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mpi

Development of Cascade Reactions to Ring-Fused Quinolizines for the Synthesis of a Natural Product-Inspired Compound Collection

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1. General Introduction

Chemical biology research dissects different biological phenomena with small molecules. In the corresponding forward chemical genetics approach,[1,2] changes in phenotype upon compound treatment are recorded, and biologically active molecules are used as chemical probes to identify and validate the target proteins associated with the observed phenotype. In reverse chemical genetics on the other hand, high-throughput screening of large compound collections against a known biological target is employed (Figure 1), and the hits are then investigated in biological systems.[3]

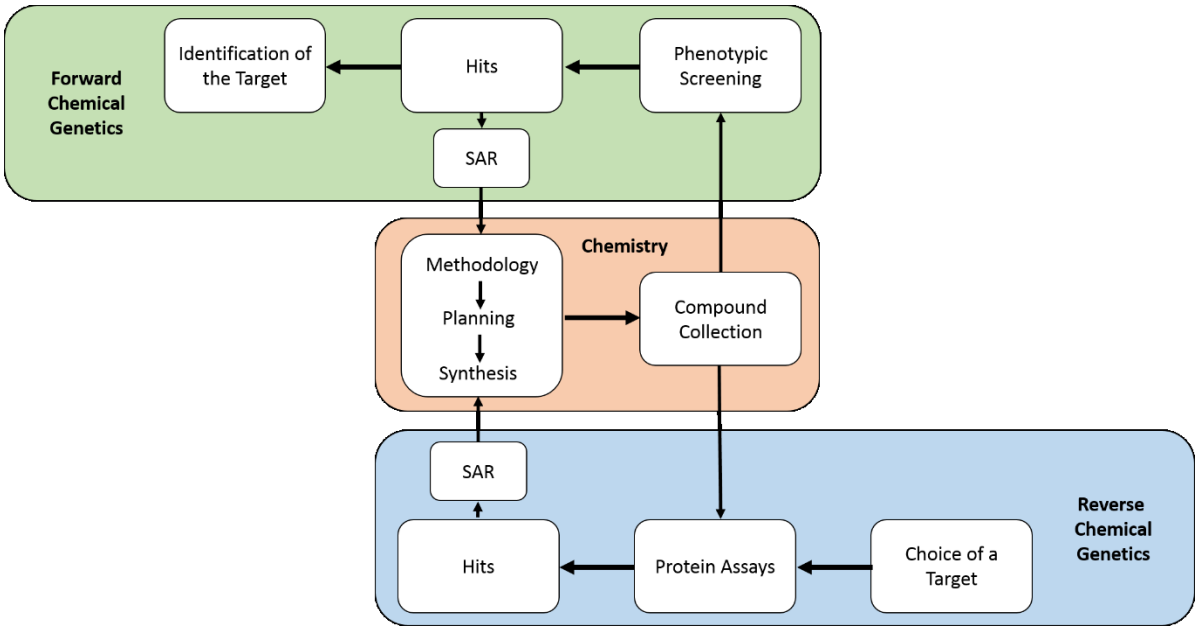

Figure 1: Forward and reverse chemical genetics. SAR: Structure-Activity Relationship.

Novel biologically active small molecules are key to investigate different biological processes and to gain better understanding of their role in diseases and for the development of possible therapeutics.[4] In the absence of a specific protein target in a forward chemical

genetics exploration, the development of new biologically relevant small molecules in principle can target any synthetically accessible compound. However, practically, it is impossible to synthesize all the possible small molecules, even by keeping limits in molecular properties depicted by the Lipinski rule of five.[5,6] Alternatively, targeting biologically relevant chemical architectures derived from natural products or drug molecules might provide higher chances to identify potent active molecules that can be developed into chemical probes for chemical biology research as well as into candidates for medicinal chemistry investigations.[7]

Natural products represent only a small fraction of the chemical space representing all the energetically stable compounds, but more than half of the existing drugs[8,9] are either directly derived from them or have natural products as starting points. Many natural products show multiple activities against a spectrum of targets, and therefore the exploration of the chemical space around these inherently active molecules is highly desirable to find candidates with better activity for a given target. Owing to their biosynthetic origins, natural products have evolved to interact with biomolecules and interestingly, unlike combinatorial compound collections, posess important properties, like solubility and membrane permeability.[10,11] While the core-structures of natural products play a key role in the interactions with biological targets, these scaffolds can be used as templates to build up natural product inspired libraries. In contrast to the total synthesis of natural products that provides only few molecules in a highly tedious synthetic design for further studies, natural products inspired compound collection synthesis targets synthetic access to numerous compound for the discovery of new active molecules.[12] Thus, synthetic designs leading to compound collections inspired from natural products retain the main structure of the natural product of interest and build up a library by possible modifications and decorations with various functional and appending moieties on the periphery of the core-framework.[13,14] These libraries are highly useful sources of chemical probes for chemical biology research and novel structures for drug discovery and may provide hit rates 10 to 100 fold higher than libraries generated on the basis of chemical feasibility.[15,16] In many cases, natural product inspired molecules surpass the efficiency and selectivities of the parent natural products and exhibit lower toxicity .

The structural complexity and diversity of these natural products and thereby natural product based compound collections, calls for the development of efficient synthesis methods that provide concise and stereoselective syntheses amenable to construct numerous complex compounds in the most straightforward way. With this in mind, concepts like atom[17,18] and step economy[19] are important to design a pathway that builds up varying structural complexity.

This work describes the development and the optimization of such a natural product-inspired compound collection with two different synthesis strategies. In chapter 2, the investigations about the mechanism and the scope of the synthesis of indoloquinolizines by an unprecedented 12-step cascade reaction are described. Then, the development of an asymmetric inverse electron demand imino Diels-Alder (IEDIDA) reaction as an alternative synthesis of the indoloquinolizines is detailed in chapter 3. Finally in chapter 4, the scope of the IEDIDA reaction is studied, and the biological activity of the natural product-inspired compound collection is evaluated in an phenotypic screening.

2. Cascade Synthesis Routes to Centrocountins

Chapter relating to: Cascade Synthesis Routes to the Centrocountins

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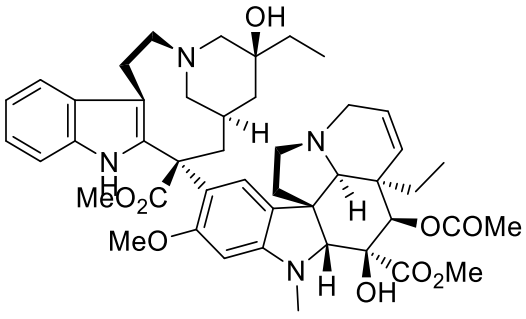
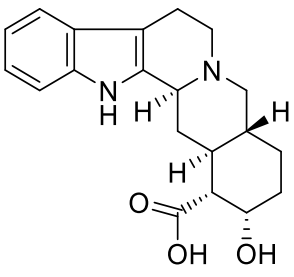
Chem. Eur. J. ***2013****, 19, 2294 – 2304.*

2.1. Introduction

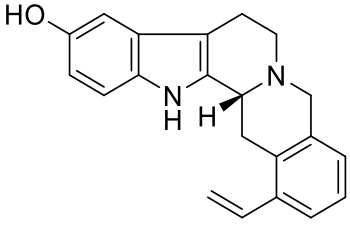
The indole ring system represents one of the most abundant and important heterocycles in nature.[20] It is found in a diverse group of biologically relevant natural compounds, from very simple neurotransmitters like serotonin, to complex alkaloids used as anticancer agents like vinblastine **1**. Furthermore, polycyclic indole alkaloids are potent modulators of the mitotic cycle. Indoloquinolizines like vinblastin **1**, yohimbin **2** or 10-hydroxyaugustin **3** are interesting molecules for the study of mitosis and therefore potential anticancer drugs[21–26] (Figure 2).



Vinblastin **1**
antimitotic, anticancer drug



Yohimbin **2**
stimulant
anticancer agent



10-Hydroxyaugustine **3**
cytotoxic to human T14
bladder-cancer cells

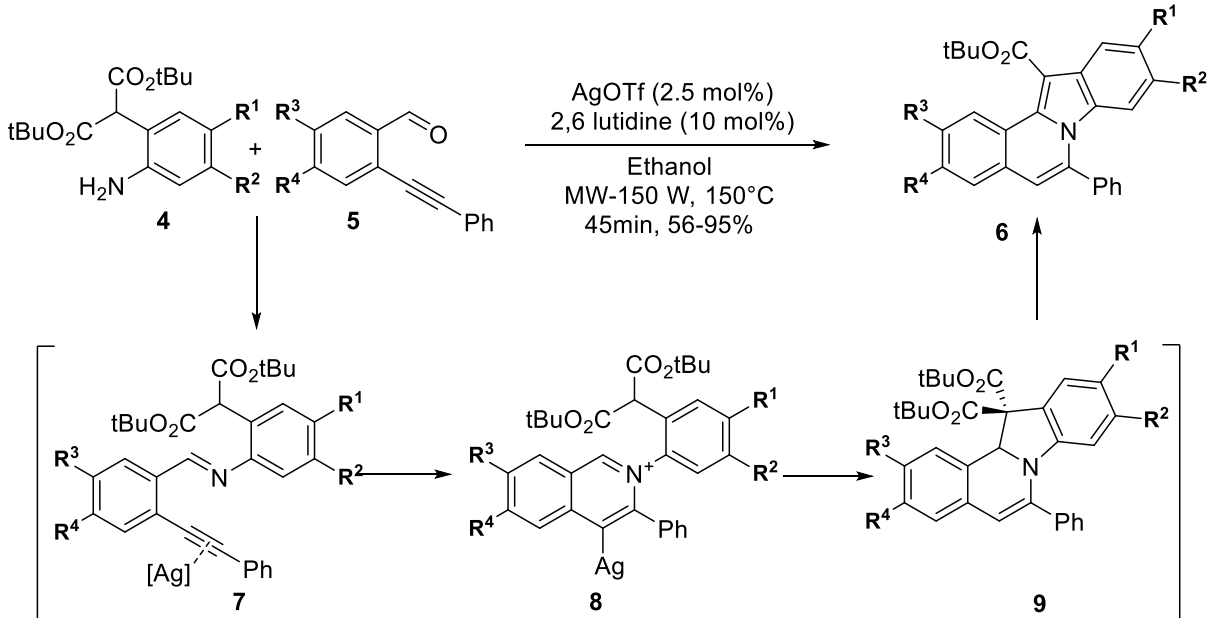
Figure 2: Structures of representative polycyclic indole alkaloids related to mitosis and cancer.

2.1.1. Domino or Cascade Reactions in Organic Synthesis

Building molecules of varying complexity is a unique ability and characteristic of organic synthesis. Despite major developments made in this field of science, the synthesis of small molecules with desired functional decorations remains a major challenge. Long and multistep synthesis routes are often unavoidable to synthesize complex molecules containing for instance, many stereogenic centres.[27]

Cascade or domino reactions, wherein several reactions proceed are viable alternatives to multistep sequences to synthesize structurally diverse and complex compound collections[28,29] and, therefore, strategies based on these reactions are highly desired. In recent years, various domino- and one-pot multi-component reaction strategies yielding various classes of molecules were developed,[30] but there is still a lot to be achieved in this field, for instance asymmetric construction of complex molecules decorated with stereogenic centers. The development of robust, scalable, economical, and stereoselective domino or cascade reactions that are also amenable to compound library synthesis is a formidable challenge. Chirality of the products is an important factor that determines the biological effects of a molecule.[31–33] Therefore enantioselective and diastereoselective cascade reactions are of particular interest in this area. Notably unlike multistep syntheses that often employ protection and deprotection steps, these reactions also address the challenge of atom economy in most of the cases.[34]

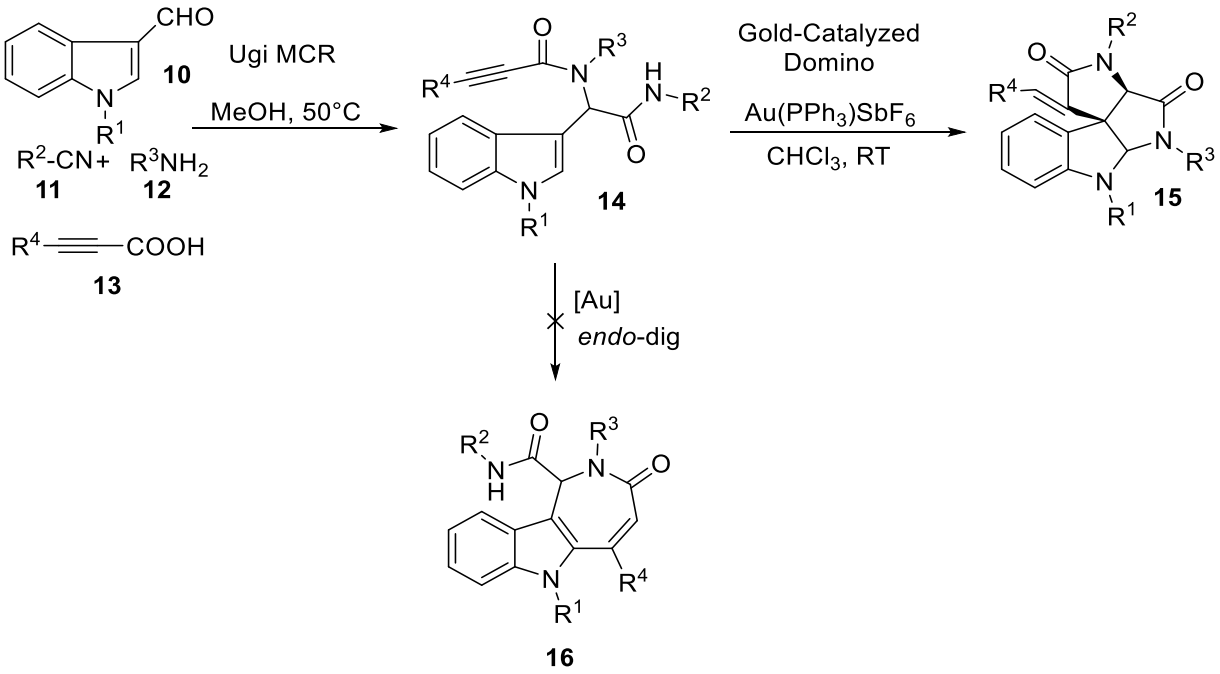
Among the few strategically designed cascade reactions towards natural product inspired compounds, the Waldmann group developed a silver catalyzed domino sequence leading to different classes of isoquinolines (Scheme 1). This cascade reaction was also used as a key step in the concise synthesis of the natural product fascaplysin. This sponge derived alkaloid is a CDK-4 inhibitor[35,36]. In their approach, aniline **4** and acetylenic benzaldehyde **5** form imine **7**, which then undergoes a silver-catalyzed cycloisomerization to form isoquinolinium intermediate **8**.[37] An intramolecular nucleophilic attack of the pendant malonate nucleophile followed by decarboxylation of the tetracyclic intermediate **9** ends the cascade with the formation of the targeted indoloisoquinolines **6** (Scheme 1).



Scheme 1: Silver catalyzed cascade synthesis of indoloisoquinolines **6**.

This strategy led to the synthesis of a small compound library of indoloisoquinolines with substitutions at both aromatic rings (R^1 – R^4) and yields up to 95%. Furthermore, a concise synthesis of the natural products fascaplysin and homofascaplysin was achieved employing this domino reaction sequence as a key transformation.

Another example of the synthesis of a small-molecule library from a cascade sequence providing a complex indole alkaloid-inspired compound collection was reported by Van der Eycken *et al*.[38] In this case, an Ugi four-component reaction[39] with indole-carboxaldehyde **10**, nitrile **11**, amine **12**, and carboxylic acid **13** yielded the highly functionnalized indole **14** that was used as a substrate for a subsequent gold-catalyzed cyclization reaction (Scheme 2). In the presence of a gold(I) catalyst a tetracyclic spiroindoline **16** was formed diastereoselectively instead of the expected indoloazepinone **15** that could be formed via an *endo*-dig cyclization.



Scheme 2: Synthetic strategy to produce a spiroindole **15** library

2.1.2. Centrocountins: Previous Work

The Waldmann group describes a one-pot cascade reaction sequence of unprecedented length that combines commercially available reagents as starting materials to yield tetracyclic indoloquinolizines embodying the basic scaffold of polycyclic alkaloids like Yohimbine **1**.[40] These compounds delayed mitosis in HeLa cells, induced chromosomal congressional defects, formation of multipolar spindles (Figure 3b), and targeted the centrosome associated proteins nucleophosmin (NPM) and Crm1. As they impair the mechanism that ensures the correct duplication of one centrosome per cell into two daughter centrosomes in the course of mitosis, they were termed centrocountins **17** (Figure 3a).

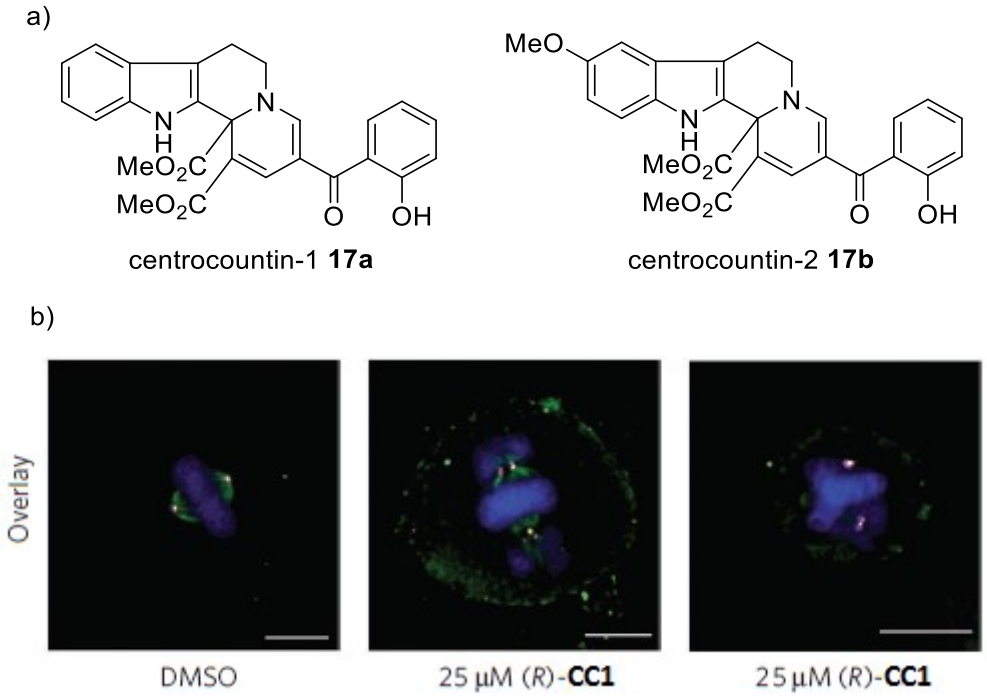
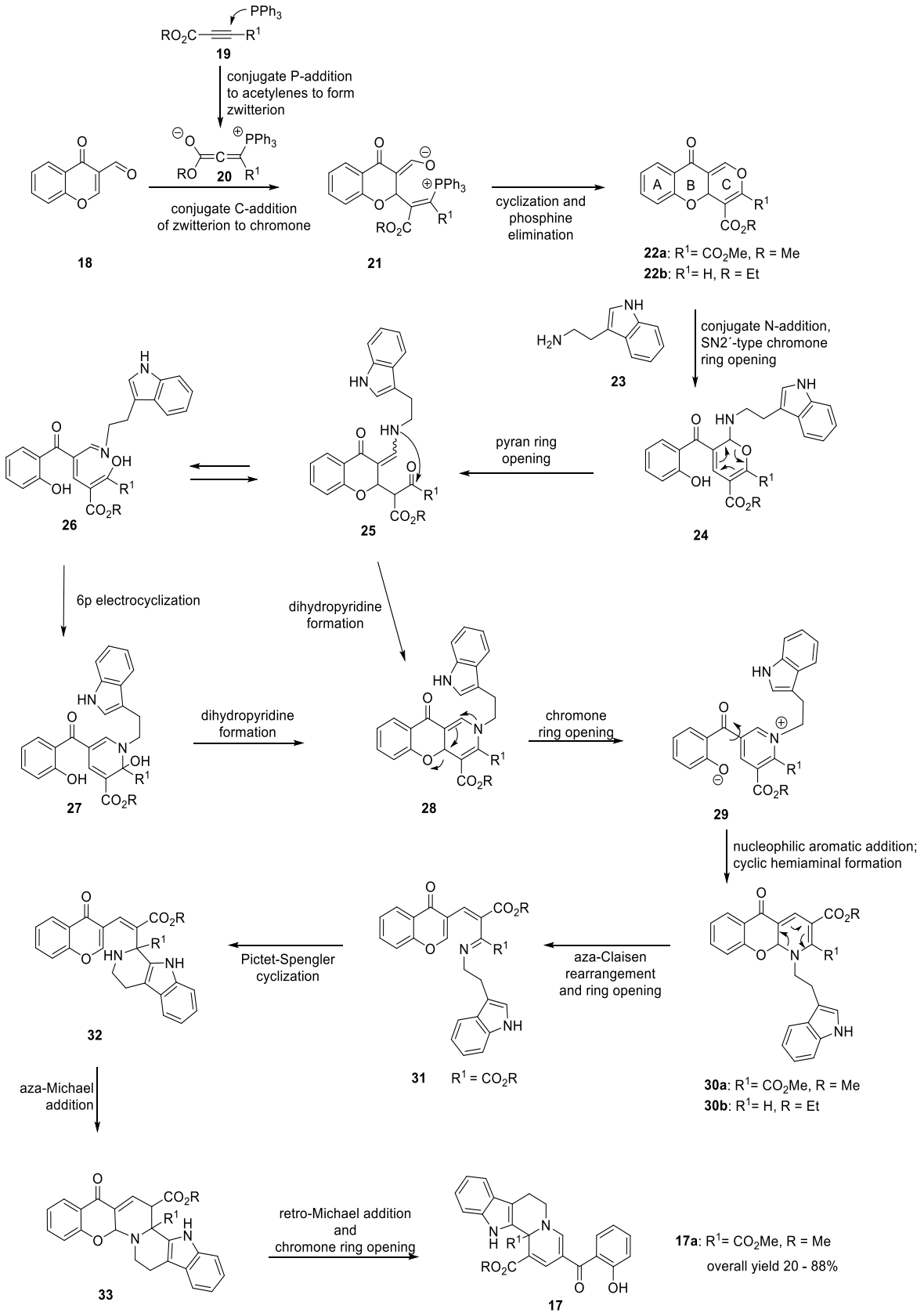


Figure 3: Centrocountin-1 **17a** and its mitotic modulation activity on HeLa cells. a) Structure of centrocountin-1 **17a** and -2 **17b** as hits from the screening of indoloquinolizines. b) Influence of (*R*)-**17a** on chromosome congression and spindle pole formation in HeLa cells. Multiple defects including chromosome congression defects (middle picture) and aberrant spindle structures (right picture) induced by (*R*)-**17a**. HeLa cells were treated with 25 µM **17a** for 18h before staining with DAPI for DNA (blue), α-tubulin (green) and γ-tubulin (green).

The one-pot cascade synthesis of the centrocountins proceeded with the attack of the triphenylphosphine catalyst on an alkyne **19** to form nucleophilic phosphozwitterion **20,** that subsequently adds to formylchromones **18** to form intermediates **21**.[41–43] These would then cyclize by means of an addition–elimination mechanism to yield tricyclic benzopyrones **22** with regeneration of the catalyst (Scheme 3). Tryptamine derivatives **23** then attack the electrophilic benzopyrone **22** by adding to the C ring of the tricyclic benzopyrones, followed by ring opening in which a phenol group acts as a leaving group to generate intermediates **24**. The phenols **24** can add again to the generated α,β-unsaturated carbonyl compounds, thereby initiating a pyran ring opening to generate intermediates **25** with an enamine and an α-ketoester in close vicinity. Addition of acid at that point of the cascade sequence initiates the condensation with the ketone, thus forming dihydropyridines **28** followed by another chromone ring opening with a phenol leaving group, and readdition of the phenol

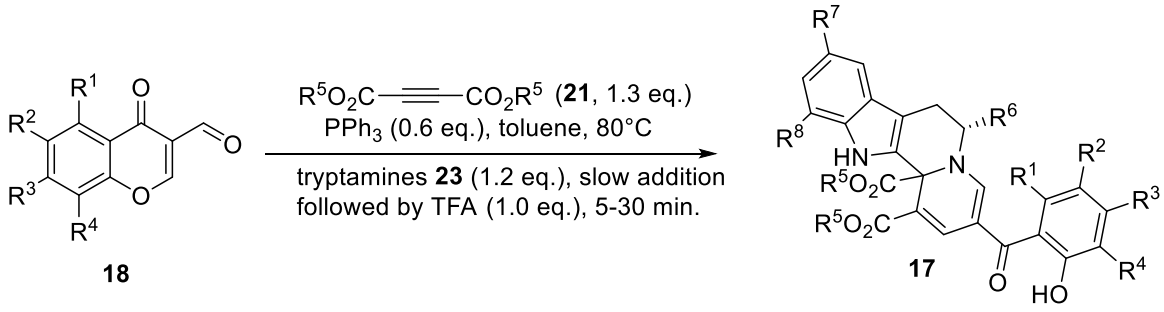
to form pyridinium salts **29**, these give rise to tricyclic dienes **30** and set the stage for a sigmatropic aza-Claisen rearrangement that yields α-iminoesters **31**. The neighboring indole ring then serves as a substrate for an intramolecular Pictet–Spengler cyclization to generate secondary amines **32**. The final steps of the sequence consists of a conjugate aza-Michael addition of the secondary amine to the doubly vinylogous esters to yield addition products **33**. Then a final acid-mediated pyran ring opening with phenol serving again as a leaving group culminates in the formation of centrocountins **17**.[44]

The optimized procedure for the cascade synthesis of the centrocountins **17** consists in the reaction of 1.0 equivalent of formylchromone **18** with 1.3 equivalents of DMAD **19**, in the presence of 0.6 equivalents of triphenylphosphine in toluene at 80°C. Subsequently 1.0 equivalent of tryptamine was added, followed by the addition of 1.0 equivalent of trifluoroacetic acid (TFA) or camphor sulphonic acid (CSA) (after disappearance of the tryptamine, monitored by thin layer chromatography) and the reaction mixture is stirred at the same temperature for 5 to 30 minutes. Flash column chromatographic purification of the concentrated reaction mixture led to centrocountins in yields varying from 20 to 88% (Centrocountin-1 **17a**, 88%). By this method, a small compound collection of thirty indoloquinolzines was synthesized, using differently substituted tryptamines and chromones, as described in Table 1**.**



Scheme 3: Proposed mechanism of the one-pot cascade sequence leading to the formation of centrocountins **17**.

Table 1: Cascade synthesis of centrocountins **17**.



