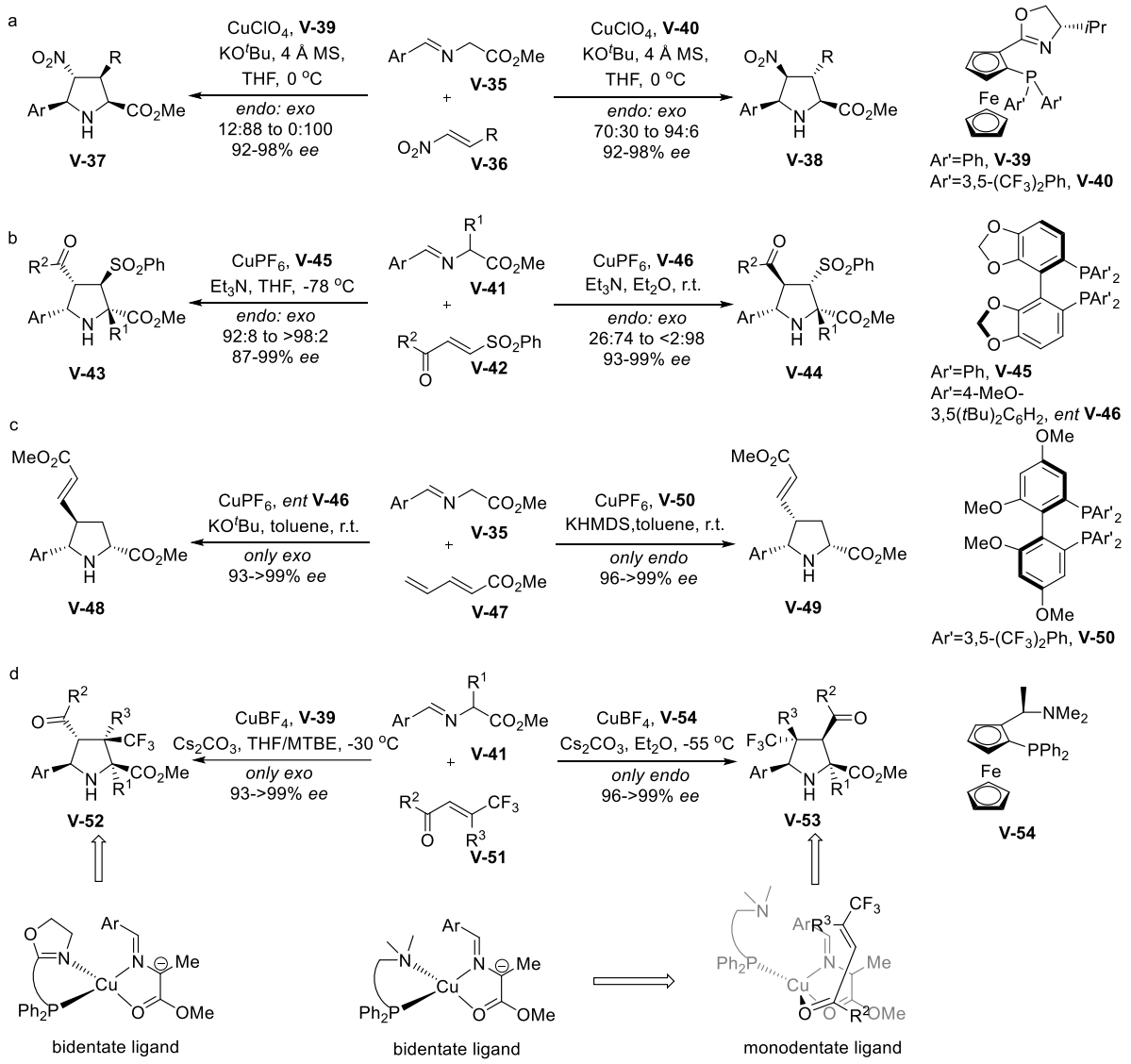


Figure 5.4. Stereochemical diversity in 1,3-dipolar cycloaddition.

Elaborate dipolarophiles can also lead to unprecedented stereochemical diversity. In 2018, Zhang and coworkers reported a regiodivergent 1,3-dipolar cycloaddition of azomethine ylides with β-fluoromethyl β,β-disubstituted enones **V-51**, where two quaternary stereocenters were constructed (Fig. 5.4d).[104] Computational analysis suggest that the abnormal regioselectivity was induced by the different coordination states of catalysts. When ligand **V-39** was used, copper would form a stable complex with the bidentate P,N-ligand. However, in the presence of ligand **V-54**, the interaction between catalyst and ligand was not strong enough because of the steric hindrance caused by dimethyl group of **V-54**. The oxygen

atom from enone **V-51** will then coordinate with copper accompanied with the dissociation of nitrogen atom of the ligand, and thus yield product **V-53** selectively (Fig. 5.4d). These four examples well-illustrate the tunability of 1,3-dipolar cycloaddition to afford stereochemical diversity by varying the electronic properties and steric effects of ligands, and coordination states of catalysts.

5.2 Project design

In Chapter 3 and 4, many efforts were devoted to develop novel methodologies for the synthesis of pseudo natural product libraries. Even though 9 compound classes were synthesized, all of them shared the same concept, that is to combine two NP fragments unprecedently. As presented in previous chapters and other published work from our group[19, 34-35, 39, 47, 49, 105], the pseudo natural product design principle has led to the discovery of novel inhibitors of Hh and Wnt signaling pathway, glucose transporters, autophagy, kinases and mitochondrial complexes.

However, the key questions still remain. Firstly, which fragments should be combined? In our previous work, indole, pyrrolidine and tetrahydroquinoline served as privileged NP fragments because of the synthetic feasibility and their common occurrence in natural products. Even fragment-sized natural products have been used as the fragments for recombination.[39, 49] All of the reports claimed that structurally complex and diverse compound collections were accessed using pseudo natural product design. However, most of the employed NP fragments are lacking structural relationship, thus resulting in both chemical and biological diversity. To explore the current boundaries of pseudo natural product studies, the combination of NP fragments which are structurally or biologically related was envisioned.

The second question is how to recombine fragments. Systematic recombination as presented in pyrroquinolines would be an option.[106] However, considering all the potential connections of two fragments, it is extremely challenging for synthetic methodology as well as construction of the library. Nature always serves as an excellent source of inspiration. Actually, nature has been synthesizing NP hybrids by merging two different biosynthetic pathways. Sesquiterpene lactones are fragment-sized natural products encoded with diverse biological activities. Most of them are equipped with an electrophilic α-methylene-γ-lactone. Because of the high reactivity of the moiety, not only biological nucleophiles like cysteines add to them, but also other natural products or biosynthetic intermediates will react with

them.[93] According to the phytochemistry analysis, most of the hybrid sesquiterpenoids are formed *via* Diels-Alder reactions of the electron deficient double bond. The Diels-Alder reaction has many common properties with 1,3-dipolar cycloaddition, for example some dienophiles are used as dipolarophiles in 1,3-dipolar cycloaddition. Inspired by this, a 1,3-dipolar cycloaddition of azomethine ylides with sesquiterpene lactones was envisioned.

As mentioned above, the chosen NP fragments should have structural or biological relevance. Sesquiterpene lactones are biosynthesized *via* cation-mediated ring formation, ring rearrangement and cleavage, which is exactly the strategy used in the complexity-to-diversity synthesis. The structurally related sesquiterpene lactones can be reached by ring distortion or using commercially available sesquiterpenes directly. This is the primary goal of the project, i.e., fragment-sized sesquiterpene lactones are firstly converted to other scaffolds while the structural relevance is still retained. Then, the synthesized lactones are recombined with alkaloid-derived NP fragment pyrrolidine at C11-C13 position (Fig. 5.5). To increase the structural diversity of the compound collection, a stereodivergent 1,3-dipolar cycloaddition is developed.

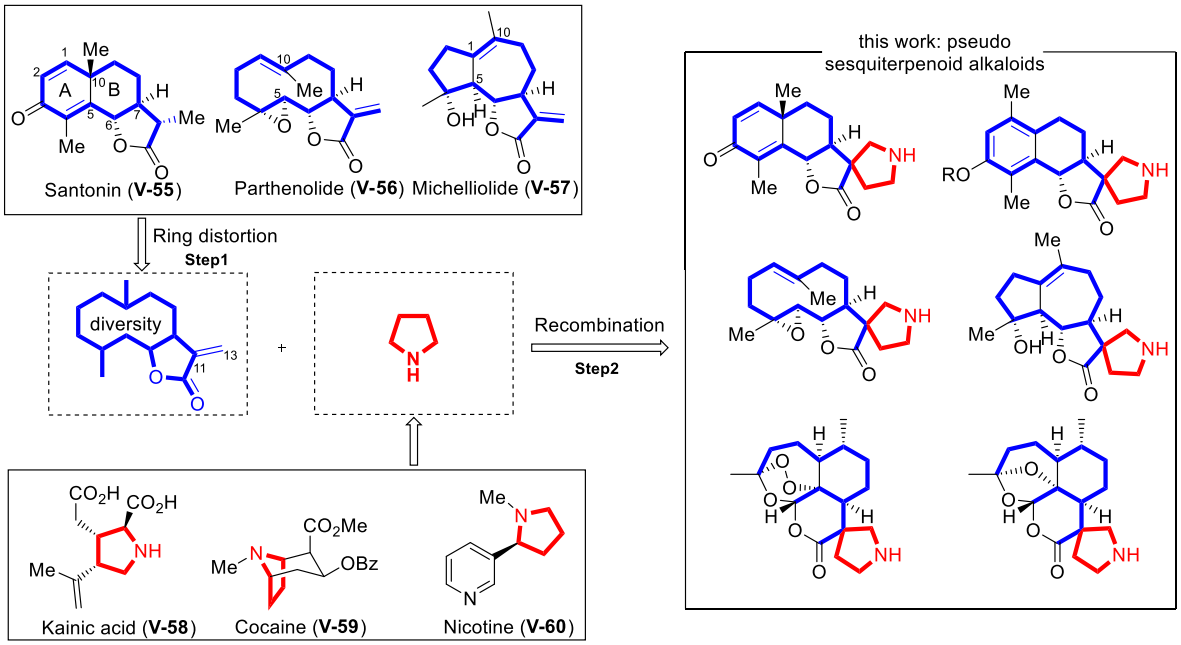


Figure 5.5. Project design of pseudo sesquiterpenoid alkaloids.

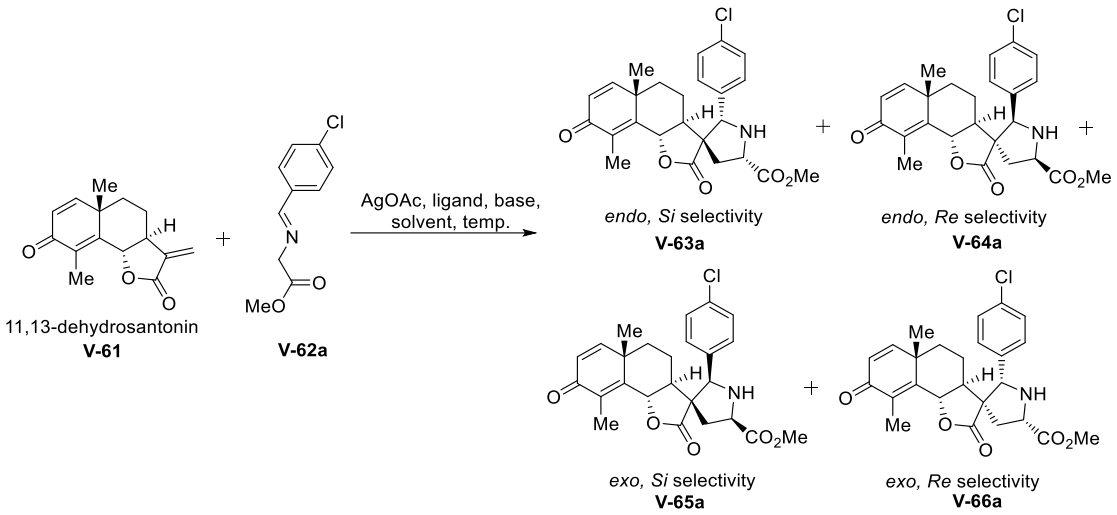
5.3 Results and discussion

5.3.1 Condition screening for stereodivergent cycloaddition with dehydrosantonin

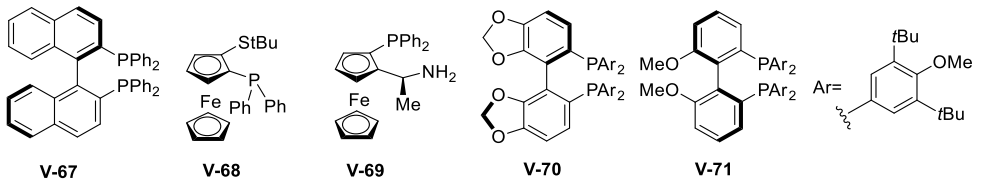
At the outset, santonin derived α-methylene-γ-lactone **V-61** was chosen as the model substrate to identify suitable reaction conditions[107]. AgOAc was found to provide mainly *endo* selectivity in the absence of any ligands (Table 5.1, entry 1). When triphenyl phosphine (PPh_3) was applied as the ligand, there was a small decrease in the *endo* selectivity (Table 5.1, entry 2). (*R*)-Fesulphos **V-68**[59] delivered moderate *endo* selectivity (Tab. 5.1, entry 5). Inspired by our previous report that hydrogen bonding between the ligand and dipolarophile can improve the *endo* selectivity[42], ligand **V-69** was then used and good *endo/exo* and excellent facial selectivities were achieved (Table 5.1, entry 6). When THF was used as the solvent, **V-69** gave excellent *endo-Si* selectivity (Table 5.1, entry 7, condition A), the same as its *ent*-ligand at 0 °C (Table 5.1, entry 8, condition B). These two conditions suggest that there were few effects of substrate on the *endo* selectivity.

However, bulky phosphine ligand BINAP **V-67** reversed the *endo/exo* selectivity and the (*R*)-configuration favored *Si* facial attack (**V-65a**:**66a**=71:2) (Table 5.1, entry 3). Comparison with low *Re* facial selectivity (**V-65a**:**66a**=19:45) under the (*S*)-BINAP (*ent*-**V-67**) suggests that (*S*)-configured phosphine ligands mismatched with the substrate (Table 5.1, entry 4). Then, bulky phosphine ligands were used to furnish the *exo* selective products. When (*R*)-DTBM Segphos **V-70** was used as the ligand with DCE as the solvent, the reaction showed almost quantitively *exo-Si* selectivity (Table 5.1, entry 9, condition C). However, the enantiomeric ligand failed to produce a satisfying result of *exo-Re* facial selectivity (Table 5.1, entry 10). A large number of ligands were further screened, where (*S*)-DTBM Biphep **V-71** performed best in terms of diastereoselectivity (Table 5.1, entry 11-13). The solvent played a curial role in the reaction selectivity. When THF was employed, the reaction was fully *endo-Re* favored (Table 5.1, entry 11). However, the selectivity was totally switched to *exo-Si* when chloroform was used as the solvent (Table 5.1, entry 12). This is the first example of solvent effects on the 1,3-dipolar cycloaddition using azomethine ylides. Finally, this transformation gave comparable yields and selectivities by lowering the temperature and increasing the amount of Schiff base (Table 5.1, entry 13, condition D).

Table 5.1. Development of the stereodivergent synthesis of santonin-pyrrolidines



Entry	Ligand	Base	Solvent	Temp	Yield	d.r. (**63a**:**64a**:**65a**:**66a**)
1	-	Et_3N	CH_2Cl_2	r.t.	74%	72:23:04:01
2	PPh_3	Et_3N	CH_2Cl_2	r.t.	79%	68:18:11:03
3	**V-67**	Et_3N	CH_2Cl_2	r.t.	93%	21:06:71:02
4	*ent*-**V-67**	Et_3N	CH_2Cl_2	r.t.	78%	22:14:19:45
5	**V-68**	Et_3N	CH_2Cl_2	r.t.	88%	60:05:09:26
6	**V-69**	Et_3N	CH_2Cl_2	r.t.	91%	89:00:11:00
7	**V-69**	Et_3N	THF	r.t.	82% (73%)†	91:02:07:00
8	*ent*-**V-69**	Et_3N	THF	0 °C	79% (95%)†	03:95:01:01
9	**V-70**	Et_3N	DCE	r.t.	92% (89%)†	00:00:100:00
10	*ent*-**V-70**	Et_3N	CH_2Cl_2	r.t.	68%	28:01:03:68
11¶	**V-71**	Cs_2CO_3	THF	r.t.	53%	88:00:00:12
12¶	**V-71**	Cs_2CO_3	$CHCl_3$	r.t.	77%	13:00:02:86
13*	**V-71**	Cs_2CO_3	$CHCl_3$	0 °C	72% (88%)†	04:00:00:96



Unless otherwise specified, all reactions were conducted with dehydrosantonin **V-61** (0.10 mmol, 1.0 equiv.), Schiff base **V-62a** (0.15 mmol, 1.5 equiv.) and base (0.02 mmol, 0.20 equiv.) in solvent (0.10 M, 1 mL) with 5 mol% AgOAc and 6 mol% ligand for 24-48 hours. Yield for all isomers and d.r. (**V-63a:64a:65a:66a**) were determined from the reaction mixture by means of ^{1}H NMR with CH_2Br_2 as the internal standard. †The main isomer was purified by column chromatography; isolated yields are shown in brackets. ¶0.50 equiv. Cs_2CO_3 was used. *2.0 equiv. Schiff base **V-62a** was used.

When the substrates approached in an *endo* manner, the chiral environment of the dehydrosantonin would not affect the reaction pocket, leading to good stereoselectivity with ligand **V-69** and its enantiomer (Table 5.1, entry 7-8; Fig. 5.6). However, in the *exo*

selectivity cases, the substrate had an inherent facial bias because of the quaternary center of the santonin scaffold (Fig. 5.6). When the reaction occurred at the *Si* face of dehydrosantonin, the methyl group was oriented away from the phosphine ligands, that is, the substrate matched well with the chiral ligand leading to excellent selectivity (reinforced stereoselection). Upon *Re* facial attack of the azomethine ylide, repulsion between the methyl group and ylide would disfavor such a pathway resulting in poor *endo*/*exo* selectivity (mismatched effect). Fortunately, condition screening of solvents and ligands enabled access to the *exo*-*Re* product in high stereoselectivity.

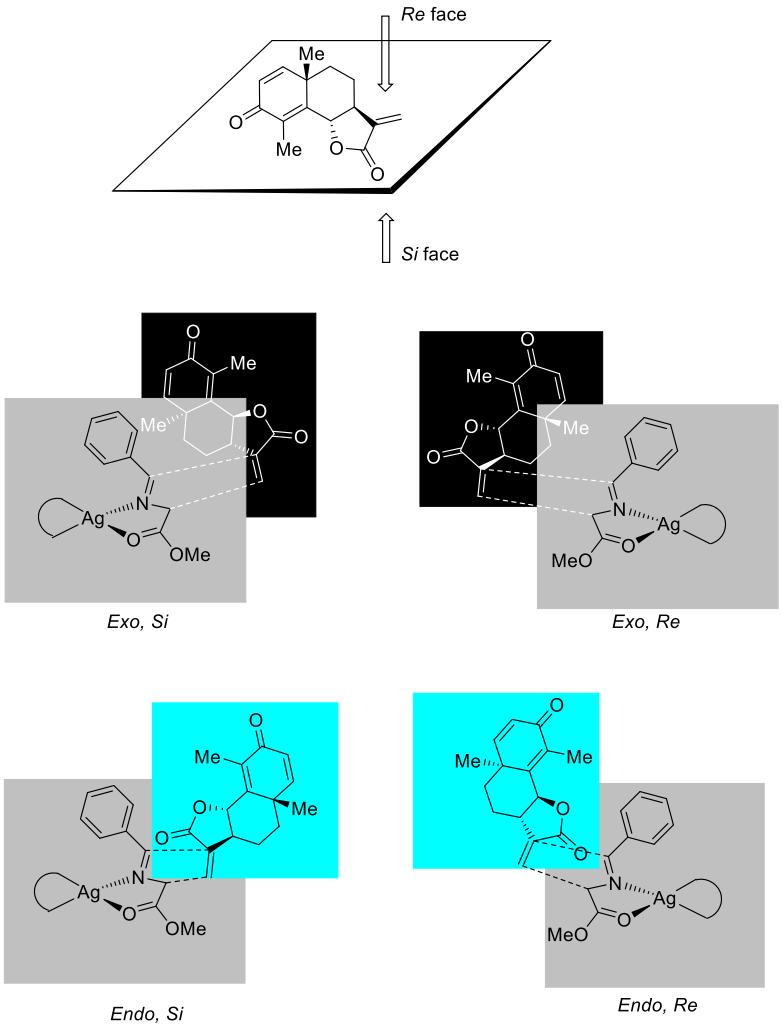
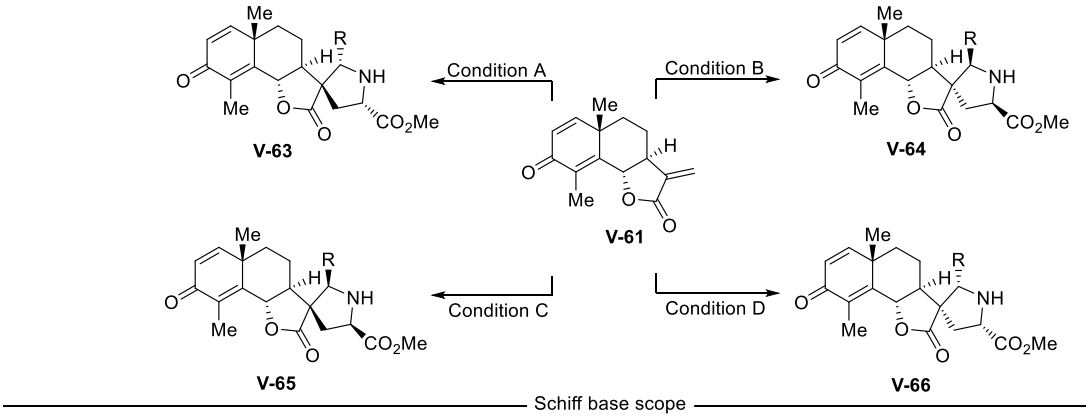


Figure 5.6. Overview of stereodivergent 1,3-dipolar cycloaddition of dehydrosantonin. In the *exo*,*Re*-selectivity, the repulsion between methyl group of santonin scaffold and azomethine ylide made such a pathway less favored (mismatched cases).

5.3.2 Substrate scope of Schiff bases

With all these four optimized conditions in hand, a series of Schiff bases was employed (Fig. 5.7). Most of these substrates were compatible with the reaction conditions. The reactions tolerated diverse substitutions on the *para*- and *meta*- positions of phenyl groups. Condition B delivered higher yields and diastereoselectivities compared with condition A. However, Condition C was not compatible with sterically hindered *ortho*-substituted Schiff bases. None of them (**V-65m** – **65o**) afforded satisfying results. Following these methodologies, 61 stereochemically diverse compounds were efficiently accessed. The absolute configuration of **V-63b**, **V-64f** and **V-66e** was unambiguously confirmed by the X-ray crystallographic analysis (see experiment part 7.4.5).



Cl	Cond.	Prod.	Yield	d.r.
	A	**63a**	73%	91:9
	B	**64a**	95%	>95:5
	C	**65a**	89%	>95:5
	D	**66a**	88%	94:6

Br	Cond.	Prod.	Yield	d.r.
	A	**63b**	67%	95:5
	B	**64b**	85%	>95:5
	C	**65b**	94%	>95:5
	D	**66b**	88%	>95:5

F	Cond.	Prod.	Yield	d.r.
	A	**63c**	53%	94:6
	B	**64c**	99%	>95:5
	C	**65c**	81%	>95:5
	D	**66c**	86%	>95:5

CF_3	Cond.	Prod.	Yield	d.r.
	A	**63d**	72%	>95:5
	B	**64d**	95%	>95:5
	C	**65d**	83%	90:10
	D	**66d**	92%	>95:5

Me	Cond.	Prod.	Yield	d.r.
	A	**63e**	63%	91:9
	B	**64e**	89%	>95:5
	C	**65e**	97%	>95:5
	D	**66e**	87%	>95:5

OMe	Cond.	Prod.	Yield	d.r.
	A	**63f**	67%	90:10
	B	**64f**	84%	>95:5
	C	**65f**	94%	>95:5
	D	**66f**	79%	95:5

CN	Cond.	Prod.	Yield	d.r.
	A	**63g**	73%	>95:5
	B	**64g**	88%	>95:5
	C	**65g**	86%	>95:5
	D	**66g**	80%	81:19

H	Cond.	Prod.	Yield	d.r.
	A	**63h**	57%	92:8
	B	**64h**	91%	>95:5
	C	**65h**	82%	n.d.
	D	**66h**	94%	>95:5

Cl	Cond.	Prod.	Yield	d.r.
	A	**63i**	66%	93:7
	B	**64i**	89%	>95:5
	C	**65i**	80%	n.d.
	D	**66i**	61%	n.d.

Br	Cond.	Prod.	Yield	d.r.
	A	**63j**	76%	93:7
	B	**64j**	95%	>95:5
	C	**65j**	75%	n.d.
	D	**66j**	55%	n.d.

Me	Cond.	Prod.	Yield	d.r.
	A	**63k**	75%	92:8
	B	**64k**	94%	>95:5
	C	**65k**	73%	n.d.
	D	**66k**	81%	81:19

MeO	Cond.	Prod.	Yield	d.r.
	A	**63l**	50%	83:17
	B	**64l**	95%	>95:5
	C	**65l**	63%	n.d.
	D	**66l**	49%	n.d.

Cl	Cond.	Prod.	Yield	d.r.
	A	**63m**	76%	>95:5
	B	**64m**	95%	>95:5
	C	**65m**	Low conv.	
	D	**66m**	64%	n.d.

Br	Cond.	Prod.	Yield	d.r.
	A	**63n**	76%	>95:5
	B	**64n**	89%	>95:5
	C	**65n**	Low conv.	
	D	**66n**	61%	90:10

Me	Cond.	Prod.	Yield	d.r.
	A	**63o**	66%	92:8
	B	**64o**	92%	>95:5
	C	**65o**	Low conv.	
	D	**66o**	88%	>95:5

S	Cond.	Prod.	Yield	d.r.
	A	**63p**	46%	82:18
	B	**64p**	87%	>95:5
	C	**65p**	93%	>95:5
	D	**66p**	81%	82:18

Figure 5.7. Substrate scope for the stereodivergent synthesis of santonin-pyrrolidines. Condition **A**: dehydrosantonin (0.1 mmol, 1.0 equiv.) and Schiff base (0.15 mmol, 1.5 equiv.), Et_3N (0.02 mmol, 20 mol%) in 1 mL THF with 5 mol% AgOAc and 6 mol% **V-69** at r.t. for 24-48 hours; Condition **B**: as condition A but *ent*-**V-69** was used at 0°C; Condition **C**: as condition A except **V-70** was used in 1 mL DCE; Condition **D**: dehydrosantonin (0.1 mmol, 1.0 equiv.) and Schiff base (0.2 mmol, 2.0 equiv.), Cs_2CO_3 (0.05 mmol, 50 mol%) in 1 mL $CHCl_3$ with 5 mol% AgOAc and 6 mol% **V-71** at 0 °C for 24-48 hours.

5.3.3 Substrate scope of sesquiterpene lactones (SLs)

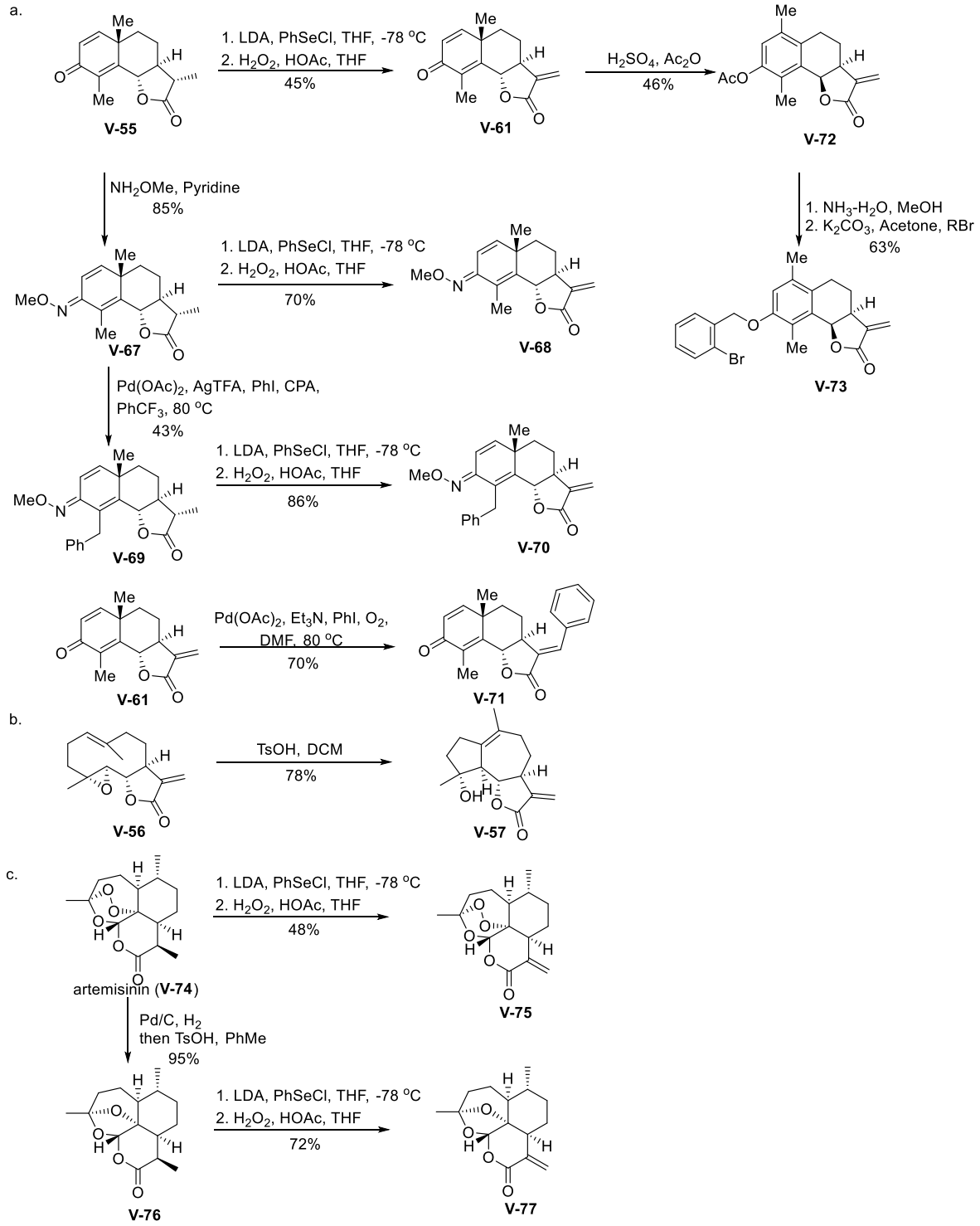


Figure 5.8. Synthesis of sesquiterpene lactones and their derivatives.

Encouraged by the good substitution tolerance of Schiff bases, more sesquiterpene derivatives were employed (Fig. 5.7). Diverse appendages were incorporated into the santonin scaffold *via* oxime formation, C-H activation[108] and Heck reaction[109] to give **V-68**, **V-70** and **V-71** respectively. Under acidic conditions, dehydrosantonin rearranged into a

phenyl product **V-72** with the stereoinversion of C6[110]. This compound was then alkylated to give **V-73**, a covalent inhibitor of ubiquitin-conjugating enzyme UbcH5c. Parthenolide **V-56** is another commercially available sesquiterpenoid, which can be viewed as a ring-opened analog of santonin.[111] Transannulation between the alkene and epoxide in **V-56** delivered the [5,7,6]-tricycle micheliolide **V-57**[112]. Artemisinin and its deoxo derivative were converted to the *α*-methylene-*δ*-lactone **V-75** and **V-77** *via* a two-step manipulation[113].

At last, 9 sesquiterpene lactones and their derivatives were synthesized (Fig. 5.9). Diverse "point" modifications were focused on santonin scaffold to yield 4 members. Rearrangement and aromatization of dehydrosantonin yielded 6/6/5 tricycles. Even though parthenolide is not directly synthesized from santonin, it can be viewed as a ring opened analog of dehydrosantonin *via* cleavage of C5-C10 bond. Compound **V-57** is a formally rearranged analog of santonin featuring 5/7/5 tricycle. The structural relationship between santonin and artemisinin is not obvious. According to the biosynthetic hypothesis, santonin and artemisinin shared a common precursor. Therefore, the biological and structural relevance are still retained.

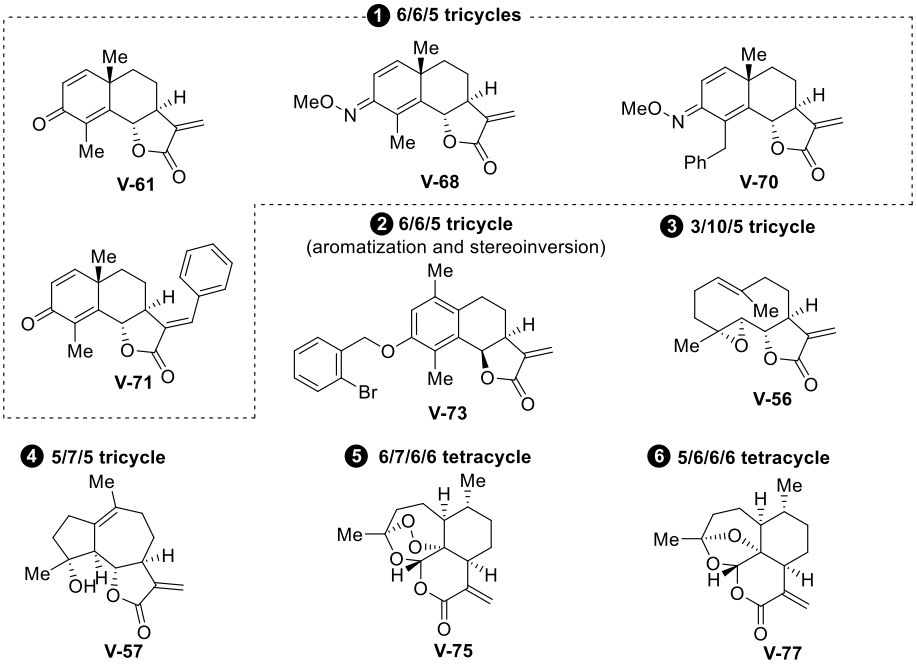


Figure 5.9. Santonin-derived compound classes employed in the synthesis of the pseudo sesquiterpenoid alkaloids.

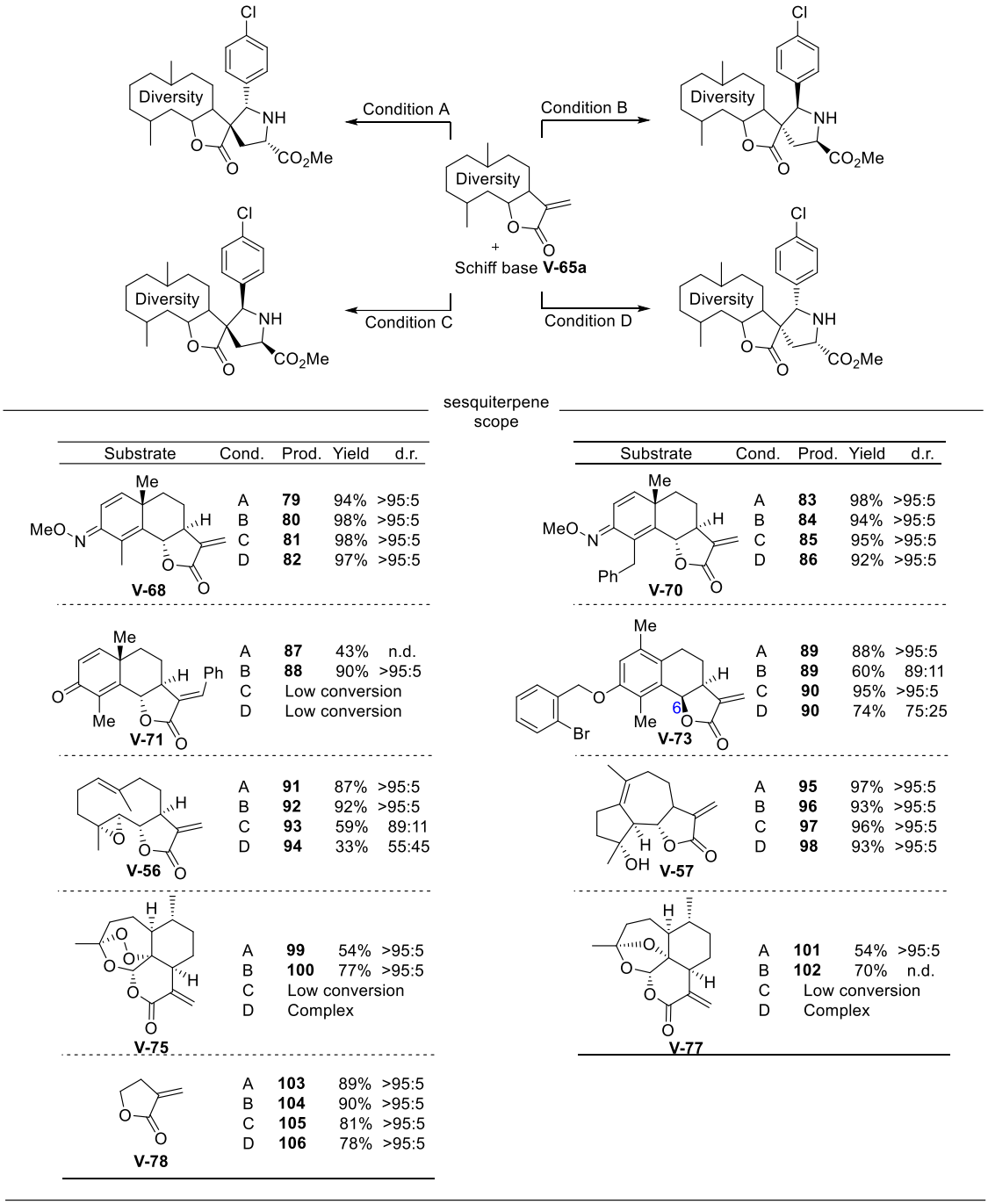


Figure 5.10. Substrate scope for diverse sesquiterpenes. All reactions were carried out under the conditions described above (Fig. 5.7). 1,3-dipolar cycloadditions with **V-71**, **73**, **75** and **77** were performed on 0.05 mmol scale.

Then, the substrate scope of sesquiterpene lactones was explored (Fig. 5.9). The reactions tolerated the changes on the ring A and B of dehydrosantonin. The oxime and phenyl group attachment afforded desired products **V-79** – **82** and **V-83** – **86** in excellent yields and selectivities respectively. Even the formally ring-opened (**V-56**) or rearranged scaffold (**V-57**) still exhibited satisfying results. However, the reaction was highly sensitive to the modifications of the γ-lactone. Compound **V-71** with a phenyl group at the end of methylene

showed low reactivity under the *exo*-selective conditions. Inversion of the stereocenters at C6 (**V-73**) confined the reaction to occur at the *Si* face. Notably, product **V-89** and **V-90** were the main isomers even under the condition B and D. Ring size of the lactone was also crucial for the reaction. The artemisinin derivative **V-75** and **V-77** only resulted in the formation of *endo* products. The reaction conditions can also be applied to simple lactone **V-78** to yield the product in excellent stereoselectivity.

5.3.4 Plausible mechanism

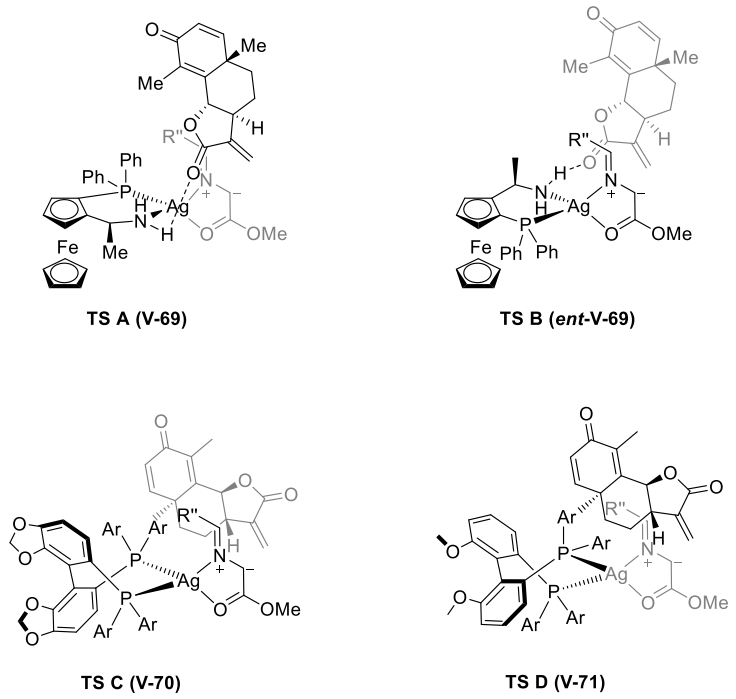


Figure 5.11. Plausible transition states (TS) of stereodivergent 1,3-dipolar cycloaddition. Ligand numbers are shown in brackets.

After the library construction, plausible transition states were then proposed. As depicted in Fig. 5.11 TS-A, in the presence of ligand **V-69**, the back face was shielded by the aryl group on P atom. On the other hand, the amine in the ligand can serve as a directing group to form hydrogen bond with dipolarophiles, so that dehydrosantonin adopted an *endo* approaching style. And its enantiomer catalyzed the formation of another *endo* isomer (TS-B). To be noted, almost no substrate bias was observed when dehydrosantonin cycloadded to azomethine ylide in *endo* selectivity. This might be attributed to the fact that quaternary center is too far away from the catalytic center to affect the reaction results.

Bulky ligands afforded the *exo* selectivity because the *endo* approaching was totally blocked by steric hindrance around Ag(I). In the presence of (*R*)-DTBM Segphos **V-70**,

dehydrosantonin approached from the back side to afford single isomer. However, when its enantiomer was used, the reaction failed to yield another *exo* isomer in satisfying selectivity, which is caused by the substrate bias. As depicted in Fig. 5.11 TS-D, the quaternary center on dehydrosantonin scaffold is close to the catalyst's center. When it approached from the front side, the methyl group is oriented toward the ligand, and thus severe steric repulsion was induced. That is why condition screening for *exo/Re* selectivity is so challenging. After many trials, (*S*)-DTBM Biphep **V-71** was found to give *exo/Re* product when $CHCl_3$ was used as solvent. The condition was highly sensitive to the changes of solvents. When THF was used, the reaction selectivity was switched from *exo/Re* to *endo/Si*. As introduced in the beginning of this chapter, electronic/steric effects of ligands and coordination states of metals can affect the reaction selectivity. In this case, THF can serve as a ligand for Ag(I), so that the coordination state of metal was changed. When dehydrosantonin approached to azomethine ylide, Ag(I) coordinated with the oxygen atom of lactone **V-61** and confined the reaction to take place in *endo* selectivity to give **V-63**.

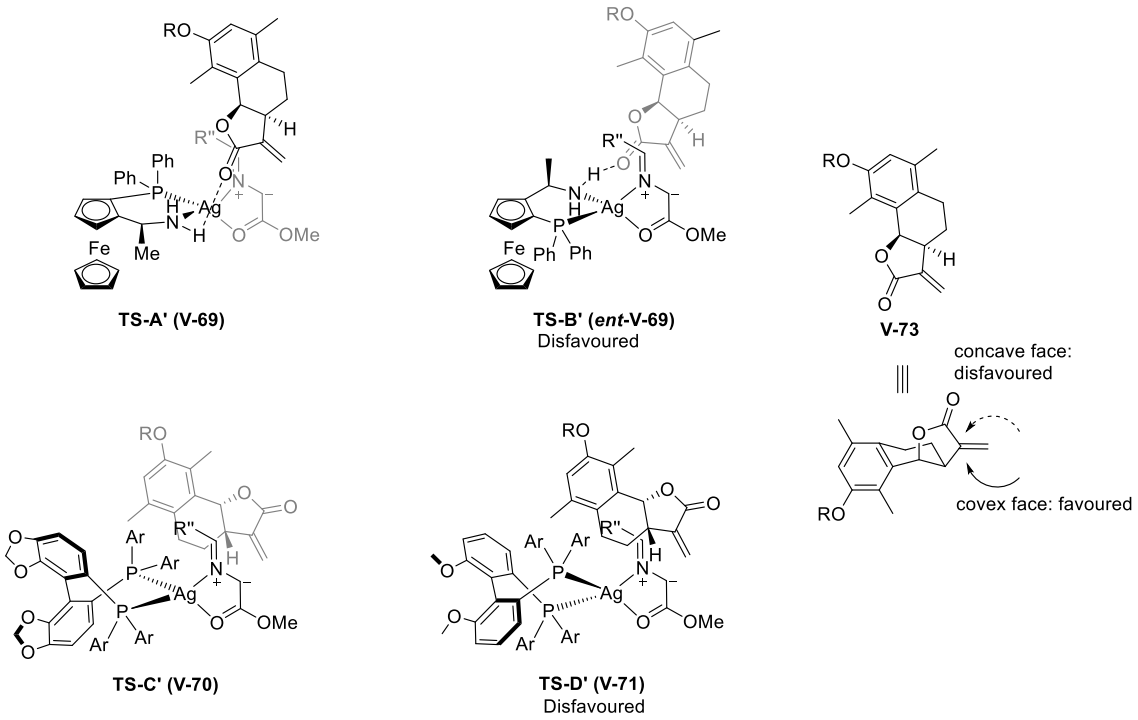


Figure 5.12. Plausible transition state (TS) of stereodivergent 1,3-dipolar cycloaddition to aromatized santonin derivative **V-73**. Ligand numbers are shown in brackets.

In the exploration of substrate scope of sesquiterpene lactones, the inversion of stereocenter at C6 position can confine the reaction to take place in *Re* face even under conditions B and D (Fig. 5.12). This is also the effect of matched/mismatched pairs. In the structure of *cis* fused lactone **V-73** as shown in Fig. 5.12, the whole molecule will form a concave shape and

the reactions can only take place in the convex face. Therefore, under condition A and C, the substrate and catalysts will form matched pairs, while mismatched pairs are formed under conditions B and D (Fig. 5.12 TS-B' and D').

As expected, no conversion should be observed in conditions B and D. However, these two conditions still afforded products, but in unexpected selectivities. As drawn in Fig. 5.13 TS-B'1 – B'4, all possible transitions states are listed. The expected B'1 complex was not favored because of the forbidden concave attack, and the same as TS-B'4. Because the steric effect of phosphine ligand is not severe so that *endo* selectivity can also take place on front face (TS-B'2). In comparison, the repulsion between the methyl group of ligand and **V-73** scaffold will disfavor the transition state B'3. Notably, even though condition A and B used enantiomeric ligands, they finally resulted in the same product.

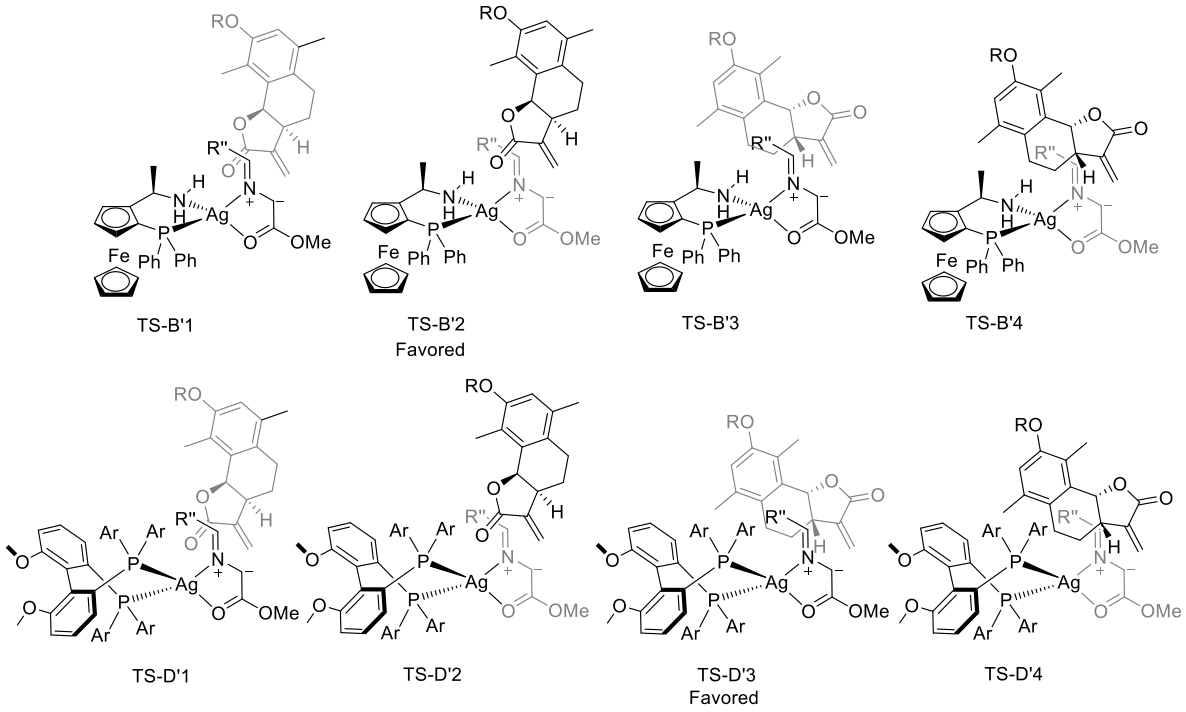


Figure 5.13. All possible transition states of 1,3-dipolar cycloaddition to aromatized santonin derivative **V-73** under condition B and D.

Similarly, condition C and D also led to the same product. Transition states D'1 and D'4 were prohibited because of the extremely huge steric hindrance of the substrates (Fig. 5.13). As stated above, bulky ligands shielded the *endo* reaction pathway, so that only transition state D'3 was favored. At last, the proposed transition states are reasonable to explain most of the unusual results.

5.3.5 Systematic analysis of pseudo sesquiterpenoid alkaloids

Data was produced by the compound management and screening center (COMAS) and analyzed by Jie Liu.

With the synthesized compound collections in hand, we then started to conduct a systematic analysis using cheminformatic tools and cell painting technology. NP-likeness score[36] was first applied to provide an overview of the structural similarity with natural products. This cheminformatic tool was first developed by Ertl and coworkers.[36] It sums up the frequency of substructures found in natural products. As introduced in Chapter 3, score more than 0 indicates that the compound is more similar to NPs. Firstly, NP-likeness scores of natural products from ChEMBL database[37] and molecules from DrugBank[38] are calculated (Fig. 5.14a). Not surprisingly, natural products display higher NP-likeness scores compared to drug molecules. The scores for pseudo sesquiterpenoid alkaloids are around 1-2, overlapping with the area covered by natural products. This observation is highly different from our previous reports of pseudo natural products that recombination of different NP fragments afforded compounds more similar to drug molecules than to natural products.[34] In this case, the retainment of high NP-likeness score might be attributed to ring distortion. Considering that ring distortion is a bioinspired strategy that many natural products use to diversify the structures,[114] retainment of high NP-likeness score after ring distortion is reasonable. Pseudo sesquiterpenoid alkaloids and sesquiterpene lactones are then compared with each other (Fig. 5.14b). As expected, an apparent decrease of NP-likeness score is observed after combination with pyrrolidine fragment which suggests that pyrrolidine is not combined with sesquiterpene lactones in natural products.

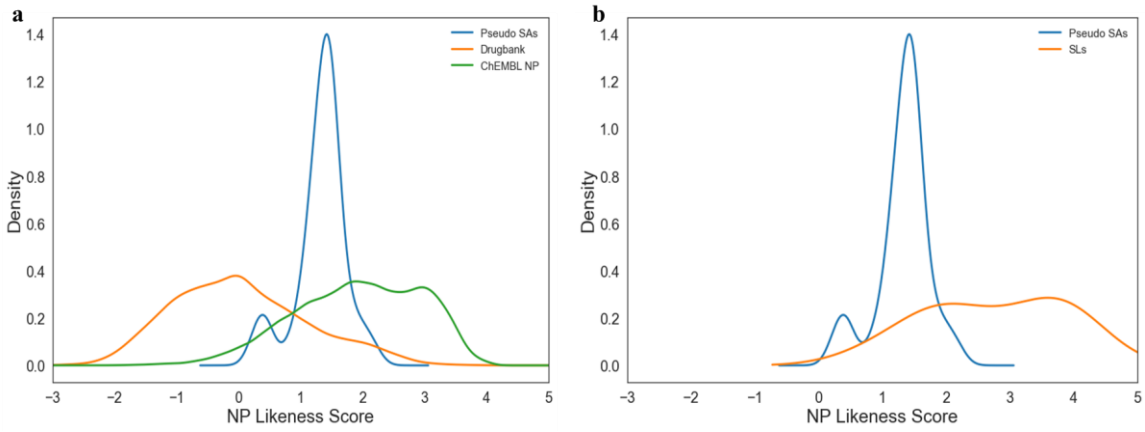


Figure 5.14. NP-likeness score revealed that pseudo sesquiterpenoid alkaloids displayed high NP-likeness. (a) Comparison of pseudo sesquiterpenoid alkaloids with natural products from ChEMBL database[37] and molecules from DrugBank[38]. (b) Comparison of pseudo sesquiterpenoid alkaloids with sesquiterpene lactones.

Then the chemical similarity between different classes of pseudo sesquiterpenoid alkaloids and sesquiterpene lactones was calculated using Tanimoto coefficients. Sesquiterpene lactones and their derivatives displayed low chemical similarity as shown in region A (Fig. 5.15). However, artemisinin **V-75** and its deoxo derivative **V-77** exhibited high chemical similarity (82%) because of their highly similar structures. Nevertheless, ring distortion is an efficient way to afford diverse scaffolds. After recombination of pyrrolidine fragment, the cross-chemical similarity between sesquiterpene lactones and pseudo sesquiterpenoid alkaloids were low (Fig. 5.15, Region B), which suggest that pseudo natural product design enabled the exploration of novel chemical space beyond that encoded by guiding natural products. An increase of intra-class chemical similarity of pseudo natural products was observed (Fig. 5.15 Region C vs Region A). This result is caused by the fact that all the compared compounds share the same pyrrolidine fragment.

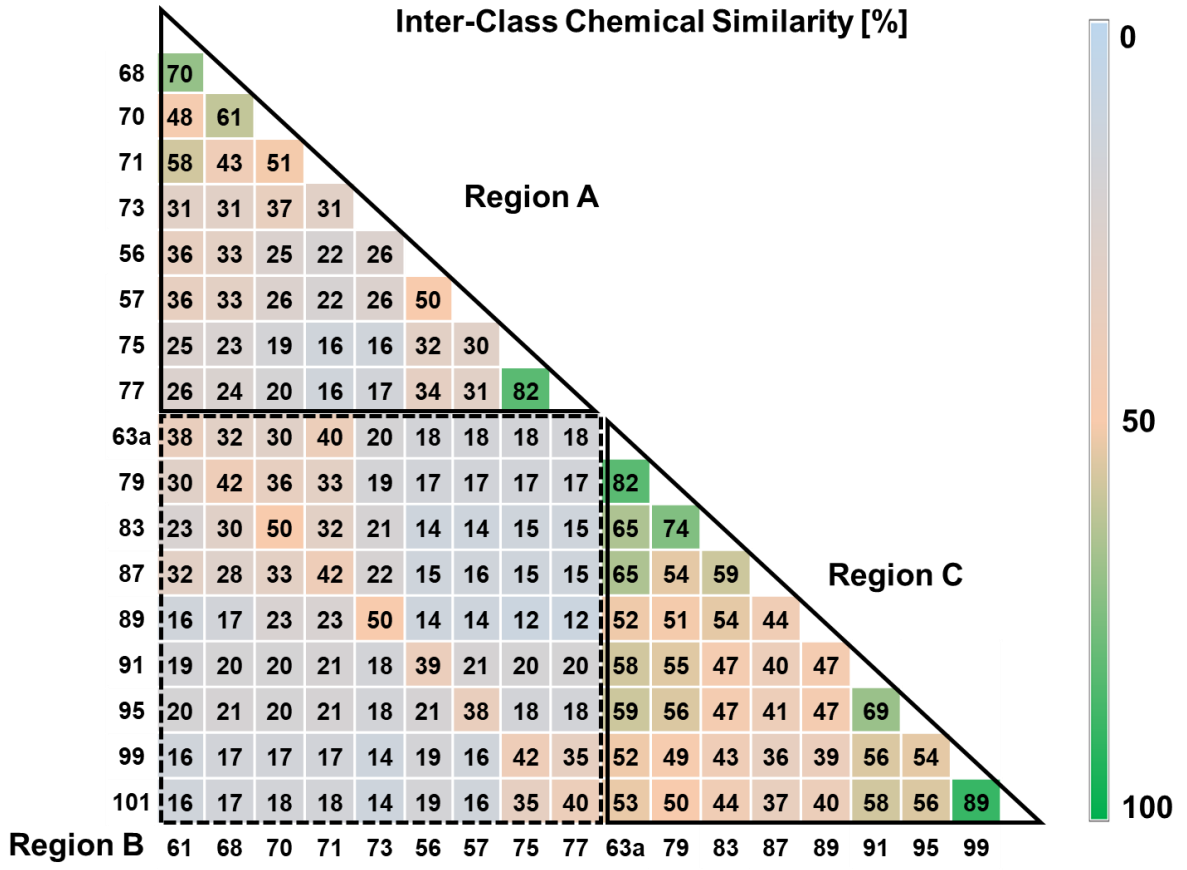


Figure 5.15. Chemical similarity between pseudo sesquiterpenoid alkaloids.

Because NP-likeness score and chemical similarity are unable to differentiate stereoisomers, principal moments of inertia (PMI) [115] was then calculated. PMI plot is a cheminformatic tool to depict the molecular shape of the lowest-energy conformations, and thus it

distinguishes between stereoisomers. In the ternary plot (Fig. 5.16), rod-shaped compounds reside on top-left corner, sphere-shaped ones reside on top-right region, while the bottom corner represents disc-shaped compounds. As shown in Fig. 5.16, the synthesized compounds occupied broad area with sesquiterpene lactones residing along the rod-disc side of the plot. After the combination of pyrrolidine, an obvious right shift was observed in the plot. Interestingly, different stereoisomers (**V-63c** – **66c**) can be distinctly differentiated. All of the cheminformatic analysis indicated that the conceptual combination of ring distortion and pseudo natural product design delivered structurally diverse compound collections.

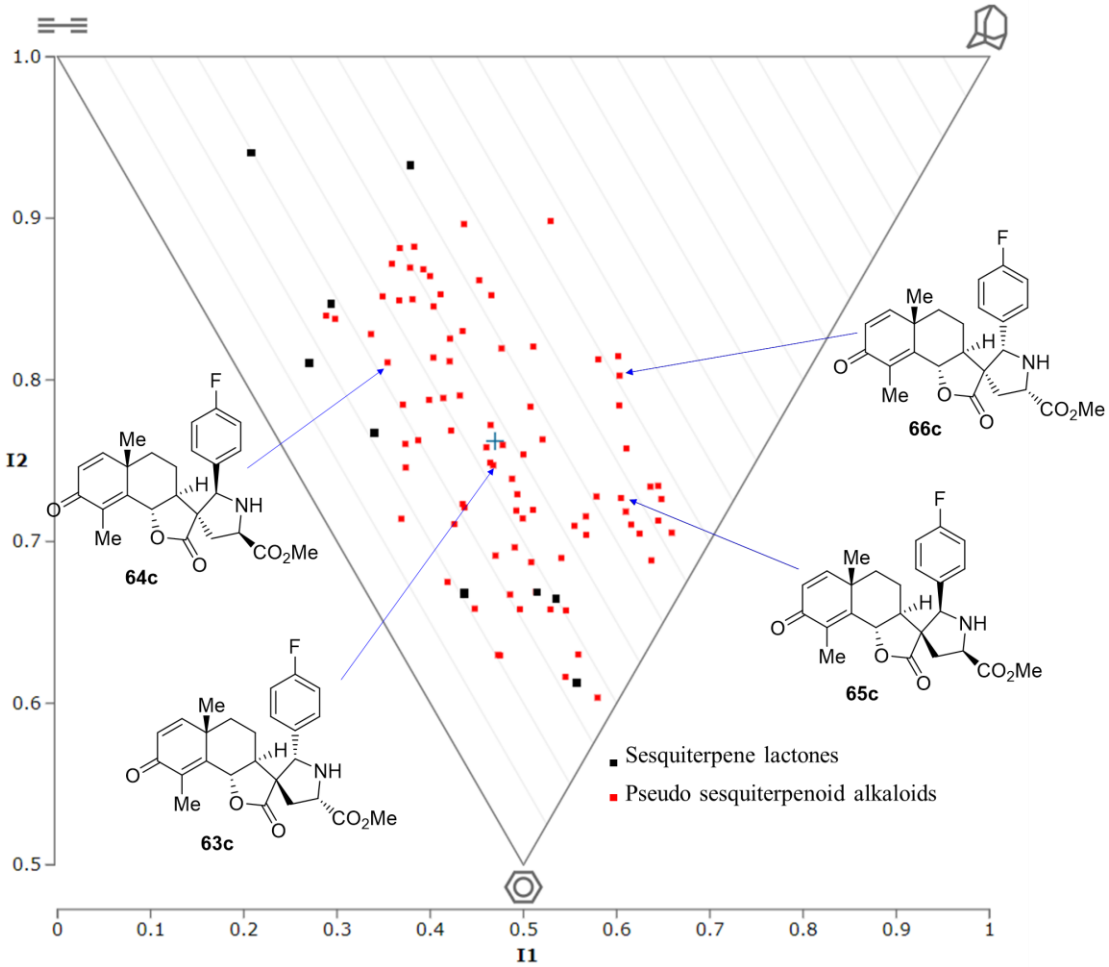


Figure 5.16. PMI plot of pseudo sesquiterpenoid alkaloids and sesquiterpene lactones.

To evaluate the biological performance of the compound collections, cell painting, a high-content and throughput morphological screening method, was employed. As introduced in Chapter 3, U2OS cells were treated with compounds at 10, 30 and 50 μM concentrations and then stained ("painted") by six orthogonal fluorescent dyes to reveal the perturbations of seven cellular compartments and organelles, such as nucleus, mitochondria, endoplasmic reticulum, golgi/plasma membrane and F-actin.[45a] Then, 579 parameters were extracted for comparison using image analysis. Induction values were calculated based on the significantly

changed phenotypic parameters compared with DMSO control.[45b] Most of the pseudo sesquiterpenoid alkaloids exhibited low induction at 10 μM concentration. 49 compounds induced significant morphological changes (induction > 5%) when tested at 50 μM concentration. Biosimilarity is calculated according to the correlation distance between two profiles. High biosimilarity between tested compounds and reference compounds (those annotated with validated MoA) will suggest the possible bioactivity or targets. As mentioned above, α-methylene-γ-lactone is a promiscuous covalent binder. However, ring distortion of sesquiterpene lactones can distinguish their biological performance with biosimilarity below 60% compared to dehydrosantonin **V-61** (Fig. 5.17a).

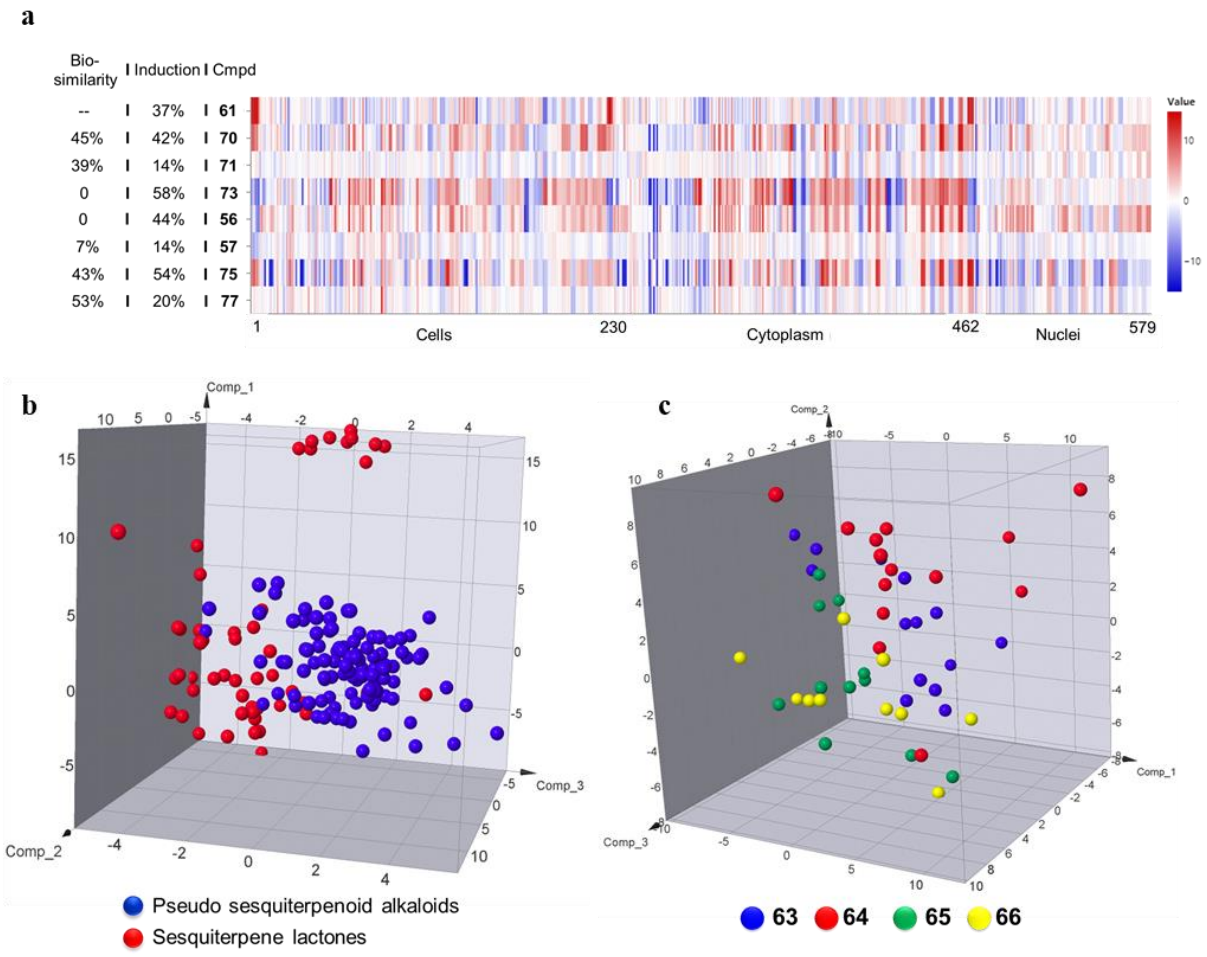


Figure 5.17. Cell painting analysis of all the compounds. (a) Biosimilarity of cell painting profiles induced by sesquiterpene lactones. (b-c) PCA of pseudo sesquiterpenoid alkaloids. (b) Comparison between pseudo sesquiterpenoid alkaloids and sesquiterpene lactones. Explained variance: 62%. (c) Comparison between different stereoisomers. Explained variance: 52%.

To condense the morphological profiles, principle component analysis (PCA) was then employed. As depicted in Fig. 5.17 b, pseudo natural products (blue dots) occupied a highly different biological space compared with sesquiterpene lactones (red dots). This was

consistent with the previous observation that α-methylene-γ-lactone moiety is key to the bioactivity. After the recombination of pyrrolidine fragment at this position, the primary MoA was totally abolished. As shown in Schreiber's work, cell painting is able to differentiate stereoisomers.[116] Herein, the same tendency was observed in Fig. 5.17c where different stereoisomers occupied distinctly different space in PCA plot.

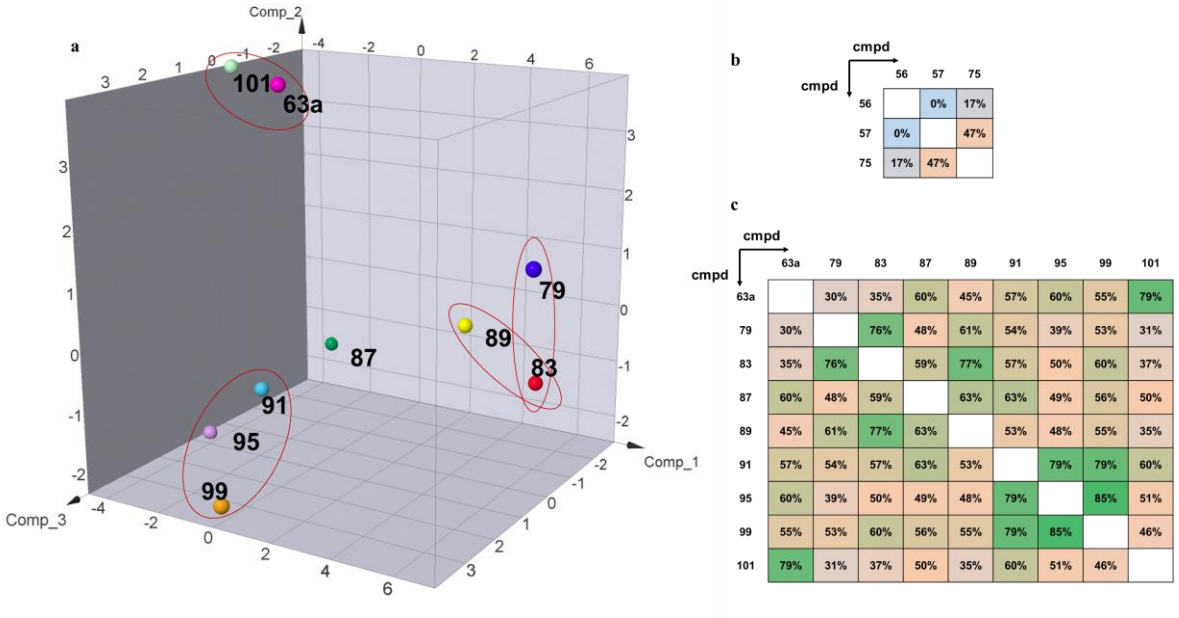
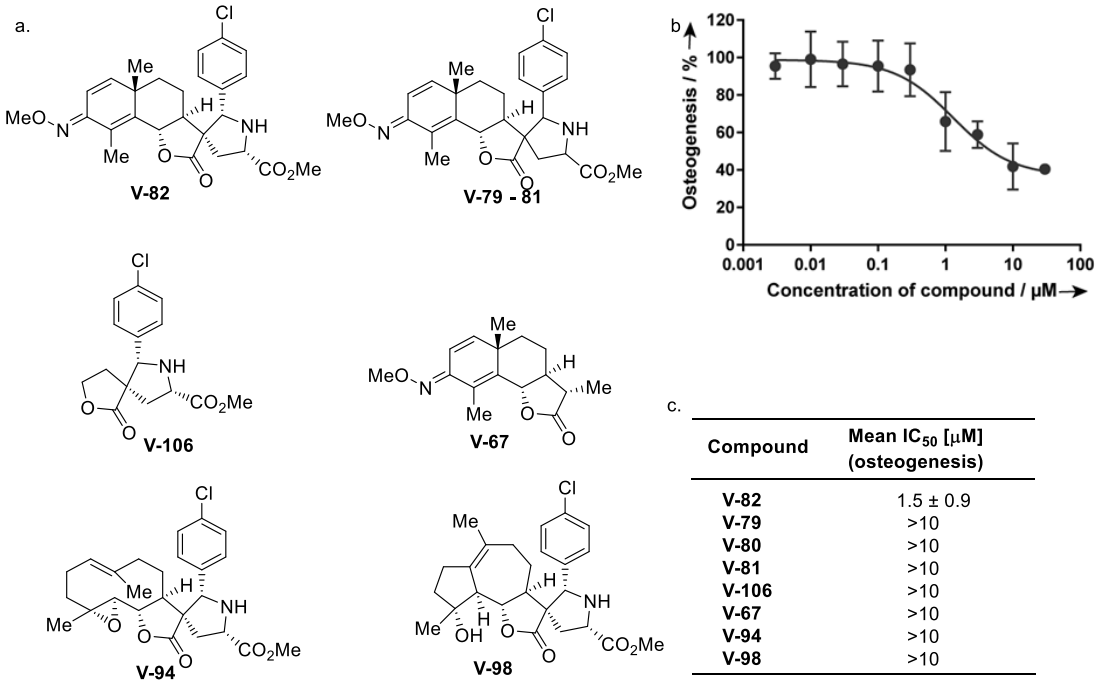


Figure 5.18. Ring distortion can lead to diverse biological clusters based on PCA results. (a) Principle component analysis of cell painting profiles. Compounds in red circle displayed >75% cross biological similarity. Explained variance: 78%. (b) Cross biosimilarity of sesquiterpene lactones **V-56**, **57** and **75**. (c) Cross biosimilarity of pseudo sesquiterpenoid alkaloids.

Then different pseudo sesquiterpenoid alkaloids with diverse sesquiterpene scaffolds *via* ring distortion were analyzed. Different scaffolds afforded diverse biological clusters as shown in Fig. 5.18a,c. Even the extremely similar structures **V-99** and **101** displayed highly different biological performance. For the structures derived from point modification of santonin, they (**V-79**, **83** and **89**) showed relatively high biological similarity (>70%) with each other. However, **V-91**, **95** and **99** exhibited unexpectedly high similarity with each other despite their strikingly different scaffolds (Fig. 5.18a,c). As shown in Fig. 5.18b, the sesquiterpene lactones **V-56**, **57** and **75** shared low cross biosimilarity and cell painting was able to differentiate these diverse scaffolds. However, the biological performance of the resulting pseudo sesquiterpenoid alkaloids after recombination of the same pyrrolidine fragment converged at last. To test if the convergence of biological performance was induced by the dominant effect of pyrrolidine fragment, truncated structure **V-103** was then tested using cell painting. This simplified structure did not induce any significant morphological changes.

Therefore, the high biosimilarity of **V-91**, **95** and **99** is not caused by the dominant effect of pyrrolidine fragments.

To gain more insight into the compound collections, the whole library was screened against a panel of cell-based assays. Compound **V-82** exhibited high inhibitory potency toward Hh-dependent osteoblast differentiation in C3H/10T1/2 cells (Data from COMAS; Confirmed by Jana Flegel). In this assay, Hh agonist purmorphamine was used to induce osteoblast differentiation. Then, the cells were treated with DMSO or tested compounds. The activity was calculated by detecting the biomarker alkaline phosphatase. This compound displayed a half-maximal inhibitory concentration (IC_{50}) of 1.5±0.9 μM (Fig. 5.19). Interestingly, other stereoisomers displayed no detectable activity at 10 μM. Truncated structures **V-106** and **67** were inactive, which emphasized the significance of pseudo natural product design to combine these two fragments together. Furthermore, other pseudo sesquiterpenoid alkaloids **V-94** and **V-98** exhibited no inhibitory activity. This is a strong support to combine ring distortion and pseudo natural product design.



Compound	Mean IC_{50} [μM] (osteogenesis)
V-82	1.5 ± 0.9
V-79	>10
V-80	>10
V-81	>10
V-106	>10
V-67	>10
V-94	>10
V-98	>10

Figure 5.19. Pseudo sesquiterpenoid alkaloid **V-82** is a new chemotype inhibiting Hedgehog dependent differentiation of multipotent murine mesenchymal progenitor stem cells into osteoblasts. (a) Structures of **V-82** and other analogs. (b) IC_{50} plot of Hh-dependent osteoblast differentiation assay. Data are mean values ±SD and representative of four biological replicates, each performed in three technical replicates. (c) IC_{50} values of compounds depicted in (a).

5.4 Summary and outlook

In this project, pseudo natural product design and ring distortion strategy were conceptually combined together to afford structurally complex and diverse compound collections. Pseudo natural product design relies on the development of highly efficient and convergent synthetic methodologies. This bottom-up strategy can be seen as a complexity-generating process. While ring distortion is a top-down strategy using natural products as the starting point for the manipulation. After the chemical transformation of ring systems, the primary natural products can be derived into strikingly different scaffolds, the whole process of which can be viewed as a diversity-generating manipulation. These two complementary concepts have inspired many fruitful results in chemical biology. However, no reports discussed the combination of these two strategies together. Herein, ring distortion of sesquiterpene lactones yielded diverse fragment-sized NP derivatives, which were sequentially recombined with alkaloid-derived NP fragment pyrrolidine to afford pseudo sesquiterpenoid alkaloids. The conceptual combination enabled the exploration of novel chemical space and resulted in diverse biological performance. Evaluation of compounds in a Hedgehog-dependent osteoblast differentiation assay resulted in the discovery of novel inhibitor. The activity comparison between compound **V-82** and other inactive analogs again confirmed the necessity and significance to combine ring distortion and pseudo natural product design.

Besides the conceptual innovation, a highly efficient and stereodivergent 1,3-dipolar cycloaddition was developed. Even though efficient synthetic methodology has enabled selective modification of natural products, most of them are only able to yield single isomer, which limits the explored chemical space. Considering that stereochemical properties parallel with biological activities, selective and stereodivergent reaction of natural products is highly promising, and thus in high demand. However, the limited accessibility of chiral ligands and highly complex stereochemical environment of natural products makes this transformation extremely challenging. To our knowledge, selective and stereodivergent 1,3-dipolar cycloadditions between azomethine ylides and natural products has never been reported. In this project, four optimal conditions were obtained after more than 40 entries of screening to afford stereochemically diverse compound collections. A solvent controlled 1,3-dipoar cycloaddition was discovered which highlighted the tunability of this reaction. Furthermore, this strategic reaction is well-tolerated with other strikingly different substrates. It is almost a common sense in asymmetric catalysis that enantiomeric ligands lead to enantiomeric products. However, under the control of catalysts and substrates, sesquiterpene derivative **V-**

73 afforded the same product even under the enantiomeric ligands. These discoveries not only emphasize the tunability and versatility of 1,3-dipolar cycloaddition, but also provide new insights for asymmetric catalysis.

Pseudo natural products employ the concept of recombination of biosynthetically unrelated NP fragments to afford structurally unprecedented compound collections. The whole strategy is based on the currently available natural products library, like the fragment generation and NP-likeness score. However, the discovery of novel NP structures is still ongoing.[117] Additionally, gene manipulation of plants and microorganisms may activate the silent biosynthetic pathways leading to the formation of novel scaffolds.[118] With the discovery of more natural products, some of the pseudo natural products synthesized previously may find their natural origins in the future. Notably, it was during our research that the isolation of vlasoulamine A was reported,[119] whose scaffold resembled that of **V-95**.

Chapter 6. Summary and outlook of the thesis

6. Summary and outlook of the thesis

Natural products serve as a great source of inspiration for the research in chemical biology and drug discovery. Their diverse and complex structures determine the correspondingly different and selective biological activities. However, NP chemical space is only partially explored and the discovery of novel NPs is still continuing. On the other hand, NPs are a small cluster explored by nature in vast chemical space because of the limited precursors and biosynthetic machineries in NP-producing organisms. Therefore, a unified and feasible synthetic strategy to afford compound collections whose properties resemble those of NPs is in high demand.

This thesis was conducted from April 2018 to May 2021 including systematic syntheses (Chapter 3), Rhodium catalysis (Chapter 4) and stereodivergent 1,3-dipolar cycloadditions (Chapter 5). With an aim to produce structurally complex and diverse compound collections, novel synthetic methodologies and concepts were developed. Systematic analysis of different compound classes supported and inspired pseudo natural product design.

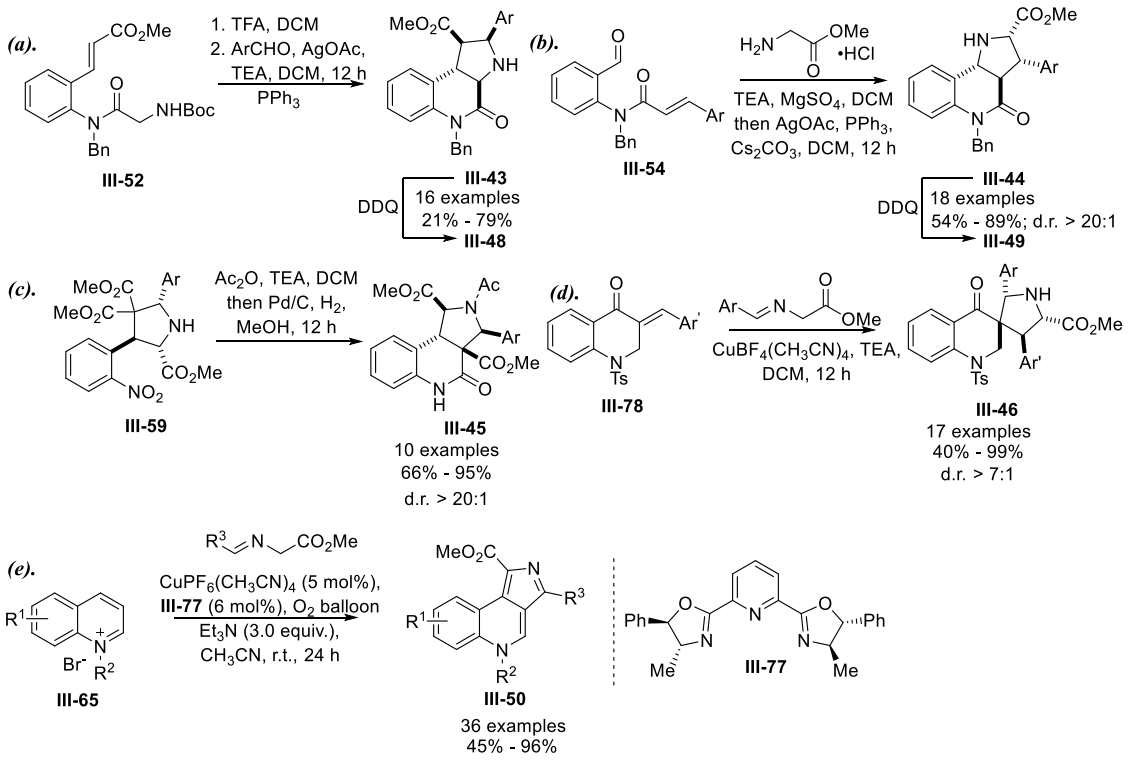


Figure 6.1. Systematic synthesis of pseudo natural product pyrroquinolines through 1,3-dipolar cycloaddition.

In Chapter 3, a systematic synthesis was established where alkaloid-derived NP fragments pyrrolidine and tetrahydroquinoline were unprecedentedly combined by varying the connectivity patterns and positions (Fig. 6.1). The synthesis campaigns featured a highly

diastereoselective intramolecular 1,3-dipolar cycloaddition (Fig. 6.1b), a novel synthetic route toward pyrrolo[3,4-*c*]quinoline **III-45** (Fig. 6.1c) and a dearomative 1,3-dipolar cycloaddition of quinolinium salts (Fig. 6.1e). Systematic analysis revealed that chemically and biologically diverse compound collections were enabled by varying the connections between the same NP fragments.