Product	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Yield(%)[a]
17a	H	H	H	H	Me	H	H	H	58
17b	H	Me	H	H	Me	H	H	H	56
17c	H	iPr	H	H	Me	H	H	H	66
17d	H	H	H	H	Et	H	H	H	88
17e	H	Me	H	H	Et	H	H	H	65
17f	H	Cl	H	H	Me	H	H	H	39
17g	H	H	H	H	Me	H	OMe	H	76
17h	H	H	H	H	Me	H	Br	H	73
17i	H	H	H	H	Me	H	Me	H	74
17j	H	H	OBn	Me	Me	H	H	H	59
17k	H	H	H	H	Et	H	OMe	H	76
17l	H	H	H	H	Me	H	OH	H	67
17m	H	Br	H	H	Me	H	OMe	H	62
17n	H	Br	H	H	Me	H	H	H	39
17o	H	Cl	H	Cl	Me	H	H	H	20
17p	H	Br	H	Br	Me	H	H	H	20
17q	H	Cl	Me	H	Me	H	H	H	60
17r	H	H	H	H	Me	CO_2Me	H	H	69
17s	H	H	H	H	tBu	H	H	H	42
17t	OMe	H	H	H	Me	H	H	H	26
17u	H	H	H	H	Me	H	H	Me	78[b]
17v	H	Me	H	H	Et	H	OMe	H	45
17w	H	iPr	H	H	Et	H	OMe	H	65

[a] isolated yields

2.1.3. Goals for the Further Development of the Cascade Reaction

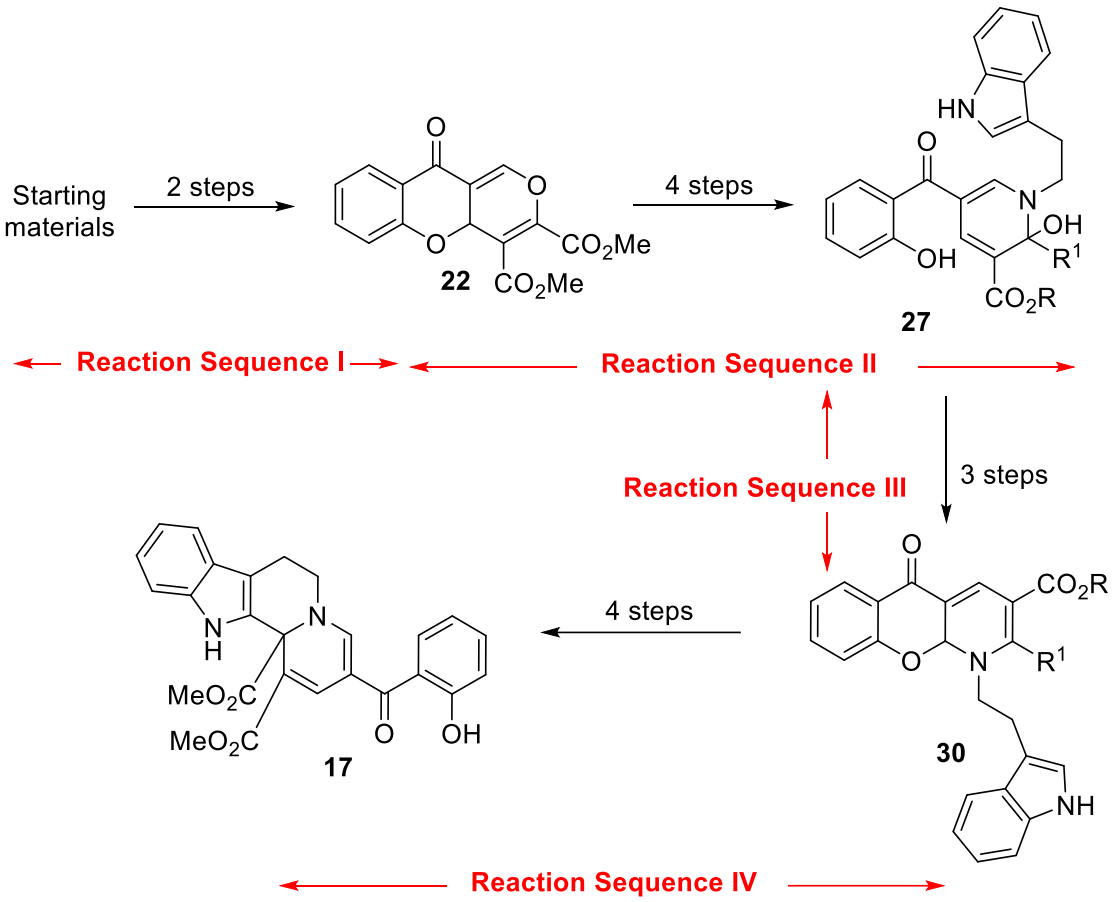
Thus, a very easy and efficient cascade synthesis of natural product inspired indoloquinolizines was established. In order to establish the proposed mechanism of this long and complex cascade sequence, key intermediates in the sequences were to be isolated. Also, it was observed that the initial [4+2] annulation between 3-formylchromones **18** and acetylenedicarboxylates **19** was quite sensitive to substitutions on the chromone. For instance, halogen-substituted 3-formylchromones always provided very low yields of indoloquinolizines (Table 1) and these were corresponding to the yields of the phosphine-catalyzed formation of the initial tricyclic benzopyrones **22**. That means, the cascade reaction sequence from tricyclic benzopyrones onwards to indoloquinolizines **17** was almost quantitive in yield. The major limitation of the cascade reaction was the irreplaceability of the tryptamines. Only tryptamines yielded the cascade products and carbo- or heterocyclic analogues could not be obtained with the cascade synthesis. Therefore, alternative methods for the synthesis of a diverse centrocountin collection were developed. In the following sections, investigations to prove the proposed reaction mechanism of the reaction cascade, and alternative cascade reactions that provide efficient and broader access to centrocountin analogues is described.

2.2. Confirmation of the Proposed Mechanism

This part of the work was conducted in collaboration with Heiko Dückert and Hanna Bruss.

The isolation and the characterization of key intermediates of the cascade reaction supports the proposed mechanism. The synthesis of tricyclic benzopyrones **22** was first developed as a separate reaction by the group. These intermediates are stable and can be stored in non acidic conditions and were fully characterized by NMR and HRMS.[41] Tricyclic aminal **27** was isolated and characterized by NMR spectroscopy as well. However its reactivity under acidic conditions rendered the recording of its NMR spectra difficult. Also, formation of indoloquinolizine from **27** was observed in the NMR sample in $CDCl_3$. In contrast, intermediate **30** was isolable, stable and crystallizable, so that X-ray analysis was performed, which unambiguously confirmed the structure of this aminal. These intermediates however define only some of the cornerstones of this unprecedentedly long cascade process, and

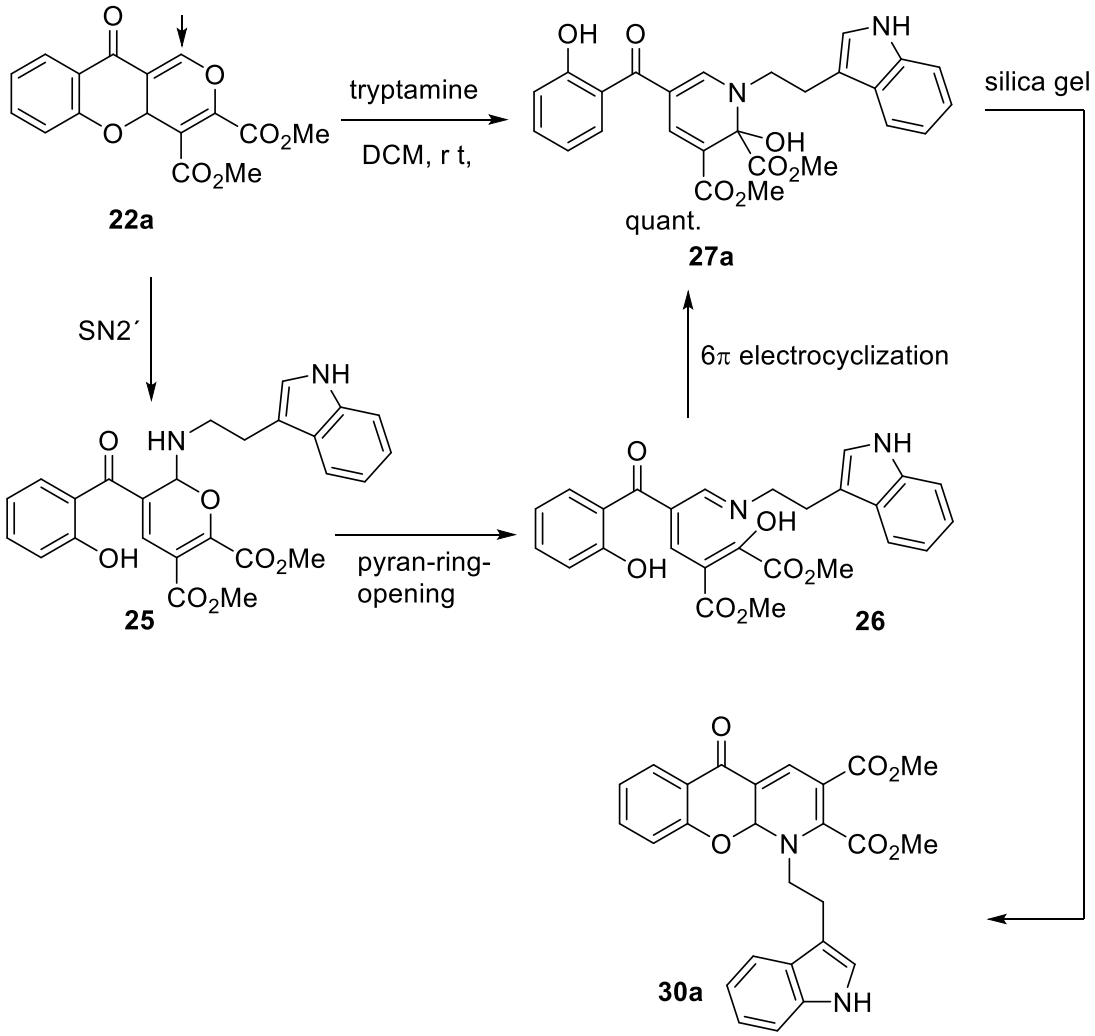
careful stepwise investigations of the remaining steps of the mechanism is necessary for its confirmation (Scheme 4).



Scheme 4: Isolated intermediates in the cascade sequence to centrocountins **17**. The isolated and characterized intermediates constitute the cornerstones to dissect the reaction sequence of the whole cascade process into smaller sequences (I to IV).

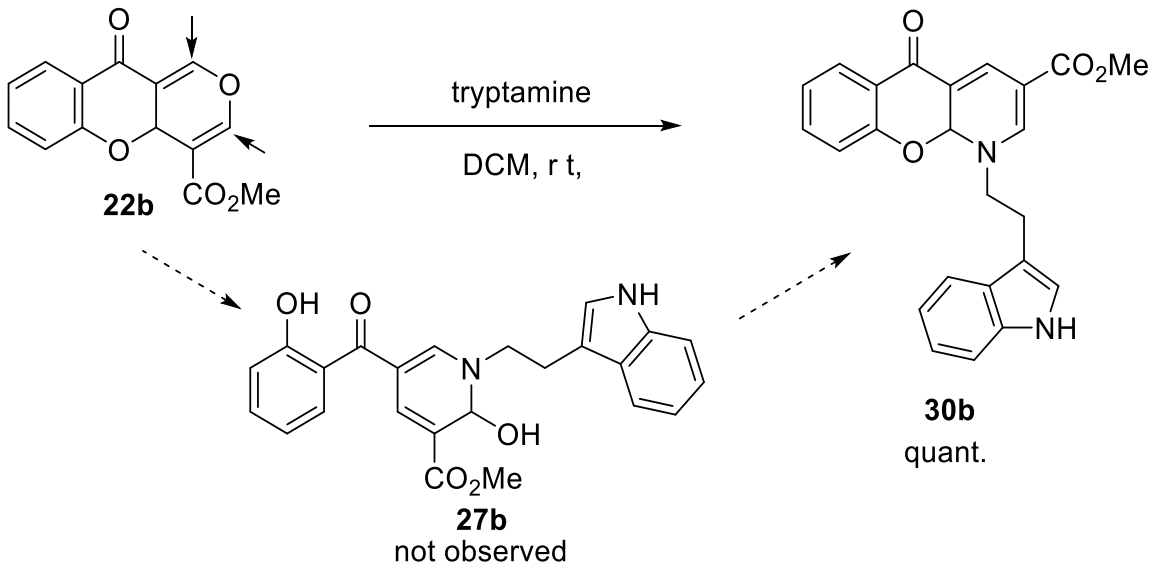
The phosphine catalyzed [4+2] cycloaddition of 3-formylchromones **18** with acetylenecarboxylates **19** to yield benzopyrones **22** sets the start of the sequence of the formation of indoloquinolizines **17**. However, the addition of tryptamine to the electrophilic benzopyrones **22** may occur at different steps of the proposed cascade by attacking either the tri- or the tetra-substituted olefin. The addition of nucleophiles to tri-substituted olefins is shown by the arrow in Scheme 5, thereby leading to a chromone ring opening to yield aminal **25**. Aminal **25** then opens up to form aza-triene **26**, that undergoes 6π-electrocyclization to form the 2-hydroxy-dihydropyridine **27** (Schemes 4 and 5, Reaction Sequence II). Indeed, compound **27** could be isolated in quantitative yield from a reaction of **22** with tryptamine in dichloromethane by directly evaporating the solvent. However, the

flash chromatography purification of aminal **27a** on silica gel converted it quantitatively into tricyclic aminal **30a** (Scheme 5, Reaction Sequence III).



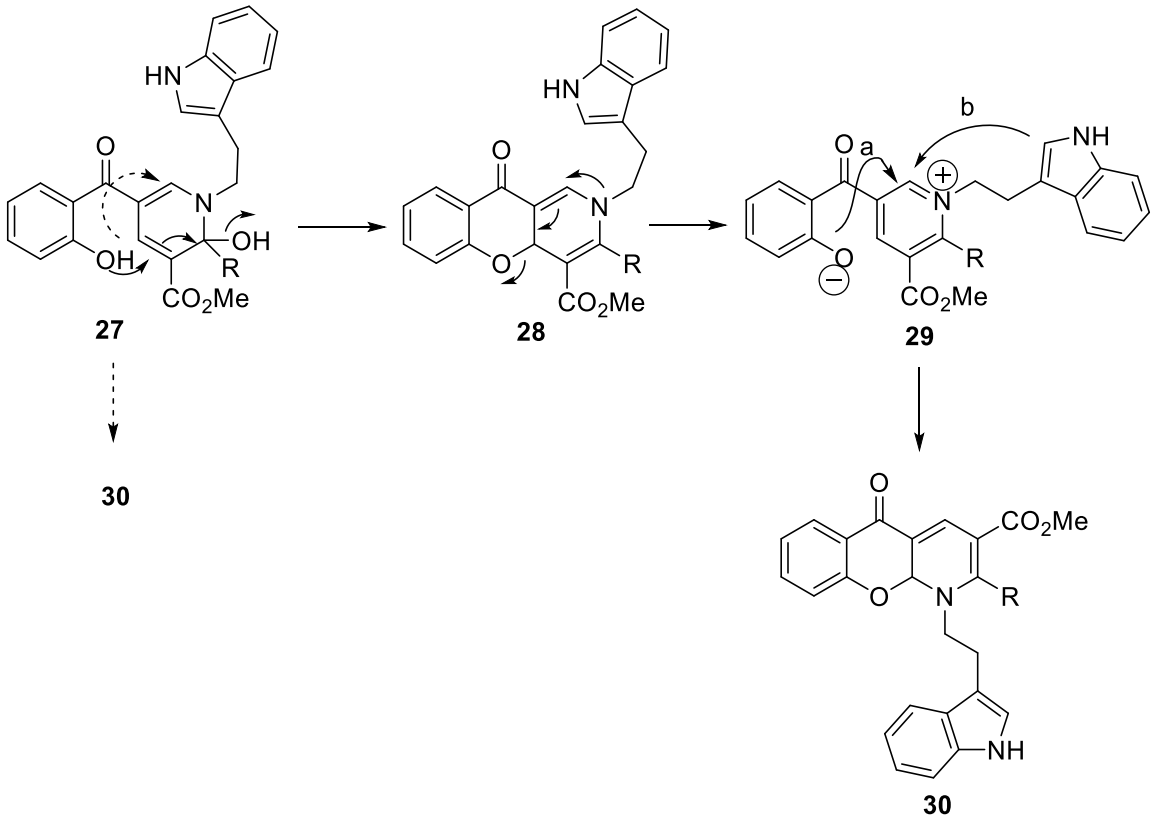
Scheme 5: Stepwise analysis and isolation of intermediates in the cascade reaction sequence: isolation of dihydropyridine **27** as precursor to tricyclic aminal **30**.

However, tricyclic benzopyrone **22b** led to the direct and quantitative formation of **30b**, and the formation of intermediate **27b** was not observed (Scheme 6). Intermediate **27b** might be formed by the addition of tryptamine to any of the two electrophilic olefinic sites (indicated by arrows). Probably, in the absence of an ester moiety, intermediate **27b** is not stable enough and quickly rearranges to form an azadiene that yields **30b**.



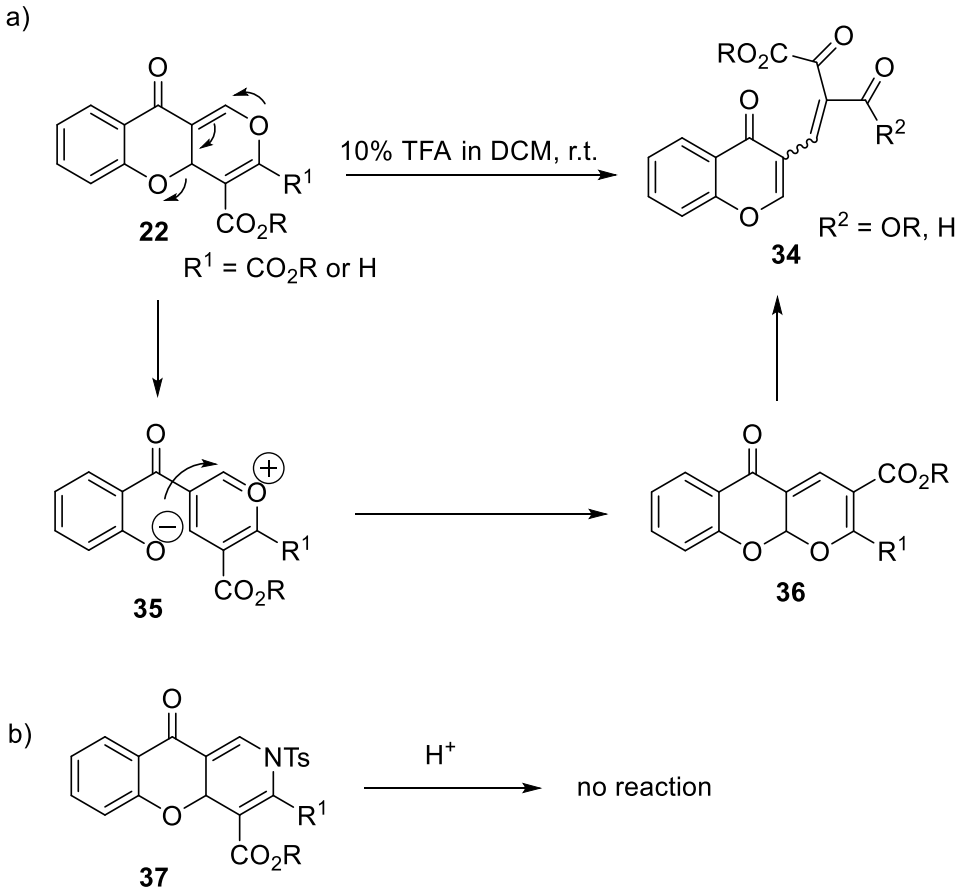
Scheme 6: Tricyclic intermediates **30b** generated from **22b** by the addition of tryptamine.

The transformation of **27a** in the presence of silica gel into tricyclic aminal **30a** is a further proof of the influence of mild acidic conditions on this transformation. If aminals **27** are indeed leading to intermediates **30**, two different pathways are possible (Scheme 7). Tricyclic aminals **30** may be directly formed by addition of the phenol to the α,β-unsaturated vinylogous amide (dotted arrow in Scheme 7) or through the formation of pyridinium salts **29** as intermediates. The isolation of indoloquinolizines **17** (Scheme 3) as side products suggests the formation of the pyridinium salts as they would be synthesized by an addition-elimination sequence from dihydropyridines **28** derived from **27**.



Scheme 7: Proposed reaction sequence from aminal **27** to tricyclic aminal **30** via pyridinium salt **29** and isolation of indoloquinolizine side product **30**.

Intermediates **28** embody a push–pull system that favors the formation of aromatic pyridinium salts **29**. The tricyclic benzopyrones **28** are structurally related to compounds **22** which are known to undergo rearrangement leading to ring-open ketoesters/aldehydes **34** (Scheme 8a).[45] This rearrangement, proceeds through pyrylium cations **35**, similar to the proposed transformation of **28** into **29**. In addition, we observed that the *N*-tosyl analogue **37** did not rearrange because the push–pull effect is lacking in this acid-stable dihydropyridine (Scheme 8b).



Scheme 8: Insights into the formation of key intermediates and side products in the cascade reaction sequence: a) ring opening of tricyclic benzopyrones **22**; b) attempted ring opening of *N*-tosyl analogues of **37** under acidic conditions.

The ^{1}H NMR spectra of tricyclic intermediates **30a** and **30b** in $CDCl_3$ at room temperature showed similar broadened peaks. Moreover, **30a** showed slow conversion to indoloquinolizine **17a**. It was therefore necessary to modify the conditions in which the NMR measurements were performed for refined results. The best results were obtained in deuterated DMSO at 60 °C. However, even under these conditions, all the expected signals did not appear properly in the spectrum (21 signals observed in the 13C NMR spectrum instead of 26 expected from HRMS calculations). Thus, a conclusive structural assignment of **30a** was not possible by means of NMR spectroscopy, but the comparison of the NMR spectra of **30a** and **30b** clearly proved their structural resemblance as depicted in Figure 4.

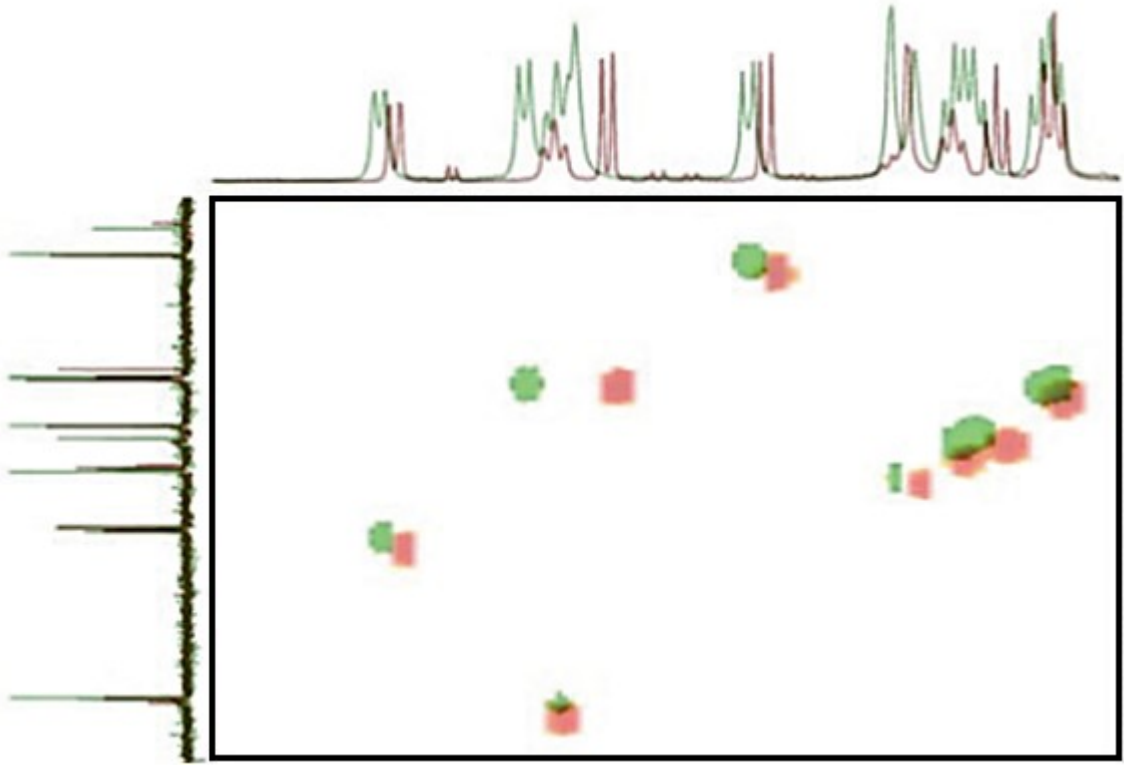
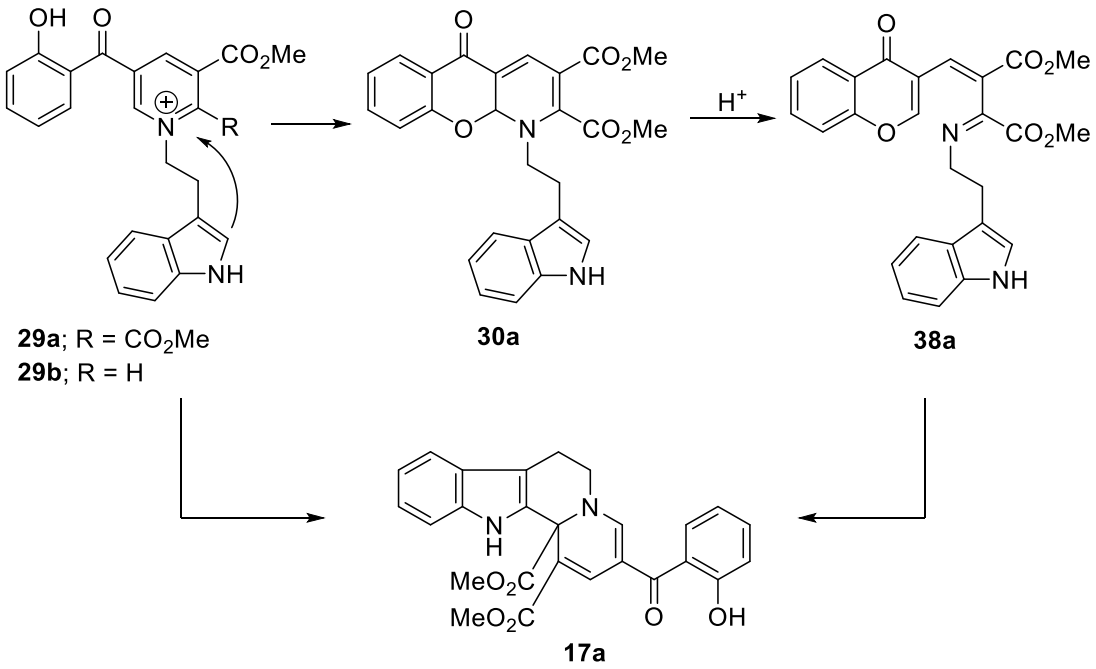


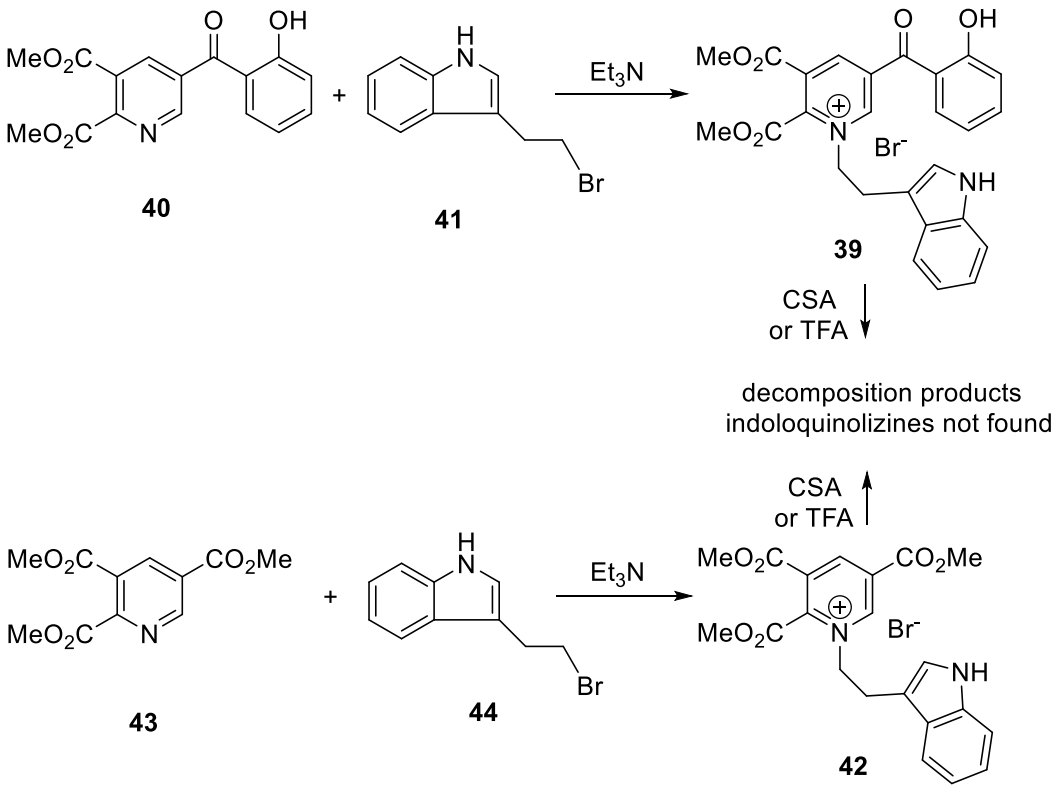
Figure 4. Overlay of the gHSQC spectra of the aromatic regions of **30a** and **30b**. The depicted sections of the spectra show all detected gHSQC signals except the CH_2 signals and the ethyl ester or methyl ester signal, respectively.

To rule out a hypothetic direct transformation of pyridinium salt **29** to indoloquinolizine **17** by the addition of the indole ring to the iminium salts (Scheme 9), further experiments were performed. An equimolar solution of **30a** in the presence of triethylamine in toluene resulted in no reaction, thus ruling out another possible addition of the indole moiety to the dihydropyridine ring in the intermediate **30a**. However, **30a** is stable under acidic and basic conditions. These observations clearly stand against the possible direct conversion of either pyridinium salts **29a** or tricyclic aminals **30a** to the indoloquinolizine **17a**.



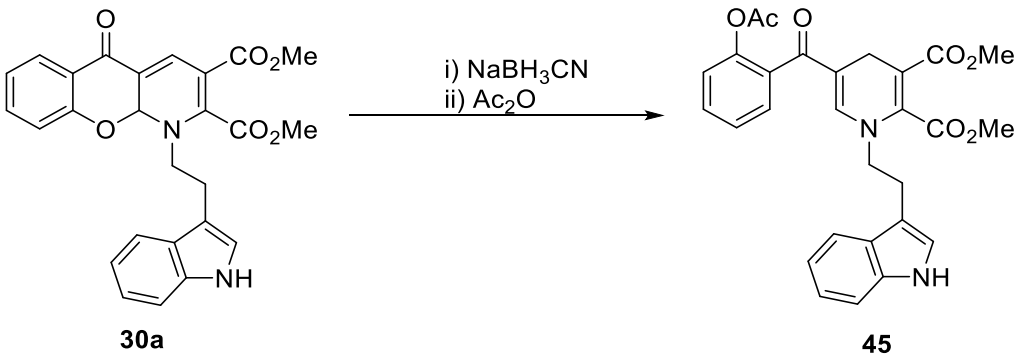
Scheme 9: Proposed reaction sequence from pyridinium salts **29** to inodoloquinolizines **17**

To further validate this notion, pyridinium salt **39** was synthesized by treating trisubstituted pyridine **40** with 3-(2-bromoethyl)indole **41** in the presence of triethylamine. Under basic reaction conditions, centrocountin **17a** was not formed. Unexpectedly, the treatment of **39** with trifluoroacetic acid (TFA) or camphorsulphonic acid (CSA) led to decomposition and the formation of indoloquinolizine **17a** was not observed by means of LC-MS analysis of the crude reaction mixture (Scheme 10). By analogy, pyridinium salt **42** decomposed under acidic conditions. These results thus strongly argue against the direct formation of indoloquinolizines **17** from pyridinium salts **29**.



Scheme 10: Synthesis of pyridinium salts **39** and **42** and their attempted conversion to centrocountins.

In the proposed cascade sequence, α-iminoesters **31** are formed from tricyclic aminals embodying two ester groups (Scheme 3). We assume that the aza-Claisen rearrangement is facilitated by an energetically low-lying LUMO of **30a**. In **30b**, the LUMO will be higher in energy, resulting in a less facile rearrangement. The α-iminoesters are potent electrophiles and Pictet–Spengler substrates due to their electrophilicity[46] and yield the secondary amines **32** in a fast cyclization reaction (Scheme 3). This intermediate contains a reactive secondary amine in proximity to a conjugated chromone moiety, so that a conjugate addition leads to hexacyclic intermediates **33** that undergo a retro-Michael-reaction and concerted chromone ring opening, thereby yielding centrocountins **17** (Scheme 3).



30a **45**

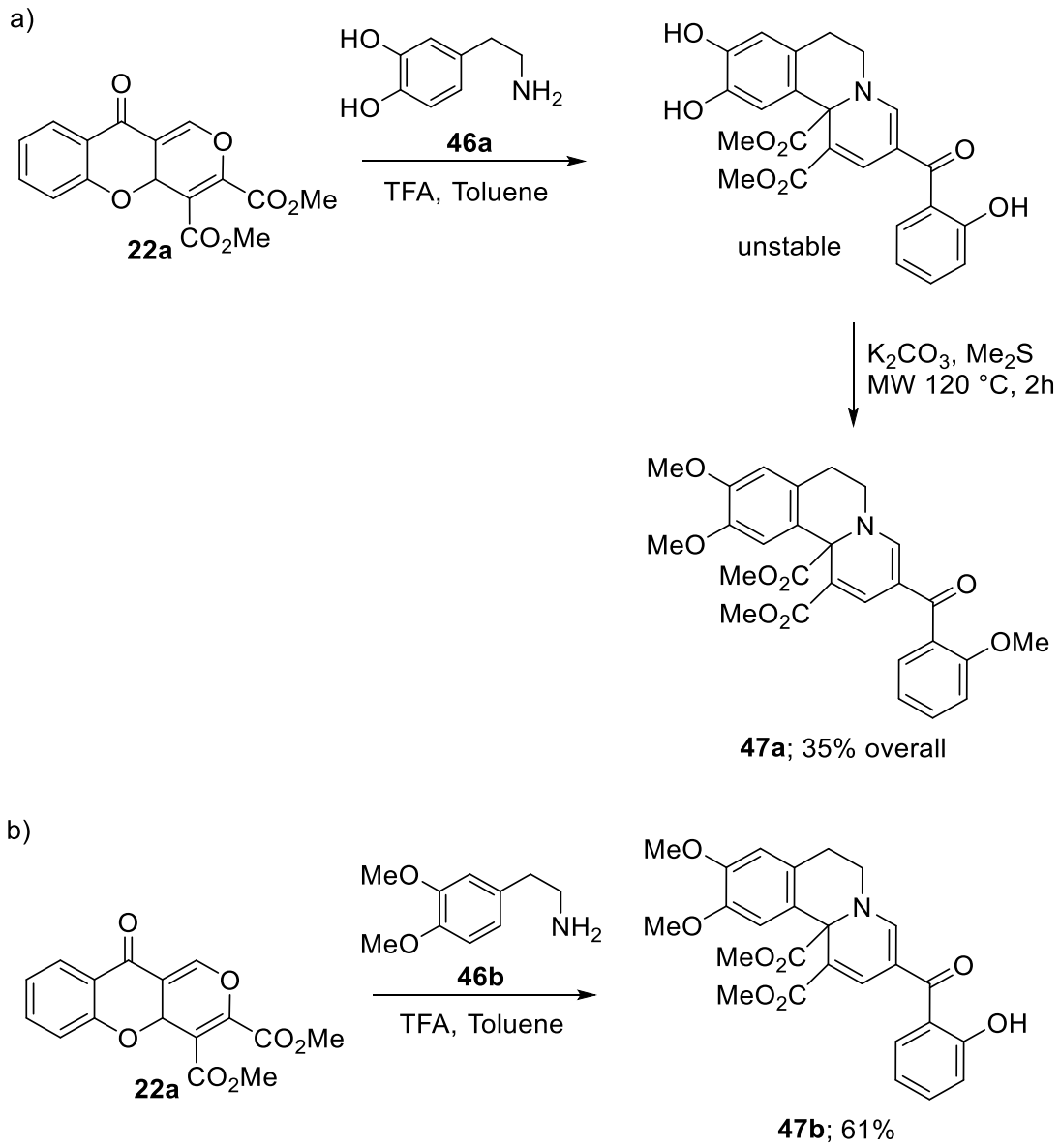
Scheme 11: Attemped reduction of **30a**.

The proposed transformations of **30** to **17** proceeded in quick succession and all attempts to trap intermediates **31**, **32**, or **33** failed. Thus, the attempted reduction of intermediate **30a** with sodium cyanoborohydride led to dihydropyridines **45** (Scheme 11). This formation can be explained by either a direct 1,4-addition of hydride or the reduction of α-iminoester **31a** to a secondary amine that adds to the chromone ring, which then opens up.

2.3. Scope of the Reaction

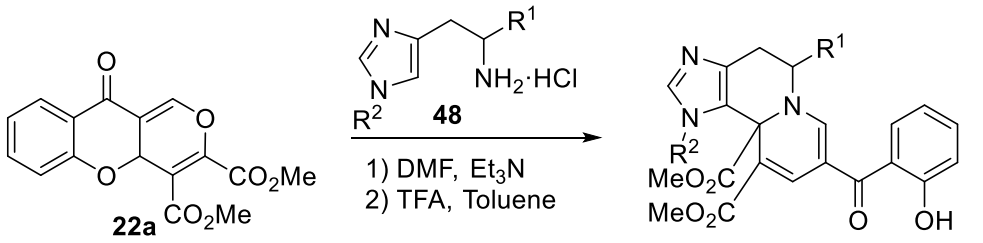
2.3.1. Use of Other Amines in the Cascade Reaction

For the synthesis of new analogues of the mitosis modulating centrocountins, replacement of the indole ring by other heterocyclic or aromatic cycles in the cascade was assumpted to expand the scope of the cascade reaction. To simplify the execution of the cascade reactions, pre-formed tricyclic benzopyrone **22a** was used and directly underwent amine addition, and side reactions due to trace amounts of triphenylphosphine were avoided. Tricyclic benzopyrone **22** reacted with electron-rich dopamine **46a** to provide the expected product, which was O-methylated to yield stable tetrahydroisoquinoline **47a** in 35 % overall yield. A cascade reaction with 2-(3,4-dimethoxyphenyl)ethylamine **46b** led to the desired product **47b** in 61 % yield. The less electron-rich 2-phenylethylamine did not yield the expected product (Scheme 12).



Scheme 12: Cascade synthesis of diverse tetrahydroisoquinolines **47**.

Electron-rich histamine and histidine derivatives **48** yielded the desired annulation products **49**, albeit in low yields. The N-methylated histamine and histidine derivatives also reacted with the tricyclic benzopyrone to give the expected products in higher yields than obtained with their NH counterparts (Scheme 13).

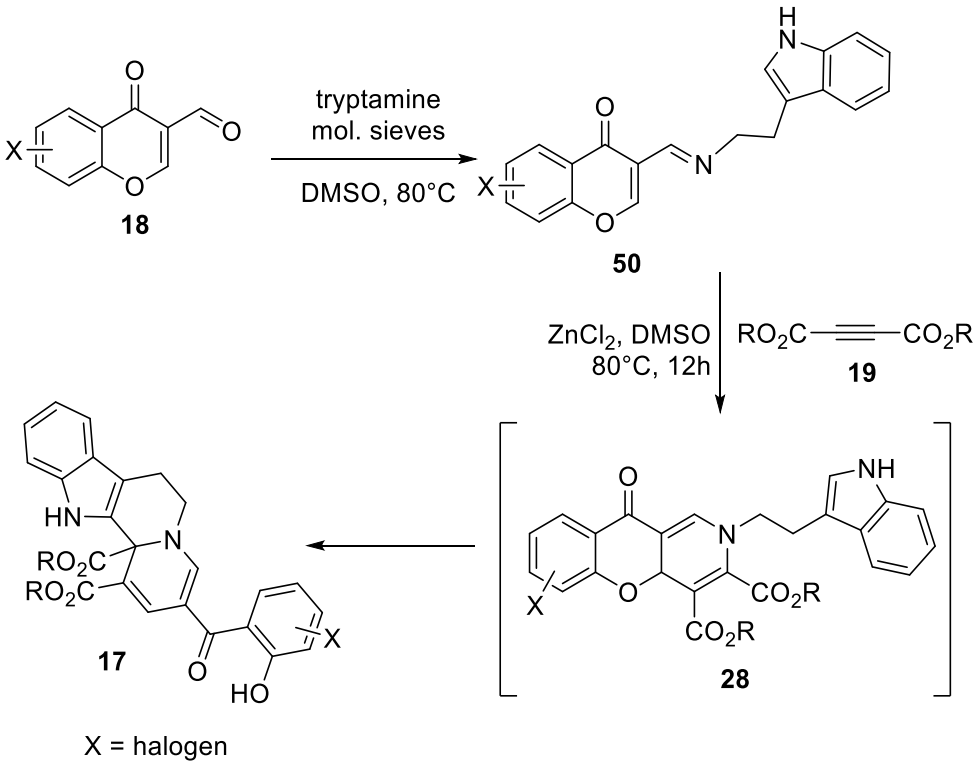


49a; $R^1 = CO_2H$; $R^2 = H$; 17%
49b; $R^1 = CO_2Me$; $R^2 = H$; 10%
49c; $R^1 = H$; $R^2 = H$; 5%
49d; $R^1 = CO_2Me$; $R^2 = Me$; 43%
49e; $R^1 = H$; $R^2 = Me$; 59%

Scheme 13: Cascade synthesis of imidazoquinolizines **49**.

2.3.2. Alternative Cascade Route to the Centrocountins

Variations in the appended substitutions on a scaffold are required for the synthesis of a compound collection. Halogens are handles for combinatorial coupling reactions in library synthesis. It was observed that the synthesis of halogenated indoloquinolizines is low yielding in the long cascade reaction. The formation of the tricyclic benzopyrones **22** is the limiting factor in the cascade reaction sequence. To solve this problem, an alternative cascade route was envisioned in which dihydropyridine intermediate **28** could be formed by an aza-Diels–Alder reaction between choromonylimines **50** and DMAD **19**. This route should yield halogenated indoloquinolizines in higher yields than in the 12-step cascade, by avoiding the low yielding [4+2] annulation of halogenated 3-formychromones with acetylenedicarboxylates (Scheme 14).



Scheme 14: Alternative cascade synthesis of centrocountins **17** by means of an aza-Diels–Alder reaction.

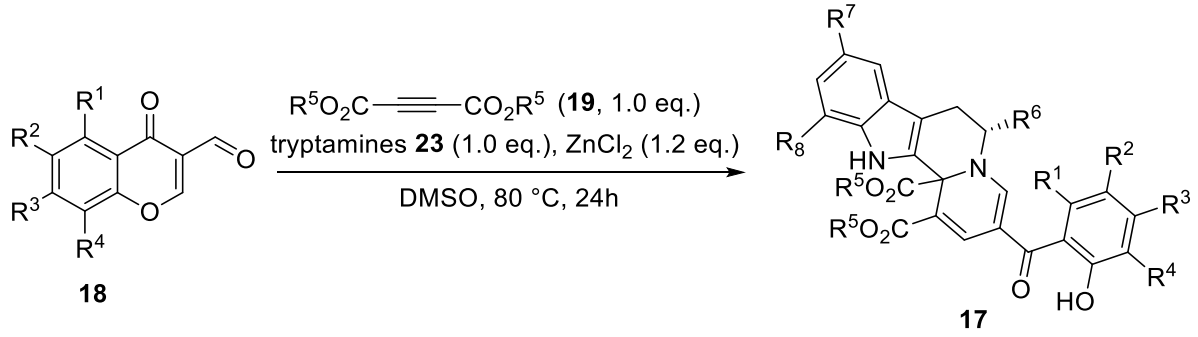
Different reaction conditions for the aza-Diels–Alder reaction were screened by increasing the reaction time and temperature and by testing different solvents and Lewis acids (Table 2). The best results were observed by using 1.2 equivalents of $ZnCl_2$ in DMSO at 80 °C for 24 hours to yield **17a** in 79 % yield (Table 2, Entry 4). Gratifyingly, differently substituted 3-formylchromones, in particular with halogen substituents, reacted smoothly with acetylenedicarboxylates and provided indoloquinolizines **17** in higher yields than recorded before for the 12-step cascade reaction. (Table 3)

Table 2: Optimization of the reactions conditions for the alternative synthesis of **17a**.

Entry	Lewis Acid	Solvent	Temperature	Reaction time	Yield[a] [%]
1	$ZnCl_2$	toluene	r.t.	12h	-
2	$ZnCl_2$	toluene	40 °C	12h	28
3	$ZnCl_2$	toluene	80 °C	12h	41
4	**$ZnCl_2$**	**DMSO**	**80 °C**	**1h**	**79**
5	$ZnCl_2$	DMSO	r.t.	1h	-

[a] Isolated yields

Table 3: Aza-Diels-Alder cascade synthesis of indoloquinolizines.



Product	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield[a,b] [%]	Yield[a,c] [%]
17a	H	H	H	H	Me	H	H	58	**79**
17f	H	Cl	H	H	Me	H	H	39	**91**
17g	H	H	H	H	Me	H	OMe	76	**64**
17m	H	Br	H	H	Me	H	OMe	62	**62**
17n	H	Br	H	H	Me	H	H	39	**77**
17o	H	Cl	H	Cl	Me	H	H	20	**53**
17p	H	Br	H	Br	Me	H	H	20	**83**
17t	OMe	H	H	H	Me	H	H	26	**29**
17v	H	Br	H	H	Et	H	H	45	**64**
17w	H	Cl	H	Cl	Et	H	H	65	**40**
17aa	H	Cl	H	H	Et	H	H	-	**93**
17ab	H	Cl	H	Cl	Et	H	OMe	-	**87**
17ac	H	Br	H	H	Et	H	OMe	-	**69**
17ae	H	Br	H	H	Et	H	H	-	**82**
17af	H	Cl	H	H	Me	H	OMe	-	**74**
17ag	H	Cl	H	Cl	Me	H	OMe	-	**91**
17ah	H	Br	H	Br	Me	H	OMe	-	**51**
17ai	H	Cl	H	Cl	Et	H	OMe	-	**31**
17aj	H	Br	H	Br	Et	H	OMe	-	**42**

[a] isolated yields, [b] synthesis by the 12-step cascade, [c]synthesis by the cascade aza-Diels-Alder reaction

2.4. Conclusion and Outlook

Analogues of centrocountin **17a** were synthesized to further develop a natural product inspired compound collection by means of an efficient and particularly long cascade sequence, involving at least twelve distinct reaction steps and nine distinct reaction types from commercially available starting material. The cascade synthesis also provides new tetrahydroquinolizines fused to other aromatic rings. The proposed mechanism of this reaction sequence was further proved by performing different control experiments, and led to an alternative shortcut cascade reaction from readily accessible substrates employing an aza-Diels-Alder reaction with DMAD as a key step. Nevertheless, the scope of the synthesis could not be substantially expanded, and the necessity of developing a new synthetic strategy for the elaboration of more various centrocountins analogues remains essential for an efficient use in chemical biological investigations.

3. Inverse Electron Demand Imino-Diels-Alder Reaction

Chapter relating to:

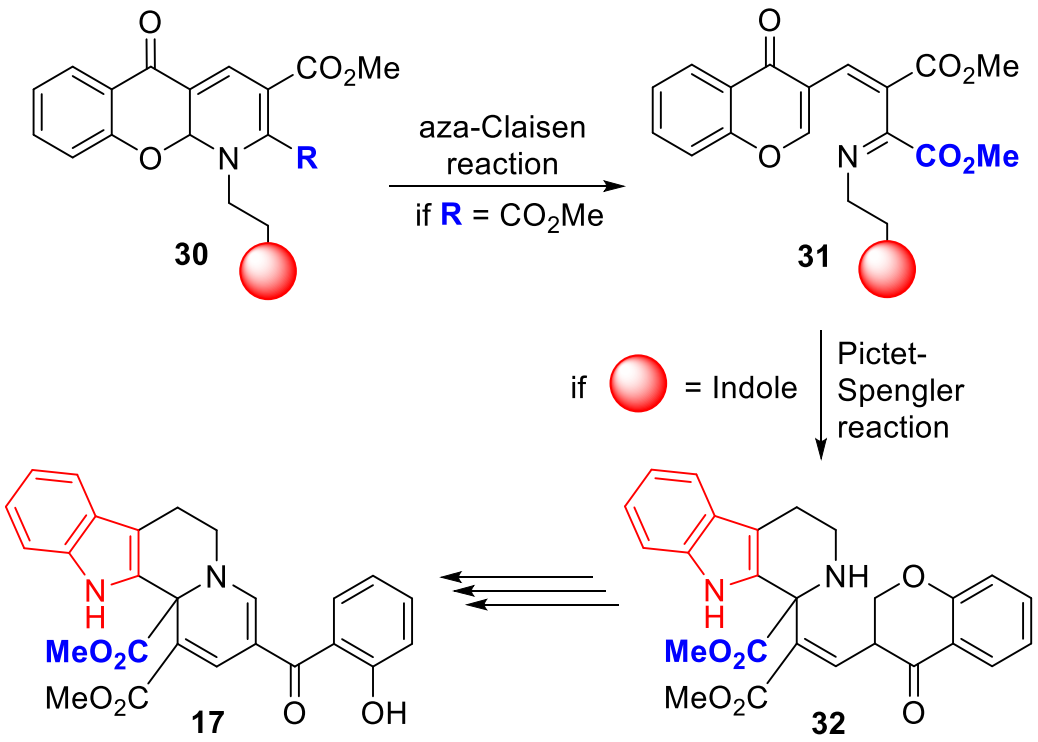
An Enantioselective Inverse Electron Demand Imino Diels-Alder Reaction

V. Eschenbrenner-Lux, P. Küchler, S. Ziegler, K. Kumar, H. Waldmann

Angew. Chem. Int. Ed. ***2014****, 53, 2134 - 2137.*

3.1. Introduction

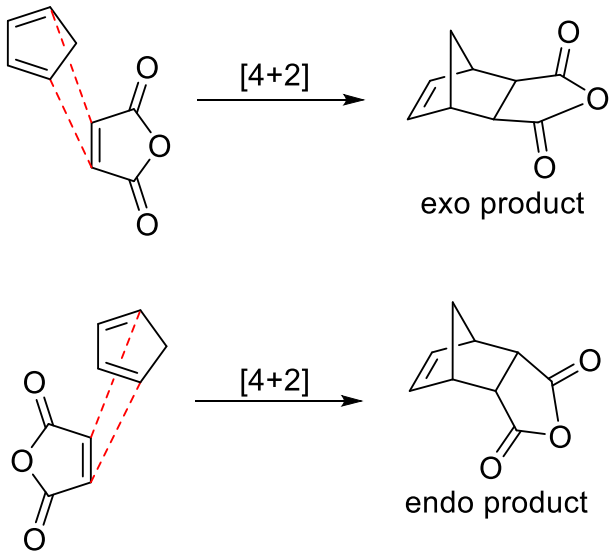
In order to further explore the unusual bioactivity of the centrocountins, and given the limited scope of the long cascade synthesis of this heterocyclic class, an alternative enantioselective synthesis was envisaged. The aza-Claisen rearrangement and the Pictet-Spengler cyclization steps limited the potential of the long cascade reaction sequence leading to the centrocountins. While the aza-Claisen reaction required the presence of an α-iminoester, the Pictet-Spengler proceeds efficiently only for indole derivatives. Therefore, a strategy was developed to overcome these limitations (Scheme 15).



Scheme 15: Limitating steps of the cascade synthesis of Centrocountin **17**.

3.1.1. Synthesis of Indoloquinolizines by an imino Diels Alder reaction

The [4+2] cycloaddition between dienophiles and dienes, the Diels-Alder reaction, is a very useful method for the formation of substituted 6-membered rings.[47,48] The concerted mechanism and the stereospecific character of this reaction was formally accepted, even before the importance of the orbital symmetry was recognized.[49,50] For a non-symmetrical diene, two stereochemical orientations toward the diene are possible. These two orientations, *endo* or *exo*, are illustrated in Scheme 16. In the endo transition state, the substituent is oriented in the direction of the diene, when in the exo state it is oriented in the opposite direction. The preference of the transition state depends on different factors like steric or electrostatic interactions, and yields different stereoisomers. For instance, the endo selectivity is prefered in the presence of a carbonyl functional groups in the dienophile.[51,52] Also, the preferred mode of cycloaddition depends on the type of catalysis used to accelerate the reaction.[53]



Scheme 16: *Endo-exo* selectivity of the Diels-Alder reaction between cyclopentadiene and maleic anhydride.