Enantioselective catalysis was also attempted in Chapter 3. A $CuBF_4$/(*R*)-Fesulphos catalyzed 1,3-dipolar cycloaddition yielded cycloadducts in excellent diastereo- and enantioselectivity with a broad substrate scope (Fig. 6.2a). The resulting pyrrolidines were converted sequentially to the pyrroquinolines in high efficiency *via* selective lactamization. For the asymmetric intramolecular 1,3-dipolar cycloaddition, tremendous efforts revealed that Ag(I)/DM-Biphep catalyzed the reaction in moderate to high stereoselectivity (Fig. 6.2 b). Biological screening of the resulting pyrroquinoline libraries resulted in the discovery of a novel chemotype **III-44** targeting Hedgehog signaling pathway by binding *Smo* protein.

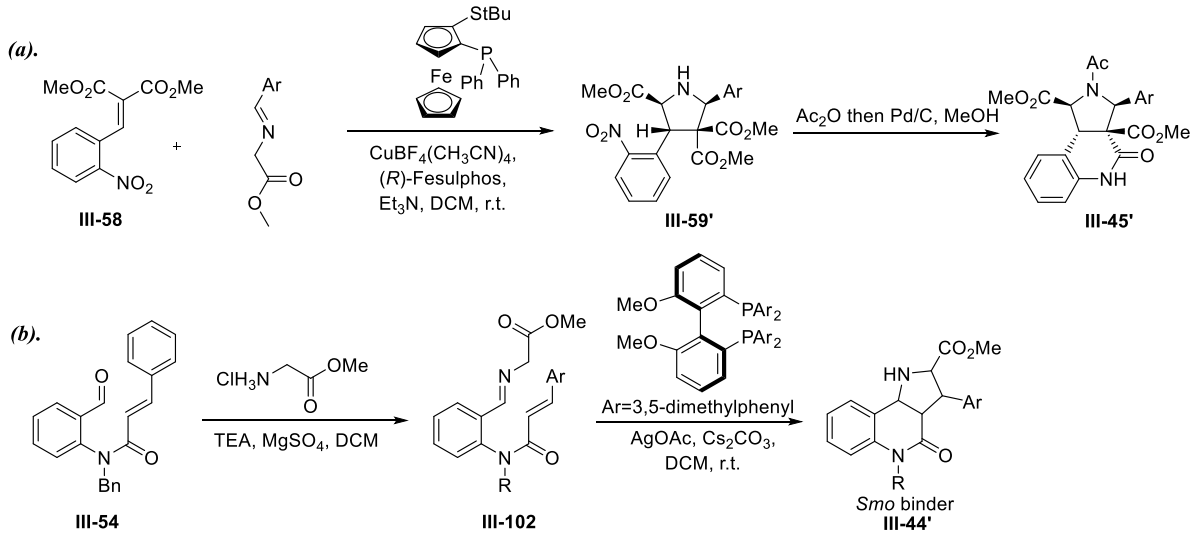


Figure 6.2. Asymmetric synthesis of pyrroquinolines.

In Chapter 4, a Rh(III)-catalyzed scaffold divergent synthesis is disclosed where the spirooxindole fragment was modularly combined with other scaffolds. A highly efficient Rh(III)-catalyzed C-H functionalization without or with Lossen rearrangement cascade was developed (Fig. 6.3). The reaction selectivity was controlled by the protecting group of diazooxindoles, where *N*-Bn favored the direct annulation product **IV-95** while *N*-Ms favored the Lossen rearrangement **IV-96**. The mild reaction conditions tolerated diverse substrates, even the natural products. With diversification of the product, a 52-membered compound collection was constructed. A careful mechanistic study and substrate scope exploration

revealed that the reaction was controlled by the stereoelectronic effects. Most of the results can be well explained by the proposed reaction mechanism.

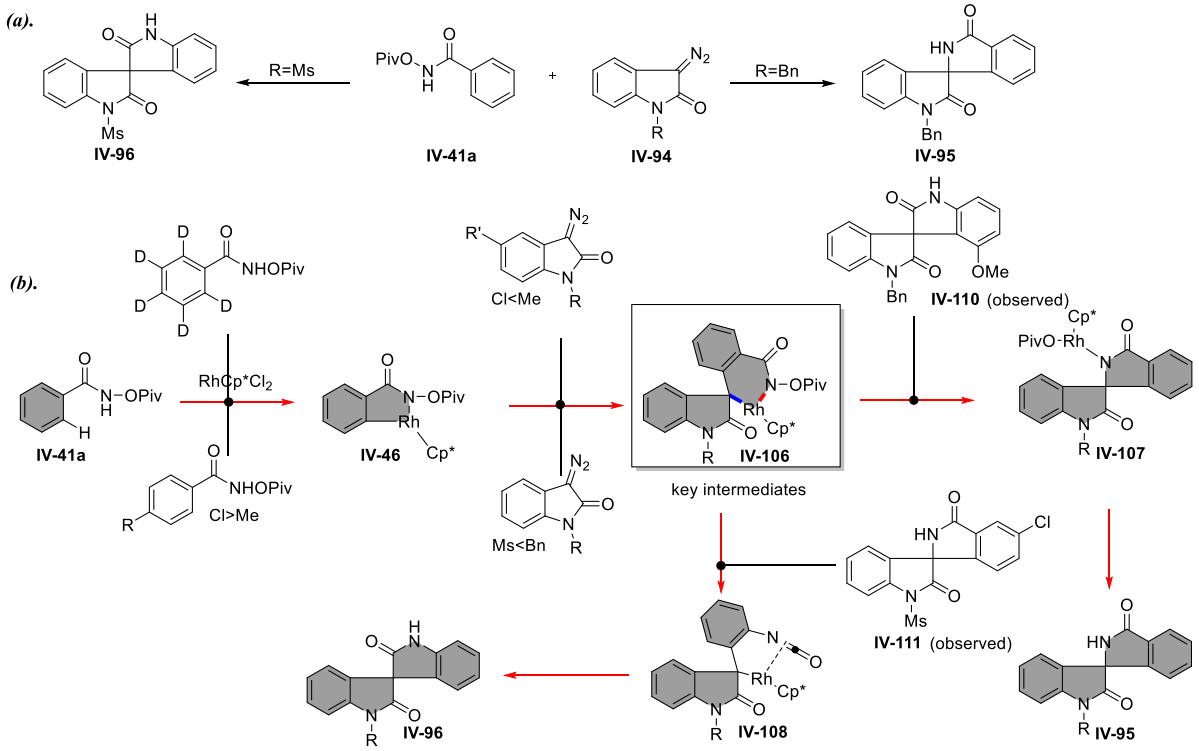


Figure 6.3. Rh(III)-catalyzed C-H functionalization enabled scaffold divergent synthesis of compound collections containing spirooxindole. (a) Scaffold divergent synthesis of spirooxindoles. (b) Plausible reaction mechanism to explain the product formation.

In Chapter 5, a stereodivergent incorporation of the alkaloid-derived pyrrolidine fragment into sesquiterpene lactones was enabled *via* stereocomplementary 1,3-dipolar cycloadditions. This project featured a conceptual combination of ring distortion and pseudo natural product design (Fig. 6.4a). The condition screening of *exo/Re* selectivity was hampered by mismatched pair of substrate and catalysts. Solvent played a significant role in controlling the reaction pathway (Fig. 6.4b). Not only santonin, but also other sesquiterpene lactones were well tolerated under the stereodivergent conditions. Notably, substrate **V-73** confined the reaction to take place in convex side, so that even enantiomeric ligands afforded the same products (Fig. 6.4c). Cheminformatic analysis and morphological profiling revealed that this strategic 1,3-dipolar cycloaddition afforded both chemically and biologically diverse pseudo sesquiterpenoid alkaloids. A novel chemotype inhibiting Hedgehog-dependent osteoblast differentiation was discovered through cell-based assays. All of these results emphasize the necessity and significance of combining ring distortion, pseudo natural product and stereodivergent synthesis together.

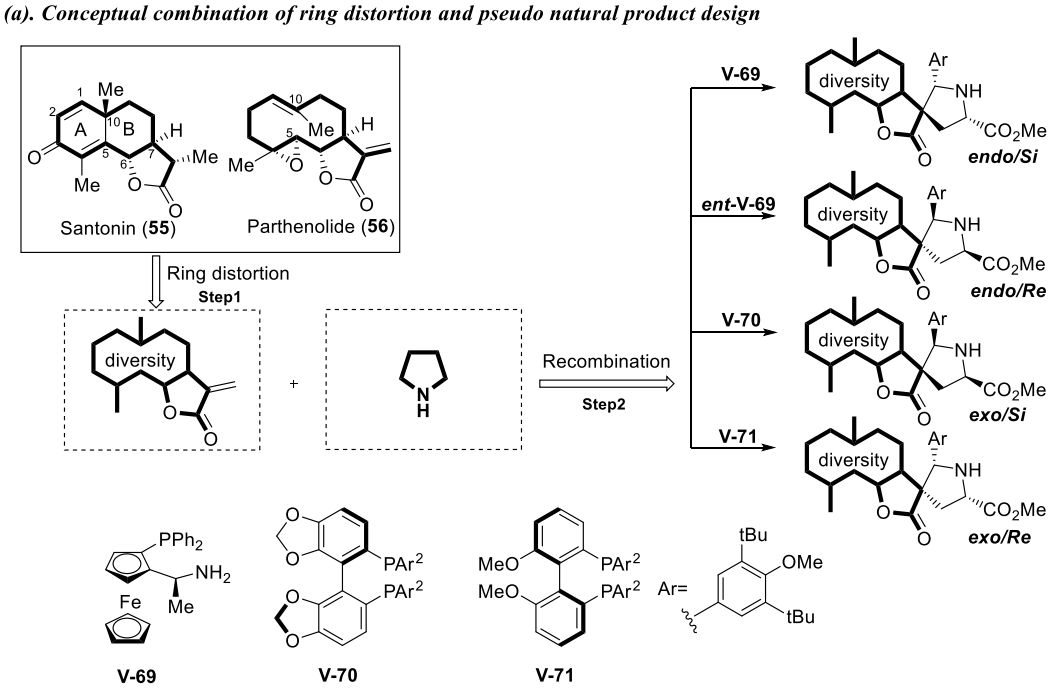


Figure 6.4. Conceptual combination of ring distortion and pseudo natural product design yielded pseudo sesquiterpenoid alkaloids. (a) Stereodivergent 1,3-dipolar cycloaddition. (b) Solvent effects in stereodivergent 1,3-dipolar cycloaddition. (c) Substrate effects in stereodivergent 1,3-dipolar cycloaddition.

In practice of pseudo natural product design, NP fragments are generated by algorithm-based fragmentation of reported natural products. Then NP-likeness scores of pseudo natural products were calculated in comparison with those of natural products. The magnificent palace of pseudo natural products is built on the reported natural products. Thus, with more

novel NPs discovered from nature or enabled by gene activation of silent biosynthetic pathways,[118] previously synthesized pseudo natural products may find their natural origins. The synthesis of **III-43**, a member of pseudo natural product pyrroquinolines, was firstly reported in 2015 (Fig. 6.5). Four years later, albogrisins, of the same scaffold, were isolated from *Streptomyces albogriseolus* MGR072.[120] In the project of pseudo sesquiterpenoid alkaloids, **V-95** was synthesized while its scaffold was found in recently isolated natural product vlasoulamine A (Fig. 6.5).[119] This indicates that pseudo natural product design is a unified synthetic strategy yielding structurally complex and diverse compound collections with retained biological relevance. It explores vast biologically relevant chemical space including those enabled by natural evolution. It can be expected that more pseudo natural products will find their natural origins in the future with the development of natural product isolation and synthetic biology.

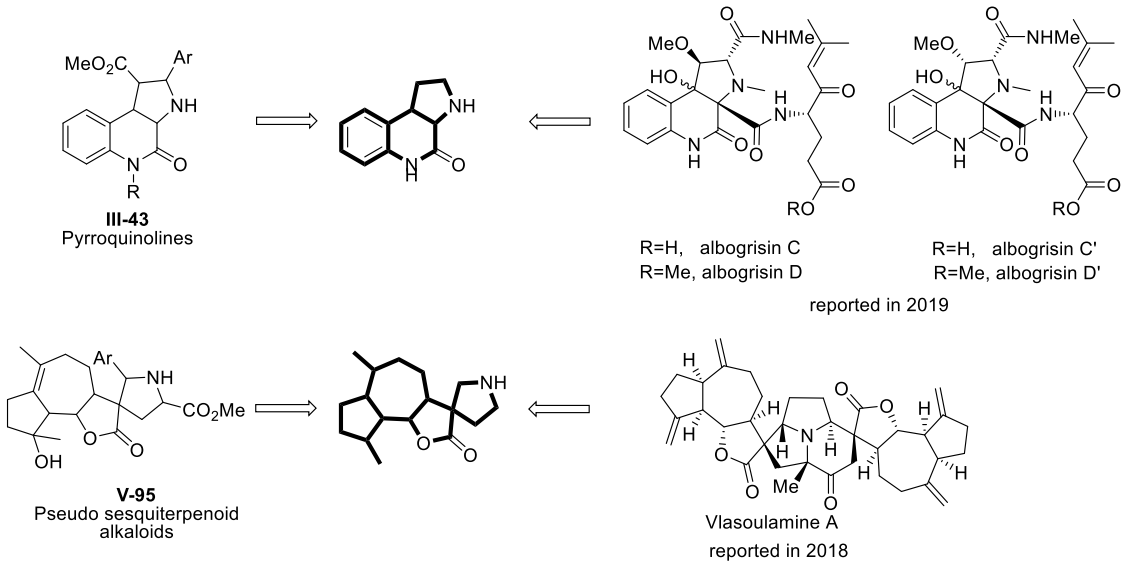


Figure 6.5. Pseudo NP scaffolds occurred in newly discovered natural products.

Direct incorporation of fragments into fragment-sized NPs or NP fragments is an attractive strategy to efficiently access diverse and complex compound collections as depicted in Chapter 3 and 4 (Fig. 6.6a,b). Conceptual combination of ring distortion and pseudo natural product design shed a novel insight into the development of pseudo natural product (Fig. 6.6b). However, the limited accessibility to natural products is still a bottleneck for this concept. With the development of synthetic strategies and methodologies, more and more complex natural products can be accessed in practical scales.[6] Therefore, the *de novo* synthetic route may enable the sufficient supply of natural products and their fragments. The combination of scalable total synthesis and pseudo natural product design may inspire more exciting discoveries in this field (Fig. 6.6c).

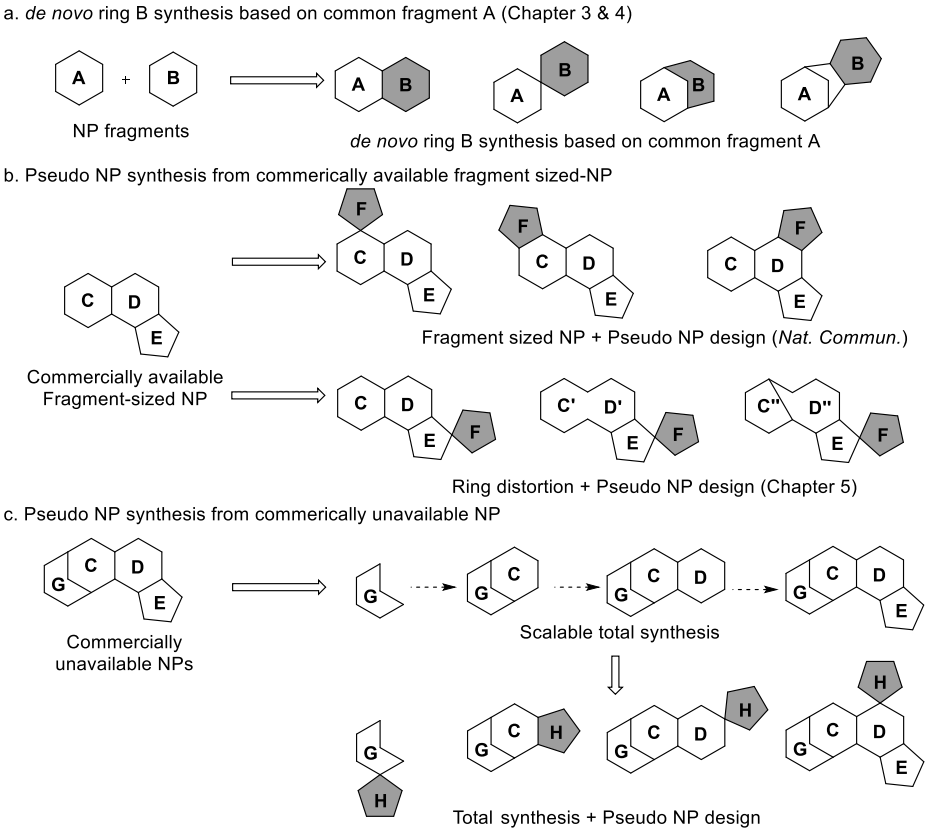


Figure 6.6. Synthetic strategies used in pseudo natural product synthesis. (a) *De novo* fragment combination as shown in Chapter 3 and 4. (b) Commercially available fragment-sized NPs are used as starting points for pseudo-NP synthesis as shown in *Nat. Commun.*[49] and Chapter 5. (c) Scalable total synthesis of complex natural products supplies structurally diverse NP fragments. Then another NP fragment **H** can be recombined.

Pseudo natural product design emphasizes the significance of scaffold diversity. Considering that diverse appendages on the same scaffold can still lead to different biological performance, more efforts should be devoted to decorating the scaffold as much as possible. Schreiber and coworkers combined DOS concept with DNA-encoded library (DEL) to give a novel synthetic strategy DOSEDO (diversity-oriented synthesis encoded by DNA oligonucleotides).[121] Inspired by their work, pseudo natural products can also be equipped with DEL technology enabling the broader exploration of chemical space encoded by pseudo natural products and the discovery of novel chemotypes against interesting targets (Fig. 6.7).

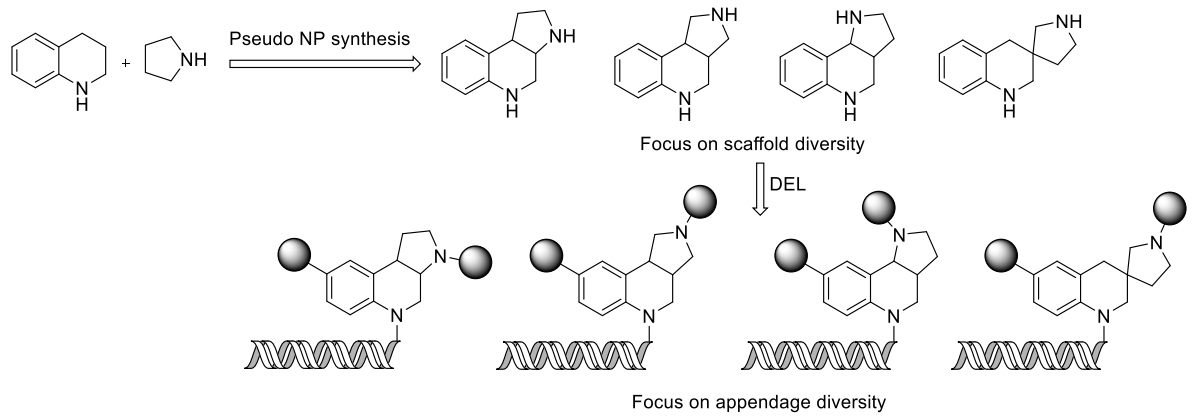


Figure 6.7. Application of DEL technology in pseudo-NP synthesis.

Chapter 7. Experimental section

7. Experimental section

7.1 General methods and materials

Unless otherwise noted, all commercially available compounds were used as received without further purifications. Dry solvents were purchased from Acros or Sigma Aldrich and used without further treatment. Solvents for chromatography were technical grade. The iminoesters used for 1,3-dipolar cycloaddition were prepared according to the reference 9. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminum plates with F-254 indicator. Compounds were visualized by irradiation with UV light and stained with an appropriate staining reagent. Column chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm) or aluminum oxide (activated, neutral, Brockmann I, Sigma-Aldrich).

^{1}H-NMR and ^{13}C-NMR were recorded on a *Bruker DRX400* (400 MHz), *Bruker DRX500* (500 MHz), *INOVA500* (500 MHz) and *Bruker DRX700* using CD_2Cl_2, $CDCl_3$ or DMSO-*d6* as solvent. Data are reported in the following order: chemical shift (δ) values are reported in ppm with the solvent resonance as internal standard (CD_2Cl_2: δ = 5.32 ppm for ^{1}H, δ = 53.84 ppm for ^{13}C; $CDCl_3$: δ = 7.26 ppm for ^{1}H, δ = 77.16 ppm for ^{13}C; DMSO-*d6*: δ = 2.50 ppm for ^{1}H, δ = 39.52 ppm for ^{13}C); multiplicities are indicated br s (broadened singlet), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (*J*) are given in Hertz (Hz). Chemical yields refer to isolated substances. *ee* was determined by chiral HPLC. Schiff bases used for 1,3-dipolar cycloadditions were synthesized according to the reported procedures.[42]

High resolution mass spectra were recorded on a *LTQ Orbitrap* mass spectrometer coupled to an *Accela HPLC*-System (HPLC column: *Hypersyl GOLD*, 50 mm x 1 mm, particle size 1.9 µm, ionization method: electron spray ionization).

Data collection for single crystal X-ray structure analyses was conducted on a *Bruker D8 Venture* four-circle diffractometer by *Bruker AXS GmbH* using a *PHOTON II* CPAD detector by *Bruker AXS GmbH*. X-ray radiation was generated by microfocus sources *IµS 3.0* Mo by *Incoatec GmbH* with HELIOS mirror optics and a single-hole collimator by *Bruker AXS GmbH*. For the data collection, the programs APEX 3 Suite (v.2018.7-2) with the integrated programs SAINT (integration) and SADABS (adsorption correction) by Bruker AXS GmbH were used. Using Olex2[122], the structures were solved with the ShelXT[123] structure solution

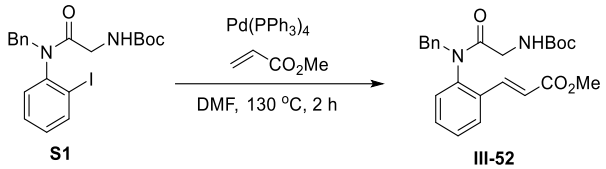
program using Intrinsic Phasing and refined with the XL[124] refinement package using Least Squares minimization.

7.2 Experimental part for synthesis of pyrroquinolines

7.2.1 Racemic synthesis of 7 classes of pyrroquinolines

7.2.1.1 Racemic synthesis of III-43

Precursor Synthesis:



S1 **III-52**

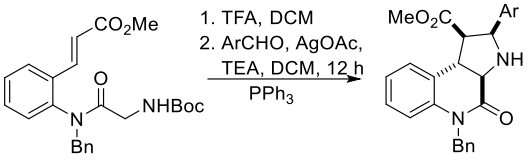
To a solution of arene **S1** (synthesized according to Ref [6])[54] (0.97 g, 2.1 mmol, 1.0 equiv.) in dry DMF (14 mL, 0.15 M), $Pd(PPh_3)_4$ (121 mg, 5 mol %), alkene (207 µL, 2.3 mmol, 1.1 equiv.) and triethylamine (590 µL, 4.2 mmol, 2.0 equiv.) were added under argon and the mixture was heated to 130 °C for 2 h. The reaction mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate (3*50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography using pentane/EA 10:1 to 4:1 gave the final substrates **III-52** (550 mg, 62% yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 16.0 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.23-7.17 (m, 3H), 7.14-7.09 (m, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.32 (dd, *J* = 16.0, 1.5 Hz, 1H), 5.45 (t, *J* = 4.6 Hz, 1H), 5.17 (dd, *J* = 14.1, 2.7 Hz, 1H), 4.46 (d, *J* = 14.1 Hz, 1H), 3.78 – 3.72 (m, 3H), 3.63 (dd, *J* = 18.0, 5.2 Hz, 1H), 3.30 (dd, *J* = 17.8, 4.0 Hz, 1H), 1.38 (s, 9H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 168.6, 166.5, 155.6, 138.9, 138.2, 135.9, 132.9, 131.5, 130.2, 129.5 (2C), 128.5 (2C), 127.9, 127.9, 121.3, 79.6, 53.3, 51.8, 43.3, 28.3 (3C).

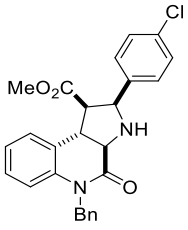
HRMS(ESI): $[M+H]^+$ calcd. $C_{24}H_{29}N_2O_5$ m/z 425.2071, found 425.2066.

General Procedure 1:



The synthesis was performed according to a literature procedure[54]: To a solution of *N*-Boc alkenyamine **III-52** (0.2 mmol, 1 equiv.) in DCM, TFA (2.0 mmol, 10 equiv.) was added at 0 °C. The mixture was stirred for 3 h at this temperature until TLC showed complete deprotection. The solvent was removed under reduced pressure. The remains were co-evaporated three times with DCM to remove excess TFA. Subsequently, dry DCM was added followed by TEA (0.4 mmol, 2.0 equiv.) and the mixture was stirred for 10 min. Aldehyde (0.24 mmol, 1.2 equiv.) and freshly activated 4 Å MS powder were added followed by AgOAc (10 mol%) and PPh_3 (10 mol%). Upon completion (typically 6-12 h), the reaction mixture was directly transferred onto a column and purified using silica gel chromatography to obtain the desired PQ **III-43** as a single diastereoisomer.

(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-2-(4-chlorophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43a)



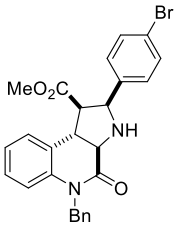
III-43a

PQ **III-43a** (60 mg, 134 µmol, 67% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.37 – 7.28 (m, 5H), 7.26 – 7.22 (m, 3H), 7.16 (dd, *J* = 8.2, 7.4, 1H), 7.05 – 6.91 (m, 3H), 5.50 (d, *J* = 16.2 Hz, 1H), 5.01 – 4.90 (m, 2H), 3.92 – 3.75 (m, 2H), 3.60 (t, *J* = 10.4 Hz, 1H), 3.29 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.3, 170.3, 140.2, 139.0, 137.0, 133.8, 129.6 (2C), 129.0 (2C), 128.3 (2C), 128.1, 127.7, 127.4, 126.6 (2C), 124.6, 123.6, 116.4, 63.4, 61.9, 52.0, 51.9, 46.5, 43.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Cl$ m/z 447.1470, found 447.1468.

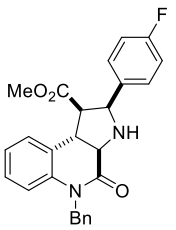
(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-2-(4-bromophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43b)

PQ **III-43b** (69 mg, 140 µmol, 70% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.


III-43b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.42 (m, 2H), 7.37 – 7.29 (m, 4H), 7.27 – 7.22 (m, 3H), 7.15 (dd, *J* = 8.2, 1.6, 1H), 7.01 (td, *J* = 7.4, 1.1 Hz, 1H), 6.98-6.92 (m, 2H), 5.49 (d, *J* = 16.2 Hz, 1H), 5.03 – 4.88 (m, 2H), 3.93 – 3.72 (m, 2H), 3.65 – 3.55 (m, 1H), 3.30 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.3, 170.3, 140.2, 139.5, 137.0, 131.2 (2C), 129.9 (2C), 129.0 (2C), 128.1, 127.7, 127.4, 126.6 (2C), 124.6, 123.6, 121.9, 116.4, 63.4, 61.9, 52.0, 51.9, 46.5, 43.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Br$ m/z 491.0965, found 491.0961.

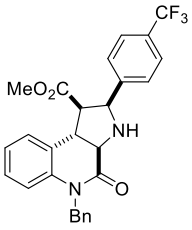
(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-2-(4-fluorophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43c)


III-43c

PQ **III-43c** (58 mg, 134 μmol, 67% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.35-7.30 (m, 2H), 7.25 (m, 3H), 7. 16 (t, *J* =7.8 Hz, 1H), 7.04 – 6.98 (m, 3H), 6.97-6.94 (m, 2H), 5.50 (d, *J* = 16.2 Hz, 1H), 5.05 – 4.91 (m, 2H), 3.87 (dd, *J* = 14.0, 10.7 Hz, 1H), 3.80 (d, *J* = 14.0 Hz, 1H), 3.59 (t, *J* = 10.6 Hz, 1H), 3.28 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 171.4, 170.3, 162.5 (d, *J*CF = 246.1 Hz), 140.2, 137.0, 136.1 (d, *J*CF = 3.0 Hz), 129.8 (d, *J*CF = 9.1 Hz, 2C), 128.9 (2C), 128.1, 127.7, 127.4, 126.6 (2C), 124.7, 123.6, 116.3, 114.9 (d, *J*CF = 21.1 Hz, 2C), 63.4, 61.9, 52.0, 51.9, 46.5, 43.1. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -114.4 (m, 1F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3F$ m/z 431.1766, found 431.1764.

(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-4-oxo-2-(4-(trifluoromethyl)phenyl)-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43d)

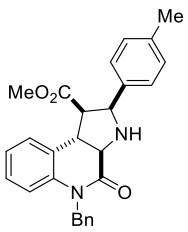

III-43d

PQ **III-43d** (62 mg, 129 μmol, 65% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62-7.58 (m, 4H), 7.36-7.30 (m, 2H), 7.26-7.24 (m, 3H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.02 (td, *J* = 7.5, 1.1 Hz, 1H), 6.98 – 6.93 (m, 2H), 5.50 (d, *J* = 16.2 Hz, 1H), 5.02 (d, *J* = 10.6 Hz, 1H), 4.98 (d, *J* = 16.2 Hz, 1H), 3.94 – 3.75 (m, 2H), 3.65 (t, *J* = 10.6 Hz, 1H), 3.24 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 171.2, 170.2, 144.6, 140.2, 136.9, 130.2 (q, *J*CF = 33.0 Hz), 129.0 (2C), 128.6 (2C), 128.1, 127.5, 127.4, 126.6 (2C), 125.0 (q, *J*CF = 3.0 Hz, 2C), 124.6, 124.3 (q, *J*CF = 271.8 Hz),

123.7, 116.4, 63.4, 61.9, 52.1, 51.9, 46.5, 43.0. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -62.4 (s, 3F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{24}N_2O_3F_3$ m/z 481.1733, found 481.1728.

(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-4-oxo-2-(p-tolyl)-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43e)

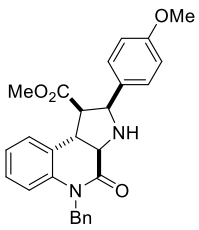


III-43e

PQ **III-43e** (48 mg, 112 μmol, 56% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 3H), 7.32 – 7.24 (m, 5H), 7.19 – 7.11 (m, 3H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 5.48 (d, *J* = 16.1 Hz, 1H), 5.04 (d, *J* = 16.1 Hz, 1H), 4.78 (d, *J* = 10.6 Hz, 1H), 4.30 – 4.18 (m, 2H), 3.23 (t, *J* = 10.4 Hz, 1H), 3.20 (s, 3H), 2.34 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 171.4, 171.2, 138.4, 138.2, 137.2, 136.6, 130.1, 129.0 (2C), 128.7 (2C), 128.5, 127.8 (2C), 127.5, 126.5 (2C), 124.2, 123.6, 115.9, 61.4, 59.2, 54.8, 51.5, 46.7, 41.5, 21.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{27}N_2O_3$ m/z 427.2016, found 427.2015.

(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-2-(4-methoxyphenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43f)



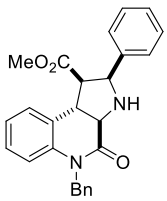
III-43f

PQ **III-43f** (22 mg, 50 μmol, 25% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 5H), 7.29 – 7.21 (m, 3H), 7.15 (dd, *J* = 8.2, 7.5 Hz, 1H), 6.98 (td, *J* = 7.5, 1.1 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.88 – 6.83 (m, 2H), 5.47 (d, *J* = 16.1 Hz, 1H), 5.01 (d, *J* = 16.1 Hz, 1H), 4.76 (d, *J* = 10.7 Hz, 1H), 4.26-4.18 (m, 2H), 3.80 (s, 3H), 3.24-3.17 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.4, 171.3, 159.1, 138.2, 136.6, 133.5, 130.1, 129.0 (2C), 129.0 (2C), 128.5, 127.5, 126.5 (2C), 124.2, 123.6, 115.9, 113.4 (2C), 61.1, 59.2, 55.4, 54.7, 51.6, 46.7, 41.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{27}N_2O_4$ m/z 443.1965, found 443.1963.

(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-4-oxo-2-phenyl-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43g)

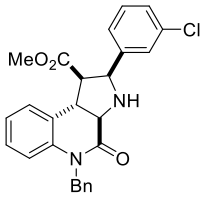
PQ **III-43g** (34 mg, 81 μmol, 41% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.



III-43g

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2H), 7.38-7.30 (m, 5H), 7.29-7.24 (m, 4H), 7.16 (ddd, *J* = 8.7, 7.5, 1.7 Hz, 1H), 6.99 (td, *J* = 7.5, 1.1 Hz, 1H), 6.92 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.49 (d, *J* = 16.1 Hz, 1H), 5.02 (d, *J* = 16.1 Hz, 1H), 4.80 (d, *J* = 10.7 Hz, 1H), 4.32 – 4.19 (m, 2H), 3.25 (t, *J* = 10.6 Hz, 1H), 3.16 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.3, 171.1, 141.5, 138.2, 136.6, 130.1, 129.0 (2C), 128.5, 128.0 (2C), 128.0 (2C), 127.7, 127.5, 126.5 (2C), 124.1, 123.6, 115.9, 61.6, 59.2, 54.8, 51.5, 46.7, 41.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{25}N_2O_3$ m/z 413.1860, found 413.1858.

(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-2-(3-chlorophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43h)

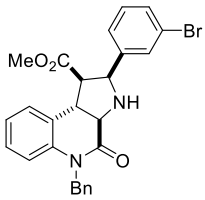


III-43h

PQ **III-43h** (60 mg, 135 µmol, 67% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 2.0 Hz, 1H), 7.37 – 7.31 (m, 3H), 7.31 – 7.23 (m, 6H), 7.16 (ddd, *J* = 8.2, 7.5, 1.7 Hz, 1H), 6.99 (td, *J* = 7.5, 1.1 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 5.48 (d, *J* = 16.1 Hz, 1H), 5.01 (d, *J* = 16.1 Hz, 1H), 4.77 (d, *J* = 10.7 Hz, 1H), 4.25 (d, *J* = 7.6 Hz, 1H), 4.18 (dd, *J* = 11.1, 7.6 Hz, 1H), 3.64 (s, 1H), 3.26-3.22 (m, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.2, 170.8, 143.8, 138.2, 136.5, 134.0, 130.2, 129.3, 129.1 (2C), 128.6, 128.2, 127.8, 127.5, 126.5 (2C), 126.1, 123.7, 116.0, 60.9, 59.2, 54.6, 51.7, 46.8, 41.4. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Cl$ m/z 447.1470, found 447.1467.

(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-2-(3-bromophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43i)



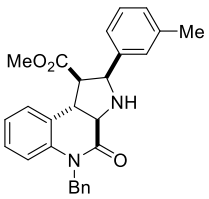
III-43i

PQ **III-43i** (77 mg, 157 µmol, 79% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (t, *J* = 1.9 Hz, 1H), 7.42 – 7.31 (m, 5H), 7.29 – 7.23 (m, 3H), 7.22 – 7.13 (m, 2H), 6.99 (td, *J* = 7.5, 1.1 Hz, 1H), 6.92 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.48 (d, *J* = 16.1 Hz, 1H), 5.02 (d, *J* = 16.1 Hz, 1H), 4.76 (d, *J* = 10.6 Hz, 1H), 4.25 (d, *J* = 7.7 Hz, 1H), 4.18 (dd, *J* = 11.0, 7.6 Hz, 1H), 3.26-3.21 (m, 4H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.2, 170.7, 144.1, 138.2, 136.6, 131.1, 130.8, 130.2, 129.6,

129.1 (2C), 128.6, 127.5, 126.6, 126.5 (2C), 123.7, 123.7, 122.2, 116.0, 60.9, 59.2, 54.7, 51.7, 46.8, 41.4. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Br$ m/z 491.0965, found 491.0960.

(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-4-oxo-2-(*m*-tolyl)-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43j)

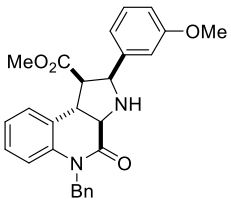


III-43j

PQ **III-43j** (49 mg, 116 µmol, 58% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 3H), 7.30 – 7.19 (m, 6H), 7.16 (ddd, *J* = 8.8, 7.6, 1.6 Hz, 1H), 7.10 – 7.05 (m, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 5.48 (d, *J* = 16.1 Hz, 1H), 5.03 (d, *J* = 16.1 Hz, 1H), 4.77 (d, *J* = 10.6 Hz, 1H), 4.37 – 4.16 (m, 2H), 3.64 (s, 1H), 3.25 (d, *J* = 10.3 Hz, 1H), 3.19 (s, 3H), 2.37 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.3, 171.1, 141.4, 138.2, 137.6, 136.6, 130.1, 129.0 (2C), 128.5, 128.5, 128.4, 127.9, 127.5, 126.5 (2C), 125.0, 124.1, 123.6, 115.9, 61.6, 59.2, 54.8, 51.5, 46.7, 41.5, 21.6. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{27}N_2O_3$ m/z 427.2016, found 427.2015.

(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-2-(3-methoxyphenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43k)

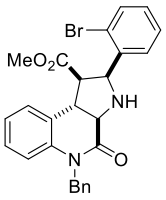


III-43k

PQ **III-43k** (34 mg, 76 µmol, 67% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 3H), 7.30 – 7.21 (m, 4H), 7.19 – 7.12 (m, 1H), 7.04 – 6.95 (m, 3H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.81 (dd, *J* = 8.2, 2.7 Hz, 1H), 5.48 (d, *J* = 16.1 Hz, 1H), 5.02 (d, *J* = 16.1 Hz, 1H), 4.78 (d, *J* = 10.6 Hz, 1H), 4.32 – 4.16 (m, 2H), 3.83 (s, 3H), 3.26-3.21 (m, 4H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.3, 171.1, 159.5, 143.2, 138.2, 136.6, 130.1, 129.0 (2C), 129.0, 128.5, 127.5, 126.5 (2C), 124.1, 123.6, 120.3, 115.9, 113.4, 113.3, 61.5, 59.2, 55.4, 54.8, 51.6, 46.7, 41.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{27}N_2O_4$ m/z 443.1965, found 443.1963.

(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-2-(2-bromophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43l)

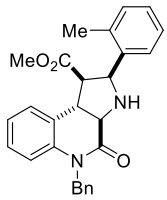


III-43l

PQ **III-43l** (68 mg, 139 µmol, 70% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.52 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.37-7.29 (m, 3H), 7.27 – 7.26 (m, 2H), 7.25 (q, *J* = 1.0 Hz, 1H), 7.19 – 7.11 (m, 2H), 7.06 – 6.99 (m, 2H), 6.99 – 6.94 (m, 1H), 5.47 (d, *J* = 16.2 Hz, 1H), 5.32 (d, *J* = 10.4 Hz, 1H), 5.01 (d, *J* = 16.2 Hz, 1H), 4.00 – 3.88 (m, 1H), 3.84 – 3.72 (m, 2H), 3.25 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.7, 170.2, 140.1, 139.2, 137.0, 132.2, 130.9, 129.3, 129.0 (2C), 128.0, 127.9, 127.5, 127.4, 126.6 (2C), 124.6, 123.8, 123.6, 116.3, 62.9, 61.7, 51.8, 50.1, 46.4, 43.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Br$ m/z 491.0965, found 491.0962.

(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-4-oxo-2-(*o*-tolyl)-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43m)

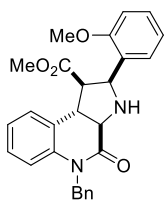


III-43m

PQ **III-43m** (19 mg, 43 µmol, 22% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.29 – 7.21 (m, 5H), 7.19 – 7.11 (m, 2H), 7.10 – 7.07 (m, 1H), 6.99 (td, *J* = 7.5, 1.1 Hz, 1H), 6.94 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.47 (d, *J* = 16.1 Hz, 1H), 5.09 (d, *J* = 16.1 Hz, 1H), 4.95 (d, *J* = 10.7 Hz, 1H), 4.38 – 4.24 (m, 2H), 3.23 (dd, *J* = 10.7, 9.3 Hz, 1H), 3.09 (s, 3H), 2.32 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.6, 171.4, 138.9, 138.1, 136.6, 135.8, 129.8, 129.8, 129.0 (2C), 128.5, 127.7, 127.5, 127.3, 126.6 (2C), 125.9, 124.7, 123.7, 116.0, 59.1, 57.8, 54.1, 51.5, 46.6, 42.2, 19.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{27}N_2O_3$ m/z 427.2016, found 427.2015.

(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-2-(2-methoxyphenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43n)



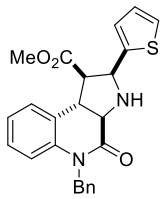
III-43n

PQ **III-43n** (58 mg, 130 µmol, 65% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.30 – 7.22 (m, 5H), 7.19 – 7.12 (m, 1H), 7.04-6.95 (m, 2H), 6.93 (d, *J* = 8.2 Hz, 1H),

6.82 (d, *J* = 8.2 Hz, 1H), 5.49 (d, *J* = 16.2 Hz, 1H), 5.17 – 5.04 (m, 2H), 4.33 – 4.20 (m, 2H), 3.80 (s, 3H), 3.27 (dd, *J* = 10.1, 9.5 Hz, 1H), 3.20 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.0, 171.4, 156.8, 138.1, 136.6, 129.7, 129.3 (2C), 129.0, 128.4 (2C), 128.3, 127.4, 126.5 (2C), 124.6, 123.6, 120.5, 115.9, 109.7, 59.0, 55.7, 55.4, 54.3, 51.5, 46.6, 42.6. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{27}N_2O_4$ m/z 443.1965, found 443.1963.

(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-4-oxo-2-(thiophen-2-yl)-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43o)

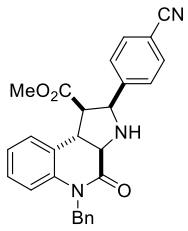


III-43o

PQ **III-43o** (55 mg, 131 µmol, 65% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 3H), 7.29 – 7.26 (m, 1H), 7.26-7.22 (m, 3H), 7.15 (ddd, *J* = 8.1, 7.4, 1.6 Hz, 1H), 7.01 – 6.95 (m, 2H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 3.5 Hz, 1H), 5.45 (d, *J* = 16.0 Hz, 1H), 5.12 (d, *J* = 10.1 Hz, 1H), 4.99 (d, *J* = 16.1 Hz, 1H), 4.30 – 4.14 (m, 2H), 3.39 (s, 3H), 3.26 – 3.18 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.1, 170.5, 147.5, 138.2, 136.5, 130.3, 129.1 (2C), 128.6, 127.5, 126.9, 126.5 (2C), 125.1, 124.0, 123.7, 123.5, 115.9, 58.8, 57.1, 54.7, 51.8, 46.8, 40.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{23}N_2O_3S$ m/z 419.1424, found 419.1423.

(±)-Methyl (1*R*,2*S*,3a*R*,9b*S*)-5-benzyl-2-(4-cyanophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-43p)



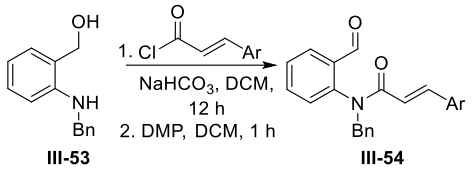
III-43p

PQ **III-43p** (60 mg, 137 µmol, 69% Yield) was synthesized according to the general procedure 1; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 4H), 7.35 – 7.29 (m, 2H), 7.27 – 7.23 (m, 3H), 7.17 (d, *J* = 1.5 Hz, 1H), 7.01 (td, *J* = 7.4, 1.0 Hz, 1H), 6.98 – 6.91 (m, 2H), 5.49 (d, *J* = 16.2 Hz, 1H), 5.08 – 4.92 (m, 2H), 3.87-3.80 (m, 2H), 3.65 (ddd, J = 10.7, 8.2, 2.6 Hz, 1H), 3.27 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 170.9, 170.1, 146.1, 140.1, 136.8, 131.9 (2C), 129.0 (4C), 128.2, 127.4, 127.2, 126.6 (2C), 124.5, 123.7, 118.9, 116.4, 111.7, 63.1, 61.8, 52.0, 52.0, 46.5, 42.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{24}N_3O_3$ m/z 438.1812, found 438.1803.

7.2.1.2 Racemic synthesis of III-44

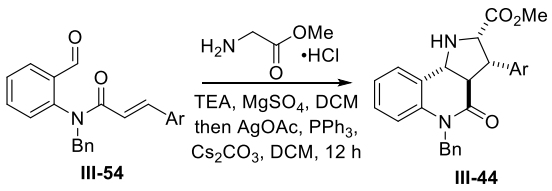
General Procedure 2



To a solution of **III-53**[125] (1.0 equiv.) in dry DCM (20 mL), $NaHCO_3$ (5.0 equiv.) was added followed by the desired acid chloride (1.1 equiv.). The reaction was stirred overnight at room temperature and quenched with saturated $NaHCO_3$ solution (20 mL) and then extracted with DCM (3*20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The reaction residue was purified with flash column using pentane/EA.

The intermediate alcohol was dissolved in dry DCM (10 mL), and DMP (1.1 equiv.) was added in small portions at room temperature. The reaction was stirred for 1 h until full conversion of the starting material was observed. The reaction mixture was quenched with saturated $Na_2S_2O_3$ (10 mL) and extracted with DCM (3*20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The reaction residue was purified by column chromatography using pentane/EA to give the desired product **III-54**.

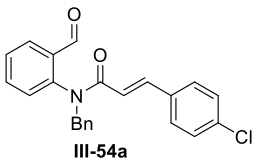
General Procedure 3



Glycine methyl ester salt (0.3 mmol, 1.3 equiv.) was suspended in dry DCM (1 mL) and $MgSO_4$ (0.3 mmol, 1.3 equiv.) and TEA (0.44 mmol, 2.0 equiv.) were added. The mixture was stirred for 30 mins followed by the addition of aldehyde **III-54** (0.22 mmol, 1.0 equiv.). The reaction was stirred for 12 h then filtered. The solution was diluted with EA (20 mL) and washed with $NaHCO_3$ solution (20 mL) and brine (20 mL) sequentially. The organic phase was dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Then the residue was dissolved in the dry DCM (1.0 mL) followed by the addition of a solution of AgOAc (0.02 mmol, 0.1 equiv.) and PPh_3 (0.03 mmol, 0.12 equiv.) in DCM (0.5 mL).

Cs_2CO_3 (0.04 mmol, 0.2 equiv.) was added to the reaction and stirred overnight. The solvent was removed under reduced pressure. PQs **III-44** were purified by silica gel chromatography using cyclohexane/EA.

(*E*)-*N*-benzyl-3-(4-chlorophenyl)-*N*-(2-formylphenyl)acrylamide (III-54a)

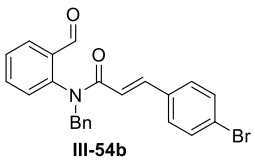


III-54a

Acrylamide **III-54a** (352 mg, 0.94 mmol, 52% Yield) was synthesized according to the general procedure 2 from **3** in 1.8 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.01 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.79 (d, *J* = 15.4 Hz, 1H), 7.72 (td, *J* = 7.6, 1.7 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.34 – 7.30 (m, 3H), 7.28-7.25 (m, 4H), 7.24-7.20 (m, 3H), 6.12 (d, *J* = 15.4 Hz, 1H), 5.38 – 4.97 (m, 2H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 188.9, 165.6, 143.5, 142.6, 135.9, 135.8, 135.4, 133.6, 133.2, 130.2, 129.5 (2C), 129.4, 129.1, 129.1 (2C), 129.0 (2C), 128.7 (2C), 128.1, 118.1, 54.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{19}NO_2Cl$ m/z 376.1099, found 376.1096.

(*E*)-*N*-benzyl-3-(4-bromophenyl)-*N*-(2-formylphenyl)acrylamide (III-54b)

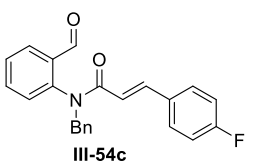


III-54b

Acrylamide **III-54b** (343 mg, 0.82 mmol, 46% Yield) was synthesized according to the general procedure 2 from **3** in 1.8 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.95 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.73 – 7.63 (m, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.29-7.22 (m, 3H), 7.22-7.18 (m, 2H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.12 – 7.05 (m, 2H), 6.06 (d, *J* = 15.4 Hz, 1H), 5.13-5.00 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 189.0, 165.7, 143.5, 142.8, 135.9, 135.5, 133.7, 133.6, 132.0 (2C), 130.2, 129.6 (2C), 129.5, 129.4 (2C), 129.2, 128.8 (2C), 128.2, 124.3, 118.2, 54.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{19}NO_2Br$ m/z 420.0594, found 420.0598.

(*E*)-*N*-benzyl-3-(4-fluorophenyl)-*N*-(2-formylphenyl)acrylamide (III-54c)



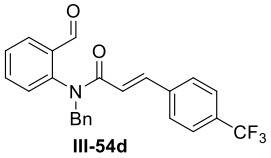
III-54c

Acrylamide **III-54c** (316 mg, 0.88 mmol, 49% Yield) was synthesized according to the general procedure 2 from **3** in 1.8 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.96 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.75 (d, *J* = 15.4 Hz, 1H), 7.67 (td, *J* = 7.6, 1.7 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.34 – 7.16 (m, 8H), 6.97-

6.90 (m, 2H), 6.02 (d, *J* = 15.4 Hz, 1H), 5.16 – 4.88 (m, 2H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 189.0, 165.8, 163.7 (d, *J*CF = 250.9 Hz), 143.7, 142.8, 136.0, 135.4, 133.7, 131.0 (d, *J* = 3.3 Hz), 130.2, 129.9 (d, *J*CF = 8.5 Hz, 2C), 129.6 (2C), 129.4, 129.1, 128.7 (2C), 128.2, 117.4, 115.9 (d, *J*CF = 22.0 Hz, 2C), 54.1. **^{19}F NMR (470 MHz, CDCl$_3$)** δ -109.9 (ddd, *J* = 13.8, 8.5, 5.4 Hz, 1F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{19}NO_2F$ m/z 360.1394, found 360.1391.

(*E*)-*N*-benzyl-*N*-(2-formylphenyl)-3-(4-(trifluoromethyl)phenyl)acrylamide (III-54d)

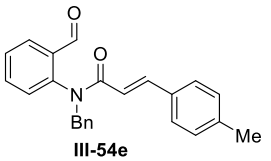


III-54d

Acrylamide **III-54d** (206 mg, 0.5 mmol, 28% Yield) was synthesized according to the general procedure 2 from **3** in 1.8 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (700 MHz, CDCl$_3$) δ 9.66 (s, 1H), 7.95 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.77 (d, *J* = 15.4 Hz, 1H), 7.66 (td, *J* = 7.6, 1.7 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.28 – 7.22 (m, 3H), 7.21 – 7.18 (m, 2H), 7.17 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.14 (d, *J* = 15.4 Hz, 1H), 5.10 – 5.05 (m, 2H). **^{13}C NMR (176 MHz, CDCl$_3$)** δ 189.0, 165.4, 143.4, 142.3, 138.2, 135.8, 135.5, 133.7, 131.5 (q, *J* = 32.6 Hz), 130.3, 129.7 (3C), 129.3, 128.8 (2C), 128.3, 128.2 (2C), 125.80 (q, *J* = 3.8 Hz, 2C), 123.89 (q, *J* = 272.3 Hz), 120.2, 54.3. **^{19}F NMR (470 MHz, CDCl$_3$)** δ -62.9 (s, 3F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{19}NO_2F_3$ m/z 410.1362, found 410.1358.

(*E*)-*N*-benzyl-*N*-(2-formylphenyl)-3-(*p*-tolyl)acrylamide (III-54e)

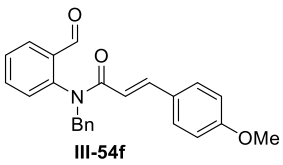


III-54e

Acrylamide **III-54e** (141 mg, 0.4 mmol, 40% Yield) was synthesized according to the general procedure 2 from **3** in 1.0 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (700 MHz, CDCl$_3$) δ 9.67 (s, 1H), 7.94 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.75 (d, *J* = 15.4 Hz, 1H), 7.65 (td, *J* = 7.6, 1.7 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.27-7.24 (m, 3H), 7.22-7.19 (m, 2H), 7.16 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 6.02 (d, *J* = 15.4 Hz, 1H), 5.15 – 4.99 (m, 2H), 2.30 (s, 3H). **^{13}C NMR (176 MHz, CDCl$_3$)** δ 189.1, 166.3, 144.2, 144.0, 140.5, 136.1, 135.4, 133.8, 132.1, 130.3, 129.7 (2C), 129.6 (2C), 129.3, 129.1, 128.8 (2C), 128.2, 128.1 (2C), 116.6, 54.2, 21.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{22}NO_2$ m/z 356.1645, found 356.1646.

(*E*)-*N*-benzyl-*N*-(2-formylphenyl)-3-(4-methoxyphenyl)acrylamide (III-54f)

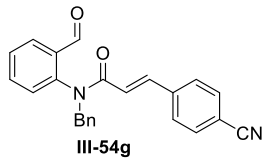


III-54f

Acrylamide **III-54f** (90 mg, 0.24 mmol, 24% Yield) was synthesized according to the general procedure 2 from **3** in 1.0 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.94 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.73 (d, *J* = 15.4 Hz, 1H), 7.65 (td, *J* = 7.7, 1.7 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.26 – 7.23 (m, 3H), 7.22 – 7.15 (m, 5H), 6.85 – 6.72 (m, 2H), 5.93 (d, *J* = 15.3 Hz, 1H), 5.15 – 4.97 (m, 2H), 3.77 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 189.2, 166.4, 161.2, 144.1, 143.9, 136.1, 135.5, 133.8, 130.3, 129.8 (2C), 129.6 (2C), 129.2, 129.0, 128.8 (2C), 128.2, 127.5, 115.1, 114.3 (2C), 55.5, 54.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{22}NO_3$ m/z 372.2594, found 372.1596.

(*E*)-*N*-benzyl-3-(4-cyanophenyl)-*N*-(2-formylphenyl)acrylamide (III-54g)

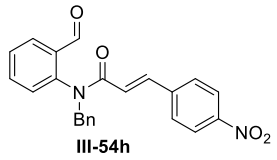


III-54g

Acrylamide **III-54g** (130 mg, 0.36 mmol, 36% Yield) was synthesized according to the general procedure 2 from **3** in 1.0 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.95 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.74 (d, *J* = 15.5 Hz, 1H), 7.67 (td, *J* = 7.6, 1.7 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.54 – 7.52 (m, 2H), 7.32 – 7.29 (m, 2H), 7.27-7.23 (m, 3H), 7.20-7.17 (m, 2H), 7.16 (d, *J* = 7.9 Hz, 1H), 6.14 (d, *J* = 15.4 Hz, 1H), 5.06 (s, 2H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 188.9, 165.1, 143.2, 141.7, 139.1, 135.7, 135.6, 133.7, 132.6 (2C), 130.2, 129.9, 129.7 (2C), 129.4, 128.8 (2C), 128.4 (2C), 128.3, 121.1, 118.5, 113.1, 54.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{19}N_2O_2$ m/z 367.1441, found 367.1443.

(*E*)-*N*-benzyl-*N*-(2-formylphenyl)-3-(4-nitrophenyl)acrylamide (III-54h)

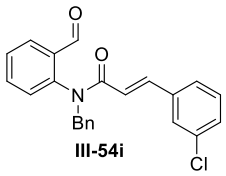


III-54h

Acrylamide **III-54h** (201 mg, 0.52 mmol, 52% Yield) was synthesized according to the general procedure 2 from **3** in 1.0 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.09 (d, *J* = 8.7 Hz, 2H), 7.95 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.79 (d, *J* = 15.4 Hz, 1H), 7.68 (td, *J* = 7.6, 1.7 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 8.9 Hz, 1H), 7.28 – 7.23 (m, 3H), 7.21-7.16 (m, 3H), 6.20 (d, *J* = 15.4 Hz, 1H), 5.10-5.04 (m, 2H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 188.9, 165.0, 148.3, 143.0, 141.1, 140.9, 135.7, 135.5, 133.6, 130.2, 129.9, 129.6 (2C), 129.4, 128.8 (2C), 128.6 (2C), 128.3, 124.1 (2C), 121.9, 54.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{19}NO_2Cl$ m/z 387.1339, found 387.1344.

(*E*)-*N*-benzyl-3-(3-chlorophenyl)-*N*-(2-formylphenyl)acrylamide (III-54i)

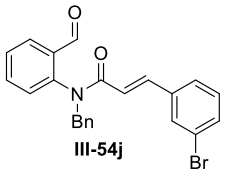


III-54i

Acrylamide **III-54i** (292 mg, 0.78 mmol, 65% Yield) was synthesized according to the general procedure 2 from **3** in 1.2 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.96 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.74 – 7.62 (m, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.29-7.24 (m, 4H), 7.22 – 7.15 (m, 5H), 7.11 (dt, *J* = 7.7, 1.5 Hz, 1H), 6.06 (d, *J* = 15.4 Hz, 1H), 5.15 – 4.93 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 189.0, 165.6, 143.5, 142.7, 136.6, 135.9, 135.6, 134.8, 133.7, 130.3, 130.1, 130.0, 129.7 (2C), 129.7, 129.3, 128.8 (2C), 128.3, 127.7, 126.5, 119.0, 54.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{19}NO_2Cl$ m/z 376.1099, found 376.1099.

(*E*)-*N*-benzyl-3-(3-bromophenyl)-*N*-(2-formylphenyl)acrylamide (III-54j)

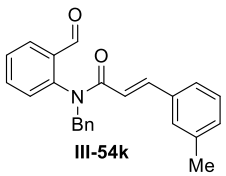


III-54j

Acrylamide **III-54j** (338 mg, 0.8 mmol, 67% Yield) was synthesized according to the general procedure 2 from **3** in 1.2 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.95 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.73 – 7.64 (m, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.39 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.35 (t, *J* = 1.9 Hz, 1H), 7.28-7.24 (m, 3H), 7.21 – 7.18 (m, 2H), 7.17 – 7.15 (m, 2H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.07 (d, *J* = 15.4 Hz, 1H), 5.09-5.03 (m, 2H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 188.9, 165.5, 143.4, 142.4, 136.9, 135.8, 135.5, 133.6, 132.8, 130.6, 130.3, 130.2, 129.7, 129.6 (2C), 129.3, 128.8 (2C), 128.2, 126.7, 122.9, 119.0, 54.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{19}NO_2Br$ m/z 420.0594, found 420.0594.

(*E*)-*N*-benzyl-*N*-(2-formylphenyl)-3-(*m*-tolyl)acrylamide (III-54k)



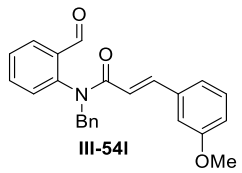
III-54k

Acrylamide **III-54k** (288 mg, 0.81 mmol, 68% Yield) was synthesized according to the general procedure 2 from **3** in 1.2 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.95 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.75 (d, *J* = 15.4 Hz, 1H), 7.66 (td, *J* = 7.7, 1.7 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.28-7.23 (m, 3H), 7.22 – 7.12 (m, 4H), 7.09 (d, *J* = 7.4 Hz, 1H), 7.05 – 7.01 (m, 2H), 6.05 (d, *J* = 15.4 Hz, 1H), 5.15 – 4.97 (m, 2H), 2.27 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 189.1, 166.1, 144.5, 143.9, 138.5, 136.0, 135.5, 134.7, 133.7, 131.0, 130.3, 129.7 (2C), 129.3, 129.1, 128.9,

128.8 (2C), 128.7, 128.2, 125.2, 117.4, 54.2, 21.4. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{22}NO_2$ m/z 356.1645, found 356.1645.

(*E*)-*N*-benzyl-*N*-(2-formylphenyl)-3-(3-methoxyphenyl)acrylamide (III-54l)

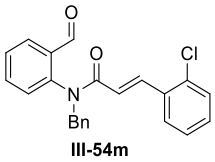


III-54l

Acrylamide **III-54g** (252 mg, 0.68 mmol, 57% Yield) was synthesized according to the general procedure 2 from **3** in 1.2 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.94 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.73 (d, *J* = 15.4 Hz, 1H), 7.65 (td, *J* = 7.7, 1.7 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.28-7.24 (m, 3H), 7.22 – 7.15 (m, 4H), 6.89 – 6.80 (m, 2H), 6.76 (t, *J* = 2.1 Hz, 1H), 6.05 (d, *J* = 15.4 Hz, 1H), 5.14 – 4.99 (m, 2H), 3.74 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 189.1, 166.0, 159.8, 144.1, 143.8, 136.2, 136.0, 135.5, 133.7, 130.3, 129.9, 129.7 (2C), 129.4, 129.2, 128.8 (2C), 128.2, 120.6, 118.0, 115.3, 113.8, 55.4, 54.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{22}NO_3$ m/z 372.1594, found 372.1592.

(*E*)-*N*-benzyl-3-(2-chlorophenyl)-*N*-(2-formylphenyl)acrylamide (III-54m)

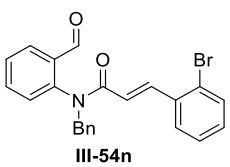


III-54m

Acrylamide **III-54m** (247 mg, 0.66 mmol, 55% Yield) was synthesized according to the general procedure 2 from **3** in 1.2 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.16 (d, *J* = 15.4 Hz, 1H), 7.95 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.67 (td, *J* = 7.6, 1.7 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.30 – 7.25 (m, 3H), 7.24-7.22 (m, 2H), 7.21-7.18 (m, 2H), 7.13 – 7.06 (m, 2H), 6.13 (d, *J* = 15.4 Hz, 1H), 5.19 – 4.97 (m, 2H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 188.9, 165.4, 143.5, 139.9, 135.8, 135.4, 134.8, 133.6, 133.0, 130.7, 130.2, 130.1, 129.6 (2C), 129.4, 129.1, 128.7 (2C), 128.1, 127.7, 126.9, 120.5, 54.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{19}NO_2Cl$ m/z 376.1099, found 376.1099.

(*E*)-*N*-benzyl-3-(2-bromophenyl)-*N*-(2-formylphenyl)acrylamide (III-54n)



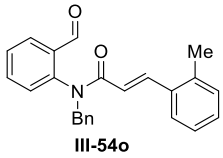
III-54n

Acrylamide **III-54n** (232 mg, 0.55 mmol, 46% Yield) was synthesized according to the general procedure 2 from **3** in 1.2 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.09 (d, *J* = 15.4 Hz, 1H), 7.94 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.65 (td, *J* = 7.6, 1.7 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.29 – 7.24 (m, 3H), 7.23 – 7.19

(m, 2H), 7.17 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.15-7.10 (m, 2H), 7.07 (dd, *J* = 7.3, 2.3 Hz, 1H), 6.04 (d, *J* = 15.4 Hz, 1H), 5.26 – 4.88 (m, 2H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 189.1, 165.5, 143.7, 142.6, 135.9, 135.5, 135.0, 133.8, 133.5, 130.9, 130.3, 129.7 (2C), 129.5, 129.2, 128.8 (2C), 128.3, 128.0, 127.6, 125.3, 120.7, 54.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{19}NO_2Br$ m/z 420.0594, found 420.0593.

(*E*)-*N*-benzyl-*N*-(2-formylphenyl)-3-(*o*-tolyl)acrylamide (III-54o)

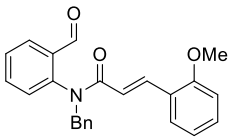


III-54o

Acrylamide **III-54o** (224 mg, 0.63 mmol, 53% Yield) was synthesized according to the general procedure 2 from **3** in 1.2 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.06 (d, *J* = 15.3 Hz, 1H), 7.94 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.65 (td, *J* = 7.6, 1.7 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.29 – 7.24 (m, 3H), 7.23-7.21 (m, 2H), 7.20-7.15 (m, 2H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.06 – 7.01 (m, 2H), 6.00 (d, *J* = 15.3 Hz, 1H), 5.21 – 4.98 (m, 2H), 2.37 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 189.0, 166.1, 143.8, 141.9, 137.7, 136.0, 135.4, 133.9, 133.7, 130.8, 130.1, 129.7, 129.6 (2C), 129.3, 129.0, 128.7 (2C), 128.1, 126.4, 126.1, 119.0, 54.2, 19.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{22}NO_2$ m/z 356.1645, found 356.1644.

(*E*)-*N*-benzyl-*N*-(2-formylphenyl)-3-(2-methoxyphenyl)acrylamide (III-54p)

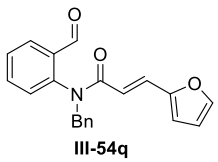


III-54p

Acrylamide **III-54p** (126 mg, 0.34 mmol, 28% Yield) was synthesized according to the general procedure 2 from **3** in 1.2 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.98 (d, *J* = 15.5 Hz, 1H), 7.94 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.64 (td, *J* = 7.6, 1.7 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.27 – 7.19 (m, 6H), 7.17 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.14 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.86 – 6.75 (m, 2H), 6.26 (d, *J* = 15.5 Hz, 1H), 5.14 (d, *J* = 14.1 Hz, 1H), 5.01 (d, *J* = 14.0 Hz, 1H), 3.67 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 189.2, 166.7, 158.5, 144.3, 139.9, 136.2, 135.4, 133.9, 131.2, 130.3, 129.8, 129.7 (2C), 129.0, 128.8, 128.8 (2C), 128.2, 123.9, 120.6, 118.9, 111.2, 55.3, 54.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{22}NO_3$ m/z 372.1594, found 372.1594.

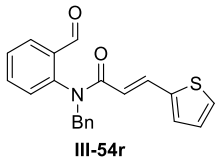
(*E*)-*N*-benzyl-*N*-(2-formylphenyl)-3-(furan-2-yl)acrylamide (III-54q)


III-54q

Acrylamide **III-54q** (77 mg, 0.23 mmol, 19% Yield) was synthesized according to the general procedure 2 from **3** in 1.2 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.94 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.64 (td, *J* = 7.6, 1.7 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.28 (d, *J* = 1.8 Hz, 1H), 7.26-7.23 (m, 3H), 7.20 – 7.16 (m, 2H), 7.14 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.50 (d, *J* = 3.4 Hz, 1H), 6.37 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.95 (d, *J* = 15.1 Hz, 1H), 5.13 – 4.97 (m, 2H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 189.2, 166.1, 151.3, 144.5, 143.8, 136.1, 135.5, 133.8, 130.6, 130.3, 129.7 (2C), 129.4, 129.1, 128.8 (2C), 128.2, 115.2, 115.0, 112.3, 54.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{21}H_{18}NO_3$ m/z 332.1281, found 332.1282.

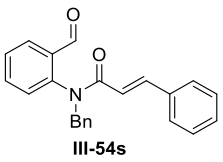
(*E*)-*N*-benzyl-*N*-(2-formylphenyl)-3-(thiophen-2-yl)acrylamide (III-54r)


III-54r

Acrylamide **III-54r** (143 mg, 0.41 mmol, 34% Yield) was synthesized according to the general procedure 2 from **3** in 1.2 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.95 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.87 (d, *J* = 15.1 Hz, 1H), 7.65 (td, *J* = 7.6, 1.7 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.27-7.24 (m, 3H), 7.23 (d, *J* = 5.0 Hz, 1H), 7.21-7.18 (m, 2H), 7.15 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.12 (d, *J* = 3.7 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.86 (d, *J* = 15.1 Hz, 1H), 5.09-5.00 (m, 2H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 189.1, 165.9, 143.7, 140.0, 136.6, 136.0, 135.4, 133.7, 130.8, 130.3, 129.6 (2C), 129.4, 129.1, 128.8 (2C), 128.2, 128.1, 128.1, 116.5, 54.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{21}H_{18}NO_2S$ m/z 348.1053, found 348.1053.

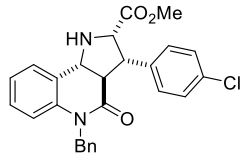
***N*-benzyl-*N*-(2-formylphenyl)cinnamamide (III-54s)**


III-54s

Acrylamide **III-54s** (559 mg, 1.63 mmol, 55% Yield) was synthesized according to the general procedure 2 from **3** in 3.0 mmol scale; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.95 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.78 (d, *J* = 15.4 Hz, 1H), 7.66 (td, *J* = 7.6, 1.7 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.29 – 7.22 (m, 8H), 7.22-7.19 (m, 2H), 7.16 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.07 (d, *J* = 15.4 Hz, 1H), 5.16 – 4.97 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 189.1, 166.1, 144.2, 143.8, 136.0, 135.5, 134.8, 133.8, 130.3, 130.1, 129.7 (2C), 129.4, 129.1, 128.9 (2C), 128.8 (2C), 128.2, 128.1 (2C), 117.7, 54.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{20}NO_2$ m/z 342.1489, found 342.1486.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-3-(4-chlorophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44a)

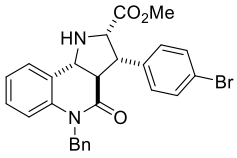


III-44a

PQ **III-44a** (87 mg, 0.2 mmol, 89% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.43 (dt, *J* = 7.4, 1.4 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.25 – 7.19 (m, 4H), 7.18 – 7.10 (m, 5H), 7.00 (d, *J* = 8.1 Hz, 1H), 5.25 (d, *J* = 16.2 Hz, 1H), 5.02 (s, 1H), 4.48 (d, *J* = 10.4 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 1H), 4.04 (t, *J* = 10.7 Hz, 1H), 3.21 (s, 3H), 3.01 (dd, *J* = 13.5, 11.1 Hz, 1H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 172.4, 169.5, 139.5, 137.3, 137.0, 133.1, 129.5 (2C), 128.9 (2C), 128.7 (2C), 128.4, 127.4, 126.7 (2C), 123.8, 123.3, 116.5, 66.7, 60.2, 54.5, 52.0, 49.1, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Cl$ m/z 447.1470, found 447.1468.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-3-(4-bromophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44b)

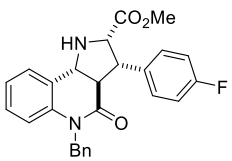


III-44b

PQ **III-44b** (81 mg, 0.17 mmol, 75% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.45 – 7.39 (m, 3H), 7.30 – 7.25 (m, 2H), 7.24 – 7.19 (m, 2H), 7.18 – 7.15 (m, 2H), 7.15 – 7.08 (m, 3H), 7.00 (d, *J* = 8.1 Hz, 1H), 5.26 (d, *J* = 16.2 Hz, 1H), 5.01 (d, *J* = 16.2 Hz, 1H), 4.48 (d, *J* = 10.4 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 1H), 4.03 (t, *J* = 10.7 Hz, 1H), 3.21 (s, 3H), 3.01 (dd, *J* = 13.5, 11.0 Hz, 1H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 172.4, 169.5, 139.5, 137.9, 136.9, 131.6 (2C), 129.9 (2C), 129.5, 128.9 (2C), 128.4, 127.4, 126.7 (2C), 123.8, 123.3, 121.2, 116.4, 66.6, 60.2, 54.5, 52.0, 49.1, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Br$ m/z 491.0965, found 491.0961.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-3-(4-fluorophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44c)



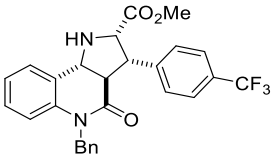
III-44c

PQ **III-44c** (63 mg, 0.15 mmol, 67% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.44 (d, *J* = 7.5 Hz, 1H), 7.32 – 7.11 (m,

9H), 7.03-6.94 (m, 3H), 5.25 (d, *J* = 16.0 Hz, 1H), 5.02 (d, *J* = 16.2 Hz, 1H), 4.48 (d, *J* = 10.4 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 1H), 4.10 – 3.99 (m, 1H), 3.20 (s, 3H), 3.02 (dd, *J* = 13.3, 11.0 Hz, 1H). **^{13}C NMR (126MHz, $CDCl_3$)** δ 172.5, 169.6, 162.1 (d, *J*CF = 245.7 Hz), 139.5, 137.0, 134.5 (d, *J*CF = 2.5 Hz), 129.7 (d, *J*CF = 7.6 Hz, 2C), 129.6, 128.9 (2C), 128.4, 127.4, 126.7 (2C), 123.8, 123.3, 116.4, 115.4 (d, *J*CF = 21.4 Hz, 2C), 66.7, 60.2, 54.5, 52.0, 49.0, 46.3. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -115.6 (ddd, *J* = 13.8, 8.8, 5.3 Hz, 1F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3F$ m/z 431.1766, found 431.1764.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-4-oxo-3-(4-(trifluoromethyl)phenyl)-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44d)

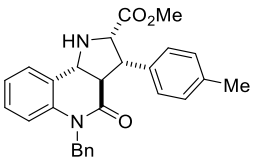


III-44d

PQ **III-44d** (84 mg, 0.18 mmol, 80% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.30 – 7.26 (m, 2H), 7.24 – 7.12 (m, 5H), 7.01 (d, *J* = 8.1 Hz, 1H), 5.26 (d, *J* = 16.2 Hz, 1H), 5.02 (d, *J* = 16.2 Hz, 1H), 4.53 (d, *J* = 10.4 Hz, 1H), 4.26 (d, *J* = 13.4 Hz, 1H), 4.13 (t, *J* = 10.7 Hz, 1H), 3.15 (s, 3H), 3.08 (dd, *J* = 13.4, 11.1 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.2, 169.3, 143.0, 139.4, 136.9, 129.6 (q, *J*CF = 32.8 Hz), 129.3, 128.9 (2C), 128.6 (2C), 128.5, 127.4, 126.7 (2C), 125.4 (q, *J*CF = 5.0 Hz, 2C), 124.2 (d, *J*CF = 272.2 Hz), 123.9, 123.4, 116.5, 66.7, 60.2, 54.4, 51.9, 49.4, 46.4. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -62.5 (s, 3F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{24}N_2O_3F_3$ m/z 481.1734, found 481.1727.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-4-oxo-3-(*p*-tolyl)-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44e)



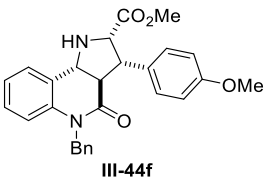
III-44e

PQ **III-44e** (71 mg, 0.17 mmol, 75% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.4 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.23 – 7.16 (m, 4H), 7.15 – 7.06 (m, 5H), 6.99 (d, *J* = 8.1 Hz, 1H), 5.25 (d, *J* = 16.2 Hz, 1H), 5.01 (d, *J* = 16.2 Hz, 1H), 4.47 (d, *J* = 10.4 Hz, 1H), 4.21 (d, *J* = 13.5 Hz, 1H), 4.04 (t, *J* = 10.7 Hz, 1H), 3.17 (s, 3H), 3.05 (dd, *J* = 13.5, 11.1 Hz, 1H), 2.29 (s, 3H). **^{13}C NMR (126MHz, $CDCl_3$)** δ 172.6, 169.7, 139.6, 137.1, 136.8, 135.6, 129.7, 129.2 (2C), 128.8 (2C),

128.3, 127.9 (2C), 127.3, 126.7 (2C), 123.7, 123.3, 116.3, 66.9, 60.2, 54.4, 51.9, 49.4, 46.2, 21.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{27}N_2O_3$ m/z 427.2016, found 427.2014.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-3-(4-methoxyphenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44f)

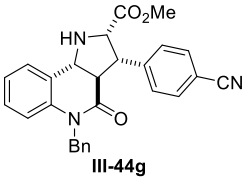


III-44f

PQ **III-44f** (53 mg, 0.12 mmol, 55% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 1:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dt, *J* = 7.4, 1.5 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.24 – 7.10 (m, 7H), 6.99 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.85 – 6.77 (m, 2H), 5.25 (d, *J* = 16.2 Hz, 1H), 5.02 (d, *J* = 16.2 Hz, 1H), 4.46 (d, *J* = 10.4 Hz, 1H), 4.21 (d, *J* = 13.5 Hz, 1H), 4.03 (t, *J* = 10.7 Hz, 1H), 3.76 (s, 3H), 3.20 (s, 3H), 3.02 (dd, *J* = 13.5, 11.1 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.7, 169.7, 158.8, 139.6, 137.1, 130.7, 129.7, 129.1 (2C), 128.9 (2C), 128.3, 127.3, 126.7 (2C), 123.7, 123.3, 116.4, 114.0 (2C), 66.8, 60.2, 55.4, 54.3, 52.0, 49.0, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{27}N_2O_4$ m/z 443.1965, found 443.1963.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-3-(4-cyanophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44g)



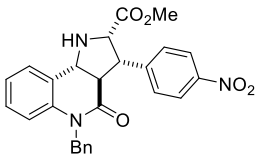
III-44g

PQ **III-44g** (60 mg, 0.14 mmol, 62% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.55 (m, 2H), 7.43 (dt, *J* = 7.4, 1.4 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.30 – 7.25 (m, 2H), 7.24 – 7.19 (m, 2H), 7.18 – 7.12 (m, 3H), 7.02 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.25 (d, *J* = 16.2 Hz, 1H), 5.01 (d, *J* = 16.2 Hz, 1H), 4.54 (d, *J* = 10.4 Hz, 1H), 4.26 (d, *J* = 13.4 Hz, 1H), 4.18 – 4.04 (m, 1H), 3.19 (s, 3H), 3.05 (dd, *J* = 13.4, 11.1 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.0, 169.1, 144.6, 139.4, 136.8, 132.3 (2C), 129.2, 129.1 (2C), 128.9 (2C), 128.6, 127.5, 126.7 (2C), 124.0, 123.4, 118.8, 116.6, 111.3, 66.6, 60.3, 54.5, 52.0, 49.6, 46.4. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{24}N_3O_3$ m/z 438.1812, found 438.1810.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-3-(4-nitrophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44h)

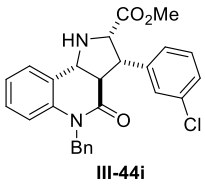
PQ **III-44h** (73 mg, 0.16 mmol, 73% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.



III-44h

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.50 – 7.38 (m, 3H), 7.33 – 7.11 (m, 7H), 7.03 (d, *J* = 8.2 Hz, 1H), 5.27 (d, *J* = 16.2 Hz, 1H), 5.01 (d, *J* = 16.2 Hz, 1H), 4.57 (d, *J* = 10.4 Hz, 1H), 4.29 (d, *J* = 13.4 Hz, 1H), 4.17 (t, *J* = 10.7 Hz, 1H), 3.21 (s, 3H), 3.10 (dd, *J* = 13.4, 11.1 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.0, 169.1, 147.2, 146.7, 139.4, 136.8, 129.2, 129.1 (2C), 128.9 (2C), 128.5, 127.4, 126.6 (2C), 124.0, 123.7 (2C), 123.4, 116.5, 66.6, 60.2, 54.7, 52.1, 49.3, 46.4. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_3O_5$ m/z 458.1711, found 458.1701.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-3-(3-chlorophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44i)

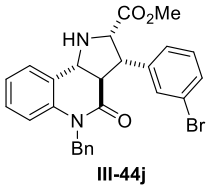


III-44i

PQ **III-44i** (77 mg, 0.17 mmol, 78% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.4 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.25 – 7.16 (m, 7H), 7.15-7.09 (m, 2H), 7.01 (d, *J* = 8.1 Hz, 1H), 5.25 (d, *J* = 16.2 Hz, 1H), 5.03 (d, *J* = 16.2 Hz, 1H), 4.49 (d, *J* = 10.4 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 1H), 4.03 (t, *J* = 10.7 Hz, 1H), 3.22 (s, 3H), 3.02 (dd, *J* = 13.5, 11.1 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.3, 169.4, 140.9, 139.5, 136.9, 134.3, 129.7, 129.5, 128.9 (2C), 128.4, 128.4, 127.5, 127.4, 126.7 (2C), 126.3, 123.8, 123.3, 116.5, 66.8, 60.2, 54.4, 52.0, 49.3, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Cl$ m/z 447.1470, found 447.1468.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-3-(3-bromophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44j)



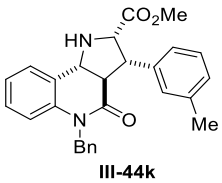
III-44j

PQ **III-44j** (59 mg, 0.12 mmol, 59% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.4 Hz, 1H), 7.39 – 7.34 (m, 2H), 7.30-7.26 (m, 2H), 7.25 – 7.11 (m, 7H), 7.01 (d, *J* = 8.2 Hz, 1H), 5.25 (d, *J* = 16.2 Hz, 1H), 5.03 (d, *J* = 16.2 Hz, 1H), 4.49 (d, *J* = 10.4 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 1H), 4.02 (t, *J* = 10.8 Hz, 1H), 3.22 (s, 3H), 3.01 (dd, *J* = 13.5, 11.1 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.2, 169.4, 141.2, 139.5, 136.9, 131.3, 130.4, 130.1, 129.5, 128.9 (2C), 128.4, 127.4,

126.8, 126.7 (2C), 123.8, 123.3, 122.5, 116.5, 66.8, 60.2, 54.4, 52.0, 49.3, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Br$ m/z 491.0965, found 491.0962.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-4-oxo-3-(*m*-tolyl)-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44k)

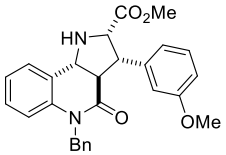


III-44k

PQ **III-44k** (54 mg, 0.13 mmol, 57% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.4 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.24 – 7.10 (m, 6H), 7.04 – 6.97 (m, 4H), 5.24 (d, *J* = 16.2 Hz, 1H), 5.03 (d, *J* = 16.2 Hz, 1H), 4.48 (d, *J* = 10.4 Hz, 1H), 4.21 (d, *J* = 13.5 Hz, 1H), 4.03 (t, *J* = 10.7 Hz, 1H), 3.15 (s, 3H), 3.05 (dd, *J* = 13.6, 11.0 Hz, 1H), 2.30 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.5, 169.8, 139.6, 138.6, 138.0, 137.1, 129.7, 129.0, 128.8 (2C), 128.4, 128.3, 128.1, 127.3, 126.7 (2C), 125.0, 123.7, 123.3, 116.4, 67.0, 60.3, 54.5, 51.8, 49.7, 46.3, 21.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{27}N_2O_3$ m/z 427.2016 found 427.2014.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-3-(3-methoxyphenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44l)

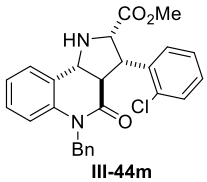


III-44l

PQ **III-44l** (66 mg, 0.15 mmol, 68% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 1:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.4 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.25 – 7.24 (m, 1H), 7.23 – 7.16 (m, 5H), 7.15 – 7.11 (m, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.82 – 6.72 (m, 3H), 5.25 (d, *J* = 16.2 Hz, 1H), 5.03 (d, *J* = 16.2 Hz, 1H), 4.50 (d, *J* = 10.4 Hz, 1H), 4.23 (d, *J* = 13.6 Hz, 1H), 4.04 (t, *J* = 10.7 Hz, 1H), 3.77 (s, 3H), 3.19 (s, 3H), 3.06 (dd, *J* = 13.6, 11.0 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.4, 169.6, 159.7, 140.2, 139.6, 137.1, 129.5, 129.5, 128.9 (2C), 128.4, 127.3, 126.7 (2C), 123.8, 123.4, 120.4, 116.4, 113.8, 113.1, 66.9, 60.3, 55.4, 54.4, 52.0, 49.7, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{27}N_2O_4$ m/z 443.1965, found 443.1955.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-3-(2-chlorophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44m)

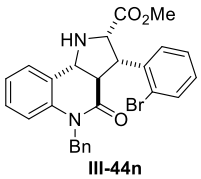


III-44m

PQ **III-44m** (68 mg, 0.15 mmol, 69% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 2H), 7.30-7.27 (m, 2H), 7.25 – 7.06 (m, 8H), 7.01 (d, *J* = 8.2 Hz, 1H), 5.27 (d, *J* = 16.2 Hz, 1H), 5.04 (d, *J* = 16.2 Hz, 1H), 4.67 (d, *J* = 10.1 Hz, 1H), 4.57 (dd, *J* = 11.5, 10.0 Hz, 1H), 4.33 (d, *J* = 13.3 Hz, 1H), 3.22 (dd, *J* = 13.4, 11.4 Hz, 1H), 3.11 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.0, 169.2, 139.5, 137.0, 135.8, 135.5, 129.8, 129.6, 128.9 (2C), 128.4, 128.3, 127.4, 126.8, 126.7 (2C), 123.8, 123.4, 116.4, 64.6, 60.0, 51.8, 51.5, 46.3, 46.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Cl$ m/z 447.1470, found 447.1468.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-3-(2-bromophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44n)

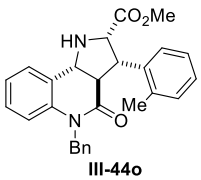


III-44n

PQ **III-44n** (76 mg, 0.15 mmol, 70% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.44 (dt, *J* = 7.4, 1.5 Hz, 1H), 7.31-7.26 (m, 2H), 7.25 – 7.17 (m, 5H), 7.16 – 7.04 (m, 3H), 7.01 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.27 (d, *J* = 16.2 Hz, 1H), 5.03 (d, *J* = 16.2 Hz, 1H), 4.70 (d, *J* = 10.1 Hz, 1H), 4.56 (dd, *J* = 11.6, 10.1 Hz, 1H), 4.34 (d, *J* = 13.3, 1H), 3.22 (dd, *J* = 13.3, 11.5 Hz, 1H), 3.11 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.8, 169.1, 139.5, 137.5, 137.0, 132.9, 129.7, 128.9 (2C), 128.6, 128.3, 127.5, 127.4, 127.3, 126.7 (2C), 126.5, 123.8, 123.4, 116.4, 64.5, 59.9, 51.8, 48.7, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Br$ m/z 491.0965, found 491.0960.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-4-oxo-3-(*o*-tolyl)-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44o)



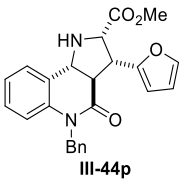
III-44o

PQ **III-44o** (59 mg, 0.14 mmol, 63% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.2 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.25 – 7.04 (m, 8H), 7.01-6.96 (m, 2H), 5.28 (d, *J* = 16.1 Hz, 1H), 5.01 (d, *J* = 16.2 Hz, 1H), 4.54 (d, *J* = 10.3 Hz, 1H), 4.33 (t, *J* = 10.7 Hz, 1H), 4.25 (d, *J* = 13.4 Hz, 1H), 3.17 (dd,

J = 13.4, 10.9 Hz, 1H), 3.07 (s, 3H), 2.53 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.6, 169.8, 139.7, 137.4, 137.1, 136.9, 130.3, 129.8, 128.9 (2C), 128.3, 127.3, 126.9, 126.7 (2C), 126.0, 125.6, 123.7, 123.3, 116.4, 65.7, 60.3, 53.9, 51.7, 46.3, 45.1, 20.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{27}N_2O_3$ m/z 427.2016, found 427.2014.