It is possible to control the regioselectivity, as well as the stereoselectivity by modulating the reaction conditions or using an asymmetric catalyst, making this reaction suitable for the total synthesis of natural products or for the construction of natural-product derived compound collections.[54]

3.1.2. The Inverse Electron Demand Imino Diels-Alder Reaction

A Diels-Alder cycloaddition reaction where a diene or a dienophile has at least one hetero-atom incorporated is termed hetero Diels-Alder reaction.[55] For an oxygen atom as heteroatom, the reaction is called oxa-Diels-Alder reaction[56] and when it is a nitrogen atom, the term aza-Diels-Alder reaction is used. A nitroso Diels-Alder[57] reaction is a variant where both N and O are implied in the cycloaddition (Figure 5). Despite its efficiency and potential, the aza-Diels-Alder reaction has been far less exploited and explored in organic syntheses compared to the all-carbon Diels-Alder cycloaddition. The first hetero Diels-Alder reaction was for instance only reported 22 years after the first Diels-Alder reaction, in 1949.[58]

The aza-Diels-Alder reaction is one of the most powerful reactions for the construction of polyfunctional heterocyclic molecules with high chemo-, regio-, and stereoselectivity.[59] The imino Diels-Alder reaction[60] a subclass of the aza-Diels-Alder reaction, in which an imine

serves as dienophile, is one of the most direct methods for the formation of six-membered nitrogen-containing rings such as tetrahydroquinolines. These reactions are also of high interest for the total synthesis of natural products, as they give access to a variety of structures in an atom-economic manner, in most of the cases, with a very high tolerance of functional groups present in the substrates. Considerable efforts have been committed to the development of asymmetric aza-Diels-Alder reactions with 1- or 2-azadienes, or imino dienophiles.[61,62] However only few examples describe the application of asymmetric imino-Diels-Alder reactions to the synthesis of biologically or pharmacologically relevant products.[63]

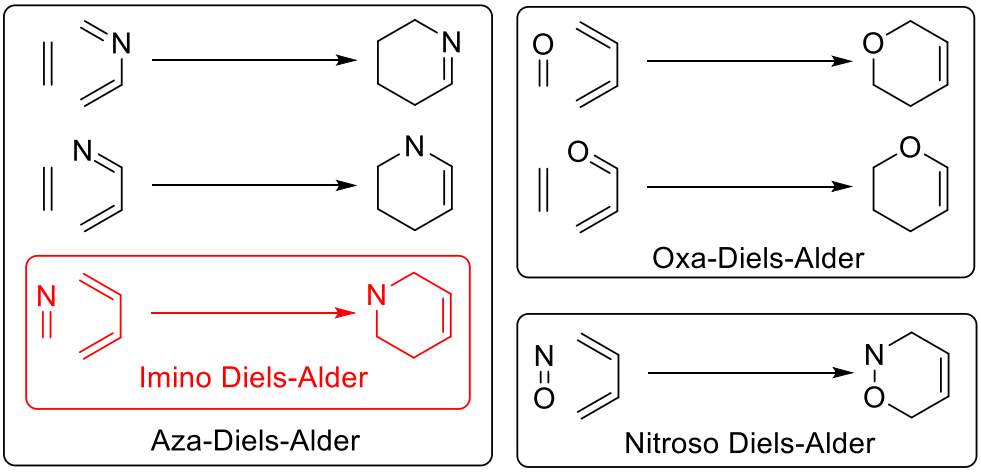


Figure 5: Hierarchy of the hetero-Diels-Alder reactions.

While major improvements have been achieved in the development of asymmetric carbo-Diels-Alder reactions, efforts to develop stereoselective hetero Diels-Alder reactions are less important. Interestingly, for several natural products it has been hypothesized that their biosynthesis includes a hetero Diels-Alder step.[64] Despite the discovery of enzymes catalysing Diels-Alder reactions for the synthesis of secondary metabolites[65], the Diels-Alderases, no enzyme was discovered to date for the catalysis of hetero Diels-Alder reactions.[66] Nevertheless, the formation of six-membered heterocycles in one step by [4+2] cycloaddition between heterodienes or heterodienophiles is a logical method in synthetic strategies designed to yield biologically active small molecules.

The relative HOMO-LUMO orbital energies of the diene and the dienophile can be modulated with appropriate reaction conditions and catalysts, like Lewis-acids, nucleophilic organocatalysts or just thermal promotion.[62] The type of activation required depends on the electronic configuration of the molecular orbitals of the diene and dienophile. Thus, in the case of a normal demand imino Diels-Alder reaction between an electron-poor imine and an electron-rich diene[67], a Lewis acid is used to lower the energy of the LUMO of the dienophile, making it more reactive for the [4+2] cycloaddition (Figure 6). Similarly, in the case on an inverse electron demand imino Diels-Alder reaction, for instance between an electron-poor diene and an electron-rich dienophile, the Lewis acid lowers the energy of the diene.[68] Typical Lewis acids used in [4+2] cycloadditions are among others $ZnCl_2$, BF_3, $AlCl_3$, $SnCl_4$.[69] There are however to the best of my knowledge, no reports to date of an asymmetric inverse electron demand imino Diels-Alder reaction.

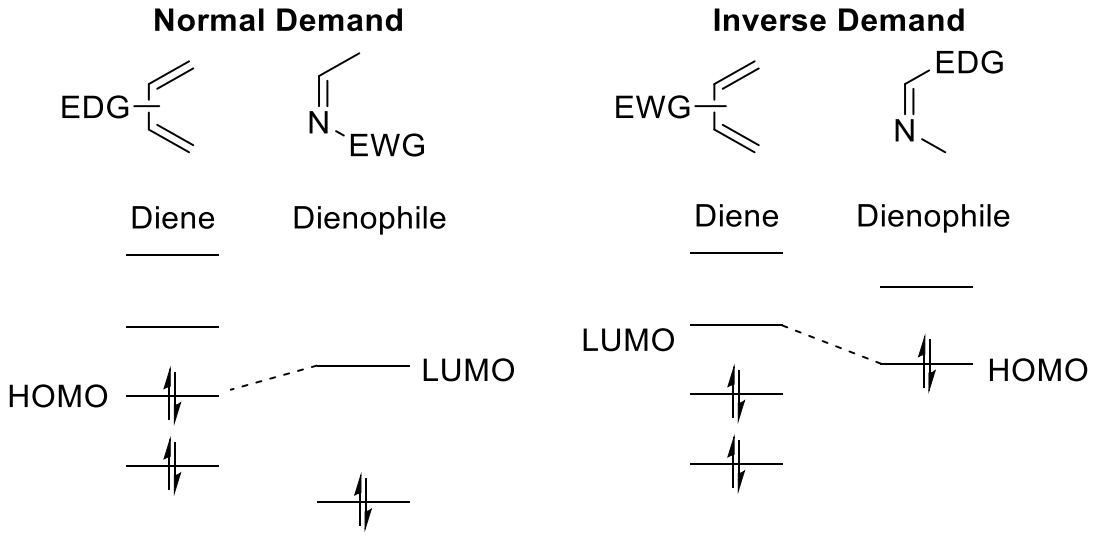


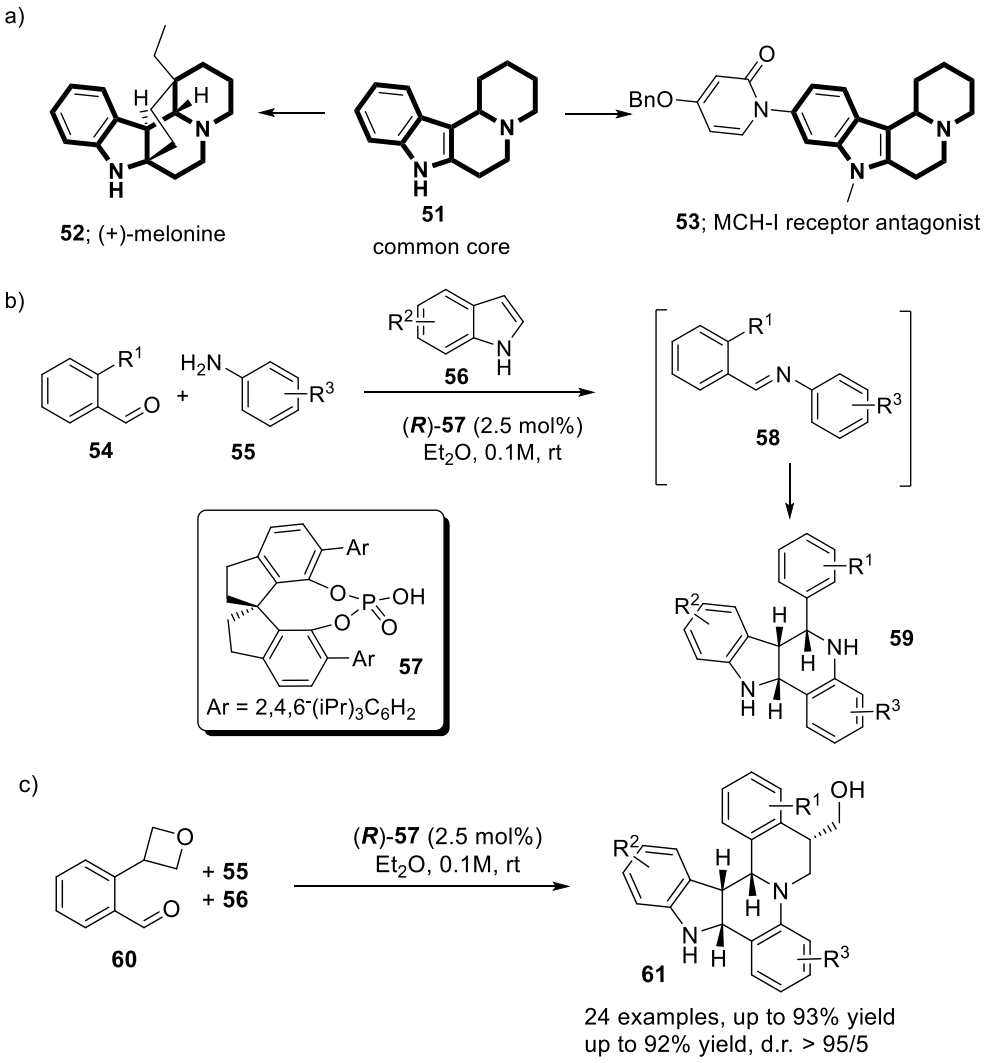
Figure 6: Comparison of the normal electron demand and inverse electron demand imino Diels Alder reaction and its translation concerning the orbital interactions between HOMOs and LUMOs. (EWG = electron withdrawing group, EDG = electron donating group)

3.1.3. Application of aza-Diels-Alder Reactions in the Synthesis of Natural Products and Analogues

The application of asymmetric hetero Diels-Alder reactions in the synthesis of small bioactive molecules has successfully yielded diastereo- and enantioselective methods which employ

either chiral catalysts or chiral auxiliaries embedded in the substrates to induce the desired chirality to the products.

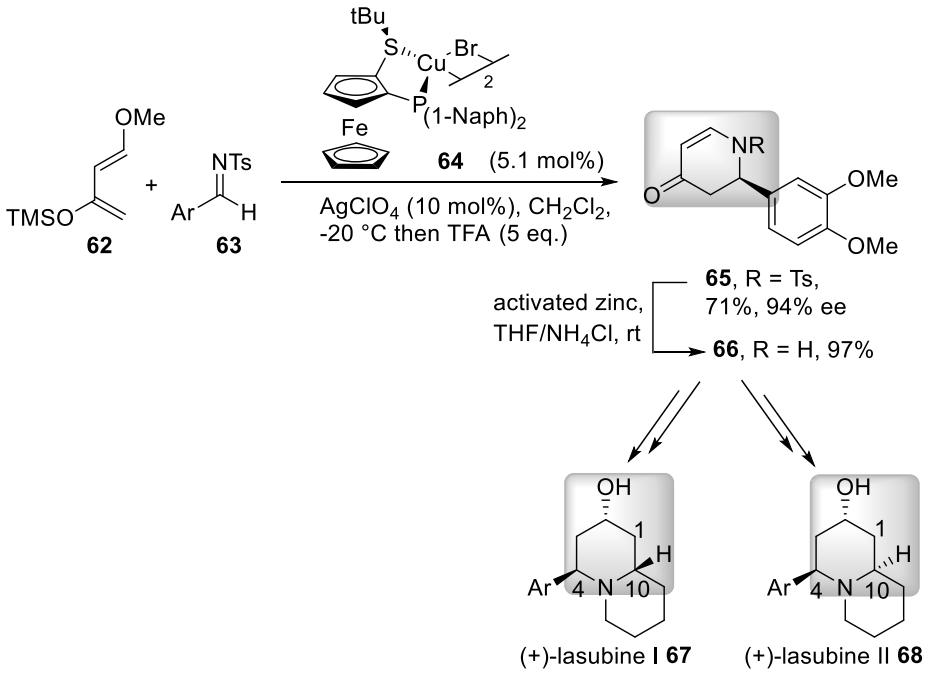
Melonine (**52**, Scheme 17a), a tetracyclic indole alkaloid, is used in the treatment of various diseases, including obesity, anxiety, depression, non-alcoholic fatty liver disease, and psychiatric disorders.[70,71] An aza-Diels-Aldre reaction was used for the synthesis of a compounds collection inspired from the tetracyclic scaffold of this bioactive molecule.[72] In this case, a one-pot three component reaction leads to the tetrahydroquinoline scaffold in one direct step with up to 92% yield and 93% ee.



Scheme 17*:* Synthesis of a indole alkaloid-inspired compound collection. a) Example of bioactive products containing the common scaffold. b) One-pot three component reaction hetero Diels-Alder reaction. c) Synthesis of a Melonine-inspired compound library **61**.

Aldehydes **54** and anilines **55** form imines **58**, which undergo an aza-Diels-Alder reaction with indoles **56** assisted by catalysis with phosphoric acid **57** to form tetrahydroquinolines **59** (Scheme 17b). Three stereogenic centres are installed by the chiral catalyst with high enantiomeric excess as well as high diastereoselectivity (95:5) in tetracylic indoles **59**. The presence of an oxetane ring on aldehyde **60** as a directing group is necessary for the synthesis of a melonine-inspired tetracyclic indoles **61**. Indeed, addition of secondary amine induces oxetane ring-opening and thereby the formation of the targeted compound **61** in good yields and diastereoselectivity (Scheme 17c).

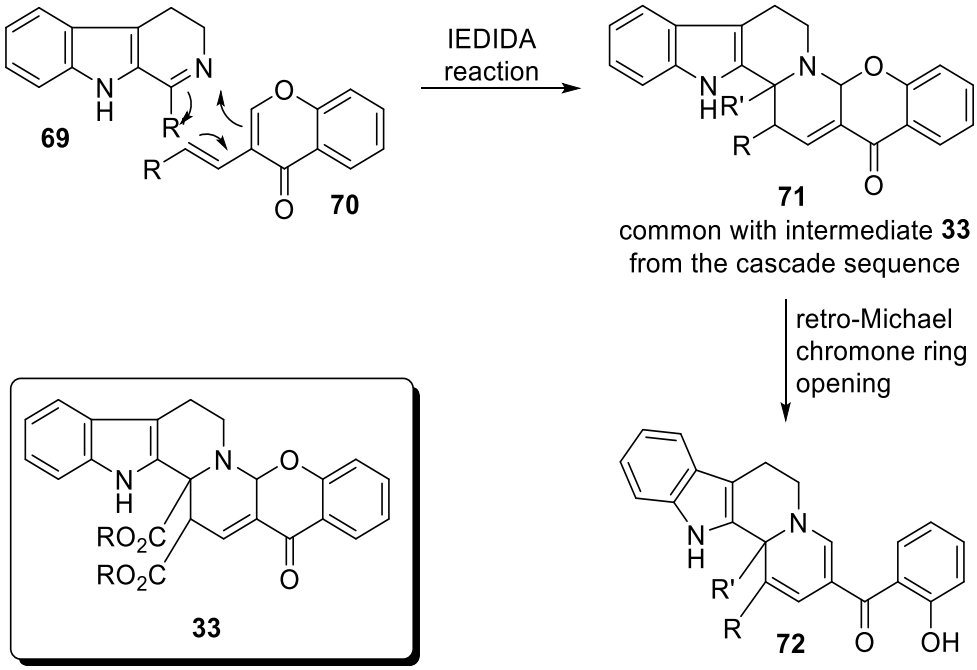
Other alkaloids, like indolizidines, quinolizidines, and piperidines can also be synthesized with an asymmetric imino Diels-Alder reaction. Lasubines are quinolizidine alkaloids isolated from plants of the *Lythraceae* family.[73] A chiral ferrocene complex is used, in this case, as the catalyst for the asymmetric HDA reaction.[74] Thus, the piperidinone core was generated by imino Diels-Alder reaction between diene **62** and aryltosylimide **63** catalyzed by Cu-Fesulphos bromo dimer complex **64** and $AgClO_4$ in DCM leading to cycloadduct **65** in 71% yield and 94% ee. Further functionalization steps of **65** yielded lasubines I and II **67**-**68** through the common building blocks **65** and **66** (Scheme 18).



Scheme 18: Synthesis of lasubines **67**-**68** using an enantioselective normal electron demand imino Diels-Alder reaction as the key step.

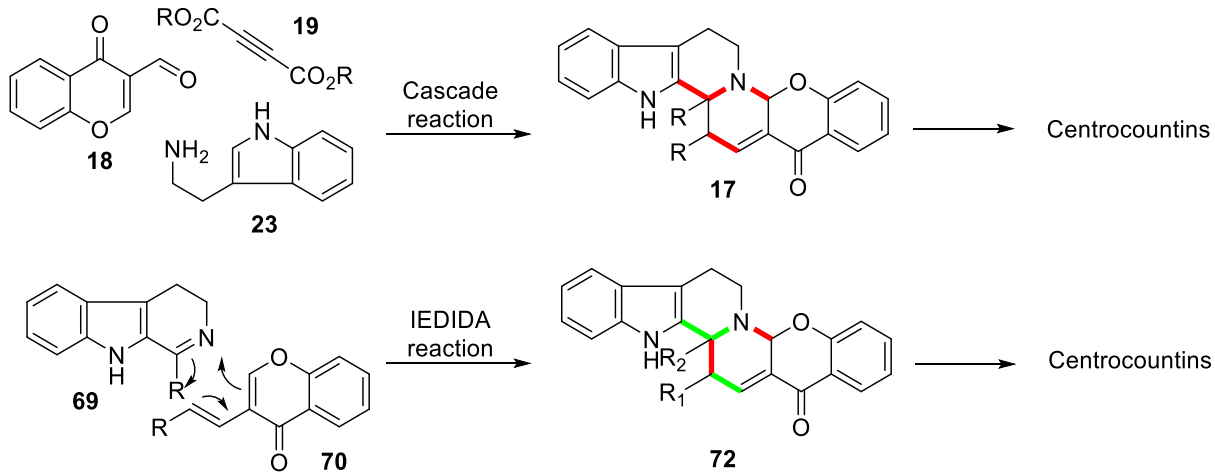
3.2. Design of the Synthetic Pathway to Centrocountin Analogues with the Hetero Diels-Alder Strategy

A [4+2] cycloaddition to form directly intermediate **33** (Scheme 3) was considered as the key step for the synthesis of centrocountin analogues and in general of natural product-inspired ring-fused quinolizines. With this aim, the reaction of indole-derived cyclic imines **69** as dienophiles with chromone olefins **70** as dienes was envisioned to synthesize tetrahydro[2,3-*b*]indoloquinolizines **72** via intermediate **71** (Scheme 19).



Scheme 19: Alternative synthesis of centrocountin analogues **72** by [4+2] cycloaddition.

The IEDIDA strategy would allow to introduce different substitutes at the positions R_1 and R_2, as these groups would be originating from each the diene and the dienophiles. This would allow to decorate the indoloquinolizine scaffold with different functional groups. (Scheme 20).



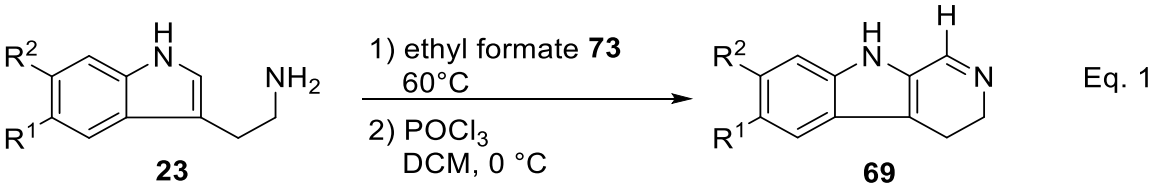
Scheme 20: Difference in the bond formation between the cascade reaction and the proposed IEDIDA reaction. The red line indicates the bonds formed during the main cycloaddition step. The green ones are formed by the synthesis of the substrates prior to the cycloaddition cascades.

3.3. Preparation of the IEDIDA Substrates

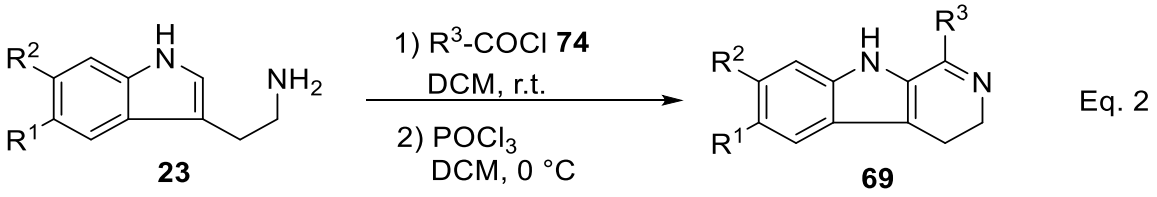
3.3.1. Preparation of the Cyclic Imines

The cyclic imines were synthesized following a reported procedure[75], in which tryptamines **23** were reacted with ethyl formate **73** leading to tryptamine-derived imines **69** (Eq. 1), or with an acyl chloride **74** to form the corresponding amide. After evaporation of the solvent was dissolved in DCM and treated with phosphorous oxychloride under argon to yield after purification by acid and basic extraction of the product the cyclic α-substituted imines **69** in good yields (Eq. 2 and Table 4).

Table 4: Preparation of cyclic imines **69**.



Eq. 1



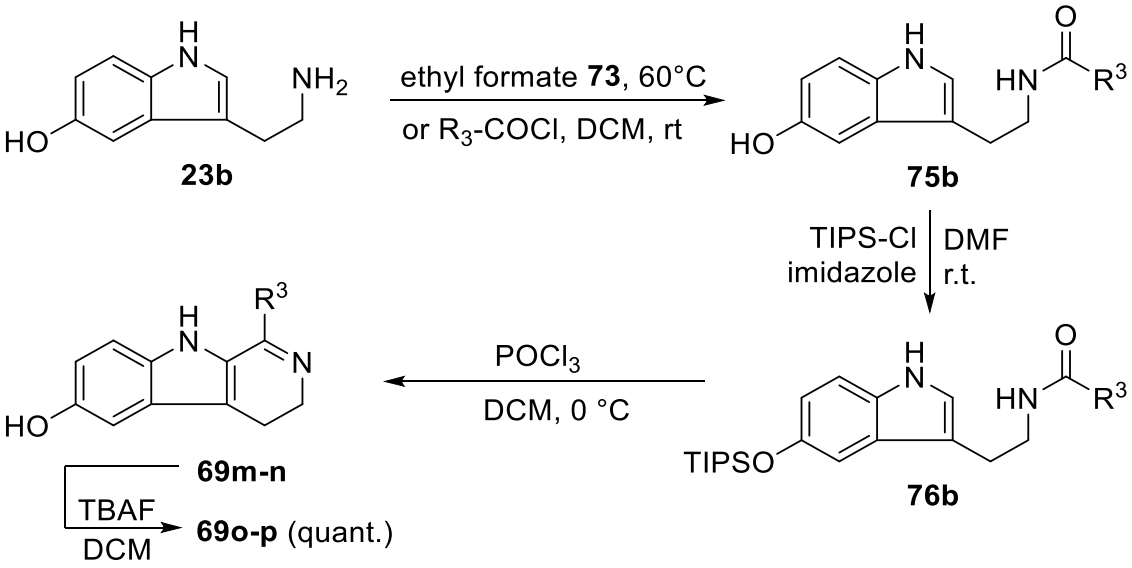
Eq. 2

Compound	R^1	R^2	R^3	Yield[a]
69a	H	H	H	63
69b	OMe	H	H	68
69c	OBn	H	H	59
69d	Me	H	H	64
69e	Cl	H	H	51
69f	H	H	Me	81
69g	OMe	H	Me	86
69h	H	H	Ph	59
69i	OMe	H	Ph	64
69j	OMe	H	Et	71

[a] Isolated yields

For imines derived from serotonin hydrochloride **23b**, the amine was first pre-dissolved in DMF due to solubility issues in ethyl formate and was then acylated to yield intermediate **75**. To avoid the reaction of the free hydroxyl group of serotonin with phosphorous oxychloride, amides **75** were protected with a triisopropylsilyl group to yield silyl ethers **76**, subsequent dehydratation proceeded smoothly to yield the targeted imines, albeit in low yields (Table 5). The same method was used for the formation of substituted imines through the acyl chloride pathway.

Table 5: Synthesis of cyclic imines from serotonin hydrochloride **23b**.



Compound	R^1	R^2	R^3	Yield[a]
69m	OTIPS	H	H	49
69n	OH	H	H	48
69o	OTIPS	H	Me	53
69p	OH	H	Me	52

[a] Isolated overall yields

3.3.2. Preparation of the Chromone Dienes

The dienes for the IEDIDA reaction were prepared by Wittig reaction[76], in which the chromone dienes were synthesized from 3-formylchromones **18** with various phosphoranylidenes **77** in DCM at room temperature (Table 6). The Z and E isomers were readily separated by flash chromatography, and were obtained in a (Z/E) ratio of 1:2 for the different chromone dienes **70** synthesized.

Table 6: Preparation of the chromone dienes **70**.

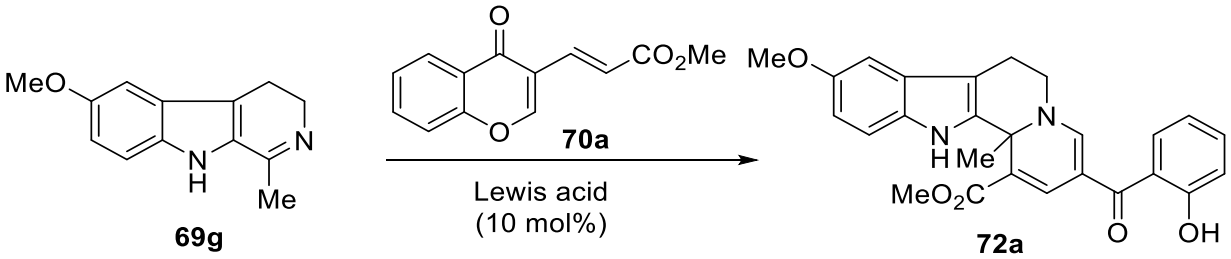
Compound	R^4	R^5	R^6	R^7	Yield[a] [%]
70a	H	H	H	CO_2Me	82
70b	F	H	H	CO_2Me	85
70c	Cl	H	H	CO_2Me	59
70d	Br	H	H	CO_2Me	54
70e	Me	H	H	CO_2Me	67
70f	Et	H	H	CO_2Me	64
70g	iPr	H	H	CO_2Me	63
70h	NO_2	H	H	CO_2Me	39
70i	H	H	H	CN	81
70j	F	H	H	CN	75
70k	Cl	H	H	CN	76
70l	Br	H	H	CN	69
70m	Me	H	H	CN	84
70n	Et	H	H	CN	85
70o	iPr	H	H	CN	74
70p	NO_2	H	H	CN	38
70q	H	H	H	CO_2Et	64
70r	F	H	H	CO_2Et	69
70s	Cl	H	H	CO_2Et	60
70w	H	H	H	COOH	48
70x	F	H	H	COOH	52
70y	Cl	H	H	COOH	46
70z	H	H	H	COPh	78

[a] Isolated yields of (Z)- and (E)-Isomers combined

3.4. Optimization of the Reaction Conditions for IEDIDA Reaction

Treatment of imine **69g** with diene **70a** in DMSO at 80 °C for 48 hours without any catalyst induced the IEDIDA reaction to form the desired indoloquinolizine **72a** in 61% yield. Both (Z)- and (E)-stereoisomers of the chromone diene **70a** led to the expected product in similar yields. However, for the sake of clarity, all the further attempted reactions were performed using the (E)-isomer exclusively. Different reaction conditions were tested to optimize the yield, the reaction time and the side product spectrum. Variation of solvent and temperature and exploration of different Lewis acids revealed that the cycloaddition proceeds best in the presence of $ZnCl_2$ in toluene or DMSO at 80 °C (Table 7). Similar results were obtained when the reaction was performed at lower temperature for longer time.

Table 7: IEDIDA reaction between imine **69g** and chromone diene **70a**.

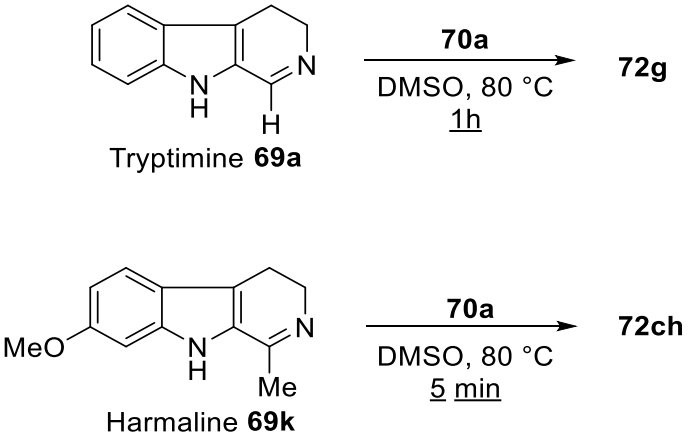


Entry	Lewis Acid	Solvent	Temperature	Reaction time	Yield[a] [%]
1	None	DMSO	80 °C	48h	61
2	$AlCl_3$	DCM	r.t.	12h	[b]
3	$ZnCl_2$	THF	60 °C	12h	-
4	$ZnCl_2$	DMF	80 °C	12h	-
5	$ZnCl_2$	DCM	r.t.	12h	69
6	$ZnCl_2$	toluene	80 °C	12h	83
7	$ZnCl_2$	DMSO	80 °C	1h	94
8	$ZnCl_2$	DMSO	r.t.	1h	85

[a] Isolated yields, [b] decomposition of the starting materials

3.5. Scope of the IEDIDA Reaction in the Synthesis of Indoloquinolizines

A total of 97 indoloquinolizines were synthesized using the optimised reaction conditions with substitutions on the indole-derived imine, as well as on the chromone diene. The yields of indoloquinolizines ranged from 67 to 93%. Harmaline **69k** was most reactive with reaction times of a few minutes, whereas unsubstituted tryptimines, like **69a**, required 1h for complete conversion (Scheme 21). α-Substitutients R^3 on the imine had a drastic effect on the reaction, the reaction was found impossible to happen with for R^3 different to H or methyl. Also, the reaction of α-methyl imines **69** only proceeded when a methoxy group was present on the indole ring. On the other hand, no influence of the substitution pattern on the chromone ring was observed regarding yield or reaction velocity. The indoloquinolizine **72** synthesized by the inverse electron demand imino Diels-Alder reaction are collected in Table 8.



Scheme 21: Reaction velocity for IEDIDA reactions with tryptimine **69a** and harmaline **69k**.

Table 8: Scope of the IEDIDA reaction to the indoloquinolizines.

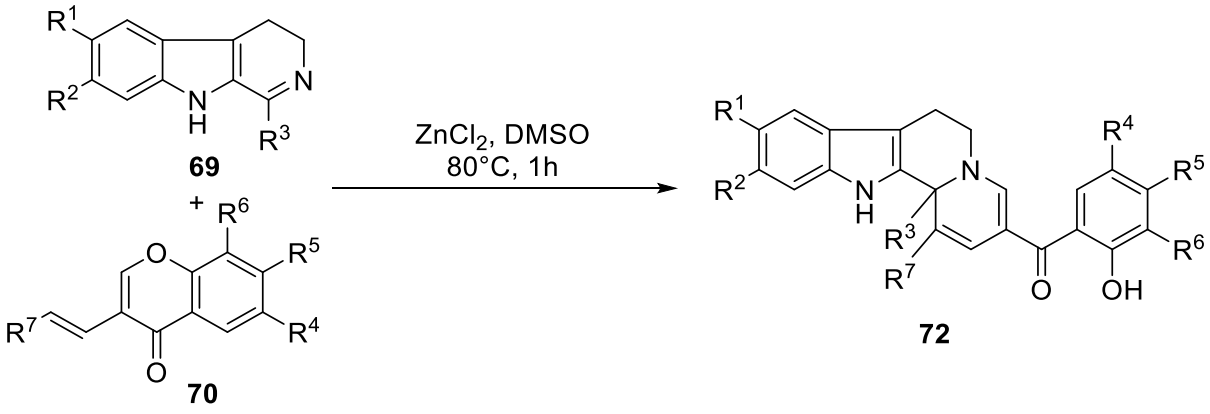


Table 8: Indoloquinolizine compound collection

Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield [%][a]
72a	OMe	H	Me	H	H	H	CO_2Me	94
72b	H	H	H	H	H	H	CO_2Et	82
72c	H	H	H	H	H	H	CO_2tBu	81
72d	H	H	H	H	H	H	CN	87
72e	H	H	H	H	H	H	COOH	74
72f	H	H	H	H	H	H	CO_2Me	71
72g	OMe	H	H	H	H	H	CO_2Me	95
72h	OMe	H	H	H	H	H	CO_2Et	82
72i	OMe	H	H	H	H	H	CO_2tBu	89
72j	OMe	H	H	H	H	H	CN	91
72k	OMe	H	H	H	H	H	COOH	72
72l	H	OMe	Me	H	H	H	CO_2Et	83
72m	H	OMe	Me	H	H	H	CO_2tBu	85
72n	H	OMe	Me	H	H	H	CN	89
72o	H	OMe	Me	H	H	H	COOH	72
72p	H	H	H	F	H	H	CO_2Me	77
72q	H	H	H	Cl	H	H	CO_2Me	79
72r	H	H	H	Br	H	H	CO_2Me	74
72s	H	H	H	Me	H	H	CO_2Me	83
72t	H	H	H	Et	H	H	CO_2Me	81
72u	H	H	H	iPr	H	H	CO_2Me	80
72v	H	H	H	NO_2	H	H	CO_2Me	84
72w	OMe	H	H	F	H	H	CO_2Me	90
72x	OMe	H	H	Cl	H	H	CO_2Me	88
72y	OMe	H	H	Br	H	H	CO_2Me	79
72z	OMe	H	H	Me	H	H	CO_2Me	84
72aa	OMe	H	H	Et	H	H	CO_2Me	91
72ab	OMe	H	H	iPr	H	H	CO_2Me	81
72ac	H	OMe	Me	F	H	H	CO_2Me	91
72ad	H	OMe	Me	Cl	H	H	CO_2Me	97
72ae	H	OMe	Me	Br	H	H	CO_2Me	80
72af	H	OMe	Me	Me	H	H	CO_2Me	94

[a] isolated yields

Table 8 (continued): Indoloquinolizine compound collection

Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield [%][a]
72ag	H	OMe	Me	Et	H	H	CO_2Me	85
72ah	H	OMe	Me	iPr	H	H	CO_2Me	79
72ai	H	OMe	Me	NO_2	H	H	CO_2Me	61
72aj	H	H	H	F	H	H	CN	92
72ak	H	H	H	Cl	H	H	CN	92
72al	H	H	H	Br	H	H	CN	83
72am	H	H	H	Me	H	H	CN	81
72an	H	H	H	Et	H	H	CN	90
72ao	H	H	H	iPr	H	H	CN	87
72ap	OMe	H	H	F	H	H	CN	91
72aq	OMe	H	H	Cl	H	H	CN	82
72ar	OMe	H	H	Br	H	H	CN	80
72as	OMe	H	H	Me	H	H	CN	87
72at	OMe	H	H	Et	H	H	CN	85
72au	OMe	H	H	iPr	H	H	CN	79
72av	H	OMe	Me	F	H	H	CN	91
72aw	H	OMe	Me	Cl	H	H	CN	97
72ax	H	OMe	Me	Br	H	H	CN	90
72ay	H	OMe	Me	Me	H	H	CN	98
72az	H	OMe	Me	Et	H	H	CN	92
72ba	H	OMe	Me	iPr	H	H	CN	89
72bb	OTIPS	H	H	H	H	H	CO_2Me	47
72bc	OTIPS	H	H	F	H	H	CO_2Me	51
72bd	OTIPS	H	H	Me	H	H	CO_2Me	47
72be	OTIPS	H	H	H	H	H	CN	51
72bf	OTIPS	H	H	F	H	H	CN	56
72bg	OTIPS	H	H	Me	H	H	CN	52
72bh	OEt	H	H	H	H	H	CO_2Me	74
72bi	OEt	H	H	F	H	H	CO_2Me	77
72bj	OEt	H	H	Me	H	H	CO_2Me	79
72bk	OEt	H	H	H	H	H	CN	79
72bl	OEt	H	H	F	H	H	CN	79
72bm	OEt	H	H	Me	H	H	CN	71

[a] isolated yields

Table 8 (continued): Indoloquinolizine compound collection

Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield [%][a]
72bn	Cl	H	H	H	H	H	CO_2Me	80
72bo	Cl	H	H	F	H	H	CO_2Me	71
72bp	Cl	H	H	Me	H	H	CO_2Me	82
72bq	Cl	H	H	H	H	H	CN	84
72br	Cl	H	H	F	H	H	CN	77
72bs	Cl	H	H	Me	H	H	CN	82
72bt	Me	H	H	H	H	H	CO_2Me	79
72bu	Me	H	H	F	H	H	CO_2Me	84
72bv	Me	H	H	Me	H	H	CO_2Me	84
72bw	Me	H	H	H	H	H	CN	90
72bx	Me	H	H	F	H	H	CN	87
72by	Me	H	H	Me	H	H	CN	92
72bz	H	OMe	Me	H	H	H	CO_2Me	91
72ca	OMe	H	Me	F	H	H	CO_2Me	90
72cb	OMe	H	Me	Me	H	H	CO_2Me	88
72cc	OMe	H	Me	H	H	H	CN	85
72cd	OMe	H	Me	F	H	H	CN	81
72ce	OMe	H	Me	Me	H	H	CN	78
72cf	H	OMe	H	H	H	H	CO_2Me	79
72cg	H	OMe	H	F	H	H	CO_2Me	71
72ch	H	OMe	H	Me	H	H	CO_2Me	72
72ci	H	OMe	H	H	H	H	CN	87
72cj	H	OMe	H	F	H	H	CN	89
72ck	H	OMe	H	Me	H	H	CN	83
72cl	H	H	H	H	Me	Cl	CO_2Me	81
72cm	H	H	H	H	Me	Cl	CN	84
72cn	H	OMe	Me	H	Me	Cl	CO_2Me	90
72co	H	OMe	Me	H	Me	Cl	CN	93
72cp	H	H	H	Cl	H	Cl	CO_2Me	89
72cq	H	H	H	Cl	H	Cl	CN	87
72cr	H	OMe	Me	Cl	H	Cl	CO_2Me	94
72cs	H	OMe	Me	Cl	H	Cl	CN	95

[a] isolated yields

3.6. Development of an Enantioselective Inverse Electron Demand Imino Diels-Alder Reaction

3.6.1. The Use of Chiral Catalysts

Enantioselective steering of a reaction may be accomplished by use of a chiral catalyst. Therefore, different metal-chiral ligand complexes were investigated as Lewis acids to form indoloquinolizines **72** enantioselectively.[77]

One important feature in the development of a stereoselective reaction, is the straightforward measurement of the stereoselectivity, in this case the determination of the enantioselective excess with which the product is obtained. The expression of the enantioselectivity is most commonly described as an enantiomeric excess.[78]

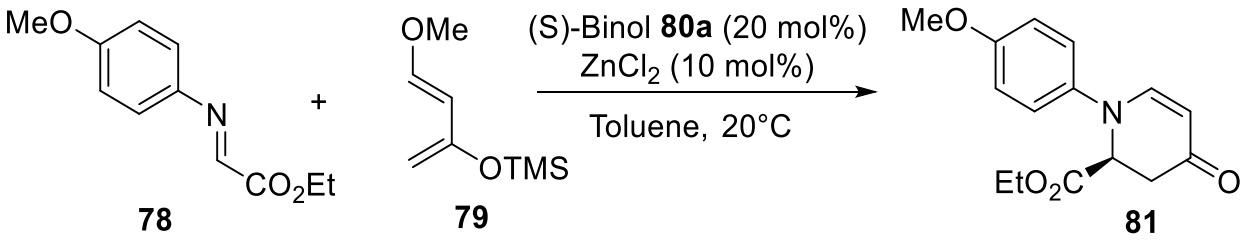
$$\%ee = \frac{R - S}{R + S} \times 100$$

The determination of the enantiomeric excess was, in this work, performed by the separation and the evaluation of the quantity of each enantiomer by high-pressure liquid chromatography employing a chiral stationary phase and UV detection. The CHIRALPAK® IC HPLC bulk stationary phase used in this work consists of a 20 µm silica support onto which the polymeric chiral selector: cellulose tris (3,5-dichlorophenylcarbamate) has been immobilized.

For the separation of the indoloquinolizines produced by imino Diels-Alder, the same solvent mixture was used as for the separation of the racemic mixture of centrocountins **17a** obtained in the 12-step cascade reaction as a racemic mixture, isohexane: dichloromethane: ethanol 80:20:1. The separation of a racemic mixture of a product was first performed to test the separation performance as well as to determine the position of the peaks for each enantiomer. The enantioselective excess was then determined by the comparison of the area below each peaks for the separation of stereoselective reaction products.

3.6.2. Development of the Enantioselective IEDIDA

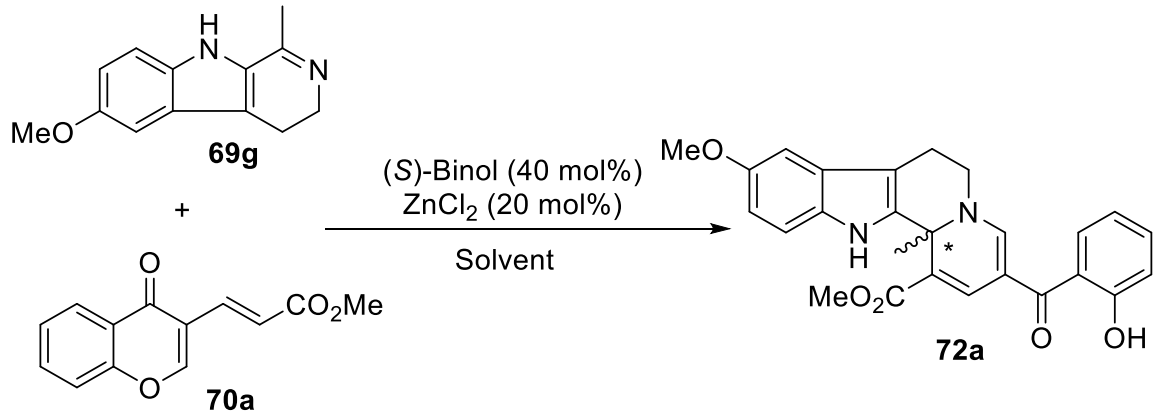
Binol ligands have previously been successfully used in the enantioselective catalysis of aza-Diels-Alder reactions catalyzed by Zn-Lewis acids.[67] Guillarme and Whiting employed a Zn-Binol complex in DCM or toluene at -78°C to room temperature to catalyze the normal electron demand imino Diels-Alder reaction of electron-poor α-iminoester **78** with electron-rich Danishefsky's Diene **79** (Scheme 22).



Scheme 22: Enantioselective normal electron demand imino Diels-Alder reaction with Danishefsky's diene **79**.

It was envisioned that tetra-coordination of zinc by the Binol ligand **80a**, the imine nitrogen and the vinylogous ester incorporated into the chromone-derived diene would allow for efficient steric discrimination in the ensuing cycloaddition reactions in the case of an inverse electron demand reaction as well.[79] With this hypothesis in mind, a procedure was crafted where the zinc complex was pre-formed from 20 mol% of the diethylzinc and 40 mol% Binol in the reaction solvent followed by the sequential addition of imine **69g** and diene **70a**. The mixture was then left reacting for 12h, purified and the enantiomeric excess was then determined by chiral HPLC. The reaction was investigated in different solvents: DMSO, DCM, toluene, THF and methanol (Table 9).

Table 9: Enantioselective IEDIDA reaction of **69g** and **70a**.

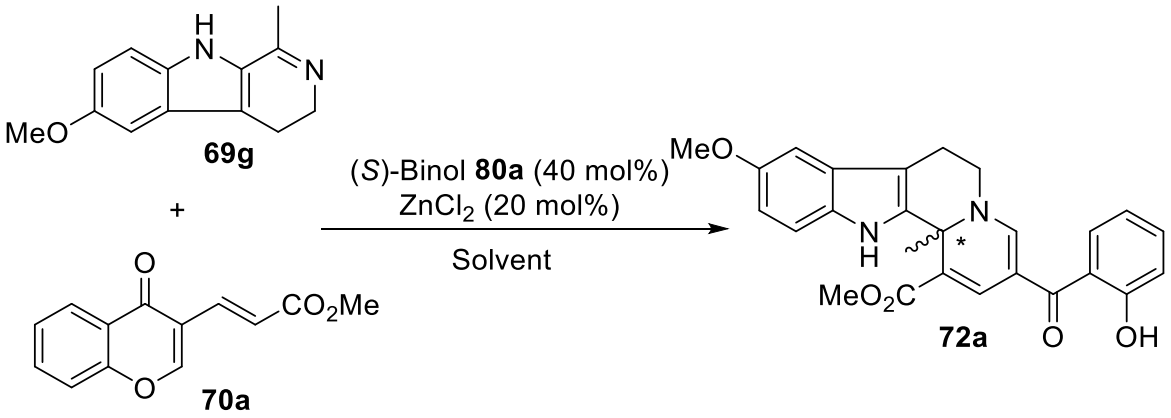


Entry	Metal	Ligand	Solvent	Temp.	Time	Yield [%][a]	ee%[b]
1	$ZnEt_2$	(*S*)-Binol	DCM	R.T.	1h	95	20
2	$ZnEt_2$	(*S*)-Binol	Toluol	R.T.	1h	83	24
3	$ZnEt_2$	(*S*)-Binol	MeOH	R.T.	1h	83	14
4	$ZnEt_2$	(*S*)-Binol	THF	R.T.	1h	75	5
5	**$ZnEt_2$**	**(*S*)-Binol**	**DMSO**	**R.T.**	**1h**	**88**	**27**

[a] Isolated yields, [b] Enantiomeric excess determined by chiral HPLC

The thermal imino Diels-Alder reaction between **69g** and **70a** proceeds without catalyst at room temperature, therefore only a low enantiomeric excess was observed in the test reactions. A decrease in the reaction temperature was considered as a parameter that would increase the enantiomeric excess, by slowing down the non-catalyzed racemic IEDIDA reaction. The screening of temperature was performed in DCM and toluene as these were the solvents showing the best yields and enantiomeric excess at room temperature (Table 10). Although the reaction in DMSO showed the highest enantioselectivity, it was not further used in the temperature screening as DMSO freezes at lower temperatures.

Table 10: Temperature screening for the enantioselective IEDIDA

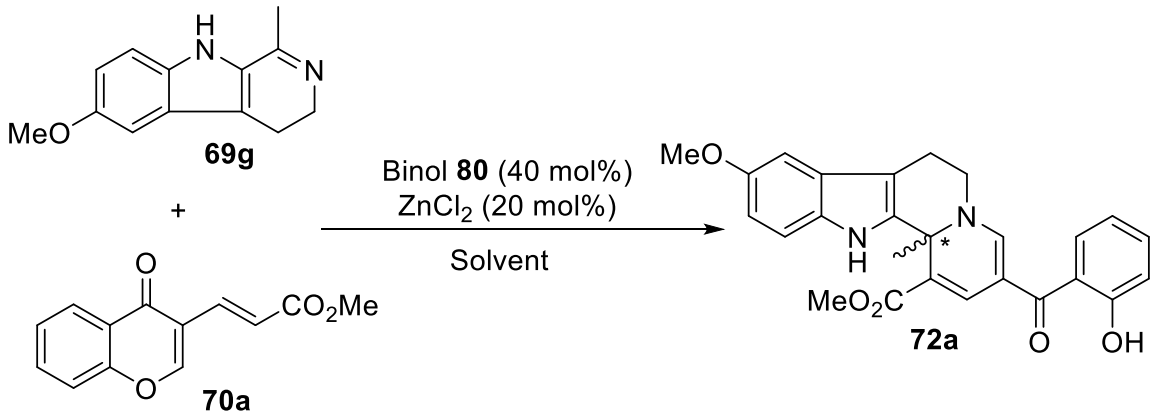


Entry	Metal	Ligand	Solvent	Temp. [°C]	Time	Yield %][a]	ee%[b]
1	$ZnEt_2$	(*S*)-Binol **80a**	DCM (0.02M)	20	1h	95	20
2	$ZnEt_2$	(*S*)-Binol **80a**	DCM (0.02M)	0	4h	80	31
3	$ZnEt_2$	(*S*)-Binol **80a**	DCM (0.02M)	-78	12h	71	47
4	$ZnEt_2$	(*S*)-Binol **80a**	Toluene (0.02M)	20	1h	83	24
5	$ZnEt_2$	(*S*)-Binol **80a**	Toluene (0.02M)	0	4h	72	39
6	**$ZnEt_2$**	**(*S*)-Binol 80a**	**Toluene (0.02M)**	**-78**	**12h**	**66**	**88**

[a] Isolated yields, [b] Enantiomeric excess determined by chiral HPLC

Treatment of imine **69g** and diene **70a** with a catalyst formed from 20 mol% of $ZnEt_2$ and 40 mol% of Binol in toluene at -78°C yields product **74a** in 66% yield and 88% ee. To explore the influence of the Binol ligands, Binol derivatives **80** substituted at the 3-position (Figure 7) were screened using the best reaction conditions determined (Table 11). The highest enantiomeric excess, 93%, was obtained using **80e** as a chiral ligand. This ligand embodies sterically demanding substituents at the 3- positions of the naphtalene rings. The use of dibromo-Binol **80b**, on the other hand led to the decomposition of the starting materials.

Table 11: Screening of the Binol ligands **80** in the development of the enantioselective IEDIDA.



Entry	Ligand	Temp.	Time	Yield [%][a]	ee%[b]
1	(*S*)-**80a** (40mol%)	-78°C	12h	66	88
2	(*R*)-**80a** (40mol%)	-78°C	12h	63	90
3	(*R*)-**80b** (40mol%)	-78°C	12h	-	-
4	(*R*)-**80c** (40mol%)	-78°C	12h	70	83
5	(*R*)-**80d** (40mol%)	-78°C	12h	51	93
6	**(*R*)-80e (40mol%)**	**-78°C**	**12h**	**13**	**89**

[a] Isolated yields, [b] Enantiomeric excess determined by chiral HPLC

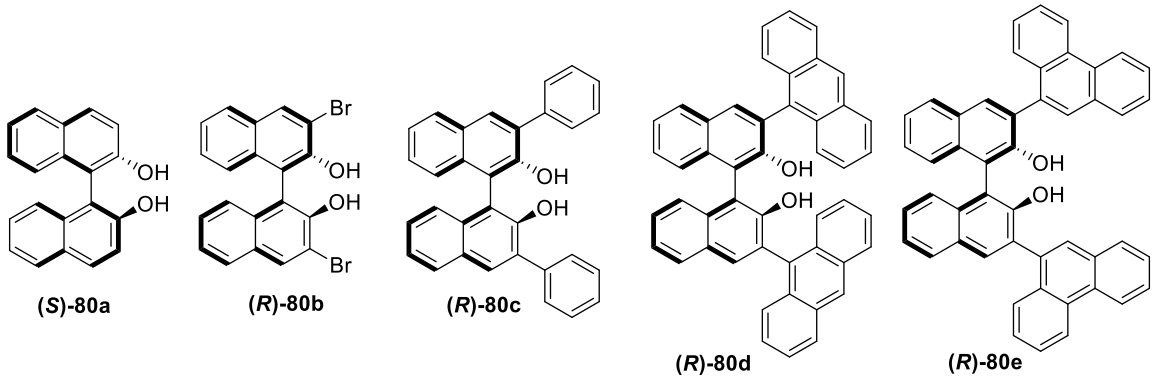


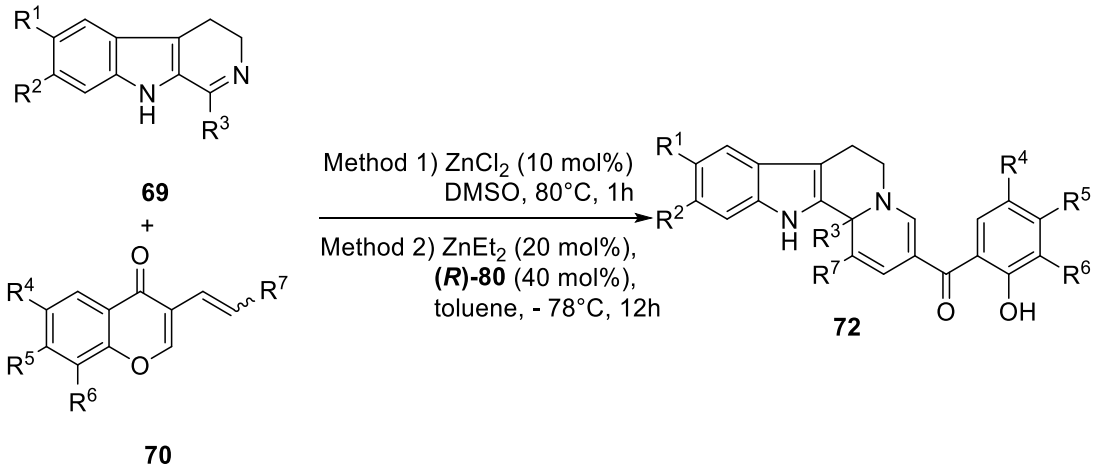
Figure 7: Binaphtol derivatives **80** tested in the screening of the enantioselective imino Diels-Alder reaction

3.6.4. Scope of the Enantioselective Reaction

In the IEDIDA reaction introduction of substituents into the chromone ring of the diene consistently yields cycloadducts with high ee and does not markedly influence the reactivity.

Thus, both chromenyl acrylates (**70a**, $R^7 = CO_2Me$) as well as chromenyl acrylonitriles (**70i**, R^7 = CN) react smoothly with imines **69** to provide indoloquinolizines **72** in excellent yields (Table 12).[80]

Table 12: Enantioselective synthesis of tetrahydroindoloquinolizines **72** by means of the IEDIDA reaction.