(±)-Methyl (2*S*,3*R*,3a*R*,9b*R*)-5-benzyl-3-(furan-2-yl)-4-oxo-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44p)

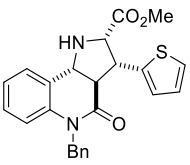


III-44p

PQ **III-44p** (55 mg, 0.14 mmol, 63% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.4 Hz, 1H), 7.31 – 7.26 (m, 3H), 7.23-7.18 (m, 4H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.35 – 6.27 (m, 1H), 6.20 (d, *J* = 3.3 Hz, 1H), 5.28 (d, *J* = 16.2 Hz, 1H), 5.02 (d, *J* = 16.3 Hz, 1H), 4.41 (d, *J* = 10.1 Hz, 1H), 4.29 – 4.11 (m, 2H), 3.43 (s, 3H), 3.06 (dd, *J* = 13.6, 11.0 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.2, 169.4, 152.0, 141.9, 139.5, 137.0, 129.4, 128.9 (2C), 128.4, 127.4, 126.7 (2C), 123.8, 123.3, 116.4, 110.8, 107.4, 65.2, 60.2, 52.8, 52.6, 46.3, 43.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{23}N_2O_4$ m/z 403.1652, found 403.1651.

(±)-Methyl (2*S*,3*R*,3a*R*,9b*R*)-5-benzyl-4-oxo-3-(thiophen-2-yl)-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44q)



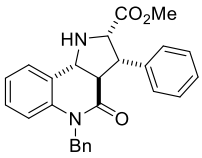
III-44q

PQ **III-44q** (68 mg, 0.16 mmol, 74% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.4 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.25 – 7.09 (m, 6H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.89 – 6.85 (m, 1H), 5.28 (d, *J* = 16.1 Hz, 1H), 5.02 (d, *J* = 16.2 Hz, 1H), 4.47 (d, *J* = 10.2 Hz, 1H), 4.35 (t, *J* = 10.5 Hz, 1H), 4.19 (dt, *J* = 13.6, 1.1 Hz, 1H), 3.32 (s, 3H), 3.01 (dd, *J* = 13.5, 10.9 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.2, 169.2, 141.4, 139.5, 137.0, 129.4, 128.9 (2C), 128.4, 127.4, 127.1, 126.7 (2C), 125.3, 124.1, 123.8, 123.3, 116.4, 67.0, 60.2, 56.0, 52.2, 46.3, 44.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{23}N_2O_3S$ m/z 419.1424, found 419.1423.

(±)-Methyl (2*S*,3*S*,3a*R*,9b*R*)-5-benzyl-4-oxo-3-phenyl-2,3,3a,4,5,9b-hexahydro-*1H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44r)

PQ **III-44r** (71 mg, 0.18 mmol, 78% Yield, >20:1 d.r.) was synthesized according to the general procedure 3; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

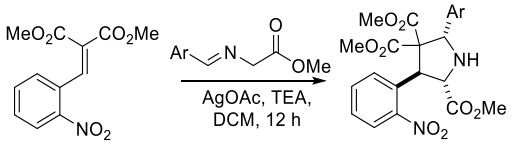


III-44r

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dt, *J* = 7.4, 1.3 Hz, 1H), 7.30 – 7.25 (m, 4H), 7.24 – 7.16 (m, 7H), 7.12 (td, *J* = 7.4, 1.1 Hz, 1H), 7.00 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.25 (d, *J* = 16.2 Hz, 1H), 5.03 (d, *J* = 16.1 Hz, 1H), 4.50 (d, *J* = 10.4 Hz, 1H), 4.23 (d, *J* = 13.5 Hz, 1H), 4.08 (t, *J* = 10.7 Hz, 1H), 3.13 (s, 3H), 3.07 (dd, *J* = 13.5, 11.1 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.5, 169.7, 139.6, 138.7, 137.1, 129.7, 128.9 (2C), 128.5 (2C), 128.3, 128.1 (2C), 127.3, 127.3, 126.7 (2C), 123.7, 123.3, 116.4, 67.0, 60.3, 54.4, 51.8, 49.8, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{25}N_2O_3$ m/z 413.1860, found 413.1854.

7.2.1.3 Racemic synthesis of III-45

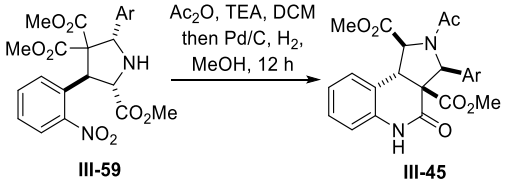
General Procedure 4



III-58 **III-59**

Ester **III-58**[126] (0.15 mmol, 1.0 equiv.) and the desired iminoester[42] (0.23 mmol, 1.5 equiv.) were dissolved in dry DCM (1.0 mL). Then silver acetate (2.5 mg, 0.015 mmol, 0.1 equiv.) was added to the mixture followed by TEA (21 µL, 0.15 mmol, 1.0 equiv.). The reaction was stirred until full conversion of the starting material was observed by TLC. The solvent was removed under reduced pressure and the product was purified by column chromatography using cyclohexane/EA mixtures as a single diastereoisomer.

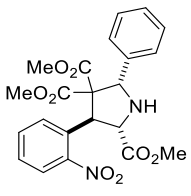
General Procedure 5



III-59 **III-45**

Pyrrolidine **III-59** (30 mg, 1.0 equiv.) was dissolved in DCM (1.0 mL). Then the acetic anhydride (3.0 equiv.) was added followed by TEA (4.0 equiv.) and the mixture was stirred overnight. Then the reaction was diluted with EA (20 mL) and washed with sat. aq. $NaHCO_3$ solution (10 mL) and brine (10 mL) sequentially. The organic phase was dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The residue was dissolved in MeOH (2.0 mL) and 10% Pd/C (30 mg) were added. The reaction vessel was flushed three times with H_2. The reaction was stirred under a H_2 atmosphere until full conversion of the starting material was observed. The reaction was filtered through a short pad of Celite and the solvent was then removed under reduced pressure. PQs **III-45** were purified by column chromatography using cyclohexane/acetone mixtures as a single diastereoisomer.

(±)-Trimethyl (2*S*,3*S*,5*S*-3-(2-nitrophenyl)-5-phenylpyrrolidine-2,4,4-tricarboxylate (III-59a)

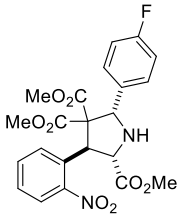


III-59a

Pyrrolidine **III-59a** (68 mg, 0.1 mmol, quant. Yield) was synthesized according to the general procedure 4; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.49 – 7.40 (m, 3H), 7.37 – 7.26 (m, 3H), 5.33 (s, 1H), 5.20 (d, *J* = 6.1 Hz, 1H), 4.20 (d, *J* = 6.3 Hz, 1H), 3.82 (s, 3H), 3.20 (s, 3H), 3.13 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.4, 169.2, 168.9, 151.0, 137.0, 133.4, 132.7, 129.5, 128.6, 128.5, 128.5 (2C), 127.4 (2C), 124.5, 71.2, 68.8, 67.4, 52.9, 52.6, 52.3, 49.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{22}H_{23}N_2O_8$ m/z 443.1449, found 443.1440.

(±)-Trimethyl (*2S,3S,5S*)-5-(4-fluorophenyl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59b)



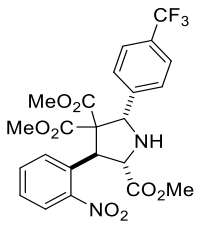
III-59b

Pyrrolidine **III-59b** (68 mg, 0.15 mmol, Yield 98%) was synthesized according to the general procedure 4; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.65 – 7.55 (m, 2H), 7.52 – 7.37 (m, 3H), 7.08 – 6.96 (m, 2H), 5.30 (s, 1H), 5.18 (d, *J* = 6.4 Hz, 1H), 4.16 (d, *J* = 6.4 Hz, 1H), 3.80 (s, 3H), 3.19 (s, 3H+3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.4, 169.1, 169.0, 162.8 (d, *J*CF = 247.1 Hz), 151.0, 133.4, 133.2 (d, *J*CF = 3.2

Hz), 132.7, 129.4, 129.2 (d, *J*CF = 8.1 Hz, 2C), 128.6, 124.5, 115.3 (d, *J*CF = 21.5 Hz, 2C), 71.0, 68.1, 67.3, 52.9, 52.6, 52.3, 49.2. **^{19}F NMR (470 MHz, CDCl$_3$)** δ -113.6 (ddd, *J* = 13.8, 8.8, 5.3 Hz, 1F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{22}H_{22}N_2O_8F$ m/z 461.1355, found 461.1345.

(±)-Trimethyl (*2S,3S,5S*)-3-(2-nitrophenyl)-5-(4-(trifluoromethyl)phenyl)pyrrolidine-2,4,4-tricarboxylate (III-59c)

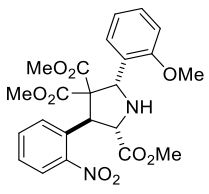


III-59c

Pyrrolidine **III-59c** (75 mg, 0.15 mmol, Yield 98%) was synthesized according to the general procedure 4; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.68 – 7.52 (m, 6H), 7.45 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H), 5.38 (s, 1H), 5.22 (d, *J* = 6.3 Hz, 1H), 4.19 (d, *J* = 6.3 Hz, 1H), 3.82 (s, 3H), 3.20 (s, 3H), 3.14 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 172.4, 168.9, 168.8, 151.0, 141.6, 133.3, 132.8, 130.7 (q, *J*CF = 32.4 Hz), 129.4, 128.7, 128.0 (2C), 125.3 (q, *J*CF = 3.7 Hz, 2C), 124.6, 124.1 (q, *J*CF = 272.7 Hz), 71.1, 68.1, 67.4, 52.9, 52.6, 52.4, 49.1. **^{19}F NMR (470 MHz, CDCl$_3$)** δ -62.7 (s, 3F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{22}N_2O_8F_3$ m/z 511.1323, found 511.1299.

(±)-Trimethyl (*2S,3S,5S*)-5-(2-methoxyphenyl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59d)



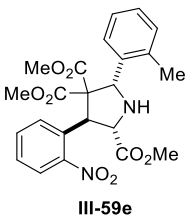
III-59d

Pyrrolidine **III-59d** (48 mg, 0.10 mmol, Yield 68%) was synthesized according to the general procedure 4; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.76 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.48 – 7.40 (m, 2H), 7.30-7.26 (m, 1H), 6.94 (td, *J* = 7.5, 1.1 Hz, 1H), 6.85 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.41 (s, 1H), 5.31 (d, *J* = 9.2 Hz, 1H), 4.28 (d, *J* = 9.1 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.24 (s, 3H), 3.22 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 171.5, 169.0, 157.8, 151.8, 131.9, 131.7, 131.4, 129.8, 129.2, 128.4, 124.7, 120.9, 110.5, 70.9, 68.5, 66.1, 55.1, 52.7, 52.5, 52.3, 49.5. **MS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{25}N_2O_9$ m/z 473.2, found 473.2.

(±)-Trimethyl (*2S,3S,5S*)-3-(2-nitrophenyl)-5-(*o*-tolyl)pyrrolidine-2,4,4-tricarboxylate (III-59e)

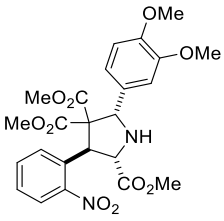
Pyrrolidine **III-59e** (60 mg, 0.13 mmol, Yield 88%) was synthesized according to the general procedure 4; column chromatography eluting with cyclohexane/EA 5:1 to 3:1.



III-59e

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.57 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.45 – 7.36 (m, 2H), 7.21 (td, *J* = 7.3, 2.3 Hz, 1H), 7.18 – 7.11 (m, 2H), 5.61 (s, 1H), 5.20 (d, *J* = 9.0 Hz, 1H), 4.26 (d, *J* = 9.0 Hz, 1H), 3.74 (s, 3H), 3.27 (s, 3H), 3.09 (s, 3H), 2.45 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.0, 169.9, 169.1, 151.7, 137.5, 137.3, 131.9, 131.3, 130.7, 129.2, 128.5, 128.2, 126.5, 126.2, 124.7, 71.9, 65.7, 64.1, 52.8, 52.5, 52.4, 49.3, 20.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{25}N_2O_8$ m/z 457.1605, found 457.1596.

(±)-Trimethyl (*2S,3S,5S*)-5-(3,4-dimethoxyphenyl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59f)

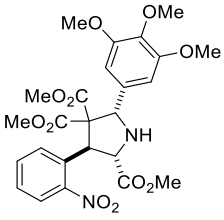


III-59f

Pyrrolidine **III-59f** (61 mg, 0.12 mmol, Yield 81%) was synthesized according to the general procedure 4; column chromatography eluting with cyclohexane/EA 5:1 to 1:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 1H), 7.67-7.54 (m, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 1.5 Hz, 1H), 6.98 (dt, *J* = 8.3, 1.6 Hz, 1H), 6.87 – 6.78 (m, 1H), 5.26 (s, 1H), 5.23 – 5.17 (m, 1H), 4.20 (d, *J* = 6.4 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.22 (s, 3H), 3.20 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.5, 169.2, 169.0, 151.0, 149.0, 148.8, 133.1, 132.7, 129.6, 129.4, 128.6, 124.5, 119.5, 110.8, 110.8, 70.8, 68.4, 66.9, 56.0, 56.0, 53.0, 52.8, 52.3, 48.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{27}N_2O_{10}$ m/z 503.1660, found 503.1651.

(±)-Trimethyl (*2S,3S,5S*)-3-(2-nitrophenyl)-5-(3,4,5-trimethoxyphenyl)pyrrolidine-2,4,4-tricarboxylate (III-59g)

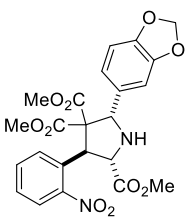


III-59g

Pyrrolidine **III-59g** (68 mg, 0.13 mmol, Yield 85%) was synthesized according to the general procedure 4; column chromatography eluting with cyclohexane/EA 5:1 to 1:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.9 Hz, 1H), 7.64 – 7.60 (m, 2H), 7.43 (dt, *J* = 8.4, 4.3 Hz, 1H), 6.75 (s, 2H), 5.27 (d, *J* = 6.4 Hz, 1H), 5.25 (s, 1H), 4.23 (d, *J* = 6.4 Hz, 1H), 3.87 (s, 6H), 3.82 (s, 3H), 3.81 (s, 3H), 3.25 (s, 3H), 3.22 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 172.5, 169.1, 168.9, 153.2 (2C), 151.1, 138.0, 133.1, 132.8, 132.6, 129.5, 128.7, 124.6, 104.7 (2C), 70.8, 68.7, 66.8, 61.0, 56.3 (2C), 53.0, 52.8, 52.4, 48.4. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{29}N_2O_{11}$ m/z 533.1766, found 533.1755.

(±)-Trimethyl (*2S,3S,5S*)-5-(benzo[*d*][1,3]dioxol-5-yl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59h)

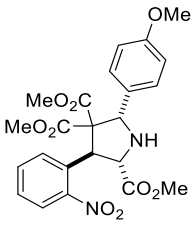


III-59h

Pyrrolidine **III-59h** (70 mg, 0.14 mmol, Yield 96%) was synthesized according to the general procedure 4; column chromatography eluting with cyclohexane/EA 5:1 to 1:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.43 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H), 6.99 (d, *J* = 1.8 Hz, 1H), 6.94 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.00 – 5.90 (m, 2H), 5.23 (s, 1H), 5.18 (d, *J* = 6.2 Hz, 1H), 4.16 (d, *J* = 6.1 Hz, 1H), 3.81 (s, 3H), 3.27 (s, 3H), 3.19 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.4, 169.2, 168.9, 150.9, 147.7, 147.7, 133.4, 132.7, 130.8, 129.5, 128.6, 124.5, 120.5, 108.4, 108.2, 101.3, 70.8, 68.5, 67.1, 52.9, 52.8, 52.3, 49.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{23}N_2O_{10}$ m/z 487.1347, found 487.1340.

(±)-Trimethyl (*2S,3S,5S*)-5-(4-methoxyphenyl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59i)

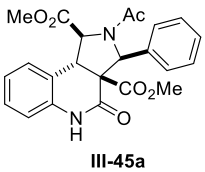


III-59i

Pyrrolidine **III-59i** (43 mg, 0.09 mmol, Yield 60%) was synthesized according to the general procedure 4; column chromatography eluting with cyclohexane/EA 5:1 to 1:1.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.43 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H), 7.41 – 7.37 (m, 2H), 6.90 – 6.83 (m, 2H), 5.27 (s, 1H), 5.17 (d, *J* = 6.3 Hz, 1H), 4.16 (d, *J* = 6.3 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.20 (s, 3H+3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 172.5, 169.4, 169.1, 159.7, 151.0, 133.6, 132.7, 129.5, 129.2, 128.6 (2C), 128.5, 124.5, 113.8 (2C), 71.1, 68.5, 67.4, 55.4, 52.9, 52.7, 52.2, 49.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{25}N_2O_9$ m/z 473.1555, found 473.1549.

(±)-Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-4-oxo-3-phenyl-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45a)

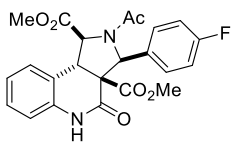


III-45a

PQ **III-45a** (60 mg, 0.14 mmol, 68% Yield) was synthesized according to the general procedure 5; column chromatography eluting with cyclohexane/EA 5:1 to 1:1 then cyclohexane/acetone 1:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.85 – 7.77 (m, 2H), 7.46 – 7.39 (m, 2H), 7.37 – 7.33 (m, 1H), 7.30 – 7.25 (m, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.05 (td, *J* = 7.5, 1.1 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.09 (s, 1H), 4.32 (d, *J* = 11.3 Hz, 1H), 4.18 (d, *J* = 11.4 Hz, 1H), 3.82 (s, 3H), 3.30 (s, 3H), 1.90 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.6, 170.7, 165.0, 164.6, 137.2, 135.0, 129.6, 129.4, 129.0 (2C), 128.9, 127.7 (2C), 124.3, 119.2, 116.3, 66.3, 64.1, 63.2, 53.2, 52.7, 44.9, 22.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{23}N_2O_6$ m/z 423.1551, found 423.1550.

(±)-Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-3-(4-fluorophenyl)-4-oxo-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45b)

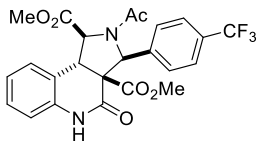


III-45b

PQ **III-45b** (15 mg, 0.03 mmol, 53% Yield) was synthesized according to the general procedure 5; column chromatography eluting with cyclohexane/EA 5:1 to 1:1 then cyclohexane/acetone 1:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.92 – 7.76 (m, 2H), 7.30 – 7.26 (m, 1H), 7.14-7.09 (m, 3H), 7.06 (td, *J* = 7.5, 1.1 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.07 (s, 1H), 4.27 (d, *J* = 11.3 Hz, 1H), 4.15 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 3H), 3.33 (s, 3H), 1.89 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.7, 170.6, 164.9, 164.3, 163.0 (d, *J*CF = 248.2 Hz), 134.9, 133.1 (d, *J*CF = 3.8 Hz), 129.6, 129.6 (d, *J*CF = 7.6 Hz, 2C), 129.4, 124.3, 119.0, 116.3, 116.0 (d, *J*CF = 22.7 Hz, 2C), 65.6, 64.1, 63.2, 53.3, 52.7, 44.8, 22.1. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -112.7 (ddd, *J* = 13.6, 8.5, 5.2 Hz, 1F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{22}N_2O_6F$ m/z 441.1456, found 441.1454.

(±)-Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-4-oxo-3-(4-(trifluoromethyl)phenyl)-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45c)



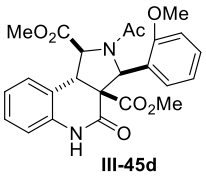
III-45c

PQ **III-45c** (20 mg, 0.04 mmol, 70% Yield) was synthesized according to the general procedure 5; column chromatography eluting with cyclohexane/EA 5:1 to 1:1 then cyclohexane/acetone 1:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.99 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.29 (td, *J* = 7.6, 1.6 Hz, 1H), 7.13-7.04 (m, 2H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.15 (s, 1H), 4.26 (d, *J* = 11.4 Hz, 1H), 4.18 (d, *J* = 11.3 Hz, 1H), 3.82 (s, 3H), 3.32 (s, 3H), 1.88 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.6, 170.5, 164.8, 164.1, 141.4, 134.8, 131.2 (q, *J*CF = 32.8 Hz), 129.7, 129.4, 128.2 (2C), 126.0 (q, *J*CF = 3.8 Hz, 2C), 124.4, 124.0 (q, *J*CF = 272.2 Hz), 118.8, 116.3, 65.7, 64.2, 63.2, 53.3, 52.8, 45.0, 22.1. **^{19}F NMR**

(470 MHz, $CDCl_3$) δ -62.7 (s, 3F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{22}N_2O_6F_3$ m/z 491.1425, found 491.1420.

(±)-Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-3-(2-methoxyphenyl)-4-oxo-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45d)

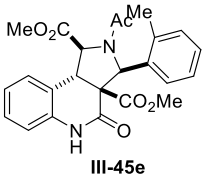


III-45d

PQ **III-45d** (14 mg, 0.03 mmol, 45% Yield) was synthesized according to the general procedure 5; column chromatography eluting with cyclohexane/EA 5:1 to 1:1 then cyclohexane/acetone 1:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.25 (s, 1H), 7.33 (td, *J* = 7.8, 1.7 Hz, 1H), 7.27 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.87-6.84 (m, 2H), 6.53 (s, 1H), 4.19 – 4.11 (m, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.31 (s, 3H), 1.88 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 171.5, 170.7, 166.0, 165.4, 156.4, 135.4, 129.8, 129.6, 129.4, 129.2, 125.7, 124.0, 121.4, 119.0, 116.0, 109.6, 62.9, 62.8, 61.0, 55.4, 52.9, 52.6, 46.7, 21.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{25}N_2O_7$ m/z 453.1656, found 453.1653.

(±)-Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-4-oxo-3-(*o*-tolyl)-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45e)

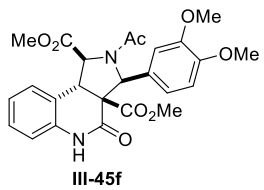


III-45e

PQ **III-45e** (20 mg, 0.05 mmol, 69% Yield) was synthesized according to the general procedure 5; column chromatography eluting with cyclohexane/EA 5:1 to 1:1 then cyclohexane/acetone 1:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.9 Hz, 1H), 8.13 (s, 1H), 7.39 – 7.33 (m, 1H), 7.29 (td, *J* = 7.7, 1.5 Hz, 1H), 7.24 (td, *J* = 7.4, 1.3 Hz, 1H), 7.19 – 7.11 (m, 2H), 7.06 (td, *J* = 7.5, 1.1 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.39 (s, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.14 (d, *J* = 11.4 Hz, 1H), 3.82 (s, 3H), 3.20 (s, 3H), 2.50 (s, 3H), 1.82 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.6, 170.5, 165.4, 164.8, 135.6, 135.0, 130.7, 129.7, 129.5, 128.8, 128.4, 127.3, 124.3, 118.8, 116.1, 63.9, 63.3, 62.7, 53.0, 52.7, 45.7, 21.8, 19.4. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{25}N_2O_6$ m/z 437.1707, found 437.1705.

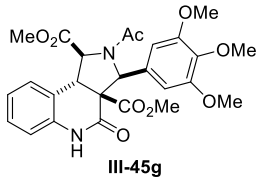
(±)-Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-3-(3,4-dimethoxyphenyl)-4-oxo-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45f)


III-45f

PQ **III-45f** (25 mg, 0.05 mmol, 86% Yield) was synthesized according to the general procedure 5; column chromatography eluting with cyclohexane/EA 5:1 to 1:1 then cyclohexane/acetone 1:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.54 (s, 1H), 7.31 – 7.24 (m, 2H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 1H), 4.29 (d, *J* = 11.3 Hz, 1H), 4.14 (d, *J* = 11.3 Hz, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H), 3.37 (s, 3H), 1.90 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.7, 170.6, 164.9, 164.5, 149.5, 149.2, 134.8, 129.6, 129.6, 129.5, 124.3, 119.9, 119.3, 116.1, 111.0, 110.6, 66.0, 64.1, 63.2, 56.4, 56.0, 53.3, 52.7, 45.0, 22.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}N_2O_8$ m/z 483.1762, found 483.1757.

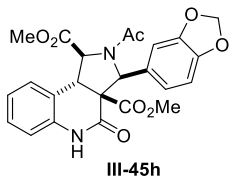
(±)-Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-4-oxo-3-(3,4,5-trimethoxyphenyl)-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45g)


III-45g

PQ **III-45g** (27 mg, 0.05 mmol, 95% Yield) was synthesized according to the general procedure 5; column chromatography eluting with cyclohexane/EA 5:1 to 1:1 then cyclohexane/acetone 1:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.29 (td, *J* = 7.7, 1.5 Hz, 1H), 7.15 – 7.10 (m, 3H), 7.07 (td, *J* = 7.5, 1.1 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.00 (s, 1H), 4.26 (d, *J* = 11.3 Hz, 1H), 4.13 (d, *J* = 11.3 Hz, 1H), 3.93 (s, 6H), 3.86 (s, 3H), 3.79 (s, 3H), 3.38 (s, 3H), 1.92 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 171.7, 170.6, 164.9, 164.3, 153.7, 138.0, 134.8, 132.7, 129.7, 129.5, 124.4, 119.3, 116.0, 104.6, 66.3, 64.3, 63.2, 61.0, 56.6 (2C), 53.3, 52.7, 45.1, 22.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{29}N_2O_9$ m/z 513.1868, found 513.1863.

(±)-Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-3-(benzo[*d*][1,3]dioxol-5-yl)-4-oxo-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45h)

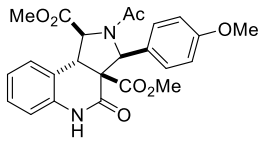

III-45h

PQ **III-45h** (20 mg, 0.04 mmol, 71% Yield) was synthesized according to the general procedure 5; column chromatography eluting with cyclohexane/EA 5:1 to 1:1 then cyclohexane/acetone 1:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.47 (d, *J* = 1.8 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.20 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.12 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.06 (td, *J* = 7.5, 1.1 Hz, 1H), 6.89 – 6.81 (m, 2H), 6.05 – 5.95 (m, 3H), 4.28 (d, *J* = 11.3 Hz, 1H), 4.13 (d, J = 11.3 Hz, 1H), 3.81 (s, 3H), 3.39 (s, 3H), 1.91 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 171.5, 170.6, 164.9, 164.4, 148.5, 148.1, 134.9, 131.0, 129.6, 129.5, 124.4, 121.3, 119.3, 116.1, 108.5, 108.2,

101.5, 66.1, 64.1, 63.2, 53.3, 52.7, 44.9, 22.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{23}N_2O_8$ m/z 467.1449, found 467.1445.

(±)-Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-3-(4-methoxyphenyl)-4-oxo-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45i)

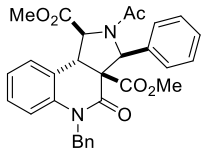


III-45i

PQ **III-45i** (9 mg, 20 µmol, 31% Yield) was synthesized according to the general procedure 5; column chromatography eluting with cyclohexane/EA 5:1 to 1:1 then cyclohexane/acetone 1:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.81 – 7.66 (m, 2H), 7.30 – 7.25 (m, 1H), 7.12 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.05 (td, *J* = 7.5, 1.1 Hz, 1H), 6.96 – 6.91 (m, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.03 (s, 1H), 4.30 (d, *J* = 11.3 Hz, 1H), 4.14 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 6H), 3.33 (s, 3H), 1.89 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.7, 170.7, 165.0, 164.5, 160.0, 135.0, 129.5, 129.4, 129.1, 129.0 (2C), 124.3, 119.3, 116.2, 114.3 (2C), 65.9, 64.1, 63.2, 55.4, 53.2, 52.6, 44.8, 22.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{25}N_2O_7$ m/z 453.1656, found 453.1654.

(±)-Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-5-benzyl-4-oxo-3-phenyl-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45j)



III-45j

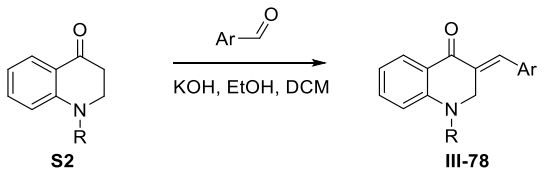
PQ **III-45j** (11 mg, 25 µmol, 1.0 equiv.) was dissolved in dry DMF (0.25 ml) and cooled in an ice bath. NaH (60% in mineral oil, 1.1 mg, 28 µmol, 1.1 equiv.) was added and the reaction was stirred for 30 minutes. Benzyl bromide (13 mg, 75 µmol, 3.0 equiv.) was added and the reaction was stirred at room temperature overnight. The reaction was quenched with sat. aq. NH_4Cl solution (20 mL) and extracted with DCM (3*20 mL). The combined organic phases were washed four times with water and dried over Na_2SO_4. The solvent was removed under reduced pressure. The product was purified by column chromatography using cyclohexane/acetone 4:1 to 2:1 affording PQ **C10** (9.6 mg, 19 µmol, 75% Yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.38 – 7.31 (m, 3H), 7.28 – 7.26 (m, 1H), 7.24-7.19 (m, 3H), 7.12 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.04 (td, *J* = 7.5, 1.0 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.22 (s, 1H), 5.76 (d, *J* = 16.1 Hz, 1H), 4.75 (d, *J* = 16.1 Hz, 1H), 4.30 (d, *J* = 11.4 Hz, 1H), 4.19 (d, *J* = 11.3 Hz, 1H), 3.83 (s, 3H), 3.33 (s, 3H), 1.90 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 171.6, 170.7, 165.2, 164.3, 137.9, 137.4, 136.5, 129.7, 129.6, 129.1 (2C), 129.1 (2C), 128.9, 127.6, 127.6 (2C), 126.4 (2C), 124.2, 120.4,

116.4, 66.9, 64.4, 63.0, 53.0, 52.7, 48.5, 44.6, 22.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{30}H_{29}N_2O_6$ m/z 513.2020, found 513.2015.

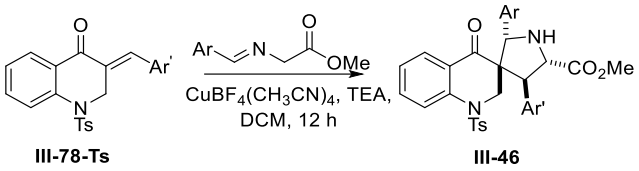
7.2.1.4 Racemic synthesis of III-46

General Procedure 6



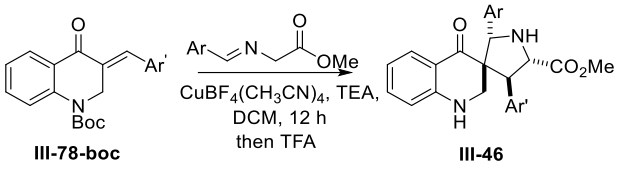
Ketone **S2** (synthesized according to Ref 10)[127] (1.0 equiv.) was dissolved in a EtOH/DCM (1:2, 0.1 M) mixture followed by the addition of aldehyde (1.0 equiv.) and KOH (2.0 equiv.). The reaction was stirred until the full conversion of the starting material was observed by TLC (less than 10 min). The reaction was quenched with sat. NH_4Cl solution (30 mL) and extracted with DCM (3*50 mL). The combined organic phases were then washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The products **III-78** were purified by column chromatography using cyclohexane/EA.

General Procedure 7



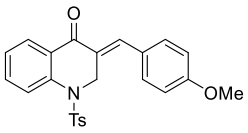
Ketone **III-78a** (0.1 mmol, 1.0 equiv.) and the desired iminoester (0.15 mmol, 1.5 equiv.) were dissolved in dry DCM (1.0 mL). Then $Cu(CH_3CN)_4BF_4$ (3.1 mg, 0.01 mmol, 0.1 equiv.) was added to the mixture followed by TEA (14 µL, 0.1 mmol, 1.0 equiv.). The reaction was stirred until full conversion of the starting material was observed. The solvent was removed under reduced pressure and the residue used to determine the diastereomeric ratio of the products. PQs **III-46** were purified by column chromatography using cyclohexane/EA.

General Procedure 8



Ketone **III-78c** (0.1 mmol, 1.0 equiv.) and the desired iminoester (0.15 mmol, 1.5 equiv.) were dissolved in dry DCM (1.0 mL). Then $Cu(CH_3CN)_4BF_4$ (3.1 mg, 0.01 mmol, 0.1 equiv.) was added to the mixture followed by TEA (14 µL, 0.1 mmol, 1.0 equiv.). After full conversion was observed, TFA (10 equiv.) was added to the reaction mixture and stirred for another 1 h. The solvent was removed under reduced pressured. The remains were three times dissolved in DCM and the solvent evaporated to remove excess TFA. Then the residue was dissolved in EA (20 mL) and washed with $NaHCO_3$ solution (10 mL) and brine (10 mL) sequentially. The organic phase was dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and deprotected PQs **III-46** were purified by column chromatography using cyclohexane/EA as a single diastereoisomer.

(*E*)-3-(4-Methoxybenzylidene)-1-tosyl-2,3-dihydroquinolin-4(*1H*)-one (III-78a)

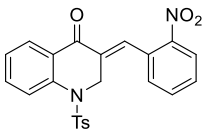


III-78a

Ketone **III-78a** (1.4 g, 3.34 mmol, 50% Yield) was synthesized according to the general procedure 6 from **S2** (2g, 6.64 mmol); column chromatography eluting with cyclohexane/EA 10:1 to 3:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.82 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.63 (ddd, *J* = 8.1, 7.3, 1.7 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.34 – 7.28 (m, 2H), 7.05 – 6.99 (m, 4H), 6.99 – 6.92 (m, 2H), 5.07 (d, *J* = 1.8 Hz, 2H), 3.91 (s, 3H), 2.33 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 182.8, 161.1, 144.3, 141.3, 138.5, 134.6, 134.1, 132.2 (2C), 129.6 (2C), 129.2, 128.3, 127.7, 127.5, 127.5 (2C), 127.2, 127.0, 114.7 (2C), 55.6, 48.2, 21.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{22}NO_4S$ m/z 420.1264, found 420.1263.

(*E*)-3-(2-Nitrobenzylidene)-1-tosyl-2,3-dihydroquinolin-4(*1H*)-one (III-78b)



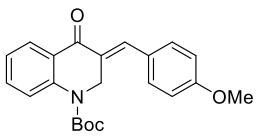
III-78b

Ketone **III-78b** (0.63 g, 1.45 mmol, 44% Yield) was synthesized according to the general procedure 6 from **S2** (1g, 3.32 mmol); column chromatography eluting with cyclohexane/EA 10:1 to 3:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.95 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.92 (s, 1H), 7.83 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.75 (td, *J* = 7.5, 1.3 Hz, 1H),

7.67 – 7.62 (m, 2H), 7.38 (td, *J* = 7.6, 1.1 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.15 – 7.12 (m, 2H), 7.11 – 7.08 (m, 2H), 4.90 (d, *J* = 2.0 Hz, 2H), 2.36 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 181.8, 148.2, 145.0, 141.7, 134.7, 134.7, 134.2, 133.9, 131.6, 130.9, 130.5, 130.1, 129.9 (2C), 128.8, 128.7, 127.4 (2C), 127.3, 127.0, 125.9, 48.3, 21.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{19}N_2O_5S$ m/z 435.1009, found 435.1008.

Tert-butyl (_E_)-3-(4-methoxybenzylidene)-4-oxo-3,4-dihydroquinoline-1(_2H_)-carboxylate (III-78c)

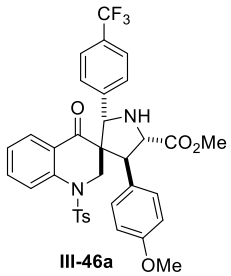


III-78c

Ketone **III-78c** (0.42 g, 1.15 mmol, 28% Yield) was synthesized according to the general procedure 6 from **S2** (1g, 4.04 mmol); column chromatography eluting with cyclohexane/EA 10:1 to 4:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.80 (d, *J* = 1.8 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.50 (ddd, *J* = 8.5, 7.2, 1.7 Hz, 1H), 7.48 – 7.45 (m, 2H), 7.21 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 6.99 – 6.95 (m, 2H), 5.06 (d, *J* = 1.7 Hz, 2H), 3.86 (s, 3H), 1.44 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 184.7, 160.8, 152.8, 143.2, 137.1, 133.4, 132.1 (2C), 130.2, 128.2, 127.4, 127.2, 124.6, 124.2, 114.4 (2C), 82.1, 55.5, 45.9, 28.3 (3C). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{22}H_{24}NO_4$ m/z 366.1700, found 366.1700.

(±)-Methyl (2_S_,3_R_,4_S_,5_S_)-4-(4-methoxyphenyl)-4'-oxo-1'-tosyl-2-(4-(trifluoromethyl)phenyl)-1',4'-dihydro-2'_H_-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46a)

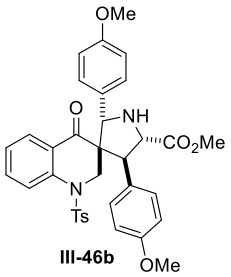


III-46a

PQ **III-46a** (65 mg, 0.1 mmol, 98% Yield, d.r. 12:1) was synthesized according to the general procedure 7; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 2H), 7.52 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.39 (m, 3H), 7.29 (m, 6H), 7.23 (ddd, *J* = 8.8, 7.2, 1.8 Hz, 1H), 6.90 – 6.86 (m, 2H), 6.83 (dd, *J* = 8.0, 7.1 Hz, 1H), 5.05 (s, 1H), 4.66 (d, *J* = 10.0 Hz, 1H), 4.53 – 4.47 (m, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.05 (d, *J* = 12.8 Hz, 1H), 2.38 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 192.6, 172.9, 159.2, 144.9, 142.7, 141.5, 136.0, 134.7, 130.3 (2C), 130.0 (q, *J*CF = 32.8 Hz), 130.0 (2C), 128.9, 128.7 (2C), 127.2, 126.9 (2C), 124.0 (q, *J*CF = 272.2 Hz), 124.8 (q, *J*CF = 3.8 Hz, 2C), 123.1, 122.7, 117.5, 114.3 (2C), 68.0, 63.1, 60.3, 55.4, 53.4, 52.7, 51.2, 21.7. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -62.7 (s, 3F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{35}H_{32}N_2O_6F_3S$ m/z 665.1928, found 665.1928.

(±)-Methyl (2*S*,3*R*,4*S*,5*S*)-2,4-bis(4-methoxyphenyl)-4'-oxo-1'-tosyl-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46b)

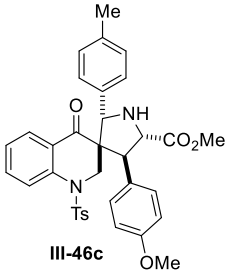


III-46b

PQ **III-46b** (31 mg, 0.05 mmol, 50% Yield, d.r. >20:1) was synthesized according to the general procedure 7; column chromatography eluting with cyclohexane/EA 5:1 to 1:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 2H), 7.56 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.30 – 7.24 (m, 4H), 7.20 (ddd, *J* = 8.8, 7.2, 1.8 Hz, 1H), 7.17 – 7.14 (m, 2H), 6.89 – 6.84 (m, 2H), 6.82 (dd, *J* = 8.0, 7.2 Hz, 1H), 6.59 – 6.55 (m, 2H), 4.95 (s, 1H), 4.61 (d, *J* = 9.9 Hz, 1H), 4.50 – 4.41 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 3.01 (d, *J* = 12.7 Hz, 1H), 2.37 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 193.3, 172.9, 159.3, 159.1, 144.7, 141.6, 136.2, 134.3, 130.2 (2C), 130.0 (2C), 129.4 (2C), 128.8, 127.7, 126.9 (2C), 122.9, 122.9, 117.5, 114.2 (2C), 113.4 (2C), 68.7, 63.1, 60.0, 55.4, 55.3, 53.7, 52.6, 52.0, 21.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{35}H_{35}N_2O_7S$ m/z 627.2160, found 627.2158.

(±)-Methyl (2*S*,3*R*,4*S*,5*S*)-4-(4-methoxyphenyl)-4'-oxo-2-(*p*-tolyl)-1'-tosyl-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46c)



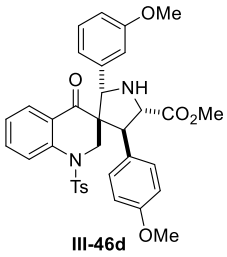
III-46c

PQ **III-46c** (52 mg, 0.09 mmol, 85% Yield, d.r. >20:1) was synthesized according to the general procedure 7; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.62 – 7.60 (m, 2H), 7.54 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.26 – 7.24 (m, 2H), 7.21 (ddd, *J* = 8.7, 7.2, 1.8 Hz, 1H), 7.11 – 7.08 (m, 2H), 6.89 – 6.86 (m, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.81 (dd, *J* = 8.0, 7.2 Hz, 1H), 4.95 (s, 1H), 4.61 (d, *J* = 10.0 Hz, 1H), 4.50 – 4.43 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.03 (d, *J* = 12.7 Hz, 1H), 2.37 (s, 3H), 2.14 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 193.2, 173.0, 159.2, 144.7, 141.6, 137.7, 136.2, 134.3, 130.2 (2C), 130.0 (2C), 128.9, 128.7 (2C), 128.1 (2C), 127.7, 126.9 (2C), 123.0, 122.8, 117.5, 114.2 (2C), 68.9, 63.2, 60.3, 55.4, 53.6, 52.6, 52.1, 21.7, 21.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{35}H_{35}N_2O_6S$ m/z 611.2210, found 611.2208.

(±)-Methyl (2*S*,3*R*,4*S*,5*S*)-2-(3-methoxyphenyl)-4-(4-methoxyphenyl)-4'-oxo-1'-tosyl-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46d)

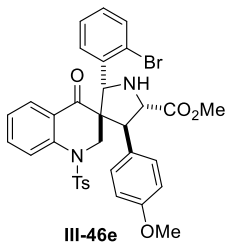
PQ **III-46d** (47 mg, 0.07 mmol, 74% Yield, d.r. >20:1) was synthesized according to the general procedure 7; column chromatography eluting with cyclohexane/EA 5:1 to 1:1.



III-46d

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.5 Hz, 2H), 7.56 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 1H), 7.30 – 7.25 (m, 4H), 7.21 (ddd, *J* = 8.8, 7.2, 1.8 Hz, 1H), 6.96 (t, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.84 – 6.77 (m, 3H), 6.59 – 6.53 (m, 1H), 4.96 (s, 1H), 4.64 (d, *J* = 10.2 Hz, 1H), 4.50 (d, *J* = 12.7 Hz, 1H), 4.45 (d, *J* = 10.2 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.62 (s, 3H), 3.04 (d, *J* = 12.7 Hz, 1H), 2.37 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 192.8, 173.1, 159.1, 159.1, 144.7, 141.6, 140.2, 136.3, 134.2, 130.2 (2C), 130.0 (2C), 129.0, 128.9, 127.6, 126.9 (2C), 123.0, 122.9, 120.2, 117.4, 115.0, 114.2 (2C), 112.8, 69.1, 63.1, 60.5, 55.4, 55.2, 53.6, 52.6, 51.8, 21.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{35}H_{35}N_2O_7S$ m/z 627.2160, found 627.2151.

(±)-Methyl (2*R*,3*R*,4*S*,5*S*)-2-(2-bromophenyl)-4-(4-methoxyphenyl)-4'-oxo-1'-tosyl-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46e)



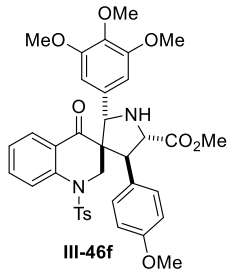
III-46e

PQ **III-46e** (67 mg, 0.1 mmol, 99% Yield, d.r. 14:1) was synthesized according to the general procedure 7; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.57 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.34 – 7.21 (m, 7H), 6.98 (td, *J* = 7.6, 1.7 Hz, 1H), 6.91 – 6.86 (m, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.65 (s, 1H), 4.76 (d, *J* = 11.3 Hz, 1H), 4.60 (dd, *J* = 12.0, 6.2 Hz, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 3.18 (d, *J* = 12.7 Hz, 1H), 2.38 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 191.5, 173.6, 159.1, 144.7, 142.5, 139.8, 136.0, 134.5, 132.5, 130.9, 130.2 (2C), 130.2 (2C), 129.1, 128.6, 127.0 (2C), 126.3, 123.8, 123.7, 123.0, 118.0, 114.0 (2C), 64.8, 61.9, 55.3, 52.6, 52.1, 50.7, 21.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{34}H_{32}N_2O_6BrS$ m/z 675.1160, found 675.1161.

(±)-Methyl (2*S*,3*R*,4*S*,5*S*)-4-(4-methoxyphenyl)-4'-oxo-1'-tosyl-2-(3,4,5-trimethoxyphenyl)-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46f)

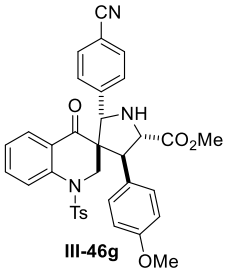
PQ **III-46f** (42 mg, 0.06 mmol, 62% Yield, d.r. >20:1) was synthesized according to the general procedure 7; column chromatography eluting with cyclohexane/EA 5:1 to 1:1.



III-46f

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 3H), 7.42 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.30 – 7.24 (m, 4H), 7.21 (ddd, *J* = 8.8, 7.2, 1.8 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.84 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H), 6.53 (s, 2H), 4.91 (s, 1H), 4.67 (d, *J* = 10.1 Hz, 1H), 4.48 (d, *J* = 12.7 Hz, 1H), 4.43 (d, *J* = 10.1 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.71 (s, 6H), 3.66 (s, 3H), 2.98 (d, *J* = 12.7 Hz, 1H), 2.38 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 193.0, 173.1, 159.1, 152.6 (2C), 144.8, 141.6, 137.3, 136.1, 134.1, 130.2 (2C), 129.9 (2C), 128.8, 127.6, 126.8 (2C), 123.0, 122.9, 117.3, 114.2 (2C), 105.4 (2C), 69.5, 63.0, 60.8, 59.9, 56.0 (2C), 55.4, 53.8, 52.5, 51.4, 21.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{37}H_{39}N_2O_9S$ m/z 687.2371, found 687.2374.

(±)-Methyl (2*S*,3*R*,4*S*,5*S*)-2-(4-cyanophenyl)-4-(4-methoxyphenyl)-4'-oxo-1'-tosyl-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46g)

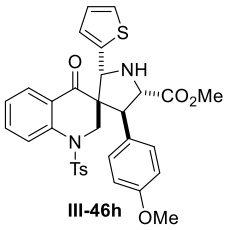


III-46g

PQ **III-46g** (54 mg, 0.09 mmol, 86% Yield, d.r. 13:1) was synthesized according to the general procedure 7; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.55 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.31 – 7.23 (m, 5H), 6.90 – 6.84 (m, 3H), 5.06 (s, 1H), 4.67 (d, *J* = 10.3 Hz, 1H), 4.57 – 4.46 (m, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.10 (d, *J* = 12.8 Hz, 1H), 2.40 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 192.2, 173.0, 159.2, 145.0, 145.0, 141.5, 136.2, 134.7, 131.6 (2C), 130.3 (2C), 130.0 (2C), 129.1 (2C), 128.9, 126.9, 126.8 (2C), 123.3, 122.8, 118.9, 117.7, 114.2 (2C), 111.5, 67.6, 62.9, 60.7, 55.4, 53.3, 52.6, 50.8, 21.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{35}H_{32}N_3O_6S$ m/z 622.2006, found 622.1992.

(±)-Methyl (2*R*,3*R*,4*S*,5*S*)-4-(4-methoxyphenyl)-4'-oxo-2-(thiophen-2-yl)-1'-tosyl-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46h)



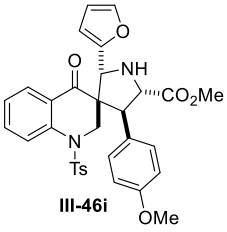
III-46h

PQ **III-46h** (49 mg, 0.08 mmol, 82% Yield, d.r. >20:1) was synthesized according to the general procedure 7; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.33 – 7.22 (m, 5H), 7.03 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.91 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.78 (dd, *J* = 3.5, 1.2 Hz, 1H), 6.66 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.29 (s, 1H), 4.70 (d, *J* = 10.4 Hz, 1H), 4.52 (d, *J* = 12.8 Hz,

1H), 4.44 (d, *J* = 10.4 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.10 (d, *J* = 12.8 Hz, 1H), 2.39 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 192.4, 172.6, 159.1, 144.8, 142.8, 141.7, 136.2, 134.4, 130.2 (2C), 130.0 (2C), 129.0, 127.3, 126.9 (2C), 126.4, 126.4, 125.3, 123.1, 123.0, 117.7, 114.1 (2C), 63.8, 62.6, 60.1, 55.4, 53.2, 52.6, 50.9, 21.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{32}H_{31}N_2O_6S_2$ m/z 603.1618, found 603.1602.

(±)-Methyl (2*R*,3*R*,4*S*,5*S*)-2-(furan-2-yl)-4-(4-methoxyphenyl)-4'-oxo-1'-tosyl-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46i)

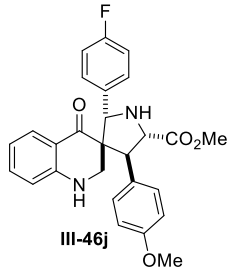


III-46i

PQ **III-46i** (41 mg, 0.07 mmol, 70% Yield, d.r. >20:1) was synthesized according to the general procedure 7; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.32 – 7.23 (m, 5H), 7.08 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.94 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.25 (d, *J* = 3.3 Hz, 1H), 6.03 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.00 (s, 1H), 4.58 (d, *J* = 9.5 Hz, 1H), 4.43 (d, *J* = 12.9 Hz, 1H), 4.34 (d, *J* = 9.4 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.08 (d, *J* = 12.9 Hz, 1H), 2.39 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 192.7, 172.9, 159.1, 150.4, 144.7, 142.2, 141.8, 136.5, 134.4, 130.2 (2C), 129.9 (2C), 128.8, 127.9, 126.8 (2C), 123.0, 122.6, 117.7, 114.2 (2C), 110.2, 109.5, 63.8, 63.2, 59.4, 55.4, 53.1, 52.6, 52.2, 21.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{32}H_{31}N_2O_7S$ m/z 587.1847, found 587.1828.

(±)-Methyl (2*S*,3*R*,4*S*,5*S*)-2-(4-fluorophenyl)-4-(4-methoxyphenyl)-4'-oxo-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46j)



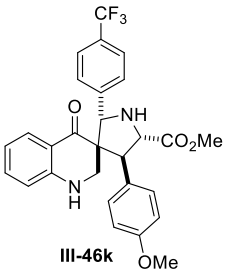
III-46j

PQ **III-46j** (28 mg, 0.06 mmol, 60% Yield) was synthesized according to the general procedure 8; column chromatography eluting with cyclohexane/acetone 5:1 to 1:1.

^{1}H NMR (700 MHz,CD_2Cl_2) δ 7.32 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.17-7.14 (m, 2H), 7.11 (ddd, *J* = 8.3, 7.1, 1.6 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.72-6.68 (m, 2H), 6.49 (t, *J* = 6.9 Hz, 1H), 6.44 (dd, *J* = 8.3, 1.2 Hz, 1H), 4.76 (s, 1H), 4.50 (d, *J* = 9.5 Hz, 1H), 4.27 (d, *J* = 9.5 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.24 – 3.15 (m, 1H), 3.01 (dd, *J* = 12.4, 6.7 Hz, 1H). **^{13}C NMR (176 MHz, CD_2Cl_2)** δ 193.4, 174.0, 162.4 (d, *J*CF = 244.6 Hz), 159.3, 150.7, 136.1 (d, *J*CF = 1.8 Hz), 135.0, 130.3 (2C), 130.1 (d, *J*CF = 8.8 Hz, 2C), 129.2, 127.9, 119.9, 117.9, 115.4, 114.3

(d, *J*CF = 21.1 Hz, 2C), 114.1 (2C), 68.8, 63.9, 60.2, 55.6, 52.6, 51.5, 49.8. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -115.0 (ddd, *J* = 14.2, 8.9, 5.4 Hz, 1F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{26}N_2O_4F$ m/z 461.1871, found 461.1859.

(±)-Methyl (2*S*,3*R*,4*S*,5*S*)-4-(4-methoxyphenyl)-4'-oxo-2-(4-(trifluoromethyl)phenyl)-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46k)

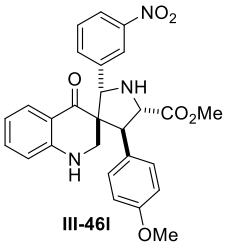


III-46k

PQ **III-46k** (25 mg, 0.05 mmol, 48% Yield) was synthesized according to the general procedure 8; column chromatography eluting with cyclohexane/acetone 5:1 to 1:1.

^{1}H NMR (700 MHz, CD_2Cl_2) δ 7.31 (d, *J* = 8.1 Hz, 2H), 7.30 – 7.25 (m, 3H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.11 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.48 (t, *J* = 7.5 Hz, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 4.85 (s, 1H), 4.53 (d, *J* = 9.5 Hz, 1H), 4.32 (d, *J* = 9.6 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.23 (dd, *J* = 12.4, 3.9 Hz, 1H), 3.04 (d, *J* = 12.4 Hz, 1H). **^{13}C NMR (176 MHz, CD_2Cl_2)** δ 193.0, 173.9, 159.4, 150.6, 144.8, 135.1, 130.3 (2C), 129.5 (q, *J*CF = 31.7 Hz), 129.0, 128.9 (2C), 128.0, 124.6 (q, *J*CF = 271.0 Hz), 124.5 (q, *J*CF = 3.5 Hz, 2C), 119.9, 118.1, 115.4, 114.1 (2C), 68.7, 63.9, 60.6, 55.6, 52.6, 51.1, 49.6. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -62.7 (s, 3F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{28}H_{26}N_2O_4F_3$ m/z 511.1839, found 511.1824.

(±)-Methyl (2*S*,3*R*,4*S*,5*S*)-4-(4-methoxyphenyl)-2-(3-nitrophenyl)-4'-oxo-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46l)

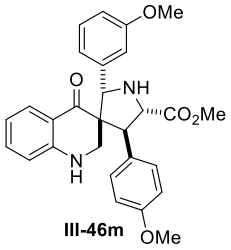


III-46l

PQ **III-46l** (21 mg, 0.04 mmol, 44% Yield) was synthesized according to the general procedure 8; column chromatography eluting with cyclohexane/acetone 5:1 to 1:1.

^{1}H NMR (700 MHz, CD_2Cl_2) δ 8.09 (s, 1H), 7.84 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.18 (m, 3H), 7.12 – 7.08 (m, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.49 – 6.44 (m, 2H), 4.91 (s, 1H), 4.56 (d, *J* = 9.5 Hz, 1H), 4.36 (d, *J* = 9.6 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.24 (d, *J* = 12.5 Hz, 1H), 3.04 (d, *J* = 12.4 Hz, 1H). **^{13}C NMR (176 MHz, CD_2Cl_2)** δ 192.8, 173.8, 159.4, 150.6, 147.7, 143.0, 135.3, 134.4, 130.3 (2C), 128.7, 128.6, 127.9, 123.8, 122.6, 119.9, 118.3, 115.5, 114.2 (2C), 68.1, 63.8, 60.4, 52.6, 50.9, 50.6, 49.6. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{26}N_3O_6$ m/z 488.1816, found 488.1807.

(±)-Methyl (2*S*,3*R*,4*S*,5*S*)-2-(3-methoxyphenyl)-4-(4-methoxyphenyl)-4'-oxo-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46m)

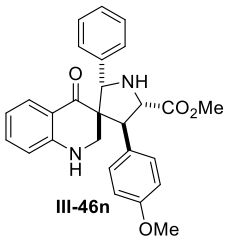


III-46m

PQ **III-46m** (19 mg, 0.04 mmol, 40% Yield) was synthesized according to the general procedure 8; column chromatography eluting with cyclohexane/acetone 5:1 to 1:1.

^{1}H NMR (700 MHz, CD_2Cl_2) δ 7.33 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.12 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 6.95 (t, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 7.7 Hz, 1H), 6.71 – 6.68 (m, 1H), 6.57 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.53 – 6.49 (m, 2H), 4.79 (s, 1H), 4.50 (d, *J* = 9.9 Hz, 1H), 4.30 (d, *J* = 10.0 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.58 (s, 3H), 3.26 (dd, *J* = 12.3, 3.9 Hz, 1H), 3.05 (d, *J* = 12.3 Hz, 1H). **^{13}C NMR (176 MHz, CD_2Cl_2)** δ 193.1, 174.1, 159.3, 159.3, 150.8, 142.3, 134.8, 130.4 (2C), 129.0, 128.7, 128.0, 120.6, 120.2, 117.8, 115.4, 114.0 (2C), 113.8, 113.7, 68.8, 63.7, 60.8, 55.6, 55.4, 52.5, 51.4, 49.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{28}H_{29}N_2O_5$ m/z 473.2071, found 473.2061.

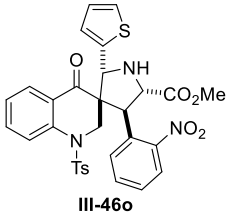
(±)-Methyl (2*S*,3*R*,4*S*,5*S*)-4-(4-methoxyphenyl)-4'-oxo-2-phenyl-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46n)



III-46n

PQ **III-46n** (24 mg, 0.05 mmol, 54% Yield) was synthesized according to the general procedure 8; column chromatography eluting with cyclohexane/acetone 5:1 to 1:1.

^{1}H NMR (700 MHz, CD_2Cl_2) δ 7.29 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.18 – 7.13 (m, 2H), 7.08 (ddd, *J* = 8.4, 7.0, 1.6 Hz, 1H), 7.03-7.00 (m, 3H), 6.84 (d, *J* = 8.7 Hz, 2H),, 6.51 – 6.39 (m, 2H), 4.77 (s, 1H), 4.50 (d, *J* = 9.6 Hz, 1H), 4.45 (d, *J* = 3.8 Hz, 1H), 4.28 (d, *J* = 9.6 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.27 – 3.19 (m, 1H), 3.03 (d, *J* = 12.4 Hz, 1H). **^{13}C NMR (176 MHz, CD_2Cl_2)** δ 193.4, 174.0, 159.3, 150.8, 140.2, 134.8, 130.3 (2C), 129.3, 128.4 (2C), 127.9, 127.7 (2C), 120.0, 117.7, 115.3, 114.0 (2C), 69.6, 64.0, 60.6, 55.6, 52.6, 51.8, 49.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{27}N_2O_4$ m/z 443.1965, found 443.1950.



III-46o

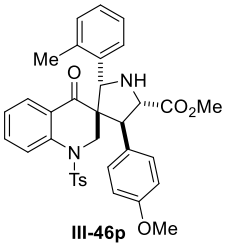
(±)-Methyl (2*R*,3*R*,4*S*,5*S*)-4-(2-nitrophenyl)-4'-oxo-2-(thiophen-2-yl)-1'-tosyl-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46o)

PQ **III-46o** (16 mg, 0.03 mmol, 51% Yield) was synthesized as a single

diastereoisomer according to the general procedure 7 from **9b** (22 mg, 0.05 mmol); column chromatography eluting with cyclohexane/EA 5:1 to 1:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.0 Hz, 1H), 7.87 – 7.79 (m, 3H), 7.56 – 7.52 (m, 1H), 7.48 (d, *J* = 8.4 Hz, 2H),, 7.38 (d, *J* = 8.6 Hz, 1H), 7.25-7.20 (m, 3H), 7.12 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.01 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.94 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H), 6.71 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.30 (s, 1H), 4.88 (d, *J* = 6.1 Hz, 1H), 4.32 (d, *J* = 6.1 Hz, 1H), 4.26 (d, *J* = 12.5 Hz, 1H), 3.83 (s, 3H), 3.46 (d, *J* = 12.5 Hz, 1H), 2.36 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 193.9, 172.1, 151.0, 144.7, 141.9, 136.0, 134.7, 133.5, 132.7, 130.3, 130.2 (2C), 129.2, 129.0, 128.4, 127.0, 126.7 (2C), 126.5, 125.8, 124.8, 123.2, 122.7, 117.5, 67.5, 66.4, 59.3, 53.1, 52.8, 48.6, 21.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{31}H_{28}N_3O_7S_2$ m/z 618.1363, found 618.1361.

(±)-Methyl (2*S*,3*R*,4*S*,5*S*)-4-(4-methoxyphenyl)-4'-oxo-2-(*o*-tolyl)-1'-tosyl-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46p)

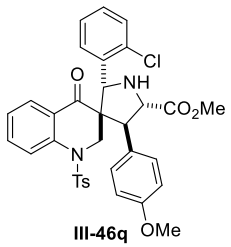


III-46p

PQ **III-46p** (55 mg, 0.09 mmol, 91% Yield, d.r. 7:1) was synthesized according to the general procedure 7; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.7 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.47 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.25 – 7.18 (m, 3H), 7.07 – 7.03 (m, 1H), 6.93 (td, *J* = 7.5, 1.4 Hz, 1H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.82 – 6.78 (m, 2H), 5.28 (s, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.54 – 4.45 (m, 2H), 3.79 (s, 3H), 3.71 (s, 3H), 2.92 (d, *J* = 12.5 Hz, 1H), 2.34 (d, *J* = 2.7 Hz, 3H), 2.20 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 192.7, 173.1, 159.1, 144.9, 141.3, 137.4, 136.5, 134.9, 134.3, 130.3, 130.1 (2C), 130.0 (2C), 128.8, 128.2, 127.5, 127.1 (2C), 126.0, 123.2, 123.0, 117.4, 114.1 (2C), 63.4, 62.7, 61.3, 55.4, 53.3, 52.6, 52.5, 21.6, 19.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{35}H_{35}N_2O_6S$ m/z 611.2210, found 611.2196.

(±)-Methyl (2*R*,3*R*,4*S*,5*S*)-2-(2-chlorophenyl)-4-(4-methoxyphenyl)-4'-oxo-1'-tosyl-1',4'-dihydro-2'*H*-spiro[pyrrolidine-3,3'-quinoline]-5-carboxylate (III-46q)

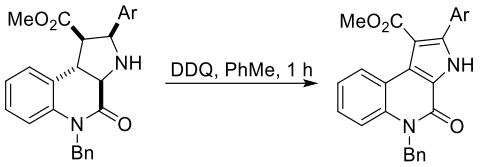


III-46q

PQ **III-46q** (52 mg, 0.08 mmol, 82% Yield, d.r. >20:1) was synthesized according to the general procedure 7; column chromatography eluting with cyclohexane/EA 5:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.61-7.56 (m, 2H), 7.32 – 7.22 (m, 6H), 7.08 – 7.01 (m, 2H), 6.91 – 6.86 (m, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.68 (s, 1H), 4.74 (d, J = 11.3 Hz, 1H), 4.61 (dd, J = 12.0, 10.2 Hz, 2H), 3.77 (s, 3H), 3.73 (s, 3H), 3.22 (d, J = 12.7 Hz, 1H), 2.39 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 191.6, 173.6, 159.1, 144.7, 142.4, 136.2, 134.5, 133.3, 130.6, 130.2 (2C), 130.2 (2C), 129.1, 128.8, 128.6, 127.0 (2C), 126.9, 126.3, 123.6, 123.0, 117.9, 114.0 (2C), 62.2, 62.0, 61.9, 55.3, 52.6, 52.1, 50.7, 21.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{34}H_{32}N_2O_6ClS$ m/z 631.1664, found 631.1662.

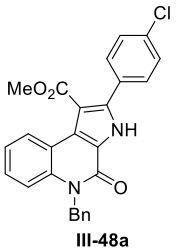
7.2.1.5 Synthesis of III-48



III-43 **III-48**

PQ **III-43** (0.05 mmol, 1.0 equiv.) was dissolved in toluene (0.5 mL) and DDQ (0.2 mmol, 4.0 equiv.) was added. The reaction was stirred for 1 h. Sat. $NaHCO_3$ solution (10 mL) was then added to quench the reaction and the mixture was extracted with DCM (3*10 mL). The combined organic phases were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the PQs **III-48** were purified by column chromatography using DCM/MeOH mixtures.

Methyl 5-benzyl-2-(4-chlorophenyl)-4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-48a)

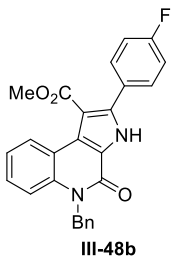


III-48a

PQ **III-48a** (21 mg, 48 µmol, 96% Yield) was synthesized according to the general procedure 10; column chromatography eluting with cyclohexane/EA 1:1 then DCM/MeOH 20:1.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 13.30 (s, 1H), 8.52 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.62 – 7.54 (m, 4H), 7.45 – 7.35 (m, 2H), 7.31 (dd, *J* = 8.3, 6.6 Hz, 2H), 7.27 – 7.18 (m, 4H), 5.68 (s, 2H), 3.72 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 166.4, 154.6, 141.5, 137.1, 136.0, 133.7, 130.9 (2C), 129.8, 128.7 (2C), 128.3 (2C), 127.7, 127.1, 126.4 (2C), 125.1, 124.6, 123.0, 122.2, 117.4, 116.3, 108.7, 51.9, 44.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_3Cl$ m/z 443.1157, found 443.1171.

Methyl 5-benzyl-2-(4-fluorophenyl)-4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-48b)

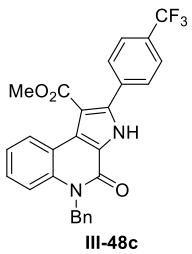


III-48b

PQ **III-48b** (18 mg, 41 µmol, 83% Yield) was synthesized according to the general procedure 10; column chromatography eluting with cyclohexane/EA 1:1 then DCM/MeOH 20:1.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 13.24 (s, 1H), 8.53 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.43 (dd, *J* = 8.7, 1.3 Hz, 1H), 7.41 – 7.28 (m, 5H), 7.28 – 7.19 (m, 4H), 5.68 (s, 2H), 3.71 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 166.4, 162.4 (d, *J*CF = 247.0 Hz), 154.6, 141.8, 137.2, 136.0, 131.4 (d, *J*CF = 8.8 Hz, 2C), 128.7 (2C), 127.6, 127.5, 127.4, 127.0, 126.4 (2C), 125.1, 124.6, 122.8, 122.1, 117.5, 116.3, 115.2 (d, *J*CF = 21.4 Hz, 2C), 108.5, 51.8, 44.5. **^{19}F NMR (470 MHz, DMSO-*d6*)** δ -112.6 (ddd, *J* = 14.3, 8.9, 5.3 Hz, 1F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_3F$ m/z 427.1453, found 427.1452.

Methyl 5-benzyl-4-oxo-2-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-48c)

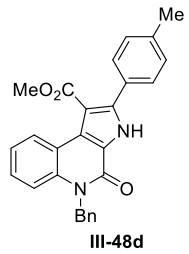


III-48c

PQ **III-48c** (18 mg, 37 µmol, 74% Yield) was synthesized according to the general procedure 10; column chromatography eluting with cyclohexane/EA 1:1 then DCM/MeOH 20:1.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 13.44 (s, 1H), 8.54 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.92 – 7.73 (m, 4H), 7.49 – 7.36 (m, 2H), 7.34 – 7.19 (m, 6H), 5.69 (s, 2H), 3.72 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 166.2, 154.6, 140.9, 137.1, 136.0, 135.0, 130.0 (2C), 128.9 (q, *J*CF = 31.5 Hz), 128.7 (2C), 127.8, 127.1, 126.4 (2C), 125.1 (2C), 124.6, 124.2 (q, *J*CF = 272.2 Hz), 123.4, 122.2, 117.4, 116.4, 109.3, 51.9, 44.5. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -62.3 (s, 3F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{20}F_3N_2O_3$ m/z 477.1421, found 477.1417.

Methyl 5-benzyl-4-oxo-2-(*p*-tolyl)-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-48d)

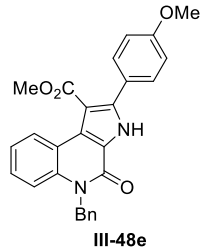


III-48d

PQ **III-48d** (10 mg, 24 µmol, 56% Yield) was synthesized according to the general procedure 10 from **III-43d** (18 mg, 42 µmol); column chromatography eluting with cyclohexane/EA 1:1 then DCM/MeOH 20:1.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 13.13 (s, 1H), 8.43 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.42 (dd, *J* = 8.7, 1.3 Hz, 1H), 7.37 (ddd, *J* = 8.6, 7.0, 1.5 Hz, 1H), 7.33 – 7.28 (m, 4H), 7.27 – 7.19 (m, 4H), 5.68 (s, 2H), 3.72 (s, 3H), 2.38 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 166.9, 154.6, 142.5, 138.4, 137.2, 135.9, 128.9 (2C), 128.8 (2C), 128.7 (2C), 128.0, 127.6, 127.0, 126.4 (2C), 124.8, 124.6, 122.6, 122.1, 117.5, 116.3, 108.2, 51.8, 44.4, 21.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_3$ m/z 423.1703, found 423.1703.

Methyl 5-benzyl-2-(4-methoxyphenyl)-4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-48e)

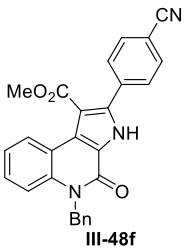


III-48e

PQ **III-48e** (13 mg, 30 µmol, 60% Yield) was synthesized according to the general procedure 10; column chromatography eluting with cyclohexane/EA 1:1 then DCM/MeOH 20:1.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 13.07 (s, 1H), 8.44 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.42 (dd, *J* = 8.7, 1.3 Hz, 1H), 7.37 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.33-7.28 (m, 2H), 7.27 – 7.19 (m, 4H), 7.08 – 7.03 (m, 2H), 5.68 (s, 2H), 3.83 (s, 3H), 3.73 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 166.9, 159.8, 154.5, 142.5, 137.2, 135.9, 130.3 (2C), 128.7 (2C), 127.5, 127.0, 126.4 (2C), 124.8, 124.6, 123.1, 122.4, 122.1, 117.5, 116.3, 113.7 (2C), 107.9, 55.3, 51.8, 44.4. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_4$ m/z 439.1652, found 439.1651.

Methyl 5-benzyl-2-(4-cyanophenyl)-4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-48f)

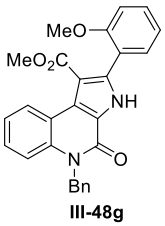


III-48f

PQ **III-48f** (16 mg, 38 µmol, 75% Yield) was synthesized according to the general procedure 10; column chromatography eluting with cyclohexane/EA 1:1 then DCM/MeOH 20:1.

^{1}H NMR (600 MHz, DMSO-*d6*) δ 13.45 (s, 1H), 8.55 (dd, J = 8.0, 1.5 Hz, 1H), 8.12 – 7.89 (m, 2H), 7.89 – 7.68 (m, 2H), 7.47 – 7.37 (m, 2H), 7.34 – 7.19 (m, 6H), 5.69 (s, 2H), 3.72 (s, 3H). **^{13}C NMR (151 MHz, DMSO-*d6*)** δ 166.0, 154.6, 140.7, 137.0, 136.0, 135.5, 132.0 (2C), 130.0 (2C), 128.7 (2C), 127.8, 127.0, 126.4 (2C), 125.1, 124.6, 123.5, 122.2, 118.6, 117.3, 116.3, 111.2, 109.4, 51.9, 44.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{20}N_3O_3$ m/z 434.1499, found 434.1497.

Methyl 5-benzyl-2-(2-methoxyphenyl)-4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-48g)

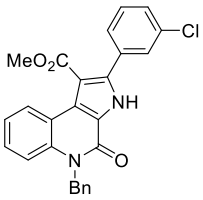


III-48g

PQ **III-48g** (22 mg, 49 µmol, 98% Yield) was synthesized according to the general procedure 10; column chromatography eluting with cyclohexane/EA 1:1 then DCM/MeOH 20:1.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 13.03 (s, 1H), 8.70 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.47 – 7.40 (m, 3H), 7.37 (ddd, *J* = 8.6, 7.0, 1.6 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.26 – 7.18 (m, 4H), 7.13 – 7.09 (m, 1H), 7.06 (td, *J* = 7.5, 1.0 Hz, 1H), 5.68 (s, 2H), 3.75 (s, 3H), 3.59 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 166.2, 156.5, 154.5, 139.9, 137.2, 135.9, 130.9, 130.4, 128.7 (2C), 127.4, 127.0, 126.4 (2C), 125.4, 124.4, 122.5, 121.9, 120.5, 120.1, 117.7, 116.2, 110.9, 110.1, 55.4, 51.3, 44.4. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_4$ m/z 439.1652, found 439.1651.

Methyl 5-benzyl-2-(3-chlorophenyl)-4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-48h)

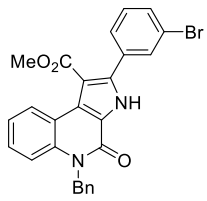


III-48h

PQ **III-48h** (20 mg, 45 µmol, 90% Yield) was synthesized according to the general procedure 10; column chromatography eluting with cyclohexane/EA 1:1 then DCM/MeOH 20:1.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 13.34 (s, 1H), 8.52 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.69-7.68 (m, 1H), 7.55-7.51 (m, 3H), 7.45 – 7.36 (m, 2H), 7.33 – 7.28 (m, 2H), 7.28 – 7.19 (m, 4H), 5.68 (s, 2H), 3.72 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 166.2, 154.6, 141.0, 137.1, 136.0, 132.9, 132.8, 130.0, 128.8, 128.7 (2C), 127.9, 127.7, 127.0, 126.4 (2C), 125.1, 124.6, 123.1, 122.2, 117.4, 116.3, 108.9, 51.8, 44.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_3Cl$ m/z 443.1157, found 443.1155.

Methyl 5-benzyl-2-(3-bromophenyl)-4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-48i)



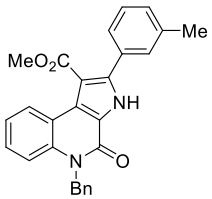
III-48i

PQ **III-48i** (20 mg, 42 µmol, 83% Yield) was synthesized according to the general procedure 10; column chromatography eluting with cyclohexane/EA 1:1 then DCM/MeOH 20:1.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 13.32 (s, 1H), 8.52 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.82 (t, *J* = 1.9 Hz, 1H), 7.67 (ddd, *J* = 8.0, 2.1, 1.0 Hz, 1H), 7.56 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.39 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.31-7.29 (m, 2H), 7.28 – 7.18 (m, 4H), 5.68 (s, 2H), 3.73 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 166.2, 154.5, 140.8, 137.1, 136.0, 133.1, 131.6, 131.6, 130.2, 128.7 (2C), 128.2, 127.7, 127.0,

126.4 (2C), 125.0, 124.5, 123.1, 122.2, 121.3, 117.4, 116.3, 108.9, 51.8, 44.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_3Br$ m/z 487.0652, found 487.0648.

Methyl 5-benzyl-4-oxo-2-(*m*-tolyl)-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-48j)

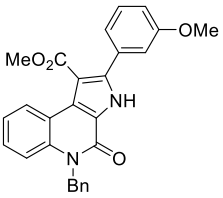


III-48j

PQ **III-48j** (16 mg, 38 µmol, 76% Yield) was synthesized according to the general procedure 10; column chromatography eluting with cyclohexane/EA 1:1 then DCM/MeOH 20:1.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 13.14 (s, 1H), 8.44 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.46 – 7.11 (m, 12H), 5.68 (s, 2H), 3.72 (s, 3H), 2.39 (s, 3H). **^{13}C NMR (101 MHz, DMSO-*d6*)** δ 166.8, 154.5, 142.5, 137.4, 137.2, 135.9, 130.7, 129.5, 128.7 (2C), 128.1, 127.5, 127.0, 126.4 (2C), 126.0, 124.8, 124.5, 122.6, 122.1, 117.4, 116.3, 108.4, 51.8, 44.4, 21.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_3$ m/z 423.1703, found 423.1702.

Methyl 5-benzyl-2-(3-methoxyphenyl)-4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-48k)

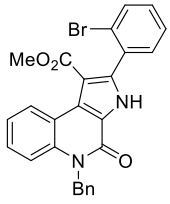


III-48k

PQ **III-48k** (20 mg, 45 µmol, 89% Yield) was synthesized according to the general procedure 10; column chromatography eluting with cyclohexane/EA 1:1 then DCM/MeOH 20:1.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 13.18 (s, 1H), 8.39 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.46 – 7.35 (m, 3H), 7.34 – 7.19 (m, 7H), 7.14 – 7.09 (m, 1H), 7.02 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 5.69 (s, 2H), 3.85 (s, 3H), 3.75 (s, 3H). **^{13}C NMR (101 MHz, DMSO-*d6*)** δ 166.8, 159.0, 154.5, 141.8, 137.1, 135.9, 132.0, 129.4, 128.7 (2C), 127.5, 127.0, 126.4 (2C), 124.6, 124.4, 122.6, 122.1, 121.1, 117.4, 116.3, 115.0, 113.7, 108.6, 55.2, 51.9, 44.4. **MS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_4$ m/z 439.2, found 439.1.

Methyl 5-benzyl-2-(2-bromophenyl)-4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylate (III-48l)



III-48l

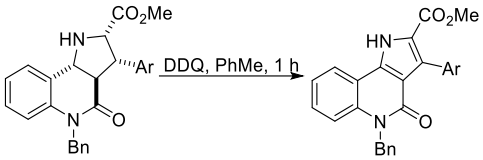
PQ **III-48l** (11 mg, 22 µmol, 90% Yield) was synthesized according to the general procedure 10 from **III-43l** (12 mg, 24 µmol); column chromatography eluting with cyclohexane/EA 1:1 then DCM/MeOH 20:1.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 13.29 (s, 1H), 9.00 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.76 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.53-7.49 (m, 2H), 7.46 – 7.38 (m, 3H),

7.32 (dd, *J* = 8.7, 6.8 Hz, 2H), 7.29 – 7.21 (m, 4H), 5.68 (s, 2H), 3.53 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 165.0, 154.5, 143.1, 137.1, 136.1, 133.7, 132.0, 132.0, 130.7, 128.7 (2C), 127.7, 127.2, 127.0, 126.4 (2C), 126.2, 124.6, 123.3, 122.9, 122.0, 117.7, 116.1, 109.8, 51.3, 44.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_3Br$ m/z 487.0652, found 487.0647.

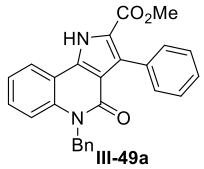
7.2.1.6 Synthesis of III-49

General Procedure 11



PQ **III-44** (0.05 mmol, 1.0 equiv.) was dissolved in toluene (0.5 mL) and DDQ (0.2 mmol, 4.0 equiv.) was added. The reaction was stirred for 1 h. Sat. $NaHCO_3$ solution (10 mL) was added to quench the reaction and the mixture was extracted with DCM (3*10 mL). The combined organic phases were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and PQs **III-49** were purified by column chromatography using cyclohexane/EA mixtures.