Entry	Prod.	Ligand	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield[a,b] [%]	Yield[a,c]/ee[d] [%]
1	**72a**	**(R)-80e**	H	OMe	Me	H	H	H	CO_2Me	94	81/95
2	**72a**	**(R)-80a**	H	OMe	Me	H	H	H	CO_2Me	94	94/93
3	**72d**	**(R)-80a**	H	H	H	H	H	H	CN	97	84/23
4	**72g**	**(R)-80a**	H	H	H	H	H	H	CO_2Me	71	82/19
5	**72j**	**(R)-80e**	H	OMe	Me	H	H	H	CN	89	79/91
6	**72p**	**(R)-80a**	H	OMe	Me	H	H	H	CN	89	97/86
7	**72ah**	**(R)-80a**	H	OMe	Me	Cl	H	H	CO_2Me	97	80/91
8	**72aj**	**(R)-80a**	H	OMe	Me	Me	H	H	CO_2Me	94	94/90
9	**72ch**	**(R)-80e**	OMe	H	Me	H	H	H	CO_2Me	91	51/93
10	**72ch**	**(R)-80a**	OMe	H	Me	H	H	H	CO_2Me	91	67/90
11	**72ck**	**(R)-80e**	OMe	H	Me	H	H	H	CN	85	82/92
12	**72ck**	**(R)-80a**	OMe	H	Me	H	H	H	CN	85	75/86
13	**72cz**	**(R)-80a**	H	OMe	Me	Cl	H	Cl	CO_2Me	94	95/71

[a] Isolated yields, [b] racemic synthesis, [c] enantioselective synthesis, [d] enantiomeric excess determined by chiral HPLC

However, electron-rich indole-derived imines incorporating at least one methoxy group are required for efficient product formation. Imines with a substituent R^3 at the imine carbon yielded the desired indoloquinolizines in very high yields and predominantly with high enantioselectivity. In contrast, in the absence of a substituent at the imine carbon (**69a**, R^3 = H) the enantioselectivity was only low. Despite the higher enantioselectivity observed with the use of anthracenyl binol **80e**, most of the investigation on the scope of the enantioselective version of the reaction was carried out for economic considerations with the unsubstituted binol **80a**. Indeed, the molar cost of **80e** is 100 times higher than for **80a**.

3.7. Determination of the Absolute Configuration

The three most common methods for the determination of the absolute configuration of a compound are X-ray crystallography, NMR analysis of chirally derivatized compounds, and CD-spectroscopy.

3.7.1. X-Ray Crystallography

X-Ray crystallography is the most reliable way to obtain the three-dimensional absolute structure of a molecule, and by extension its absolute configuration.[81,82] Once a single crystal is obtained and isolated, a beam of X-ray is projected on it and the intensity and angles of the diffraction patterns are analyzed to obtain the structure of the molecule.

Disappointingly, due to the low solubility of the indoloqunolizines in the most common solvents used in crystallization or recrystallization processes,[83] no single crystal was obtained for any of the compounds depicted in Figure 8a. Some crystallisation was attempted from concentrated solutions in DMSO, but none of these experiments led to satisfying results: the products either stayed in solution or precipitated abruptly, thus not producing any crystal.

Compounds containing nitro groups are known to crystallize better than the equivalent lacking the nitro group, therefore indoloquinolizine **72am** was synthesized for further crystallization attempts (Figure 8). This works as well with compounds containing bromine, with the additional advantage, that the determination of the absolute configuration is easier

for halogenated compounds. (Compound **72ap**). Nevertheless, none of these compounds crystallized either, so that X-ray crystallography was abandoned for the determination of the absolute configuration of the indoloquinolizines synthesized by imino-Diels-Alder reaction.

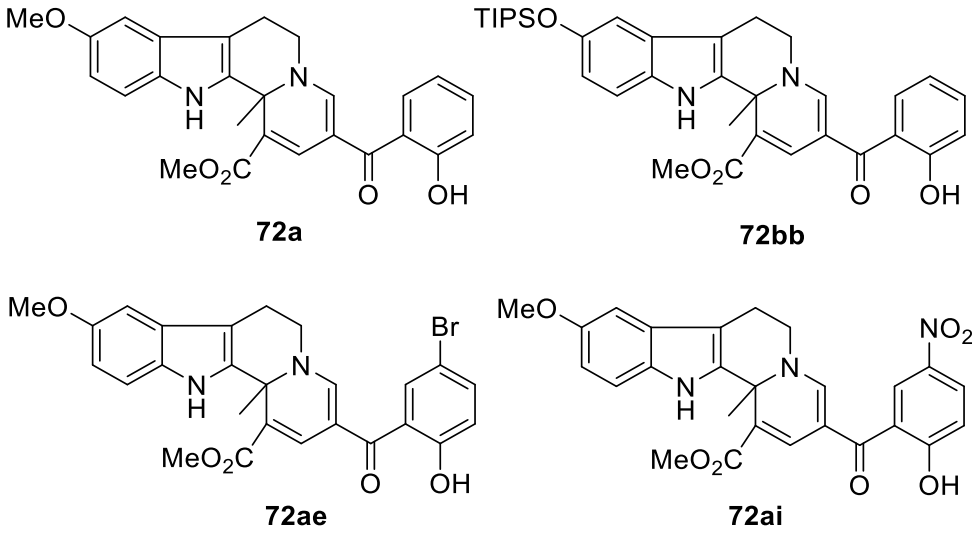


Figure 8: Attempted crystallisation of indoloquinolizines **72**.

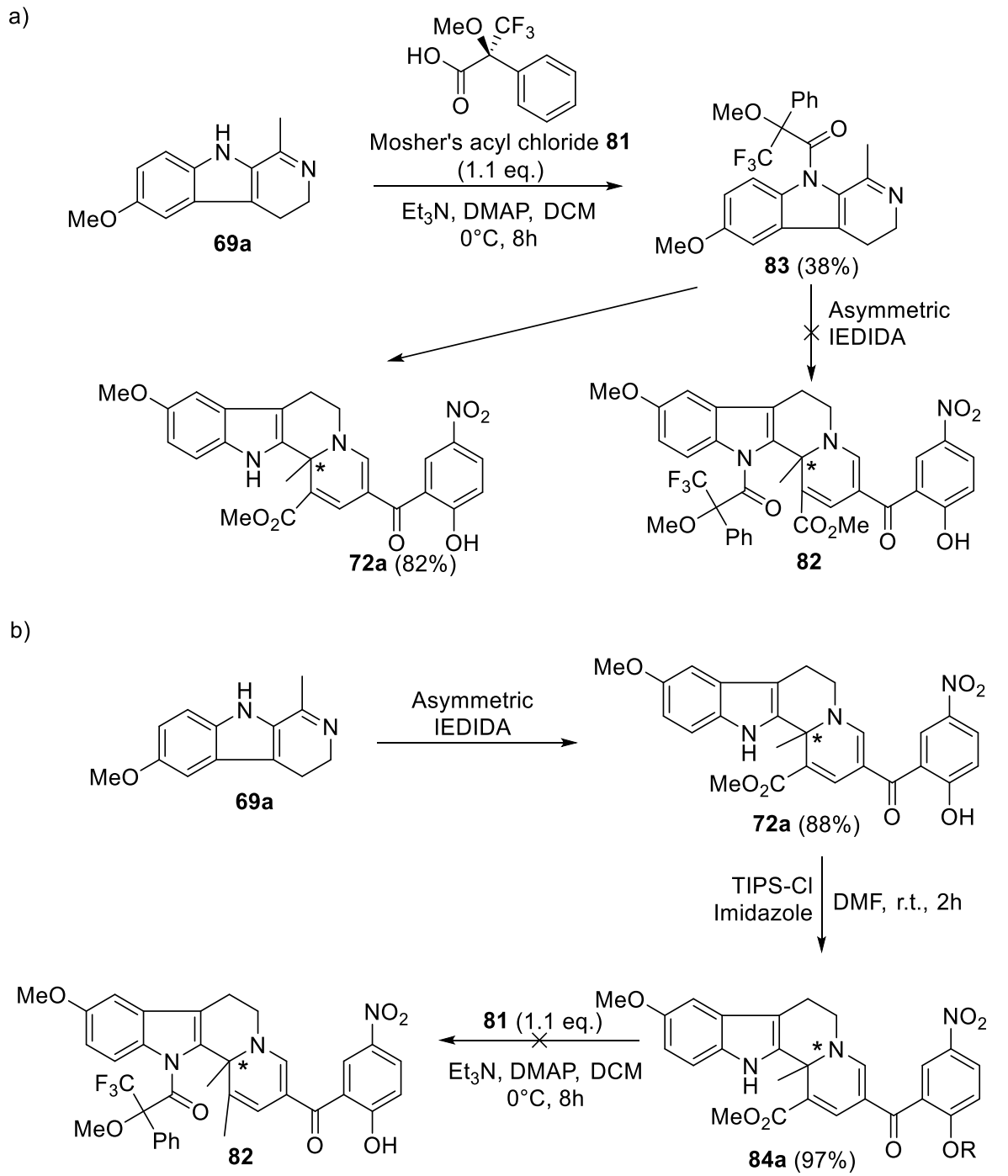
3.7.2. Chiral Derivatization

The chiral derivatization of indoloquinolizine **72** was envisaged for the determination of the absolute configuration by NMR analysis. It consists in the addition of a chiral auxillary with known stereochemistry to the Diels-Alder product, thus forming diastereoisomers with one known stereogenic center. The NMR properties of diastereoisomers may be different, and it is therefore possible to deduce the configuration of the remaining unknown stereogenic center based on a Nuclear Overhauser Effect (nOe) spectroscopy experiments.[84,85] In these experiments, the orientation and the distances of the protons in the molecule may be determined to discriminate the diastereoisomers, thus determining the absolute configuration of the unknown stereogenic center.[86,87]

Mosher's acyl chloride, or α-methoxy-α-trifluoromethylphenylacetyl choride **81** is a commercially available chiral derivatizing agent and is widely used for the determination of the enantiomeric composition of alcohols and amines. It is possible to determine the enantiomeric excess by separation and quantification of the formed diastereoisomers but also to determine the absolute configuration by NMR spectroscopy.[88–90]

Two strategies were followed for the synthesis of Mosher-derivatized indoloquinolizine **82**: on one hand, Mosher-functionalized tryptamine derived imine **83** was employed as a substrate for a subsequent enantioselective IEDIDA reaction with chromone diene **70a**. On the other hand, the synthesis of indoloquinolizine **72a** by asymmetric IEDIDA was followed by protection of the phenol and addition of the Mosher acyl chloride on the indole (Scheme 23). The formation of the Mosher-functionalized tryptamine derived imine **83** was performed following a described procedure[91], in the presence of triethylamine and DMAP in DCM at 0 °C.

Disappointingly, none of these experiments led to the targeted compound. The IEDIDA reaction resulted in the hydrolysis of the Mosher amide and the recovery of the non-functionnalized indoloquinolizine **72a** in high yields. The attempts at forming the Mosher amide from enantioselectively generated indoloquinolizines were not successful either, leading to no reaction. This is probably due to the steric hindrance between the Mosher acid and the quite rigid indoloquinolizine tetracycle.



Scheme 23: Strategies for the synthesis of Mosher-functionalized indoloquinolizine **82**.

3.7.3. CD Spectroscopy

The determination of the chirality by circular dichroism is a non-empirical method based on the Cotton effect, variation of optical rotation as a function of wavelength, and on the difference of absorption between left and right circularly polarized light.

The absolute configuration of imino Diels-Alder product **72a** was determined by comparison of its CD-spectrum with the spectrum recorded for the structurally closely related centrocountin-1 **17a** reported earlier (Figure 9).[40] The absolute configuration of centrocountins-1 was determined by circular dichroism as well. A circular dichroism spectrum was computed from ab-initio time dependent DFT calculations of its molecular chiroptical properties for one enantiomer of centrocountin-1 and compared with the experimental spectrum.[92,93] As depicted in Figures 9a and 9b, the profiles of the CD-spectra match very well with synchronized phase inversions, for both (*R)*- and (*S*)-enantiomers. The good agreement between the two spectra justifies the assignment of the absolute configuration by analogy as (*R*) for (-)-**72a** and (*S*) for (+)-**72a**. Thus (*S*)-configured ligand **80** induces the prefered formation of (*S*)-configured cycloadducts **72**.

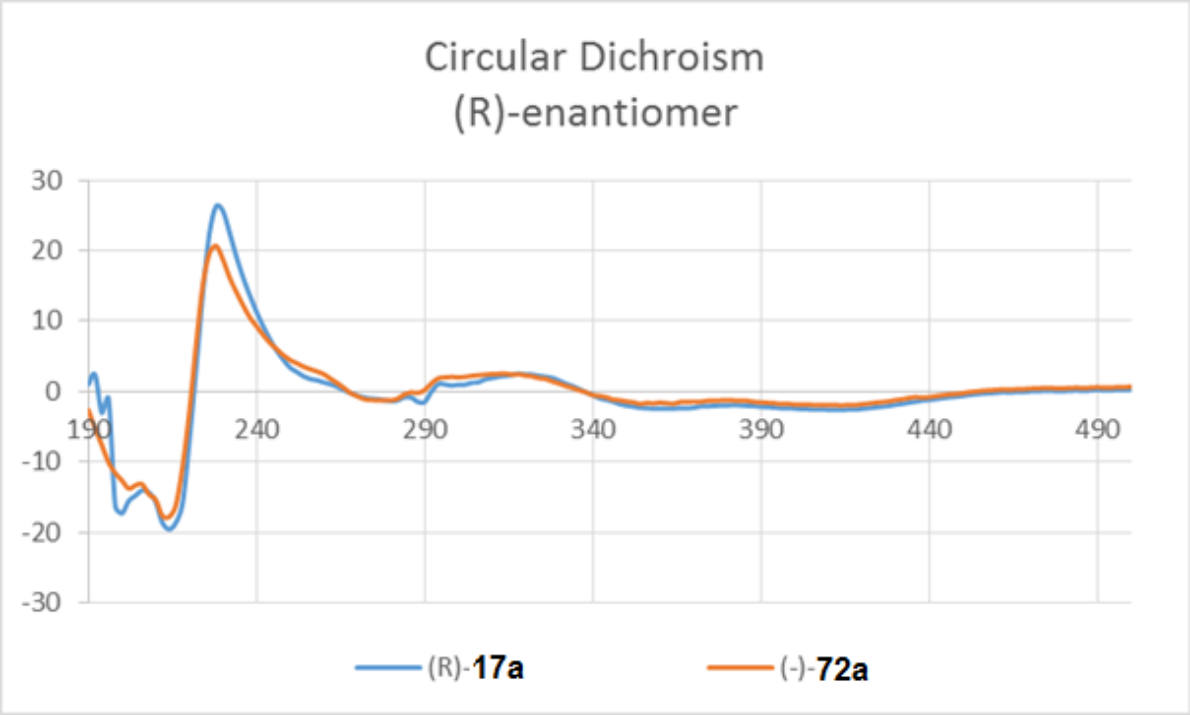


Figure 9a: Experimental CD-spectra of (*R*)-centrocountin-1 **17a** and (-)-**72a** in ethanol (wavelength in nm, CD in mdeg).

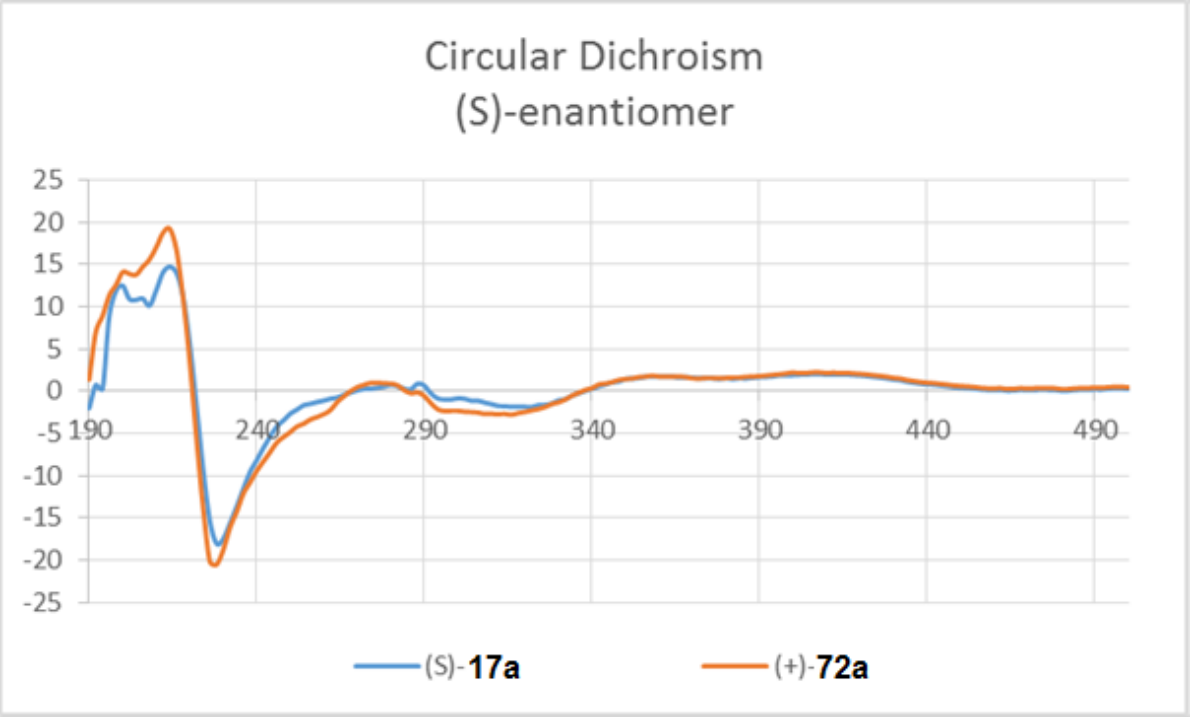


Figure 9b: Experimental CD-spectra of (*S*)-centrocountin-1 **17a** and (+)-**72a** in ethanol (wavelength in nm, CD in mdeg).

The CD spectra for four more enantiopure IEDIDA products were measured to determine the consistency of the measurements. The absolute configuration of the other indoloquinolizines was assigned by analogy. Analysis of the HPLC traces revealed that the (*R*) enantiomers have shorter retention times in all the separations.

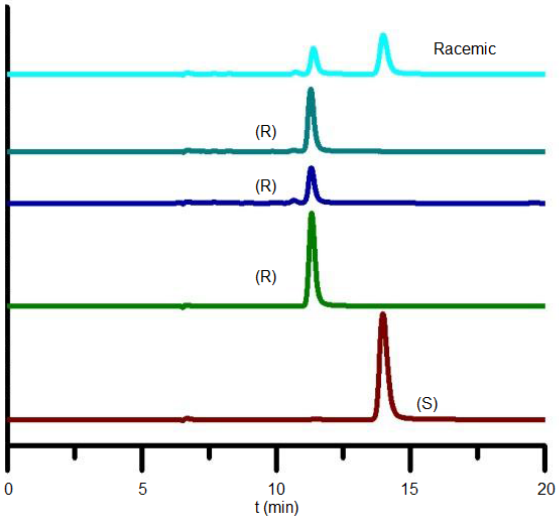


Figure 10: Superposition of chiral HPLC trace for determination of the absolute configuration of the centrocountins and indoloquinolizine analogues.

3.7.4. Mechanistic Considerations

The stereochemical course of the IEDIDA reaction can be rationalized by the formation of a preformed zinc-Binol complex which then coordinates the imine-nitrogen and the vinylogous ester oxygen of the diene (Scheme 24). In the ensuing complex **85**, one naphthalene ring would be oriented orthogonal to the plane of the heterodienophile and thus shields the *Si*-face of the imine. Thereby the attack of the diene is directed to the *Re*-face of the imines. α-Alkyl groups on the imines also avoid the steric bulk of the naphthalene ring which provides further steric bias and leads to high stereoselectivity.

c**Scheme 24:** Rationale for stereoselection in the asymmetric imino Diels-Alder reaction.

3.8. Conclusion and Outlook

An enantioselective inverse electron demand imino Diels-Alder reaction was developed for the synthesis of centrocountin-like indoloquinolizines **72**. The IEDIDA reaction of cyclic tryptamine-derived imines **69** with chromone dienes **70** went smoothly, in good yields and with enantioselectivity up to 94%. However, new classes of quinolizine molecules could also be synthesized using this reaction by replacing indole rings by other cycles in the imines. The expanded centrocountin-analogue compound collection accessible thereby opens up to establish a structure-activity relationship in plurotypical assays monitoring.

4. Synthesis of Ring-fused Tetrahydroisoquinolizines by IEDIDA

4.1. Introduction

It was planned to synthesize a compound collection of centrocountin-analogues in order to identify potent biologically active molecules exhibiting similar phenotypic effects on cancer cell lines as displayed by centrocountin-1 **17a**, and with improved activity and selectivity for the targets. Therefore, all compounds synthesized by the cascade or the imino Diels-Alder reaction were screened in a cell based assay. The extension of the compound library was then guided by the results of these screening results.

4.2. Phenotypical Screening and Structure-Activity Relationship

The cell biology work was performed by Philipp Küchler and Dr Slava Ziegler.

The synthesized compound collection was subjected to a phenotypic cell based screening in order to determine if it shares the bioactivity recorded for the centrocountins **17**.[94,95] Centrocountins impair centrosome integrity which leads to defects in chromosome congression and to an arrest of the cells in metaphase of mitosis. Human cervical carcinoma (HeLa) cells were treated with the compounds for 24 h, and the cells were then stained for DNA and the mitotic marker phospho-histone H3 to determine the proportion of cells arrested in mitosis. For the compounds inducing a mitotic arrest in cells higher than the

threshold of 10% of the cell population, a further experiment was performed in order to obtain pictures of the cells blocked in mitosis. Thus, HeLa cells were treated with 25µM of the hit compounds for 18h before staining for tubulin (green) and DNA (blue). In figure 11, for example, compound (*R*)-centrocountin-1 **17a** blocked mitosis in cells and induced chromosome congression defects (middle image) or aberrant spindle structures (right image) in comparison to the negative DMSO control.

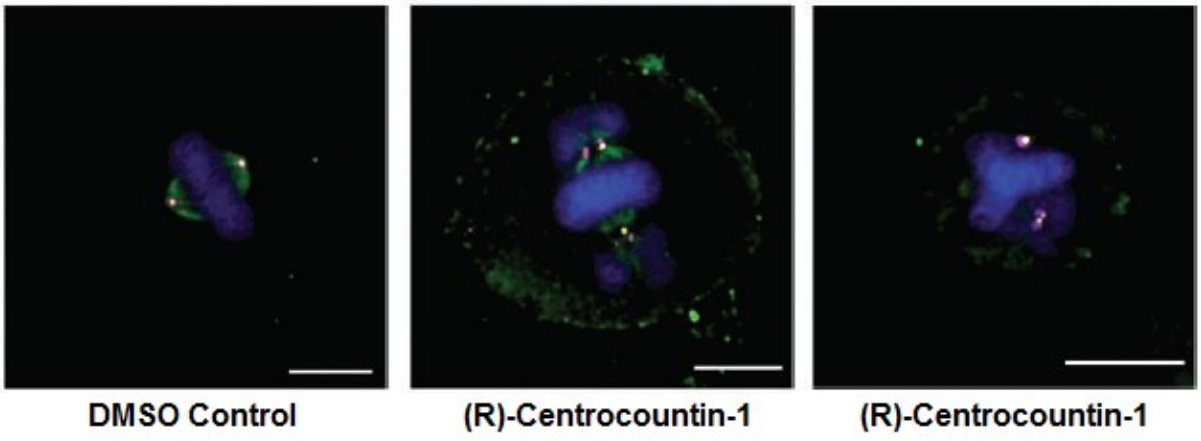


Figure 11: Representative images of mitotic cells treated with 25µM (R)-**17a**.

The screening of the indoloquinolizine library revealed 2 compounds, indoloquinolizines **72b** and **72h** showing a biological activity with similar phenotype as displayed by centrocountin-1 **17a** (Figure 12). However, the mitotic ratio of HeLa cells upon treatment with these compounds was lower than for centrocountin-1, and higher concentrations of the substances were required for a similar activity profile. These results led to further expansion of the compound collection by applying the inverse electron demand imino Diels-Alder reaction to new subclasses of molecules, and for instance replacing the indole ring with other heterocycles.

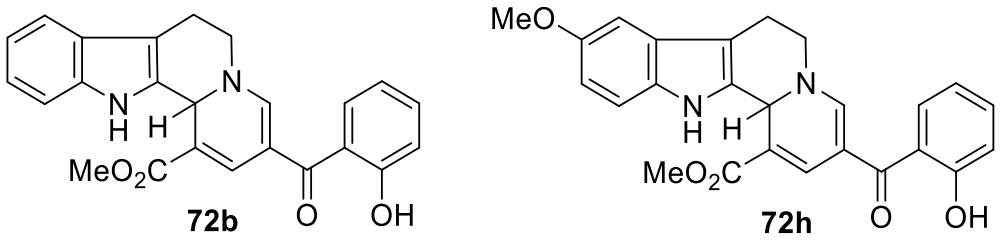


Figure 12: New active indoloquinolizines **72b** and **72h**.

4.3. Stability Considerations of Indoloquinolizines and Synthesis of Indolopyridinium Salts

4.3.1. Stability of Indoloquinolizine Samples

The mass analysis of indoloquinolizine **72h** stored as a 10 mM solution in DMSO at room temperature, 0°C or -25°C showed the formation of a new by-product over time with a molecular weight 2 units lower than the original compound (Figure 13). Some indoloquinolizines also showed a mass corresponding to the addition of an equivalent of water to the molecules.

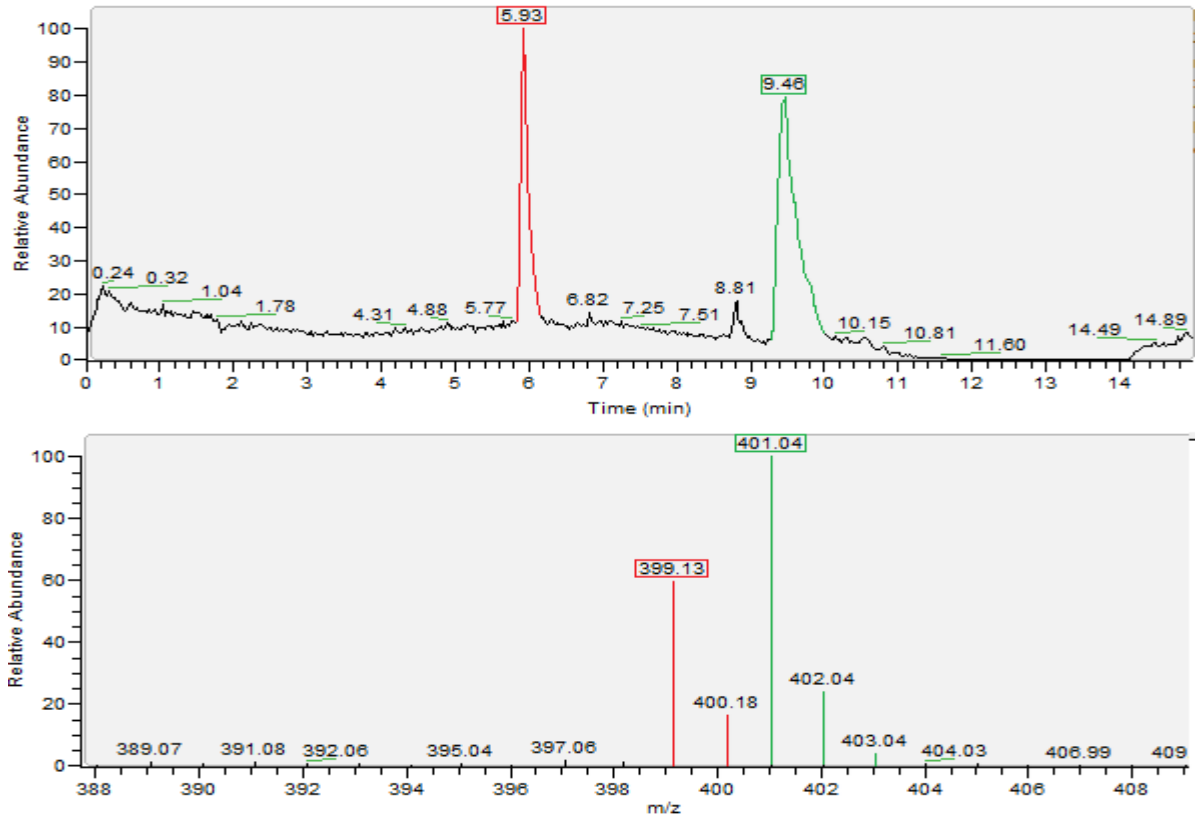


Figure 13: LC-MS Spectrum of a sample of **72h** conserved for 2 weeks in DMSO at room temperature. The substance with a retention time of 5.93 min displays a mass $[M+H]^+$ of 399, and the one at 9.46 min, a mass $[M+H]^+$ of 401.