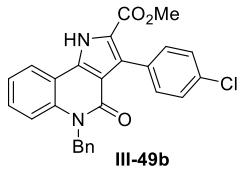
Methyl 5-benzyl-4-oxo-3-phenyl-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-49a)



PQ **III-49a** (17 mg, 41 µmol, 82%) was synthesized using the general procedure 11; column chromatography eluting with cyclohexane/EA 10:1 to 2:1.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.44 – 7.37 (m, 3H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.28 – 7.22 (m, 4H), 7.22-7.16 (m, 3H), 3.77 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 162.0, 159.6, 138.5, 137.1, 135.7, 132.6, 131.4, 130.8 (2C), 129.8, 128.8 (2C), 127.7, 127.3 (2C), 127.1, 126.6 (2C), 122.1, 121.9, 121.5, 116.6, 113.7, 113.1, 52.1, 45.6. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{21}N_2O_3$ m/z 409.1547, found 409.1546.

Methyl 5-benzyl-3-(4-chlorophenyl)-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-49b)

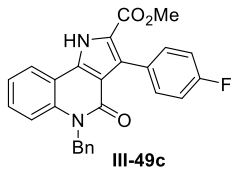


III-49b

PQ **III-49b** (20 mg, 50 µmol, quantitative yield) was synthesized using the general procedure 11; column chromatography eluting with cyclohexane/EA 10:1 to 2:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.02 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.38 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1H), 7.29 (dd, *J* = 8.7, 1.0 Hz, 1H), 7.27 – 7.22 (m, 4H), 7.22 – 7.15 (m, 4H), 5.56 (s, 2H), 3.69 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.9, 159.8, 138.4, 137.0, 136.1, 133.6, 132.2 (2C), 131.2, 130.0, 129.8, 128.8 (2C), 127.4 (2C), 127.2, 126.6 (2C), 122.2, 122.1, 122.1, 116.5, 113.4, 113.2, 52.1, 45.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_3Cl$ m/z 443.1157, found 443.1155.

Methyl 5-benzyl-3-(4-fluorophenyl)-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-49c)

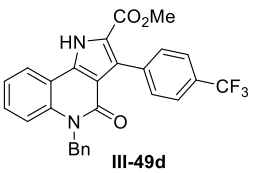


III-49c

PQ **III-49c** (13 mg, 31 µmol, 63% Yield) was synthesized using the general procedure 11; column chromatography eluting with cyclohexane/EA 10:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.01 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.57 – 7.44 (m, 2H), 7.39 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1H), 7.32 – 7.17 (m, 7H), 7.08 – 6.97 (m, 2H), 5.57 (s, 2H), 3.74 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 162.5 (d, *J*CF = 247.0 Hz), 162.0, 159.7, 138.4, 137.0, 136.0, 132.5 (d, *J*CF = 7.6 Hz, 2C), 130.3, 129.8, 128.8 (2C), 128.5 (d, *J*CF = 2.5 Hz), 127.2, 126.5 (2C), 122.2, 122.0, 121.9, 116.5, 114.2 (d, *J*CF = 21.4 Hz, 2C), 113.5, 113.2, 52.1, 45.6. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -115.0 (ddd, *J* = 14.4, 8.8, 5.5 Hz, 1F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_3F$ m/z 427.1453, found 427.1451.

Methyl 5-benzyl-4-oxo-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-49d)



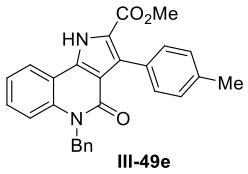
III-49d

PQ **III-49d** (17 mg, 35 µmol, 71% Yield) was synthesized using the general procedure 11; column chromatography eluting with cyclohexane/EA 10:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.04 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.41 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1H), 7.31 (dd, *J* = 8.7, 1.0 Hz,

1H), 7.28 – 7.15 (m, 6H), 5.57 (s, 2H), 3.72 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 161.8, 159.7, 138.4, 136.9, 136.6, 136.2, 131.2 (2C), 129.9, 129.6, 129.4 (q, *J*CF = 31.5 Hz), 128.8 (2C), 127.2, 126.5 (2C), 124.5 (q, *J*CF = 272.2 Hz), 124.1 (q, *J*CF = 3.8 Hz, 2C), 122.3, 122.2, 122.1, 116.6, 113.4, 113.1, 52.2, 45.7. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -62.4 (s, 3F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{20}N_2O_3F_3$ m/z 477.1421, found 477.1416.

Methyl 5-benzyl-4-oxo-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-49e)

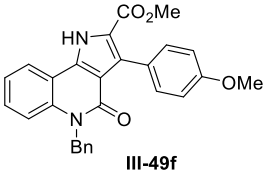


III-49e

PQ **III-49e** (18 mg, 43 μmol, 87% Yield) was synthesized using the general procedure 11; column chromatography eluting with cyclohexane/EA 10:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.01 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 2H),, 7.37 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1H), 7.29 (dd, *J* = 8.7, 1.0 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.21 – 7.16 (m, 4H), 7.15 (d, *J* = 7.8 Hz, 2H), 5.57 (s, 2H), 3.73 (s, 3H), 2.30 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 162.1, 159.7, 138.4, 137.2, 137.2, 135.9, 131.6, 130.6 (2C), 129.6, 129.5, 128.7 (2C), 128.0 (2C), 127.1, 126.6 (2C), 122.1, 122.0, 121.8, 116.4, 113.5, 113.3, 52.0, 45.6, 21.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_3$ m/z 423.1703, found 423.1702.

Methyl 5-benzyl-3-(4-methoxyphenyl)-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-49f)

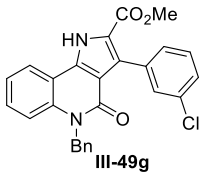


III-49f

PQ **III-49f** (18 mg, 41 μmol, 81% Yield) was synthesized using the general procedure 11; column chromatography eluting with cyclohexane/EA 10:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.02 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.63 – 7.44 (m, 2H), 7.37 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1H), 7.29 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.28 – 7.23 (m, 2H), 7.22 – 7.16 (m, 4H), 6.99 – 6.71 (m, 2H), 5.58 (s, 2H), 3.75 (s, 3H), 3.73 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 162.1, 159.8, 159.1, 138.3, 137.1, 136.0, 132.1 (2C), 131.3, 129.6, 128.8 (2C), 127.1, 126.6 (2C), 124.7, 122.1, 122.0, 121.8, 116.4, 113.4, 113.3, 112.7 (2C), 55.2, 52.0, 45.6. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_4$ m/z 439.1652, found 439.1650.

Methyl 5-benzyl-3-(3-chlorophenyl)-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-49g)

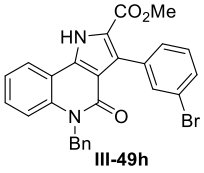


III-49g

PQ **III-49g** (16 mg, 36 µmol, 71% Yield) was synthesized using the general procedure 11; column chromatography eluting with cyclohexane/EA 10:1 to 2:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 7.99 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.51-7.50 (m, 1H), 7.44 – 7.40 (m, 1H), 7.40 – 7.36 (m, 1H), 7.32 – 7.16 (m, 9H), 5.57 (s, 2H), 3.75 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.9, 159.6, 138.4, 137.0, 136.0, 134.6, 132.9, 130.9, 129.8, 129.6, 129.1, 128.8 (2C), 128.4, 127.7, 127.2, 126.6 (2C), 122.3, 121.9, 116.6, 113.5, 113.1, 52.2, 45.6. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_3Cl$ m/z 443.1157, found 443.1156.

Methyl 5-benzyl-3-(3-bromophenyl)-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-49h)

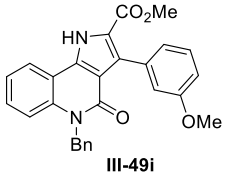


III-49h

PQ **III-49h** (24 mg, 49 µmol, 97% Yield) was synthesized using the general procedure 11; column chromatography eluting with cyclohexane/EA 10:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.01 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.67 (t, *J* = 1.8 Hz, 1H), 7.48 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.31 – 7.16 (m, 8H), 5.57 (s, 2H), 3.74 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 161.9, 159.6, 138.4, 137.0, 136.0, 134.9, 133.7, 130.5, 129.8, 129.6, 129.4, 128.8 (2C), 128.6, 127.2, 126.6 (2C), 122.3, 122.2, 122.0, 121.1, 116.5, 113.4, 113.2, 52.2, 45.6. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_3Br$ m/z 487.0652, found 487.0648.

Methyl 5-benzyl-3-(3-methoxyphenyl)-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-49i)

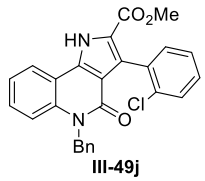


III-49i

PQ **III-49i** (36 mg, 37 µmol, 74% Yield) was synthesized using the general procedure 11; column chromatography eluting with cyclohexane/EA 10:1 to 2:1.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.99 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.38 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1H), 7.30 – 7.23 (m, 4H), 7.22 – 7.16 (m, 4H), 7.12 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.07 (dd, *J* = 2.6, 1.5 Hz, 1H), 6.84 (dd, *J* = 8.3, 2.7 Hz, 1H), 5.57 (s, 2H), 3.76 (s, 3H), 3.74 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 162.1, 159.6, 158.5, 138.4, 137.1, 135.9, 134.0, 131.0, 129.6, 128.8 (2C), 128.1, 127.1, 126.6 (2C), 123.3, 122.1, 122.1, 121.9, 116.7, 116.5, 113.6, 113.2, 112.9, 55.2, 52.1, 45.6. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_4$ m/z 439.1652, found 439.1651.

Methyl 5-benzyl-3-(2-chlorophenyl)-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-49j)

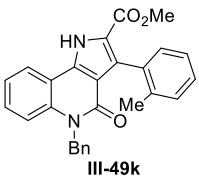


III-49j

PQ **III-49j** (18 mg, 41 µmol, 82% Yield) was synthesized using the general procedure 11; column chromatography eluting with cyclohexane/EA 10:1 to 2:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.43 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.40-7.34 (m, 2H), 7.31 – 7.16 (m, 9H), 5.57 (s, 2H), 3.70 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.0, 159.6, 138.3, 137.1, 136.1, 134.1, 132.9, 131.9, 129.6, 128.9, 128.8, 128.8 (2C), 127.4, 127.2, 126.6 (2C), 125.9, 122.8, 122.3, 122.1, 116.4, 114.1, 113.5, 52.2, 45.6. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_3Cl$ m/z 443.1157, found 443.1156.

Methyl 5-benzyl-4-oxo-3-(*o*-tolyl)-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-49k)

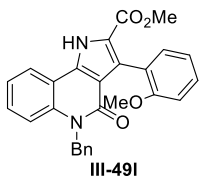


III-49k

PQ **III-49k** (16 mg, 39 µmol, 77% Yield) was synthesized using the general procedure 11; column chromatography eluting with cyclohexane/EA 10:1 to 2:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.04 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.38 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1H), 7.32 – 7.23 (m, 4H), 7.21 – 7.12 (m, 7H), 5.57 (s, 2H), 3.69 (s, 3H), 2.20 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.3, 159.6, 138.4, 137.2, 136.7, 136.1, 133.3, 130.5, 130.0, 129.5, 129.4, 128.8 (2C), 127.6, 127.1, 126.6 (2C), 124.9, 122.2, 122.1, 122.0, 116.4, 114.2, 113.5, 52.1, 45.5, 20.5. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_3$ m/z 423.1703, found 423.1702.

Methyl 5-benzyl-3-(2-methoxyphenyl)-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-49l)



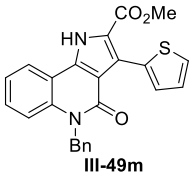
III-49l

PQ **III-49l** (14 mg, 32 µmol, 65% Yield) was synthesized using the general procedure 11; column chromatography eluting with cyclohexane/EA 10:1 to 1:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 7.97 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.39 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.31 – 7.22 (m, 4H), 7.21 – 7.13 (m, 4H), 6.98 (td, *J* = 7.5, 1.1 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 5.53 (s, 2H), 3.76 (s, 3H), 3.71 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 159.5, 157.5, 138.4, 137.3, 136.0, 131.9, 129.3, 129.1, 128.7 (2C), 127.1, 126.9, 126.6 (2C), 122.6, 122.4, 121.9, 121.9, 119.9, 116.3, 114.3, 113.5, 110.6, 55.7, 52.0, 45.4. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_4$ m/z 439.1652, found 439.1651.

Methyl 5-benzyl-4-oxo-3-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-49m)



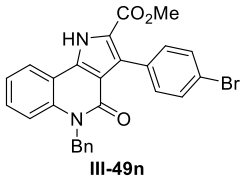
III-49m

PQ **III-49m** (12 mg, 29 µmol, 58% Yield) was synthesized using the general procedure 11; column chromatography eluting with cyclohexane/EA 10:1 to 2:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.99 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.29 (dd, *J* = 5.1, 3.8 Hz, 2H), 7.25 – 7.16 (m, 6H), 7.05 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.57 (s, 2H), 3.80 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.8, 159.4, 138.4, 137.0, 136.0, 132.4, 129.8, 129.6, 128.8 (2C), 127.2, 126.6 (2C), 126.4, 126.3, 123.2, 123.1, 122.2, 121.9, 116.5, 114.1, 113.0, 52.2, 45.6. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{19}N_2O_3S$ m/z 415.1111, found 415.1110.

Methyl 5-benzyl-3-(4-bromophenyl)-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-49n)

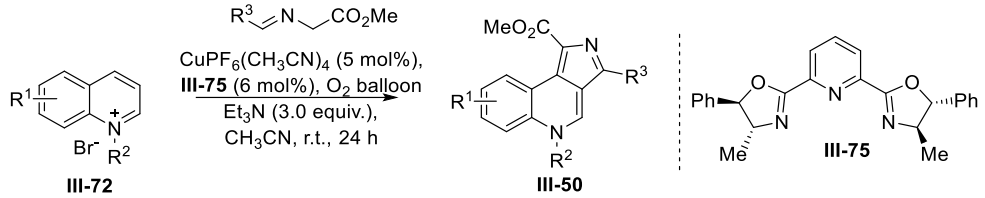
PQ **III-49n** (18 mg, 37 µmol, 75% Yield) was synthesized using the general procedure 11; column chromatography eluting with cyclohexane/EA 10:1 to 2:1.



III-49n

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.04 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.43 – 7.37 (m, 5H), 7.31 (d, *J* = 8.7 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.23 – 7.17 (m, 4H), 5.57 (s, 2H), 3.70 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 161.9, 159.8, 138.4, 137.0, 136.2, 132.5 (2C), 131.7, 130.3 (2C), 129.9, 129.8, 128.8 (2C), 127.2, 126.6 (2C), 122.2, 122.2, 122.0, 121.9, 116.5, 113.4, 113.2, 52.1, 45.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_3Br$ m/z 487.0652, found 487.0648.

7.2.1.7 Synthesis of III-50



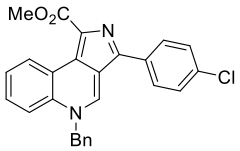
General Procedure 12

To a solution of quinolinium salt **III-72**[128] (0.1 mmol, 1.0 equiv.) and the iminoester[42] (0.15 mmol, 1.5 equiv.) in CH_3CN (1.0 mL) was added $Cu(CH_3CN)_4PF_6$ (0.005 mmol, 0.05 equiv.), TEA (0.3 mmol, 3.0 equiv.) and ligand **III-75** (0.005 mmol, 0.05 equiv.) in one portion. The reaction vessel was three times evacuated and refilled with O_2. The reaction was stirred for 24 h under an O_2 atmosphere. Then 20% KOH solution (20 mL) was added to quench the reaction and the mixture was extracted with EA (3*50 mL). The combined organic phases were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and PQs **III-50** were purified by column chromatography using cyclohexane/acetone.

General Procedure 13

To a solution of quinolinium salt **III-72** (0.1 mmol, 1.0 equiv.) and iminoester (0.15 mmol, 1.5 equiv.) in CH_3CN (1.0 mL) was added $Cu(CH_3CN)_4PF_6$ (0.015 mmol, 0.15 equiv.), TEA (0.3 mmol, 3.0 equiv.) and 10% Pd/C (30 mg) in one portion. The reaction was stirred for 24 h and then filtered through a short pad of Celite. Then 20% KOH solution (20 mL) was added to the filtrate and the mixture was extracted with EA (3*50 mL). The combined organic phases were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and PQs **III-75** were purified by column chromatography using cyclohexane/acetone.

Methyl 5-benzyl-3-(4-chlorophenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50a)



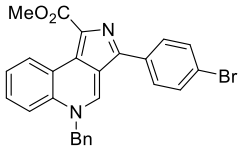
III-50a

PQ **III-50a** (38 mg, 89 µmol, 89%) was synthesized according to the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.58 (s, 1H), 7.81 – 7.67 (m, 2H), 7.58 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.44 (ddd, *J* = 8.6, 7.0, 1.6 Hz, 1H), 7.35 (m, 5H), 7.15 – 7.02 (m, 2H), 5.68 (s, 2H), 4.06 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.2, 146.5, 141.3, 134.1, 133.8 (2C), 132.5, 129.9, 129.6

(2C), 129.4 (2C), 129.0 (2C), 129.0, 128.3, 128.1, 127.4, 127.1, 126.3 (2C), 123.5, 119.3, 116.9, 59.5, 52.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_2Cl$ m/z 427.1208, found 427.1204.

Methyl 5-benzyl-3-(4-bromophenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50b)

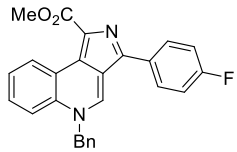


III-50b

PQ **III-50b** (37 mg, 79 µmol, 79% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.57 (s, 1H), 7.66 – 7.61 (m, 2H), 7.57 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.55 – 7.47 (m, 3H), 7.43 (ddd, *J* = 8.6, 6.9, 1.5 Hz, 1H), 7.38 – 7.32 (m, 3H), 7.15 – 7.03 (m, 2H), 5.67 (s, 2H), 4.05 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.2, 146.5, 141.3, 134.5, 133.8, 132.5, 132.0 (2C), 129.8, 129.6 (2C), 129.6 (2C), 129.0, 128.3, 128.1, 127.4, 127.1, 126.3 (2C), 123.5, 122.1, 119.2, 116.9, 59.5, 52.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_2Br$ m/z 471.0703, found 471.0693.

Methyl 5-benzyl-3-(4-fluorophenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50c)

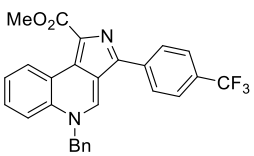


III-50c

PQ **III-50c** (36 mg, 87 µmol, 87% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.55 (s, 1H), 7.80 – 7.69 (m, 2H), 7.57 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.46 – 7.39 (m, 1H), 7.38 – 7.29 (m, 3H), 7.20 – 7.01 (m, 4H), 5.66 (s, 2H), 4.06 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.2, 162.8 (d, *J*CF = 248.2 Hz), 147.0, 141.4, 133.9, 132.5, 131.8 (d, *J*CF = 3.8 Hz), 129.9 (d, *J*CF = 7.6 Hz, 2C), 129.9, 129.6 (2C), 128.9, 128.2, 127.8, 127.2, 127.0, 126.3 (2C), 123.5, 119.3, 116.9, 115.8 (d, *J*CF = 22.7 Hz, 2C), 59.5, 52.0. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -114.0 (m, 1F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_2F$ m/z 411.1503, found 411.1493.

Methyl 5-benzyl-3-(4-(trifluoromethyl)phenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50d)



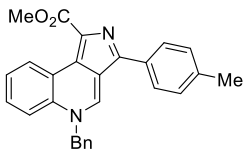
III-50d

PQ **III-50d** (39 mg, 86 µmol, 86% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.06 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.63 (s,

1H), 7.99 – 7.81 (m, 2H), 7.65 – 7.53 (m, 4H), 7.51 – 7.40 (m, 1H), 7.37-7.32 (m, 3H), 7.15 – 7.04 (m, 2H), 5.70 (s, 2H), 4.06 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.2, 145.8, 141.3, 139.0, 133.7, 132.5, 129.8, 129.6 (2C), 129.5 (q, *J*CF = 32.8 Hz), 129.1, 129.0, 128.4, 128.2 (2C), 127.6, 127.2, 126.3 (2C), 125.8 (q, *J*CF = 3.8 Hz, 2C), 124.3 (q, *J*CF = 272.2 Hz), 123.5, 119.3, 116.9, 59.6, 52.1. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -62.4 (s, 3F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{20}N_2O_2F_3$ m/z 461.1471, found 461.1458.

Methyl 5-benzyl-3-(*p*-tolyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50e)

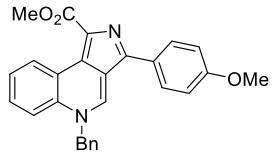


III-50e

PQ **III-50e** (32 mg, 78 µmol, 78% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (700 MHz, $CDCl_3$) δ 10.06 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.57 (s, 1H), 7.68 (d, *J* = 7.9 Hz, 2H), 7.55 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.39 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.34 – 7.29 (m, 3H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 7.7 Hz, 2H), 5.63 (s, 2H), 4.06 (s, 3H), 2.36 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 166.3, 148.2, 141.7, 137.8, 134.1, 132.7, 132.6, 129.8, 129.6 (2C), 129.5 (2C), 128.8, 128.2 (2C), 127.7, 127.1, 126.9, 126.2 (2C), 123.6, 119.5, 116.8, 59.4, 51.9, 21.4. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_2$ m/z 407.1754, found 407.1746.

Methyl 5-benzyl-3-(4-methoxyphenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50f)

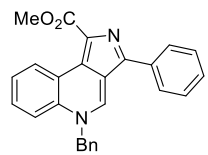


III-50f

PQ **III-50f** (28 mg, 65 µmol, 65% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:3.

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.05 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.61 (s, 1H), 7.75 – 7.65 (m, 2H), 7.62 – 7.51 (m, 2H), 7.44 (ddd, *J* = 8.6, 7.0, 1.5 Hz, 1H), 7.36 – 7.28 (m, 3H), 7.12 – 7.05 (m, 2H), 6.93 – 6.85 (m, 2H), 5.68 (s, 2H), 4.03 (s, 3H), 3.78 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 165.8, 159.8, 147.6, 142.3, 134.1, 132.7, 129.9, 129.6 (2C), 129.5 (2C), 128.8, 128.3, 127.6, 127.0, 126.9, 126.8, 126.2 (2C), 123.6, 119.1, 117.0, 114.3 (2C), 59.5, 55.4, 51.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_3$ m/z 423.1703, found 423.1700.

Methyl 5-benzyl-3-phenyl-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50g)

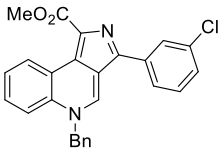


III-50g

PQ **III-50g** (26 mg, 66 µmol, 66% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.09 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.64 (s, 1H), 7.85 – 7.74 (m, 2H), 7.58 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.53 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.46 – 7.38 (m, 3H), 7.37 – 7.30 (m, 4H), 7.09-7.07 (m, 2H), 5.67 (s, 2H), 4.06 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.2, 148.0, 141.8, 135.4, 134.0, 132.6, 129.9, 129.6 (2C), 128.9 (2C), 128.9, 128.4 (2C), 128.2, 128.0, 127.8, 127.2, 127.0, 126.2 (2C), 123.6, 119.4, 116.9, 59.5, 52.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{21}N_2O_2$ m/z 393.1598, found 393.1589.

Methyl 5-benzyl-3-(3-chlorophenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50h)

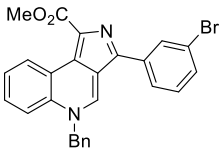


III-50h

PQ **III-50h** (26 mg, 61 µmol, 61% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.10 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.62 (s, 1H), 7.81 (t, *J* = 1.8 Hz, 1H), 7.65 – 7.55 (m, 3H), 7.46 (ddd, *J* = 8.6, 7.0, 1.5 Hz, 1H), 7.40 – 7.34 (m, 3H), 7.33 – 7.26 (m, 2H), 7.11 (dd, *J* = 7.6, 2.0 Hz, 2H), 5.71 (s, 2H), 4.07 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.2, 146.1, 141.3, 137.3, 134.8, 133.7, 132.6, 130.1, 129.9, 129.7 (2C), 129.1, 128.4, 128.1, 128.1, 127.8, 127.4, 127.2, 126.5 (2C), 126.3, 123.6, 119.2, 116.9, 59.6, 52.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_2Cl$ m/z 427.1208, found 427.1203.

Methyl 5-benzyl-3-(3-bromophenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50i)

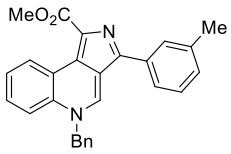


III-50i

PQ **III-50i** (37 mg, 78 µmol, 78% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.09 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.59 (s, 1H), 7.98 (t, *J* = 1.8 Hz, 1H), 7.65 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.45 (ddd, *J* = 8.6, 6.9, 1.5 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.38 – 7.32 (m, 3H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.11 (dd, *J* = 7.4, 2.2 Hz, 2H), 5.70 (s, 2H), 4.06 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.2, 145.9, 141.2, 137.6, 133.7, 132.6, 130.9, 130.7, 130.3, 129.9, 129.7 (2C), 129.1, 128.3, 128.1, 127.4, 127.2, 126.7, 126.5 (2C), 123.5, 123.1, 119.2, 116.9, 59.5, 52.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_2Br$ m/z 471.0703, found 471.0696.

Methyl 5-benzyl-3-(*m*-tolyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50j)

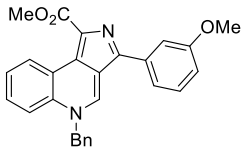


III-50j

PQ **III-50j** (33 mg, 80 µmol, 80% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.97 (dd, *J* = 8.2, 1.6 Hz, 1H), 9.66 (s, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.86-7.80 (m, 2H), 7.67-7.58 (m, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.31 – 7.24 (m, 3H), 7.23 – 7.18 (m, 1H), 6.13 (s, 2H), 3.89 (s, 3H), 2.43 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 165.7, 146.1, 144.1, 137.9, 135.8, 135.7, 132.1, 129.0 (2C), 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 126.7, 126.5, 126.5 (2C), 126.5, 125.0, 122.9, 118.4, 118.3, 57.9, 51.0, 21.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_2$ m/z 407.1754, found 407.1750.

Methyl 5-benzyl-3-(3-methoxyphenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50k)

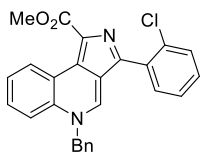


III-50k

PQ **III-50k** (31 mg, 73 µmol, 73% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:3.

^{1}H NMR (500 MHz, CDCl$_3$) δ 10.11 (dd, *J* = 8.2, 4.5 Hz, 1H), 8.81 – 8.59 (m, 1H), 7.63 – 7.52 (m, 2H), 7.47 – 7.41 (m, 2H), 7.37 – 7.27 (m, 5H), 7.11-7.06 (m, 2H), 6.90-6.87 (m, 1H), 5.68 (s, 2H), 4.06 (s, 3H), 3.86 (s, 3H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 166.2, 160.1, 147.8, 141.9, 136.9, 133.9, 132.6, 129.9, 129.8, 129.6 (2C), 128.9, 128.2, 127.3, 127.0, 126.2 (2C), 123.6, 123.6, 120.8, 119.5, 116.9, 114.1, 113.4, 59.5, 55.6, 51.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_3$ m/z 423.1703, found 423.1695.

Methyl 5-benzyl-3-(2-chlorophenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50l)



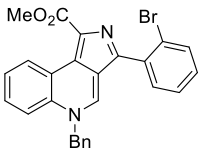
III-50l

PQ **III-50l** (28 mg, 66 µmol, 66% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, CDCl$_3$) δ 10.21 (dd, *J* = 8.7, 1.5 Hz, 1H), 8.64 (s, 1H), 7.78 – 7.72 (m, 1H), 7.69 – 7.64 (m, 2H), 7.55 – 7.49 (m, 1H), 7.49 – 7.43 (m, 1H), 7.39 – 7.29 (m, 5H), 7.13 (dd, *J* = 7.7, 1.8 Hz, 2H), 5.72 (s, 2H), 4.05 (s, 3H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 166.1, 145.4, 142.8, 134.7, 133.9, 133.3, 132.9, 132.5, 130.2, 129.9, 129.6 (2C),

129.6, 129.0, 128.3, 128.1, 127.3, 127.3, 127.2, 126.2 (2C), 124.0, 119.8, 117.1, 59.8, 52.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_2Cl$ m/z 427.1208, found 427.1198.

Methyl 5-benzyl-3-(2-bromophenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50m)

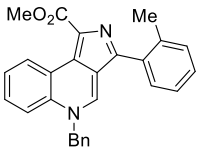


III-50m

PQ **III-50m** (29 mg, 62 µmol, 62% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.00 (dd, *J* = 8.2, 1.6 Hz, 1H), 9.39 (s, 1H), 7.99 (dd, *J* = 8.7, 1.3 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.72 – 7.60 (m, 3H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.36 – 7.31 (m, 2H), 7.30 – 7.25 (m, 3H), 6.06 (s, 2H), 3.86 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 165.6, 145.8, 144.4, 136.8, 135.7, 133.0, 132.9, 132.0, 129.8, 129.0 (2C), 128.5, 128.0, 128.0, 127.7, 126.7, 126.5 (2C), 126.0, 123.0, 123.0, 118.9, 118.5, 57.7, 50.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_2O_2Br$ m/z 471.0703, found 471.0694.

Methyl 5-benzyl-3-(*o*-tolyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50n)

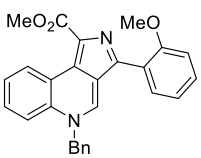


III-50n

PQ **III-50n** (29 mg, 70 µmol, 70% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.18 (dt, *J* = 8.4, 1.7 Hz, 1H), 8.42 (s, 1H), 7.67 – 7.58 (m, 2H), 7.49 (t, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.27 (m, 5H), 7.25 – 7.21 (m, 1H), 7.08 (d, J = 7.3 Hz, 2H), 5.68 (s, 2H), 4.04 (s, 3H), 2.39 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.3, 148.7, 141.8, 137.8, 134.7, 134.1, 132.7, 130.8, 130.8, 130.1, 129.6 (2C), 128.8, 128.2, 127.5, 127.1, 126.3, 126.0 (2C), 125.6, 123.8, 120.9, 117.0, 59.5, 51.9, 20.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_2$ m/z 407.1754, found 407.1742.

Methyl 5-benzyl-3-(2-methoxyphenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50o)



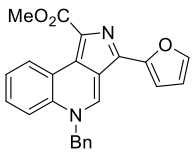
III-50o

PQ **III-50o** (20 mg, 46 µmol, 46% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:3.

^{1}H NMR (700 MHz, $CDCl_3$) δ 10.18 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.87 (s, 1H), 7.92 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.67-7.62 (m, 2H), 7.53 – 7.48 (m, 1H), 7.38 – 7.31 (m, 4H),

7.19 – 7.14 (m, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 5.72 (s, 2H), 4.05 (s, 3H), 3.70 (s, 3H). **^{13}C NMR (176 MHz, CDCl$_3$)** δ 166.1, 156.6, 145.0, 143.8, 134.3, 132.6, 132.5, 130.2, 129.6, 129.6 (2C), 128.9, 128.2, 127.7, 127.4, 127.0, 126.3 (2C), 125.0, 124.0, 121.8, 120.1, 116.9, 111.9, 59.5, 56.1, 51.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{23}N_2O_3$ m/z 423.1703, found 423.1698.

Methyl 5-benzyl-3-(furan-2-yl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50p)

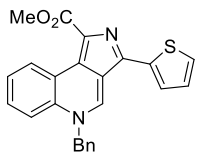


III-50p

PQ **III-50p** (17 mg, 45 µmol, 45% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (600 MHz, CDCl$_3$) δ 10.09 (dd, *J* = 8.3, 1.5 Hz, 1H), 9.16 (s, 1H), 7.64 – 7.51 (m, 2H), 7.51 – 7.39 (m, 2H), 7.38 – 7.30 (m, 3H), 7.21 – 7.09 (m, 3H), 6.54 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.73 (s, 2H), 4.06 (s, 3H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 165.9, 152.2, 143.0, 141.9, 138.5, 134.0, 132.7, 130.0, 129.6 (2C), 128.9, 128.3, 128.0, 127.2, 126.4, 126.3 (2C), 123.8, 118.9, 117.1, 112.1, 107.5, 59.7, 52.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{19}N_2O_3$ m/z 383.1390, found 383.1391.

Methyl 5-benzyl-3-(thiophen-2-yl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50q)

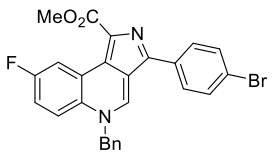


III-50q

PQ **III-50q** (29 mg, 73 µmol, 73% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, CDCl$_3$) δ 10.14 (dd, *J* = 8.7, 1.5 Hz, 1H), 8.86 (s, 1H), 7.67 – 7.61 (m, 2H), 7.54 – 7.48 (m, 2H), 7.41 – 7.36 (m, 3H), 7.34 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.19 – 7.15 (m, 2H), 7.12 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.75 (s, 2H), 4.06 (s, 3H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 166.0, 141.9, 141.3, 138.6, 133.8, 132.8, 130.2, 129.7 (2C), 129.1, 128.4, 128.0, 127.9, 127.3, 127.0, 126.5 (2C), 125.6, 124.8, 123.8, 119.4, 116.9, 59.7, 52.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{19}N_2O_2S$ m/z 399.1162, found 399.1154.

Methyl 5-benzyl-3-(4-bromophenyl)-8-fluoro-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50r)

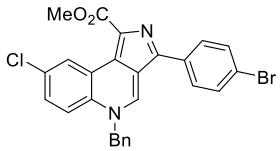


III-50r

PQ **III-50r** (31 mg, 64 µmol, 64% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (dd, *J* = 11.1, 2.9 Hz, 1H), 8.67 (s, 1H), 7.70 – 7.63 (m, 2H), 7.57 (dd, *J* = 9.4, 4.8 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.39-7.33 (m, 3H), 7.17 (ddd, *J* = 9.8, 7.0, 3.0 Hz, 1H), 7.13 – 7.08 (m, 2H), 5.75 (s, 2H), 4.05 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.6, 160.6 (d, *J*CF = 248.2 Hz), 146.3, 141.8, 133.7, 133.5, 132.0 (2C), 129.7 (4C), 129.2 (2C), 127.8, 126.7 (d, *J*CF = 3.8 Hz), 126.4 (2C), 125.4 (d, *J*CF = 11.3 Hz), 122.5, 119.1 (d, *J*CF = 10.1 Hz), 118.4, 116.8 (d, *J*CF = 25.2 Hz), 114.9 (d, *J*CF = 26.5 Hz), 60.0, 52.2. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -110.1 (m, 1F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{19}N_2O_2BrF$ m/z 489.0609, found 489.0597.

Methyl 5-benzyl-3-(4-bromophenyl)-8-chloro-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50s)



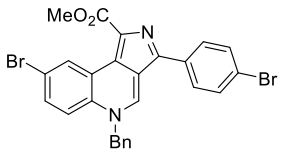
III-50s

PQ **III-50s** (42 mg, 83 µmol, 83% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.13 (d, *J* = 2.5 Hz, 1H), 9.76 (s, 1H), 8.05 – 7.99 (m, 2H), 7.97 (d, *J* = 9.3 Hz, 1H), 7.72 – 7.64 (m, 3H), 7.37-7.31 (m, 2H), 7.31 – 7.23 (m, 3H), 6.11 (s, 2H), 3.91 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 165.7, 145.0, 144.7, 135.5, 134.7, 131.6 (2C), 131.2, 130.7, 129.7 (2C), 129.0 (2C), 128.1, 127.8, 127.4, 127.3, 126.4 (2C), 125.6, 124.2, 120.8, 120.6, 118.3, 58.3, 51.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{19}N_2O_2ClBr$ m/z 505.0313, found 505.0305.

Methyl 5-benzyl-8-bromo-3-(4-bromophenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50t)

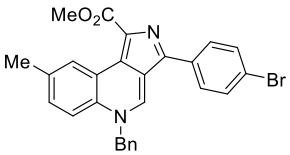
PQ **III-50t** (37 mg, 67 µmol, 67% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.



III-50t

^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.28 (d, *J* = 2.4 Hz, 1H), 9.76 (s, 1H), 8.09 – 7.99 (m, 2H), 7.89 (d, *J* = 9.3 Hz, 1H), 7.78 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.73 – 7.63 (m, 2H), 7.36 – 7.32 (m, 2H), 7.31 – 7.27 (m, 1H), 7.27 – 7.23 (m, 2H), 6.10 (s, 2H), 3.91 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 165.7, 145.0, 144.8, 135.5, 134.7, 131.6 (2C), 131.1, 130.6, 130.4, 129.7 (2C), 129.0 (2C), 128.0, 127.4, 126.4 (2C), 125.5, 124.5, 120.8, 120.7, 119.7, 118.4, 58.2, 51.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{19}N_2O_2Br_2$ m/z 548.9808, found 548.9805.

Methyl 5-benzyl-3-(4-bromophenyl)-8-methyl-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50u)

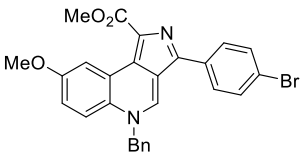


III-50u

PQ **III-50u** (39 mg, 81 µmol, 81% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (d, *J* = 2.1 Hz, 1H), 8.73 (s, 1H), 7.75 – 7.68 (m, 2H), 7.56 – 7.48 (m, 3H), 7.37 – 7.32 (m, 4H), 7.13-7.09 (m, 2H), 5.77 (s, 2H), 4.06 (s, 3H), 2.57 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.5, 145.6, 141.8, 137.8, 133.9, 132.0 (2C), 130.9, 130.1, 129.9 (2C), 129.6 (2C), 129.5, 129.0, 127.2, 126.3 (2C), 123.7, 122.4, 118.7, 116.9, 59.8, 52.1, 21.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{22}N_2O_2Br$ m/z 485.0859, found 485.0853.

Methyl 5-benzyl-3-(4-bromophenyl)-8-methoxy-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50v)

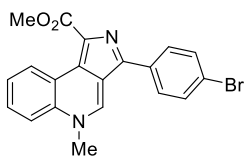


III-50v

PQ **III-50v** (39 mg, 78 µmol, 78% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:3.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.70 – 9.59 (m, 2H), 8.09 – 7.98 (m, 2H), 7.89 (d, *J* = 9.5 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.38 – 7.21 (m, 6H), 6.09 (s, 2H), 3.93 (s, 3H), 3.89 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 165.8, 157.4, 143.8, 142.5, 135.8, 135.1, 131.5 (2C), 129.5 (2C), 129.0 (2C), 128.0, 127.1, 126.8, 126.6, 126.4 (2C), 124.7, 120.4, 120.0, 117.8, 117.3, 109.5, 58.2, 55.5, 51.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{22}N_2O_3Br$ m/z 501.0808, found 501.0799.

Methyl 3-(4-bromophenyl)-5-methyl-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50w)



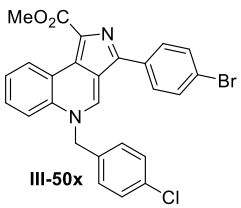
III-50w

PQ **III-50w** (35mg, 88 µmol, 88% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.10 (d, *J* = 7.8 Hz, 1H), 8.56 (s, 1H), 7.73 – 7.61 (m, 5H), 7.59 – 7.55 (m, 2H), 4.20 (s, 3H), 4.05 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.0, 146.0, 141.8, 134.4, 133.2, 132.0 (2C), 129.9, 129.8 (2C), 128.4, 127.7,

127.4, 127.3, 123.3, 122.2, 119.0, 116.0, 52.1, 44.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{20}H_{16}N_2O_2Br$ m/z 395.0390, found 395.0382.

Methyl 3-(4-bromophenyl)-5-(4-chlorobenzyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50x)

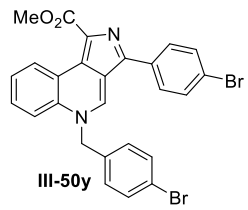


III-50x

PQ **III-50x** (46 mg, 79 µmol, 90% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.96 (dd, *J* = 8.2, 1.7 Hz, 1H), 9.74 (s, 1H), 8.07 – 7.97 (m, 2H), 7.92 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.71 – 7.58 (m, 4H), 7.43 – 7.37 (m, 2H), 7.34 – 7.27 (m, 2H), 6.11 (s, 2H), 3.89 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 165.7, 144.5, 144.4, 134.9, 134.9, 132.5, 131.9, 131.6 (2C), 129.7 (2C), 128.9 (2C), 128.5 (2C), 128.5, 128.1, 127.0, 126.7, 126.7, 122.9, 120.6, 118.3, 118.2, 57.4, 51.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{19}N_2O_2ClBr$ m/z 505.0313, found 505.0307.

Methyl 5-(4-bromobenzyl)-3-(4-bromophenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50y)

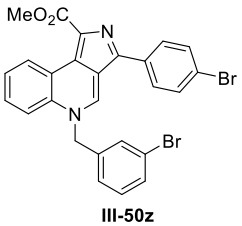


III-50y

PQ **III-50y** (47 mg, 85 µmol, 85% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.97 (dd, *J* = 8.2, 1.6 Hz, 1H), 9.73 (s, 1H), 8.07 – 7.98 (m, 2H), 7.91 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.71 – 7.59 (m, 4H), 7.56 – 7.51 (m, 2H), 7.26 – 7.20 (m, 2H), 6.09 (s, 2H), 3.89 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 165.7, 144.5, 144.3, 135.3, 135.0, 131.9, 131.8 (2C), 131.6 (2C), 129.7 (2C), 128.8 (2C), 128.5, 128.1, 127.1, 126.7, 122.9, 121.1, 120.6, 118.3, 118.2, 57.5, 51.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{19}N_2O_2Br_2$ m/z 548.9808, found 548.9798.

Methyl 5-(3-bromobenzyl)-3-(4-bromophenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50z)



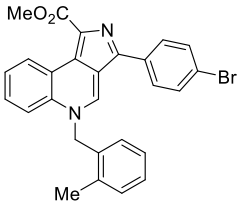
III-50z

PQ **III-50z** (53 mg, 96 µmol, 96% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.97 (dd, *J* = 8.1, 1.8 Hz, 1H), 9.73 (s,

1H), 8.08 – 7.98 (m, 2H), 7.95 – 7.87 (m, 1H), 7.71 – 7.61 (m, 4H), 7.60 (t, *J* = 1.9 Hz, 1H), 7.49 (ddd, *J* = 8.0, 2.1, 1.0 Hz, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.18 (dt, *J* = 8.1, 1.2 Hz, 1H), 6.11 (s, 2H), 3.89 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 165.7, 144.5, 138.6, 134.9, 131.9, 131.6 (2C), 131.1, 130.9, 129.7 (2C), 129.3, 128.5, 128.1, 127.0, 126.7, 126.7, 125.4, 122.9, 122.1, 120.6, 118.2, 118.2, 57.4, 51.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{19}N_2O_2Br_2$ m/z 548.9808, found 548.9803.

Methyl 3-(4-bromophenyl)-5-(2-methylbenzyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50aa)

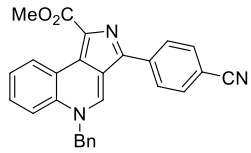


III-50aa

PQ **III-50aa** (44 mg, 90 µmol, 90% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.01 (dd, *J* = 8.4, 1.5 Hz, 1H), 9.62 (s, 1H), 8.03 – 7.92 (m, 2H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.69 (dd, *J* = 8.4, 7.0 Hz, 1H), 7.67 – 7.59 (m, 3H), 7.38 – 7.27 (m, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 7.7 Hz, 1H), 6.36 – 6.23 (m, 1H), 6.07 (s, 2H), 3.90 (s, 3H), 2.49 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 165.7, 144.3, 144.2, 134.9, 134.9, 134.0, 132.3, 131.6 (2C), 130.4, 129.5 (2C), 128.4, 128.2, 127.5, 127.1, 126.8, 126.7, 126.4 (2C), 122.7, 120.5, 118.4, 118.3, 56.4, 51.1, 18.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{22}N_2O_2Br$ m/z 485.0859, found 485.0850.

Methyl 5-benzyl-3-(4-cyanophenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50bb)

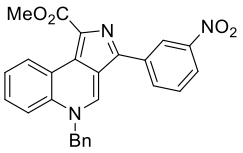


III-50bb

PQ **III-50bb** (8 mg, 20 µmol, 20%) was synthesized according to the general procedure 13; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (700 MHz, DMSO-*d6*) δ 9.97 (dd, *J* = 8.3, 1.6 Hz, 1H), 9.87 (s, 1H), 8.36 – 8.24 (m, 2H), 7.99 (d, *J* = 8.7 Hz, 1H), 7.96 – 7.89 (m, 2H), 7.68 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.64 (ddd, *J* = 8.6, 6.9, 1.6 Hz, 1H), 7.36-7.32 (m, 2H), 7.32 – 7.25 (m, 3H), 6.15 (s, 2H), 3.91 (s, 3H). **^{13}C NMR (176 MHz, DMSO-*d6*)** δ 165.6, 144.4, 143.0, 140.1, 135.6, 132.6 (2C), 132.0, 128.9 (2C), 128.4, 128.2, 128.0, 128.0 (2C), 127.7, 127.2, 126.8, 126.4 (2C), 122.9, 119.2, 118.5, 118.4, 109.1, 58.3, 51.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{20}N_3O_2$ m/z 418.1550, found 418.1548.

Methyl 5-benzyl-3-(3-nitrophenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50cc)

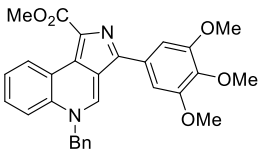


III-50cc

PQ **III-50cc** (7 mg, 16 µmol, 16%) was synthesized according to the general procedure 13; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (600 MHz, DMSO-*d6*) δ 9.98 (dd, *J* = 8.3, 1.6 Hz, 1H), 9.88 (s, 1H), 8.82 (t, *J* = 2.0 Hz, 1H), 8.52 (d, *J* = 7.8 Hz, 1H), 8.20 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.79 (t, *J* = 8.0 Hz, 1H), 7.68 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.64 (ddd, *J* = 8.6, 7.0, 1.7 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.31 – 7.26 (m, 3H), 6.14 (s, 2H), 3.92 (s, 3H). **^{13}C NMR (151 MHz, DMSO-*d6*)** δ 165.6, 148.4, 144.3, 142.7, 137.3, 135.6, 133.6, 132.0, 130.3, 128.9 (2C), 128.4, 128.1, 128.0, 127.3, 127.0, 126.8, 126.5 (2C), 122.9, 121.7, 121.5, 118.5, 118.1, 58.3, 51.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{20}N_3O_4$ m/z 438.1448, found 438.1443.

Methyl 5-benzyl-3-(3,4,5-trimethoxyphenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50dd)

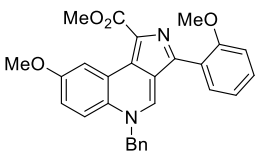


III-50dd

PQ **III-50dd** (11 mg, 23 µmol, 23%) was synthesized according to the general procedure 13; column chromatography eluting with cyclohexane/acetone 2:1 to 1:3.

^{1}H NMR (700 MHz, DMSO-*d6*) δ 9.95 (dd, *J* = 8.2, 1.7 Hz, 1H), 9.61 (s, 1H), 7.99 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.66-7.60 (m, 2H), 7.37 – 7.32 (m, 2H), 7.30 – 7.27 (m, 3H), 7.17 (s, 2H), 6.10 (s, 2H), 3.91 (s, 6H), 3.89 (s, 3H), 3.73 (s, 3H). **^{13}C NMR (176 MHz, DMSO-*d6*)** δ 165.7, 153.2 (2C), 146.4, 144.2, 137.3, 135.8, 132.2, 131.3, 128.9 (2C), 128.4, 128.0, 127.9, 126.7 (2C), 126.5, 126.3, 122.9, 118.3, 118.2, 105.3 (2C), 60.1, 57.8, 56.0 (2C), 51.0, 26.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{29}H_{27}N_2O_5$ m/z 483.1915, found 483.1907.

Methyl 5-benzyl-8-methoxy-3-(2-methoxyphenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50ee)



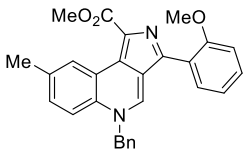
III-50ee

PQ **III-50ee** (9 mg, 21 µmol, 21% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:3.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (d, *J* = 2.9 Hz, 1H), 8.91 (s, 1H), 7.96 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.59 (d, *J* = 9.4 Hz, 1H), 7.39 – 7.29 (m, 4H), 7.17 – 7.09 (m, 4H), 6.99 (d, *J* = 8.3 Hz, 1H), 5.77 (s, 2H), 4.06 (s, 3H), 4.04 (s, 3H), 3.73 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.6, 158.3, 156.5, 143.7, 142.7, 134.3, 132.6, 129.7, 129.5 (2C),

128.9, 127.6, 127.0, 126.4, 126.3 (2C), 125.7, 124.3, 121.9, 119.3, 118.7, 118.5, 111.9, 110.3, 59.7, 56.1, 56.1, 52.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{28}H_{25}N_2O_4$ m/z 453.1809, found 453.1801.

Methyl 5-benzyl-3-(2-methoxyphenyl)-8-methyl-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50ff)

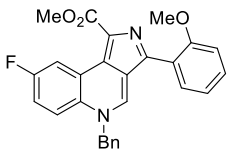


III-50ff

PQ **III-50ff** (18 mg, 40 µmol, 40% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:3.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (d, *J* = 2.1 Hz, 1H), 8.83 (s, 1H), 7.91 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.38 – 7.31 (m, 5H), 7.16-7.12 (m, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.70 (s, 2H), 4.04 (s, 3H), 3.70 (s, 3H), 2.58 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 165.9, 156.5, 144.6, 143.4, 137.3, 134.3, 132.6, 130.6, 129.7, 129.6, 129.6, 129.5 (2C), 128.9, 127.4, 127.2, 126.3 (2C), 124.8, 124.0, 121.8, 119.9, 116.8, 111.8, 59.5, 56.1, 51.9, 21.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{28}H_{25}N_2O_3$ m/z 437.1860, found 437.1854.

Methyl 5-benzyl-8-fluoro-3-(2-methoxyphenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50gg)

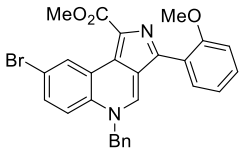


III-50gg

PQ **III-50gg** (25 mg, 57 µmol, 57% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:3.

^{1}H NMR (700 MHz, $CDCl_3$) δ 10.00 (dd, *J* = 11.2, 3.0 Hz, 1H), 8.85 (s, 1H), 7.90 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.63 (dd, *J* = 9.4, 4.8 Hz, 1H), 7.39-7.34 (m, 4H), 7.22 (ddd, *J* = 9.6, 7.0, 3.0 Hz, 1H), 7.18 – 7.14 (m, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 5.71 (s, 2H), 4.06 (s, 3H), 3.71 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 166.0, 160.5 (d, *J*CF = 248.2 Hz), 156.6, 145.3, 143.6, 134.0, 132.6, 129.7 (2C), 129.5, 129.1, 129.0, 128.4, 126.9 (d, *J*CF = 3.5 Hz), 126.3 (2C), 125.9 (d, *J*CF = 10.6 Hz), 124.9, 121.9, 119.7, 118.9 (d, *J*CF = 8.8 Hz), 116.5 (d, *J*CF = 24.6 Hz), 115.2 (d, *J*CF = 26.4 Hz), 111.9, 59.9, 56.1, 52.0. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -110.8 (m, 1F). **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{22}N_2O_3F$ m/z 441.1609, found 441.1604.

Methyl 5-benzyl-8-bromo-3-(2-methoxyphenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50hh)

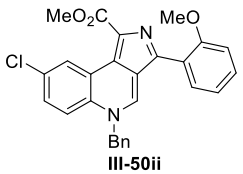


III-50hh

PQ **III-50hh** (9 mg, 19 µmol, 19% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:3.

^{1}H NMR (500 MHz, CDCl$_3$) δ 10.35 (d, *J* = 2.2 Hz, 1H), 8.85 (s, 1H), 7.83 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.58 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.52 (d, *J* = 9.1 Hz, 1H), 7.40 – 7.32 (m, 4H), 7.15-7.12 (m, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.71 (s, 2H), 4.04 (s, 3H), 3.71 (s, 3H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 165.3, 156.5, 144.8, 144.5, 133.7, 132.4, 132.3, 131.4, 131.3, 130.1, 129.7 (2C), 129.1, 127.1, 126.3 (2C), 125.7, 125.2, 123.6, 121.8, 121.2, 119.8, 118.7, 111.8, 59.8, 56.0, 52.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{22}N_2O_3Br_2$ m/z 501.0808, found 501.0797.

Methyl 5-benzyl-8-chloro-3-(2-methoxyphenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50ii)

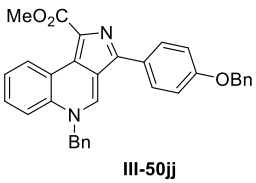


III-50ii

PQ **III-50ii** (13 mg, 28 µmol, 28% Yield) was synthesized using the general procedure 12; column chromatography eluting with cyclohexane/acetone 2:1 to 1:3.

^{1}H NMR (500 MHz, CDCl$_3$) δ 10.24 (d, *J* = 2.4 Hz, 1H), 8.78 (s, 1H), 7.87 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.53 (d, *J* = 9.1 Hz, 1H), 7.41 – 7.33 (m, 5H), 7.15-7.12 (m, 2H), 7.10 (td, *J* = 7.5, 1.1 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.66 (s, 2H), 4.06 (s, 3H), 3.69 (s, 3H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 166.1, 156.5, 145.8, 143.6, 133.9, 132.7, 132.5, 130.7, 129.7 (2C), 129.6, 129.2, 129.1, 128.7, 128.2, 126.3 (2C), 126.2, 125.0, 125.0, 121.7, 120.3, 118.2, 111.8, 59.6, 56.0, 52.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{22}N_2O_3Cl$ m/z 457.1314, found 457.1303.

Methyl 5-benzyl-3-(4-(benzyloxy)phenyl)-5*H*-pyrrolo[3,4-*c*]quinoline-1-carboxylate (III-50jj)



III-50jj

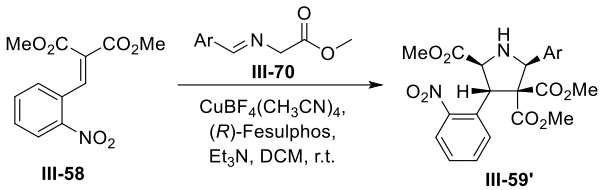
PQ **III-50jj** (64 mg, 128 µmol, 64% Yield) was synthesized using the general procedure 12 for 0.2 mmol scale; column chromatography eluting with cyclohexane/acetone 2:1 to 1:2.

^{1}H NMR (700 MHz, DMSO-*d6*) δ 9.96 (dd, *J* = 8.2, 1.6 Hz, 1H), 9.63 (s, 1H), 8.02 – 7.95 (m, 2H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.60 – 7.55 (m, 1H), 7.51 – 7.48 (m, 2H), 7.43-7.39 (m, 2H), 7.36 – 7.31 (m, 3H), 7.29 – 7.23 (m, 3H), 7.18 – 7.11 (m, 2H), 6.09 (s, 2H), 5.19 (s, 2H), 3.88 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ

165.8, 158.2, 146.1, 144.3, 137.2, 135.9, 132.2, 129.2 (2C), 129.1 (2C), 128.6 (3C), 128.5, 128.1, 128.0 (2C), 127.8 (3C), 126.6, 126.5 (2C), 126.3, 123.0, 118.4, 118.2, 115.2 (2C), 69.4, 58.0, 51.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{33}H_{27}N_2O_3$ m/z 499.2016, found 499.2004.

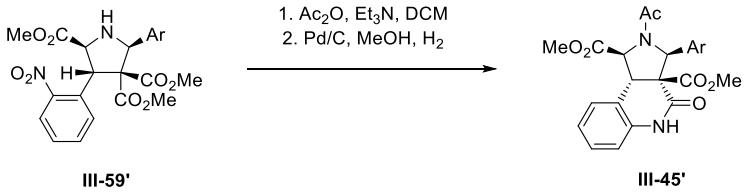
7.2.2 Asymmetric synthesis of pyrro[3,4-*c*]quinolines

General procedure 14



A solution of (*R*)-Fesulphos (0.018 mmol, 6 mol %) and $Cu(CH_3CN)_4BF_4$ (0.015 mmol, 5 mol %) in CH_2Cl_2 (3 mL) was stirred for 30 min at room temperature. To the resulting solution were successively added Schiff base **2** (0.60 mmol, 2.0 equiv.), dipolarophile **III-58** (0.30 mmol, 1.0 equiv), and Et_3N (8.3 μL, 20 mol %). When the reaction was complete as monitored by TLC, the reaction mixture was directly purified by silica gel flash chromatography using Cyclohexane: Ethyl acetate (3:1 to 1:1) as eluent to give desired product.

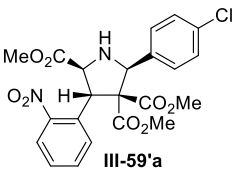
General procedure 15



The specific pyrrolidine **III-59'** (0.1 mmol) was dissolved into 2 mL CH_2Cl_2 followed by addition of Ac_2O (28 μL, 0.3 mmol) and Et_3N (69 μL, 0.5 mmol). The reaction was stirred overnight until the starting material was fully consumed. Then saturated $NaHCO_3$ solution (5 mL) was added to the reaction mixture, and extracted with CH_2Cl_2 (10 mL *3). The resulting organic layer was combined and dried over $MgSO_4$, and then the solvent was removed under reduced pressure. The residue was dissolved in MeOH (3 mL) and 10% Pd/C (30 mg) was added sequentially. The reaction vessel was flushed three times with H_2. The reaction was stirred under a H_2 atmosphere until full conversion of the starting material was observed. The reaction was filtered through a short pad of Celite and the solvent was then removed under

reduced pressure. The residue was purified by column chromatography using cyclohexane/acetone mixtures as a single diastereomer.

Trimethyl (2*S*,3*S*,5*S*)-5-(4-chlorophenyl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59'a)

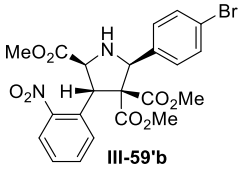


III-59'a

The title product compound **III-59'a** is prepared using general procedure 14 and isolated by column chromatography (2:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (127.3 mg, 0.27 mmol, 89% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.62 (td, *J* = 7.6, 1.4 Hz, 1H), 7.56 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.45-7.43 (m, 3H), 7.31 (d, *J* = 8.5 Hz, 2H), 5.30 (d, *J* = 2.1 Hz, 1H), 5.19 (d, *J* = 6.2 Hz, 1H), 4.17 (d, *J* = 6.3 Hz, 1H), 3.81 (s, 3H), 3.20 (s, 3H), 3.20 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 172.4, 169.1, 168.9, 151.0, 135.9, 134.3, 133.4, 132.7, 129.4, 128.9, 128.6, 124.6, 71.0, 68.1, 67.4, 52.9, 52.7, 52.3, 49.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{22}H_{22}N_2O_8Cl$ m/z 477.1059, found 477.1056. **$[\alpha]_D^{20}$** = +21.4 (c = 0.14, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 20/80, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 22.9 min; minor enantiomer: t_R = 26.7 min. *ee* >99%.

Trimethyl (2*S*,3*S*,5*S*)-5-(4-bromophenyl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59'b)

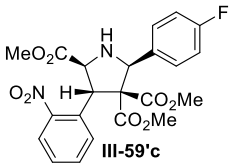


III-59'b

The title product compound **III-59'b** is prepared using general procedure 14 and isolated by column chromatography (2:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (137.1 mg, 0.26 mmol, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.47 – 7.41 (m, 3H), 7.39 – 7.34 (m, 2H), 5.27 (s, 1H), 5.18 (d, *J* = 6.3 Hz, 1H), 4.16 (d, *J* = 6.4 Hz, 1H), 3.80 (s, 3H), 3.19 (s, 3H), 3.19 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.3, 169.0, 168.9, 151.0, 136.5, 133.4, 132.7, 131.6, 129.4, 129.2, 128.6, 124.5, 122.5, 70.9, 68.1, 67.3, 52.9, 52.7, 52.3, 49.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{22}H_{22}N_2O_8Br$ m/z 521.0554, found 521.0551. **$[\alpha]_D^{20}$** = +20.9 (c = 0.22, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 20/80, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 24.1 min; minor enantiomer: t_R = 28.7 min. *ee*=99%.

Trimethyl (2*S*,3*S*,5*S*)-5-(4-fluorophenyl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59'c)

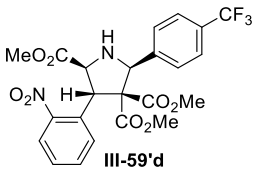


III-59'c

The title product compound **III-59'c** is prepared using general procedure 14 and isolated by column chromatography (2:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (100.7 mg, 0.22 mmol, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.65 – 7.55 (m, 2H), 7.52 – 7.37 (m, 3H), 7.08 – 6.96 (m, 2H), 5.30 (s, 1H), 5.18 (d, *J* = 6.4 Hz, 1H), 4.16 (d, *J* = 6.4 Hz, 1H), 3.80 (s, 3H), 3.19 (s, 3H+3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.4, 169.1, 169.0, 162.8 (d, *J*CF = 247.1 Hz), 151.0, 133.4, 133.2 (d, *J*CF = 3.2 Hz), 132.7, 129.4, 129.2 (d, *J*CF = 8.1 Hz, 2C), 128.6, 124.5, 115.3 (d, *J*CF = 21.5 Hz, 2C), 71.0, 68.1, 67.3, 52.9, 52.6, 52.3, 49.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{22}H_{22}N_2O_8F$ m/z 461.1355, found 461.1345. **$[\alpha]_D^{20}$** = +21.6 (c = 0.13, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 20/80, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 22.3 min; minor enantiomer: t_R = 27.7 min. *ee*=99%.

Trimethyl (2*S*,3*S*,5*S*)-3-(2-nitrophenyl)-5-(4-(trifluoromethyl)phenyl)pyrrolidine-2,4,4-tricarboxylate (III-59'd)

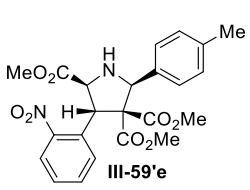


III-59'd

The title product compound **III-59'd** is prepared using general procedure 14 and isolated by column chromatography (2:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (122.4 mg, 0.24 mmol, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.68 – 7.52 (m, 6H), 7.45 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H), 5.38 (s, 1H), 5.22 (d, *J* = 6.3 Hz, 1H), 4.19 (d, *J* = 6.3 Hz, 1H), 3.82 (s, 3H), 3.20 (s, 3H), 3.14 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.4, 168.9, 168.8, 151.0, 141.6, 133.3, 132.8, 130.7 (q, *J*CF = 32.4 Hz), 129.4, 128.7, 128.0 (2C), 125.3 (q, *J*CF = 3.7 Hz, 2C), 124.6, 124.1 (q, *J*CF = 272.7 Hz), 71.1, 68.1, 67.4, 52.9, 52.6, 52.4, 49.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{22}N_2O_8F_3$ m/z 511.1323, found 511.1299. **$[\alpha]_D^{20}$** = +17.0 (c = 0.14, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 20/80, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 14.9 min; minor enantiomer: t_R = 18.6 min. *ee*=98%.

Trimethyl (2*S*,3*S*,5*S*)-3-(2-nitrophenyl)-5-(*p*-tolyl)pyrrolidine-2,4,4-tricarboxylate (III-59'e)

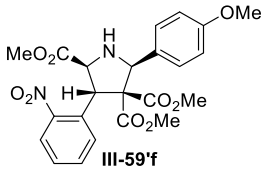


III-59'e

The title product compound **III-59'e** is prepared using general procedure 14 and isolated by column chromatography (2:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (106.8 mg, 0.23 mmol, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.73 (m, 1H), 7.66 – 7.54 (m, 2H), 7.42 (ddd, *J* = 8.1, 7.0, 1.8 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.18 – 7.11 (m, 2H), 5.28 (s, 1H), 5.17 (d, *J* = 6.4 Hz, 1H), 4.16 (d, *J* = 6.4 Hz, 1H), 3.80 (s, 3H), 3.19 (s, 3H), 3.18 (s, 3H), 2.31 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.4, 169.3, 169.0, 151.0, 138.2, 134.1, 133.6, 132.6, 129.5, 129.1, 128.5, 127.3, 124.5, 71.2, 68.8, 67.5, 52.8, 52.6, 52.2, 49.5, 21.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{25}N_2O_8$ m/z 457.1605, found 457.1602. **$[\alpha]_D^{20}$** = +31.8 (c = 0.26, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 29.0 min; minor enantiomer: t_R = 23.3 min. *ee*=97%.

Trimethyl (2*S*,3*S*,5*S*)-5-(4-methoxyphenyl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59'f)

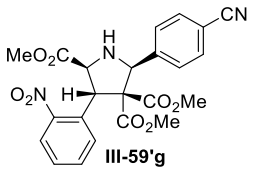


III-59'f

The title product compound **III-59'f** is prepared using general procedure 14 and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (113.8 mg, 0.24 mmol, 80% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.43 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H), 7.41 – 7.37 (m, 2H), 6.90 – 6.83 (m, 2H), 5.27 (s, 1H), 5.17 (d, *J* = 6.3 Hz, 1H), 4.16 (d, *J* = 6.3 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.20 (s, 3H+3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 172.5, 169.4, 169.1, 159.7, 151.0, 133.6, 132.7, 129.5, 129.2, 128.6 (2C), 128.5, 124.5, 113.8 (2C), 71.1, 68.5, 67.4, 55.4, 52.9, 52.7, 52.2, 49.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{25}N_2O_9$ m/z 473.1555, found 473.1549. **$[\alpha]_D^{20}$** = +34.5 (c = 0.38, CH_2Cl_2)

Trimethyl (2*S*,3*S*,5*S*)-5-(4-cyanophenyl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59'g)

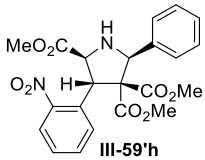


III-59'g

The title product compound **III-59'g** is prepared using general procedure 14 and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (120.9 mg, 0.26 mmol, 86% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.66 – 7.61 (m, 5H), 7.57 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.45 (ddd, *J* = 8.5, 7.4, 1.4 Hz, 1H), 5.37 (s, 1H), 5.22 (d, *J* = 6.2 Hz, 1H), 4.19 (d, *J* = 6.2 Hz, 1H), 3.82 (s, 3H), 3.21 (s, 3H), 3.16 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 172.3, 168.7, 168.7, 151.0, 143.1, 133.1, 132.8, 132.2, 129.3, 128.8, 128.5, 124.7, 118.7, 112.3, 71.0, 68.0, 67.3, 53.0, 52.7, 52.5, 48.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{22}N_3O_8$ m/z 468.1401, found 468.1398. **$[\alpha]_D^{20}$** = +16.9 (c = 0.29, CH_2Cl_2) **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 35.1 min; minor enantiomer: t_R = 48.4 min. *ee*=96%.

Trimethyl (2*S*,3*S*,5*S*)-3-(2-nitrophenyl)-5-phenylpyrrolidine-2,4,4-tricarboxylate (III-59'h)

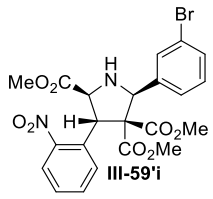


III-59'h

The title product compound **III-59'h** is prepared using general procedure 14 and isolated by column chromatography (2:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (120.9 mg, 0.27 mmol, 91% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.49 – 7.40 (m, 3H), 7.37 – 7.26 (m, 3H), 5.33 (s, 1H), 5.20 (d, *J* = 6.1 Hz, 1H), 4.20 (d, *J* = 6.3 Hz, 1H), 3.82 (s, 3H), 3.20 (s, 3H), 3.13 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.4, 169.2, 168.9, 151.0, 137.0, 133.4, 132.7, 129.5, 128.6, 128.5 (3C), 127.4 (2C), 124.5, 71.2, 68.8, 67.4, 52.9, 52.6, 52.3, 49.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{22}H_{23}N_2O_8$ m/z 443.1449, found 443.1440. **$[\alpha]_D^{20}$** = +7.0 (c = 0.43, CH_2Cl_2)

Trimethyl (2*S*,3*S*,5*S*)-5-(3-bromophenyl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59'i)



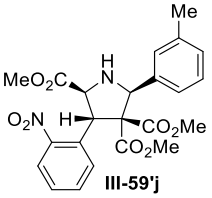
III-59'i

The title product compound **III-59'i** is prepared using general procedure 14 and isolated by column chromatography (2:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (155.1 mg, 0.30 mmol, 99% yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.55 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.46 – 7.41 (m, 3H), 7.21 (t, *J* = 7.9 Hz, 1H), 5.27 (s, 1H), 5.19 (d, *J* = 6.5 Hz, 1H), 4.17 (d, *J* = 6.4 Hz, 1H), 3.81 (s, 3H), 3.22 (s, 3H), 3.20 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 172.2, 168.9, 168.8, 151.0, 139.7, 133.3, 132.7, 131.6, 130.7, 130.0, 129.4, 128.6, 126.1, 124.6, 122.5, 71.0, 68.1, 67.3, 52.9, 52.7, 52.3, 49.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{22}H_{22}N_2O_8Br$ m/z 521.0554, found 521.0551. **$[\alpha]_D^{20}$** = +6.9 (c = 0.59, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 15/85,

flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 54.1 min; minor enantiomer: t_R = 57.5 min. *ee*=98%.

Trimethyl (2*S*,3*S*,5*S*)-3-(2-nitrophenyl)-5-(*m*-tolyl)pyrrolidine-2,4,4-tricarboxylate (III-59'j)

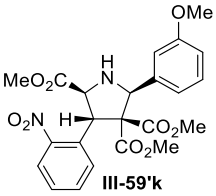


III-59'j

The title product compound **III-59'j** is prepared using general procedure 14 and isolated by column chromatography (2:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (127.6 mg, 0.28 mmol, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.43 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.26 – 7.19 (m, 3H), 7.12 – 7.07 (m, 1H), 5.27 (s, 1H), 5.18 (d, *J* = 6.5 Hz, 1H), 4.17 (d, *J* = 6.4 Hz, 1H), 3.81 (s, 3H), 3.19 (s, 3H), 3.17 (s, 3H), 2.34 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.4, 169.3, 169.0, 151.0, 138.1, 137.0, 133.5, 132.7, 129.5, 129.3, 128.5, 128.4, 128.1, 124.5, 124.4, 71.2, 68.9, 67.5, 52.9, 52.5, 52.2, 49.4, 21.6. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{25}N_2O_8$ m/z 457.1605, found 457.1602. **$[\alpha]_D^{20}$** = +21.5 (c = 0.21, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 32.5 min; minor enantiomer: t_R = 23.4 min. *ee*=99%.

Trimethyl (2*S*,3*S*,5*S*)-5-(3-methoxyphenyl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59'k)

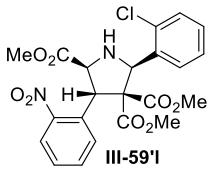


III-59'k

The title product compound **III-59'k** is prepared using general procedure 14 and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (120.1 mg, 0.25 mmol, 85% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.63-7.60 (m, 2H), 7.43 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.10 – 7.06 (m, 1H), 7.05 – 7.00 (m, 1H), 6.83 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 5.27 (s, 1H), 5.20 (d, *J* = 6.4 Hz, 1H), 4.18 (d, *J* = 6.4 Hz, 1H), 3.81 (s, 3H), 3.81 (s, 3H), 3.21 (s, 3H), 3.18 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.5, 169.2, 169.0, 159.7, 151.0, 139.0, 133.3, 132.7, 129.5, 129.4, 128.6, 124.5, 119.3, 114.3, 113.1, 71.1, 68.7, 67.3, 55.4, 52.9, 52.6, 52.3, 49.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{25}N_2O_9$ m/z 473.1555, found 473.1550. **$[\alpha]_D^{20}$** = +26.7 (c = 0.18, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 46.5 min; minor enantiomer: t_R = 36.0 min. *ee*=95%.

Trimethyl (2*S*,3*S*,5*R*)-5-(2-chlorophenyl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59'l)

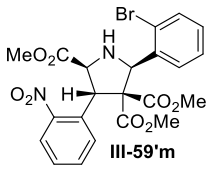


III-59'l

The title product compound **III-59'l** is prepared using general procedure 14 and isolated by column chromatography (2:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (107.4 mg, 0.23 mmol, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.61 – 7.53 (m, 2H), 7.46 – 7.40 (m, 2H), 7.33 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.29 (td, *J* = 7.6, 1.4 Hz, 1H), 7.19 (td, *J* = 7.6, 1.7 Hz, 1H), 5.87 (s, 1H), 5.22 (d, *J* = 9.9 Hz, 1H), 4.35 (d, *J* = 10.0 Hz, 1H), 3.71 (s, 3H), 3.33 (s, 3H), 3.11 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.9, 169.6, 168.6, 151.8, 137.4, 134.6, 131.7, 130.2, 129.6, 129.4, 129.1, 129.0, 128.6, 127.3, 124.8, 71.3, 64.8, 63.6, 52.7, 52.6, 52.3, 47.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{22}H_{22}N_2O_8Cl$ m/z 477.1059, found 477.1057. **$[\alpha]_D^{20}$** = +185.4 (c = 0.21, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 22.2 min; minor enantiomer: t_R = 34.0 min. *ee*=94%.

Trimethyl (2*S*,3*S*,5*R*)-5-(2-bromophenyl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59'm)

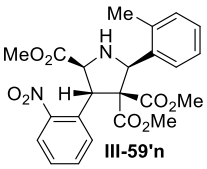


III-59'm

The title product compound **III-59'm** is prepared using general procedure 14 and isolated by column chromatography (2:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (137.6 mg, 0.26 mmol, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.72 (m, 1H), 7.62 – 7.51 (m, 3H), 7.46 – 7.38 (m, 2H), 7.35 (td, *J* = 7.6, 1.3 Hz, 1H), 7.12 (ddd, *J* = 7.9, 7.3, 1.7 Hz, 1H), 5.86 (s, 1H), 5.23 (d, *J* = 10.2 Hz, 1H), 4.38 (d, *J* = 10.2 Hz, 1H), 3.71 (s, 3H), 3.36 (s, 3H), 3.10 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.9, 169.7, 168.5, 151.9, 139.4, 133.0, 131.6, 130.1, 129.7, 129.2, 129.1, 128.7, 128.0, 125.3, 124.9, 71.4, 66.2, 64.6, 52.7, 52.7, 52.3, 47.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{22}H_{22}N_2O_8Br$ m/z 521.0554, found 521.0553. **$[\alpha]_D^{20}$** = +232.0 (c = 0.25, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 22.7 min; minor enantiomer: t_R = 35.1 min. *ee*=95%.

Trimethyl (2*S*,3*S*,5*S*)-3-(2-nitrophenyl)-5-(*o*-tolyl)pyrrolidine-2,4,4-tricarboxylate (III-59'n)

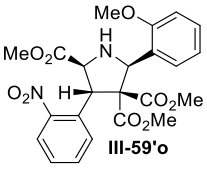


III-59'n

The title product compound **III-59'n** is prepared using general procedure 14 and isolated by column chromatography (2:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (113.9 mg, 0.25 mmol, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.57 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.45 – 7.36 (m, 2H), 7.21 (td, *J* = 7.3, 2.3 Hz, 1H), 7.18 – 7.11 (m, 2H), 5.61 (s, 1H), 5.20 (d, *J* = 9.0 Hz, 1H), 4.26 (d, *J* = 9.0 Hz, 1H), 3.74 (s, 3H), 3.27 (s, 3H), 3.09 (s, 3H), 2.45 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.0, 169.9, 169.1, 151.7, 137.5, 137.3, 131.9, 131.3, 130.7, 129.2, 128.5, 128.2, 126.5, 126.2, 124.7, 71.9, 65.7, 64.1, 52.8, 52.5, 52.4, 49.3, 20.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{25}N_2O_8$ m/z 457.1605, found 457.1596. **$[\alpha]_D^{20}$** = +191.3 (c = 0.54, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 20/80, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 14.9 min; minor enantiomer: t_R = 18.6 min. *ee*=98%.

Trimethyl (2*S*,3*S*,5*S*)-5-(2-methoxyphenyl)-3-(2-nitrophenyl)pyrrolidine-2,4,4-tricarboxylate (III-59'o)

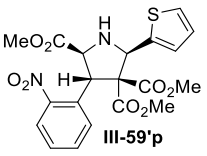


III-59'o

The title product compound **III-59'o** is prepared using general procedure 14 and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (84.8 mg, 0.18 mmol, 60% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.48 – 7.40 (m, 2H), 7.29 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H), 6.95 (td, *J* = 7.5, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.44 (s, 1H), 5.38 (d, *J* = 8.6 Hz, 1H), 4.37 (d, *J* = 8.7 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.25 (s, 3H), 3.24 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.0, 168.8, 157.6, 151.5, 132.3, 131.8, 131.4, 130.2, 129.5, 128.7, 124.8, 121.1, 110.5, 70.9, 68.2, 65.7, 55.2, 53.0, 52.6, 52.5, 48.8. **MS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{25}N_2O_9$ m/z 473.2, found 473.2. **$[\alpha]_D^{20}$** = +31.1 (c = 0.18, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 39.2 min; minor enantiomer: t_R = 55.8 min. *ee*=93%.

Trimethyl (2*S*,3*S*,5*R*)-3-(2-nitrophenyl)-5-(thiophen-2-yl)pyrrolidine-2,4,4-tricarboxylate (III-59'p)

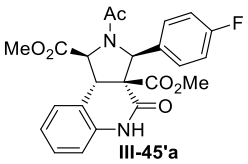


III-59'p

The title product compound **III-59'p** is prepared using general procedure 14 and isolated by column chromatography (2:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (89.1 mg, 0.20 mmol, 66% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.60 (td, *J* = 7.7, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.43 (ddd, *J* = 8.5, 7.4, 1.3 Hz, 1H), 7.24 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.14 (dt, *J* = 3.5, 1.0 Hz, 1H), 6.97 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.50 (s, 1H), 5.17 (d, *J* = 6.6 Hz, 1H), 4.17 (d, *J* = 6.6 Hz, 1H), 3.79 (s, 3H), 3.31 (s, 3H), 3.24 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.0, 169.1, 168.8, 150.9, 139.9, 133.4, 132.7, 129.2, 128.6, 126.8, 125.6, 125.3, 124.6, 71.1, 67.4, 65.0, 53.0, 52.9, 52.3, 49.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{20}H_{21}N_2O_8S$ m/z 449.1013, found 449.1011. **$[\alpha]_D^{20}$** = +23.1 (c = 0.16, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 43.8 min; minor enantiomer: t_R = 39.2 min. *ee*=91%.

Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-3-(4-fluorophenyl)-4-oxo-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45'a)

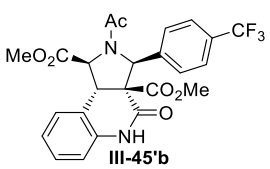


III-45'a

The title product compound **III-45'a** is prepared using general procedure 15 and isolated by column chromatography (1:1 Cyclohexane: acetone) giving an amorphous solid (34.8 mg, 0.08 mmol, 79% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.8 Hz, 1H), 7.92 – 7.76 (m, 2H), 7.30 – 7.26 (m, 1H), 7.14-7.09 (m, 3H), 7.06 (td, *J* = 7.5, 1.1 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.07 (s, 1H), 4.27 (d, *J* = 11.3 Hz, 1H), 4.15 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 3H), 3.33 (s, 3H), 1.89 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.7, 170.6, 164.9, 164.3, 163.0 (d, *J*CF = 248.2 Hz), 134.9, 133.1 (d, *J*CF = 3.8 Hz), 129.6, 129.6 (d, *J*CF = 7.6 Hz, 2C), 129.4, 124.3, 119.0, 116.3, 116.0 (d, *J*CF = 22.7 Hz, 2C), 65.6, 64.1, 63.2, 53.3, 52.7, 44.8, 22.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{22}N_2O_6F$ m/z 441.1456, found 441.1454. **$[\alpha]_D^{20}$** = -86.9 (c = 0.16, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 20/80, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 22.6 min; minor enantiomer: t_R = 43.8 min. *ee*=99%.

Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-4-oxo-3-(4-(trifluoromethyl)phenyl)-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45'b)

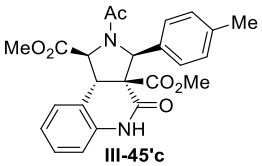


III-45'b

The title product compound **III-45'b** is prepared using general procedure 15 and isolated by column chromatography (1:1 Cyclohexane: acetone) giving an amorphous solid (32.3 mg, 0.07 mmol, 66% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.99 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.29 (td, *J* = 7.6, 1.6 Hz, 1H), 7.11 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.07 (td, *J* = 7.4, 1.1 Hz, 1H), 6.88 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.15 (s, 1H), 4.26 (d, *J* = 11.4 Hz, 1H), 4.18 (d, *J* = 11.3 Hz, 1H), 3.82 (s, 3H), 3.32 (s, 3H), 1.88 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.6, 170.5, 164.8, 164.1, 141.4, 134.8, 131.2 (q, *J*CF = 32.8 Hz), 129.7, 129.4, 128.2 (2C), 126.0 (q, *J*CF = 3.8 Hz, 2C), 124.4, 124.0 (q, *J*CF = 272.2 Hz), 118.8, 116.3, 65.7, 64.2, 63.2, 53.3, 52.8, 45.0, 22.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{22}N_2O_6F_3$ m/z 491.1425, found 491.1420. **$[\alpha]_D^{20}$** = -90.3 (c = 0.16, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 20/80, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 21.7 min; minor enantiomer: t_R = 45.1 min. *ee*=98%.

Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-3-(*p*-tolyl)-4-oxo-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45'c)

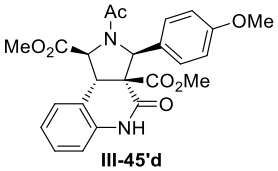


III-45'c

The title product compound **III-45'c** is prepared using general procedure 15 and isolated by column chromatography (1:1 Cyclohexane: acetone) giving an amorphous solid (24.4 mg, 0.06 mmol, 56% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.73 – 7.65 (m, 2H), 7.30 – 7.26 (m, 1H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.13 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.06 (td, *J* = 7.5, 1.1 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.04 (s, 1H), 4.31 (d, *J* = 11.3 Hz, 1H), 4.15 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 3H), 3.34 (s, 3H), 2.35 (s, 3H), 1.88 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.5, 170.6, 165.0, 164.4, 138.7, 134.9, 134.1, 129.7, 129.6, 129.5, 127.6, 124.3, 119.3, 116.1, 66.1, 64.1, 63.2, 53.2, 52.6, 44.8, 22.1, 21.4. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{25}N_2O_6$ m/z 437.1707, found 437.1707. **$[\alpha]_D^{20}$** = -27.0 (c = 0.27, CH_2Cl_2)

Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-3-(4-methoxyphenyl)-4-oxo-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45'd)



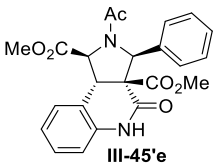
III-45'd

The title product compound **III-45'd** is prepared using general procedure 15 and isolated by column chromatography (1:1 Cyclohexane: acetone) giving an amorphous solid (13.9 mg, 0.03 mmol, 31% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.81 – 7.66 (m, 2H), 7.30 – 7.25 (m, 1H), 7.12 (dd, J = 7.6, 1.5 Hz, 1H), 7.05 (td, J = 7.5, 1.1 Hz, 1H), 6.96 – 6.91 (m, 2H), 6.85 (dd, J = 8.0,

1.2 Hz, 1H), 6.03 (s, 1H), 4.30 (d, J = 11.3 Hz, 1H), 4.14 (d, J = 11.3 Hz, 1H), 3.81 (s, 6H), 3.33 (s, 3H), 1.89 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.7, 170.7, 165.0, 164.5, 160.0, 135.0, 129.5, 129.4, 129.1, 129.0 (2C), 124.3, 119.3, 116.2, 114.3 (2C), 65.9, 64.1, 63.2, 55.4, 53.2, 52.6, 44.8, 22.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{25}N_2O_7$ m/z 453.1656, found 453.1654. **$[\alpha]_D^{20}$** = -117.7 (c = 0.13, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 16.7 min; minor enantiomer: t_R = 34.6 min. *ee*=99%.

Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-4-oxo-3-phenyl-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45'e)



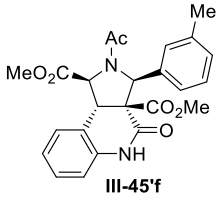
III-45'e

The title product compound **III-45'e** is prepared using general procedure 15 and isolated by column chromatography (1:1 Cyclohexane: acetone) giving an amorphous solid (33.5 mg, 0.08 mmol, 79% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.85 – 7.77 (m, 2H), 7.46 – 7.39 (m, 2H), 7.37 – 7.33 (m, 1H), 7.30 – 7.25 (m, 1H), 7.12 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.05 (td, *J* = 7.5, 1.1 Hz, 1H), 6.88 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.09 (s, 1H), 4.32 (d, *J* = 11.3 Hz, 1H), 4.18 (d, *J* = 11.4 Hz, 1H), 3.82 (s, 3H), 3.30 (s, 3H), 1.90 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.6, 170.7, 165.0, 164.6, 137.2, 135.0, 129.6, 129.4, 129.0 (2C), 128.9, 127.7 (2C), 124.3, 119.2, 116.3, 66.3, 64.1, 63.2, 53.2, 52.7, 44.9, 22.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{23}N_2O_6$ m/z 423.1551, found 423.1550. **$[\alpha]_D^{20}$** = -54.6 (c = 0.26, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 14.8 min; minor enantiomer: t_R = 28.3 min. *ee*=95%.

Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-4-oxo-3-(*m*-tolyl)-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45'f)

The title product compound **III-45'f** is prepared using general procedure 15 and isolated by column chromatography (1:1 Cyclohexane: acetone) giving an amorphous solid (40.4 mg, 0.09 mmol, 93% yield).

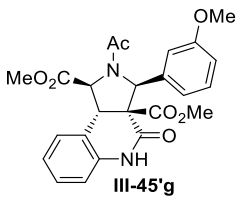


III-45'f

^{1}H NMR (500 MHz, DMSO-d*6*) δ 10.96 (s, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.51 (s, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.26 (ddd, *J* = 7.7, 5.7, 1.4 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.06 – 6.88 (m, 2H), 5.97 (s, 1H), 4.07 (d, *J* = 11.3 Hz, 1H), 3.88 (d, *J* = 11.3 Hz, 1H), 3.73 (s, 3H), 3.26 (s, 3H), 2.34 (s, 3H), 1.75 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 171.1, 169.7, 165.3, 163.4, 138.3, 137.8,

136.2, 129.9, 129.6, 129.6, 129.1, 128.2, 124.7, 123.5, 119.0, 116.4, 65.8, 63.5, 62.9, 53.2, 52.8, 44.7, 22.0, 21.6. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{25}N_2O_6$ m/z 437.1707, found 437.1707. **$[\alpha]_D^{20}$** = -67.8 (c = 0.20, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 12.7 min; minor enantiomer: t_R = 25.3 min. *ee*=98%.

Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-4-oxo-3-(3-methoxyphenyl -1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45'g)

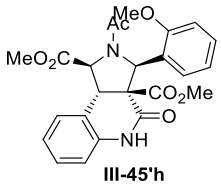


III-45'g

The title product compound **III-45'g** is prepared using general procedure 15 and isolated by column chromatography (1:1 Cyclohexane: acetone) giving an amorphous solid (38.5 mg, 0.09 mmol, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.56 (s, 1H), 7.33 – 7.25 (m, 4H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.08 – 7.03 (m, 1H), 6.88 (ddd, *J* = 7.8, 2.6, 1.3 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.05 (s, 1H), 4.30 (d, *J* = 11.4 Hz, 1H), 4.15 (d, *J* = 11.3 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.34 (s, 3H), 1.90 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.5, 170.6, 164.9, 164.4, 160.4, 138.9, 134.9, 129.9, 129.6, 129.5, 124.3, 119.8, 119.3, 116.1, 114.8, 112.9, 66.2, 64.2, 63.2, 55.6, 53.2, 52.6, 45.1, 22.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{25}N_2O_7$ m/z 453.1656, found 453.1655. **$[\alpha]_D^{20}$** = -41.3 (c = 0.16, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 15.5 min; minor enantiomer: t_R = 57.2 min. *ee*=97%.

Dimethyl (1*S*,3*S*,3a*S*,9b*S*)-2-acetyl-3-(2-methoxyphenyl)-4-oxo-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,4-*c*]quinoline-1,3a-dicarboxylate (III-45'h)



III-45'h

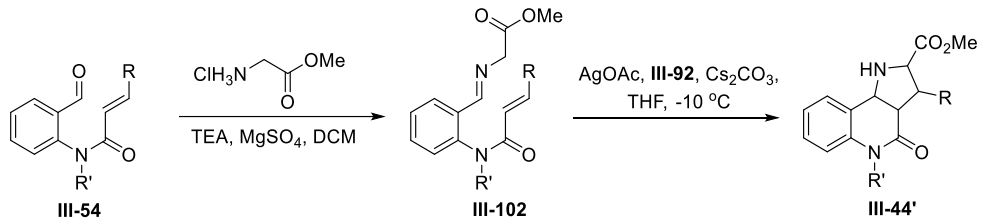
The title product compound **III-45'h** is prepared using general procedure 15 and isolated by column chromatography (1:1 Cyclohexane: acetone) giving an amorphous solid (18.0 mg, 0.04 mmol, 47% yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.25 (s, 1H), 7.33 (td, *J* = 7.8, 1.7 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.11 (td, *J* = 7.6, 1.0 Hz, 1H), 7.06 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.02 (td, *J* = 7.5, 1.1 Hz, 1H), 6.87 – 6.84 (m, 2H), 6.53 (s, 1H), 4.28 – 4.08 (m, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.31 (s, 3H), 1.88 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 171.5, 170.7, 166.0, 165.3, 156.4, 135.4, 129.8, 129.6, 129.4, 129.2, 125.7, 124.0, 121.4, 119.0, 116.0, 109.6, 62.9, 62.8, 60.9, 55.4, 52.9, 52.6, 46.7, 21.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{24}H_{25}N_2O_7$ m/z 453.1656, found 453.1655. **$[\alpha]_D^{20}$** = -69.3 (c = 0.08, CH_2Cl_2).

HPLC conditions: CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 16.6 min; minor enantiomer: t_R = 25.2 min. *ee*=95%.

7.2.3 Asymmetric synthesis of pyrro[3,2-*c*]quinolines

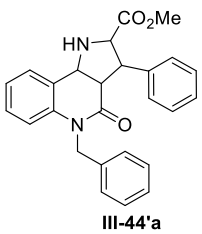
General Procedure 16



Glycine methyl ester salt (37.6 mg, 0.3 mmol, 3.0 equiv.) was suspended in dry DCM (1 mL) and $MgSO_4$ (36.1 mg, 0.3 mmol, 3.0 equiv.) and TEA (42 µL, 0.44 mmol, 3.0 equiv.) were added. The mixture was stirred for 30 mins followed by the addition of aldehyde **III-54** (0.1 mmol, 1.0 equiv.). The reaction was stirred overnight then filtered. The solution was diluted with EA (20 mL) and washed with $NaHCO_3$ solution (20 mL) and brine (20 mL) sequentially. The organic phase was dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure.

A solution of **III-92** (8.3 mg, 0.012 mmol, 12 mol %) and AgOAc (1.7 mg, 0.001 mmol, 10 mol %) in dry THF (1 mL) was stirred for 30 min at room temperature, followed by the addition of **III-102** from prior step in dry THF (1 mL) at -10 °C. The reaction was stirred at the same temperature for 24 h then quenched by the addition of silica (2 g), diluted with DCM and stirred at room temperature for another 1 h. Then, the solvent was removed and purified by column chromatography using cyclohexane/EA.

Methyl 5-benzyl-4-oxo-3-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'a)



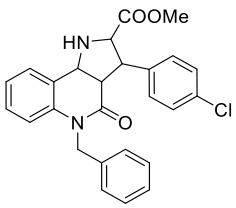
III-44'a

The title product compound **III-44'a** is prepared using general procedure 16 and isolated by column chromatography (1:1 Cyclohexane: acetone) giving an amorphous solid (27.7 mg, 0.07 mmol, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dt, *J* = 7.4, 1.3 Hz, 1H), 7.30 – 7.25

(m, 4H), 7.24 – 7.16 (m, 7H), 7.12 (td, *J* = 7.4, 1.1 Hz, 1H), 7.00 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.25 (d, *J* = 16.2 Hz, 1H), 5.03 (d, *J* = 16.1 Hz, 1H), 4.50 (d, *J* = 10.4 Hz, 1H), 4.23 (d, *J* = 13.5 Hz, 1H), 4.08 (t, *J* = 10.7 Hz, 1H), 3.13 (s, 3H), 3.07 (dd, *J* = 13.5, 11.1 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.5, 169.7, 139.6, 138.7, 137.1, 129.7, 128.9 (2C), 128.5 (2C), 128.3, 128.1 (2C), 127.3, 127.3, 126.7 (2C), 123.7, 123.3, 116.4, 67.0, 60.3, 54.4, 51.8, 49.8, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{25}N_2O_3$ m/z 413.1860, found 413.1854. **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 68.8 min; minor enantiomer: t_R = 40.7 min. *ee*=91%.

Methyl 5-benzyl-3-(4-chlorophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'b)

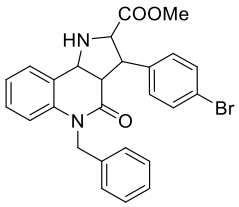


III-44'b

The title product compound **III-44'b** is prepared using general procedure 16 and isolated by column chromatography (1:1 PE:EA) giving a white solid (41 mg, 0.09 mmol, 92% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dt, *J* = 7.4, 1.4 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.25 – 7.19 (m, 4H), 7.18 – 7.10 (m, 5H), 7.00 (d, *J* = 8.1 Hz, 1H), 5.25 (d, *J* = 16.2 Hz, 1H), 5.02 (s, 1H), 4.48 (d, *J* = 10.4 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 1H), 4.04 (t, *J* = 10.7 Hz, 1H), 3.21 (s, 3H), 3.01 (dd, *J* = 13.5, 11.1 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.4, 169.5, 139.5, 137.3, 137.0, 133.1, 129.5 (2C), 128.9 (2C), 128.7 (2C), 128.4, 127.4, 126.7 (2C), 123.8, 123.3, 116.5, 66.7, 60.2, 54.5, 52.0, 49.1, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Cl$ m/z 447.1470, found 447.1468. **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 49.6 min; minor enantiomer: t_R = 24.7 min. *ee*=85%.

Methyl 5-benzyl-3-(4-bromophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'c)



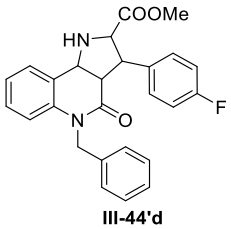
III-44'c

The title product compound **III-44'c** is prepared using general procedure 16 and isolated by column chromatography (1:1 PE:EA) giving an amorphous solid (45 mg, 0.09 mmol, 92% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 3H), 7.30 – 7.25 (m, 2H), 7.24 – 7.19 (m, 2H), 7.18 – 7.15 (m, 2H), 7.15 – 7.08 (m, 3H), 7.00 (d, *J* = 8.1 Hz, 1H), 5.26 (d, *J* = 16.2 Hz, 1H), 5.01 (d, *J* = 16.2 Hz, 1H), 4.48 (d, *J* = 10.4 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 1H), 4.03 (t, *J* = 10.7 Hz, 1H), 3.21 (s, 3H), 3.01 (dd, *J* = 13.5, 11.0 Hz, 1H). **^{13}C NMR**

(126 MHz, $CDCl_3$) δ 172.4, 169.5, 139.5, 137.9, 136.9, 131.6 (2C), 129.9 (2C), 129.5, 128.9 (2C), 128.4, 127.4, 126.7 (2C), 123.8, 123.3, 121.2, 116.4, 66.6, 60.2, 54.5, 52.0, 49.1, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Br$ m/z 491.0965, found 491.0961. **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 52.4 min; minor enantiomer: t_R = 25.4 min. *ee*=82%.

Methyl 5-benzyl-3-(4-fluorophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'd)

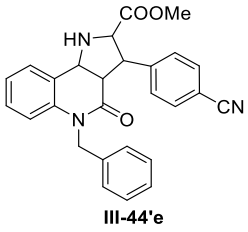


III-44'd

The title product compound **III-44'd** is prepared using general procedure 16 and isolated by column chromatography (1:1 PE:EA) giving an amorphous solid (38.1 mg, 0.09 mmol, 89% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.5 Hz, 1H), 7.32 – 7.11 (m, 9H), 7.03-6.94 (m, 3H), 5.25 (d, *J* = 16.0 Hz, 1H), 5.02 (d, *J* = 16.2 Hz, 1H), 4.48 (d, *J* = 10.4 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 1H), 4.10 – 3.99 (m, 1H), 3.20 (s, 3H), 3.02 (dd, *J* = 13.3, 11.0 Hz, 1H). **^{13}C NMR (126MHz, $CDCl_3$)** δ 172.5, 169.6, 162.1 (d, *J*CF = 245.7 Hz), 139.5, 137.0, 134.5 (d, *J*CF = 2.5 Hz), 129.7 (d, *J*CF = 7.6 Hz, 2C), 129.6, 128.9 (2C), 128.4, 127.4, 126.7 (2C), 123.8, 123.3, 116.4, 115.4 (d, *J*CF = 21.4 Hz, 2C), 66.7, 60.2, 54.5, 52.0, 49.0, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3F$ m/z 431.1766, found 431.1764. **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 40.3 min; minor enantiomer: t_R = 23.2 min. *ee*=86%.

Methyl 5-benzyl-3-(4-cyanophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'e)



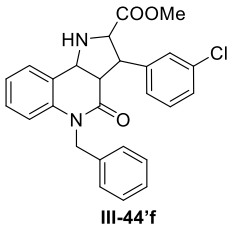
III-44'e

The title product compound **III-44'e** is prepared using general procedure 16 and isolated by column chromatography (1:1 PE:EA) giving an amorphous solid (19.0 mg, 0.04 mmol, 43% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.55 (m, 2H), 7.43 (dt, *J* = 7.4, 1.4 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.30 – 7.25 (m, 2H), 7.24 – 7.19 (m, 2H), 7.18 – 7.12 (m, 3H), 7.02 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.25 (d, *J* = 16.2 Hz, 1H), 5.01 (d, *J* = 16.2 Hz, 1H), 4.54 (d, *J* = 10.4 Hz, 1H), 4.26 (d, *J* = 13.4 Hz, 1H), 4.18 – 4.04 (m, 1H), 3.19 (s, 3H), 3.05 (dd, *J* = 13.4, 11.1 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.0, 169.1, 144.6, 139.4, 136.8, 132.3 (2C), 129.2, 129.1 (2C), 128.9 (2C), 128.6, 127.5, 126.7 (2C), 124.0, 123.4, 118.8, 116.6, 111.3, 66.6, 60.3, 54.5, 52.0, 49.6, 46.4. **HRMS(ESI):** $[M+H]^+$

calcd. $C_{27}H_{24}N_3O_3$ m/z 438.1812, found 438.1810. **HPLC conditions**: CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 30/70, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 55.1 min; minor enantiomer: t_R = 34.9 min. *ee*=2%.

Methyl-5-benzyl-3-(3-chlorophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'f)

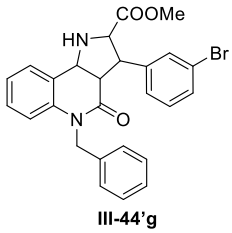


III-44'f

The title product compound **III-44'f** is prepared using general procedure 16 and isolated by column chromatography (1:1 PE:EA) giving an amorphous solid (36.1 mg, 0.08 mmol, 81% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.4 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.25 – 7.16 (m, 7H), 7.15-7.09 (m, 2H), 7.01 (d, *J* = 8.1 Hz, 1H), 5.25 (d, *J* = 16.2 Hz, 1H), 5.03 (d, *J* = 16.2 Hz, 1H), 4.49 (d, *J* = 10.4 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 1H), 4.03 (t, *J* = 10.7 Hz, 1H), 3.22 (s, 3H), 3.02 (dd, *J* = 13.5, 11.1 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.3, 169.4, 140.9, 139.5, 136.9, 134.3, 129.7, 129.5, 128.9 (2C), 128.4, 128.4, 127.5, 127.4, 126.7 (2C), 126.3, 123.8, 123.3, 116.5, 66.8, 60.2, 54.4, 52.0, 49.3, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Cl$ m/z 447.1470, found 447.1468. **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 49.1 min; minor enantiomer: t_R = 32.9 min. *ee*=75%.

Methyl-5-benzyl-3-(3-bromophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'g)

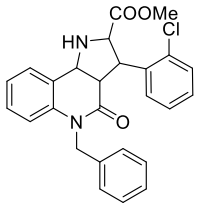


III-44'g

The title product compound **III-44'g** is prepared using general procedure 16 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (27.0 mg, 0.05 mmol, 55% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.4 Hz, 1H), 7.39 – 7.34 (m, 2H), 7.30-7.26 (m, 2H), 7.25 – 7.11 (m, 7H), 7.01 (d, *J* = 8.2 Hz, 1H), 5.25 (d, *J* = 16.2 Hz, 1H), 5.03 (d, *J* = 16.2 Hz, 1H), 4.49 (d, *J* = 10.4 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 1H), 4.02 (t, *J* = 10.8 Hz, 1H), 3.22 (s, 3H), 3.01 (dd, *J* = 13.5, 11.1 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.2, 169.4, 141.2, 139.5, 136.9, 131.3, 130.4, 130.1, 129.5, 128.9 (2C), 128.4, 127.4, 126.8, 126.7 (2C), 123.8, 123.3, 122.5, 116.5, 66.8, 60.2, 54.4, 52.0, 49.3, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Br$ m/z 491.0965, found 491.0962. **HPLC conditions**: CHIRAPAK IA column, *iso*-propanol / *iso*-hexane = 10/90, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 82.6 min; minor enantiomer: t_R = 74.2 min. *ee*=77%.

Methyl-5-benzyl-3-(2-chlorophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'h)



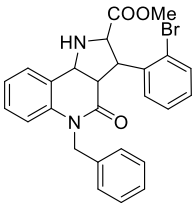
III-44'h

The title product compound **III-44'h** is prepared using general procedure 16 and isolated by column chromatography (1:1 PE:EA) giving an amorphous solid (32.8 mg, 0.07 mmol, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 2H), 7.30-7.27 (m, 2H), 7.25 – 7.06 (m, 8H), 7.01 (d, *J* = 8.2 Hz, 1H), 5.27 (d, *J* = 16.2 Hz, 1H), 5.04 (d, *J* = 16.2 Hz, 1H), 4.67 (d, *J* = 10.1 Hz, 1H), 4.57 (dd, *J* = 11.5, 10.0 Hz, 1H), 4.33 (d, *J* = 13.3 Hz, 1H), 3.22 (dd, *J* = 13.4, 11.4 Hz, 1H), 3.11 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.0, 169.2, 139.5, 137.0, 135.8, 135.5, 129.8, 129.6, 128.9 (2C), 128.4, 128.3, 127.4, 126.8, 126.7 (2C), 123.8, 123.4, 116.4, 64.6, 60.0, 51.8, 51.5, 46.3, 46.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Cl$ m/z 447.1470, found 447.1468. **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 52.8 min; minor enantiomer: t_R = 31.2 min. *ee*=75%.

Methyl-5-benzyl-3-(2-bromophenyl)-4-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'i)

The title product compound **III-44'i** is prepared using general procedure 16 and isolated by column chromatography (1:1 PE:EA) giving an amorphous solid (30.8 mg, 0.06 mmol, 63% yield).

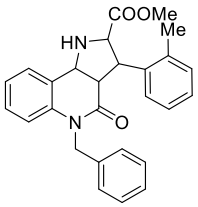


III-44'i

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.44 (dt, *J* = 7.4, 1.5 Hz, 1H), 7.31-7.26 (m, 2H), 7.25 – 7.17 (m, 5H), 7.16 – 7.04 (m, 3H), 7.01 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.27 (d, *J* = 16.2 Hz, 1H), 5.03 (d, *J* = 16.2 Hz, 1H), 4.70 (d, *J* = 10.1 Hz, 1H), 4.56 (dd, *J* = 11.6, 10.1 Hz, 1H), 4.34 (d, *J* = 13.3, 1H), 3.22 (dd, *J* = 13.3, 11.5 Hz, 1H), 3.11 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.8, 169.1, 139.5, 137.5, 137.0, 132.9, 129.7, 128.9 (2C), 128.6, 128.3, 127.5, 127.4, 127.3, 126.7 (2C), 126.5, 123.8, 123.4, 116.4, 64.5, 59.9, 51.8, 48.7, 46.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{24}N_2O_3Br$ m/z 491.0965, found 491.0960. **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 47.5 min; minor enantiomer: t_R = 31.4 min. *ee*=76%.

Methyl-5-benzyl-4-oxo-3-(*o*-tolyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'j)

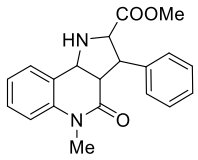
The title product compound **III-44'j** is prepared using general procedure 16 and isolated by column chromatography (1:1 PE:EA) giving an amorphous solid (20.5 mg, 0.05 mmol, 48% yield).



III-44'j

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.2 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.25 – 7.04 (m, 8H), 7.01-6.96 (m, 2H), 5.28 (d, *J* = 16.1 Hz, 1H), 5.01 (d, *J* = 16.2 Hz, 1H), 4.54 (d, *J* = 10.3 Hz, 1H), 4.33 (t, *J* = 10.7 Hz, 1H), 4.25 (d, *J* = 13.4 Hz, 1H), 3.17 (dd, *J* = 13.4, 10.9 Hz, 1H), 3.07 (s, 3H), 2.53 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.6, 169.8, 139.7, 137.4, 137.1, 136.9, 130.3, 129.8, 128.9 (2C), 128.3, 127.3, 126.9, 126.7 (2C), 126.0, 125.6, 123.7, 123.3, 116.4, 65.7, 60.3, 53.9, 51.7, 46.3, 45.1, 20.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{27}H_{27}N_2O_3$ m/z 427.2016, found 427.2014. **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 34.8 min; minor enantiomer: t_R = 24.7 min. *ee*=85%.

Methyl-5-methyl-4-oxo-3-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'k)

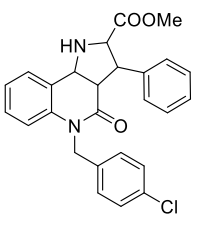


III-44'k

The title product compound **III-44'k** is prepared using general procedure 16 and isolated by column chromatography (1:1 PE:EA) giving an amorphous solid (18.8 mg, 0.06 mmol, 56% yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.4 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.30 – 7.26 (m, 2H), 7.23 – 7.18 (m, 4H), 7.09 (d, *J* = 8.1 Hz, 1H), 4.49 (d, *J* = 10.4 Hz, 1H), 4.18 (d, *J* = 13.6 Hz, 1H), 4.01 (t, *J* = 10.8 Hz, 1H), 3.36 (s, 3H), 3.14 (s, 3H), 2.94 (dd, *J* = 13.5, 11.2 Hz, 1H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 172.5, 169.4, 140.4, 138.6, 129.3, 128.4, 128.4, 128.1, 127.2, 123.6, 123.2, 115.5, 66.8, 60.0, 54.2, 51.8, 49.7, 29.8. **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 58.2 min; minor enantiomer: t_R = 41.4 min. *ee*=79%.

Methyl-5-(4-chlorobenzyl)-4-oxo-3-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'l)



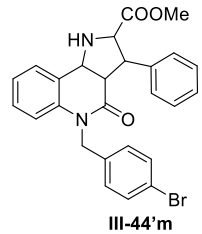
III-44'l

The title product compound **III-44'l** is prepared using general procedure 16 and isolated by column chromatography (1:1 PE:EA) giving an amorphous solid (26.4 mg, 0.06 mmol, 59% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.5 Hz, 1H), 7.31 – 7.18 (m,

8H), 7.17 – 7.10 (m, 3H), 6.96 (d, *J* = 8.2 Hz, 1H), 5.19 (d, *J* = 16.2 Hz, 1H), 5.00 (d, *J* = 16.2 Hz, 1H), 4.52 (d, *J* = 10.4 Hz, 1H), 4.24 (dd, *J* = 13.7 Hz, 1H), 4.07 (t, *J* = 10.7 Hz, 1H), 3.14 (s, 3H), 3.08 (dd, *J* = 13.4, 11.0 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.4, 169.5, 139.3, 138.4, 138.4, 135.6, 133.1, 129.0, 128.5, 128.4, 128.2, 128.1, 127.4, 124.0, 123.5, 116.2, 66.8, 60.2, 54.1, 54.1, 51.9, 49.6, 49.5, 45.7. **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 52.3 min; minor enantiomer: t_R = 34.6 min. *ee*=85%

Methyl-5-(4-bromobenzyl)-4-oxo-3-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'm)

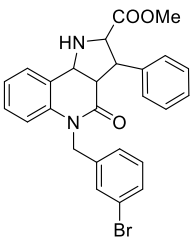


III-44'm

The title product compound **III-44'm** is prepared using general procedure 16 and isolated by column chromatography (1:1 PE:EA) giving an amorphous solid (29.0 mg, 0.06 mmol, 59% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.4 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.31 – 7.19 (m, 6H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.09 – 7.04 (m, 2H), 6.95 (d, *J* = 8.1 Hz, 1H), 5.17 (d, *J* = 16.3 Hz, 1H), 4.98 (d, *J* = 16.2 Hz, 1H), 4.50 (d, *J* = 10.4 Hz, 1H), 4.22 (d, *J* = 13.5 Hz, 1H), 4.06 (t, *J* = 10.7 Hz, 1H), 3.13 (s, 3H), 3.07 (dd, *J* = 13.5, 11.0 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.5, 169.6, 139.3, 138.5, 136.1, 131.9, 129.6, 128.5, 128.5, 128.4, 128.0, 127.3, 123.9, 123.5, 121.2, 116.2, 66.8, 60.2, 54.2, 51.9, 49.6, 45.7. **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 58.2 min; minor enantiomer: t_R = 37.6 min. *ee*=81%.

Methyl-5-(3-bromobenzyl)-4-oxo-3-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'n)



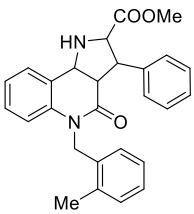
III-44'n

The title product compound **III-44'n** is prepared using general procedure 16 and isolated by column chromatography (1:1 PE:EA) giving an amorphous solid (23.1 mg, 0.05 mmol, 47% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.4 Hz, 1H), 7.37-7.33 (m, 2H), 7.31 – 7.19 (m, 6H), 7.18 – 7.11 (m, 2H), 7.09 (d, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 5.20 (d, *J* = 16.3 Hz, 1H), 5.00 (d, *J* = 16.4 Hz, 1H), 4.50 (d, *J* = 10.4 Hz, 1H), 4.23 (d, *J* = 13.4 Hz, 1H), 4.07 (t, *J* = 10.7 Hz, 1H), 3.13 (s, 3H), 3.09 (dd, *J* = 13.5, 11.1 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.5, 169.7, 139.4, 139.2, 138.5, 130.6, 130.4, 129.7,

129.6, 128.5, 128.4, 128.0, 127.3, 125.3, 123.9, 123.5, 123.0, 116.1, 66.8, 60.2, 54.1, 51.9, 49.6, 45.7. **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 58.3 min; minor enantiomer: t_R = 37.6 min. *ee*=85%.

Methyl-5-(2-methylbenzyl)-4-oxo-3-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (III-44'o)



III-44'o

The title product compound **III-44'o** is prepared using general procedure 16 and isolated by column chromatography (1:1 PE:EA) giving an amorphous solid (26.4 mg, 0.06 mmol, 62% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.3 Hz, 1H), 7.31 – 7.24 (m, 2H), 7.23 – 7.18 (m, 4H), 7.17 – 7.10 (m, 3H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.85-6.82 (m, 2H), 5.31 (d, *J* = 16.9 Hz, 1H), 4.84 (d, *J* = 16.9 Hz, 1H), 4.51 (d, *J* = 10.4 Hz, 1H), 4.30 (d, *J* = 13.6 Hz, 1H), 4.07 (t, *J* = 10.7 Hz, 1H), 3.16 – 3.07 (m, 4H), 2.36 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.5, 169.5, 139.8, 138.6, 135.0, 134.2, 130.5, 129.5, 128.5, 128.4, 128.1, 127.3, 127.0, 126.4, 124.9, 123.8, 123.3, 116.3, 66.9, 60.3, 54.4, 51.9, 49.7, 44.7, 19.3. **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1} , major enantiomer: t_R = 58.3 min; minor enantiomer: t_R = 41.5 min. *ee*=88%.

7.2.4 X-ray crystallographic data of III-50m, III-59'b and III-45'c (by Dr. Otte and Prof. Dr. Strohmann)

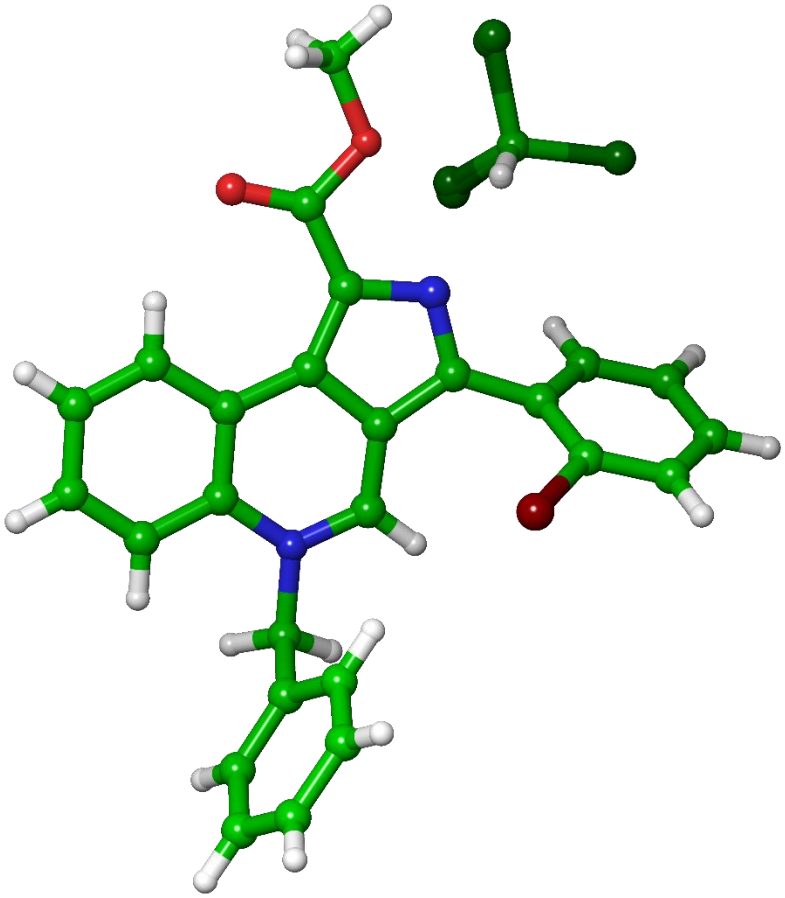


Figure S1. Crystal structure of the cycloadduct **III-50m**. ORTEP plot of $C_{27}H_{20}BrCl_3N_2O_2$ (M =590.71 g/mol) (**III-50m·CHCl$_3$**) at the 50% probability level. See Supplementary Table S1 for additional details. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC 2017048.

Table S1. Crystal data and structure refinement for **III-50m·CHCl$_3$**.

Empirical formula	$C_{27}H_{20}BrCl_3N_2O_2$
Formula weight	590.71
Temperature/K	99.98
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.297(2)
b/Å	8.1074(10)
c/Å	26.975(5)
α/°	90
β/°	100.752(6)
γ/°	90
Volume/Å^3	2427.3(7)
Z	4
ρ_{calc}g/cm^3	1.616
μ/mm^{-1}	2.054
F(000)	1192
Crystal size/mm^3	0.195 × 0.139 × 0.055
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.208 to 61.996
Index ranges	$-16 \leq h \leq 16$, $-11 \leq k \leq 11$, $-39 \leq l \leq 39$
Reflections collected	132541
Independent reflections	7730 [R_{int} = 0.0407, R_{sigma} = 0.0152]
Data/restraints/parameters	7730/0/336
Goodness-of-fit on F^2	1.06
Final R indexes [I>=2σ (I)]	R_1 = 0.0310, wR_2 = 0.0791
Final R indexes [all data]	R_1 = 0.0380, wR_2 = 0.0838
Largest diff. peak/hole / e Å^{-3}	1.68/-0.80

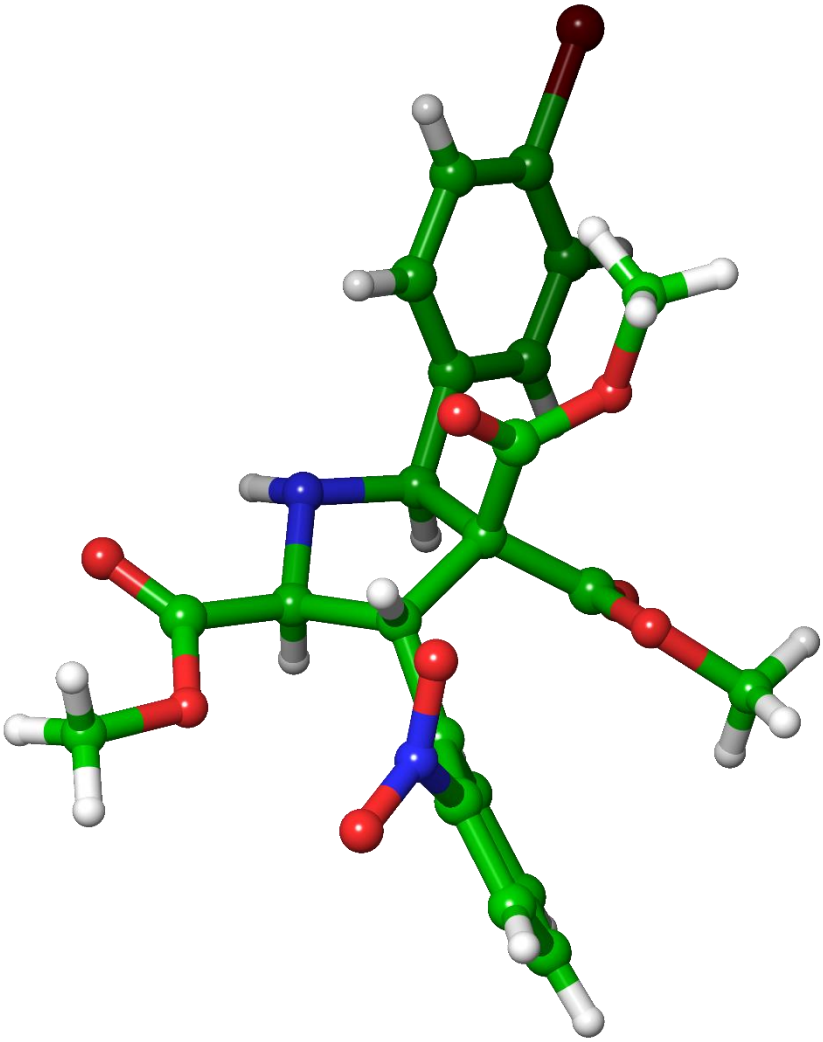


Figure S2. Crystal structure of the cycloadduct **III-59'b**. ORTEP plot of $C_{22}H_{21}BrN_2O_8$ (M =521.32 g/mol) at the 50% probability level. See Supplementary Table S2 for additional details. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC 2062836.

Table S2. Crystal data and structure refinement for **III-59'b**.

Empirical formula	$C_{22}H_{21}BrN_2O_8$
Formula weight	521.32
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1$
a/Å	11.0295(4)
b/Å	8.0843(3)
c/Å	12.5939(6)
α/°	90
β/°	105.806(2)
γ/°	90
Volume/Å^3	1080.49(8)
Z	2
ρ_{calc}g/cm^3	1.602
μ/mm^{-1}	1.956
F(000)	532
Crystal size/mm^3	0.742 × 0.235 × 0.096
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.36 to 81.996
Index ranges	$-20 \leq h \leq 20$, $-14 \leq k \leq 14$, $-23 \leq l \leq 23$
Reflections collected	212914
Independent reflections	14212 [R_{int} = 0.0293, R_{sigma} = 0.0129]
Data/restraints/parameters	14212/1/305
Goodness-of-fit on F^2	1.032
Final R indexes [I>=2σ (I)]	R_1 = 0.0174, wR_2 = 0.0485
Final R indexes [all data]	R_1 = 0.0182, wR_2 = 0.0489
Largest diff. peak/hole / e Å^{-3}	0.39/-0.38
Flack parameter	-0.0033(11)

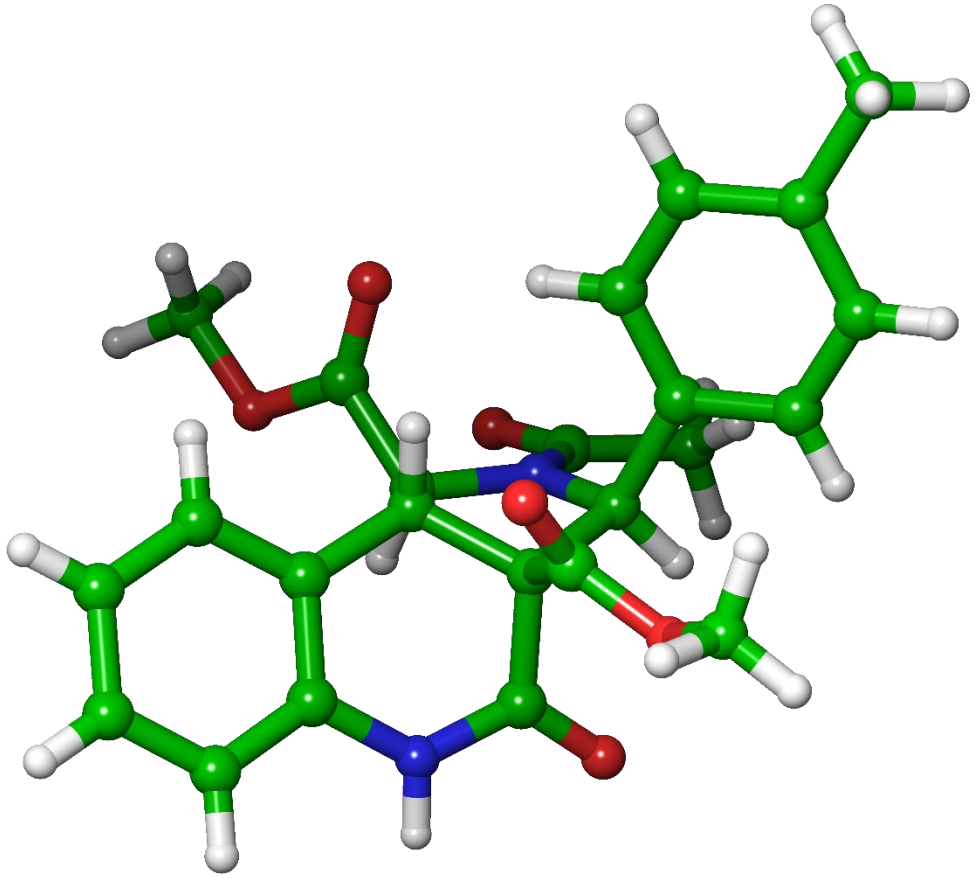


Figure S3. Crystal structure of the cycloadduct **III-45'c**. ORTEP plot of $C_{24}H_{24}N_2O_6$ (M =436.45 g/mol) at the 50% probability level. See Supplementary Table S3 for additional details. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC 2062837.

Table S3. Crystal data and structure refinement for **III-45'c**.

Empirical formula	$C_{24}H_{24}N_2O_6$
Formula weight	436.45
Temperature/K	102.26
Crystal system	trigonal
Space group	$P3_1$
a/Å	13.1782(8)
b/Å	13.1782(8)
c/Å	10.9411(7)
α/°	90
β/°	90
γ/°	120
Volume/Å^3	1645.5(2)
Z	3
ρ_{calc}g/cm^3	1.321
μ/mm^{-1}	0.792
F(000)	690
Crystal size/mm^3	0.375 × 0.126 × 0.059
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.746 to 148.83
Index ranges	$-16 \leq h \leq 16$, $-12 \leq k \leq 16$, $-13 \leq l \leq 13$
Reflections collected	18732
Independent reflections	4448 [R_{int} = 0.0210, R_{sigma} = 0.0176]
Data/restraints/parameters	4448/1/298
Goodness-of-fit on F^2	1.031
Final R indexes [I>=2σ (I)]	R_1 = 0.0243, wR_2 = 0.0650
Final R indexes [all data]	R_1 = 0.0243, wR_2 = 0.0651
Largest diff. peak/hole / e Å^{-3}	0.24/-0.15
Flack parameter	0.03(3)

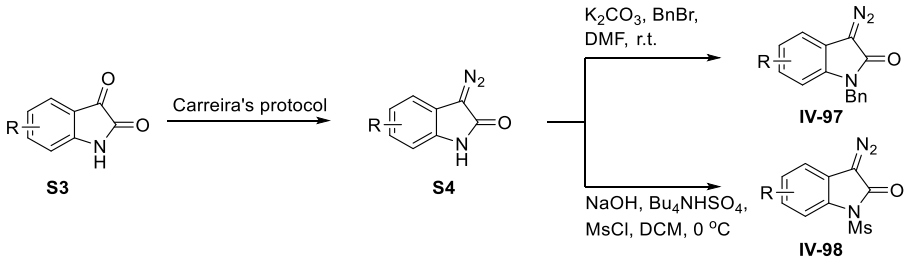
7.2.5 Cell painting datasets of pyrroquinolines

No.	**Induction @ 10 µM**	**Induction @ 30 µM**	**Induction @ 50 µM**	*No.*	**Induction @ 10 µM**	**Induction @ 30 µM**	**Induction @ 50 µM**
III-43a	1	28	54	**III-43i**	6	27	34
III-43b	6	37	64	**III-43j**	2	31	37
III-43c	0	22	34	**III-43k**	1	29	34
III-43d	0	69	87	**III-43l**	1	30	33
III-43e	1	31	40	**III-43m**	1	29	32
III-43f	1	36	48	**III-43n**	2	28	36
III-43g	1	18	20	**III-43o**	0	20	12
III-43h	7	28	16	**III-43p**	2	n.d.	n.d.
III-44a	2	29	31	**III-44j**	3	32	34
III-44b	0	27	31	**III-44k**	0	28	42
III-44c	0	19	24	**III-44l**	0	8	14
III-44d	7	32	66	**III-44m**	4	38	51
III-44e	1	37	30	**III-44n**	10	41	41
III-44f	0	23	25	**III-44o**	2	55	45
III-44g	2	16	21	**III-44p**	0	9	13
III-44h	4	52	29	**III-44q**	0	12	23
III-44i	4	25	47	**III-44r**	0	18	24
III-45a	0	0	0	**III-45f**	2	0	1
III-45b	0	0	1	**III-45g**	0	0	1
III-45c	0	0	1	**III-45h**	1	0	0
III-45d	0	n.d.	n.d.	**III-45i**	0	0	2
III-45e	0	1	0	**III-45j**	0	22	29
III-46a	5	5	2	**III-46j**	n.d.	17	23
III-46b	8	3	4	**III-46k**	0	24	12
III-46c	n.d.	4	6	**III-46l**	0	16	14
III-46d	4	14	3	**III-46m**	1	8	30
III-46e	n.d.	1	3	**III-46n**	1	13	30
III-46f	5	5	2	**III-46o**	8	n.d.	n.d.
III-46g	1	24	9	**III-46p**	3	n.d.	n.d.
III-46h	8	9	4	**III-46q**	3	2	2
III-46i	0	12	5				
III-48a	1	n.d.	n.d.	**III-48g**	10	61	66
III-48b	0	n.d.	n.d.	**III-48h**	0	26	25
III-48c	0	n.d.	2	**III-48i**	4	5	7
III-48d	0	50	64	**III-48j**	0	10	19
III-48e	1	n.d.	9	**III-48k**	10	59	66
III-48f	0	52	71	**III-48l**	2	25	39

No.	**Induction @ 10 µM**	**Induction @ 30 µM**	**Induction @ 50 µM**	*No.*	**Induction @ 10 µM**	**Induction @ 30 µM**	**Induction @ 50 µM**
III-49a	0	23	27	**III-49h**	7	n.d.	n.d.
III-49b	10	33	23	**III-49i**	12	15	28
III-49c	25	64	49	**III-49j**	9	18	21
III-49d	11	20	26	**III-49k**	8	23	29
III-49e	8	14	12	**III-49l**	11	31	19
III-49f	15	21	12	**III-49m**	5	32	27
III-49g	5	9	10	**III-49n**	2	15	6
III-50a	4	n.d.	n.d.	**III-50s**	5	n.d.	n.d.
III-50b	16	n.d.	n.d.	**III-50t**	19	n.d.	n.d.
III-50c	8	n.d.	n.d.	**III-50u**	39	n.d.	n.d.
III-50d	24	n.d.	n.d.	**III-50v**	10	73	75
III-50e	36	n.d.	n.d.	**III-50w**	39	n.d.	n.d.
III-50f	26	n.d.	n.d.	**III-50x**	26	n.d.	n.d.
III-50g	6	n.d.	n.d.	**III-50y**	20	n.d.	n.d.
III-50h	5	58	56	**III-50z**	20	n.d.	n.d.
III-50i	23	n.d.	n.d.	**III-50aa**	21	n.d.	n.d.
III-50j	18	n.d.	n.d.	**III-50bb**	8	n.d.	n.d.
III-50k	19	n.d.	n.d.	**III-50cc**	11	n.d.	n.d.
III-50l	3	n.d.	n.d.	**III-50dd**	31	n.d.	n.d.
III-50m	9	n.d.	n.d.	**III-50ee**	46	n.d.	n.d.
III-50n	5	70	88	**III-50ff**	43	n.d.	n.d.
III-50o	25	n.d.	n.d.	**III-50gg**	26	n.d.	n.d.
III-50p	2	n.d.	n.d.	**III-50hh**	14	83	81
III-50q	11	n.d.	n.d.	**III-50ii**	27	n.d.	n.d.
III-50r	13	n.d.	n.d.	**III-50jj**	62	n.d.	n.d.

7.3 Experimental part for synthesis of spirooxindoles

7.3.1 Synthesis of diazooxindoles

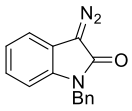


Diazo **S4** was prepared according to Carreira's protocol.[129] The resulting diazo was then converted to **IV-97** or **IV-98** *via* one step manipulation as listed below.

General procedure 17: Diazo **S4** (1.0 equiv.) was dissolved in DMF (0.25 M) followed by the addition of K_2CO_3 (3.0 equiv.) and BnBr (1.5 equiv.) and stirred at room temperature for overnight. Then the reaction was dilute with ether (50 mL) and wash the mixture with water (10 mL * 3). The organic layer was dried with Na_2SO_4. The solvent was removed under reduced pressure. The remaining residue was purified by flash column chromatography to give product **IV-97**.

General procedure 18: Diazo **S4** (1.0 equiv.), NaOH (3.0 equiv.) and Bu_4NHSO_4 (0.05 equiv.) were stirred at CH_2Cl_2 (0.5 M) at 0 °C for 20 min. Then MsCl (1.5 equiv.) was then added to the rection mixture. The reaction was then warmed to room temperature and stirred overnight. The reaction mixture was loaded directly onto the column and eluted with CH_2Cl_2 directly to give product **IV-98**.

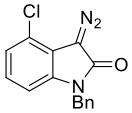
1-benzyl-3-diazoindolin-2-one (IV-97a)



The title product compound **IV-97a** was prepared using general procedure 17 from diazo **S4a** (0.96 g, 6.0 mmol) and isolated by column chromatography (4:1 *n*-pentane:EA) giving a solid (1.04 g, 4.2 mmol, 69% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.19 (m, 5H), 7.18 – 7.14 (m, 1H), 7.05 (td, *J* = 7.6, 1.5 Hz, 1H), 7.01 (td, *J* = 7.5, 1.4 Hz, 1H), 6.78 (dd, *J* = 7.1, 1.3 Hz, 1H), 4.98 (s, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 167.0, 136.1, 133.8, 128.9, 127.8, 127.4, 125.6, 122.3, 118.4, 116.9, 109.7, 44.4.

1-benzyl-4-chloro-3-diazoindolin-2-one (IV-97b)

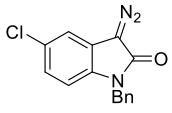


IV-97b

The title product compound **IV-97b** was prepared using general procedure 17 from diazo **S4b** (193 mg, 1.0 mmol) and isolated by column chromatography (4:1 PE:EA) giving a solid (150 mg, 0.53 mmol, 53% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.29 (m, 2H), 7.29 – 7.26 (m, 3H), 7.02-6.97 (m, 2H), 6.71 (dd, *J* = 6.9, 1.9 Hz, 1H), 5.02 (s, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.8, 135.8, 134.9, 129.0, 128.0, 127.4, 126.2, 126.1, 122.6, 114.6, 108.0, 44.7.

1-benzyl-5-chloro-3-diazoindolin-2-one (IV-97c)

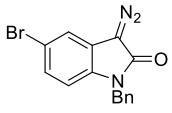


IV-97c

The title product compound **IV-97c** was prepared using general procedure 17 from diazo **S4c** (0.5 g, 2.6 mmol) and isolated by column chromatography (4:1 PE:EA) giving a solid (200 mg, 0.71 mmol, 27% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 2H), 7.29 – 7.25 (m, 4H), 7.19 (d, *J* = 2.0 Hz, 1H), 7.04 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 5.01 (s, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.4, 135.7, 132.3, 129.0, 128.0, 127.8, 127.4, 125.6, 118.4, 118.3, 110.5, 77.2, 44.6.

1-benzyl-5-bromo-3-diazoindolin-2-one (IV-97d)

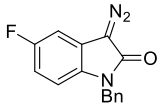


IV-97d

The title product compound **IV-97d** was prepared using general procedure 17 from diazo **S4d** (170 mg, 0.71 mmol) and isolated by column chromatography (5:1 PE:EA) giving a solid (133 mg, 0.41 mmol, 57% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.23 (m, 6H), 7.22 – 7.15 (m, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 5.00 (s, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.3, 135.7, 132.7, 129.0, 128.4, 128.0, 127.4, 121.1, 118.8, 114.9, 111.0, 77.2, 44.5.

1-benzyl-3-diazo-5-fluoroindolin-2-one (IV-97e)

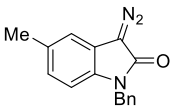


IV-97e

The title product compound **IV-97e** was prepared using general procedure 17 from diazo **S4e** (177 mg, 1.0 mmol) and isolated by column chromatography (5:1 PE:EA) giving a solid (161 mg, 0.6 mmol, 60% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.25 (m, 5H), 6.95 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.79 (ddd, *J* = 9.3, 8.6, 2.5 Hz, 1H), 6.70 (dd, *J* = 8.6, 4.2 Hz, 1H), 5.01 (s, 2H).

1-benzyl-3-diazo-5-methylindolin-2-one (IV-97f)

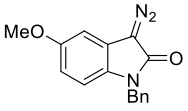


IV-97f

The title product compound **IV-97f** was prepared using general procedure 17 from diazo **S4f** (260 mg, 1.5 mmol) and isolated by column chromatography (4:1 PE:EA) giving a solid (364 mg, 1.4 mmol, 92% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 6H), 7.03 (s, 1H), 6.89 (ddd, *J* = 8.1, 1.7, 0.9 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.00 (s, 2H), 2.33 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 167.1, 136.2, 132.0, 131.6, 128.9, 127.7, 127.4, 126.2, 119.1, 116.9, 109.5, 44.4, 21.3.

1-benzyl-3-diazo-5-methoxyindolin-2-one (IV-97g)

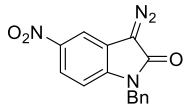


IV-97g

The title product compound **IV-97g** was prepared using general procedure 17 from diazo **S4g** (500 mg, 2.6 mmol) and isolated by column chromatography (4:1 PE:EA) giving a light yellow solid (411 mg, 1.5 mmol, 56 yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 5H), 6.79 (d, *J* = 2.4 Hz, 1H), 6.69 (d, *J* = 8.6 Hz, 1H), 6.63 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.99 (s, 2H), 3.78 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.9, 155.8, 136.2, 128.9, 127.8, 127.8, 127.4, 118.0, 111.2, 110.2, 104.9, 56.0, 44.5.

1-benzyl-3-diazo-5-nitroindolin-2-one (IV-97h)

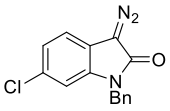


IV-97h

The title product compound **IV-97h** was prepared using general procedure 17 from diazo **S4h** (204 mg, 1.0 mmol) and isolated by column chromatography (5:1 PE:EA) giving a light yellow solid (93 mg, 0.3 mmol, 31% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.2 Hz, 1H), 8.04 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.40 – 7.25 (m, 5H), 6.89 (d, *J* = 8.7 Hz, 1H), 5.08 (s, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.3, 143.2, 138.5, 135.0, 129.2, 128.3, 127.4, 122.2, 117.8, 113.8, 109.0, 44.9.

1-benzyl-6-chloro-3-diazoindolin-2-one (IV-97i)



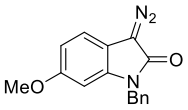
IV-97i

The title product compound **IV-97i** was prepared using general procedure 17 from diazo **S4i** (194 mg, 1.0 mmol) and isolated by column chromatography (4:1 PE:EA) giving a light yellow solid (160 mg, 0.6 mmol, 57% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 5H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.43 (d, *J* = 2.3 Hz, 1H), 4.99 (s, 2H), 3.74 (s, 3H). **^{13}C NMR (126 MHz,**

$CDCl_3$) δ 168.1, 158.7, 136.0, 135.0, 128.9, 127.8, 127.4, 119.1, 108.7, 107.2, 97.8, 55.7, 44.5.

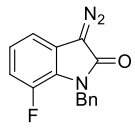
1-benzyl-3-diazo-6-methoxyindolin-2-one (IV-97j)



IV-97j

The title product compound **IV-97j** was prepared using general procedure 17 from diazo **S4j** (189 mg, 1.0 mmol) and isolated by column chromatography (4:1 PE:EA) giving a light yellow solid (233 mg, 0.8 mmol, 83% yield).

1-benzyl-3-diazo-7-fluoroindolin-2-one (IV-97k)

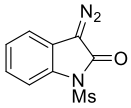


IV-97k

The title product compound **IV-97k** was prepared using general procedure 17 from diazo **S4k** (177 mg, 1.0 mmol) and isolated by column chromatography (4:1 PE:EA) giving a light yellow solid (176 mg, 0.7 mmol, 66% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 2H), 7.33 – 7.28 (m, 2H), 7.27 – 7.24 (m, 1H), 7.03 – 6.94 (m, 2H), 6.86 (ddd, *J* = 11.7, 7.5, 1.9 Hz, 1H), 5.16 (s, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 166.4, 148.01 (d, *J* = 243.9 Hz), 137.3, 128.7, 127.8, 127.7 (d, *J* = 1.6 Hz), 122.9 (d, *J* = 7.2 Hz), 120.6 (d, *J* = 11.7 Hz), 119.7 (d, *J* = 5.5 Hz), 114.3 (d, *J* = 3.2 Hz), 113.0 (d, *J* = 19.7 Hz), 46.1 (d, *J* = 4.7 Hz).

3-diazo-1-(methylsulfonyl)indolin-2-one (IV-98a)

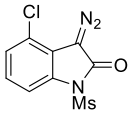


IV-98a

The title product compound **IV-98a** was prepared using general procedure 18 from diazo **S4a** (1 g, 6.3 mmol) and isolated by column chromatography (DCM) giving a solid (0.85 g, 3.6 mmol, 57% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 1H), 7.38 – 7.15 (m, 3H), 3.47 (s, 3H).

4-chloro-3-diazo-1-(methylsulfonyl)indolin-2-one (IV-98b)

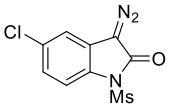


IV-98b

The title product compound **IV-98b** was prepared using general procedure 18 from diazo **S4b** (387 mg, 2.0 mmol) and isolated by column chromatography (DCM) giving a solid (183 mg, 0.7 mmol, 34% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 6.0, 3.2 Hz, 1H), 7.18 (s, 1H), 7.16 (d, *J* = 2.8 Hz, 1H), 3.48 (s, 3H).

5-chloro-3-diazo-1-(methylsulfonyl)indolin-2-one (IV-98c)

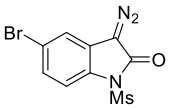


IV-98c

The title product compound **IV-98c** was prepared using general procedure 18 from diazo **S4c** (300 mg, 1.55 mmol) and isolated by column chromatography (DCM) giving a solid (147 mg, 0.5 mmol, 35% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 9.5 Hz, 1H), 7.21 – 7.17 (m, 2H), 3.47 (s, 3H).

5-bromo-3-diazo-1-(methylsulfonyl)indolin-2-one (IV-98d)

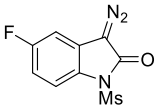


IV-98d

The title product compound **IV-98d** was prepared using general procedure 18 from diazo **S4d** (476 mg, 2.0 mmol) and isolated by column chromatography (DCM) giving a solid (83 mg, 0.3 mmol, 13% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.65 (m, 1H), 7.38 – 7.32 (m, 2H), 3.47 (s, 3H).

3-diazo-5-fluoro-1-(methylsulfonyl)indolin-2-one (IV-98e)

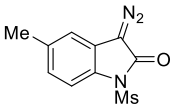


IV-98e

The title product compound **IV-98e** was prepared using general procedure 18 from diazo **S4e** (354 mg, 2.0 mmol) and isolated by column chromatography (DCM) giving a solid (194 mg, 0.8 mmol, 38% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 9.7, 4.5 Hz, 1H), 7.00 – 6.89 (m, 2H), 3.47 (s, 3H).

3-diazo-5-methyl-1-(methylsulfonyl)indolin-2-one (IV-98f)

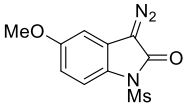


IV-98f

The title product compound **IV-98f** was prepared using general procedure 18 from diazo **S4f** (346 mg, 2.0 mmol) and isolated by column chromatography (DCM) giving a solid (178 mg, 0.71 mmol, 35% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.07 – 6.98 (m, 2H), 3.45 (s, 3H), 2.38 (s, 3H).

3-diazo-5-methoxy-1-(methylsulfonyl)indolin-2-one (IV-98g)

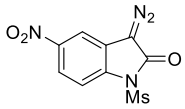


IV-98g

The title product compound **IV-98g** was prepared using general procedure 18 from diazo **S4g** (378 mg, 2.0 mmol) and isolated by column chromatography (DCM) giving a solid (95 mg, 0.4 mmol, 18% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 8.9, 0.5 Hz, 1H), 6.76 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.73 (d, *J* = 2.2 Hz, 1H), 3.82 (s, 3H), 3.44 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.5, 157.4, 123.9, 117.2, 115.3, 112.2, 104.1, 55.9, 42.0.

3-diazo-1-(methylsulfonyl)-5-nitroindolin-2-one (IV-98h)

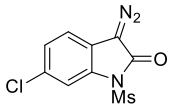


IV-98h

The title product compound **IV-98h** was prepared using general procedure 18 from diazo **S4h** (408 mg, 2.0 mmol) and isolated by column chromatography (DCM) giving a solid (171 mg, 0.6 mmol, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 9.0, 2.3 Hz, 1H), 8.12 (d, *J* = 2.2 Hz, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 3.54 (s, 3H).

6-chloro-3-diazo-1-(methylsulfonyl)indolin-2-one (IV-98i)

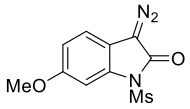


IV-98i

The title product compound **IV-98i** was prepared using general procedure 18 from diazo **S4i** (387 mg, 2.0 mmol) and isolated by column chromatography (DCM) giving a solid (254 mg, 0.9 mmol, 47% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 1.8 Hz, 1H), 7.23 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 3.48 (s, 3H).

3-diazo-6-methoxy-1-(methylsulfonyl)indolin-2-one (IV-98j)

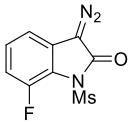


IV-98j

The title product compound **IV-98j** was prepared using general procedure 18 from diazo **S4j** (378 mg, 2.0 mmol) and isolated by column chromatography (DCM) giving a solid (173 mg, 0.6 mmol, 32% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.3 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.80 (dd, *J* = 8.5, 2.3 Hz, 1H), 3.83 (s, 3H), 3.47 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.4, 159.2, 131.0, 118.9, 111.5, 107.4, 101.4, 55.9, 42.2.

3-diazo-7-fluoro-1-(methylsulfonyl)indolin-2-one (IV-98k)

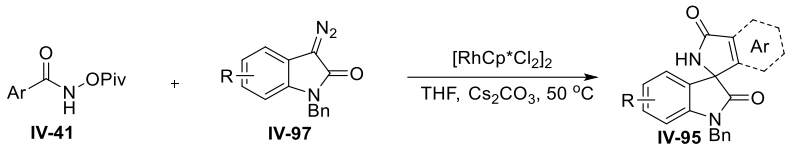


IV-98k

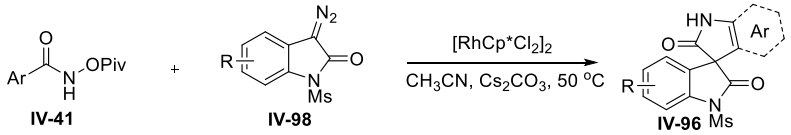
The title product compound **IV-98k** was prepared using general procedure 18 from diazo **S4k** (354 mg, 2.0 mmol) and isolated by column chromatography (DCM) giving a solid (133 mg, 0.5 mmol, 26% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.20 (m, 1H), 7.07 – 6.96 (m, 2H), 3.52 (s, 3H).

7.3.2 Synthesis of spirooxindoles

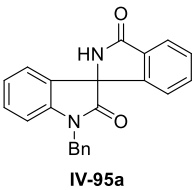


General procedure 19: To a solution of $[RhCp^*Cl_2]_2$ (0.6 mg, 0.001 mmol, 0.01 equiv.) in THF (1.0 mL) was added benzhydroxamate **IV-41** (0.1 mmol, 1.0 equiv.) and Cs_2CO_3 (0.02 mmol, 0.2 equiv.). The reaction mixture was stirred at room temperature for 2 min. Then, diazo **IV-97** (0.1 mmol, 1.0 equiv.) was added to the solution and stirred at 50 °C overnight. The reaction was concentrated and crude ^{1}H NMR was performed directly. Then, the reaction mixture was purified by column chromatography (2:1 to 1:1 PE:EA).



General procedure 20: To a solution of $[RhCp^*Cl_2]_2$ (0.6 mg, 0.001 mmol, 0.01 equiv.) in CH_3CN (1.0 mL) was added benzhydroxamate **IV-41** (0.1 mmol, 1.0 equiv.) and Cs_2CO_3 (0.02 mmol, 0.2 equiv.). The reaction mixture was stirred at room temperature for 2 min. Then, diazo **IV-98** (0.12 mmol, 1.2 equiv.) was added to the solution and stirred at 50 °C overnight. The reaction was concentrated and crude ^{1}H NMR was performed directly. Then, the reaction mixture was purified by column chromatography (2:1 to 1:1 PE:EA).

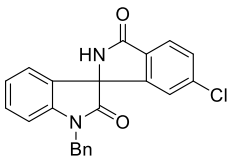
1-benzylspiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95a)



The title product compound **IV-95a** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (30.9 mg, 0.09 mmol, 91% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.21 (s, 1H), 7.84 – 7.76 (m, 1H), 7.59-7.52 (m, 2H), 7.44 – 7.27 (m, 6H), 7.10 (d, *J* = 7.9 Hz, 1H), 7.06 – 7.00 (m, 2H), 7.03 – 6.94 (m, 1H), 5.01 (s, 2H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 173.8, 170.2, 145.5, 143.0, 135.9, 132.7, 131.8, 130.1, 129.4, 128.8, 127.6, 127.3, 127.3, 124.0, 123.5, 123.4, 121.6, 110.2, 66.7, 43.4.

1-benzyl-6'-chlorospiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95b)

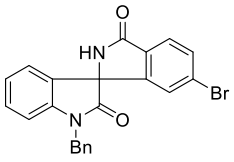


IV-95b

The title product compound **IV-95b** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (34.5 mg, 0.09 mmol, 92% yield).

^{1}H NMR (700 MHz, DMSO-*d6*) δ 9.34 (s, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.63 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.44 – 7.34 (m, 5H), 7.33 – 7.28 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 1.8 Hz, 1H), 7.08 – 7.01 (m, 2H), 5.08 (d, *J* = 15.8 Hz, 1H), 4.92 (d, *J* = 15.8 Hz, 1H). **^{13}C NMR (176 MHz, DMSO-*d6*)** δ 173.1, 169.0, 147.2, 143.1, 137.3, 135.9, 130.7, 130.3, 129.8, 128.7, 127.4, 126.5, 125.3, 124.1, 123.4, 121.8, 110.4, 66.4, 43.6.

1-benzyl-6'-bromospiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95c)

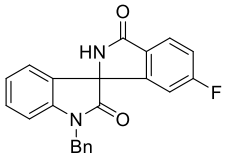


IV-95c

The title product compound **IV-95c** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (39.3 mg, 0.09 mmol, 94% yield).

^{1}H NMR (700 MHz, DMSO-*d6*) δ 9.32 (s, 1H), 7.79 – 7.72 (m, 2H), 7.43 – 7.34 (m, 5H), 7.34 – 7.29 (m, 1H), 7.22 (d, *J* = 1.6 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.09 – 7.02 (m, 2H), 5.07 (d, *J* = 15.8 Hz, 1H), 4.92 (d, *J* = 15.9 Hz, 1H). **^{13}C NMR (176 MHz, DMSO-*d6*)** δ 173.1, 169.1, 147.4, 143.1, 135.9, 132.6, 131.0, 130.3, 128.7, 127.4, 126.5, 126.0, 125.4, 124.7, 124.1, 123.4, 110.3, 66.3, 43.6.

1-benzyl-6'-fluorospiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95d)

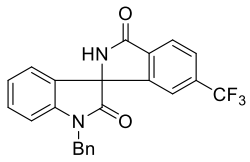


IV-95d

The title product compound **IV-95d** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (35.7 mg, 0.10 mmol, 99% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.28 (s, 1H), 7.86 (dd, *J* = 8.4, 5.0 Hz, 1H), 7.46 – 7.27 (m, 7H), 7.10 (d, *J* = 7.9 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.91 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.07 (d, *J* = 15.9 Hz, 1H), 4.92 (d, *J* = 15.9 Hz, 1H). **^{13}C NMR (176 MHz, DMSO-*d6*)** δ 173.3, 169.0, 164.8 (d, *J* = 250.2 Hz), 147.9 (d, *J* = 9.9 Hz), 143.1, 135.8, 130.3, 128.7, 128.2, 127.6, 127.4, 126.7, 125.9 (d, *J* = 9.8 Hz), 124.1, 123.4, 117.1 (d, *J* = 23.5 Hz), 110.4, 109.2 (d, *J* = 24.5 Hz), 66.4, 66.4, 43.6. **^{19}F NMR (470 MHz, DMSO-*d6*)** δ -106.7 (td, *J* = 8.9, 5.1 Hz).

1-benzyl-6'-(trifluoromethyl)spiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95e)

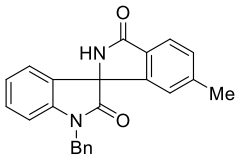


IV-95e

The title product compound **IV-95e** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (39.1 mg, 0.10 mmol, 96% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.58 (s, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.97 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.43 – 7.34 (m, 6H), 7.33 – 7.28 (m, 1H), 7.16 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.10 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.04 (td, *J* = 7.5, 1.0 Hz, 1H), 5.08 (d, *J* = 15.8 Hz, 1H), 4.93 (d, *J* = 15.8 Hz, 1H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 173.0, 168.6, 146.1, 143.2, 135.9, 135.6, 132.6 (d, *J* = 32.3 Hz), 130.5, 128.7, 127.7, 127.4, 126.9, 126.2, 125.8 (q, *J* = 275.9 Hz), 124.8, 124.2, 123.5, 118.8 (q, *J* = 5.0 Hz), 110.5, 66.8, 43.6. **^{19}F NMR (470 MHz, DMSO-*d6*)** δ -60.9 (s).

1-benzyl-6'-methylspiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95f)

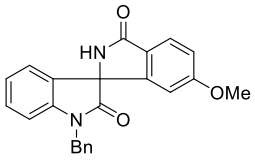


IV-95f

The title product compound **IV-95f** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (33.2 mg, 0.09 mmol, 94% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.10 (s, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.44 – 7.27 (m, 7H), 7.12 (d, *J* = 7.9 Hz, 1H), 7.06 – 6.98 (m, 2H), 6.74 (s, 1H), 5.15 – 4.88 (m, 2H), 2.30 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 173.9, 170.2, 146.0, 143.1, 143.0, 136.0, 130.2, 130.1, 129.2, 128.7, 127.7, 127.4, 127.4, 124.0, 123.4, 123.3, 121.7, 110.2, 66.5, 43.4, 21.2.

1-benzyl-6'-methoxyspiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95g)

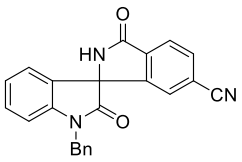


IV-95g

The title product compound **IV-95g** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (33.5 mg, 0.09 mmol, 90% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.00 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.44 – 7.28 (m, 6H), 7.15 – 7.07 (m, 2H), 7.07 – 7.00 (m, 2H), 6.37 (d, *J* = 2.2 Hz, 1H), 5.03 – 4.91 (m, 2H), 3.69 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 173.8, 170.0, 163.0, 147.9, 143.0, 136.1, 130.1, 128.8, 127.7, 127.4, 127.4, 124.9, 124.2, 124.0, 123.4, 116.1, 110.2, 105.8, 66.4, 55.8, 43.4.

1-benzyl-2,3'-dioxospiro[indoline-3,1'-isoindoline]-6'-carbonitrile (IV-95h)

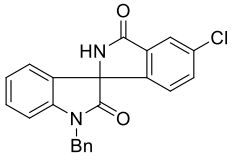


IV-95h

The title product compound **IV-95h** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (21.8 mg, 0.06 mmol, 60% yield).

^{1}H NMR (700 MHz, DMSO-*d6*) δ 9.61 (s, 1H), 8.05 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.99 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.67 (d, *J* = 1.3 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.38-7.35 (m, 3H), 7.34 – 7.29 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.05 (td, *J* = 7.5, 1.0 Hz, 1H), 5.10 (d, *J* = 15.9 Hz, 1H), 4.89 (d, *J* = 15.9 Hz, 1H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 172.8, 168.4, 145.7, 143.3, 135.7, 135.7, 133.7, 130.5, 128.7, 127.6, 127.4, 126.2, 126.0, 124.6, 124.2, 123.4, 117.8, 114.9, 110.4, 66.6, 43.7.

1-benzyl-5'-chlorospiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95i)

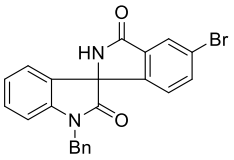


IV-95i

The title product compound **IV-95i** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (21.8 mg, 0.06 mmol, 58% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.40 (s, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 7.61 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.43 – 7.29 (m, 6H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.09 – 7.03 (m, 3H), 5.10 – 4.84 (m, 2H).

1-benzyl-5'-bromospiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95j)

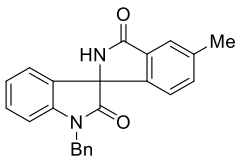


IV-95j

The title product compound **IV-95j** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (24.8 mg, 0.06 mmol, 59% yield).

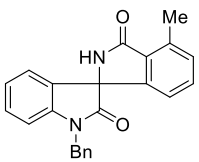
^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.38 (s, 1H), 7.95 (d, *J* = 1.8 Hz, 1H), 7.74 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.48 – 7.27 (m, 6H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.13 – 6.96 (m, 3H), 5.05 – 4.94 (m, 2H).

1-benzyl-5'-methylspiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95k)



IV-95k

+

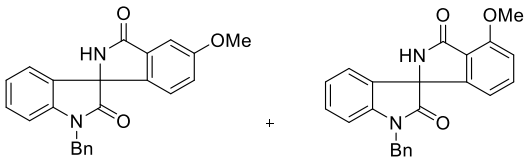


IV-95k'

The title product compound **IV-95k** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (29.0 mg, 0.08 mmol, 82% yield) with inseparable isomer **IV-95k'** (2.6 mg, 0.01 mmol, 7% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.15 (s, 1H), 7.60 (s, 1H), 7.41 – 7.28 (m, 7H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.07 – 6.96 (m, 2H), 6.85 (d, *J* = 7.6 Hz, 1H), 5.00 (s, 2H), 2.40 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 174.0, 170.3, 143.0, 142.9, 139.2, 136.0, 133.5, 132.0, 130.0, 128.8, 127.3, 123.9, 123.6, 123.4, 121.3, 110.1, 66.5, 43.4, 20.9.

1-benzyl-5'-methoxyspiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95l)

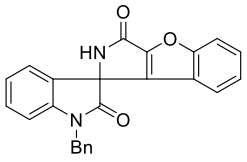


IV-95l IV-95l'

The title product compound **IV-95l** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (18.5 mg, 0.05 mmol, 50% yield) with inseparable isomer **IV-95l'** (11.5 mg, 0.03 mmol, 31% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.19 (s, 1.6 H), 9.16 (s, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.42 – 7.26 (m, 17H), 7.16 (d, *J* = 8.1 Hz, 1H), 7.11 – 7.06 (m, 4H), 7.05 – 6.92 (m, 6H), 6.88 (d, *J* = 8.4 Hz, 1.6 H), 5.12 (d, *J* = 15.9 Hz, 1H), 4.99 s, 3H), 4.88 (d, *J* = 15.9 Hz, 1H), 3.84 (s, 5H), 3.47 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 174.0, 170.3, 143.0, 142.9, 139.2, 136.0, 133.5, 132.0, 130.0, 128.8, 127.3, 123.9, 123.6, 123.4, 121.3, 110.1, 66.5, 43.4, 20.9.

1'-benzylspiro[benzofuro[2,3-*c*]pyrrole-1,3'-indoline]-2',3(2*H*)-dione (IV-95n)

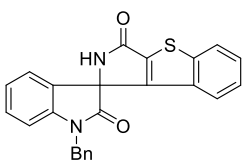


IV-95n

The title product compound **IV-95n** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (19.0 mg, 0.05 mmol, 50% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.32 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.47 – 7.28 (m, 6H), 7.28 – 7.19 (m, 3H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 5.12 – 5.01 (m, 2H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 171.8, 161.1, 160.1, 152.7, 142.5, 135.9, 134.5, 130.6, 128.8, 127.8, 127.6, 127.5, 124.7, 124.5, 124.4, 123.5, 120.8, 119.6, 113.9, 110.5, 62.2, 43.6.

1'-benzylspiro[benzo[4,5]thieno[2,3-*c*]pyrrole-1,3'-indoline]-2',3(2*H*)-dione (IV-95o)



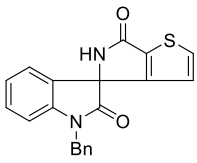
IV-95o

The title product compound **IV-95o** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (28.5 mg, 0.07 mmol, 72% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.34 (s, 1H), 8.17 (dt, *J* = 8.3, 0.9 Hz,

1H), 7.48 – 7.31 (m, 7H), 7.30 – 7.28 (m, 1H), 7.20 (ddd, *J* = 8.2, 7.2, 1.0 Hz, 1H), 7.16 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.03 (td, *J* = 7.5, 1.0 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.08 (q, *J* = 15.5 Hz, 2H).**^{13}C NMR (126 MHz, DMSO-*d6*)** δ 172.0, 166.4, 148.7, 145.8, 142.6, 136.4, 135.9, 130.6, 130.2, 128.8, 127.9, 127.0, 125.7, 125.2, 125.1, 124.4, 123.6, 121.1, 110.5, 65.9, 43.7.

1-benzylspiro[indoline-3,4'-thieno[2,3-*c*]pyrrole]-2,6'(5'*H*)-dione (IV-95p)

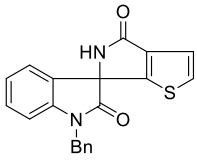


IV-95p

The title product compound **IV-95p** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (25.2 mg, 0.07 mmol, 73% yield).

^{1}H NMR (700 MHz, DMSO-*d6*) δ 9.05 (s, 1H), 7.99 (dd, *J* = 4.8, 0.9 Hz, 1H), 7.39 – 7.35 (m, 4H), 7.35 – 7.29 (m, 2H), 7.12 – 7.08 (m, 1H), 7.08 – 7.01 (m, 2H), 6.80 (d, *J* = 4.8 Hz, 1H), 5.03 – 4.95 (m, 2H). **^{13}C NMR (176 MHz, DMSO-*d6*)** δ 172.4, 165.8, 155.0, 142.7, 137.7, 135.8, 135.6, 130.2, 128.7, 127.5, 127.2, 125.9, 124.0, 123.3, 119.8, 110.2, 65.6, 43.4.

1-benzylspiro[indoline-3,6'-thieno[2,3-*c*]pyrrole]-2,4'(5'*H*)-dione (IV-95q)

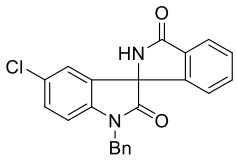


XX

The title product compound **IV-95q** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (22.8 mg, 0.07 mmol, 66% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.06 – 9.02 (m, 1H), 7.76 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.40 – 7.27 (m, 7H), 7.18 – 7.11 (m, 1H), 7.10 – 7.01 (m, 2H), 5.03-4.96 (m, 2H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 172.6, 166.5, 153.9, 142.4, 141.1, 135.8, 133.4, 130.5, 128.8, 127.7, 127.2, 126.6, 124.2, 123.6, 119.9, 110.4, 65.6, 43.3.

1-benzyl-5-chlorospiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95s)

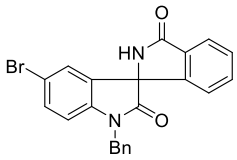


IV-95s

The title product compound **IV-95s** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (36.7 mg, 0.10 mmol, 98% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.20 (s, 1H), 7.83 – 7.78 (m, 1H), 7.62-7.53 (m, 2H), 7.43 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.42 – 7.36 (m, 4H), 7.39 – 7.27 (m, 1H), 7.17 (d, *J* = 2.2 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 6.9 Hz, 1H), 5.07 – 4.95 (m, 2H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 173.6, 170.1, 144.8, 141.9, 135.6, 132.8, 131.7, 130.0, 129.6, 129.4, 128.8, 127.7, 127.6, 127.3, 124.2, 123.6, 121.6, 111.7, 66.5, 55.0, 43.5.

1-benzyl-5-bromospiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95t)

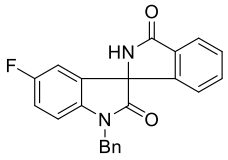


IV-95t

The title product compound **IV-95t** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (40.1 mg, 0.10 mmol, 96% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.21 (s, 1H), 7.84 – 7.78 (m, 1H), 7.63 – 7.52 (m, 3H), 7.42 – 7.35 (m, 4H), 7.31 (ddd, *J* = 5.4, 4.2, 2.2 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 7.06 – 7.01 (m, 1H), 5.07 – 4.95 (m, 2H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 173.5, 170.1, 144.8, 142.4, 135.6, 132.9, 132.8, 131.8, 129.7, 129.6, 128.8, 127.7, 127.3, 126.9, 123.6, 121.6, 115.2, 112.3, 66.5, 43.5.

1-benzyl-5-fluorospiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95u)

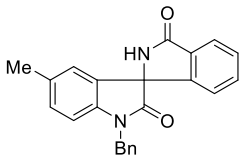


IV-95u

The title product compound **IV-95u** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (32.7 mg, 0.09 mmol, 91% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.23 (s, 1H), 7.83 – 7.77 (m, 1H), 7.62 – 7.52 (m, 2H), 7.43 – 7.35 (m, 4H), 7.31 (ddt, *J* = 8.6, 5.8, 3.0 Hz, 1H), 7.26 – 7.16 (m, 1H), 7.10 (dd, *J* = 8.7, 4.1 Hz, 1H), 7.04 (dd, *J* = 7.9, 2.7 Hz, 1H), 7.02 – 6.99 (m, 1H), 5.05 – 4.94 (m, 2H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 173.8, 170.3, 159.0 (d, *J* = 240.0 Hz), 145.0, 139.3, 139.2, 135.8, 132.9, 131.8, 129.6, 129.2 (d, *J* = 8.3 Hz), 128.9, 127.8, 127.4, 123.7, 121.6, 116.6 (d, *J* = 23.6 Hz), 112.2 (d, *J* = 25.3 Hz), 111.3 (d, *J* = 8.0 Hz), 66.9, 66.9, 43.6.

1-benzyl-5-methylspiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95v)

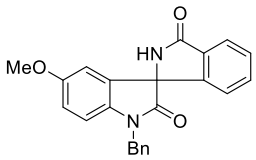


IV-95v

The title product compound **IV-95v** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (31.0 mg, 0.09 mmol, 87% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.21 (s, 1H), 7.83 – 7.76 (m, 1H), 7.61 – 7.51 (m, 2H), 7.42 – 7.34 (m, 4H), 7.34 – 7.27 (m, 1H), 7.14 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.01 – 6.93 (m, 2H), 6.84 (s, 1H), 4.98 (s, 2H), 2.17 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 173.7, 170.2, 145.6, 140.6, 136.0, 132.7, 132.7, 131.8, 130.3, 129.3, 128.7, 127.6, 127.3, 124.5, 123.5, 121.6, 110.0, 66.8, 43.4, 20.4.

1-benzyl-5-methoxyspiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95w)

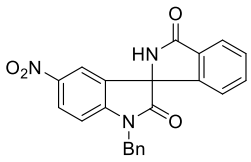


IV-95w

The title product compound **IV-95w** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (36.2 mg, 0.10 mmol, 98% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.21 (s, 1H), 7.82 – 7.77 (m, 1H), 7.61 – 7.52 (m, 2H), 7.42 – 7.35 (m, 4H), 7.35 – 7.27 (m, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.98 – 6.96 (m, 1H), 6.90 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.65 (d, *J* = 2.6 Hz, 1H), 4.97 (s, 2H), 3.62 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 173.6, 170.2, 156.1, 145.5, 136.2, 136.0, 132.7, 131.8, 129.4, 128.8, 128.5, 127.6, 127.3, 123.5, 121.5, 115.1, 110.9, 110.4, 67.1, 55.6, 43.4.

1-benzyl-5-nitrospiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95x)

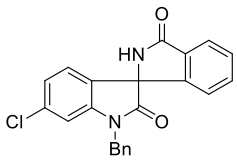


IV-95x

The title product compound **IV-95x** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (19.3 mg, 0.05 mmol, 50% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.22 (s, 1H), 8.33 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.90 (d, *J* = 2.3 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.69 – 7.54 (m, 2H), 7.43 – 7.36 (m, 5H), 7.35 – 7.30 (m, 1H), 7.09 (d, *J* = 7.2 Hz, 1H), 5.17 – 4.99 (m, 2H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 174.4, 170.0, 149.0, 144.2, 143.5, 135.2, 132.9, 131.8, 129.9, 128.9, 128.5, 127.9, 127.3, 127.2, 123.8, 121.8, 119.6, 110.6, 66.1, 43.9.

1-benzyl-6-chlorospiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95y)

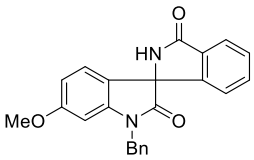


IV-95y

The title product compound **IV-95y** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (26.6 mg, 0.07 mmol, 71% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.20 (s, 1H), 7.83 – 7.78 (m, 1H), 7.62 – 7.52 (m, 2H), 7.44 – 7.36 (m, 4H), 7.34 – 7.30 (m, 1H), 7.28 (s, 1H), 7.09 – 7.05 (m, 2H), 7.05 – 7.01 (m, 1H), 5.08 – 4.97 (m, 2H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 173.9, 170.1, 145.0, 144.6, 135.6, 134.5, 132.8, 131.7, 129.6, 128.8, 127.7, 127.3, 126.1, 125.6, 123.6, 123.1, 121.7, 110.5, 66.2, 43.4.

1-benzyl-6-methoxyspiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95z)

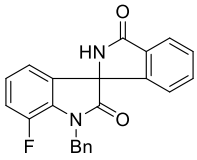


IV-95z

The title product compound **IV-95z** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (32.0 mg, 0.09 mmol, 86% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.16 (s, 1H), 7.81 – 7.75 (m, 1H), 7.59 – 7.50 (m, 2H), 7.43 – 7.34 (m, 4H), 7.34 – 7.27 (m, 1H), 7.09 – 6.95 (m, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.73 (d, *J* = 2.3 Hz, 1H), 6.56 (dd, *J* = 8.3, 2.3 Hz, 1H), 4.99 (s, 2H), 3.72 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 174.4, 170.1, 161.1, 145.8, 144.4, 136.0, 132.7, 131.8, 129.3, 128.8, 127.6, 127.4, 125.0, 123.4, 121.6, 118.6, 107.4, 98.0, 66.4, 55.5, 43.3.

1-benzyl-7-fluorospiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-95aa)



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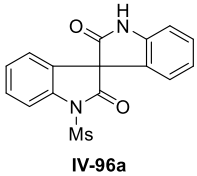
The title product compound **IV-95aa** was prepared using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (34.2 mg, 0.10 mmol, 95% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.28 (s, 1H), 7.84 – 7.78 (m, 1H), 7.63 – 7.54 (m, 2H), 7.41 – 7.28 (m, 5H), 7.25 (dd, *J* = 11.8, 8.5 Hz, 1H), 7.15 – 7.10 (m, 1H), 7.05 (ddd, *J* = 8.4, 7.4, 4.4 Hz, 1H), 6.90 (dd, *J* = 7.5, 1.1 Hz, 1H), 5.12 (d, *J* = 16.0 Hz, 1H), 5.03 (d, *J* = 16.1 Hz, 1H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 173.8, 170.1, 146.9 (d, *J* = 244.1 Hz), 145.1, 136.6, 132.9, 131.6, 130.4 (d, *J* = 2.7 Hz), 129.6, 129.5 (d, *J* = 9.2 Hz), 128.7, 127.5, 126.7, 124.6 (d, *J* = 6.4 Hz), 123.6, 121.8, 120.3 (d, *J* = 3.2 Hz), 118.2 (d, *J* = 19.1 Hz), 66.6 (d, *J* = 2.5 Hz), 45.3. **^{19}F NMR (470 MHz, DMSO-*d6*)** δ -133.4 (dd, *J* = 11.7, 4.4 Hz).

1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96a)

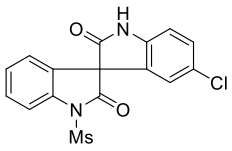


IV-96a

The title product compound **IV-96a** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (26.8 mg, 0.08 mmol, 82% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.16 (s, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.37 (td, *J* = 7.7, 1.3 Hz, 1H), 7.21 (td, *J* = 7.6, 1.0 Hz, 1H), 7.12 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.07 – 6.98 (m, 3H), 3.63 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 172.0, 171.2, 143.6, 140.4, 130.3, 129.9, 127.7, 126.8, 125.5, 124.7, 124.2, 122.9, 113.6, 110.6, 62.9, 41.1.

5'-chloro-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96b)

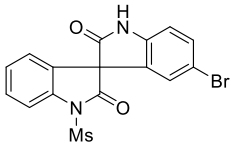


IV-96b

The title product compound **IV-96b** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (20.3 mg, 0.06 mmol, 56% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.29 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.44 – 7.40 (m, 2H), 7.21 (td, *J* = 7.6, 1.0 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 2H), 3.63 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 171.7, 170.6, 142.7, 140.6, 130.1, 130.0, 129.3, 126.7, 126.3, 125.5, 125.2, 124.2, 113.5, 112.0, 62.8, 41.2.

5'-bromo-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96c)

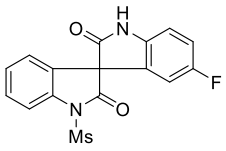


IV-96c

The title product compound **IV-96c** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (20.9 mg, 0.05 mmol, 51% yield).

^{1}H NMR (600 MHz, DMSO-*d6*) δ 11.28 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.56 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.48 (ddd, *J* = 8.4, 7.6, 1.4 Hz, 1H), 7.21 (td, *J* = 7.5, 1.0 Hz, 1H), 7.05 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 3.63 (s, 3H). **^{13}C NMR (151 MHz, DMSO-*d6*)** δ 171.6, 170.6, 143.1, 140.6, 133.0, 130.0, 129.6, 127.9, 126.3, 125.4, 124.2, 114.3, 113.5, 112.5, 62.7, 41.2.

5'-fluoro-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96d)

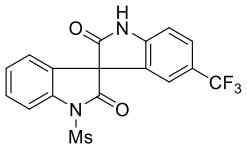


IV-96d

The title product compound **IV-96d** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (24.0 mg, 0.07 mmol, 69% yield).

^{1}H NMR (600 MHz, DMSO-*d6*) δ 11.17 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.48 (ddd, *J* = 8.3, 7.6, 1.4 Hz, 1H), 7.25 – 7.19 (m, 3H), 7.06 – 7.00 (m, 2H), 3.62 (s, 3H). **^{13}C NMR (151 MHz, DMSO-*d6*)** δ 171.9, 170.7, 158.3 (d, *J* = 238.2 Hz), 140.5, 140.0 (d, *J* = 2.0 Hz), 130.0, 128.8 (d, *J* = 9.2 Hz), 126.4, 125.5, 124.1, 116.7 (d, *J* = 23.4 Hz), 113.5, 112.9 (d, *J* = 25.7 Hz), 111.5 (d, *J* = 8.1 Hz), 63.1, 41.1. **^{19}F NMR (470 MHz, DMSO-*d6*)** δ -123.35 (td, *J* = 9.0, 4.4 Hz).

1-(methylsulfonyl)-5'-(trifluoromethyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96e)

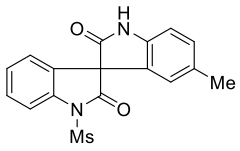


IV-96e

The title product compound **IV-96e** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (16.4 mg, 0.04 mmol, 41% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.55 (s, 1H), 7.79 – 7.72 (m, 3H), 7.54 – 7.45 (m, 1H), 7.25 – 7.18 (m, 2H), 7.06 (dd, *J* = 7.6, 1.3 Hz, 1H), 3.64 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 172.1, 170.5, 147.5, 140.8, 130.1, 128.1, 128.1 (q, *J* = 4.1 Hz), 126.2, 125.4, 124.4 (q, *J* = 273.42 Hz), 124.2, 123.3 (d, *J* = 32.3 Hz), 122.5 (d, *J* = 3.7 Hz), 113.6, 110.9, 62.7, 41.2. **^{19}F NMR (470 MHz, DMSO-*d6*)** δ -59.74 (s).

5'-methyl-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96f)

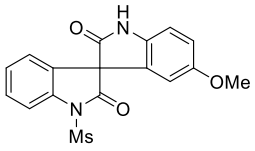


IV-96f

The title product compound **IV-96f** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (26.4 mg, 0.08 mmol, 77% yield).

^{1}H NMR (600 MHz, DMSO-*d6*) δ 11.04 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.47 (td, *J* = 8.0, 1.4 Hz, 1H), 7.21 (td, *J* = 7.6, 1.0 Hz, 1H), 7.16 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.00 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.96 – 6.89 (m, 2H), 3.63 (s, 3H), 2.20 (s, 3H). **^{13}C NMR (151 MHz, DMSO-*d6*)** δ 172.0, 171.3, 141.1, 140.3, 132.0, 130.5, 129.8, 127.7, 127.0, 125.5, 125.1, 124.2, 113.5, 110.3, 62.9, 41.1, 20.5.

5'-methoxy-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96g)

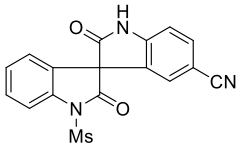


IV-96g

The title product compound **IV-96g** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (31.1 mg, 0.09 mmol, 87% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.95 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.47 (td, *J* = 8.0, 1.4 Hz, 1H), 7.21 (td, *J* = 7.6, 1.0 Hz, 1H), 7.00 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.97 – 6.90 (m, 2H), 6.84 (d, *J* = 2.1 Hz, 1H), 3.65 (s, 3H), 3.63 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 171.9, 171.2, 155.6, 140.5, 136.7, 129.8, 128.6, 127.0, 125.4, 124.1, 115.1, 113.5, 111.5, 111.0, 63.3, 55.6, 41.1.

1'-(methylsulfonyl)-2,2'-dioxo-3,3'-spirobi[indoline]-5-carbonitrile (IV-96h)

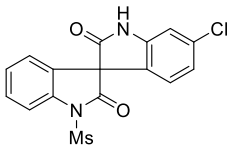


IV-96h

The title product compound **IV-96h** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (13.4 mg, 0.04 mmol, 38% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.67 (s, 1H), 7.87 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.82 (d, *J* = 1.6 Hz, 1H), 7.77 – 7.73 (m, 1H), 7.50 (ddd, *J* = 8.5, 7.6, 1.4 Hz, 1H), 7.26 – 7.15 (m, 2H), 7.10 (dd, *J* = 7.6, 1.3 Hz, 1H), 3.63 (s, 3H).

6'-chloro-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96i)

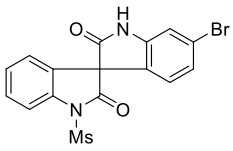


IV-96i

The title product compound **IV-96i** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (11.7 mg, 0.03 mmol, 32% yield).

^{1}H NMR (700 MHz, DMSO-*d6*) δ 11.31 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.48 (td, *J* = 7.9, 1.4 Hz, 1H), 7.24 – 7.18 (m, 2H), 7.11 – 7.04 (m, 3H), 3.62 (s, 3H).

6'-bromo-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96j)

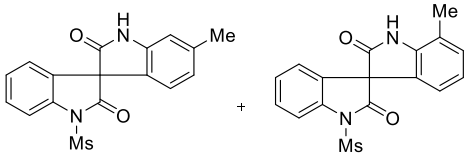


IV-96j

The title product compound **IV-96j** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (14.8 mg, 0.04 mmol, 36% yield).

^{1}H NMR (700 MHz, DMSO-*d6*) δ 11.30 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.25 – 7.17 (m, 3H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 3.62 (s, 3H). **^{13}C NMR (176 MHz, DMSO-*d6*)** δ 171.8, 170.6, 145.3, 140.4, 130.0, 126.7, 126.7, 126.2, 125.5, 124.2, 122.9, 113.6, 113.4, 62.5, 41.1.

6'-methyl-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96k)

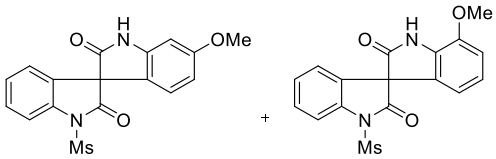


IV-96k **IV-96k'**

The title product compound **IV-96k** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (25.5 mg, 0.07 mmol, 75% yield) with inseparable isomer **IV-96k'** (3.1 mg, 0.01 mmol, 9% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.10 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.46 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.04 – 6.95 (m, 2H), 6.90 – 6.79 (m, 2H), 3.61 (s, 3H), 2.33 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 172.3, 171.4, 143.7, 140.3, 140.2, 129.8, 127.0, 125.5, 124.8, 124.4, 124.1, 123.3, 113.5, 111.2, 62.7, 41.1, 21.4.

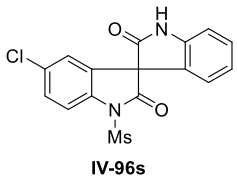
6'-methyl-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96l)



The title product compound **IV-96l** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (12.5 mg, 0.03 mmol, 35% yield) with inseparable isomer **IV-96l'** (9.5 mg, 0.03 mmol, 27% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.10 (s, 1H), 7.77 – 7.70 (m, 1H), 7.48-7.41 (m, 1H), 7.34 (dd, *J* = 8.5, 7.8 Hz, 0.4 H), 7.22-7.15 (m, 1H), 7.02 (ddd, *J* = 17.3, 7.5, 1.4 Hz, 2H), 6.69-6.66 (m, 0.8 H), 6.59 – 6.50 (m, 1.2 H), 3.78 (s, 1.7 H), 3.61 (s, 1.7 H), 3.57 (s, 1.3 H), 3.54 (s, 1.3 H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 172.6, 172.2, 171.5, 171.0, 161.0, 154.9, 144.9, 144.4, 140.3, 140.0, 131.8, 129.8, 129.7, 127.1, 126.2, 125.7, 125.4, 124.1, 123.5, 119.3, 114.1, 113.5, 113.4, 107.8, 106.1, 103.7, 97.3, 62.4, 55.8, 55.5, 55.0, 41.1, 40.7.

5-chloro-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96s)

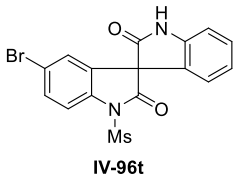


IV-96s

The title product compound **IV-96s** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (17.3 mg, 0.05 mmol, 48% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.20 (s, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.56 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.38 (td, *J* = 7.8, 1.3 Hz, 1H), 7.22 (d, *J* = 2.3 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.07 – 6.99 (m, 2H), 3.64 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 171.4, 170.8, 143.7, 139.3, 130.4, 129.8, 129.6, 128.7, 127.0, 124.8, 124.3, 122.9, 115.2, 110.7, 62.7, 41.1.

5-bromo-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96t)

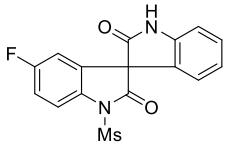


IV-96t

The title product compound **IV-96t** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (9.5 mg, 0.02 mmol, 23% yield).

^{1}H NMR (700 MHz, DMSO-*d6*) δ 11.18 (s, 1H), 7.70-7.68 (m, 2H), 7.38 (td, *J* = 7.7, 1.3 Hz, 1H), 7.31 (t, *J* = 1.3 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.05 – 7.00 (m, 2H), 3.63 (s, 3H). **^{13}C NMR (176 MHz, DMSO-*d6*)** δ 171.4, 170.6, 143.7, 139.7, 132.7, 130.4, 129.0, 127.0, 127.0, 124.7, 122.8, 117.4, 115.5, 110.7, 62.6, 41.1.

5-fluoro-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96u)

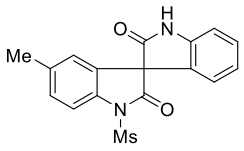


IV-96u

The title product compound **IV-96u** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (15.2 mg, 0.04 mmol, 44% yield).

^{1}H NMR (700 MHz, DMSO-*d6*) δ 11.19 (s, 1H), 7.76 (dd, *J* = 9.1, 4.4 Hz, 1H), 7.41 – 7.30 (m, 2H), 7.17 – 7.12 (m, 1H), 7.09 (dd, *J* = 7.9, 2.7 Hz, 1H), 7.06 – 6.99 (m, 2H), 3.63 (s, 3H). **^{13}C NMR (176 MHz, DMSO-*d6*)** δ 171.5, 171.0, 159.6 (d, *J* = 242.1 Hz), 143.7, 136.7, 130.4, 128.5 (d, *J* = 9.1 Hz), 127.2, 124.7, 122.9, 116.50 (d, *J* = 22.9 Hz), 115.1 (d, *J* = 8.4 Hz), 112.1 (d, *J* = 25.4 Hz), 110.7, 63.0, 41.1, 39.5. **^{19}F NMR (470 MHz, DMSO-*d6*)** δ -116.82 (td, *J* = 8.5, 4.4 Hz).

5-methyl-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96v)

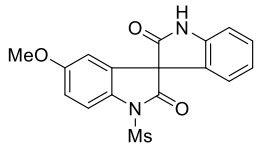


IV-96v

The title product compound **IV-96v** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (32.3 mg, 0.09 mmol, 94% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.14 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.36 (td, *J* = 7.7, 1.3 Hz, 1H), 7.27 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.06 – 6.98 (m, 2H), 6.83 (s, 1H), 3.60 (s, 3H), 2.23 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 172.1, 171.3, 143.6, 138.0, 135.0, 130.2, 130.2, 127.8, 126.8, 124.7, 124.4, 122.8, 113.4, 110.6, 62.9, 41.0, 39.5, 20.3.

5-methoxy-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96w)

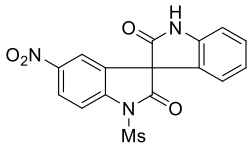


IV-96w

The title product compound **IV-96w** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (19.6 mg, 0.05 mmol, 55% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.13 (s, 1H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.36 (td, *J* = 7.7, 1.3 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.07 – 6.98 (m, 3H), 6.60 (d, *J* = 2.7 Hz, 1H), 3.67 (s, 3H), 3.58 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 172.1, 171.3, 143.6, 138.0, 135.0, 130.2, 130.2, 127.8, 126.8, 124.7, 124.4, 122.8, 113.4, 110.6, 62.9, 41.0, 20.3.

1-(methylsulfonyl)-5-nitro-3,3'-spirobi[indoline]-2,2'-dione (IV-96x)

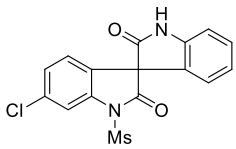


IV-96x

The title product compound **IV-96x** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (20.0 mg, 0.05 mmol, 54% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.28 (s, 1H), 8.43 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.94 (d, *J* = 2.5 Hz, 1H), 7.41 (td, *J* = 7.7, 1.3 Hz, 1H), 7.23 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.09 – 7.01 (m, 2H), 3.71 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 170.9, 170.9, 145.7, 144.7, 143.9, 130.7, 128.0, 126.4, 126.3, 125.1, 122.9, 119.7, 114.2, 110.9, 62.6, 41.5.

6-chloro-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96y)

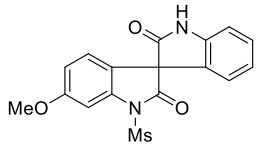


IV-96y

The title product compound **IV-96y** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (13.9 mg, 0.04 mmol, 38% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.20 (s, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.37 (td, *J* = 7.7, 1.3 Hz, 1H), 7.29 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.19 – 7.14 (m, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 7.09 – 6.97 (m, 2H), 3.67 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 171.5, 170.9, 143.6, 141.4, 134.0, 130.4, 127.1, 125.8, 125.7, 125.3, 124.8, 122.9, 113.7, 110.7, 62.5, 41.2.

6-methoxy-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96z)

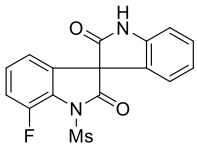


IV-96z

The title product compound **IV-96z** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (21.5 mg, 0.06 mmol, 60% yield).

^{1}H NMR (700 MHz, DMSO-*d6*) δ 11.07 (s, 1H), 7.35 (td, *J* = 7.7, 1.3 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.04 – 6.98 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.77 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.80 (s, 3H), 3.62 (s, 3H). **^{13}C NMR (176 MHz, DMSO-*d6*)** δ 172.3, 171.6, 160.3, 143.5, 141.2, 130.1, 127.9, 125.0, 124.5, 122.7, 118.4, 110.5, 110.3, 100.7, 62.3, 55.6, 41.1.

7-fluoro-1-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-96aa)

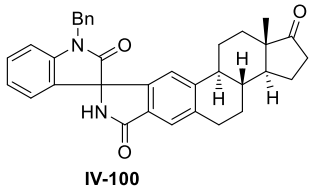


IV-96aa

The title product compound **IV-96aa** was prepared using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (23.2 mg, 0.07 mmol, 67% yield).

^{1}H NMR (700 MHz, DMSO-*d6*) δ 11.17 (s, 1H), 7.44 – 7.35 (m, 2H), 7.33 – 7.22 (m, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.05 – 7.01 (m, 2H), 6.86 (dd, *J* = 7.5, 1.1 Hz, 1H), 3.66 (s, 3H). **^{13}C NMR (176 MHz, DMSO-*d6*)** δ 171.4, 169.8, 148.0 (d, *J* = 250.3 Hz), 143.5, 130.4, 129.8 (d, *J* = 2.0 Hz), 127.21 (d, *J* = 7.4 Hz), 127.2, 127.1, 124.6, 122.9, 120.0 (d, *J* = 3.2 Hz), 118.18 (d, *J* = 21.3 Hz), 110.6, 63.3, 42.78 (d, *J* = 4.2 Hz).

(3aS,3bR,10bS,12aS)-1'-benzyl-12a-methyl-2,3,3a,3b,4,5,10b,11,12,12a-decahydro-1H-spiro[cyclopenta[5,6]naphtho[1,2-f]isoindole-9,3'-indoline]-1,2',7(8H)-trione (IV-100)

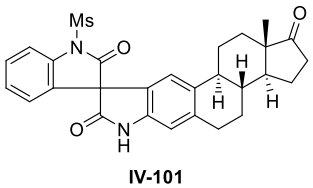


IV-100

The title product compound **IV-100** was prepared from reported substrate **IV-99** using general procedure 19 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (39.3 mg, 0.08 mmol, 76% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.05,9.02 (s, 1H), 7.48 (s, 1H), 7.42 – 7.28 (m, 6H), 7.16 (dd, *J* = 14.5, 7.9 Hz, 1H), 7.06 – 6.94 (m, 2H), 6.73,6.70 (s, 1H), 5.14 – 4.83 (m, 2H), 3.05 – 2.86 (m, 2H), 2.50 – 2.37 (m, 1H), 2.30 – 2.16 (m, 1H), 2.09 – 2.00 (m, 1H), 1.99-1.91 (m, 3H), 1.75 – 1.63 (m, 1H), 1.60 – 1.28 (m, 6H), 0.87 – 0.70 (m, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 174.1, 170.3, 145.0, 144.9, 143.4, 143.3, 142.8, 142.8, 138.2, 136.3, 136.2, 130.0, 129.2, 129.1, 128.8, 128.7, 127.7, 127.6, 127.6, 127.5, 123.8, 123.5, 123.4, 123.3, 123.3, 117.7, 110.1, 110.0, 66.6, 66.5, 49.6, 49.6, 47.2, 47.2, 44.1, 44.1, 43.3, 43.2, 37.0, 36.9, 35.4, 31.1, 31.0, 29.6, 29.0, 25.7, 25.6, 25.5, 25.2, 21.1, 13.5, 13.4.

(3aS,3bR,10bS,12aS)-12a-methyl-1'-(methylsulfonyl)-2,3,3a,4,5,7,10b,11,12,12a-decahydro-1H-spiro[cyclopenta[5,6]naphtho[1,2-f]indole-9,3'-indoline]-1,2',8(3bH)-trione (IV-101)



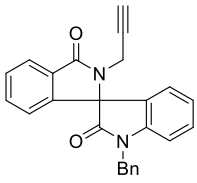
IV-101

The title product compound **IV-101** was prepared from reported substrate **IV-99** using general procedure 20 and isolated by column chromatography (2:1 to 1:1 PE:EA) giving an amorphous solid (26.5 mg, 0.05 mmol, 53% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 7.76-7.74 (m, 1H), 7.48 – 7.42 (m, 1H), 7.22 – 7.16 (m, 1H), 7.09 – 7.00 (m, 1H), 7.00 – 6.94 (m, 1H), 6.72 (s, 1H), 3.62,3.61 (s, 3H), 2.93 – 2.78 (m,

2H), 2.48 – 2.37 (m, 1H), 2.24 – 1.88 (m, 5H), 1.69 – 1.14 (m, 7H), 0.81,0.78 (s, 3H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 172.3, 172.3, 171.6, 171.5, 141.4, 141.3, 140.5, 138.6, 134.3, 129.7, 127.3, 127.3, 125.5, 125.4, 124.2, 124.1, 121.9, 121.8, 113.5, 110.5, 62.9, 49.6, 49.5, 47.4, 47.3, 43.9, 43.8, 41.1, 41.0, 37.6, 37.6, 35.4, 31.2, 31.1, 29.6, 25.8, 25.8, 25.7, 25.5, 21.1, 13.5.

1-benzyl-2'-(prop-2-yn-1-yl)spiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-102)

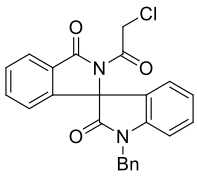


IV-102

Substrate **V-95a** (68 mg, 0.2 mmol, 1.0 equiv.) was dissolved in dry THF (1 mL, 0.2 M) followed by the addition of 60% NaH (8.8 mg, 0.22 mmol, 1.1 equiv.) at 0 °C. The reaction was stirred at the same temperature for 5 min, then 80% propargyl bromide (36 mg, 0.24 mmol, 1.2 equiv.) was added and warmed to room temperature. The reaction was stirred for 12 h then quenched with saturated NH_4Cl (5 mL). The reaction mixture was extracted with EA (10 mL * 3). All organic layers were combined, washed with brine, dried with Na_2SO_4, filtered and condensed under vacuum. The resulting residue was purified by column chromatography (10:1 – 3:1 PE:EA) giving an amorphous solid **IV-102** (53.4 mg, 0.14 mmol, 71% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 7.92 – 7.84 (m, 1H), 7.64 – 7.55 (m, 2H), 7.47 – 7.35 (m, 5H), 7.35 – 7.28 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.08 – 6.96 (m, 3H), 5.05 (d, *J* = 15.8 Hz, 1H), 4.97 (d, *J* = 15.7 Hz, 1H), 4.27 – 4.22 (m, 1H), 4.08 – 3.83 (m, 1H), 3.01 (t, *J* = 2.6 Hz, 1H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 172.3, 167.7, 144.1, 143.6, 136.0, 133.2, 130.8, 130.5, 129.7, 128.8, 127.7, 127.4, 125.0, 124.1, 123.7, 123.4, 121.4, 110.5, 77.5, 75.1, 70.4, 43.8, 29.3.

1-benzyl-2'-(2-chloroacetyl)spiro[indoline-3,1'-isoindoline]-2,3'-dione (IV-103)



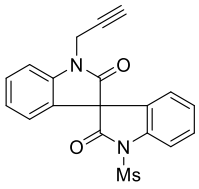
IV-103

Substrate **V-95a** (68 mg, 0.2 mmol, 1.0 equiv.) was added to dry PhMe (1 mL, 0.2 M) followed by the addition of chloroacetyl chloride (32 µL, 0.4 mmol, 2.0 equiv.) at room temperature. The reaction was stirred overnight at 90 °C. Then, it was cooled to room temperature and loaded to the column directly for purification (3:1-2:1 PE:EA) giving an amorphous solid **IV-103** (77.2 mg, 0.19 mmol, 93% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.05 (dt, *J* = 7.3, 1.0 Hz, 1H), 7.78 – 7.67 (m, 2H), 7.49 – 7.43 (m, 2H), 7.42 – 7.28 (m, 4H), 7.11 – 7.07 (m, 2H), 7.03 (dt, *J* = 7.7, 0.9 Hz, 1H), 6.99 (td, *J* = 7.6, 1.0 Hz, 1H), 5.19 – 4.99 (m, 4H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 171.5,

167.0, 165.4, 143.9, 142.9, 136.0, 135.9, 130.6, 130.1, 128.7, 128.5, 127.6, 127.2, 126.4, 125.5, 123.3, 123.2, 121.9, 110.3, 69.3, 45.1, 43.7.

1-(methylsulfonyl)-1'-(prop-2-yn-1-yl)-3,3'-spirobi[indoline]-2,2'-dione (IV-104)

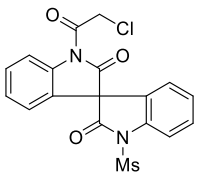


IV-104

Substrate **V-96a** (66 mg, 0.2 mmol, 1.0 equiv.) was dissolved in dry THF (1 mL, 0.2 M) followed by the addition of 60% NaH (8.8 mg, 0.22 mmol, 1.1 equiv.) at 0 °C. The reaction was stirred at the same temperature for 5 min, then 80% propargyl bromide (36 mg, 0.24 mmol, 1.2 equiv.) was added and warmed to room temperature. The reaction was stirred for 12 h then quenched with saturated NH_4Cl (5 mL). The reaction mixture was extracted with EA (10 mL * 3). All organic layers were combined, washed with brine, dried with Na_2SO_4, filtered and condensed under vacuum. The resulting residue was purified by column chromatography (10:1 – 3:1 PE:EA) giving an amorphous solid **IV-104** (17.8 mg, 0.05 mmol, 24% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 7.78 (d, *J* = 9.8 Hz, 0H), 7.50 (tdd, *J* = 8.4, 3.4, 1.3 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.25 – 7.19 (m, 2H), 7.14 (td, *J* = 7.6, 1.1 Hz, 1H), 6.94 (dd, *J* = 7.6, 1.4 Hz, 1H), 4.73 – 4.53 (m, 2H), 3.65 (s, 3H), 3.40 (t, *J* = 2.4 Hz, 1H). **^{13}C NMR (126 MHz, DMSO-*d6*)** δ 170.7, 169.8, 143.1, 140.4, 130.3, 130.2, 126.6, 126.3, 125.6, 124.6, 124.2, 123.9, 113.7, 110.4, 77.4, 75.1, 62.0, 41.2, 29.8.

1-(2-chloroacetyl)-1'-(methylsulfonyl)-3,3'-spirobi[indoline]-2,2'-dione (IV-105)



IV-105

Substrate **V-96a** (66 mg, 0.2 mmol, 1.0 equiv.) was added to dry PhMe (1 mL, 0.2 M) followed by the addition of chloroacetyl chloride (32 µL, 0.4 mmol, 2.0 equiv.) at room temperature. The reaction was stirred overnight at 90 °C. Then, it was cooled to room temperature and loaded to the column directly for purification (3:1-2:1 PE:EA) giving an amorphous solid **IV-105** (32.8 mg, 0.08 mmol, 41% yield).

^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.26 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.61 – 7.48 (m, 2H), 7.34 – 7.28 (m, 2H), 7.26 (td, *J* = 7.5, 1.0 Hz, 1H), 7.21 (dd, *J* = 7.6, 1.4 Hz, 1H), 5.07 (d, *J* = 16.2 Hz, 1H), 4.91 (d, *J* = 16.3 Hz, 1H), 3.68 (s, 3H). **^{13}C NMR (126 MHz, DMSO)** δ 171.1, 170.2, 166.7, 141.1, 140.3, 130.6, 130.5, 126.5, 126.4, 126.2, 125.6, 125.3, 124.6, 116.3, 113.7, 62.6, 46.5, 41.2.

7.3.3 X-ray crystallographic data of IV-95o (by R. Scheel and Prof. Dr. Strohmann)

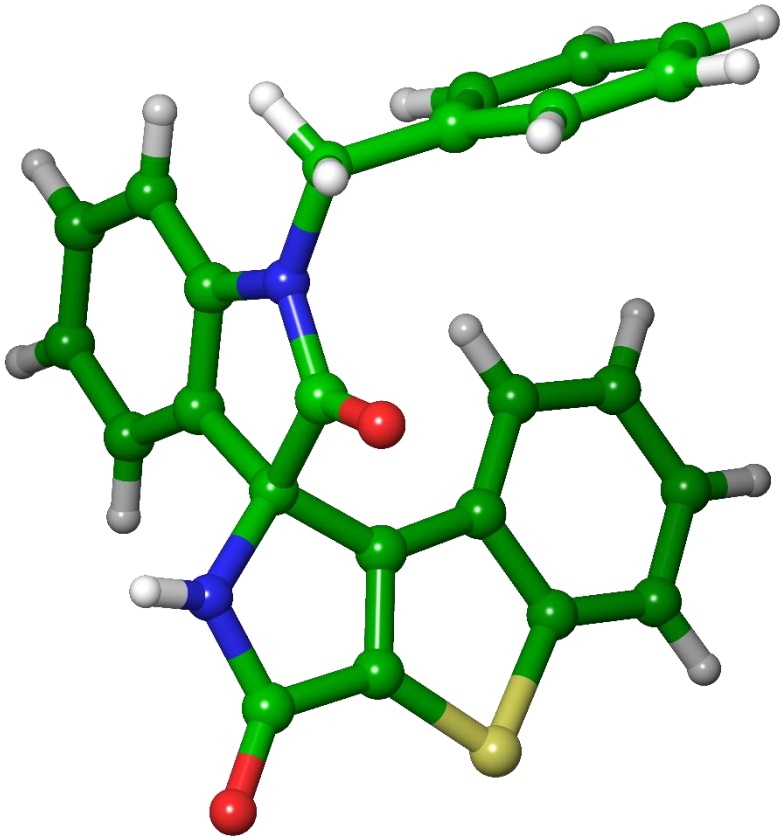


Figure S4. Crystal structure of the cycloadduct **IV-95o**. ORTEP plot of $C_{24}H_{16}N_2O_2S$ (M =396.45 g/mol) at the 50% probability level. See Supplementary Table S4 for additional details.

Table S4. Crystal data and structure refinement for **IV-95o**.

Empirical formula	$C_{24}H_{16}N_2O_2S$
Formula weight	396.45
Temperature/K	100.0
Crystal system	triclinic
Space group	P-1
a/Å	9.1071(7)
b/Å	9.9559(8)
c/Å	11.0561(9)
α/°	109.978(3)
β/°	98.033(3)
γ/°	90.575(3)
Volume/Å^3	931.08(13)
Z	2
ρ_{calc}g/cm^3	1.414
μ/mm^{-1}	0.198
F(000)	412.0
Crystal size/mm^3	1.375 × 0.963 × 0.598
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.966 to 60.908
Index ranges	$-12 \leq h \leq 12$, $-14 \leq k \leq 11$, $-15 \leq l \leq 15$
Reflections collected	30303
Independent reflections	5629 [R_{int} = 0.0471, R_{sigma} = 0.0351]
Data/restraints/parameters	5629/0/266
Goodness-of-fit on F^2	1.036
Final R indexes [I>=2σ (I)]	R_1 = 0.0448, wR_2 = 0.1046
Final R indexes [all data]	R_1 = 0.0546, wR_2 = 0.1111
Largest diff. peak/hole / e Å^{-3}	0.44/-0.26

7.4 Experimental part for synthesis of pseudo sesquiterpenoid alkaloids

7.4.1 Synthesis of SLs derivatives

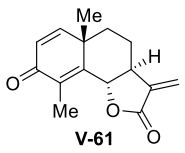
Compound **V-61**, **V-73**, **V-67**, **V-69**, **V-76**, **V-57**, **V-75**, **V-77** were synthesized according to the literature.

General procedure 21 for the synthesis of *α*-methylene-*γ/δ*-lactones:

A solution of freshly prepared lithium diisopropylamide (1.2 equiv.; 0.5 M in anhydrous THF) was added dropwise to the sesquiterpene derivatives (1.0 equiv.) in THF (0.1 M) under -78 ^{o}C and Ar protection. The whole reaction was stirred for 1 h before the addition of PhSeCl (1.2 equiv.) dissolved with few THF. When the starting material was full consumed monitored by TLC, aqueous NH_4Cl was added to quench the reaction and warm to room temperature. The solution was extracted with ethyl acetate (EA) for three times. The organic layer was combined, washed with brine, dried with Na_2SO_4 and evaporated after the filtration. The residue was then purified by column chromatography with elution of *n*-pentane and EA.

The *α*-selenation product (1.0 equiv.) was again dissolved in THF (0.1 M). Then AcOH (3.0 equiv.) and H_2O_2 (6.5 equiv.; 30% solution) were added sequentially at 0 ^{o}C. The reaction was stirred for 20 min before warmed to room temperature. When the starting material was full consumed monitored by TLC, aqueous $NaHCO_3$ was added to quench the reaction. The solution was extracted with ethyl acetate (EA) for three times. The organic layer was combined, washed with brine, dried with Na_2SO_4 and evaporated after the filtration. The residue was then purified by column chromatography with elution of *n*-pentane and EA.

(3a*S*,5a*S*,9b*S*)-5a,9-dimethyl-3-methylene-3a,5,5a,9b-tetrahydronaphtho[1,2-*b*]furan-2,8(3*H*,4*H*)-dione (V-61)

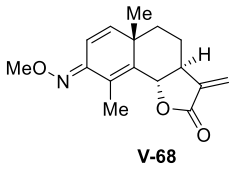


V-61

The title product compound **V-61** was prepared using general procedure 21 from santonin (2.46 g, 10 mmol) and isolated by column chromatography (1:1 *n*-pentane: Ethyl acetate) giving a solid (1.1 g, 4.50 mmol, 45% yield). The spectra were consistent with the reported data[110].

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (d, *J* = 9.9 Hz, 1H), 6.30 – 6.19 (m, 2H), 5.56 (dd, *J* = 3.1, 1.3 Hz, 1H), 4.77 (dd, *J* = 11.6, 1.4 Hz, 1H), 2.75 – 2.64 (m, 1H), 2.23-2.18 (m, 1H), 2.16 (s, 3H), 1.93 (ddd, *J* = 13.5, 3.9, 2.2 Hz, 1H), 1.84 – 1.72 (m, 1H), 1.59 (td, J = 13.3, 4.5 Hz, 1H), 1.31 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.4, 169.3, 154.9, 150.8, 137.6, 129.1, 126.1, 119.9, 81.6, 50.4, 41.5, 37.8, 25.3, 21.8, 11.0.

(3a*S*,5a*S*,9b*S*,*E*)-8-(methoxyimino)-5a,9-dimethyl-3-methylene-3a,4,5,5a,8,9b-hexahydronaphtho[1,2-*b*]furan-2(3*H*)-one (V-68)

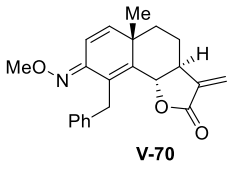


V-68

The title product compound **V-68** was prepared using general procedure 21 from reported compound **V-67** (300 mg, 1.09 mmol)[108] and isolated by column chromatography (1:1 *n*-pentane: Ethyl acetate) giving a solid (210 mg, 0.77 mmol, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, *J* = 10.2 Hz, 1H), 6.17 (d, *J* = 3.2 Hz, 1H), 5.97 (d, *J* = 10.2 Hz, 1H), 5.49 (d, *J* = 3.1 Hz, 1H), 4.74 (dd, *J* = 11.4, 1.4 Hz, 1H), 3.92 (s, 3H), 2.61-2.70 (m, 1H), 2.25 – 2.06 (m, 4H), 1.82 – 1.66 (m, 2H), 1.59 – 1.48 (m, 1H), 1.21 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.7, 149.8, 145.1, 138.3, 123.2, 119.1, 113.0, 82.5, 62.1, 50.3, 40.8, 38.2, 25.9, 22.4, 12.0.

(3a*S*,5a*S*,9b*S*,*E*)-9-benzyl-8-(methoxyimino)-5a-methyl-3-methylene-3a,4,5,5a,8,9b-hexahydronaphtho[1,2-*b*]furan-2(3*H*)-one (V-70)

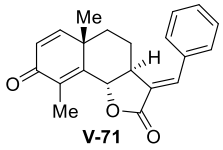


V-70

The title product compound **V-70** was prepared using general procedure 21 from reported compound **V-69** (300 mg, 0.85 mmol)[108] and isolated by column chromatography (1:1 *n*-pentane: Ethyl acetate) giving a solid (260 mg, 0.74 mmol, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 2H), 7.22 – 7.17 (m, 2H), 7.12 – 7.05 (m, 1H), 6.83 (d, *J* = 10.1 Hz, 1H), 6.13 (d, *J* = 3.3 Hz, 1H), 5.99 (d, *J* = 10.2 Hz, 1H), 5.44 (d, *J* = 3.0 Hz, 1H), 4.78 (d, *J* = 11.4 Hz, 1H), 4.28 (d, *J* = 14.7 Hz, 1H), 4.13 (d, *J* = 14.7 Hz, 1H), 3.90 (s, 3H), 2.58 – 2.50 (m, 1H), 2.16 – 2.08 (m, 1H), 1.83 – 1.67 (m, 2H), 1.63-1.55 (m, 1H), 1.27 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.4, 148.6, 144.8, 142.2, 139.5, 138.1, 128.6, 128.0, 126.5, 125.3, 119.1, 113.3, 82.1, 62.3, 50.1, 41.1, 38.5, 30.3, 26.1, 22.5.

(3a*S*,5a*S*,9b*S*)-3-((*E*)-benzylidene)-5a,9-dimethyl-3a,5,5a,9b-tetrahydronaphtho[1,2-*b*]furan-2,8(3*H*,4*H*)-dione (V-71)



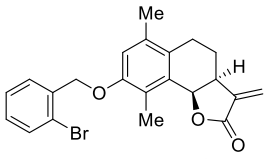
V-71

A mixture of dehydrosantonin **V-61** (150 mg, 0.61 mmol), triethylamine (255 µL, 1.83 mmol), and iodobenzene (77 µL, 0.69 mmol) in DMF (6 mL) was treated with palladium(II) acetate (7 mg, 0.03 mmol) and then heated at 80 °C under air. After 24 h, the reaction mixture was allowed to cool to rt, water (5 mL) was added, and the resultant mixture was extracted with EA (10 mL x 3). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash

chromatography (2:1 *n*-pentane/EtOAc) afforded the title product **V-71** as a solid (137 mg, 0.43 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 3.4 Hz, 1H), 7.42 – 7.35 (m, 3H), 7.36 – 7.29 (m, 2H), 6.67 (d, *J* = 9.9 Hz, 1H), 6.25 (d, *J* = 9.9 Hz, 1H), 4.79 (dq, *J* = 11.3, 1.3 Hz, 1H), 3.03 (tt, *J* = 11.4, 3.2 Hz, 1H), 2.31 – 2.24 (m, 1H), 2.18 (d, *J* = 1.3 Hz, 3H), 1.79 (ddd, *J* = 13.2, 3.6, 2.4 Hz, 1H), 1.53 (td, *J* = 13.2, 3.8 Hz, 1H), 1.47-1.35 (m, 1H), 1.26 (d, *J* = 0.6 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.3, 170.8, 154.9, 151.2, 138.3, 133.6, 129.6, 129.5, 129.0, 128.5, 128.5, 126.0, 82.0, 49.8, 41.2, 38.2, 25.3, 22.1, 10.9.

(3a*S*,9b*R*)-8-((2-bromobenzyl)oxy)-6,9-dimethyl-3-methylene-3a,4,5,9b-tetrahydronaphtho[1,2-*b*]furan-2(3*H*)-one (V-73)

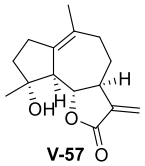


V-73

The tile compound **V-73** was synthesized from **V-61** according to the literature.[110] The spectra were consistent with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.56 (m, 2H), 7.36 (td, *J* = 7.5, 1.3 Hz, 1H), 7.20 (td, *J* = 7.7, 1.7 Hz, 1H), 6.80 (s, 1H), 6.31 (d, *J* = 2.1 Hz, 1H), 5.71 (d, *J* = 1.8 Hz, 1H), 5.63 (d, *J* = 6.7 Hz, 1H), 5.11 (s, 2H), 3.34-3.29 (m, 1H), 2.72 (ddd, *J* = 16.4, 6.2, 4.4 Hz, 1H), 2.52 (ddd, *J* = 16.4, 9.5, 4.4 Hz, 1H), 2.40 (s, 3H), 2.24 (s, 3H), 2.01-1.94 (m, 1H), 1.89 – 1.76 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.4, 154.7, 140.2, 136.8, 134.2, 132.7, 130.8, 129.2, 129.0, 128.8, 127.7, 126.2, 122.3, 121.5, 115.1, 75.2, 70.0, 39.6, 26.3, 23.8, 20.1, 11.8.

(3a*S*,9*R*,9a*S*,9b*S*)-9-hydroxy-6,9-dimethyl-3-methylene-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (V-57)

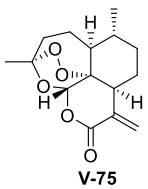


V-57

The tile compound **V-57** was synthesized from **V-56** according to the literature. The spectra were consistent with the reported data[112].

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (d, *J* = 3.3 Hz, 1H), 5.50 (d, *J* = 3.1 Hz, 1H), 3.81 (dd, *J* = 10.6, 9.9 Hz, 1H), 2.73 (d, *J* = 10.9 Hz, 1H), 2.71 – 2.61 (m, 1H), 2.47 (s, 1H), 2.39 (dd, *J* = 16.6, 8.4 Hz, 1H), 2.29 – 2.14 (m, 3H), 2.13-2.06 (m, 1H), 1.88 – 1.73 (m, 2H), 1.69 (s, 3H), 1.40 – 1.32 (m, 1H), 1.30 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.9, 139.0, 132.1, 131.0, 119.6, 84.6, 80.4, 58.9, 49.8, 38.5, 35.1, 30.3, 26.0, 24.1, 22.9.

(3*R*,5a*S*,6*R*,8a*S*,12*S*,12a*R*)-3,6-dimethyl-9-methyleneoctahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10(3*H*)-one (V-75)

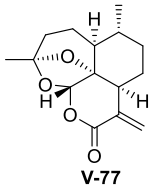


V-75

The title product compound **V-75** was prepared using general procedure 21 from artemisinin **V-74** (140 mg, 0.50 mmol) and isolated by column chromatography (5:1 *n*-pentane: Ethyl acetate) giving a solid (68 mg, 0.24 mmol, 48% yield). The spectra were consistent with the reported data[113].

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, *J* = 1.1 Hz, 1H), 5.99 (s, 1H), 5.66 (d, *J* = 1.1 Hz, 1H), 2.54 (dd, *J* = 13.6, 4.5 Hz, 1H), 2.40 (ddd, *J* = 14.8, 12.8, 3.9 Hz, 1H), 2.06 (ddd, *J* = 15.0, 4.7, 2.9 Hz, 1H), 2.00 – 1.94 (m, 1H), 1.78-1.72 (m, 2H), 1.61 – 1.40 (m, 7H), 1.24 – 1.14 (m, 1H), 1.01 (d, *J* = 5.7 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.8, 135.1, 130.5, 105.5, 93.6, 79.5, 50.3, 46.2, 37.9, 36.0, 33.8, 31.7, 25.5, 24.8, 20.0.

(3a*S*,3a1*R*,6*R*,6a*S*,9*S*,10a*R*)-6,9-dimethyl-3-methyleneoctahydro-10a*H*-3a1,9-epoxyoxepino[4,3,2-*ij*]isochromen-2(3*H*)-one (V-77)



V-77

The title product compound **V-77** was prepared using general procedure 21 from reported compound **V-76** (133 mg, 0.5 mmol) and isolated by column chromatography (5:1 *n*-pentane: Ethyl acetate) giving a solid (94.1 mg, 0.36 mmol, 72% yield). The spectra were consistent with the reported data[113].

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (d, *J* = 1.3 Hz, 1H), 5.79 (s, 1H), 5.67 – 5.60 (m, 1H), 2.80 (dd, *J* = 13.3, 4.4 Hz, 1H), 1.90 (ddd, *J* = 8.5, 4.9, 1.9 Hz, 1H), 1.83 – 1.71 (m, 3H), 1.65 – 1.59 (m, 1H), 1.54 – 1.47 (m, 4H), 1.33 – 1.18 (m, 4H), 0.96 (d, *J* = 6.0 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 163.2, 135.5, 129.5, 110.1, 99.6, 82.5, 44.8, 44.5, 35.7, 34.0, 33.8, 31.0, 24.2, 22.1, 18.7.

7.4.2 Stereodivergent synthesis of santonin-pyrrolidines

Condition A: Silver acetate (0.8 mg, 0.005 mmol, 0.05 equiv.) and chiral ligand **V-69** (2.5 mg, 0.006 mmol, 0.06 equiv.) were dissolved in dry THF (0.5 mL). After stirring for 30 min, a solution of lactones (0.10 mmol, 1.0 equiv.) and the desired iminoester (0.15 mmol, 1.5 equiv.) in THF (0.5 mL) were added dropwise followed by the addition of Et_3N (2.8 µL, 0.20 mmol, 0.2 equiv.). The reaction was stirred at room temperature until full conversion of the starting material was observed by TLC. The reaction was passed through a short pad of silica and test the crude ^1H NMR to determine the diastereoselectivity. Then the reaction was purified by column chromatography using cyclohexane/EA mixtures. Unless otherwise specified, only main isomer was isolated.

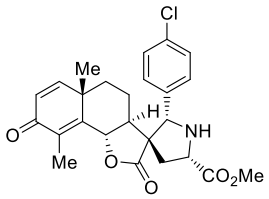
Condition B: Silver acetate (0.8 mg, 0.005 mmol, 0.05 equiv.) and chiral ligand *ent*-**V-69** (2.5 mg, 0.006 mmol, 0.06 equiv.) were dissolved in dry THF (0.5 mL). After stirring for 30 min, a solution of lactones (0.10 mmol, 1.0 equiv.) and the desired iminoester (0.15 mmol, 1.5 equiv.) in THF (0.5 mL) were added at 0 ºC dropwise followed by the addition of Et_3N (2.8 µL, 0.20 mmol, 0.2 equiv.). The reaction was stirred until full conversion of the starting material was observed by TLC. The reaction was passed through a short pad of silica and test the crude ^1H NMR to determine the diastereoselectivity. Then the reaction was purified by column chromatography using cyclohexane/EA mixtures. Unless otherwise specified, only main isomer was isolated.

Condition C: Silver acetate (0.8 mg, 0.005 mmol, 0.05 equiv.) and chiral ligand **V-70** (7.1 mg, 0.006 mmol, 0.06 equiv.) were dissolved in dry DCE (0.5 mL). After stirring for 30 min, a solution of lactones (0.10 mmol, 1.0 equiv.) and the desired iminoester (0.15 mmol, 1.5 equiv.) in DCE (0.5 mL) were added dropwise followed by the addition of Et_3N (2.8 µL, 0.20 mmol, 0.2 equiv.). The reaction was stirred until full conversion of the starting material was observed by TLC. The reaction was passed through a short pad of silica and test the crude ^1H NMR to determine the diastereoselectivity. Then the reaction was purified by column chromatography using cyclohexane/EA mixtures. Unless otherwise specified, only main isomer was isolated.

Condition D: Silver acetate (0.8 mg, 0.005 mmol, 0.05 equiv.) and chiral ligand **V-71** (6.9 mg, 0.006 mmol, 0.06 equiv.) were dissolved in $CHCl_3$ (0.5 mL). After stirring for 30 min, a solution of lactones (0.10 mmol, 1.0 equiv.) and the desired iminoester (0.20 mmol, 2.0 equiv.) in $CHCl_3$ (0.5 mL) were added dropwise at 0 ºC followed by the addition of Cs_2CO_3

(16.3 mg, 0.05 mmol, 0.5 equiv.). The reaction was stirred until full conversion of the starting material was observed by TLC. The reaction was passed through a short pad of silica and test the crude ^{1}H NMR to determine the diastereoselectivity. Then the reaction was purified by column chromatography using cyclohexane/EA mixtures. Unless otherwise specified, only main isomer was isolated.

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(4-chlorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63a)

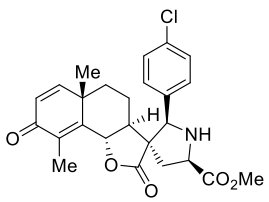


V-63a

The title product compound **V-63a** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (35 mg, 0.07 mmol, 73% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 4H), 6.67 (d, *J* = 9.9 Hz, 1H), 6.23 (d, *J* = 9.9 Hz, 1H), 4.78 (dd, *J* = 11.7, 1.5 Hz, 1H), 4.09 – 3.99 (m, 2H), 3.82 (s, 3H), 2.54 (dd, *J* = 13.5, 9.0 Hz, 1H), 2.46 (dd, *J* = 13.4, 5.4 Hz, 1H), 2.05 – 1.93 (m, 3H), 1.90 (d, *J* = 1.4 Hz, 3H), 1.88 – 1.79 (m, 1H), 1.53 (td, *J* = 13.1, 4.6 Hz, 1H), 1.30 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 175.9, 172.5, 154.5, 150.4, 134.5, 134.0, 129.7, 129.3, 128.9, 126.2, 80.0, 68.0, 58.7, 55.1, 52.8, 50.3, 41.1, 37.6, 33.8, 25.2, 19.4, 10.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Cl$ m/z 456.1572, found 456.1560. **IR** (film, cm^{-1}): 2926, 2854, 1775, 1737, 1661, 1634, 1615, 1491, 1436, 1376, 1268, 1225, 1204, 1185, 1154, 1091, 1036, 1014, 991, 961, 906, 831. **$[\alpha]_D^{20}$** = -52.3 (c = 0.17, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(4-chlorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64a)



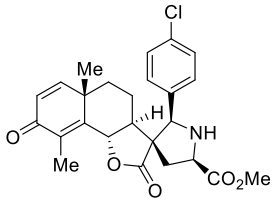
V-64a

The title product compound **V-64a** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (43.3 mg, 0.09 mmol, 95% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 6.62 (d, *J* = 9.9 Hz, 1H), 6.18 (d, *J* = 9.8 Hz, 1H), 4.39 (s, 1H), 4.21 (dd, *J* = 11.9, 1.5 Hz, 1H), 4.01-3.97 (m, 1H), 3.83 (s, 3H), 2.65 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.32 (dd, *J* = 13.7, 9.5 Hz, 1H), 2.23 (td, *J* = 12.1, 3.5 Hz, 1H), 2.11 – 1.85 (m, 6H), 1.49 – 1.40 (m, 1H), 1.08 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 177.3, 173.4, 154.5,

150.6, 136.3, 135.1, 129.7, 129.2, 128.9, 126.1, 79.5, 65.8, 58.3, 56.7, 52.7, 52.5, 41.1, 38.6, 37.8, 24.8, 19.2, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Cl$ m/z 456.1572, found 456.1562. **IR** (film, cm^{-1}): 2959, 1774, 1732,1662, 1635, 1615, 1492.99, 1435, 1372, 1336, 1315, 1287, 1263,1219, 1195, 1169, 1149, 1094, 1064, 1041, 1013, 997, 962, 939, 919, 894, 839, 827. **$[\alpha]_D^{20}$** = -122.1 (c = 0.15, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(4-chlorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-65a)

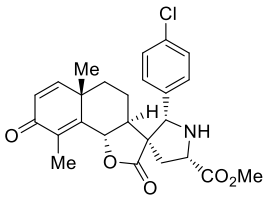


V-65a

The title product compound **V-65a** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (40.8 mg, 0.09 mmol, 89% yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 4H), 6.57 (d, *J* = 9.9 Hz, 1H), 6.18 (d, *J* = 9.9 Hz, 1H), 4.82 – 4.70 (m, 2H), 4.21 (dd, *J* = 9.0, 7.7 Hz, 1H), 3.82 (s, 3H), 2.51 (dd, *J* = 13.4, 7.7 Hz, 1H), 2.37 – 2.27 (m, 1H), 2.04 (d, *J* = 1.5 Hz, 3H), 1.66 (ddd, *J* = 13.4, 3.7, 2.4 Hz, 1H), 1.63 – 1.49 (m, 2H), 1.31 – 1.27 (m, 2H), 1.22 (s, 3H), 1.10 (td, *J* = 12.9, 4.5 Hz, 1H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 186.2, 178.3, 173.3, 154.8, 150.7, 137.4, 134.1, 129.3, 129.0, 128.5, 126.1, 79.9, 66.5, 57.1, 55.1, 52.5, 50.3, 41.1, 37.4, 31.2, 25.1, 20.1, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Cl$ m/z 456.1572, found 456.1568. **IR** (film, cm^{-1}): 2925, 1771, 1737, 1662, 1634, 1614, 1490 ,1454, 1437, 1376, 1274, 1192, 1153, 1139, 1090, 1042, 1014, 998, 968, 902, 832. **$[\alpha]_D^{20}$** = +84.0 (c = 0.15, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(4-chlorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66a)



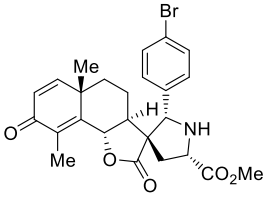
V-66a

The title product compound **V-66a** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (40.0 mg, 0.09 mmol, 88% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.9 Hz, 2H), 7.41 – 7.34 (m, 2H), 6.52 (d, *J* = 9.9 Hz, 1H), 6.15 (d, *J* = 9.9 Hz, 1H), 4.53 (s, 1H), 4.17 (ddd, *J* = 11.9, 10.6, 3.7 Hz, 2H), 3.80 (s, 3H), 3.01 (dd, *J* = 13.9, 10.7 Hz, 1H), 2.19 (dd, *J* = 13.9, 5.6 Hz, 1H), 2.05 (d, *J* = 1.4 Hz, 3H), 1.99 – 1.95 (m, 2H), 1.91 – 1.82 (m, 1H),

1.66 (ddd, *J* = 13.7, 4.1, 2.3 Hz, 1H), 1.20 (td, *J* = 13.1, 4.4 Hz, 1H), 0.65 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 186.3, 178.5, 173.3, 154.9, 151.1, 135.1, 134.6, 129.1, 128.7, 128.6, 125.9, 79.7, 67.8, 56.8, 56.6, 54.9, 52.6, 41.2, 40.4, 38.5, 24.0, 18.2, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Cl$ m/z 456.1572, found 456.1558. **IR** (film, cm^{-1}): 2930, 1770, 1737, 1661, 1633, 16141491, 1437, 1406, 1377, 1271, 1201, 1186, 1162, 1091, 1040, 1013, 989, 954, 903, 878, 830. **$[\alpha]_D^{20}$** = -100.0 (c = 0.10, $CHCl_3$)

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(4-bromophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63b)

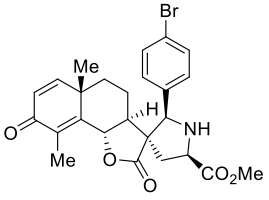


V-63b

The title product compound **V-63b** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (33.4 mg, 0.07 mmol, 67% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 2H), 7.32 – 7.17 (m, 2H), 6.67 (d, *J* = 9.9 Hz, 1H), 6.23 (d, *J* = 9.8 Hz, 1H), 4.77 (dd, *J* = 11.6, 1.4 Hz, 1H), 4.04 (m, 2H), 3.81 (s, 3H), 2.54 (dd, *J* = 13.5, 9.0 Hz, 1H), 2.45 (dd, *J* = 13.4, 5.4 Hz, 1H), 2.03 – 1.92 (m, 3H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.88-1.78 (m, 1H), 1.53 (td, *J* = 13.1, 4.6 Hz, 1H), 1.29 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 175.9, 172.5, 154.5, 150.4, 134.6, 131.8, 130.0, 129.3, 126.2, 122.7, 80.0, 67.9, 58.7, 55.0, 52.7, 50.3, 41.1, 37.5, 33.8, 25.2, 19.4, 10.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Br$ m/z 500.1067, found 500.1055. **IR** (film, cm^{-1}): 2946, 2557, 2161, 2036, 1774, 1736, 1661, 1633, 1614, 1487, 1436, 1376, 1305, 1270, 1224, 1204, 1185, 1154, 1132, 1057, 1035, 1010, 991, 961, 905, 831. **$[\alpha]_D^{20}$** = -91.4 (c = 0.11, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(4-bromophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64b)



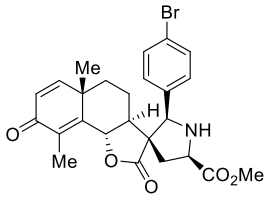
V-64b

The title product compound **V-64b** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (42.6 mg, 0.09 mmol, 85% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 9.9 Hz, 1H), 6.20 (d, *J* = 9.9 Hz, 1H), 4.37 (s, 1H), 4.24 (dd, *J* = 11.9, 1.5 Hz, 1H), 3.99 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.84 (s, 3H), 2.66 (dd, *J* =

13.6, 5.2 Hz, 1H), 2.32 (dd, *J* = 13.6, 9.6 Hz, 1H), 2.24 (td, *J* = 12.1, 4.0 Hz, 1H), 2.08 – 1.88 (m, 6H), 1.46 (td, *J* = 13.0, 4.9 Hz, 1H), 1.09 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 177.3, 173.4, 154.5, 150.6, 137.0, 132.6, 129.5, 129.0, 126.2, 123.3, 79.5, 77.5, 77.2, 76.8, 66.0, 58.5, 56.7, 52.8, 52.6, 41.2, 38.7, 37.9, 24.9, 19.2, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Br$ m/z 500.1067, found 500.1053. **IR** (film, cm^{-1}): 2960, 1773, 1732, 1661, 1635, 1615, 1490, 1435, 1372, 1336, 1314, 1292, 1263, 1218, 1194, 1168, 1149, 1115, 1094, 1064, 1041, 1009, 997, 962, 939, 919, 895, 840, 827, 806. **$[\alpha]_D^{20}$** = -129.3 (c = 0.14, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(4-bromophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-65b)

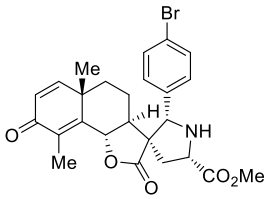


V-65b

The title product compound **V-65b** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (47.0 mg, 0.09 mmol, 94% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.57 (d, *J* = 9.8 Hz, 1H), 6.19 (d, *J* = 9.8 Hz, 1H), 4.77 (dd, *J* = 11.3, 1.5 Hz, 1H), 4.73 (s, 1H), 4.21 (dd, *J* = 9.0, 7.6 Hz, 1H), 3.82 (s, 3H), 2.51 (dd, *J* = 13.4, 7.7 Hz, 1H), 2.32 (dd, *J* = 13.4, 9.0 Hz, 1H), 2.04 (d, *J* = 1.4 Hz, 3H), 1.67 (ddd, *J* = 13.5, 3.7, 2.3 Hz, 1H), 1.62 – 1.49 (m, 2H), 1.33 – 1.27 (m, 1H), 1.22 (s, 3H), 1.15 – 1.07 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 173.2, 154.8, 154.8, 150.7, 137.9, 131.9, 129.2, 128.8, 126.0, 122.2, 79.9, 77.4, 77.2, 76.9, 66.5, 57.1, 55.0, 52.6, 50.2, 41.1, 37.3, 31.2, 25.1, 20.1, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Br$ m/z 500.1067, found 500.1061. **IR** (film, cm^{-1}): 2948, 2160, 2032, 1772, 1737, 1662, 1635, 1487, 1437, 1274, 1193, 1042, 1010, 902, 832. **$[\alpha]_D^{20}$** = +75.3 (c = 0.09, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(4-bromophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66b)



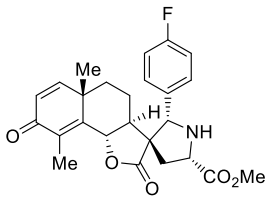
V-66b

The title product compound **V-66b** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (43.8 mg, 0.09 mmol, 88% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 6.52 (d, *J* = 9.9 Hz, 1H), 6.14 (d, *J* = 9.9 Hz, 1H), 4.50 (s,

1H), 4.20 – 4.11 (m, 2H), 3.79 (s, 3H), 3.00 (dd, *J* = 13.9, 10.7 Hz, 1H), 2.18 (dd, *J* = 13.9, 5.5 Hz, 1H), 2.05 (d, *J* = 1.4 Hz, 3H), 2.00 – 1.93 (m, 2H), 1.90 – 1.83 (m, 1H), 1.66 (ddd, *J* = 13.6, 4.1, 2.3 Hz, 1H), 1.19 (td, *J* = 13.0, 4.4 Hz, 1H), 0.65 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 186.3, 178.5, 173.3, 155.0, 151.1, 135.8, 132.1, 129.0, 128.5, 125.9, 122.5, 79.7, 77.4, 77.2, 76.9, 67.9, 56.8, 56.5, 54.8, 52.6, 41.2, 40.5, 38.4, 23.9, 18.2, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Br$ m/z 500.1067, found 500.1062. **IR** (film, cm^{-1}): 1766, 1740, 1658, 1628, 1432, 1272, 1203, 1009, 844, 821. **$[\alpha]_D^{20}$** = -97.6 (c = 0.21, $CHCl_3$)

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(4-fluorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63c)

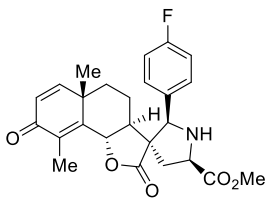


V-63c

The title product compound **V-63c** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (23.3 mg, 0.05 mmol, 53% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 2H), 7.06-6.98 (m, 2H), 6.67 (d, *J* = 9.9 Hz, 1H), 6.22 (d, *J* = 9.9 Hz, 1H), 4.78 (dd, *J* = 11.7, 1.5 Hz, 1H), 4.18 – 4.05 (m, 2H), 3.81 (s, 3H), 2.56 (dd, *J* = 13.5, 9.1 Hz, 1H), 2.48 (dd, *J* = 13.5, 5.0 Hz, 1H), 2.05 – 1.94 (m, 3H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.83 (dd, *J* = 12.7, 4.0 Hz, 1H), 1.52 (ddd, *J* = 13.6, 13.1, 4.4 Hz, 1H), 1.29 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 176.1, 172.4, 162.9 (d, *J* = 247.8 Hz), 154.6, 150.4, 130.8 (d, *J* = 3.3 Hz), 130.1 (d, *J* = 8.2 Hz), 129.2, 126.2, 115.7 (d, *J* = 21.4 Hz), 80.1, 67.8, 58.6, 55.0, 52.8, 50.1, 41.2, 37.6, 33.7, 25.1, 19.5, 10.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5F$ m/z 440.1868, found 440.1856. **IR** (film, cm^{-1}): 3349, 2938, 2346, 1784, 1733, 1657, 1626, 1609, 1509, 1438, 1404, 1371, 1338, 1292, 1266, 1223, 1187, 1164, 1155, 1135, 1084, 1056, 1024, 993, 957, 901, 837. **$[\alpha]_D^{20}$** = -64.6 (c = 0.13, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(4-fluorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64c)



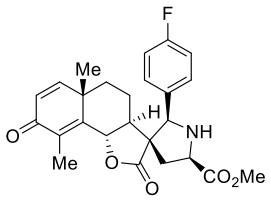
V-64c

The title product compound **V-64c** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (43.7 mg, 0.10 mmol, 99% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.40 (m, 2H), 7.12-7.05 (m, 2H),

6.61 (d, *J* = 9.9 Hz, 1H), 6.18 (d, *J* = 9.8 Hz, 1H), 4.38 (s, 1H), 4.18 (dd, *J* = 12.0, 1.4 Hz, 1H), 3.99 (dd, *J* = 9.7, 5.0 Hz, 1H), 3.83 (s, 3H), 2.64 (dd, *J* = 13.7, 5.1 Hz, 1H), 2.32 (dd, *J* = 13.7, 9.8 Hz, 1H), 2.24 (td, *J* = 12.3, 3.7 Hz, 1H), 2.09 – 2.03 (m, 1H), 1.99 – 1.84 (m, 5H), 1.44 (td, *J* = 13.2, 4.7 Hz, 1H), 1.06 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 177.5, 173.4, 163.0 (d, *J* = 248.8 Hz), 154.6, 150.7, 133.6 (d, *J* = 3.2 Hz), 129.6 (d, *J* = 8.2 Hz), 128.9, 126.1, 116.5 (d, *J* = 21.4 Hz), 79.4, 65.9, 58.3, 56.6, 52.7, 52.4, 41.1, 38.6, 37.8, 24.8, 19.1, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5F$ m/z 440.1868, found 440.1855. **IR** (film, cm^{-1}): 2951, 2161, 1759, 1734, 1661, 1634, 1614, 1510, 1437, 1406, 1374, 1335, 1307, 1265, 1217, 1155, 1132, 1107, 1061, 1038, 991, 944, 918, 904, 836. **$[\alpha]_D^{20}$** = -99.2 (c = 0.13, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(4-fluorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-65c)

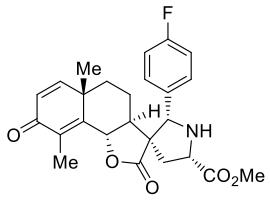


V-65c

The title product compound **V-65c** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (35.4 mg, 0.08 mmol, 81% yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 2H), 7.03-6.98 (m, 2H), 6.57 (d, *J* = 9.9 Hz, 1H), 6.19 (d, *J* = 9.8 Hz, 1H), 4.80 – 4.74 (m, 2H), 4.22 (dd, *J* = 8.9, 7.7 Hz, 1H), 3.82 (s, 3H), 2.51 (dd, *J* = 13.4, 7.8 Hz, 1H), 2.32 (dd, *J* = 13.4, 8.9 Hz, 1H), 2.04 (d, *J* = 1.4 Hz, 3H), 1.66 (ddd, *J* = 13.4, 3.8, 2.4 Hz, 1H), 1.60 (dd, *J* = 12.3, 3.1 Hz, 1H), 1.54 (dd, *J* = 12.7, 3.9 Hz, 1H), 1.28 – 1.24 (m, 1H), 1.23 (s, 3H), 1.09 (td, *J* = 13.0, 4.5 Hz, 1H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 186.3, 178.4, 173.5, 162.6 (d, *J* = 247.0 Hz), 154.8, 150.8, 134.7 (d, *J* = 3.1 Hz), 129.2, 128.7 (d, *J* = 8.0 Hz), 126.1, 115.7 (d, *J* = 21.3 Hz), 80.0, 66.5, 57.1, 55.1, 52.6, 50.3, 41.1, 37.5, 31.2, 25.1, 20.2, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5F$ m/z 440.1868, found 440.1864. **IR** (film, cm^{-1}): 2950, 1771, 1738, 1662, 1634, 1614, 1509, 1438, 1377, 1275, 1223, 1154, 1140, 1043, 1016, 998, 968, 904, 833. **$[\alpha]_D^{20}$** = +30.0 (c = 0.15, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(4-fluorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66c)

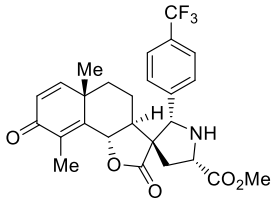


V-66c

The title product compound **V-66c** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (37.6 mg, 0.09 mmol, 86% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.48 (m, 2H), 7.14 – 7.05 (m, 2H), 6.52 (d, *J* = 9.9 Hz, 1H), 6.14 (d, *J* = 9.8 Hz, 1H), 4.51 (s, 1H), 4.19 – 4.09 (m, 2H), 3.79 (s, 3H), 3.00 (dd, *J* = 13.9, 10.8 Hz, 1H), 2.22 – 2.11 (m, 1H), 2.05 (d, *J* = 1.4 Hz, 3H), 2.00-1.93 (m, 2H), 1.89 (ddd, *J* = 14.0, 12.4, 3.9 Hz, 1H), 1.66 (ddd, *J* = 13.5, 3.9, 2.3 Hz, 1H), 1.20 (td, *J* = 12.9, 4.8 Hz, 1H), 0.64 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.4, 178.6, 173.6, 162.6 (d, *J* = 248.7 Hz), 155.0, 151.3, 132.6 (d, *J* = 3.4 Hz), 128.9 (d, *J* = 7.8 Hz), 128.5, 125.9, 115.9 (d, *J* = 21.4 Hz), 79.6, 67.8, 56.9, 56.5, 54.8, 52.6, 41.2, 40.5, 38.4, 24.0, 18.1, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5F$ m/z 440.1868, found 440.1861. **IR** (film, cm^{-1}): 2925, 2854, 1766, 1740, 1660, 1628, 1610, 1509, 1435, 1406, 1376, 1271, 1222, 1201, 1185, 1161, 1107, 1038, 988, 953, 902, 882, 834, 803. **$[\alpha]_D^{20}$** = -58.9 (c = 0.09, $CHCl_3$)

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(4- (trifluoromethyl)phenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63d)

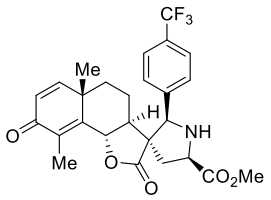


V-63d

The title product compound **V-63d** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (35.1 mg, 0.07 mmol, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 6.67 (d, *J* = 9.9 Hz, 1H), 6.22 (d, *J* = 9.9 Hz, 1H), 4.79 (dd, *J* = 11.6, 1.7 Hz, 1H), 4.16 (s, 1H), 4.06 (dd, *J* = 8.9, 5.6 Hz, 1H), 3.81 (s, 3H), 2.57 (dd, *J* = 13.5, 8.9 Hz, 1H), 2.46 (dd, *J* = 13.4, 5.6 Hz, 1H), 2.07 – 1.95 (m, 3H), 1.92 – 1.76 (m, 4H), 1.54 (ddd, *J* = 13.5, 13.0, 4.8 Hz, 1H), 1.29 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 175.8, 172.5, 154.5, 150.3, 139.9, 130.7 (q, *J* = 32.6 Hz), 129.3, 128.8, 126.2, 125.5 (q, *J* = 3.8 Hz), 124.0 (d, *J* = 272.2 Hz), 80.0, 67.9, 58.7, 55.2, 52.7, 50.6, 41.1, 37.5, 33.8, 25.1, 19.4, 10.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{27}NO_5F_3$ m/z 490.1836, found 490.1819. **IR** (film, cm^{-1}): 2936, 1774, 1738, 1662, 1634, 1617, 1437, 1379, 1324, 1269, 1225, 1162, 1116, 1068, 1017, 991, 906, 832. **$[\alpha]_D^{20}$** = -74.5 (c = 0.11, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(4- (trifluoromethyl)phenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64d)

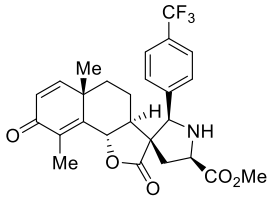


V-64d

The title product compound **V-64d** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (46.7 mg, 0.10 mmol, 95% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.53 (m, 4H), 6.63 (d, *J* = 9.9 Hz, 1H), 6.19 (d, *J* = 9.9 Hz, 1H), 4.49 (s, 1H), 4.26 (dd, *J* = 12.1, 1.5 Hz, 1H), 4.02 (dd, *J* = 9.4, 5.7 Hz, 1H), 3.84 (s, 3H), 2.69 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.33 (dd, *J* = 13.6, 9.4 Hz, 1H), 2.25 (td, *J* = 12.1, 4.0 Hz, 1H), 2.11 – 2.04 (m, 1H), 2.02 – 1.90 (m, 5H), 1.47 (td, *J* = 12.9, 4.8 Hz, 1H), 1.10 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 176.9, 173.4, 154.5, 150.4, 142.4, 131.4 (q, *J* = 32.9 Hz), 129.1, 128.4, 126.4 (q, *J* = 3.7 Hz), 126.1, 123.8 (d, *J* = 272.3 Hz), 79.4, 65.8, 58.5, 57.0, 52.9, 52.8, 41.1, 38.6, 37.8, 24.8, 19.4, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{27}NO_5F_3$ m/z 490.1836, found 490.1821. **IR** (film, cm^{-1}): 2952, 1774, 1738, 1662, 1634, 1617, 1437, 1378, 1324, 1266, 1225, 1163, 1120, 1068, 1039, 1016, 993, 959, 906, 832. **$[\alpha]_D^{20}$** = -76.5 (c = 0.17, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(4- (trifluoromethyl)phenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-65d)

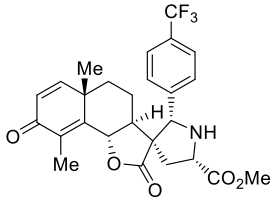


V-65d

The title product compound **V-65d** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (40.8 mg, 0.08 mmol, 83% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 6.57 (d, *J* = 9.8 Hz, 1H), 6.19 (d, *J* = 9.9 Hz, 1H), 4.83 (s, 1H), 4.79 (dq, *J* = 11.1, 1.4 Hz, 1H), 4.24 (dd, *J* = 8.8, 7.8 Hz, 1H), 3.83 (s, 3H), 2.54 (dd, *J* = 13.4, 7.9 Hz, 1H), 2.34 (dd, *J* = 13.4, 8.8 Hz, 1H), 1.69 – 1.62 (m, 1H), 1.60 – 1.49 (m, 2H), 1.23 (m, 4H), 1.12 – 1.02 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 178.2, 173.2, 154.7, 150.5, 143.1, 130.6 (q, *J* = 32.6 Hz), 129.4, 127.6, 126.1, 125.7 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 272.3 Hz), 79.9, 66.5, 57.1, 55.1, 52.6, 50.4, 41.0, 37.2, 31.1, 25.1, 20.1, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{27}NO_5F_3$ m/z 490.1836, found 490.1823. **IR** (film, cm^{-1}): 2926, 2117, 1773, 1741, 1663, 1636, 1617, 1438, 1324, 1276, 1163, 1120, 1067, 1017, 902, 833. **$[\alpha]_D^{20}$** = +44.8 (c = 0.13, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(4- (trifluoromethyl)phenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66d)

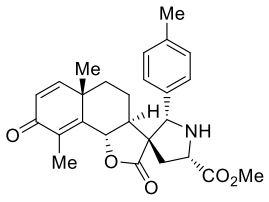


V-66d

The title product compound **V-66d** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (45.0 mg, 0.09 mmol, 92% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 – 7.62 (m, 4H), 6.50 (d, *J* = 9.8 Hz, 1H), 6.13 (d, *J* = 9.9 Hz, 1H), 4.60 (s, 1H), 4.22 – 4.14 (m, 1H), 4.08 – 4.04 (m, 1H), 3.80 (s, 3H), 3.04 (dd, *J* = 13.9, 10.8 Hz, 1H), 2.20 (dd, *J* = 13.9, 5.5 Hz, 1H), 2.04 (d, *J* = 1.1 Hz, 3H), 2.01 – 1.94 (m, 2H), 1.88 – 1.75 (m, 1H), 1.64 (ddd, *J* = 13.7, 4.1, 2.2 Hz, 1H), 1.19 (td, *J* = 13.1, 4.3 Hz, 1H), 0.54 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.3, 178.4, 173.3, 154.9, 150.9, 141.1, 130.0 (q, *J* = 32.9 Hz), 128.5, 127.8, 125.9, 125.8 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 272.4 Hz), 79.7, 67.9, 56.8, 56.5, 55.0, 52.6, 41.1, 40.6, 38.4, 23.6, 18.2, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{27}NO_5F_3$ m/z 490.1836, found 490.1824. **IR** (film, cm^{-1}): 2926, 1766, 1743, 1661, 1633, 1437, 1378, 1324, 1272, 1222, 1184, 1163, 1118, 1068, 1038, 1016, 989, 955, 913, 881, 832. **$[\alpha]_D^{20}$** = -50.0 (c = 0.21, $CHCl_3$)

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(*p*-tolyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63e)

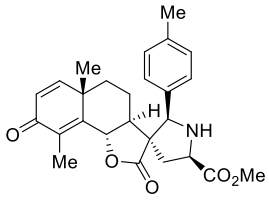


V-63e

The title product compound **V-63e** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (27.4 mg, 0.06 mmol, 63% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.1 Hz, 2H), 7.16 – 7.10 (m, 2H), 6.67 (d, *J* = 9.9 Hz, 1H), 6.22 (d, *J* = 9.9 Hz, 1H), 4.76 (dd, *J* = 11.7, 1.3 Hz, 1H), 4.10 – 4.00 (m, 2H), 3.81 (s, 3H), 2.53 (dd, *J* = 13.5, 9.1 Hz, 1H), 2.45 (dd, *J* = 13.4, 5.2 Hz, 1H), 2.31 (s, 3H), 2.05 (td, *J* = 12.3, 3.4 Hz, 1H), 1.99 – 1.92 (m, 2H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.86 – 1.77 (m, 1H), 1.52 (td, *J* = 13.1, 4.6 Hz, 1H), 1.29 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.3, 176.3, 172.7, 154.6, 150.8, 138.4, 132.1, 129.4, 129.1, 128.1, 126.2, 80.1, 77.4, 68.6, 58.8, 55.1, 52.7, 50.0, 41.2, 37.7, 34.1, 25.1, 21.2, 19.5, 10.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_5$ m/z 436.2119, found 436.2108. **IR** (film, cm^{-1}): 2924, 2160, 2036, 1777, 1737, 1659, 1627, 1611, 1514, 1434, 1404, 1377, 1338, 1303, 1267, 1211, 1189, 1163, 1141, 1088, 1056, 1026, 990, 960, 899, 842, 817. **$[\alpha]_D^{20}$** = -75.7 (c = 0.19, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(*p*-tolyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64e)

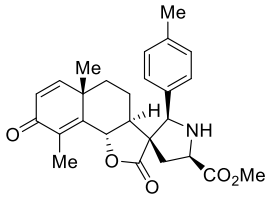


V-64e

The title product compound **V-64e** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (38.8 mg, 0.09 mmol, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 6.61 (d, *J* = 9.9 Hz, 1H), 6.17 (d, *J* = 9.9 Hz, 1H), 4.33 (s, 1H), 4.22 – 4.14 (m, 1H), 3.99 (dd, *J* = 9.9, 4.7 Hz, 1H), 3.84 (s, 3H), 2.63 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.37 – 2.29 (m, 4H), 2.23 (td, *J* = 12.2, 3.4 Hz, 1H), 2.10 (td, *J* = 12.8, 4.0 Hz, 1H), 2.00 – 1.88 (m, 5H), 1.48 – 1.39 (m, 1H), 1.04 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.3, 177.9, 173.5, 154.7, 151.1, 139.3, 134.3, 130.2, 128.7, 127.6, 126.0, 79.5, 66.7, 58.4, 56.6, 52.7, 52.3, 41.2, 38.9, 37.9, 24.7, 21.3, 19.0, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_5$ m/z 436.2119, found 436.2115. **IR** (film, cm^{-1}): 2927, 1773, 1732, 1661, 1635, 1615, 1518, 1436, 1373, 1343, 1319, 1310, 1267, 1219, 1169, 1149, 1116, 1095, 1064, 1041, 997, 961, 939, 894, 841, 823. **$[\alpha]_D^{20}$** = -119.0 (c = 0.10, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(*p*-tolyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-65e)

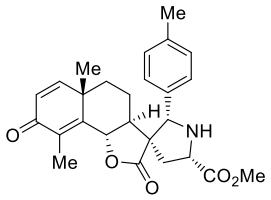


V-65e

The title product compound **V-65e** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (42.5 mg, 0.10 mmol, 97% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 9.8 Hz, 1H), 6.17 (d, *J* = 9.8 Hz, 1H), 4.80 – 4.70 (m, 2H), 4.22 (dd, *J* = 9.0, 7.7 Hz, 1H), 3.82 (s, 3H), 2.53 (dd, *J* = 13.4, 7.6 Hz, 1H), 2.39 – 2.26 (m, 4H), 2.03 (d, *J* = 1.4 Hz, 3H), 1.69 – 1.48 (m, 3H), 1.41 – 1.34 (m, 1H), 1.22 (s, 3H), 1.08 (td, *J* = 12.9, 4.5 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.4, 178.6, 173.2, 155.0, 151.1, 138.1, 135.1, 129.5, 129.1, 126.9, 126.0, 79.9, 67.2, 57.2, 55.1, 52.6, 50.2, 41.1, 37.5, 31.4, 25.0, 21.3, 20.2, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_5$ m/z 436.2119, found 436.2109. **IR** (film, cm^{-1}): 3343, 2949, 2160, 2040, 1771, 1737, 1662, 1635, 1614, 1513, 1437, 1378, 1324, 1273, 1191, 1162, 1123, 1106, 1042, 1016, 997, 967, 902, 882, 832. **$[\alpha]_D^{20}$** = +66.7 (c = 0.14, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(*p*-tolyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66e)

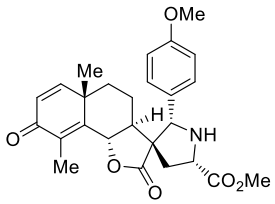


V-66e

The title product compound **V-66e** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (37.7 mg, 0.09 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.8 Hz, 2H), 7.24 – 7.15 (m, 2H), 6.50 (d, *J* = 9.9 Hz, 1H), 6.13 (d, *J* = 9.9 Hz, 1H), 4.50 (s, 1H), 4.22 – 4.08 (m, 2H), 3.80 (s, 3H), 3.02 (dd, *J* = 13.9, 10.8 Hz, 1H), 2.33 (s, 3H), 2.17 – 2.09 (m, 1H), 2.06 (d, *J* = 1.4 Hz, 3H), 2.04 – 1.90 (m, 3H), 1.69 – 1.60 (m, 1H), 1.24 – 1.12 (m, 1H), 0.58 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.4, 178.8, 173.7, 155.1, 151.6, 138.5, 133.4, 129.5, 128.4, 127.1, 125.9, 79.6, 68.4, 57.1, 56.7, 55.0, 52.5, 41.2, 40.8, 38.6, 23.8, 21.2, 18.1, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_5$ m/z 436.2119, found 436.2106. **IR** (film, cm^{-1}): 3296, 2956, 1764, 1744, 1659, 1628, 1610, 1519, 1432, 1407, 1376, 1347, 1324, 1310, 1273, 1234, 1223, 1199, 1185, 1166, 1136, 1105, 1092, 1036, 1020, 989, 954, 932, 915, 900, 884, 855, 847, 836, 821. **$[\alpha]_D^{20}$** = -78.1 (c = 0.16, $CHCl_3$)

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(4-methoxyphenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63f)

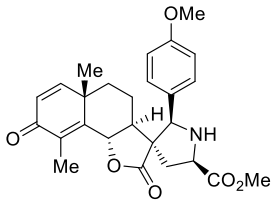


V-63f

The title product compound **V-63f** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (30.1 mg, 0.07 mmol, 67% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 2H), 6.90 – 6.81 (m, 2H), 6.66 (d, *J* = 9.9 Hz, 1H), 6.21 (d, *J* = 9.9 Hz, 1H), 4.76 (dd, *J* = 11.9, 1.4 Hz, 1H), 4.04 (dd, *J* = 9.1, 5.1 Hz, 1H), 4.01 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.51 (dd, *J* = 13.5, 9.1 Hz, 1H), 2.44 (dd, *J* = 13.5, 5.1 Hz, 1H), 2.03 – 1.98 (m, 1H), 1.97 – 1.90 (m, 2H), 1.87 (d, *J* = 1.4 Hz, 3H), 1.81 (qd, *J* = 12.8, 4.0 Hz, 1H), 1.51 (td, *J* = 13.1, 4.7 Hz, 1H), 1.28 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.3, 176.4, 172.7, 159.7, 154.7, 150.8, 129.4, 129.1, 127.1, 126.1, 114.0, 80.1, 68.4, 58.7, 55.3, 55.0, 52.7, 49.9, 41.2, 37.6, 34.0, 25.1, 19.5, 10.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_6$ m/z 452.2068, found 452.2056. **IR** (film, cm^{-1}): 2936, 2161, 1772, 1737, 1661, 1634, 1613, 1515, 1437, 1377, 1247, 1224, 1182, 1131, 1058, 1032, 991, 961, 906, 831. **$[\alpha]_D^{20}$** = -86.7 (c = 0.12, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(4-methoxyphenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64f)

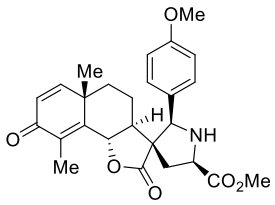


V-64f

The title product compound **V-64f** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (38.1 mg, 0.08 mmol, 84% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.61 (d, *J* = 9.9 Hz, 1H), 6.18 (d, *J* = 9.9 Hz, 1H), 4.32 (s, 1H), 4.18 (dd, *J* = 11.9, 1.5 Hz, 1H), 3.98 (dd, *J* = 9.9, 4.7 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.63 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.33 (dd, *J* = 13.6, 9.9 Hz, 1H), 2.23 (td, *J* = 12.3, 3.5 Hz, 1H), 2.14 – 2.02 (m, 1H), 1.98 (d, *J* = 1.3 Hz, 3H), 1.97 – 1.88 (m, 2H), 1.43 (td, *J* = 13.2, 4.5 Hz, 1H), 1.05 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.3, 178.0, 173.5, 160.2, 154.6, 151.1, 129.2, 128.9, 128.8, 126.1, 114.8, 79.5, 66.4, 58.3, 56.4, 55.4, 52.7, 52.3, 41.2, 38.8, 37.9, 24.8, 19.0, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_6$ m/z 452.2068, found 452.2056. **IR** (film, cm^{-1}): 2957, 1770, 1724, 1661, 1634, 1614, 1517, 1436, 1372, 1321, 1268, 1225, 1187, 1151, 1117, 1096, 1067, 1042, 1033, 990, 959, 940, 903, 890, 850, 840, 829, 822. **$[\alpha]_D^{20}$** = -92.4 (c = 0.21, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(4-methoxyphenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-65f)



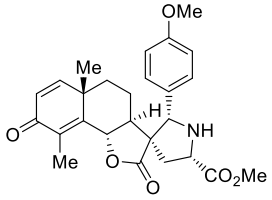
V-65f

The title product compound **V-65f** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (42.3 mg, 0.09 mmol, 94% yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.2 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 6.57 (d, *J* = 9.8 Hz, 1H), 6.18 (d, *J* = 9.8 Hz, 1H), 4.77 – 4.74 (m, 1H), 4.73 (s, 1H), 4.20 (t, *J* = 8.3 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.51 (dd, *J* = 13.4, 7.6 Hz, 1H), 2.31 (dd, *J* = 13.4, 9.0 Hz, 1H), 2.08 – 1.98 (m, 3H), 1.69 – 1.61 (m, 2H), 1.54 (qd, *J* = 12.8, 4.0 Hz, 1H), 1.39 – 1.34 (m, 1H), 1.23 (s, 3H), 1.10 (td, *J* = 13.2, 4.6 Hz, 1H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 186.4, 178.7, 173.5, 159.5, 154.9, 151.1, 130.6, 129.1, 128.2, 126.0, 114.1, 79.9, 66.9, 57.2, 55.4, 55.2, 52.5, 50.2, 41.1, 37.6, 31.4, 25.1, 20.2, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_6$ m/z 452.2068, found 452.2064. **IR** (film, cm^{-1}):

2927, 2250, 1771, 1738, 1662, 1634, 1612, 1512, 1455, 1438, 1378, 1325, 1247, 1227, 1181, 1139, 1106, 1079, 1034, 1018, 997, 967, 903, 832. **[α]D^{20}** = +50.6 (c = 0.16, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(4-methoxyphenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66f)

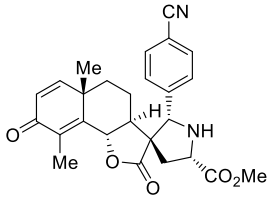


V-66f

The title product compound **V-66f** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (35.6 mg, 0.08 mmol, 79% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.2 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.51 (d, *J* = 9.9 Hz, 1H), 6.13 (d, *J* = 9.8 Hz, 1H), 4.48 (s, 1H), 4.29 – 4.05 (m, 2H), 3.78 (s, 3H+3H), 2.99 (dd, *J* = 13.9, 10.7 Hz, 1H), 2.13 (dd, *J* = 13.9, 5.7 Hz, 1H), 2.04 (d, *J* = 1.4 Hz, 3H), 1.95 (dd, *J* = 8.2, 3.8 Hz, 3H), 1.69 – 1.60 (m, 1H), 1.25 – 1.13 (m, 2H), 0.62 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.5, 178.9, 173.6, 159.7, 155.1, 151.6, 128.3, 128.3, 125.8, 114.2, 79.6, 68.1, 56.9, 56.6, 55.5, 54.8, 52.5, 41.2, 40.5, 38.5, 24.0, 18.0, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_6$ m/z 452.2068, found 452.2064. **IR** (film, cm^{-1}): 3297, 2920, 2850, 1762, 1743, 1659, 1631, 1611, 1584, 1517, 1434, 1408, 1376, 1332, 1312, 1274, 1256, 1234, 1222, 1182, 1167, 1136, 1110, 1031, 1018, 989, 952, 930, 915, 901, 883, 833, 822. **[α]D^{20}** = -95.5 (c = 0.20, $CHCl_3$)

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(4-cyanophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63g)



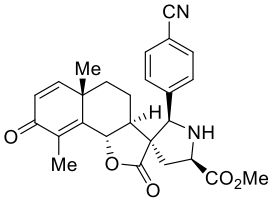
V-63g

The title product compound **V-63g** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (32.7 mg, 0.07 mmol, 73% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 9.9 Hz, 1H), 6.23 (d, *J* = 9.9 Hz, 1H), 4.80 (dq, *J* = 11.8, 1.4 Hz, 1H), 4.19 (s, 1H), 4.05 (dd, *J* = 8.7, 5.9 Hz, 1H), 3.81 (s, 3H), 2.58 (dd, *J* = 13.4, 8.7 Hz, 1H), 2.46 (dd, *J* = 13.4, 5.9 Hz, 1H), 2.06 – 1.96 (m, 4H), 1.89 (m, 4H), 1.61 – 1.50 (m, 1H), 1.31 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.1, 175.5, 172.3, 154.5, 150.1, 141.5, 132.3, 129.4, 129.1, 126.2, 118.6, 112.5, 79.9, 67.8, 58.7, 55.3, 52.8, 51.0, 41.1, 37.4, 33.7, 25.2, 19.3, 10.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{27}N_2O_5$ m/z 447.1915, found

447.1903. **IR** (film, cm^{-1}): 2932, 2227, 1774, 1735, 1661, 1633, 1612, 1504, 1437, 1374, 1305, 1267, 1225, 1205, 1185, 1155, 1133, 1025, 991, 961, 906, 832. **$[\alpha]_D^{20}$** = -82.2 (c = 0.14, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(4-cyanophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64g)

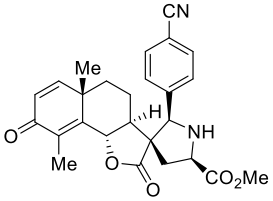


V-64g

The title product compound **V-64g** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (39.3 mg, 0.09 mmol, 88% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 9.9 Hz, 1H), 6.21 (d, *J* = 9.9 Hz, 1H), 4.52 (s, 1H), 4.37 – 4.30 (m, 1H), 4.03 (dd, *J* = 9.1, 6.3 Hz, 1H), 3.84 (s, 3H), 2.70 (dd, *J* = 13.5, 6.3 Hz, 1H), 2.31 (dd, *J* = 13.7, 9.1 Hz, 1H), 2.28 – 2.20 (m, 1H), 2.06 (dd, *J* = 12.4, 8.7 Hz, 1H), 2.02 – 1.91 (m, 5H), 1.49 (m, 1H), 1.15 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.1, 176.4, 173.4, 154.4, 150.2, 144.2, 133.0, 129.3, 128.7, 126.2, 118.3, 113.1, 79.4, 65.4, 58.6, 57.4, 53.2, 52.8, 41.1, 38.4, 37.7, 24.9, 19.6, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{27}N_2O_5$ m/z 447.1915, found 447.1903. **IR** (film, cm^{-1}): 3376, 2929, 2227, 1774, 1737, 1661, 1633, 1610, 1504, 1437, 1377, 1305, 1265, 1202, 1181, 1155, 1118, 1093, 1041, 993, 959, 905, 833. **$[\alpha]_D^{20}$** = -88.8 (c = 0.21, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(4-cyanophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-65g)



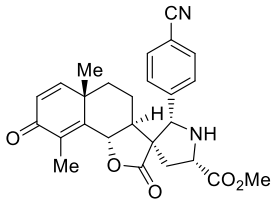
V-65g

The title product compound **V-65g** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (38.6 mg, 0.09 mmol, 86% yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 6.57 (d, *J* = 9.8 Hz, 1H), 6.19 (d, *J* = 9.9 Hz, 1H), 4.82 (s, 1H), 4.80 – 4.76 (m, 1H), 4.25 (t, *J* = 8.3 Hz, 1H), 3.83 (s, 3H), 2.52 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.34 (dd, *J* = 13.4, 8.7 Hz, 1H), 2.05 (d, *J* = 1.5 Hz, 3H), 1.69 – 1.63 (m, 1H), 1.56 – 1.53 (m, 2H), 1.23 (s, 3H), 1.17 – 1.12 (m, 1H), 1.06 (td, *J* = 12.5, 4.4 Hz, 1H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 186.1, 178.0, 173.1, 154.6, 150.3, 144.7, 132.6, 129.4, 128.1, 126.1, 118.6, 112.4, 80.0, 66.4, 57.2,

55.3, 52.6, 50.4, 41.0, 37.3, 31.1, 25.1, 20.1, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{27}N_2O_5$ m/z 447.1915, found 447.1905. **IR** (film, cm^{-1}): 2925, 2227, 1771, 1738, 1662, 1634, 1611, 1504, 1438, 1377, 1276, 1201, 1153, 1141, 1106, 1080, 1043, 1018, 998, 968, 903, 883, 833. **$[\alpha]_D^{20}$** = -32.7 (c = 0.25, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(4-cyanophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66g)

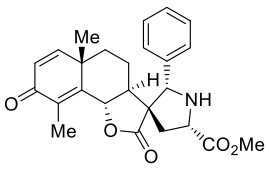


V-66g

The title product compound **V-66g** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (35.9 mg, 0.08 mmol, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 4H), 6.51 (d, *J* = 9.9 Hz, 1H), 6.15 (d, *J* = 9.9 Hz, 1H), 4.57 (s, 1H), 4.17 (dd, *J* = 10.7, 5.4 Hz, 1H), 4.07 (dd, *J* = 12.2, 1.5 Hz, 1H), 3.79 (s, 3H), 3.02 (dd, *J* = 13.9, 10.7 Hz, 1H), 2.22 (dd, *J* = 13.9, 5.4 Hz, 1H), 2.05 (d, *J* = 1.4 Hz, 3H), 1.98 (dd, *J* = 14.5, 3.7 Hz, 2H), 1.77 – 1.63 (m, 2H), 1.20 (ddd, *J* = 9.0, 8.5, 3.7 Hz, 1H), 0.60 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.2, 178.1, 173.3, 154.7, 150.7, 142.9, 132.6, 128.7, 128.2, 126.0, 118.2, 112.5, 79.7, 67.9, 56.8, 56.4, 55.1, 52.6, 41.1, 40.5, 38.4, 24.0, 18.4, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{27}N_2O_5$ m/z 447.1915, found 447.1908. **IR** (film, cm^{-1}): 2925, 2854, 2228, 1771, 1739, 1662, 1634, 1610, 1504, 1437, 1406, 1378, 1271, 1201, 1185, 1161, 1106, 1040, 1018, 989, 959, 907, 880, 831. **$[\alpha]_D^{20}$** = -82.7 (c = 0.14, $CHCl_3$)

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-phenyl-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63h)



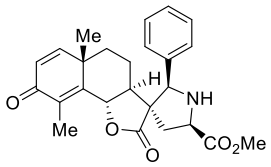
V-63h

The title product compound **V-63h** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (24.1 mg, 0.06 mmol, 57% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 5H), 6.67 (d, *J* = 9.9 Hz, 1H), 6.23 (d, *J* = 9.9 Hz, 1H), 4.77 (dd, *J* = 11.9, 1.5 Hz, 1H), 4.11 – 4.04 (m, 2H), 3.82 (s, 3H), 2.55 (dd, *J* = 13.5, 9.1 Hz, 1H), 2.47 (dd, *J* = 13.4, 5.2 Hz, 1H), 2.11 – 2.04 (m, 2H), 2.00 – 1.93 (m, 2H), 1.87 (d, *J* = 1.4 Hz, 3H), 1.86 – 1.78 (m, 1H), 1.54 (ddd, *J* = 13.7, 13.3, 4.6 Hz, 1H), 1.30 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.3, 176.2, 172.7, 154.6, 150.7, 135.2, 129.2, 128.7, 128.7,

128.3, 126.2, 80.1, 68.8, 58.9, 55.1, 52.7, 50.1, 41.2, 37.7, 34.1, 25.1, 19.6, 10.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{28}NO_5$ m/z 422.1962, found 422.1955. **IR** (film, cm^{-1}): 2938, 2162, 1787, 1732, 1657, 1626, 1610, 1495, 1438, 1404, 1385, 1338, 1292, 1267, 1223, 1189, 1164, 1131, 1091, 1072, 1056, 1020, 991, 957, 900, 844, 820. **$[\alpha]_D^{20}$** = -81.2 (c = 0.17, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-phenyl-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64h)

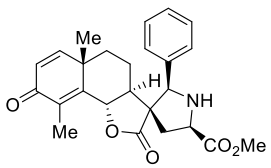


V-64h

The title product compound **V-64h** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (38.3 mg, 0.09 mmol, 91% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.46 (m, 2H), 7.46 – 7.32 (m, 3H), 6.61 (d, *J* = 9.9 Hz, 1H), 6.18 (d, *J* = 9.9 Hz, 1H), 4.36 (s, 1H), 4.14 (dd, *J* = 11.9, 1.5 Hz, 1H), 4.01 (dd, *J* = 9.9, 4.7 Hz, 1H), 3.85 (s, 3H), 2.65 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.34 (dd, *J* = 13.6, 9.9 Hz, 1H), 2.24 (td, *J* = 12.3, 3.5 Hz, 1H), 2.14 – 2.03 (m, 1H), 1.97 (d, *J* = 1.5 Hz, 3H), 1.96 – 1.84 (m, 2H), 1.44 (td, *J* = 13.1, 4.5 Hz, 1H), 1.03 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.3, 177.8, 173.5, 154.6, 151.0, 137.5, 129.5, 129.4, 128.8, 127.8, 126.0, 79.4, 67.0, 58.5, 56.7, 52.7, 52.3, 41.2, 38.9, 37.9, 24.7, 19.0, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{28}NO_5$ m/z 422.1962, found 422.1949. **IR** (film, cm^{-1}): 3351, 2930, 2156, 1771, 1729, 1663, 1636, 1616, 1495, 1455, 1433, 1405, 1376, 1322, 1268, 1226, 1207, 1182, 1153, 1111, 1095, 1061, 1041, 992, 960, 941, 902, 882, 836. **$[\alpha]_D^{20}$** = -103.6 (c = 0.28, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-phenyl-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-65h)



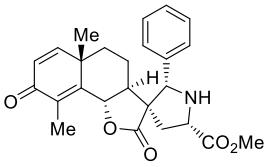
V-65h

The title product compound **V-65h** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (34.7 mg, 0.08 mmol, 82% yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 2H), 7.32-7.25 (m, 3H), 6.55 (d, *J* = 9.8 Hz, 1H), 6.16 (d, *J* = 9.8 Hz, 1H), 4.79 – 4.73 (m, 2H), 4.22 (dd, *J* = 8.8, 7.9 Hz, 1H), 3.82 (s, 3H), 2.51 (dd, *J* = 13.4, 7.9 Hz, 1H), 2.32 (dd, *J* = 13.4, 8.8 Hz, 1H), 2.03 (d, *J* = 1.4 Hz, 3H), 1.66 – 1.58 (m, 2H), 1.51 (qd, *J* = 12.9, 4.0 Hz, 1H), 1.25 – 1.20 (m, 4H), 1.05 (td, *J* = 13.2, 4.6 Hz, 1H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 186.3, 178.6, 173.4,

154.9, 151.0, 138.9, 129.1, 128.7, 128.3, 127.0, 126.0, 79.9, 67.1, 57.2, 55.2, 52.5, 50.3, 41.1, 37.5, 31.3, 25.0, 20.1, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{28}NO_5$ m/z 422.1962, found 422.1950. **IR** (film, cm^{-1}): 2950, 1771, 1738, 1661, 1634, 1614, 1493, 1454, 1437, 1378, 1274, 1192, 1153, 1139, 1055, 1017, 997, 967, 902, 833. **$[\alpha]_D^{20}$** = +37.8 (c = 0.19, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-phenyl-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66h)

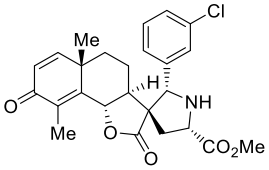


V-66h

The title product compound **V-66h** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (39.8 mg, 0.09 mmol, 94% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.5 Hz, 2H), 7.38 (dd, *J* = 8.3, 7.0 Hz, 2H), 7.35 – 7.28 (m, 1H), 6.50 (d, *J* = 9.9 Hz, 1H), 6.12 (d, *J* = 9.8 Hz, 1H), 4.53 (s, 1H), 4.20 – 4.09 (m, 2H), 3.79 (s, 3H), 3.02 (dd, *J* = 13.8, 10.8 Hz, 1H), 2.14 (dd, *J* = 13.9, 5.6 Hz, 1H), 2.05 (d, *J* = 1.4 Hz, 3H), 1.99 – 1.92 (m, 3H), 1.64 (dd, *J* = 13.5, 3.0 Hz, 1H), 1.17 (ddd, *J* = 13.2, 8.7, 6.7 Hz, 1H), 0.55 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.4, 178.8, 173.7, 155.1, 151.5, 136.6, 128.9, 128.6, 128.3, 127.1, 125.8, 79.6, 68.5, 57.1, 56.6, 54.9, 52.5, 41.2, 40.8, 38.5, 23.9, 18.1, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{28}NO_5$ m/z 422.1962, found 422.1947. **IR** (film, cm^{-1}): 2929, 1765, 1742, 1661, 1633, 1613, 1453, 1435, 1377, 1311, 1272, 1223, 1199, 1183, 1162, 1107, 1039, 989, 953, 914, 832. **$[\alpha]_D^{20}$** = -56.9 (c = 0.16, $CHCl_3$)

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(3-chlorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63i)



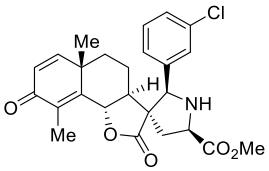
V-63i

The title product compound **V-63i** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (30.0 mg, 0.07 mmol, 66% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.28 – 7.23 (m, 3H), 6.67 (d, *J* = 9.9 Hz, 1H), 6.23 (d, *J* = 9.9 Hz, 1H), 4.78 (dd, *J* = 11.7, 1.4 Hz, 1H), 4.05 (s, 1H), 4.03 (dd, *J* = 8.9, 5.6 Hz, 1H), 3.81 (s, 3H), 2.54 (dd, *J* = 13.5, 8.9 Hz, 1H), 2.44 (dd, *J* = 13.4, 5.7 Hz, 1H), 2.07 – 2.01 (m, 1H), 1.99 – 1.92 (m, 2H), 1.91 (d, *J* = 1.4 Hz, 3H), 1.84 (qd, *J* = 13.2, 4.3 Hz, 1H), 1.55 (ddd, *J* = 13.5, 13.1, 4.6 Hz, 1H), 1.29 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 175.9, 172.4, 154.6, 150.4, 137.8, 134.5, 129.9, 129.3, 128.9, 128.6, 126.4,

126.2, 80.0, 67.9, 58.7, 55.0, 52.7, 50.5, 41.1, 37.5, 33.9, 25.2, 19.4, 10.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Cl$ m/z 456.1572, found 456.1569. **IR** (film, cm^{-1}): 3328, 2937, 2349, 2161, 1783, 1732, 1658, 1630, 1611, 1597, 1573, 1438, 1403, 1379, 1339, 1291, 1269, 1225, 1209, 1186, 1165, 1133, 1093, 1076, 1022, 990, 959, 900, 840. **$[\alpha]_D^{20}$** = -79.6 (c = 0.25, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(3-chlorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64i)

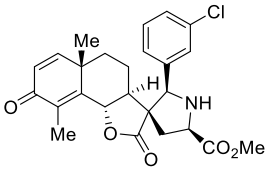


V-64i

The title product compound **V-64i** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (40.4 mg, 0.09 mmol, 89% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.41 – 7.31 (m, 3H), 6.63 (d, *J* = 9.9 Hz, 1H), 6.19 (d, *J* = 9.9 Hz, 1H), 4.36 (s, 1H), 4.24 (dd, *J* = 11.8, 1.5 Hz, 1H), 4.00 (dd, *J* = 9.7, 5.3 Hz, 1H), 3.84 (s, 3H), 2.66 (dd, *J* = 13.6, 5.3 Hz, 1H), 2.41 – 2.19 (m, 2H), 2.12 – 1.90 (m, 7H), 1.51-1.41 (m, 1H), 1.11 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 177.1, 173.3, 154.6, 150.7, 140.1, 135.1, 131.0, 129.5, 129.0, 128.4, 126.1, 125.6, 79.4, 66.0, 58.4, 56.9, 52.7, 52.6, 41.2, 38.6, 37.8, 24.6, 19.2, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Cl$ m/z 456.1572, found 456.1560. **IR** (film, cm^{-1}): 2928, 1774, 1737, 1661, 1634, 1614, 1597, 1573, 1436, 1377, 1306, 1265, 1202, 1181, 1154, 1097, 1039, 992, 959, 906, 833. **$[\alpha]_D^{20}$** = -105.3 (c = 0.15, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(3-chlorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-65i)



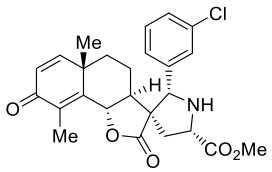
V-65i

The title product compound **V-65i** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (36.6 mg, 0.08 mmol, 80% yield).

^{1}H NMR (700 MHz, CD_2Cl_2) δ 7.47 (s, 1H), 7.29 – 7.18 (m, 3H), 6.59 (d, *J* = 9.8 Hz, 1H), 6.13 (d, *J* = 9.8 Hz, 1H), 4.79 (d, *J* = 11.4 Hz, 1H), 4.72 (s, 1H), 4.21 (t, *J* = 8.3 Hz, 1H), 3.80 (s, 3H), 2.49 (dd, *J* = 13.4, 8.0 Hz, 1H), 2.32 (dd, *J* = 13.4, 8.7 Hz, 1H), 2.00 (s, 3H), 1.69 – 1.61 (m, 2H), 1.55 – 1.50 (m, 1H), 1.22 (s, 3H), 1.19 (ddd, *J* = 13.4, 5.4, 2.9 Hz, 1H), 1.09 (td, *J* = 13.2, 4.6 Hz, 1H). **^{13}C NMR (176 MHz, CD_2Cl_2)** δ 186.2,

178.5, 173.5, 155.3, 151.3, 142.1, 134.9, 130.3, 129.0, 128.5, 127.5, 126.0, 125.9, 80.3, 66.7, 57.5, 55.5, 52.6, 50.6, 41.4, 37.6, 31.5, 27.3, 25.1, 20.4, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Cl$ m/z 456.1572, found 456.1563. **IR** (film, cm^{-1}): 3342, 2949, 2160, 1770, 1737, 1662, 1634, 1615, 1597, 1572, 1436, 1377, 1272, 1193, 1153, 1140, 1076, 1043, 1018, 998, 969, 903, 833. **$[\alpha]_D^{20}$** = +72.5 (c = 0.12, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(3-chlorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66i)

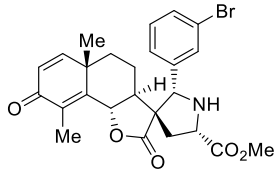


V-66i

The title product compound **V-66i** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (27.9 mg, 0.06 mmol, 61% yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.41 – 7.32 (m, 3H), 6.53 (d, *J* = 9.9 Hz, 1H), 6.16 (d, *J* = 9.9 Hz, 1H), 4.59 (s, 1H), 4.24 (dd, *J* = 10.6, 5.9 Hz, 1H), 4.20 (d, *J* = 12.1 Hz, 1H), 3.82 (s, 3H), 3.01 (dd, *J* = 13.9, 10.6 Hz, 1H), 2.24 (dd, *J* = 13.9, 5.9 Hz, 1H), 2.07 (d, *J* = 1.4 Hz, 3H), 2.02 – 1.95 (m, 2H), 1.84 (qd, *J* = 13.3, 3.9 Hz, 1H), 1.69 (ddd, *J* = 13.7, 4.0, 2.3 Hz, 1H), 1.21 (td, *J* = 13.2, 4.5 Hz, 1H), 0.67 (s, 3H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 186.3, 178.3, 172.9, 154.9, 151.0, 135.3, 130.4, 129.0, 128.7, 127.4, 126.0, 125.7, 79.7, 67.7, 56.7, 56.6, 54.9, 52.8, 41.2, 40.1, 38.5, 23.8, 18.2, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Cl$ m/z 456.1572, found 456.1559. **IR** (film, cm^{-1}): 2924, 1771, 1739, 1661, 1634, 1614, 1597, 1572, 1436, 1377, 1273, 1201, 1162, 1106, 1078, 1039, 988, 906.63, 832. **$[\alpha]_D^{20}$** = -97.6 (c = 0.13, $CHCl_3$)

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(3-bromophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63j)



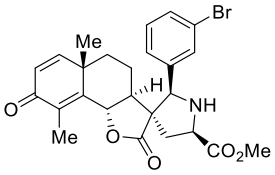
V-63j

The title product compound **V-63j** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (38.0 mg, 0.08 mmol, 76% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 6.68 (d, *J* = 9.9 Hz, 1H), 6.24 (d, *J* = 9.9 Hz, 1H), 4.79 (dd, *J* = 11.8, 1.4 Hz, 1H), 4.08 – 3.99 (m, 2H), 3.81 (s, 3H), 2.55 (dd, *J* = 13.4, 8.9 Hz, 1H), 2.44 (dd, *J* = 13.4, 5.7 Hz, 1H), 2.08 – 2.00 (m, 1H), 1.96 (ddd, *J* = 14.4, 4.1, 2.4 Hz,

2H), 1.92 (d, *J* = 1.4 Hz, 3H), 1.84 (qd, *J* = 13.1, 4.2 Hz, 1H), 1.55 (ddd, *J* = 13.5, 13.1, 4.6 Hz, 1H), 1.30 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 175.9, 172.4, 154.6, 150.4, 138.1, 131.8, 131.5, 130.2, 129.4, 126.8, 126.2, 122.7, 80.0, 67.9, 58.7, 55.0, 52.7, 50.6, 41.1, 37.5, 33.9, 25.2, 19.4, 10.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Br$ m/z 500.1067, found 500.1054. **IR** (film, cm^{-1}): 3340, 2989, 2947, 2803, 2234, 2123, 1789, 1749, 1731, 1658, 1628, 1612, 1570, 1429, 1405, 1386, 1335, 1305, 1276, 1264, 1226, 1205, 1190, 1144, 1134, 1094, 1072, 1057, 1023, 1013, 988, 962, 949, 912, 902, 846. **$[\alpha]_D^{20}$** = -55.8 (c = 0.19, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(3-bromophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64j)

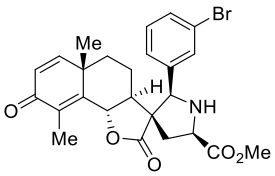


V-64j

The title product compound **V-64j** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (47.5 mg, 0.09 mmol, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 6.63 (d, *J* = 9.9 Hz, 1H), 6.20 (d, *J* = 9.9 Hz, 1H), 4.35 (s, 1H), 4.24 (dd, *J* = 11.8, 1.4 Hz, 1H), 4.00 (dd, *J* = 9.7, 5.2 Hz, 1H), 3.85 (s, 3H), 2.67 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.36 – 2.20 (m, 2H), 2.14 – 1.91 (m, 7H), 1.46 (td, *J* = 13.1, 4.8 Hz, 1H), 1.12 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.2, 177.1, 173.3, 154.6, 150.7, 140.4, 132.5, 131.4, 131.3, 129.0, 126.1, 126.0, 123.1, 79.4, 66.0, 58.5, 56.9, 52.8, 52.6, 41.2, 38.6, 37.9, 24.7, 19.3, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Br$ m/z 500.1067, found 500.1056. **IR** (film, cm^{-1}): 2928, 2248, 1774, 1737, 1661, 1634, 1614, 1569, 1436, 1377, 1306, 1264, 1202, 1181, 1154, 1096, 1039, 995, 959, 905, 833. **$[\alpha]_D^{20}$** = -85.6 (c = 0.20, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(3-bromophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-65j)



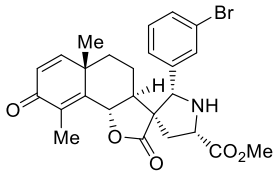
V-65j

The title product compound **V-65j** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (37.3 mg, 0.07 mmol, 75% yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.58 (d, *J* = 9.8 Hz, 1H), 6.19 (d, *J* = 9.8 Hz,

1H), 4.78 (dd, *J* = 11.5, 1.5 Hz, 1H), 4.74 (s, 1H), 4.22 (dd, *J* = 8.9, 7.8 Hz, 1H), 3.83 (s, 3H), 2.52 (dd, *J* = 13.4, 7.8 Hz, 1H), 2.32 (dd, *J* = 13.4, 8.8 Hz, 1H), 2.05 (d, *J* = 1.4 Hz, 3H), 1.71 – 1.65 (m, 1H), 1.61 (td, *J* = 11.7, 11.1, 2.8 Hz, 1H), 1.56 (dd, *J* = 12.7, 3.8 Hz, 1H), 1.28 (dt, *J* = 5.0, 2.4 Hz, 1H), 1.23 (s, 3H), 1.10 (td, *J* = 13.0, 4.5 Hz, 1H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 186.3, 178.2, 173.2, 154.8, 150.7, 141.4, 131.6, 130.4, 130.1, 129.3, 126.1, 126.0, 123.1, 80.0, 66.5, 57.2, 55.1, 52.6, 50.4, 41.1, 37.4, 31.1, 25.1, 20.2, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Br$ m/z 500.1067, found 500.1061. **IR** (film, cm^{-1}): 2946, 2248, 1771, 1736, 1661, 1634, 1614, 1568, 1436, 1376, 1272, 1193, 1153, 1140, 1043, 1018, 996, 968, 904, 832. **$[\alpha]_D^{20}$** = +73.2 (c = 0.24, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(3-bromophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66j)

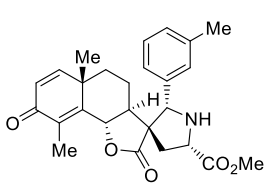


V-66j

The title product compound **V-66j** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (27.4 mg, 0.05 mmol, 55% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.52 – 7.45 (m, 1H), 7.44 – 7.35 (m, 1H), 7.29 – 7.23 (m, 1H), 6.53 (d, *J* = 9.9 Hz, 1H), 6.15 (d, *J* = 9.9 Hz, 1H), 4.49 (s, 1H), 4.20 – 4.08 (m, 2H), 3.80 (s, 3H), 2.99 (dd, *J* = 13.9, 10.7 Hz, 1H), 2.18 (dd, *J* = 13.9, 5.5 Hz, 1H), 2.06 (d, *J* = 1.4 Hz, 3H), 2.03 – 1.83 (m, 3H), 1.69 (ddd, *J* = 13.5, 3.8, 2.3 Hz, 1H), 1.20 (td, *J* = 12.9, 4.7 Hz, 1H), 0.66 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.4, 178.5, 173.5, 155.0, 151.2, 139.5, 131.7, 130.6, 130.2, 128.5, 126.1, 125.9, 123.2, 79.6, 67.8, 56.9, 56.5, 54.9, 52.6, 41.2, 40.2, 38.5, 23.7, 18.2, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Br$ m/z 500.1067, found 500.1062.

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(*m*-tolyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63k)



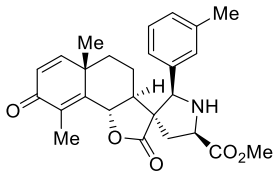
V-63k

The title product compound **V-63k** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (32.7 mg, 0.08 mmol, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.16 (m, 2H), 7.14 – 7.06 (m, 2H), 6.67 (d, *J* = 9.9 Hz, 1H), 6.23 (d, *J* = 9.9 Hz, 1H), 4.77 (dd, *J* = 11.8, 1.4 Hz, 1H), 4.12 – 4.01 (m, 2H), 3.82 (s,

3H), 2.54 (dd, *J* = 13.4, 9.1 Hz, 1H), 2.45 (dd, *J* = 13.4, 5.3 Hz, 1H), 2.33 (s, 3H), 2.07 (td, *J* = 12.3, 3.4 Hz, 1H), 2.00 – 1.91 (m, 2H), 1.90 (d, *J* = 1.4 Hz, 3H), 1.82 (ddd, *J* = 13.2, 12.7, 4.3 Hz, 1H), 1.53 (ddd, *J* = 13.6, 13.1, 4.6 Hz, 1H), 1.29 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.3, 176.3, 172.6, 154.6, 150.7, 138.3, 135.2, 129.5, 129.2, 128.8, 128.5, 126.2, 125.3, 80.1, 68.7, 58.8, 55.0, 52.7, 50.1, 41.2, 37.6, 34.2, 25.1, 21.7, 19.5, 10.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_5$ m/z 436.2119, found 436.2114. **IR** (film, cm^{-1}): 2935, 1766, 1738, 1660, 1633, 1613, 1430, 1381, 1319, 1270, 1190, 1158, 1135, 1112, 1092, 1057, 1031, 988, 966, 942, 902, 883, 856, 838. **$[\alpha]_D^{20}$** = -72.4 (c = 0.11, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(*m*-tolyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64k)

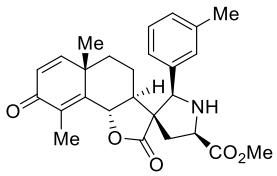


V-64k

The title product compound **V-64k** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (40.9 mg, 0.09 mmol, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 3H), 7.16 (d, *J* = 5.7 Hz, 1H), 6.61 (d, *J* = 9.9 Hz, 1H), 6.17 (d, *J* = 9.8 Hz, 1H), 4.31 (s, 1H), 4.15 (dd, *J* = 11.7, 1.5 Hz, 1H), 4.00 (dd, *J* = 10.0, 4.7 Hz, 1H), 3.84 (s, 3H), 2.63 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.38 – 2.31 (m, 4H), 2.23 (td, *J* = 12.2, 3.3 Hz, 1H), 2.11 (qd, *J* = 12.9, 4.1 Hz, 1H), 2.02 – 1.88 (m, 5H), 1.48 – 1.37 (m, 1H), 1.04 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.3, 177.8, 173.5, 154.6, 151.1, 139.2, 137.3, 130.2, 129.4, 128.7, 128.4, 126.1, 124.8, 79.4, 67.0, 58.4, 56.7, 52.7, 52.3, 41.2, 38.9, 37.9, 24.5, 21.6, 19.0, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_5$ m/z 436.2119, found 436.2106. **IR** (film, cm^{-1}): 2929, 1771, 1737, 1662, 1634, 1614, 1436, 1405, 1377, 1309, 1268, 1221, 1203, 1183, 1154, 1096, 1038, 991, 961, 907, 881, 833. **$[\alpha]_D^{20}$** = -70.0 (c = 0.16, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(*m*-tolyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-65k)

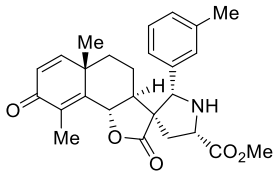


V-65k

The title product compound **V-65k** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (31.7 mg, 0.07 mmol, 73% yield).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.7 Hz, 1H), 7.15-7.12 (m, 2H), 7.06 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.56 (d, *J* = 9.9 Hz, 1H), 6.16 (d, *J* = 9.8 Hz, 1H), 4.74 (dd, *J* = 11.7, 1.5 Hz, 1H), 4.72 (s, 1H), 4.20 (dd, *J* = 9.0, 7.7 Hz, 1H), 3.82 (s, 3H), 2.51 (dd, *J* = 13.4, 7.7 Hz, 1H), 2.33 – 2.27 (m, 4H), 2.02 (d, *J* = 1.4 Hz, 3H), 1.67 – 1.58 (m, 2H), 1.52 (qd, *J* = 12.8, 3.9 Hz, 1H), 1.34 – 1.30 (m, 1H), 1.21 (s, 3H), 1.05 (td, *J* = 13.2, 4.6 Hz, 1H). **^{13}C NMR (176 MHz, $CDCl_3$)** δ 186.3, 178.6, 173.4, 154.9, 151.1, 138.6, 138.5, 129.1, 129.0, 128.6, 127.6, 126.0, 124.0, 79.9, 67.3, 57.2, 55.1, 52.5, 50.2, 41.1, 37.5, 31.4, 25.0, 21.6, 20.2, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_5$ m/z 436.2119, found 436.2106. **IR** (film, cm^{-1}): 2950, 1771, 1738, 1662, 1634, 1613, 1454, 1437, 1378, 1274, 1191, 1162, 1139, 1108, 1042, 1019, 991, 968, 908, 833. **$[\alpha]_D^{20}$** = +40.5 (c = 0.19, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(*m*-tolyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66k)

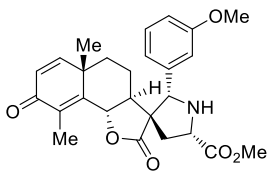


V-66k

The title product compound **V-66k** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (35.1 mg, 0.08 mmol, 81% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.23 (m, 3H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.51 (d, *J* = 9.8 Hz, 1H), 6.14 (d, *J* = 9.9 Hz, 1H), 4.48 (s, 1H), 4.21 – 4.06 (m, 2H), 3.80 (d, *J* = 1.4 Hz, 3H), 3.01 (ddd, *J* = 14.3, 10.7, 1.8 Hz, 1H), 2.36 (s, 3H), 2.13 (dd, *J* = 13.8, 5.5 Hz, 1H), 2.06 (s, 3H), 2.06 – 1.89 (m, 3H), 1.72 – 1.61 (m, 1H), 1.18 (td, *J* = 12.8, 4.7 Hz, 1H), 0.58 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.5, 178.9, 173.8, 155.1, 151.6, 138.7, 136.6, 129.3, 128.9, 128.3, 127.6, 125.9, 124.3, 79.6, 68.5, 57.2, 56.6, 55.0, 52.5, 41.2, 40.8, 38.6, 23.6, 21.6, 18.0, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_5$ m/z 436.2119, found 436.2115. **IR** (film, cm^{-1}): 3325, 2919, 2850, 2363, 2160, 2033, 1770, 1736, 1662, 1635, 1613, 1489, 1437, 1378, 1308, 1271, 1186, 1162, 1106, 1039, 989, 938, 899, 832, 805. **$[\alpha]_D^{20}$** = -56.7 (c = 0.09, $CHCl_3$).

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(3-methoxyphenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63l)



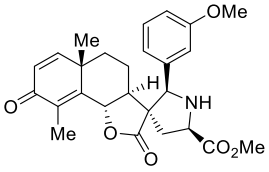
V-63l

The title product compound **V-63l** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving

an amorphous solid (22.6 mg, 0.05 mmol, 50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.9 Hz, 1H), 6.97 (s, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 9.9 Hz, 1H), 6.23 (d, *J* = 9.8 Hz, 1H), 4.77 (dd, *J* = 11.8, 1.6 Hz, 1H), 4.09 – 4.01 (m, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 2.53 (dd, *J* = 13.5, 9.1 Hz, 1H), 2.46 (dd, *J* = 13.4, 5.1 Hz, 1H), 2.08 (td, *J* = 12.3, 3.5 Hz, 1H), 2.00 – 1.92 (m, 2H), 1.90 (s, 3H), 1.82 (qd, *J* = 13.1, 4.3 Hz, 1H), 1.53 (td, *J* = 13.1, 4.7 Hz, 1H), 1.29 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.3, 176.2, 172.7, 159.7, 154.6, 150.7, 136.9, 129.6, 129.2, 126.2, 120.5, 114.3, 113.8, 80.1, 68.6, 58.8, 55.4, 55.1, 52.7, 50.1, 41.2, 37.6, 34.0, 25.1, 19.5, 10.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_6$ m/z 452.2068, found 452.2054. **IR** (film, cm^{-1}): 2951, 1768, 1739, 1660, 1633, 1612, 1585, 1489, 1456, 1432, 1381, 1275, 1267, 1261, 1202, 1190, 1156, 1135, 1111, 1091, 1031, 988, 965, 940, 902, 882, 856, 837. **$[\alpha]_D^{20}$** = -81.5 (c = 0.14, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(3-methoxyphenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64l)

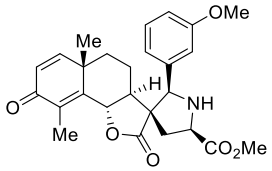


V-64l

The title product compound **V-64l** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (42.9 mg, 0.10 mmol, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.2 Hz, 1H), 7.07 – 7.02 (m, 2H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.61 (d, *J* = 9.9 Hz, 1H), 6.18 (d, *J* = 9.8 Hz, 1H), 4.33 (s, 1H), 4.25 – 4.18 (m, 1H), 4.00 (dd, *J* = 9.9, 4.8 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.64 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.32 (dd, *J* = 13.6, 9.8 Hz, 1H), 2.23 (td, *J* = 12.2, 3.4 Hz, 1H), 2.16 – 1.88 (m, 7H), 1.44 (dt, *J* = 13.1, 6.7 Hz, 1H), 1.06 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.3, 177.8, 173.5, 160.4, 154.6, 151.1, 139.2, 130.5, 128.8, 126.1, 120.0, 114.9, 113.2, 79.4, 66.9, 58.5, 56.7, 55.4, 52.7, 52.4, 41.2, 38.8, 37.9, 24.7, 19.0, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_6$ m/z 452.2068, found 452.2054. **IR** (film, cm^{-1}): 2935, 1772, 1737, 1661, 1634, 1611, 1585, 1489, 1455, 1437, 1377, 1267, 1223, 1202, 1181, 1154, 1096, 1037, 992, 961, 907, 880, 833. **$[\alpha]_D^{20}$** = -71.1 (c = 0.18, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(3-methoxyphenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-65l)

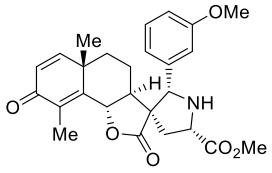


V-65l

The title product compound **V-65l** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (28.2 mg, 0.06 mmol, 63% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.9 Hz, 1H), 6.96 (s, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 9.8 Hz, 1H), 6.17 (d, *J* = 9.8 Hz, 1H), 4.75 (dd, *J* = 11.8, 1.4 Hz, 1H), 4.72 (s, 1H), 4.21 (dd, *J* = 8.8, 7.8 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 2.51 (dd, *J* = 13.4, 7.8 Hz, 1H), 2.30 (dd, *J* = 13.4, 8.9 Hz, 1H), 2.03 (s, 3H), 1.70 – 1.61 (m, 2H), 1.52 (qd, *J* = 12.8, 3.8 Hz, 1H), 1.31 – 1.25 (m, 1H), 1.21 (s, 3H), 1.08 (td, *J* = 13.1, 4.5 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.3, 178.6, 173.4, 159.9, 154.9, 151.0, 140.6, 129.8, 129.0, 126.0, 119.3, 113.7, 112.5, 79.9, 67.0, 57.2, 55.4, 55.1, 52.5, 50.2, 41.1, 37.5, 31.2, 25.0, 20.2, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_6$ m/z 452.2068, found 452.2055. **IR** (film, cm^{-1}): 3339, 2949, 2526, 2160, 2024, 1770, 1738, 1661, 1634, 1611, 1584, 1488, 1454, 1437, 1378, 1314, 1274, 1192, 1157, 1044, 1018, 995, 969, 947, 902, 833. **$[\alpha]_D^{20}$** = +57.2 (c = 0.22, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(3-methoxyphenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66l)

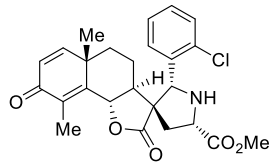


V-66l

The title product compound **V-66l** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (22.2 mg, 0.05 mmol, 49% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.0 Hz, 1H), 7.17-7.07 (m, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.52 (d, *J* = 9.9 Hz, 1H), 6.15 (d, *J* = 9.9 Hz, 1H), 4.49 (s, 1H), 4.20 (dd, *J* = 11.4, 1.6 Hz, 1H), 4.14 (dd, *J* = 10.8, 5.5 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.01 (dd, *J* = 13.9, 10.8 Hz, 1H), 2.15 (dd, *J* = 13.9, 5.6 Hz, 1H), 2.10 – 1.91 (m, 6H), 1.67 (ddd, *J* = 13.6, 3.9, 2.3 Hz, 1H), 1.19 (td, *J* = 13.0, 4.6 Hz, 1H), 0.63 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.5, 178.9, 173.7, 160.0, 155.1, 151.6, 138.4, 130.1, 128.4, 125.9, 119.4, 113.9, 113.0, 79.7, 68.4, 57.1, 56.6, 55.6, 55.0, 52.5, 41.3, 40.6, 38.6, 23.9, 18.2, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_6Cl$ m/z 452.2068, found 452.2064. **IR** (film, cm^{-1}): 2923, 2851, 2161, 1770, 1737, 1661, 1634, 1610, 1584, 1491, 1454, 1437, 1378, 1272, 1187, 1160, 1107, 1039, 989, 960, 898, 832. **$[\alpha]_D^{20}$** = -66.7 (c = 0.15, $CHCl_3$)

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(2-chlorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63m)

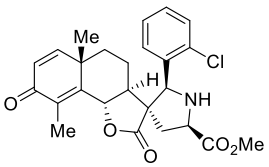


V-63m

The title product compound **V-63m** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (34.5 mg, 0.08 mmol, 76% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.9 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.22 (t, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 9.9 Hz, 1H), 6.21 (d, *J* = 9.9 Hz, 1H), 4.81 – 4.69 (m, 2H), 4.11 (dd, *J* = 9.1, 5.7 Hz, 1H), 3.81 (s, 3H), 2.57 (dd, *J* = 13.5, 9.1 Hz, 1H), 2.43 (dd, *J* = 13.4, 5.7 Hz, 1H), 2.19 (td, *J* = 12.2, 3.4 Hz, 1H), 2.10 (ddt, *J* = 10.4, 4.3, 2.3 Hz, 1H), 1.95 – 1.88 (m, 4H), 1.82 (qd, *J* = 12.7, 3.9 Hz, 1H), 1.51 (td, *J* = 13.2, 4.5 Hz, 1H), 1.28 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 186.3, 175.8, 172.8, 154.7, 150.8, 134.0, 133.9, 130.2, 129.6, 129.1, 127.4, 126.1, 79.9, 63.6, 58.6, 55.6, 52.7, 50.5, 41.2, 37.6, 33.7, 25.2, 19.9, 10.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Cl$ m/z 456.1572, found 456.1565. **IR** (film, cm^{-1}): 3387, 2925, 2160, 1775, 1719, 1658, 1630, 1609, 1439, 1401, 1383, 1327, 1303, 1289, 1266, 1225, 1202, 1183, 1164, 1150, 1117, 1093, 1076, 1026, 989, 959, 902, 835. **$[\alpha]_D^{20}$** = -67.5 (c = 0.12, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(2-chlorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64m)



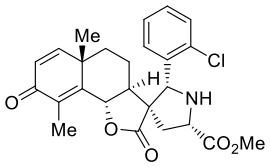
V-64m

The title product compound **V-64m** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (43.3 mg, 0.09 mmol, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 1H), 7.36 (dd, *J* = 7.4, 6.4 Hz, 2H), 7.30 – 7.24 (m, 1H), 6.66 (d, *J* = 9.9 Hz, 1H), 6.22 (d, *J* = 9.8 Hz, 1H), 5.07 (s, 1H), 4.77 (dd, *J* = 11.6, 1.5 Hz, 1H), 4.01 (t, *J* = 8.2 Hz, 1H), 3.83 (s, 3H), 2.75 (dd, *J* = 13.3, 8.5 Hz, 1H), 2.37 – 2.14 (m, 3H), 2.09 – 1.92 (m, 5H), 1.56 – 1.46 (m, 1H), 1.25 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.3, 176.5, 173.4, 154.9, 151.0, 136.6, 132.5, 130.0, 129.8, 129.1, 128.2, 126.1, 79.4, 60.6, 59.0, 57.6, 54.9, 52.7, 41.3, 39.3, 37.9, 24.9, 20.1, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Cl$ m/z 456.1572, found 456.1557. **IR** (film, cm^{-1}): 2929, 1774, 1737, 1662, 1634, 1614, 1438, 1405, 1377, 1304, 1265, 1226, 1202, 1179, 1163, 1111, 1042, 994, 959, 903, 833. **$[\alpha]_D^{20}$** = -66.7 (c = 0.23, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(2-chlorophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66m)

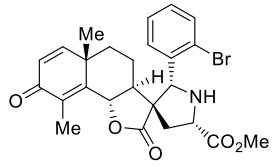
The title product compound **V-66m** was prepared using **Condition D** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (29.4 mg, 0.06 mmol, 64% yield).



V-66m

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 9.9 Hz, 1H), 6.16 (d, *J* = 9.9 Hz, 1H), 4.97 (s, 1H), 4.77 (dd, *J* = 12.2, 1.7 Hz, 1H), 4.31 (t, *J* = 8.6 Hz, 1H), 3.80 (s, 3H), 2.73 (dd, *J* = 13.4, 8.3 Hz, 1H), 2.30 (dd, *J* = 13.5, 8.8 Hz, 1H), 2.11 (s, 3H), 1.99 (td, *J* = 12.7, 3.6 Hz, 1H), 1.66 – 1.57 (m, 2H), 1.36 (dd, *J* = 13.2, 3.8 Hz, 1H), 1.15 (td, *J* = 13.0, 4.1 Hz, 1H), 0.73 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.4, 179.2, 173.3, 155.0, 151.3, 137.0, 133.5, 131.1, 130.0, 129.8, 129.1, 127.2, 125.9, 80.1, 63.1, 57.0, 55.9, 53.9, 52.5, 41.3, 39.3, 38.3, 23.9, 18.0, 11.4. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Cl$ m/z 456.1572, found 456.1563. **IR** (film, cm^{-1}): 2925, 2853, 1773, 1739, 1661, 1633, 1614, 1438, 1404, 1378, 1274, 1202, 1185, 1157, 1106, 1035, 990, 954, 907, 832. **$[\alpha]_D^{20}$** = -28.7 (c = 0.36, $CHCl_3$)

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(2-bromophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63n)



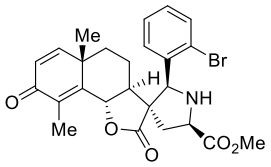
V-63n

The title product compound **V-63n** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (38.2 mg, 0.08 mmol, 76% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.16 (dd, *J* = 7.9, 7.3 Hz, 1H), 6.66 (d, *J* = 9.9 Hz, 1H), 6.22 (d, *J* = 9.9 Hz, 1H), 4.82 – 4.76 (m, 1H), 4.75 (s, 1H), 4.12 (dd, *J* = 9.0, 5.7 Hz, 1H), 3.82 (s, 3H), 2.56 (dd, *J* = 13.5, 9.1 Hz, 1H), 2.44 (dd, *J* = 13.4, 5.7 Hz, 1H), 2.25 (td, *J* = 12.1, 3.3 Hz, 1H), 2.21 – 2.14 (m, 1H), 1.97 – 1.88 (m, 4H), 1.82 (qd, *J* = 12.7, 3.9 Hz, 1H), 1.53 (td, *J* = 13.2, 4.5 Hz, 1H), 1.29 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 186.3, 175.8, 172.9, 154.7, 150.9, 135.7, 132.9, 130.6, 130.0, 129.1, 128.0, 126.1, 125.0, 79.9, 66.3, 58.7, 55.7, 52.7, 50.6, 41.2, 37.6, 33.7, 25.2, 20.2, 10.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Br$ m/z 500.1067, found 500.1055. **IR** (film, cm^{-1}): 3386, 2940, 1775, 1719, 1658,

1630, 1610, 1439, 1378, 1304, 1289, 1266, 1225, 1202, 1183, 1164, 1140, 1075, 1023, 989, 959, 902, 835. **$[\alpha]_D^{20}$** = -48.4 (c = 0.23, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(2-bromophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64n)

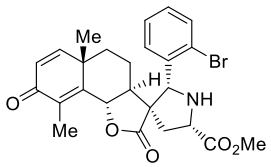


V-64n

The title product compound **V-64n** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (44.3 mg, 0.09 mmol, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.22 – 7.14 (m, 1H), 6.66 (d, *J* = 9.9 Hz, 1H), 6.21 (d, *J* = 9.9 Hz, 1H), 5.03 (s, 1H), 4.87 (dd, *J* = 11.7, 1.5 Hz, 1H), 4.01 (t, *J* = 8.3 Hz, 1H), 3.82 (s, 3H), 2.77 (dd, *J* = 13.3, 8.8 Hz, 1H), 2.41 – 2.28 (m, 1H), 2.28 – 2.11 (m, 2H), 2.06 – 1.93 (m, 5H), 1.50 (td, *J* = 13.1, 12.7, 4.6 Hz, 1H), 1.26 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.3, 176.3, 173.4, 154.8, 151.0, 138.2, 133.2, 130.4, 130.3, 129.1, 128.7, 126.0, 123.2, 79.4, 63.5, 59.0, 57.7, 55.1, 52.7, 41.3, 39.4, 37.9, 25.0, 20.4, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Br$ m/z 500.1067, found 500.1060. **IR** (film, cm^{-1}): 2930, 1773.74, 1736, 1661.78, 1633.70, 1614, 1567, 1436, 1405, 1376, 1304.72, 1274, 1263, 1225.68, 1201, 1179, 1163, 1113, 1042.71, 994, 959, 902, 832.67. **$[\alpha]_D^{20}$** = -63.5 (c = 0.26, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(2-bromophenyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66n)



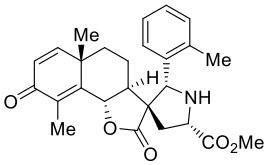
V-66n

The title product compound **V-66n** was prepared using **Condition D** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (30.3 mg, 0.06 mmol, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.38 (dd, *J* = 8.5, 7.2 Hz, 1H), 7.21 (dd, *J* = 8.0, 7.3 Hz, 1H), 6.51 (d, *J* = 9.9 Hz, 1H), 6.16 (d, *J* = 9.9 Hz, 1H), 5.00 (s, 1H), 4.96 (dd, *J* = 12.2, 1.5 Hz, 1H), 4.40 (dd, *J* = 9.4, 7.7 Hz, 1H), 3.80 (s, 3H), 2.61 (dd, *J* = 13.3, 7.7 Hz, 1H), 2.43 – 2.31 (m, 1H), 2.12 (s, 3H), 2.06 – 1.95 (m, 1H), 1.57 (dd, *J* = 9.4, 2.3 Hz, 1H), 1.51 (ddd, *J* = 9.5, 3.8, 3.0 Hz, 1H), 1.19 – 1.09 (m, 2H), 0.81 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.4, 179.2, 173.3, 155.0, 151.4, 139.3, 133.3, 131.8, 130.2, 129.2, 127.9, 126.0, 123.8, 80.3, 65.0, 57.1, 55.1, 54.3, 52.5, 41.3, 38.8, 38.3,

24.1, 18.2, 11.4. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{27}NO_5Br$ m/z 500.1067, found 500.1057. **IR** (film, cm^{-1}): 2927, 1772, 1739, 1661, 1633, 1614, 1437, 1404, 1378, 1275, 1202, 1184, 1156, 1106, 1038, 991, 950, 906, 879, 832. **$[\alpha]_D^{20}$** = -24.0 (c = 0.13, $CHCl_3$)

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(*o*-tolyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63o)

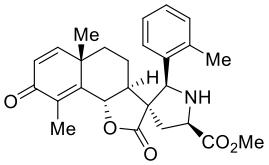


V-63o

The title product compound **V-63o** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (28.8 mg, 0.07 mmol, 66% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 1H), 7.25 – 7.11 (m, 3H), 6.65 (d, *J* = 9.9 Hz, 1H), 6.21 (d, *J* = 9.8 Hz, 1H), 4.77 (dd, *J* = 11.5, 1.5 Hz, 1H), 4.42 (s, 1H), 4.14 (dd, *J* = 8.4, 5.5 Hz, 1H), 3.82 (s, 3H), 2.56 – 2.46 (m, 2H), 2.26 (s, 3H), 2.01 – 1.89 (m, 6H), 1.88 – 1.78 (m, 1H), 1.45 (td, *J* = 13.3, 4.6 Hz, 1H), 1.29 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 176.5, 172.9, 154.5, 150.7, 136.6, 133.7, 130.9, 129.1, 128.3, 127.6, 126.7, 126.1, 80.1, 77.4, 77.2, 76.9, 63.9, 58.7, 55.2, 52.7, 49.7, 41.1, 37.6, 34.2, 25.2, 20.2, 20.2, 10.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_5$ m/z 436.2119, found 436.2108. **IR** (film, cm^{-1}): 2933, 2118, 1771, 1737, 1661, 1634, 1615, 1436, 1378, 1307, 1268, 1203, 1184, 1165, 1153, 1141, 110, 1037, 994, 960, 907, 832. **$[\alpha]_D^{20}$** = -60.0 (c = 0.27, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(*o*-tolyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64o)



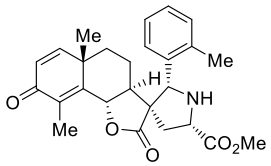
V-64o

The title product compound **V-64o** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (40.2 mg, 0.09 mmol, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.29 – 7.17 (m, 3H), 6.60 (d, *J* = 9.9 Hz, 1H), 6.19 (d, *J* = 9.9 Hz, 1H), 4.57 (s, 1H), 4.30 (dd, *J* = 11.9, 1.5 Hz, 1H), 4.01 (dd, *J* = 9.4, 5.8 Hz, 1H), 3.84 (s, 3H), 2.68 (dd, *J* = 13.4, 5.8 Hz, 1H), 2.49 (s, 3H), 2.36 – 2.19 (m, 2H), 2.03 (s, 3H), 2.02 – 1.82 (m, 3H), 1.51-1.40 (m, 1H), 1.00 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.2, 178.1, 173.4, 154.6, 150.8, 135.9, 135.4, 131.3, 129.0, 128.8, 127.6, 126.8, 126.1, 79.5, 61.8, 58.7, 56.7, 53.0, 52.7, 41.1, 39.6, 37.9, 24.6, 19.9, 19.7, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_5$ m/z 436.2119, found 436.2108. **IR** (film, cm^{-1}): 2933, 2250, 1770, 1736, 1662, 1634, 1614, 1492, 1437, 1404,

1377, 1303, 1264, 1202, 1179, 1154, 1112, 1037, 992, 959, 905, 832. **$[\alpha]_D^{20}$** = -80.0 (c = 0.21, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(*o*-tolyl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66o)

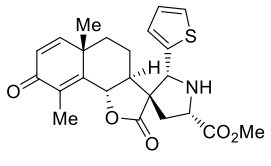


V-66o

The title product compound **V-66o** was prepared using **Condition D** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (38.5 mg, 0.09 mmol, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.97 (m, 1H), 7.26 – 7.18 (m, 3H), 6.51 (d, *J* = 9.9 Hz, 1H), 6.14 (d, *J* = 9.9 Hz, 1H), 4.76 (s, 1H), 4.29 (dd, *J* = 11.6, 1.5 Hz, 1H), 4.17 (dd, *J* = 9.6, 7.3 Hz, 1H), 3.80 (s, 3H), 2.94 (dd, *J* = 13.7, 9.6 Hz, 1H), 2.39 (s, 3H), 2.23 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.16 – 2.03 (m, 4H), 1.99-1.89 (m, 2H), 1.66 (d, *J* = 13.4 Hz, 1H), 1.17 (td, *J* = 13.0, 4.0 Hz, 1H), 0.57 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.4, 179.4, 173.0, 155.2, 151.3, 136.9, 134.8, 131.7, 128.9, 128.9, 128.6, 125.9, 125.9, 79.9, 64.9, 57.3, 56.8, 53.5, 52.6, 41.3, 39.8, 38.4, 23.8, 19.6, 17.9, 11.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}NO_5$ m/z 436.2119, found 436.2106. **IR** (film, cm^{-1}): 1775, 1732, 1662, 1432, 1373, 1244, 1154, 1098, 1079, 1030, 984, 954, 890. **$[\alpha]_D^{20}$** = -52.1 (c = 0.28, $CHCl_3$)

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(thiophen-2-yl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63p)



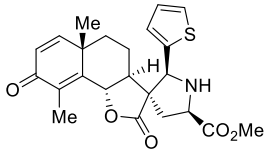
V-63p

The title product compound **V-63p** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (19.6 mg, 0.05 mmol, 46% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, *J* = 5.1 Hz, 1H), 7.08 (d, *J* = 3.6 Hz, 1H), 6.98 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.67 (d, *J* = 9.9 Hz, 1H), 6.24 (d, *J* = 9.9 Hz, 1H), 4.81 (dd, *J* = 11.9, 1.5 Hz, 1H), 4.31 (s, 1H), 4.07 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.80 (s, 3H), 2.57 – 2.44 (m, 2H), 2.20 (td, *J* = 12.2, 3.5 Hz, 1H), 1.98 (s, 3H), 1.95 (ddd, *J* = 13.5, 4.0, 2.3 Hz, 1H), 1.92 – 1.87 (m, 1H), 1.80 (qd, *J* = 12.8, 3.9 Hz, 1H), 1.53 (td, *J* = 13.1, 4.6 Hz, 1H), 1.30 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 186.3, 176.5, 172.3, 154.6, 150.7, 137.8, 129.2, 127.3, 126.5, 126.2, 125.6, 80.4, 64.6, 58.9, 55.2, 52.8, 50.0, 41.2, 37.8, 34.0, 25.1, 19.8, 10.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{26}NO_5S$ m/z 428.1526, found 428.1524. **IR** (film, cm^{-1}): 3337, 2931, 2855, 2160, 1791, 1731, 1657, 1626, 1610, 1437, 1404, 1386, 1336, 1293, 1264, 1223, 1198,

1166, 1143, 1129, 1117, 1088, 1054, 1043, 1019, 992, 955, 902, 878, 842. **$[\alpha]_D^{20}$** = -63.2 (c = 0.22, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(thiophen-2-yl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-64p)

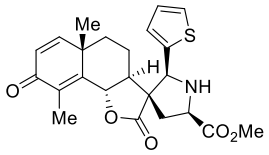


V-64p

The title product compound **V-64p** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (37.2 mg, 0.09 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 1H), 7.23 (d, *J* = 3.7 Hz, 1H), 7.05 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.62 (d, *J* = 9.9 Hz, 1H), 6.19 (d, *J* = 9.9 Hz, 1H), 4.59 (s, 1H), 4.34 (dd, *J* = 11.7, 1.4 Hz, 1H), 3.97 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.83 (s, 3H), 2.66 (dd, *J* = 13.7, 4.8 Hz, 1H), 2.44 – 2.22 (m, 2H), 2.16 – 2.05 (m, 1H), 2.00 (s, 3H), 1.97 – 1.88 (m, 2H), 1.51 – 1.39 (m, 1H), 1.11 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.3, 177.7, 173.0, 154.7, 151.1, 139.6, 128.8, 128.4, 126.0, 126.0, 125.4, 79.8, 61.6, 58.1, 56.7, 52.7, 52.0, 41.2, 38.8, 37.9, 24.9, 18.9, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{26}NO_5S$ m/z 428.1526, found 428.1517. **IR** (film, cm^{-1}): 2928, 1772, 1736, 1661, 1633, 1614, 1436, 1378, 1308, 1270, 1220, 1202, 1155, 1106, 1037, 991, 957, 902, 832. **$[\alpha]_D^{20}$** = -103.1 (c = 0.26, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*)-2'-(thiophen-2-yl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-65p)



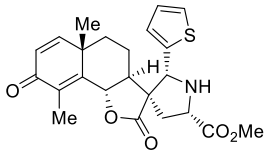
V-65p

The title product compound **V-65p** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (39.8 mg, 0.09 mmol, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.96 (dt, *J* = 7.2, 3.5 Hz, 2H), 6.59 (d, *J* = 9.8 Hz, 1H), 6.19 (d, *J* = 9.8 Hz, 1H), 5.00 (s, 1H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.20 (t, *J* = 8.3 Hz, 1H), 3.81 (s, 3H), 2.55 (dd, *J* = 13.4, 7.8 Hz, 1H), 2.31 (dd, *J* = 13.4, 8.7 Hz, 1H), 2.06 (s, 3H), 1.79 (td, *J* = 12.1, 3.5 Hz, 1H), 1.69 (dd, *J* = 13.5, 3.2 Hz, 1H), 1.55 (qd, *J* = 12.9, 3.8 Hz, 1H), 1.35 (d, *J* = 15.6 Hz, 1H), 1.24 (s, 3H), 1.18 (td, *J* = 13.2, 4.5 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.3, 178.1, 172.9, 154.9, 151.0, 143.3, 129.2, 127.5, 126.0, 125.2, 124.9, 80.0, 63.5, 57.2, 55.3, 52.5, 50.4, 41.1, 37.6, 30.7, 25.1,

20.2, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{26}NO_5S$ m/z 428.1526, found 428.1514. **IR** (film, cm^{-1}): 2948, 2160, 2032, 1770, 1738, 1661, 1633, 1614, 1437, 1378, 1307, 1270, 1193, 1054, 1016, 996, 967, 902, 832. **$[\alpha]_D^{20}$** = +34.1 (c = 0.21, $CHCl_3$)

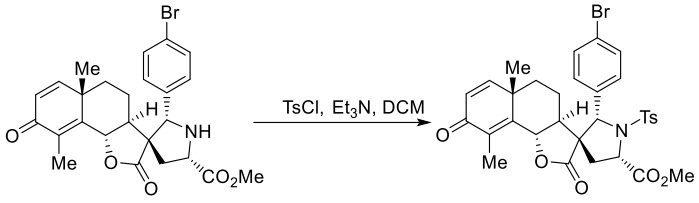
Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(thiophen-2-yl)-5a,9-dimethyl-2,8-dioxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-66p)



V-66p

The title product compound **V-66p** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (34.6 mg, 0.08 mmol, 81% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 5.0 Hz, 1H), 7.19 (d, *J* = 3.5 Hz, 1H), 7.03 (dd, *J* = 4.7, 3.6 Hz, 1H), 6.55 (d, *J* = 9.9 Hz, 1H), 6.16 (dt, *J* = 9.9, 1.2 Hz, 1H), 4.74 (s, 1H), 4.47 (dd, *J* = 11.9, 1.3 Hz, 1H), 4.16 (dd, *J* = 10.6, 5.5 Hz, 1H), 3.79 (s, 3H), 2.94 (dd, *J* = 13.1, 10.7 Hz, 1H), 2.20 (dd, *J* = 13.9, 5.6 Hz, 1H), 2.14 – 1.90 (m, 6H), 1.71 (ddd, *J* = 13.5, 4.0, 2.3 Hz, 1H), 1.29 – 1.19 (m, 2H), 0.79 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.5, 178.2, 173.4, 155.2, 151.5, 140.5, 128.5, 127.6, 125.9, 125.7, 125.3, 79.8, 64.6, 56.7, 56.5, 55.2, 52.6, 41.3, 39.9, 38.5, 24.2, 18.3, 11.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{23}H_{26}NO_5S$ m/z 428.1526, found 428.1523. **IR** (film, cm^{-1}): 3325, 2921, 2851, 1770, 1737, 1661, 1634, 1614, 1436, 1377, 1273, 1186, 1162, 1106, 1038, 990, 957, 901, 831.



V-63b **V-63b-Ts**

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*)-2'-(4-bromophenyl)-5a,9-dimethyl-2,8-dioxo-1'-tosyl-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-63b-Ts)

To a solution of **V-63b** (25.0 mg, 0.05 mmol) in DCM (1.0 mL) was added with $NaHCO_3$ (21.0 mg, 0.25 mmol) and TsCl (19.0 mg, 0.1 mmol). The reaction was stirred until full consumption of the starting material monitored by TLC. Then saturated $NaHCO_3$ solution (10 mL) was added to quench the reaction. The mixture was extracted with DCM (10 mL) for

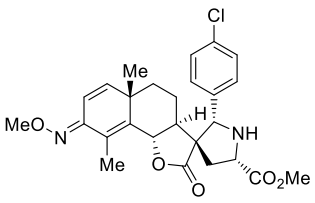
three times. And the resulting organic layers were combined, washed with brine and dried over Na_2SO_4. After evaporation, the residue was purified by flash column chromatography (*n*-pentane: ethyl acetate 3:1) giving a solid **V-63b-Ts** (25.0 mg, 0.04 mmol, 76% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.9 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 7.04 – 6.95 (m, 2H), 6.67 (d, *J* = 9.9 Hz, 1H), 6.24 (d, *J* = 9.9 Hz, 1H), 5.10 (dd, *J* = 8.9, 2.7 Hz, 1H), 4.82 – 4.72 (m, 2H), 3.82 (s, 3H), 2.71 (dd, *J* = 13.1, 2.7 Hz, 1H), 2.44 (dd, *J* = 13.1, 8.9 Hz, 1H), 2.38 (s, 3H), 2.07 (td, *J* = 12.2, 3.0 Hz, 1H), 1.97 (d, *J* = 14.1 Hz, 2H), 1.86 (d, *J* = 1.2 Hz, 3H), 1.77 (dd, *J* = 12.9, 3.7 Hz, 1H), 1.56 – 1.47 (m, 1H), 1.29 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 185.98, 173.08, 170.87, 154.39, 149.83, 144.30, 135.89, 132.96, 131.06, 131.00, 129.69, 129.12, 128.38, 126.28, 122.63, 79.56, 68.76, 60.14, 56.78, 52.94, 51.03, 41.10, 37.45, 31.44, 25.26, 21.69, 19.15, 10.89.

7.4.3 Stereodivergent synthesis of pseudo sesquiterpenoid alkaloids

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*,*E*)-2'-(4-chlorophenyl)-8-(methoxyimino)-5a,9-dimethyl-2-oxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-79)

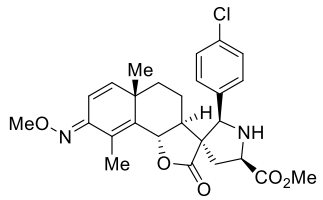
The title product compound **V-79** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (45.5 mg, 0.09 mmol, 94% yield).



V-79

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.28 (m, 4H), 6.78 (d, *J* = 10.1 Hz, 1H), 5.95 (d, *J* = 10.1 Hz, 1H), 4.77 (dd, *J* = 11.6, 1.6 Hz, 1H), 4.06-4.02 (m, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 2.52 (dd, *J* = 13.4, 8.8 Hz, 1H), 2.41 (dd, *J* = 13.4, 5.0 Hz, 1H), 1.99 (ddd, *J* = 12.0, 10.5, 5.5 Hz, 1H), 1.93-1.86 (m, 4H), 1.84 – 1.73 (m, 2H), 1.54 – 1.45 (m, 1H), 1.20 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 176.5, 172.6, 149.7, 144.8, 137.9, 134.4, 134.2, 129.7, 128.8, 123.5, 113.2, 80.9, 67.8, 62.1, 58.8, 55.0, 52.7, 50.2, 40.5, 38.0, 33.9, 25.8, 19.9, 12.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}N_2O_5Cl$ m/z 485.1838, found 485.1830. **IR** (film, cm^{-1}): 2936, 1774, 1737, 1597, 1492, 1436, 1374, 1314, 1269, 1225, 1202, 1166, 1111, 1092, 1038, 1014, 988, 904, 870, 833. **$[\alpha]_D^{20}$** = -3.3 (c = 0.15, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*,*E*)-2'-(4-chlorophenyl)-8-(methoxyimino)-5a,9-dimethyl-2-oxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-80)



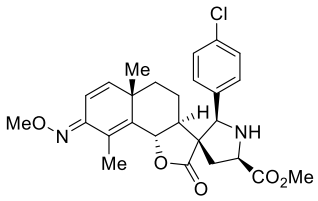
V-80

The title product compound **V-80** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (47.6 mg, 0.10 mmol, 98% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 10.1 Hz, 1H), 5.90 (d, *J* = 10.2 Hz, 1H), 4.38 (s, 1H), 4.24 (dd, *J* = 11.7, 1.6 Hz, 1H), 3.99 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 2.65 (dd, *J* = 13.5, 5.0 Hz, 1H), 2.31 (dd, *J* = 13.6, 9.5 Hz, 1H), 2.21 (td, *J* = 12.2, 3.6 Hz, 1H), 2.03 – 1.89 (m, 5H), 1.75 (ddd, *J* = 13.6, 3.9, 2.2 Hz, 1H), 1.43 (td, *J* = 13.1, 4.6 Hz, 1H), 1.00 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.7, 173.1, 149.7, 144.6, 137.9, 135.9, 135.3, 129.7, 129.3, 123.2, 113.1, 80.5, 65.7, 62.1, 58.4, 56.6, 52.9, 52.5, 40.5, 38.5, 38.3, 25.5, 19.8, 12.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}N_2O_5Cl$ m/z 485.1838, found 485.1833. **IR** (film, cm^{-1}): 2932, 1770, 1737, 1491, 1436, 1374, 1316, 1266, 1204, 1155, 1093, 1037, 1014, 988, 944, 902, 868, 835. **$[\alpha]_D^{20}$** = -90.3 (c = 0.15, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*,*E*)-2'-(4-chlorophenyl)-8-(methoxyimino)-5a,9-dimethyl-2-oxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-81)

The title product compound **V-81** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (47.5 mg, 0.10 mmol, 98% yield).

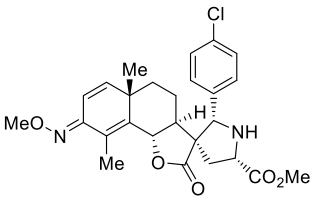


V-81

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 4H), 6.73 (d, *J* = 10.1 Hz, 1H), 5.85 (d, *J* = 10.2 Hz, 1H), 4.76 (dd, *J* = 11.3, 1.5 Hz, 1H), 4.73 (s, 1H), 4.21 (t, *J* = 8.3 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 2.48 (dd, *J* = 13.4, 7.9 Hz, 1H), 2.29 (dd, *J* = 13.3, 8.8 Hz, 1H), 2.06 (s, 3H), 1.59 (td, *J* = 11.7, 3.2 Hz, 1H), 1.54 – 1.44 (m, 2H), 1.24 – 1.18 (m, 1H), 1.13 (s, 3H), 1.11 – 1.04 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 178.8, 173.3, 149.9, 145.0, 138.1, 137.5, 134.0, 128.9, 128.6, 123.3, 113.0, 80.8, 77.4, 66.5, 62.1, 57.2, 55.0, 52.5, 50.1, 40.4, 37.8, 31.2, 25.8, 20.7, 12.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}N_2O_5Cl$ m/z 485.1838, found 485.1832. **IR** (film, cm^{-1}): 2937, 1770, 1739, 1490, 1437,

1373, 1326, 1275, 1199, 1151, 1090, 1047, 1014, 951, 913, 888, 870, 839. **[α]$_D^{20}$** = +152.4 (c = 0.11, $CHCl_3$)

Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*,*E*)-2'-(4-chlorophenyl)-8-(methoxyimino)-5a,9-dimethyl-2-oxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-82)

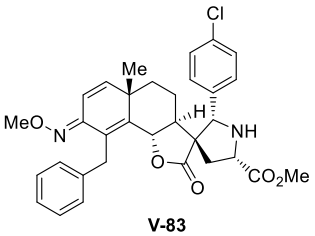


V-82

The title product compound **V-82** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (47.1 mg, 0.10 mmol, 97% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.33 (m, 2H), 6.69 (d, *J* = 10.2 Hz, 1H), 5.80 (d, *J* = 10.2 Hz, 1H), 4.48 (s, 1H), 4.17 (dd, *J* = 10.5, 1.4 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 2.99 (dd, *J* = 13.8, 10.7 Hz, 1H), 2.15 (dd, *J* = 13.9, 5.8 Hz, 1H), 2.06 (s, 3H), 1.95 (td, *J* = 12.6, 3.5 Hz, 1H), 1.91 – 1.85 (m, 1H), 1.79 (td, *J* = 13.0, 3.9 Hz, 1H), 1.48 (ddd, *J* = 13.4, 3.9, 2.3 Hz, 1H), 1.17 (td, *J* = 13.0, 4.7 Hz, 1H), 0.56 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 179.1, 173.5, 149.9, 145.1, 138.7, 135.5, 134.3, 129.0, 128.6, 122.6, 112.8, 80.6, 67.8, 62.0, 57.0, 56.7, 54.9, 52.6, 40.7, 40.5, 38.9, 24.7, 18.7, 12.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{26}H_{30}N_2O_5Cl$ m/z 485.1838, found 485.1832. **IR** (film, cm^{-1}): 2927, 1769, 1739, 1492, 1437, 1380, 1275, 1201, 1165, 1091, 1038, 1014, 987, 955, 908, 869, 826. **[α]$_D^{20}$** = -60.0 (c = 0.17, $CHCl_3$)

Methyl (2'*S*,3*R*,3a*S*,5a*S*,5'*S*,9b*S*,*E*)-9-benzyl-2'-(4-chlorophenyl)-8-(methoxyimino)-5a-methyl-2-oxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-83)



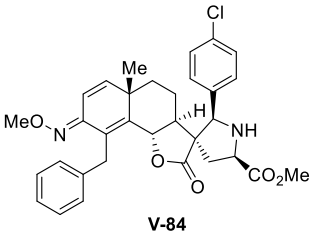
V-83

The title product compound **V-83** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (55.0 mg, 0.10 mmol, 98% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.18 (m, 4H), 7.07 – 7.00 (m, 1H), 6.97 (dd, *J* = 8.3, 6.7 Hz, 2H), 6.91 (dd, *J* = 8.1, 1.5 Hz, 2H), 6.78 (d, *J* = 10.1 Hz, 1H), 5.95 (d, *J* = 10.1 Hz, 1H), 4.81 (d, *J* = 11.6 Hz, 1H), 4.05 – 3.95 (m, 4H), 3.83 (s, 3H), 3.79 (s, 3H), 2.50 (dd, *J* = 13.5, 9.1 Hz, 1H), 2.41 (dd, *J* = 13.4, 4.8 Hz, 1H), 1.99 – 1.72 (m, 4H), 1.58 (ddd, *J* = 14.0, 13.6, 4.8 Hz, 1H), 1.25 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.9, 172.6, 148.4, 144.4, 141.5, 138.9, 134.3, 134.0, 129.7,

128.8, 128.1, 127.7, 126.6, 125.1, 113.4, 80.6, 67.6, 62.2, 58.6, 54.7, 52.7, 49.9, 40.7, 38.0, 33.8, 30.4, 26.1, 19.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{32}H_{34}N_2O_5Cl$ m/z 561.2151, found 561.2146. **IR** (film, cm^{-1}): 2937, 1774, 1737, 1663, 1600, 1494, 1452, 1436, 1374, 1314, 1266, 1223, 1186, 1154, 1092, 1052, 1014, 908, 895, 823. **$[\alpha]_D^{20}$** = -8.0 (c = 0.18, $CHCl_3$)

Methyl (2'*R*,3*S*,3a*S*,5a*S*,5'*R*,9b*S*,*E*)-9-benzyl-2'-(4-chlorophenyl)-8-(methoxyimino)-5a-methyl-2-oxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-84)

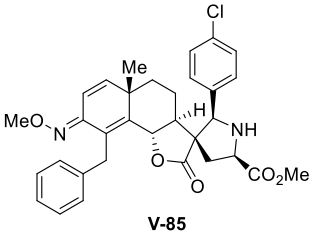


V-84

The title product compound **V-84** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (52.6 mg, 0.09 mmol, 94% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (q, *J* = 8.7 Hz, 4H), 7.18 – 7.11 (m, 2H), 7.10 – 7.04 (m, 3H), 6.79 (d, *J* = 10.1 Hz, 1H), 5.93 (d, *J* = 10.2 Hz, 1H), 4.28 (s, 1H), 4.21 – 4.16 (m, 2H), 3.93 – 3.90 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 2.29 (dd, *J* = 13.5, 5.3 Hz, 1H), 2.08 (dd, *J* = 13.6, 9.5 Hz, 1H), 2.04 (s, 1H), 1.99 – 1.83 (m, 3H), 1.77 (d, *J* = 13.2 Hz, 1H), 1.48-1.41 (m, 1H), 1.04 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.1, 173.4, 148.7, 144.6, 142.3, 139.3, 136.5, 134.9, 129.5, 129.2, 128.5, 127.8, 126.3, 125.1, 113.3, 80.0, 65.7, 62.2, 58.4, 56.4, 52.6, 51.8, 40.8, 38.8, 38.7, 29.9, 25.4, 19.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{32}H_{34}N_2O_5Cl$ m/z 561.2151, found 561.2146. **IR** (film, cm^{-1}): 2936, 1770, 1737, 1663, 1600, 1493, 1452, 1435, 1374, 1316, 1265, 1221, 1181, 1154, 1093, 1051, 1031, 1014, 959, 941, 909, 893, 860, 824. **$[\alpha]_D^{20}$** = -122.5 (c = 0.12, $CHCl_3$)

Methyl (2'*R*,3*R*,3a*S*,5a*S*,5'*R*,9b*S*,*E*)-9-benzyl-2'-(4-chlorophenyl)-8-(methoxyimino)-5a-methyl-2-oxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-85)



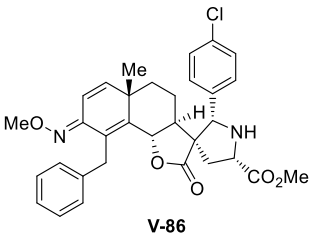
V-85

The title product compound **V-85** was prepared using **Condition C** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (53.4 mg, 0.10 mmol, 95% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 4H), 7.17 – 7.12 (m, 1H), 7.11 – 7.06 (m, 4H), 6.76 (d, *J* = 10.1 Hz, 1H), 5.87 (d, *J* = 10.1 Hz, 1H), 4.75 (d, *J* = 10.8 Hz, 1H), 4.45 (s, 1H), 4.22 – 4.14 (m, 2H), 4.03 (d, *J* = 14.9 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 2.37 (dd, *J* = 13.3, 8.3 Hz, 1H), 2.22 (dd, *J* = 13.3, 8.5 Hz, 1H), 1.54 – 1.40 (m, 3H), 1.18 (s, 3H), 1.14 –

1.04 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 178.4, 173.4, 148.7, 144.8, 142.3, 139.5, 137.7, 133.6, 128.7, 128.5, 128.4, 127.9, 126.2, 125.2, 113.1, 80.6, 66.2, 62.2, 57.2, 54.6, 52.5, 49.7, 40.7, 38.3, 31.2, 30.3, 25.6, 20.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{32}H_{34}N_2O_5Cl$ m/z 561.2151, found 561.2146. **IR** (film, cm^{-1}): 2938, 1771, 1738, 1663, 1600, 1492, 1452, 1437, 1375, 1327, 1275, 1195, 1154, 1089, 1052, 1031, 1013, 909, 886, 846. **$[\alpha]_D^{20}$** = +176.5 (c = 0.12, $CHCl_3$)

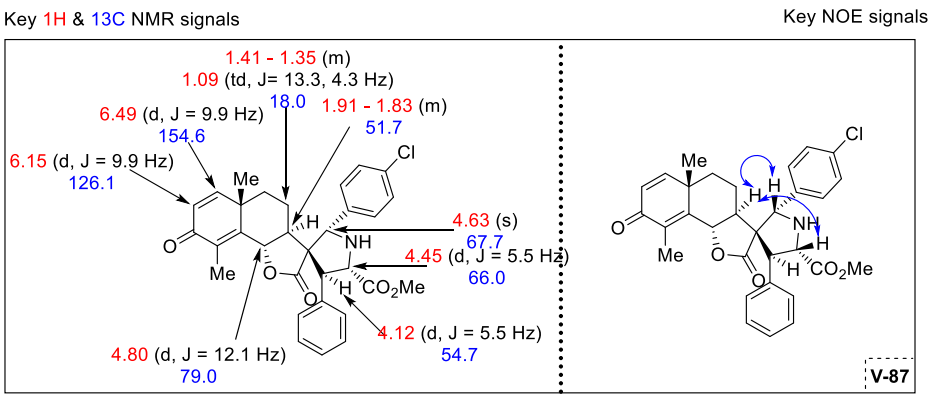
Methyl (2'*S*,3*S*,3a*S*,5a*S*,5'*S*,9b*S*,*E*)-9-benzyl-2'-(4-chlorophenyl)-8-(methoxyimino)-5a-methyl-2-oxo-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-86)



V-86

The title product compound **V-86** was prepared using **Condition D** and isolated by column chromatography (1:1 Cyclohexane: Ethyl acetate) giving an amorphous solid (51.6 mg, 0.09 mmol, 92% yield).

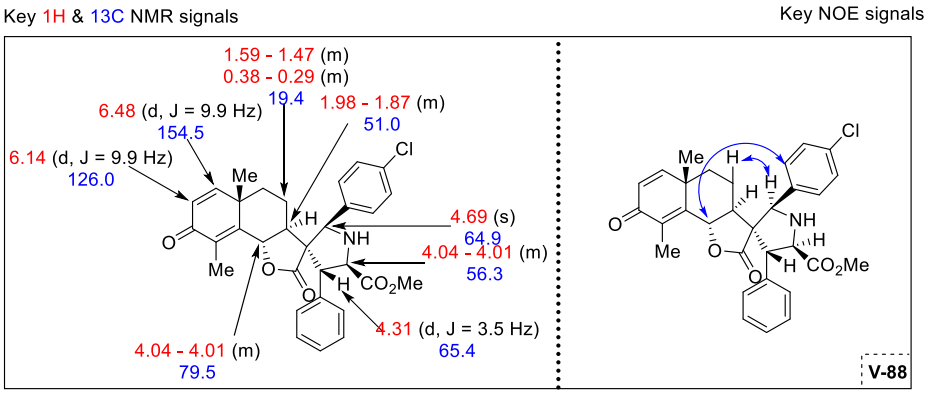
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.1 Hz, 2H), 7.38 – 7.31 (m, 2H), 7.21 - 7.16 (m, 2H), 7.14 – 7.06 (m, 3H), 6.73 (d, *J* = 10.1 Hz, 1H), 5.83 (d, *J* = 10.2 Hz, 1H), 4.37 (s, 1H), 4.24 (d, *J* = 15.0 Hz, 1H), 4.13 (d, *J* = 11.7 Hz, 1H), 4.04 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.97 (d, *J* = 15.0 Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 2.73 (dd, *J* = 13.9, 10.7 Hz, 1H), 1.85 – 1.65 (m, 4H), 1.54 – 1.48 (m, 1H), 1.20 (td, *J* = 12.7, 5.0 Hz, 1H), 0.61 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 178.6, 173.6, 148.8, 145.0, 142.4, 140.0, 135.6, 134.2, 125.6, 125.1, 113.0, 80.3, 67.8, 62.2, 56.5, 56.4, 54.6, 52.5, 40.9, 40.8, 39.4, 30.1, 24.5, 18.8. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{32}H_{34}N_2O_5Cl$ m/z 561.2151, found 561.2146. **IR** (film, cm^{-1}): 2936, 1770, 1739, 1663, 1600, 1493, 1452, 1436, 1275, 1198, 1164, 1117, 1091, 1051, 1031, 1012.89, 986, 958, 909, 887, 825. **$[\alpha]_D^{20}$** = -72.8 (c = 0.18, $CHCl_3$)



Methyl (2'*S*,3*R*,3a*S*,4'*S*,5a*S*,5'*S*,9b*S*)-2'-(4-chlorophenyl)-5a,9-dimethyl-2,8-dioxo-4'-phenyl-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-87)

The title product compound **V-87** was prepared from substrate **V-71** (16.0 mg, 0.05 mmol) using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (15.2 mg, 0.03 mmol, 57% yield) as a mixture of diastereomers (**V-87** + **V-88**; 3.17:1). The yield for the main isomer **V-87** is 43%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.31 (m, 9H), 6.49 (d, *J* = 9.9 Hz, 1H), 6.15 (d, *J* = 9.9 Hz, 1H), 4.80 (dd, *J* = 12.1, 1.6 Hz, 1H), 4.63 (s, 1H), 4.45 (d, *J* = 5.5 Hz, 1H), 4.12 (d, *J* = 5.5 Hz, 1H), 3.81 (s, 3H), 1.92 (s, 3H), 1.91 – 1.83 (m, 1H), 1.55 (ddd, *J* = 13.5, 3.9, 2.3 Hz, 1H), 1.41 – 1.35 (m, 1H), 1.09 (td, *J* = 13.3, 4.3 Hz, 1H), 0.87 (s, 3H), 0.80 (td, *J* = 13.3, 3.9 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.2, 176.2, 154.6, 150.3, 138.6, 135.0, 129.9, 129.2, 126.1, 79.0, 67.7, 66.0, 59.6, 54.7, 53.2, 51.7, 41.1, 37.9, 24.4, 18.0, 11.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{31}H_{31}NO_5Cl$ m/z 532.1885, found 532.1879. **IR** (film, cm^{-1}): 2922, 1772, 1738, 1662, 1635, 1493, 1454, 1436, 1375, 1159, 1091, 1055, 1014, 904, 831. **$[\alpha]_D^{20}$** = -25.0 (c = 0.06, $CHCl_3$)

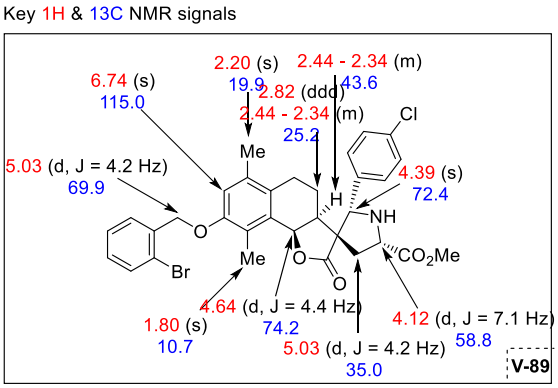


Methyl (2'*R*,3*S*,3a*S*,4'*R*,5a*S*,5'*R*,9b*S*)-2'-(4-chlorophenyl)-5a,9-dimethyl-2,8-dioxo-4'-phenyl-3a,4,5,5a,8,9b-hexahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-88)

The title product compound **V-88** was prepared from substrate **V-71** (16.0 mg, 0.05 mmol) using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (23.9 mg, 0.04 mmol, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.5 Hz, 2H), 7.43 – 7.30 (m, 7H), 6.48 (d, *J* = 9.9 Hz, 1H), 6.14 (d, *J* = 9.8 Hz, 1H), 4.69 (s, 1H), 4.31 (d, *J* = 3.5 Hz, 1H), 4.07 – 3.98 (m, 2H),

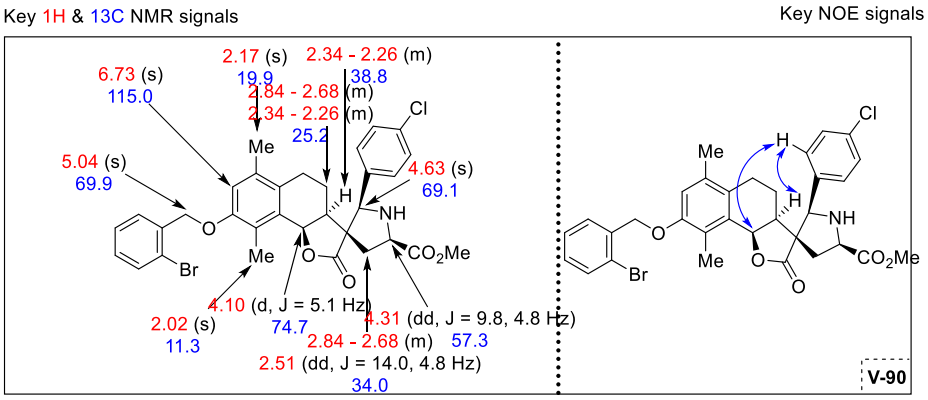
3.86 (s, 3H), 2.02 – 1.87 (m, 4H), 1.59 – 1.47 (m, 2H), 0.96 – 0.84 (m, 4H), 0.38 – 0.29 (m, 1H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 186.2, 177.5, 173.4, 154.5, 150.7, 138.5, 136.0, 135.5, 129.9, 129.5, 129.2, 128.9, 128.5, 128.3, 126.0, 79.4, 65.4, 64.9, 60.3, 56.3, 53.1, 51.0, 40.9, 37.7, 24.7, 19.3, 11.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{31}H_{31}NO_5Cl$ m/z 532.1885, found 532.1880. **IR** (film, cm^{-1}): 2925, 1771, 1736, 1662, 1635, 1615, 1492, 1454, 1435, 1406, 1376, 1307, 1264, 1226, 1184, 1157, 1093, 1055, 1013, 996, 941, 903, 832.



Methyl (2'*S*,3*R*,3a*S*,5'*S*,9b*R*)-8-((2-bromobenzyl)oxy)-2'-(4-chlorophenyl)-6,9-dimethyl-2-oxo-3a,4,5,9b-tetrahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-89)

The title product compound **V-89** was prepared from substrate **V-73** (20.7 mg, 0.05 mmol) using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (27.6 mg, 0.04 mmol, 88% yield).

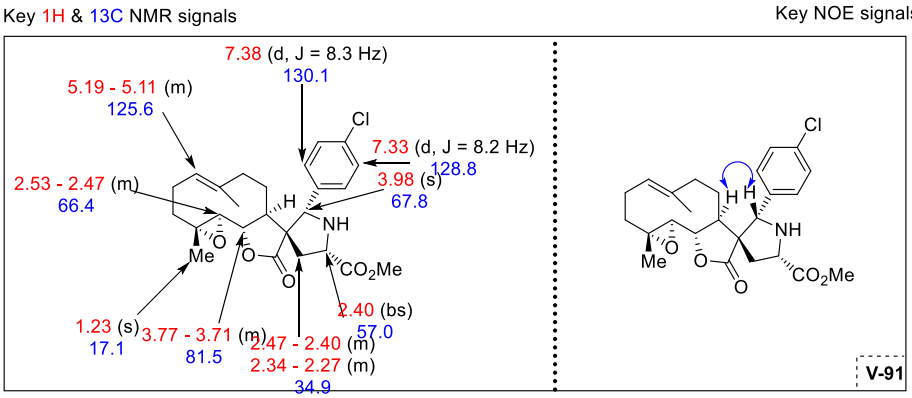
^{1}H NMR (600 MHz, CDCl$_3$) δ 7.56 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.53 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.33 (td, *J* = 7.5, 1.2 Hz, 1H), 7.18 (td, *J* = 7.7, 1.7 Hz, 1H), 6.74 (s, 1H), 5.03 (d, *J* = 4.2 Hz, 2H), 4.64 (d, *J* = 4.4 Hz, 1H), 4.39 (s, 1H), 4.12 (d, *J* = 7.1 Hz, 1H), 3.87 (s, 3H), 2.82 (d, *J* = 14.5 Hz, 1H), 2.62 (dd, *J* = 13.5, 4.2 Hz, 1H), 2.51 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.44 – 2.34 (m, 2H), 2.20 (s, 3H), 2.02 – 1.96 (m, 1H), 1.80 (s, 3H), 1.49-1.41 (m, 1H), 0.94 – 0.85 (m, 1H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 177.8, 173.5, 171.3, 154.6, 136.7, 136.2, 135.3, 134.2, 132.6, 129.5, 129.5, 129.2, 129.1, 128.7, 128.4, 127.7, 125.9, 122.2, 115.0, 74.2, 72.4, 69.9, 61.1, 60.5, 58.8, 52.8, 43.6, 35.0, 25.2, 22.1, 21.2, 19.9, 14.3, 10.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{32}H_{32}NO_5ClBr$ m/z 624.1147, found 624.1145. **IR** (film, cm^{-1}): 3356, 2926, 2852, 2160, 1762, 1738, 1601, 1484, 1437, 1384, 1353, 1339, 1304, 1212, 1194, 1172, 1132, 1112, 1087, 1045, 1028, 1012, 984, 945, 920, 862, 840. **$[\alpha]_D^{20}$** = -36.3 (c = 0.25, $CHCl_3$)



Methyl (2'*R*,3*R*,3a*S*,5'*R*,9b*R*)-8-((2-bromobenzyl)oxy)-2'-(4-chlorophenyl)-6,9-dimethyl-2-oxo-3a,4,5,9b-tetrahydro-2*H*-spiro[naphtho[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-90)

The title product compound **V-90** was prepared from substrate **V-73** (20.7 mg, 0.05 mmol) using **Condition C** and isolated by column chromatography (3:1 *n*-pentane: EA) giving an amorphous solid (29.6 mg, 0.05 mmol, 95% yield).

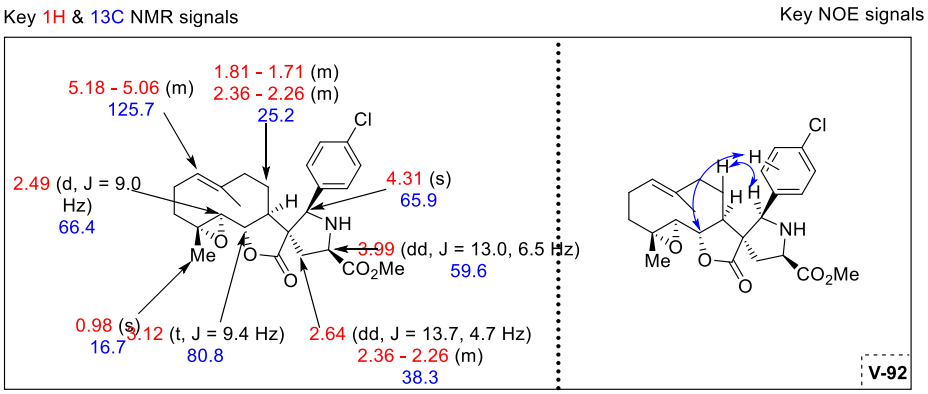
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.60 – 7.49 (m, 4H), 7.37 – 7.31 (m, 3H), 7.18 (td, *J* = 7.6, 1.7 Hz, 1H), 6.73 (s, 1H), 5.04 (s, 2H), 4.63 (s, 1H), 4.31 (dd, *J* = 9.8, 4.8 Hz, 1H), 4.10 (d, *J* = 5.1 Hz, 1H), 3.84 (s, 3H), 2.84 – 2.68 (m, 2H), 2.51 (dd, *J* = 14.0, 4.8 Hz, 1H), 2.34 – 2.26 (m, 2H), 2.17 (s, 3H), 2.02 (s, 3H), 1.85 – 1.80 (m, 1H), 1.32 – 1.27 (m, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 178.7, 174.3, 154.6, 136.7, 136.4, 134.8, 134.1, 132.6, 129.9, 129.2, 129.2, 128.8, 128.6, 128.5, 127.7, 126.0, 122.2, 115.0, 74.7, 70.0, 69.1, 59.4, 57.3, 52.7, 38.8, 34.0, 25.2, 22.2, 19.9, 11.3. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{32}H_{32}NO_5ClBr$ m/z 624.1147, found 624.1145. **IR** (film, cm^{-1}): 2925, 1745, 1602, 1486, 1437, 1413, 1381, 1335, 1306, 1281, 1201, 1169, 1111, 1090, 1059, 1046, 1026, 1013, 977, 916, 872, 824. **$[\alpha]_D^{20}$** = +13.2 (c = 0.24, $CHCl_3$)



Methyl (2'*S*,3*R*,3a*S*,5'*S*,9a*R*,10a*R*,10b*S*,*E*)-2'-(4-chlorophenyl)-6,9a-dimethyl-2-oxo-3a,4,5,8,9,9a,10a,10b-octahydro-2*H*-spiro[oxireno[2',3':9,10]cyclodeca[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-91)

The title product compound **V-91** was prepared using **Condition A** and isolated by column chromatography (30:1 DCM: MeOH) giving an amorphous solid (40.2 mg, 0.09 mmol, 87% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 5.19 – 5.11 (m, 1H), 4.06 – 3.95 (m, 2H), 3.77 – 3.71 (m, 4H), 2.55 – 2.40 (m, 3H), 2.39 – 2.26 (m, 2H), 2.13 – 2.01 (m, 2H), 1.91 (dd, *J* = 15.0, 6.8 Hz, 1H), 1.70 (s, 3H), 1.67 – 1.56 (m, 1H), 1.23 (s, 3H), 1.12 (td, *J* = 13.0, 5.9 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 207.2, 176.3, 172.5, 134.5, 134.0, 133.7, 130.1, 128.8, 125.6, 81.5, 67.8, 66.4, 61.6, 58.9, 57.0, 52.7, 47.5, 41.4, 36.7, 34.9, 31.1, 26.0, 24.0, 17.1, 17.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{31}NO_5Cl$ m/z 460.1885, found 460.1881. **IR** (film, cm^{-1}): 2926, 2855, 2346, 2158, 2048, 1957, 1765, 1491, 1437, 1387, 1317, 1292, 1270, 1204, 1092, 1074, 1045, 1012, 976, 940, 913, 892, 871, 824. **$[\alpha]_D^{20}$** = +12.3 (c = 0.16, $CHCl_3$)

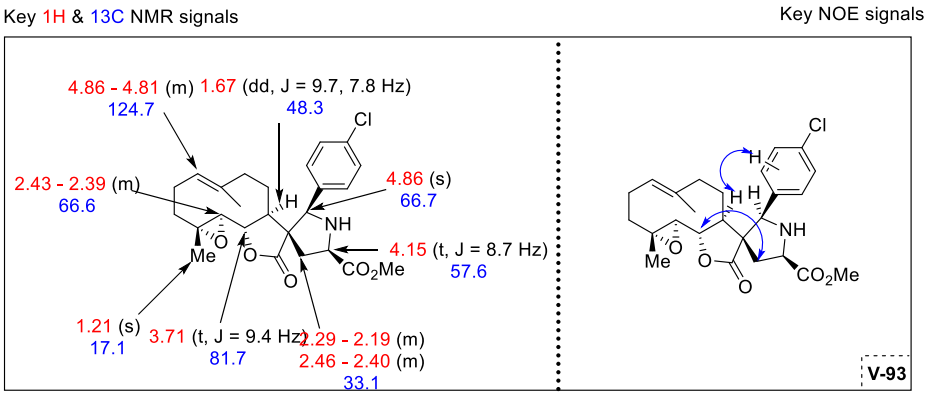


Methyl (2'*R*,3*S*,3a*S*,5'*R*,9a*R*,10a*R*,10b*S*,*E*)-2'-(4-chlorophenyl)-6,9a-dimethyl-2-oxo-3a,4,5,8,9,9a,10a,10b-octahydro-2*H*-spiro[oxireno[2',3':9,10]cyclodeca[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-92)

The title product compound **V-92** was prepared using **Condition B** and isolated by column chromatography (30:1 DCM: MeOH) giving an amorphous solid (42.3 mg, 0.09 mmol, 92% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (brs, 4H), 5.18 – 5.06 (m, 1H), 4.31 (s, 1H), 3.99 (dd, *J* = 10.2, 5.0 Hz, 1H), 3.83 (s, 3H), 3.12 (t, *J* = 9.4 Hz, 1H), 2.64 (dd, *J* = 13.7, 4.7 Hz, 1H), 2.49 (d, *J* = 9.0 Hz, 1H), 2.45 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.36 – 2.26 (m, 3H), 2.15 – 1.95 (m,

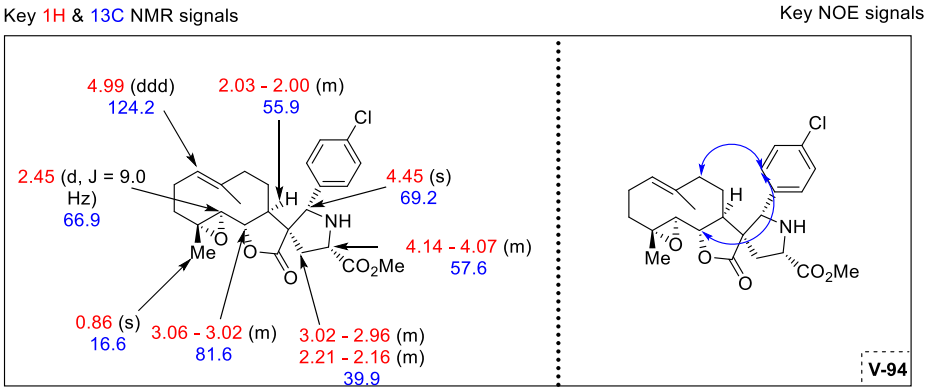
4H), 1.81 – 1.71 (m, 1H), 1.68 (s, 3H), 1.10 (td, *J* = 13.0, 5.8 Hz, 1H), 0.98 (s, 3H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 177.4, 173.1, 135.1, 135.0, 133.9, 129.3, 129.1, 125.7, 80.8, 66.4, 65.9, 61.4, 59.6, 58.4, 52.7, 50.2, 41.8, 38.3, 36.7, 25.2, 24.0, 16.9, 16.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{31}NO_5Cl$ m/z 460.1885, found 460.1880. **IR** (film, cm^{-1}): 2929, 2861, 1761, 1738, 1492, 1435, 1386, 1316, 1201, 1152, 1113, 1092, 1071, 1044, 1014, 1004, 984, 940, 910, 873, 824. **[α]$_D^{20}$** = +21.9 (c = 0.16, $CHCl_3$)



Methyl (2'*R*,3*R*,3a*S*,5'*R*,9a*R*,10a*R*,10b*S*,*E*)-2'-(4-chlorophenyl)-6,9a-dimethyl-2-oxo-3a,4,5,8,9,9a,10a,10b-octahydro-2*H*-spiro[oxireno[2',3':9,10]cyclodeca[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-93)

The title product compound **V-93** was prepared using **Condition C** and isolated by column chromatography (3:1 *n*-pentane: EA) giving an amorphous solid (27.0 mg, 0.06 mmol, 59% yield).

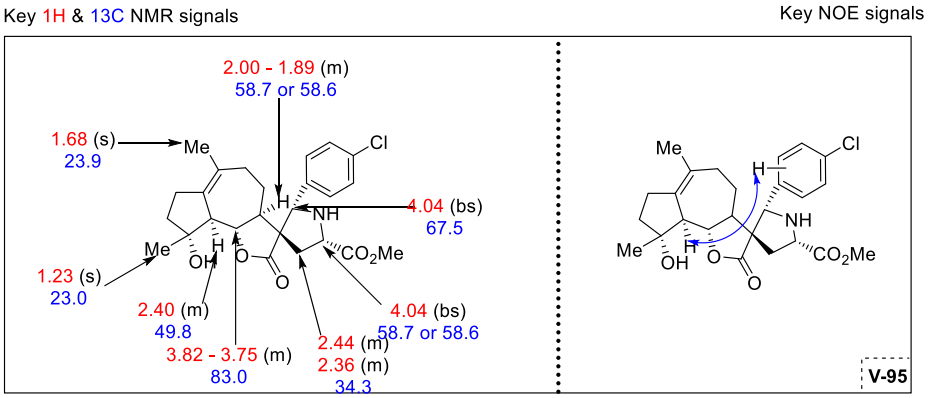
^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 (brs, 4H), 4.86 – 4.81 (m, 2H), 4.15 (t, *J* = 8.7 Hz, 1H), 3.79 (s, 3H), 3.71 (t, *J* = 9.4 Hz, 1H), 2.46 – 2.40 (m, 2H), 2.29 – 2.19 (m, 2H), 2.10 – 2.03 (m, 2H), 2.00 – 1.92 (m, 2H), 1.67 (dd, *J* = 9.7, 7.8 Hz, 1H), 1.57 (s, 3H), 1.22 – 1.19 (m, 4H), 1.10 (td, *J* = 12.9, 6.0 Hz, 1H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 178.7, 172.7, 137.1, 134.6, 134.0, 129.0, 128.9, 124.7, 81.7, 66.7, 66.6, 61.8, 57.6, 56.2, 52.5, 48.3, 40.4, 36.9, 33.1, 26.0, 23.9, 17.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{31}NO_5Cl$ m/z 460.1885, found 460.1880. **IR** (film, cm^{-1}): 2928, 2858, 1760, 1739, 1491, 1438, 1386, 1333, 1277, 1203, 1089, 1072, 1013, 976, 941, 910, 872, 824. **[α]$_D^{20}$** = +28.2 (c = 0.11, $CHCl_3$)



Methyl (2'*S*,3*S*,3a*S*,5'*S*,9a*R*,10a*R*,10b*S*,*E*)-2'-(4-chlorophenyl)-6,9a-dimethyl-2-oxo-3a,4,5,8,9,9a,10a,10b-octahydro-2*H*-spiro[oxireno[2',3':9,10]cyclodeca[1,2-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-94)

The title product compound **V-94** was prepared using **Condition D** and isolated by column chromatography (3:1 *n*-pentane: EA) giving an amorphous solid (15.1 mg, 0.03 mmol, 33% yield).

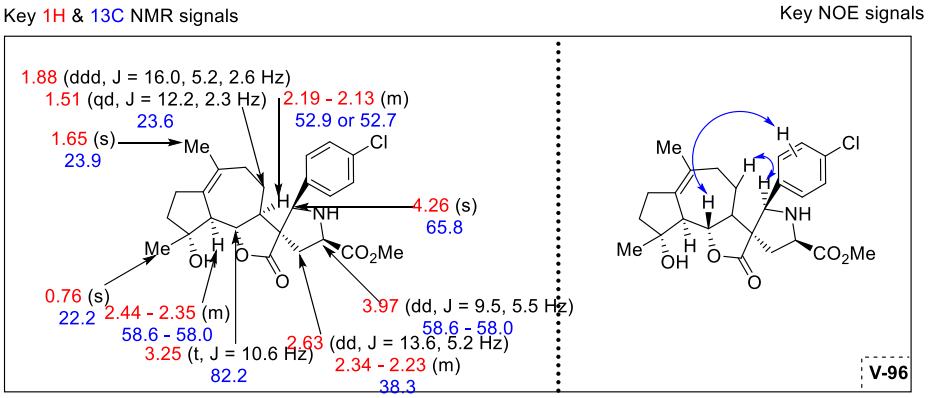
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 4.99 (ddd, *J* = 12.0, 3.8, 1.8 Hz, 1H), 4.45 (s, 1H), 4.14 – 4.07 (m, 1H), 3.81 (s, 3H), 3.07 – 2.96 (m, 2H), 2.66 (dd, *J* = 15.5, 7.3 Hz, 1H), 2.45 (d, *J* = 9.0 Hz, 1H), 2.28 – 2.16 (m, 3H), 2.11 – 1.99 (m, 3H), 1.73 (t, *J* = 12.4 Hz, 1H), 1.45 (s, 3H), 1.14 – 1.01 (m, 2H), 0.86 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 179.4, 173.1, 135.7, 134.9, 134.3, 129.2, 128.4, 124.2, 81.6, 69.2, 66.9, 61.5, 57.6, 57.3, 55.9, 52.5, 42.4, 39.9, 36.9, 23.8, 23.0, 17.0, 16.6. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{31}NO_5Cl$ m/z 460.1885, found 460.1882. **IR** (film, cm^{-1}): 2923, 2854, 1736, 1461, 1411, 1148, 1056, 967, 884, 811. **$[\alpha]_D^{20}$** = +17.8 (c = 0.14, $CHCl_3$)



Methyl (2'*S*,3*R*,3a*S*,5'*S*,9*R*,9a*S*,9b*S*)-2'-(4-chlorophenyl)-9-hydroxy-6,9-dimethyl-2-oxo-3a,4,5,7,8,9,9a,9b-octahydro-2*H*-spiro[azuleno[4,5-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-95)

The title product compound **V-95** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (44.5 mg, 0.10 mmol, 97% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 4H), 4.04 (brs, 2H), 3.82 – 3.75 (m, 4H), 2.51 – 2.24 (m, 5H), 2.21 – 2.09 (m, 2H), 1.99 (t, *J* = 11.0 Hz, 1H), 1.82 (d, *J* = 12.6 Hz, 1H), 1.74 – 1.64 (m, 5H), 1.42 – 1.32 (m, 1H), 1.23 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 176.8, 172.7, 134.5, 133.9, 132.2, 131.3, 129.9, 128.8, 83.0, 80.3, 67.5, 58.7, 58.6, 55.5, 52.7, 49.8, 38.5, 35.3, 34.3, 30.1, 23.9, 23.8, 23.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{31}NO_5Cl$ m/z 460.1885, found 460.1880. **IR** (film, cm^{-1}): 2923, 2851, 1765, 1644, 1492, 1438, 1377, 1312, 1215, 1177, 1138, 1090, 1014, 990, 911, 873, 832. **$[\alpha]_D^{20}$** = +21.5 (c = 0.14, $CHCl_3$)

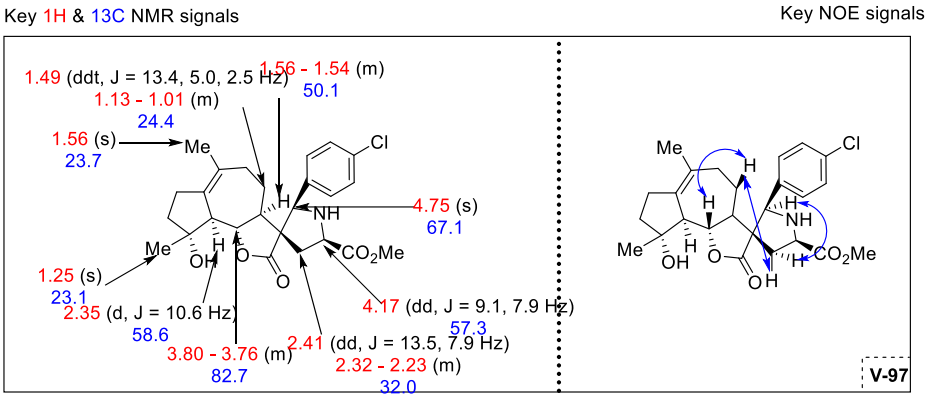


Methyl (2'*R*,3*S*,3a*S*,5'*R*,9*R*,9a*S*,9b*S*)-2'-(4-chlorophenyl)-9-hydroxy-6,9-dimethyl-2-oxo-3a,4,5,7,8,9,9a,9b-octahydro-2*H*-spiro[azuleno[4,5-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-96)

The title product compound **V-96** was prepared using **Condition B** and isolated by column chromatography (1:1 *n*-pentane: EA) giving an amorphous solid (42.7 mg, 0.09 mmol, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 4H), 4.26 (s, 1H), 3.97 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.83 (s, 3H), 3.25 (t, *J* = 10.6 Hz, 1H), 2.63 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.44 – 2.35 (m, 1H), 2.34 – 2.23 (m, 3H), 2.19 – 2.13 (m, 1H), 2.12 – 1.98 (m, 2H), 1.88 (ddd, *J* = 16.0, 5.2, 2.6 Hz, 1H), 1.71 – 1.59 (m, 5H), 1.51 (q, *J* = 12.3 Hz, 1H), 0.76 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 178.0, 173.4, 136.1, 134.7, 132.2, 131.3, 129.5, 129.2, 82.2, 80.3, 65.8, 58.6, 58.4, 58.0, 52.9, 52.7, 38.3, 38.3, 35.6, 30.0, 23.9, 23.6, 22.2. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{31}NO_5Cl$ m/z 460.1885, found 460.1880. **IR** (film, cm^{-1}): 2934, 2854, 2247, 1760, 1491,

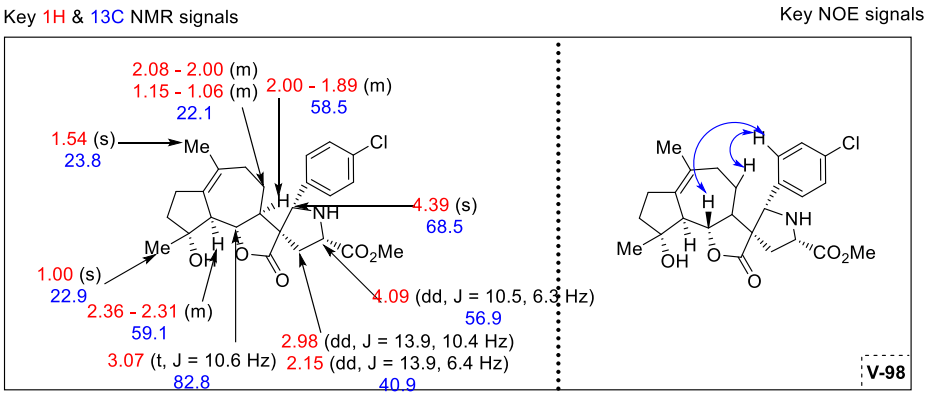
1436, 1376, 1316, 1202, 1181, 1136, 1111, 1091, 1074, 1014, 988, 909, 877, 825. **[α]D^{20}** = +46.9 (c = 0.13, $CHCl_3$)



Methyl (2'*R*,3*R*,3a*S*,5'*R*,9*R*,9a*S*,9b*S*)-2'-(4-chlorophenyl)-9-hydroxy-6,9-dimethyl-2-oxo-3a,4,5,7,8,9,9a,9b-octahydro-2*H*-spiro[azuleno[4,5-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-97)

The title product compound **V-97** was prepared using **Condition C** and isolated by column chromatography (2:1 *n*-pentane: EA) giving an amorphous solid (44.0 mg, 0.10 mmol, 96% yield).

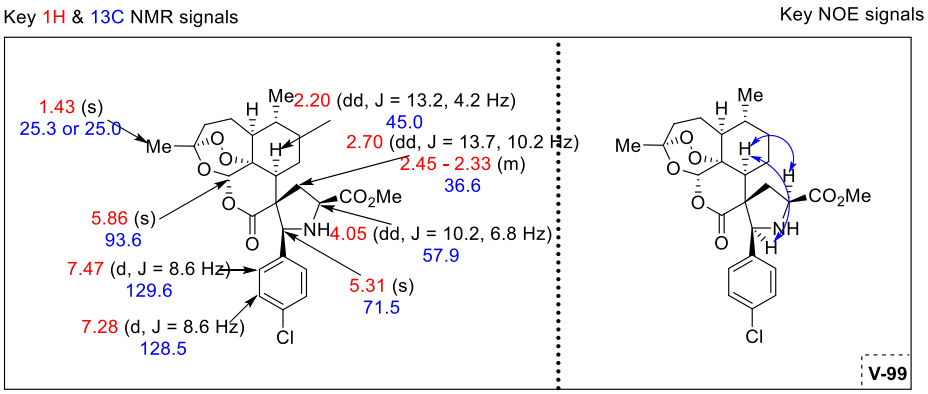
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 4.75 (s, 1H), 4.17 (dd, *J* = 9.1, 7.9 Hz, 1H), 3.80 – 3.76 (m, 4H), 2.41 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.35 (d, *J* = 10.6 Hz, 1H), 2.32 – 2.23 (m, 2H), 2.13 – 2.03 (m, 1H), 1.93 (ddd, *J* = 15.9, 5.4, 2.4 Hz, 1H), 1.72 – 1.54 (m, 7H), 1.52-1.46 (m, 1H), 1.25 (s, 3H), 1.13 – 1.01 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 179.1, 173.2, 137.4, 133.9, 131.9, 131.4, 128.8, 128.7, 82.7, 80.4, 67.1, 58.6, 57.3, 55.0, 52.4, 50.1, 38.5, 34.8, 32.0, 29.9, 24.4, 23.7, 23.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{31}NO_5Cl$ m/z 460.1885, found 460.1882. **IR** (film, cm^{-1}): 2924, 2349, 2117, 1744, 1490, 1437, 1376, 1303, 1212, 1172, 1137, 1088, 1013, 989, 910, 877, 835. **[α]D^{20}** = +25.6 (c = 0.20, $CHCl_3$)



Methyl (2'*S*,3*S*,3a*S*,5'*S*,9*R*,9a*S*,9b*S*)-2'-(4-chlorophenyl)-9-hydroxy-6,9-dimethyl-2-oxo-3a,4,5,7,8,9,9a,9b-octahydro-2*H*-spiro[azuleno[4,5-*b*]furan-3,3'-pyrrolidine]-5'-carboxylate (V-98)

The title product compound **V-98** was prepared using **Condition D** and isolated by column chromatography (1:1 *n*-pentane: EA) giving an amorphous solid (42.9 mg, 0.09 mmol, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 4.39 (s, 1H), 4.09 (dd, *J* = 10.5, 6.3 Hz, 1H), 3.80 (s, 3H), 3.07 (t, *J* = 10.6 Hz, 1H), 2.98 (dd, *J* = 13.9, 10.4 Hz, 1H), 2.36 – 2.31 (m, 1H), 2.24 (dd, *J* = 16.5, 7.8 Hz, 1H), 2.15 (dd, *J* = 13.9, 6.4 Hz, 1H), 2.08 – 1.89 (m, 4H), 1.82 (t, *J* = 13.2 Hz, 1H), 1.72 – 1.60 (m, 2H), 1.54 (s, 3H), 1.15 – 1.06 (m, 1H), 1.00 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 179.5, 173.4, 135.8, 134.0, 131.9, 131.3, 128.6, 128.5, 82.7, 80.4, 68.5, 59.1, 58.5, 56.9, 56.2, 52.5, 40.9, 38.5, 36.7, 29.8, 23.8, 22.9, 22.1. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{31}NO_5Cl$ m/z 460.1885, found 460.1880. **IR** (film, cm^{-1}): 2950, 1742, 1492, 1437, 1376, 1318, 1303, 1210, 1137, 1113, 1090, 1074, 1012, 987, 908, 883, 829. **$[\alpha]_D^{20}$** = +40.6 (c = 0.17, $CHCl_3$)



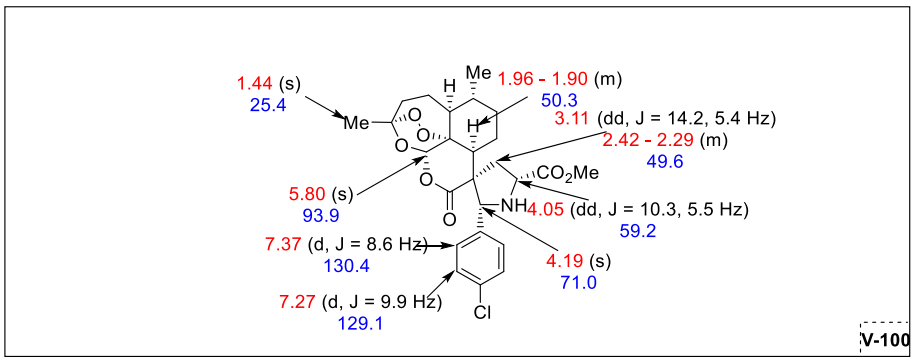
Methyl (2*S*,3*R*,3'*R*,5*S*,5a'*S*,6'*R*,8a'*S*,12'*S*,12a'*R*)-2-(4-chlorophenyl)-3',6'-dimethyl-10'-oxooctahydro-10'*H*,12'*H*-spiro[pyrrolidine-3,9'-[3,12]epoxy[1,2]dioxepino[4,3-*i*]isochromene]-5-carboxylate (V-99)

The title product compound **V-99** was prepared from substrate **V-75** (14.0 mg, 0.05 mmol) using **Condition A** and isolated by column chromatography (1:1 *n*-pentane: EA) giving an amorphous solid (13.3 mg, 0.03 mmol, 54% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 5.86 (s, 1H), 5.31 (s, 1H), 4.05 (dd, *J* = 10.2, 6.8 Hz, 1H), 3.83 (s, 3H), 2.70 (dd, *J* = 13.7, 10.2 Hz, 1H), 2.45 – 2.33 (m, 2H), 2.20 (dd, *J* = 13.2, 4.2 Hz, 1H), 2.09 – 1.98 (m, 3H), 1.85 – 1.78 (m,

1H), 1.56 – 1.48 (m, 2H), 1.43 (s, 3H), 1.41 – 1.36 (m, 1H), 1.27 – 1.22 (m, 1H), 1.21 – 1.14 (m, 1H), 1.01 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.2, 169.8, 138.7, 133.7, 129.6, 128.5, 105.5, 93.6, 80.6, 71.5, 57.9, 56.3, 53.0, 50.9, 45.0, 37.6, 36.6, 35.9, 34.0, 26.1, 25.3, 25.0, 20.0. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{31}NO_7Cl$ m/z 492.1784, found 492.1779. **IR** (film, cm^{-1}): 2926, 2112, 1733, 1633, 1494, 1437, 1377, 1205, 1154, 1138, 1110, 1091, 1052, 1035, 1011, 991, 971, 935, 880, 835.

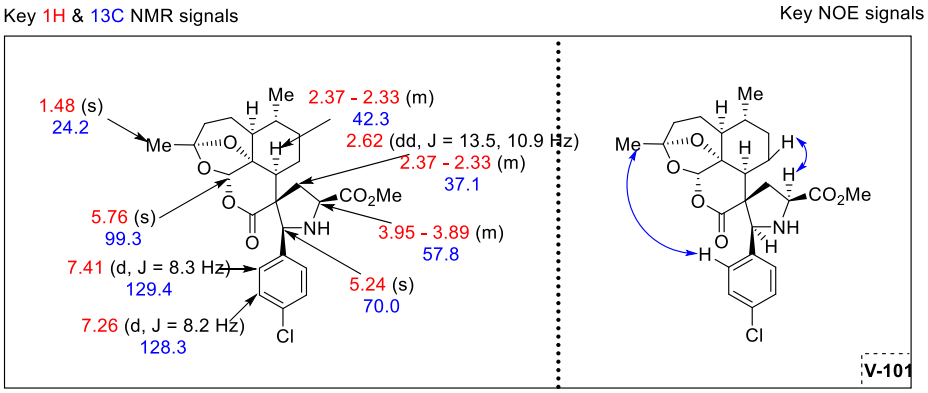
Key 1H & 13C NMR signals



Methyl (2*R*,3*S*,3'*R*,5*R*,5a'*S*,6'*R*,8a'*S*,12'*S*,12a'*R*)-2-(4-chlorophenyl)-3',6'-dimethyl-10'-oxooctahydro-10'*H*,12'*H*-spiro[pyrrolidine-3,9'-[3,12]epoxy[1,2]dioxepino[4,3-*i*]isochromene]-5-carboxylate (V-100)

The title product compound **V-100** was prepared from substrate **V-75** (14.0 mg, 0.05 mmol) using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (19.0 mg, 0.04 mmol, 77% yield).

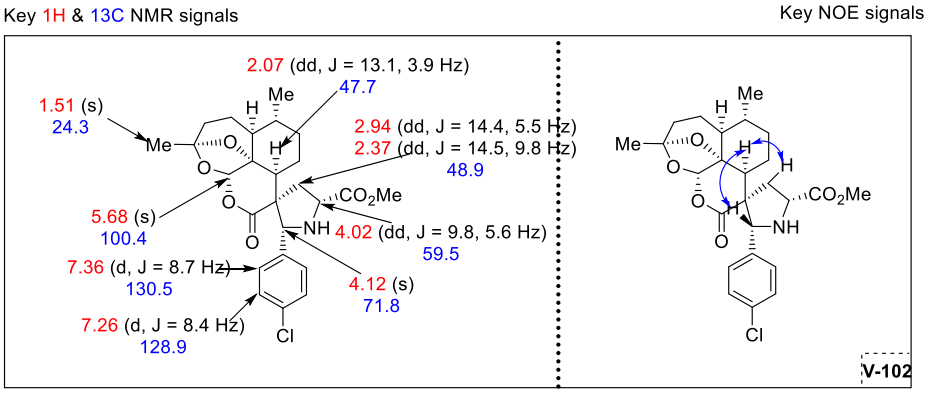
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 9.9 Hz, 2H), 5.80 (s, 1H), 4.19 (s, 1H), 4.05 (dd, *J* = 10.3, 5.5 Hz, 1H), 3.79 (s, 3H), 3.11 (dd, *J* = 14.2, 5.4 Hz, 1H), 2.42 – 2.29 (m, 2H), 2.06 – 2.00 (m, 1H), 1.96 – 1.90 (m, 2H), 1.86 – 1.81 (m, 1H), 1.67 – 1.63 (m, 1H), 1.45 – 1.37 (m, 5H), 1.25 (t, *J* = 7.2 Hz, 1H), 1.00 – 0.91 (m, 5H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.5, 172.7, 136.2, 134.3, 130.4, 129.1, 105.5, 93.9, 80.8, 71.0, 59.2, 53.2, 52.6, 50.3, 50.3, 49.6, 37.4, 36.0, 34.3, 27.3, 25.4, 25.0, 19.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{31}NO_7Cl$ m/z 492.1784, found 492.1779. **IR** (film, cm^{-1}): 2952, 1737, 1492, 1435, 1379, 1322, 1200, 1153, 1110, 1032, 1013, 992, 958, 908, 879, 832. **$[\alpha]_D^{20}$** = +52.0 (c = 0.13, $CHCl_3$)



Methyl (2*S*,3*R*,3a'*S*,3a^1'*R*,5*S*,6'*R*,6a'*S*,9'*S*,10a'*S*)-2-(4-chlorophenyl)-6',9'-dimethyl-2'-oxooctahydro-2'*H*,10a'*H*-spiro[pyrrolidine-3,3'-[3a^1,9]epoxyoxepino[4,3,2-*iJ*]isochromene]-5-carboxylate (V-101)

The title product compound **V-101** was prepared from substrate **V-77** (13.2 mg, 0.05 mmol) using **Condition A** and isolated by column chromatography (1:1 *n*-pentane: EA) giving an amorphous solid (12.8 mg, 0.03 mmol, 54% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 5.76 (s, 1H), 5.24 (s, 1H), 3.95 – 3.89 (m, 1H), 3.81 (s, 3H), 2.62 (dd, *J* = 13.5, 10.9 Hz, 1H), 2.37 – 2.33 (m, 2H), 2.09 – 2.01 (m, 1H), 1.94 (dt, *J* = 13.6, 5.1 Hz, 1H), 1.86 (dt, *J* = 9.9, 3.5 Hz, 1H), 1.77 – 1.71 (m, 1H), 1.63 (ddd, *J* = 13.6, 11.5, 5.7 Hz, 1H), 1.48 (s, 3H), 1.43 – 1.36 (m, 1H), 1.33 – 1.26 (m, 3H), 1.21 – 1.14 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.1, 169.2, 140.5, 133.3, 129.4, 128.3, 110.3, 99.3, 83.1, 70.0, 57.8, 56.0, 52.7, 45.4, 42.3, 37.1, 35.7, 34.1, 34.0, 26.5, 24.2, 22.4, 18.9. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{31}NO_6Cl$ m/z 476.1834, found 476.1829. **IR** (film, cm^{-1}): 2924, 1733, 1493, 1437, 1387, 1281, 1209, 1189, 1153, 1124, 1092, 1019, 1004, 974, 939, 883, 856. **$[\alpha]_D^{20}$** = -123.7 (c = 0.14, $CHCl_3$)

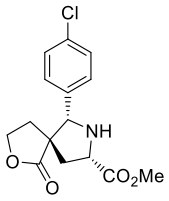


Methyl (2*R*,3*S*,3a'*S*,3a^1'*R*,5*R*,6'*R*,6a'*S*,9'*S*,10a'*S*)-2-(4-chlorophenyl)-6',9'-dimethyl-2'-oxooctahydro-2'*H*,10a'*H*-spiro[pyrrolidine-3,3'-[3a^1,9]epoxyoxepino[4,3,2-*iJ*]isochromene]-5-carboxylate (V-102)

The title product compound **V-102** was prepared from substrate **V-77** (13.2 mg, 0.05 mmol) using **Condition B** and isolated by column chromatography (1:2 *n*-pentane: EA) giving an amorphous solid (16.6 mg, 0.03 mmol, 70% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 5.68 (s, 1H), 4.12 (s, 1H), 4.02 (dd, *J* = 9.8, 5.6 Hz, 1H), 3.78 (s, 3H), 2.94 (dd, *J* = 14.4, 5.5 Hz, 1H), 2.37 (dd, *J* = 14.5, 9.8 Hz, 1H), 2.07 (dd, *J* = 13.1, 3.9 Hz, 1H), 1.91 – 1.83 (m, 1H), 1.83 – 1.76 (m, 1H), 1.76 – 1.64 (m, 2H), 1.64 – 1.54 (m, 1H), 1.51 (s, 3H), 1.26 – 1.14 (m, 6H), 1.06 – 0.92 (m, 2H), 0.88 (d, *J*=6.2 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.6, 172.9, 136.6, 134.2, 130.5, 128.9, 110.3, 100.4, 82.7, 71.8, 59.5, 53.0, 52.6, 48.9, 47.7, 44.7, 35.5, 34.3, 33.7, 27.9, 24.3, 22.4, 18.7. **HRMS(ESI):** $[M+H]^+$ calcd. $C_{25}H_{31}NO_6Cl$ m/z 476.1834, found 476.1829. **IR** (film, cm^{-1}): 2924, 2853, 1738, 1492, 1435, 1388, 1323, 1267, 1209, 1180, 1146, 1130, 1095, 1068, 1011, 983, 944, 886, 855, 822. **$[\alpha]_D^{20}$** = -54.5 (c = 0.11, $CHCl_3$)

Methyl (5*R*,6*S*,8*S*)-6-(4-chlorophenyl)-1-oxo-2-oxa-7-azaspiro[4.4]nonane-8-carboxylate (V-103)

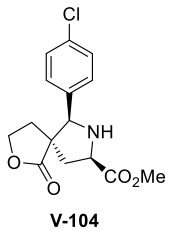


V-103

The title product compound **V-103** was prepared using **Condition A** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (27.5 mg, 0.09 mmol, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 4H), 4.19 (s, 1H), 4.09 (tt, *J* = 8.0, 4.0 Hz, 2H), 3.83 (s, 3H), 3.61 (td, *J* = 9.5, 7.0 Hz, 1H), 2.70 (dd, *J* = 13.4, 5.1 Hz, 1H), 2.46 (dt, *J* = 13.3, 9.4 Hz, 1H), 2.33 (ddd, *J* = 15.6, 8.3, 3.9 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 178.4, 173.2, 135.3, 135.0, 129.3, 128.8, 72.4, 65.4, 59.0, 53.7, 52.7, 40.3, 33.2. **$[\alpha]_D^{20}$** = +16.1 (c = 0.83, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 24.9 min; minor enantiomer: t_R = 41.5 min. *ee* = 96%.

Methyl (5*S*,6*R*,8*R*)-6-(4-chlorophenyl)-1-oxo-2-oxa-7-azaspiro[4.4]nonane-8-carboxylate (V-104)

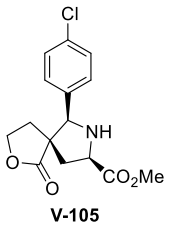


V-104

The title product compound **V-104** was prepared using **Condition B** and isolated by column chromatography (20:1 DCM: MeOH) giving an amorphous solid (27.9 mg, 0.09 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 4H), 4.19 (s, 1H), 4.09 (tt, *J* = 8.0, 4.0 Hz, 2H), 3.83 (s, 3H), 3.61 (td, *J* = 9.5, 7.0 Hz, 1H), 2.70 (dd, *J* = 13.4, 5.1 Hz, 1H), 2.46 (dt, *J* = 13.3, 9.4 Hz, 1H), 2.33 (ddd, *J* = 15.6, 8.3, 3.9 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 178.4, 173.2, 135.3, 135.0, 129.3, 128.8, 72.4, 65.4, 59.0, 53.7, 52.7, 40.3, 33.2. **$[\alpha]_D^{20}$** = -13.5 (c = 0.73, CH_2Cl_2). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 40.9 min; minor enantiomer: t_R = 25.6 min. *ee* = 95%.

Methyl (5*R*,6*R*,8*R*)-6-(4-chlorophenyl)-1-oxo-2-oxa-7-azaspiro[4.4]nonane-8-carboxylate (V-105)

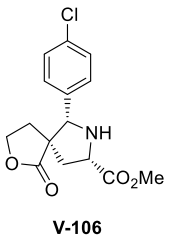


V-105

The title product compound **V-105** was prepared using **Condition C** and isolated by column chromatography (1:2 *n*-pentane: EA) giving an amorphous solid (25.1 mg, 0.08 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 4H), 4.61 (s, 1H), 4.15 (dd, *J* = 10.0, 4.7 Hz, 1H), 4.06 – 3.95 (m, 1H), 3.79 (s, 3H), 3.37 (ddd, *J* = 8.8, 7.9, 6.5 Hz, 1H), 2.76 (dd, *J* = 13.3, 10.0 Hz, 1H), 2.26 (dd, *J* = 13.3, 4.7 Hz, 1H), 2.06 (ddd, *J* = 13.7, 7.9, 5.9 Hz, 1H), 1.90 (ddd, *J* = 13.4, 8.1, 6.5 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 179.8, 174.1, 136.3, 134.3, 128.9, 128.5, 68.0, 66.0, 57.2, 52.7, 52.5, 40.6, 31.0. **$[\alpha]_D^{20}$** = +20.6 (c = 0.16, $CHCl_3$). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 24.4 min; minor enantiomer: t_R = 28.6 min. *ee* = 97%.

Methyl (5*S*,6*S*,8*S*)-6-(4-chlorophenyl)-1-oxo-2-oxa-7-azaspiro[4.4]nonane-8-carboxylate (V-106)



V-106

The title product compound **V-106** was prepared using **Condition D** and isolated by column chromatography (1:2 *n*-pentane: EA) giving an amorphous solid (24.2 mg, 0.08 mmol, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 4H), 4.61 (s, 1H), 4.15 (dd, *J* =

10.0, 4.7 Hz, 1H), 4.06 – 3.95 (m, 1H), 3.79 (s, 3H), 3.37 (ddd, *J* = 8.8, 7.9, 6.5 Hz, 1H), 2.76 (dd, *J* = 13.3, 10.0 Hz, 1H), 2.26 (dd, *J* = 13.3, 4.7 Hz, 1H), 2.06 (ddd, *J* = 13.7, 7.9, 5.9 Hz, 1H), 1.90 (ddd, *J* = 13.4, 8.1, 6.5 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 179.8, 174.1, 136.3, 134.3, 128.9, 128.5, 68.0, 66.0, 57.2, 52.7, 52.5, 40.6, 31.0. **$[\alpha]_D^{20}$** = -33.2 (c = 0.19, $CHCl_3$). **HPLC conditions**: CHIRAPAK IC column, *iso*-propanol / *iso*-hexane = 40/60, flow rate = 0.5 mL min^{-1}, major enantiomer: t_R = 24.3 min; minor enantiomer: t_R = 28.8 min. *ee* = 98%.

7.4.4 X-ray crystallographic data of V-63b-Ts, V-64f and V-66e (by Dr. Otte and Prof. Dr. Strohmann)

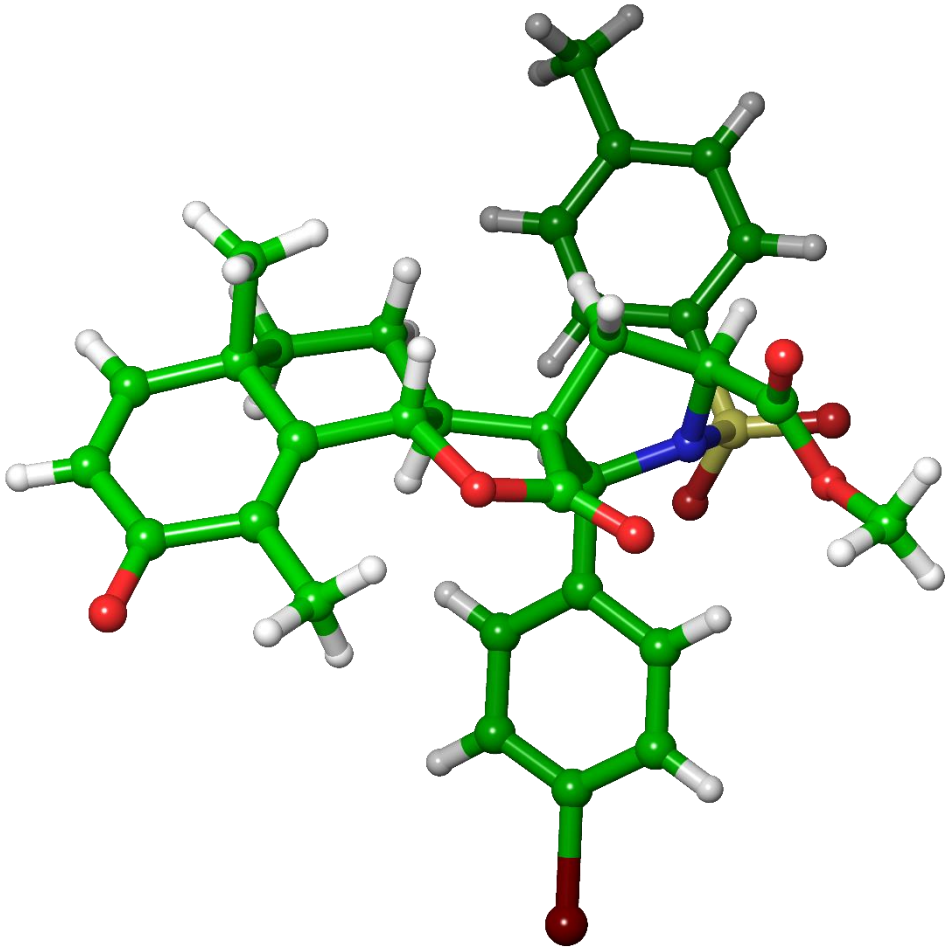


Figure S5. Crystal structure of the Ts protected cycloadduct **V-63b-Ts**. ORTEP plot of C32H32BrNO7S (M =654.55 g/mol) at the 50% probability level. See Supplementary Table S5 for additional details. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC 2055830.

Table S5. Crystal data and structure refinement for **V-63b-Ts**.

Empirical formula	$C_{32}H_{32}BrNO_7S$
Formula weight	654.55
Temperature/K	100.0
Crystal system	hexagonal
Space group	$P6_1$
a/Å	16.1442(17)
b/Å	16.1442(17)
c/Å	22.1544(15)
α/°	90
β/°	90
γ/°	120
Volume/Å^3	5000.6(11)
Z	6
ρ_{calc}g/cm^3	1.304
μ/mm^{-1}	1.340
F(000)	2028.0
Crystal size/mm^3	0.436 × 0.239 × 0.132
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.828 to 57.994
Index ranges	$-22 \leq h \leq 22$, $-22 \leq k \leq 21$, $-30 \leq l \leq 29$
Reflections collected	50608
Independent reflections	8817 [R_{int} = 0.0389, R_{sigma} = 0.0439]
Data/restraints/parameters	8817/1/383
Goodness-of-fit on F^2	1.035
Final R indexes [I>=2σ (I)]	R_1 = 0.0374, wR_2 = 0.0978
Final R indexes [all data]	R_1 = 0.0408, wR_2 = 0.0999
Largest diff. peak/hole / e Å^{-3}	0.39/-0.30
Flack parameter	0.022(3)

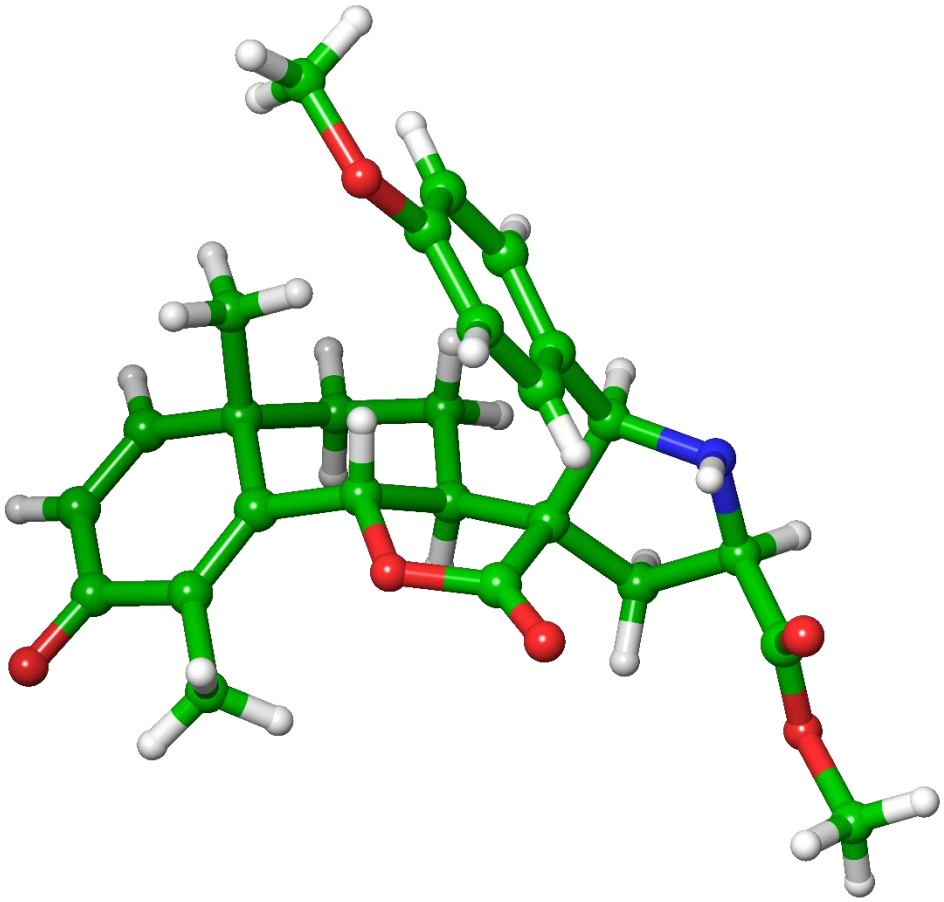


Figure S6. Crystal structure of the cycloadduct **V-64f**. ORTEP plot of C26H29NO6 (M =451.50 g/mol) at the 50% probability level. See Supplementary Table S6 for additional details. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC 2055829.

Table S6. Crystal data and structure refinement for **V-64f**.

Empirical formula	$C_{26}H_{29}NO_6$
Formula weight	451.50
Temperature/K	100.0
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	6.38220(10)
b/Å	12.9293(3)
c/Å	27.4615(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2266.05(8)
Z	4
ρ_{calc}g/cm^3	1.323
μ/mm^{-1}	0.768
F(000)	960.0
Crystal size/mm^3	0.678 × 0.048 × 0.04
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.436 to 159.68
Index ranges	$-8 \leq h \leq 8$, $-16 \leq k \leq 16$, $-35 \leq l \leq 33$
Reflections collected	75692
Independent reflections	4876 [R_{int} = 0.0279, R_{sigma} = 0.0091]
Data/restraints/parameters	4876/0/306
Goodness-of-fit on F^2	1.058
Final R indexes [I>=2σ (I)]	R_1 = 0.0270, wR_2 = 0.0718
Final R indexes [all data]	R_1 = 0.0272, wR_2 = 0.0721
Largest diff. peak/hole / e Å^{-3}	0.21/-0.17
Flack parameter	-0.02(3)

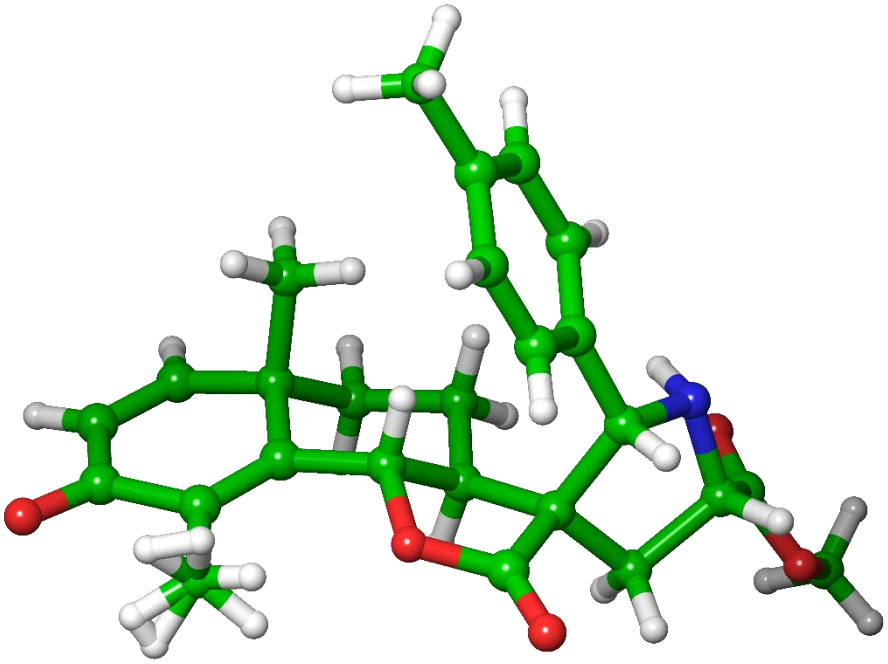


Figure S7. Crystal structure of the cycloadduct **V-66e**. ORTEP plot of C26H29NO5 (M =435.50 g/mol) at the 50% probability level. See Supplementary Table S7 for additional details. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC 2055831.

Table S7. Crystal data and structure refinement for **V-66e**.

Empirical formula	$C_{26}H_{29}NO_5$
Formula weight	435.50
Temperature/K	100.0
Crystal system	hexagonal
Space group	$P6_1$
a/Å	11.5596(2)
b/Å	11.5596(2)
c/Å	27.5631(6)
α/°	90
β/°	90
γ/°	120
Volume/Å^3	3189.66(13)
Z	6
ρ_{calc}g/cm^3	1.360
μ/mm^{-1}	0.762
F(000)	1392.0
Crystal size/mm^3	0.738 × 0.161 × 0.108
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	8.832 to 159.24
Index ranges	$-14 \leq h \leq 14$, $-14 \leq k \leq 14$, $-30 \leq l \leq 34$
Reflections collected	113217
Independent reflections	4514 [R_{int} = 0.0229, R_{sigma} = 0.0070]
Data/restraints/parameters	4514/1/310
Goodness-of-fit on F^2	1.038
Final R indexes [I>=2σ (I)]	R_1 = 0.0245, wR_2 = 0.0647
Final R indexes [all data]	R_1 = 0.0245, wR_2 = 0.0647
Largest diff. peak/hole / e Å^{-3}	0.18/-0.17
Flack parameter	-0.05(4)

7.4.5 Cell painting datasets of pseudo sesquiterpenoid alkaloids

No.	**Induction @ 10 µM**	**Induction @ 30 µM**	**Induction @ 50 µM**	*No.*	**Induction @ 10 µM**	**Induction @ 30 µM**	**Induction @ 50 µM**
V-61	36.6	94.8	95.0	**V-56**	44.4	94.5	n.d.
V-68	89.6	95.5	92.4	**V-57**	14.2	70.6	93.6
V-70	41.8	92.1	94.6	**V-75**	53.7	95.3	94.1
V-71	13.5	29.7	18.7	**V-77**	19.7	44.0	34.9
V-73	58.5	92.4	73.1				
V-63a	0.2	9.5	11.9	**V-63i**	0.3	1.4	7.1
V-63b	0.0	9.3	10.7	**V-63j**	0.0	25.9	25.0
V-63c	0.0	0.9	2.1	**V-63k**	0.0	1.6	16.1
V-63d	0.3	14.3	10.7	**V-63l**	0.0	6.9	1.4
V-63e	0.0	0.2	0.3	**V-63m**	0.0	1.4	12.3
V-63f	0.2	11.1	3.3	**V-63n**	0.3	2.4	2.8
V-63g	0.0	1.0	10.4	**V-63o**	0.0	3.3	2.1
V-63h	0.0	2.6	1.7	**V-63p**	0.0	3.3	1.7
V-64a	1.6	2.6	15.0	**V-64i**	1.0	36.1	25.2
V-64b	0.7	2.6	4.1	**V-64j**	0.9	12.4	35.2
V-64c	4.7	0.3	4.8	**V-64k**	0.3	3.1	6.4
V-64d	0.5	0.3	2.1	**V-64l**	1.0	6.6	8.3
V-64e	1.4	11.1	7.1	**V-64m**	0.3	0.9	3.5
V-64f	n.d.	n.d.	n.d.	**V-64n**	0.9	5.7	8.3
V-64g	0.3	0.7	0.3	**V-64o**	0.7	1.2	6.2
V-64h	n.d.	n.d.	n.d.	**V-64p**	0.2	2.8	10.2
V-65a	0.2	3.5	2.4	**V-65i**	0.5	3.8	11.4
V-65b	1.0	16.6	16.6	**V-65j**	0.2	14.5	8.5
V-65c	0.0	0.3	2.4	**V-65k**	0.5	18.8	6.2
V-65d	0.3	3.3	6.9	**V-65l**	0.0	0.7	3.8
V-65e	0.0	0.9	4.5	**V-65p**	0.0	0.7	0.3
V-65f	0.5	8.5	5.9				
V-65g	0.0	3.3	6.7				
V-65h	0.3	2.1	0.7				

No.	**Induction @ 10 µM**	**Induction @ 30 µM**	**Induction @ 50 µM**	***No.***	**Induction @ 10 µM**	**Induction @ 30 µM**	**Induction @ 50 µM**
V-66a	n.d.	n.d.	n.d.	**V-66i**	n.d.	n.d.	n.d.
V-66b	0.9	2.9	16.6	**V-66j**	3.3	7.3	25.9
V-66c	0.0	0.2	0.7	**V-66k**	0.7	5.7	12.3
V-66d	0.7	14.5	18.1	**V-66l**	0.5	0.7	4.1
V-66e	1.4	3.8	8.6	**V-66m**	0.0	2.1	6.7
V-66f	0.3	0.3	1.6	**V-66n**	0.3	4.1	6.7
V-66g	0.3	1.7	0.9	**V-66o**	0.3	0.5	1.9
V-66h	0.5	0.0	1.6	**V-66p**	0.2	0.0	1.2
V-79	0.9	6.9	24.5	**V-94**	0.3	1.4	10.2
V-80	0.3	3.6	21.1	**V-95**	0.7	16.6	22.5
V-81	6.4	22.8	39.7	**V-96**	0.2	1.9	2.8
V-82	5.0	42.1	64.1	**V-97**	0.3	0.2	1.6
V-83	4.8	11.7	12.3	**V-98**	0.0	5.4	0.7
V-84	1.7	23.3	30.6	**V-99**	0.3	n.d.	n.d.
V-85	7.8	26.9	28.0	**V-100**	0.0	26.4	20.4
V-86	7.8	30.1	35.4	**V-101**	1.0	10.0	3.6
V-87	1.4	12.1	13.1	**V-102**	0.0	2.9	11.7
V-88	0.5	5.2	14.2	**V-103**	0.0	0.0	0.7
V-89	2.8	5.7	10.9	**V-104**	0.0	0.0	0.3
V-90	14.5	13.0	15.5	**V-105**	0.3	0.9	0.0
V-91	1.2	15.9	22.3	**V-106**	0.0	0.2	0.0
V-92	1.9	3.1	14.9				
V-93	0.0	0.5	1.4				

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9. Appendix

9.1 Abbrevations

Ac	Acyl
Ar	Aryl
Boc	*tert*-butoxycarbonyl
Bn	Benzyl
BIOS	Biology-oreinted synthesis
Bu	Butyl
Calcd.	Calculated
cat	catalyst
$CDCl_3$	Deuterated chloroform
CETSA	Cellular thermal shift assay
$CHCl_3$	Chloroform
COMAS	Compound management and screening center
Cp*	Pentamethylcyclopentadienyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DG	Directing group
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DMP	Dess–Martin periodinane
d.r.	diastereomeric ratio
ee	enantiomeric ratio
equiv.	equivalent
Et_2O	Diethyl ether
Et	Ethyl
Et_3N	Triethylamine
FOS	Function-oriented synthesis
HMBC	Heteronuclear Multiple Bond Correlation
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy

HSQC	Heteronuclear Single Quantum Coherence
IC_{50}	Half maximal inhibitory concentration
*i*Pr	isopropyl
J	Coupling constant
LUMO	Lowest unoccupied molecular orbital
M	Metal
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
MHz	Megahertz
MoA	Mechanism of action
Ms	Mesyl
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NPs	Natural products
n.r.	no reaction
n.s.	enantiomers cannot be seperated by chiral HPLC
Ph	Phenyl
Piv	Pivaloyl
r.t.	room temperature
SILAC	Stable isotope labelling of amino acids in cell culture
T	Temperature
t-Bu	tert-Butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	Tosyl

9.2 Acknowledgement

Finally, it comes to the end of my PhD.

I would like to express my biggest and most honest gratefulness to Prof. Dr. Dr. h.c. Herbert Waldmann. Thank you for giving me the opportunity to work in the frontier of chemical biology research, and also giving me the great freedom to explore the unknown space in pseudo natural products on this excellent platform. You are a great supervisor, scientist and leader. Your wise comments constantly inspire my research work and shape my scientific thoughts. Under your supervision, I started to think some fundamental questions, such as what I wanted to do, what I could do and what I should do. And at last, my curiosity, capability and responsibility were perfectly united in my PhD projects. You set a great role model for me to bridge the gap between chemistry and biology. I often lament my littleness before your broad and deep knowledge of general chemistry. In the face of the Covid-19 pandemic, your excellent and efficient management created a safe and warm environment for us to continue the research. Your art of management enables a productive group. Thank you very much.

Thank Dr. Andreas Brunschweiger for being my second examiner of my PhD thesis. Thank Dr. Michael Grigalunas for proof reading this dissertation.

Thank my kind collaborators for their contributions in my research work. Thank my hardworking students, Timo Schönig, Denise Zickler, Benedikt Rothkegel, Noemi Ezinne Nwosu and Alexander Kartheiser. I still remember those funny moments of my poor English. Thank you all for the understanding and efficient cooperation. Thank Dr. Gregor Cremosnik. If without you, the pyrroquinoline project could not be ended so fast. I am very grateful to your suggestions and comments in my manuscript writing. Thank Dr. Yusheng Xie. Your helpful work in the Rh(III)-catalysis speeded up our work. Thank Jana Flegel for taking care of my compounds and validating the results of Hedgehog inhibitory assays.

Thank COMAS team (Dr. Sonja Sievers and Dr. Axel Paul) for the screening and analysis of my compounds. Thank HRMS team (Dr. Petra Janning and Christiane Heitbrink) for testing my molecules. Thank X-ray team (Prof. Dr. Carsten Strohmann, Dr. Felix Otte) for the unambiguous confirmation of the molecular structures.

Thank Dr. Andrey Antonchick for the kind and insightful suggestions in my chemistry. Thank my friendly colleagues Okan Yildirim, Mahesh Puthanveedu, Vasiliki Polychronidou, Chun-ngai Hui, Dr. Saad Shaaban, Dr. Sukdev Bag, Dr. Lin Wang, Aylin Binici, Dr. Sohan Patil, Dr. Yenchun Lee and Dr. Houhua Li for your kind help. Thank Svetlana Gerdt and Brigitte Rose for your helping hands in daily affairs. Thank Dr. Peng Wu, Dr. Zhijun Jia, Dr. Xin Han for your kind comments on my career plans.

Thank Prof. Dr. Dawei Ma for giving me a systematic training of organic synthesis during my master period. If without the solid background in chemistry, I would not work so efficiently in Dortmund. And your research philosophy still inspires my current work. Thank my bachelor teacher Prof. Dr. Haibing Zhou and Prof. Dr. Yuxiu Xiao for your strong support in my study.

Last but not least, thank my parents and sister for your tremendous support and encouragement in my pursuit of the doctorate. I am forever indebted to my family. If without you, I would have gone to a factory to make a living after high school like many of my classmates. Thank my girlfriend, Miss Tang. Your warm words and sweet smiles help me overcome all the obstacles in front of me.

Studying in Dortmund is one of my life-changing decisions. To everyone who has helped me along the way, thank you. If without you, I will not be here.

9.3 Eidesstattliche Versicherung (Affidavit)

Eidesstattliche Versicherung (Affidavit)

Liu, Jie
Name, Vorname
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Matrikel-Nr.
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9.4 Curriculum vitae

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[6]. **J. Liu**, J. Flegel, F. Otte, A. Pahl, S. Sievers, C. Strohmann, H. Waldmann, Combination of pseudo-natural product design and formal natural product ring distortion yields stereochemically and biologically diverse pseudo-sesquiterpenoid alkaloids, *Angew. Chemie. Int. Ed.* **2021**, 10.1002/anie.202106654.

[5]. **J. Liu**, F. Otte, C. Strohmann, H. Waldmann, Enantioselective synthesis of pyrro[3,4-*c*]quinoline pseudo-natural products, *Tetrahedron Lett.* **2021**, *76*, 153228-153231.

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[3]. G. S. Cremosnik†, **J. Liu**†, H. Waldmann, Guided by evolution: from biology oriented synthesis to pseudo natural products, *Nat. Prod. Rep.* **2020**, *37*, 1497-1510.

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04/2021	14. Tag der Chemie of TU-Dortmund (online) Oral presentation: Combination of natural product ring distortion and pseudo-natural product design yields stereochemically and biologically diverse pseudo sesquiterpenoid alkaloids
12/2020	Soochow University's Dongwu Forum for Overseas High-level Talents (online) Oral presentation: Natural products: Total synthesis, library construction and biological study
12/2020	9th East Lake International Forum for Outstanding Overseas Young Scholars (online) Oral presentation: From total synthesis of natural products to collective synthesis of pseudo natural products

Honors and Awards

2014	Outstanding graduate, Wuhan University
2013	Lei Jun Scholarship
2012	Merck Serono Chinese Elite Scholarship
2011	2011 National Scholarship

9.5 Pursuit of my doctorate