Characterization of the byproduct by means of NMR spectroscopy hinted at aromatization of the indoloquinolizines to yield the corresponding indolopyridinium salts, e.g. **87e**, in which the positively charged quaternary amine forms an internal salt with the deprotonated

phenol (Figure 14). The ^{13}C NMR spectra also confirmed the formation of the pyridinium salts as oxidation products of the indoloquinolizines. Crystallization of the purified pyridinium was attempted for X-ray crystallographic analysis, but was not achieved due to the low solubility of the pyridinium salts in the most common crystallization solvents.

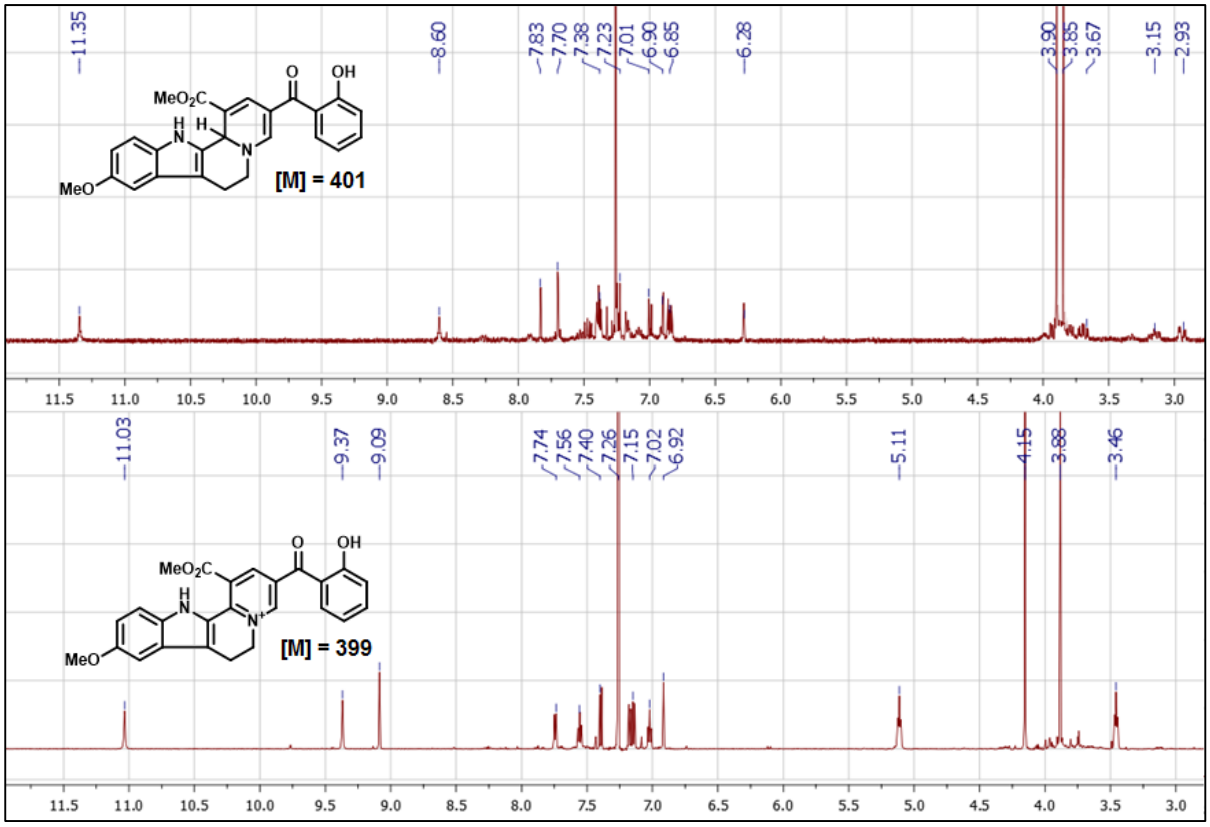
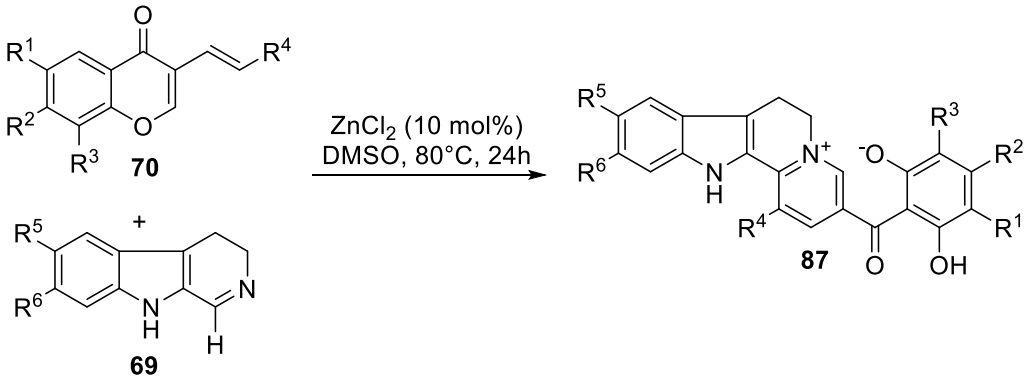


Figure 14: ^{1}H NMR spectra comparison between the fraction with mass 401 and 399. The major changes are the disappearance of the signal at 6.28ppm corresponding, and the displacement of the signals to 9.09 and 9.37 ppm corresponding to the pyridinium aromatic signals.

Monitoring the aromatization of indoloquinolizines showed that in the case of indoloquinolizine **72b**, in DMSO at room temperature 10% of pyridinium **87a** was formed over 4 weeks. Nitrile bearing indoloquinolizines showed the fastest aromatization, in which the byproducts already appear during the formation of the indoloquinolizines by IEDIDA reaction, and fully aromatize within one week at room temperature in DMSO solution as well as a dry solid.

Table 13: Synthesis of Indolopyridinium inner salts **87**.



Product	R^1	R^2	R^4	R^5	R^6	R^7	Yield[a] [%]
87a	H	H	H	H	H	CO_2Me	36
87b	H	H	H	H	H	CN	87
87c	H	H	H	H	F	CO_2Me	41
87d	H	H	H	H	F	CN	82
87e	OMe	H	H	H	H	CO_2Me	42
87f	OMe	H	H	H	H	CN	81
87g	H	H	H	H	Br	CN	92

[a] isolated yields

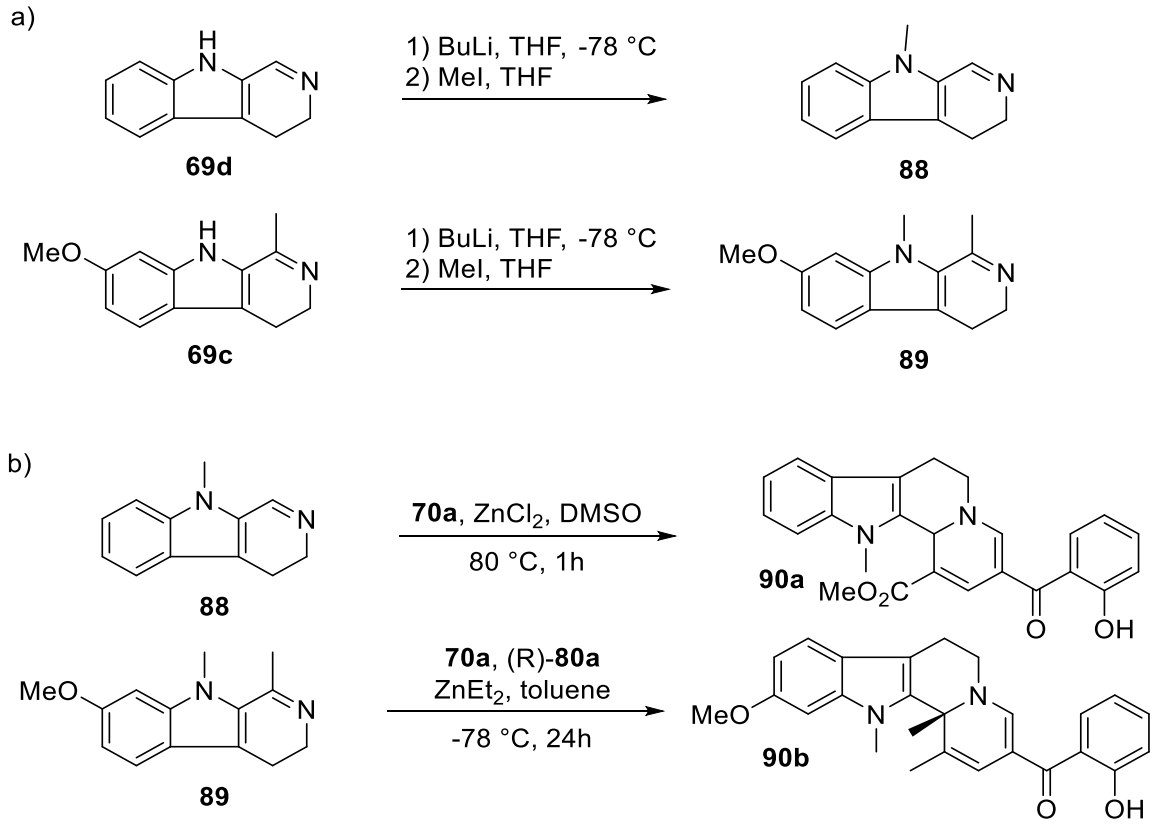
It was observed that indoloquinolizines with a hydrogen at the α-position to the amine undergo this aromatization process and not the analogues with alkyl chains. Forcing the formation of the pyridinium was achieved, on the one hand by using DDQ in DCM to oxidize the indoloquinolizine, and on the other hand in the case of nitrile bearing compounds, by simply heating to 80°C in DMSO, under these conditions oxidation of the quinolizine was complete within 24h (Table 13).

4.3.2. Attempts to Avoid Oxidation of Indoloquinolizines and to Induce Stability

To resolve the problem of the instability of the indoloquinolizines **72**, several solutions were considered in the synthesis of more stable analogues. However, the synthesis of these compounds either should not require too many additional steps from the original product, or include a direct IEDIDA reaction from easily modified imines or chromone dienes, to be suitable for a compound collection synthesis.

There are only a few positions where indoloquinolizines can be modified after their synthesis, i.e. the free NH of the indole, and the hydroxyl group of the phenol. It has been shown before for the centrocountins that modification of the phenolic OH renders the molecules inactive in HeLa cells. However, the protection of the indole was not attempted previously, and was therefore the major point of focus for the protection of indoloquinolizines against oxidation.

With this goal, tryptamine-derived imines were methylated at the indole NH following a reported procedure[96] and using methyl iodide and sodium hydride to form both methyl protected tryptimine **88** and methyl-protected harmaline **89** (Scheme 25a). These imines underwent the asymmetric IEDIDA reaction under standard conditions to yield the corresponding indoloquinolizines **90**, in very high yields and with high enantioselectivity (Scheme 25b).

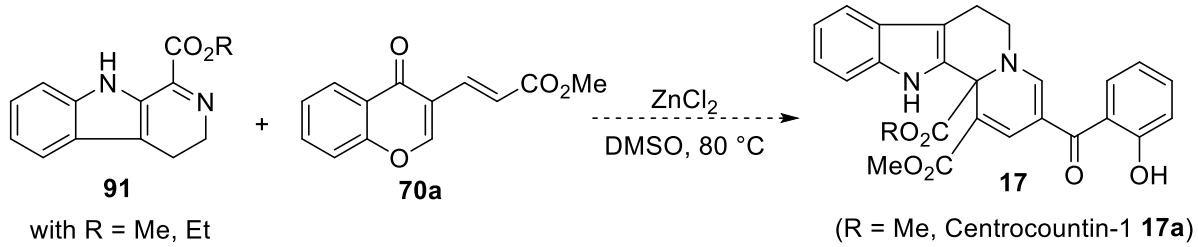


Scheme 25: Attempts at the stabilisation of the indoloquinolizines. a) Synthesis of N-methylated indole imines **88** and **89**. b) Synthesis of N-methylated indoloquinolizines **90**.

Analysis by mass spectrometry and ^{1}H NMR spectroscopy of a sample of indoloquinolizines **90** after two weeks in DMSO at room temperature indicated no decomposition or formation of the oxidation products. Thus the methyl-derivated indoloquinolizines **90** are stable alternatives to the initial indoloquinolizines. Disappointingly, the treatment of HeLa cells with these compounds did not reveal any activity with regard to mitotic arrest or chromosome alignment anomalies.

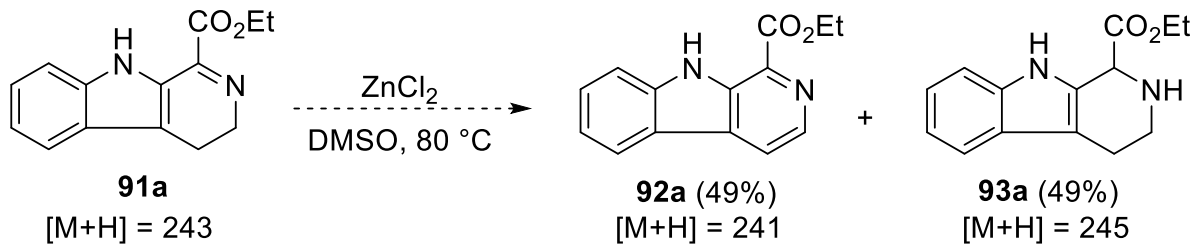
4.3.3. Synthesis of Centrocountin Analogues by IEDIDA

In order to incorporate an ester moeity in α-position to the imine in the indoloquinolizines (centrocountin has an ester at this carbon), tryptamine-derived iminoester **91** and chromone diene **70** were submitted to the imino Diels-Alder reaction (Scheme 26). The synthesis of these intermediates would have been interesting for the confirmation of the absolute configuration determination by synthesizing enantioselectively centrocountin-1 **17a** and closely related analogues by IEDIDA reaction. α-Iminoester **91** was synthesized following a procedure described by Tietze et al.[97], by reaction of tryptamine with ethyl glyoxylate in ethanol to form a cyclic amine that was then oxidized with potassium permanganate.



Scheme 26: Synthesis of centrocountin analogue **17**.

Disappointingly, the expected products were not formed. The NMR and mass analyses revealed the formation of carboline **92a** and amine **93a**, as products of the dismutation of α-iminoester **91a** (Figure 15 and Scheme 27).



91a
[M+H] = 243

92a (49%)
[M+H] = 241

93a (49%)
[M+H] = 245

Scheme 27: Dismutation of iminoester **91a**.

A set of screening reactions was performed in the absence of heating or zinc chloride and in different solvents, but the dismutation was always faster than the imino Diels-Alder reaction giving no traces of the targeted centrocountin **17**.

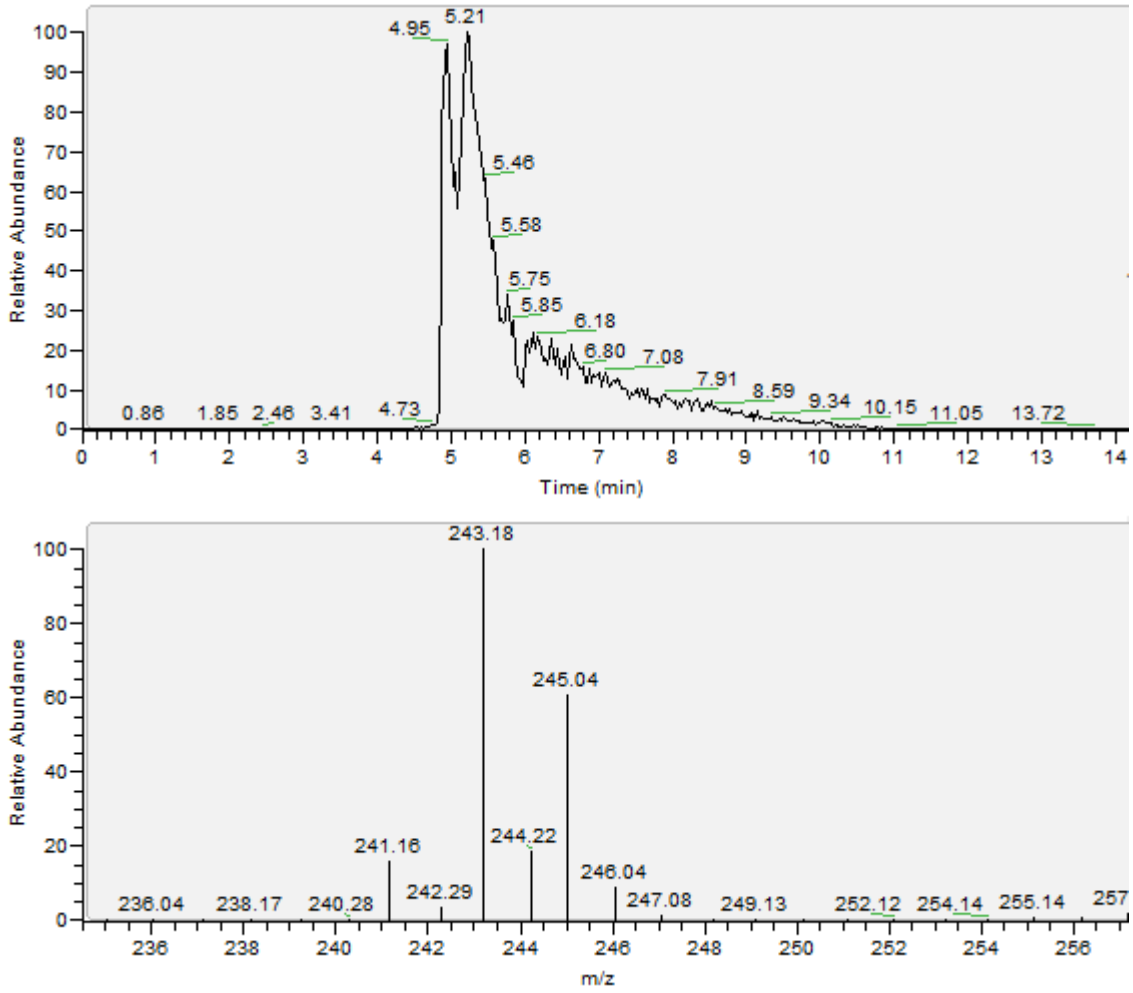


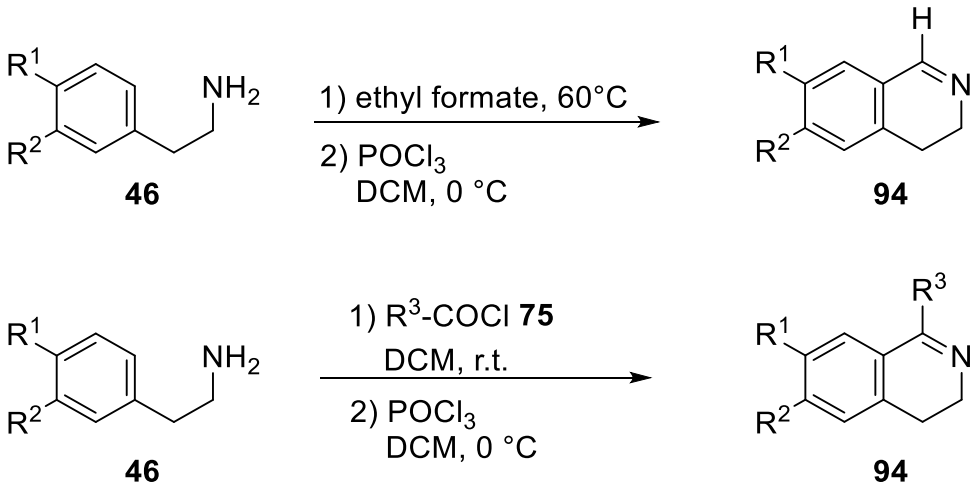
Figure 15: LCMS profile of the reaction outcome from α-iminoester **91a** after 5min in DMSO at room temperature with $ZnCl_2$.

4.4. Synthesis of Pyridoisoquinolines and Pyridoisoquinoliums

4.4.1. Preparation of the Dihydroisoquinolines

In order to study the importance of the indole ring on the biological activity, it was replaced with another ring-system. Therefore, it was planned to employ different cyclic imines embodying other aryl or hetero/carbocyclic rings. Several 3,4-dihydroisoquinolines **94** are commercially available, and in addition, further imines were synthesized from phenylethylamines **46** following the procedure described for the indole-derived imines **69** (Table 14).

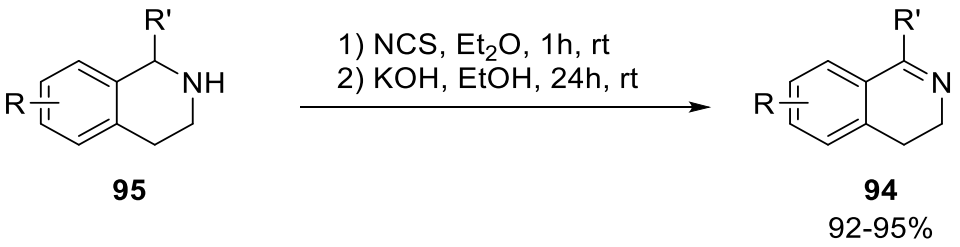
Table 14: Preparation of 3,4-dihydroisoquinolines **94** by Bischler-Napieralski reaction.



Compound	R^1	R^2	R^3	Yield[a]
94a	H	H	Et	83
94b	H	H	iPr	86
94c	H	H	Cy	74
94d	OMe	OMe	Et	89
94e	OMe	OMe	iPr	84

[a] isolated yields

An alternative method for the synthesis of these imines is the N-chlorination of cyclic amines **95** with N-chlorosuccinimide followed by treatment with KOH in ethanol (Scheme 28). This synthesis was adapted from the described procedure in Rouchaud and co-workers.[98]



Scheme 28: Preparation of 3,4-dihydroisoquinolines **94** by oxidation.

4.4.2. Development and Scope of the Reaction

The synthesis of the pyridoisoquinolines **96** was performed following the optimized general procedures for the racemic and asymmetric synthesis of indoloquinolizines **72.** Application of this method led to the formation of the desired products in appreciable yields and with enantiomeric excesses in similar ranges as observed for the indole-derived compounds. Moreover, some limitations observed previously for the IEDIDA synthesis of the indoloquinolizines were not recorded for isoquinolizines. For instance, it was possible to enantioselectively synthesize isoquinolizines bearing bigger groups on R^3 (Table 15), like ethyl-, iso-propyl- or cyclohexyl groups which was not possible for indole derivatives. A decrease of yield and enantioselectivity was observed in correlation with the increase in the size of the R^3 groups. The introduction of a phenyl group or an ester group at this position still remains challenging. 17 pyridoisoquinolines **96** were synthesized enantioselectively (Table 15), and 48 additional racemic pyridoisoquinolines **96** were synthesized with the IEDIDA reaction.

Table 15: Scope of the IEDIDA reaction to the pyridoisoquinolines **96**.

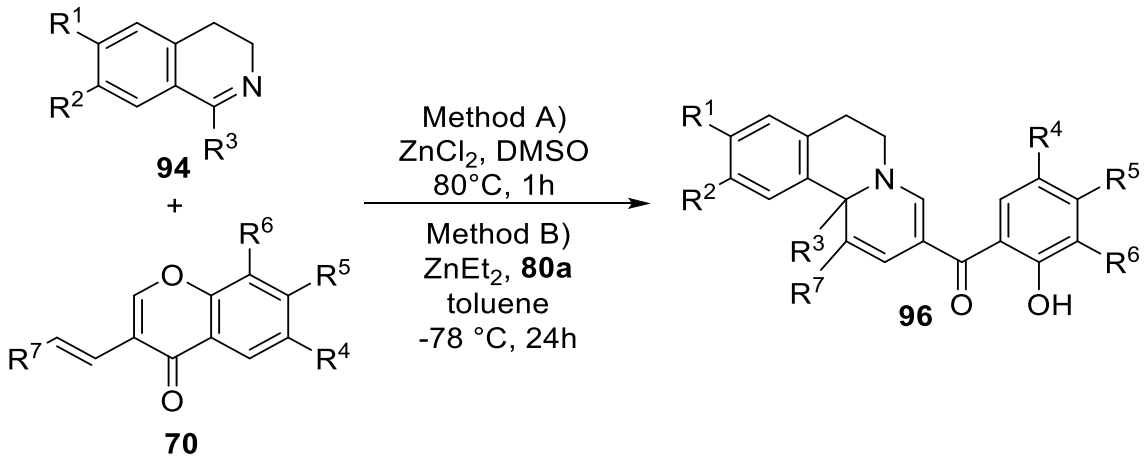


Table 15: Pyridoisoquinolines **96** compound collection.

Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield[a,b] [%]	Yield[a,c]/ee[d] [%]
96a	H	H	H	H	H	H	CO_2Me	93	81/27
96b	H	H	H	H	H	H	CO_2Et	92	-
96c	H	H	H	H	H	H	CO_2tBu	87	-
96d	H	H	H	H	H	H	CN	96	84/24
96e	H	H	H	H	H	H	COOH	79	-
96f	OMe	OMe	Me	H	H	H	CO_2Me	94	-
96g	OMe	OMe	Me	H	H	H	CO_2Et	93	-
96h	OMe	OMe	Me	H	H	H	CO_2tBu	82	-
96i	OMe	OMe	Me	H	H	H	CN	97	-
96j	OMe	OMe	Me	H	H	H	COOH	83	-
96k	OEt	OEt	Me	H	H	H	CO_2Me	76	71/83
96l	OEt	OEt	Me	H	H	H	CO_2Et	79	-
96m	OEt	OEt	Me	H	H	H	CO_2tBu	78	-
96n	OEt	OEt	Me	H	H	H	CN	77	80/83
96o	OEt	OEt	Me	H	H	H	COOH	64	-
96p	OH	OH	H	H	H	H	CO_2Me	51	-
96q	OH	OH	H	H	H	H	CN	52	-
96r	OH	OH	Me	H	H	H	CO_2Me	60	-
96s	OH	OH	Me	H	H	H	CN	63	-
96t	OH	OH	H	Cl	H	Cl	CO_2Me	49	-
96u	OH	OH	H	Cl	H	Cl	CN	47	-
96v	OH	OH	Me	Cl	H	Cl	CO_2Me	48	-
96w	OH	OH	Me	Cl	H	Cl	CN	53	-
96x	H	H	Me	H	H	H	CO_2Me	89	75/93
96y	H	H	Et	H	H	H	CO_2Me	84	54/83
96z	H	H	iPr	H	H	H	CO_2Me	80	51/69
96aa	H	H	Cy	H	H	H	CO_2Me	79	47/91
96ab	OMe	OMe	Et	H	H	H	CO_2Me	81	67/82
96ac	OMe	OMe	iPr	H	H	H	CO_2Me	84	-
96ad	OMe	OMe	Cy	H	H	H	CO_2Me	85	-
96ae	H	H	Me	H	H	H	CN	91	79/91
96af	H	H	Et	H	H	H	CN	83	-
96ag	H	H	iPr	H	H	H	CN	78	-

[a] Isolated yields, [b] racemic synthesis, [c] enantioselective synthesis, [d] enantiomeric excess determined by chiral HPLC

Table 15: Pyridoisoquinolines **96** compound collection. (continued)

Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield[a,b] [%]	Yield[a,c]/ee[d] [%]
96a	H	H	Cy	H	H	H	CN	64	-
96ai	OMe	OMe	Et	H	H	H	CN	93	-
96aj	OMe	OMe	iPr	H	H	H	CN	90	-
96ak	OMe	OMe	Cy	H	H	H	CN	83	41/83
96al	H	H	H	F	H	H	CO_2Me	90	-
96am	H	H	H	Cl	H	H	CO_2Me	90	-
96an	H	H	H	Br	H	H	CO_2Me	84	-
96ao	H	H	H	Me	H	H	CO_2Me	92	-
96ap	H	H	H	Et	H	H	CO_2Me	90	-
96aq	H	H	H	iPr	H	H	CO_2Me	93	-
96ar	OMe	OMe	Me	F	H	H	CO_2Me	97	-
96as	OMe	OMe	Me	Cl	H	H	CO_2Me	92	86/87
96at	OMe	OMe	Me	Br	H	H	CO_2Me	81	-
96au	OMe	OMe	Me	Me	H	H	CO_2Me	92	61/87
96av	OMe	OMe	Me	Et	H	H	CO_2Me	80	-
96aw	OMe	OMe	Me	iPr	H	H	CO_2Me	87	-
96ax	H	H	H	F	H	H	CN	89	-
96ay	H	H	H	Cl	H	H	CN	81	-
96az	H	H	H	Br	H	H	CN	70	-
96ba	H	H	H	Me	H	H	CN	88	-
96bb	H	H	H	Et	H	H	CN	91	-
96bc	H	H	H	iPr	H	H	CN	92	-
96bd	OMe	OMe	Me	F	H	H	CN	97	-
96be	OMe	OMe	Me	Cl	H	H	CN	96	90/83
96bf	OMe	OMe	Me	Br	H	H	CN	89	-
96bg	OMe	OMe	Me	Me	H	H	CN	94	84/80
96bh	OMe	OMe	Me	Et	H	H	CN	90	-
96bi	OMe	OMe	Me	iPr	H	H	CN	90	-
96bj	H	H	H	Cl	H	Cl	CO_2Me	90	-
96bk	H	H	H	Cl	H	Cl	CN	93	-
96bl	OMe	OMe	Me	Cl	H	Cl	CO_2Me	91	90/88
96bm	OMe	OMe	Me	Cl	H	Cl	CN	97	86/86

[a] Isolated yields, [b] racemic synthesis, [c] enantioselective synthesis, [d] enantiomeric excess determined by chiral HPLC

4.4.3. Pyridoisoquinolinium Salts

Stability experiments were performed with pyridoisoquinolines **96** (R^3 = H), to detect the formation of pyridoisoquinolinium zwitterionic salts **97**. Indeed, the formation of these pyridinium salts was also observed in DMSO samples at room temperature, however the amount (only 17% after 2 weeks for **97a**) was much smaller than for indoloquinolizines **72**. The nitrile bearing pyridoisoquinolines were oxidizing much faster here as well, and the corresponding pyridoisoquinoliniums **97** were obtained with yields up to 97% in DMSO at 80 °C (Table 16).

Table 16: Synthesis of pyridoisoquinolinium inner salts **97**.

Product	R^1	R^2	R^4	R^5	R^6	R^7	Yield[a] [%]
97a	H	H	H	H	H	CO_2Me	15
97b	H	H	H	H	H	CN	97
97c	H	H	H	H	F	CO_2Me	18
97d	H	H	H	H	F	CN	94
97e	OMe	OMe	H	H	H	CO_2Me	25
97f	OMe	OMe	H	H	H	CN	85
97g	H	H	H	H	Br	CN	96
97h	H	H	H	H	Et	CN	91
97i	H	H	H	H	iPr	CN	92
97j	H	H	H	H	NO_2	CN	79
97k	H	H	H	Cl	Me	CN	85
97l	H	H	Cl	H	Cl	CN	90

[a] isolated yields using Method A

4.4.4. Phenotypical Screening of the Pyridoisoquinolines

The screening of the compound collection of pyridoisoquinolines **96** and pyridoisoquinolinium salts **97** identified compounds that led to the accumulation of mitotic cells. When pyridinium salts **97** were found inactive, compound **96a** was identified as the

most potent, more potent than centrocountin-1 **17a** (Figure 16). Separate investigation of the enantiomers of **96a** revealed that only the (*S*)-configured cycloadduct arrested the cells in mitosis whereas the (*R*)-enantiomer was inactive at the applied concentrations (see Figure 16a). To further assess the ability of **96a** for inhibition of cell proliferation HeLa cells were treated for 48 h with (*R*)- and (*S*)-enantiopure **96a** as well as with racemic **96a** and cell viability was determined by means of the WST-1 reagent[99]. Whereas pyridoisoquinoline **96a** reduced the viability of HeLa cells with a half-maximal inhibitory concentration (IC_{50}) of 9.7 ± 1.1µM, (*S*)-**96a** more potently inhibited cell proliferation with an IC_{50} of 4.7 ± 0.5 µM (Figure 16b). The (*R*)-enantiomer again proved to be inactive. It was concluded that **96a** and (*S*)-**96a** were more potent than the centrocountin-1 **17a** (IC_{50} 17.2 ± 2.4 µM). Increase of the proportion of mitotic cells upon treatment with pyridoisoquinoline **96a** followed by cell death was independently confirmed by live cell imaging**.** Cell death was observed 24 hours after treatment of the cells with the compound. Immunostaining of DNA and tubulin revealed the same phenotype as for the centrocountins, with misaligned chromosomes during metaphase and tripolar spindles. (Figure 16c).

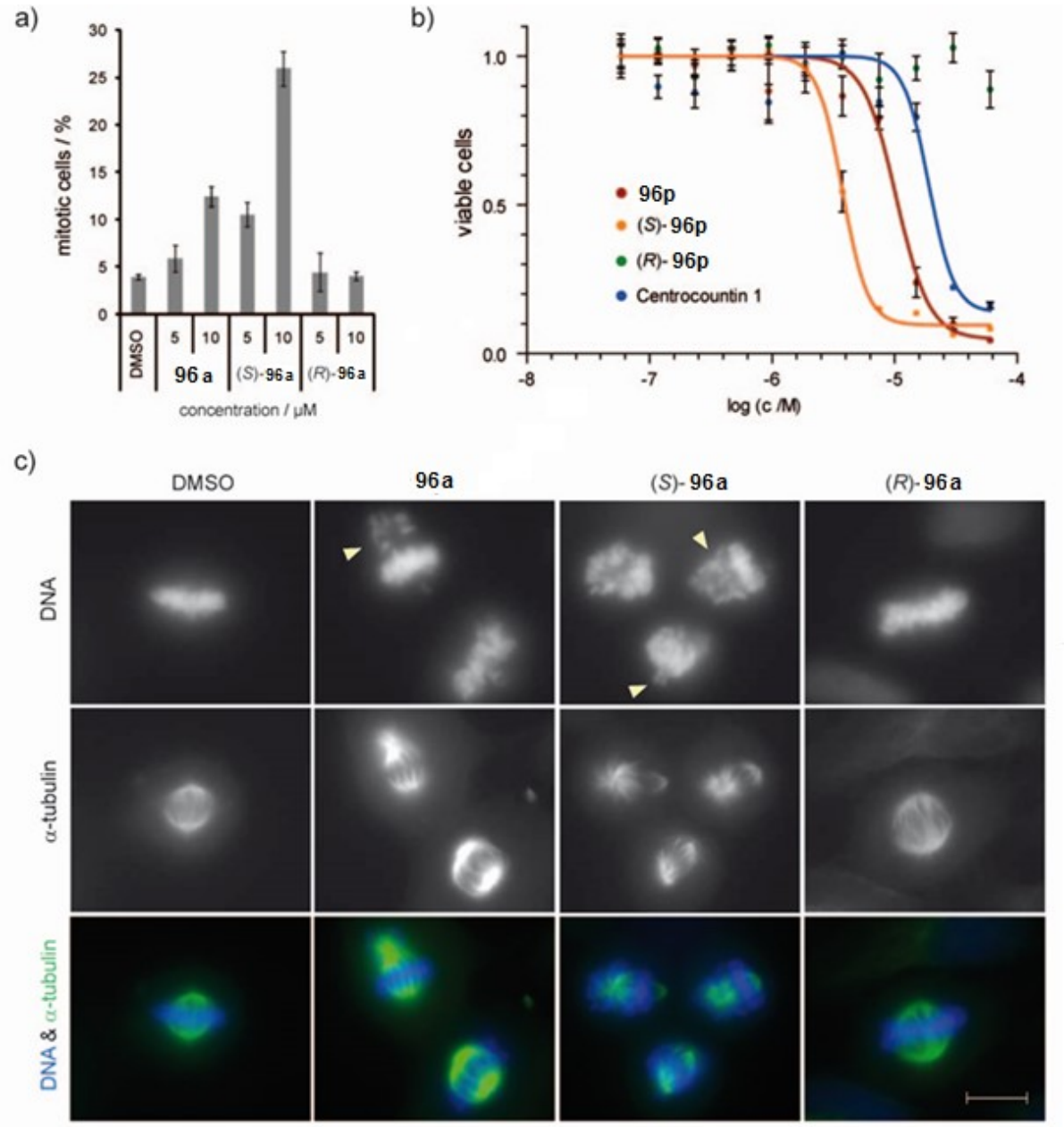


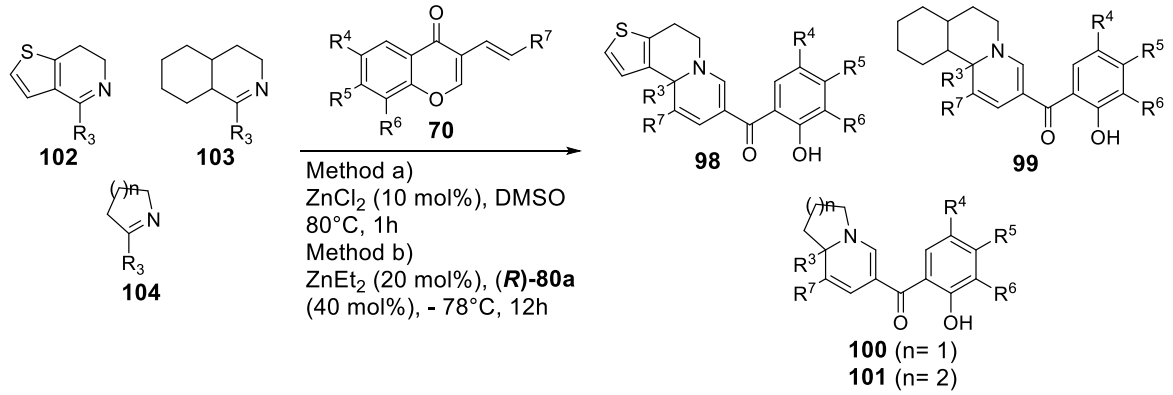
Figure 16: Pyridoisoquinoline **96a** induces chromosome congression defects and mitotic arrest in HeLa cells. a) HeLa cells were treated with enantiopure and racemic **96a** for 24 h prior to staining with anti-phospho-histone H3 antibody and DAPI to detect the mitotic marker and DNA respectively. Data are shown as mean values ± SD. b) Influence of **96a** and the enantiomers (*S/R*)-**96a** on the viability of HeLa cells. Cells were treated with the compounds for 48 h prior to determination of cell viability using the WST-1 proliferation reagent. Data were normalized to DMSO and represent mean values ± SD. c) **96a** and (*S*)-**96a** cause chromosome congression defects. (*R*)-**96a** is inactive. HeLa cells were treated with compounds at a concentration of 10 µM for 24 h prior to staining with anti-α-tubulin

antibody coupled to FITC (green) and DAPI (blue) to visualize tubulin and DNA respectively. Arrows indicate misaligned chromosomes during metaphase. *Scale bar: 10 µm.*

4.5. Synthesis of Ring-fused Quinolizines

Exploration of the scope of the reaction was attempted by replacing the indole or phenyl groups by other cycles like thiophene, cyclohexane or by the synthesis of bicyclic quinolizines. The synthesis of these new compound subclasses **98-101** (Table 17), proceeded under the same reaction conditions as applied for the synthesis of indoloquinolizines **72**.

Table 17: Synthesis of ring-fused quinolizines **98-101**.



Product	R^4	R^5	R^6	R^7	Yield[a] [%]	Yield [%][a] / ee[c] [%]
98a	H	H	H	CO_2Me	87	- / -
98b	H	H	H	CN	91	- / -
99a	F	H	H	CO_2Me	95	- / -
99b	F	H	H	CN	97	- / -
99c	H	H	H	CO_2Me	77	- / -
99d	H	H	H	CN	83	- / -
100a	Br	H	H	CO_2Me	66	62/44
100b	Et	H	H	CN	68	62/29
101a	iPr	H	H	CO_2Me	51	- / -
101b	NO_2	H	H	CN	54	- / -

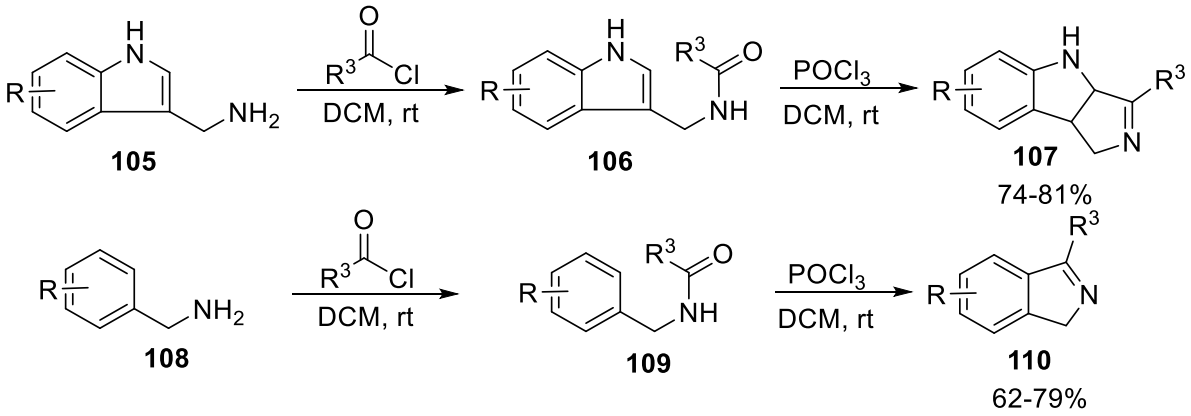
[a] isolated yields using Method A, [b] isolated yields using method B, [c] enantiomeric excess determined by chiral HPLC.

However, compounds **98, 99** and **101** proved to be unstable and the measurement of the enantiomeric excess by chiral HPLC was not successful as the compounds decomposed before or during the measurements. For dihydroquinolizines **100**, the enantiomeric excess was low, possibly due to a lack of chiral bias in the absence of any directing aromatic cycle that could interact with the naphtalene of the Binol ligands.

4.6. Synthesis of Indoloindolizines and Dihydropyridoisoindoles

4.6.1. Preparation of the Methanamine Derived Imines

The indolemethanamine derived imines **107** and benzylamine derived imines **110** were synthesized as described above for the tryptamine and the phenylethylamine derived imines by Bischler-Napieralski reaction in good yields (Scheme 29).

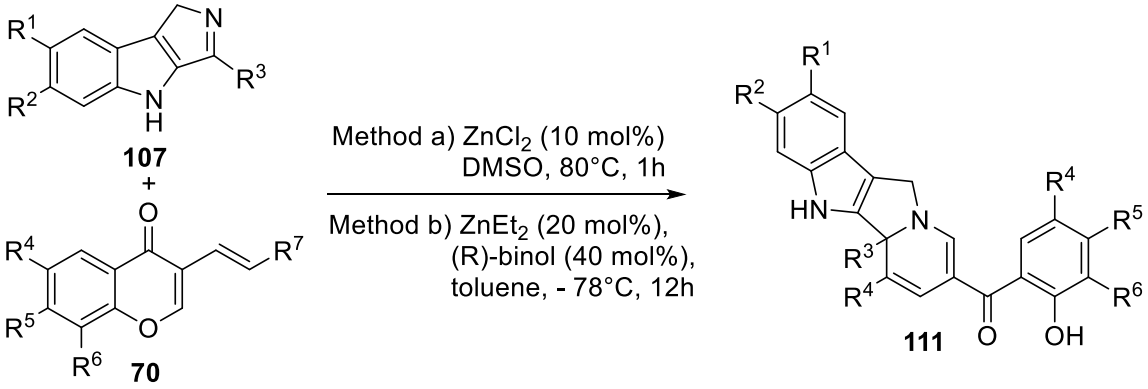


Scheme 29: Preparation of the cyclic imines **107** and **110**.

4.6.2. Development and Scope of the Reaction

No further optimization of the IEDIDA reaction was required for the reaction of cyclic imines **107** and **110** and chromone dienes **70**. A small collection of these dihydroindoloindolizines **111** was synthesized in order to evaluate their biological activity compared to centrocountin-1 **17a** as well as to compound **96a** (Table 18). The yields, reaction velocity and enantioselectivity were coherent with the observations made for the synthesis of indoloquinolizines **72** by means of the imino Diels-Alder reaction. However, none of these compounds was active in the cell based assay.

Table 18: Synthesis of dihydroindoloindolizine **111**.



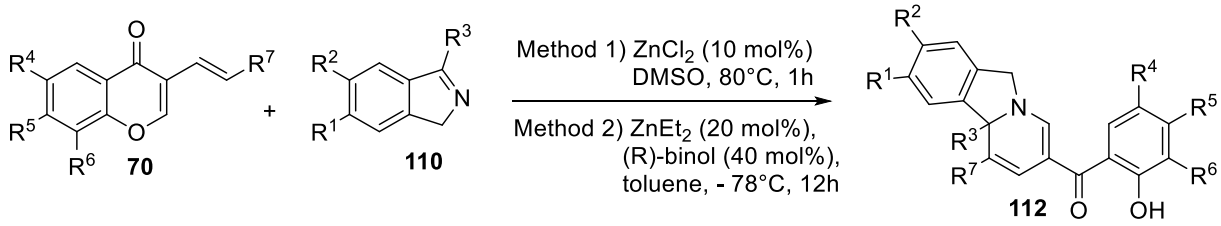
Product	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield[a/b] [%]	ee[c] [%]
111a	H	OMe	Me	H	H	H	CO_2Me	-/97	84
111b	H	OMe	Me	F	H	H	CO_2Me	-/97	74
111c	H	OMe	Me	H	H	H	CN	-/91	92
111d	H	OMe	Me	F	H	H	CN	-/92	88
111e	H	H	H	H	H	H	CO_2Me	78/-	-
111f	H	H	H	F	H	H	CO_2Me	79/-	-
111g	H	H	H	H	H	H	CN	68/-	-
111h	H	H	H	F	H	H	CN	64/-	-

[a] isolated yields using method A, [b] isolated yields using method B, [c] enantiomeric excess determined by chiral HPLC.

4.6.3. The Dihydropyridoisoindoles

Similarly, dihydropyridoisoindoles **112** were synthesized following the general procedures and using cyclic imines, synthesized from benzylamines by Bischler-Napieralski reaction (Table 19). Dihydropyridoisoindoles **112** were obtained in comparable yields and enantiomeric excesses, and had similar properties compared to the pyridoisoquinolines **96**. However, no formation of pyridinium or other byproduct was observed this time, making them interesting compounds for chemical biological investigations. Disappointingly, dihydropyridoisoindoles **112** also did not show any activity in the phenotypical screening.

Table 19: Synthesis of dihydropyridoisoindole **112**



Product	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield[a/b] [%]	ee[c] [%]
112a	OMe	OMe	Me	H	H	H	CO_2Me	-/83	79
112b	OMe	OMe	Me	F	H	H	CO_2Me	-/86	82
112c	OMe	OMe	Me	H	H	H	CN	-/79	84
112d	OMe	OMe	Me	F	H	H	CN	-/74	77
112e	H	H	H	H	H	H	CO_2Me	78/-	-
112f	H	H	H	F	H	H	CO_2Me	82/-	-
112g	H	H	H	H	H	H	CN	67/-	-
112h	H	H	H	F	H	H	CN	68/-	-

[a] isolated yields using method A, [b] isolated yields using method B, [c] enantiomeric excess determined by chiral HPLC.

Lacking of biological activity of compounds **111** and **112** might be due to the change in the 3D structure of the compound compared to the ring-fused quinolizines **72** or **96**. This difference in geometry is depicted in the computed structures shown in Figure 17.

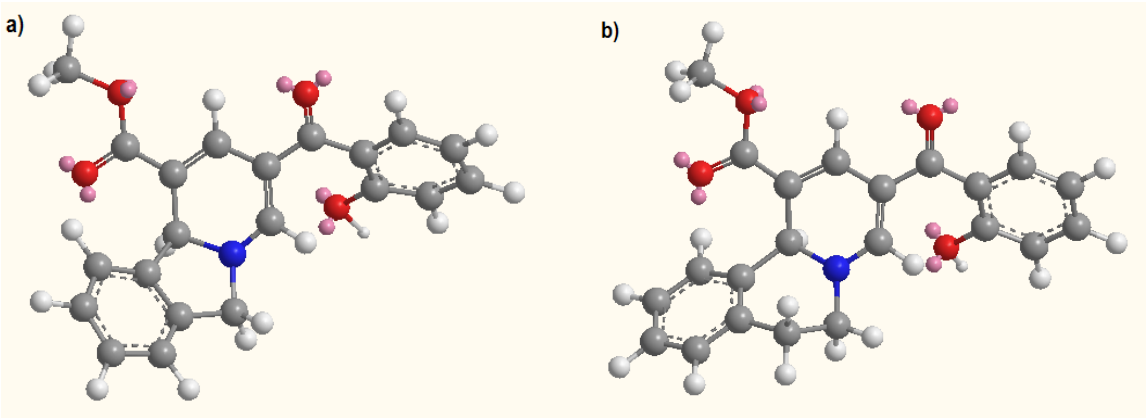
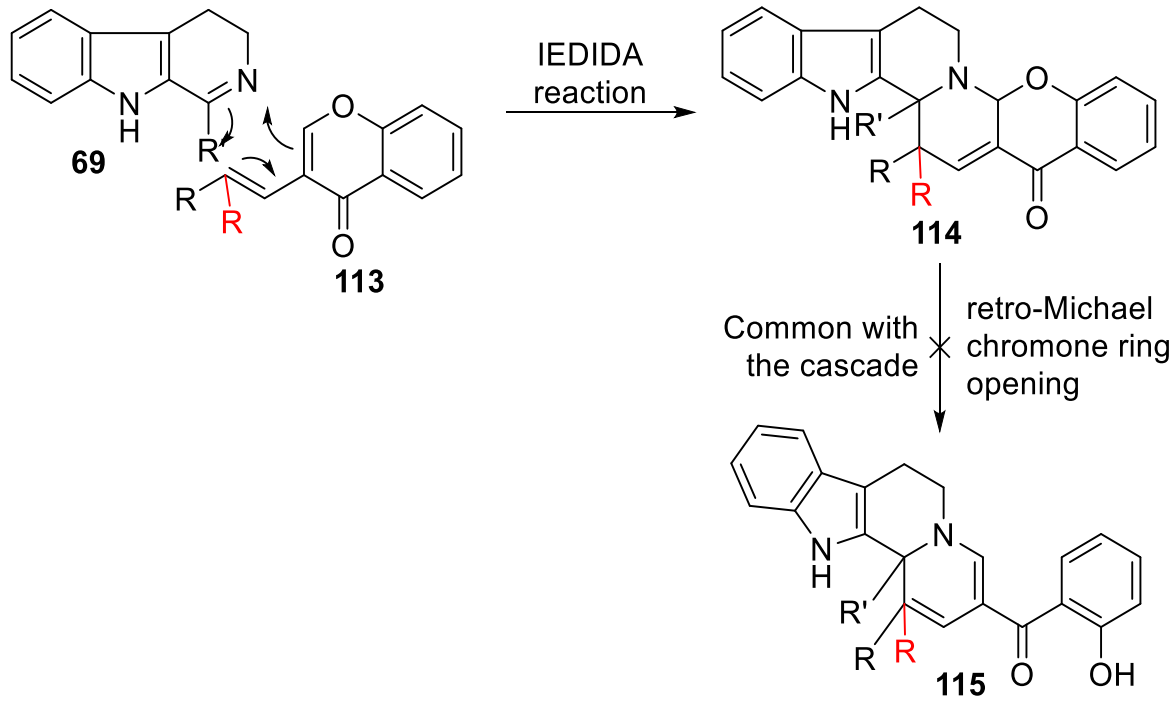


Figure 17: Three-dimensional structures of a) dihydropyridoisoindole **112a** and b) pyridoisoquinoline **96a**. These 3D structures were obtained by molecular dynamics and modelization in the MM2 force field.[100]

4.7. Synthesis of Hexacyclic indoloquinolizines

4.7.1. Design of the Synthesis

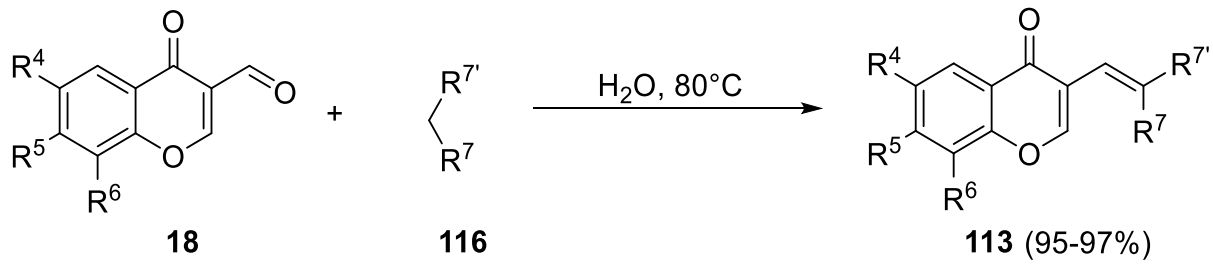
The synthesis of hexacyclic indoloquinolizines was envisaged to further expand the scope of the imino-Diels-Alder reaction as well as to elucidate the mechanistic proposal made for the IEDIDA reaction between chromone dienes **70** and indole-derived cyclic imines **69**. The use of disubstituted chromone dienes **113** was planned to prevent the retro-Michael/chromone ring opening step and thus to provide hexacyclic products (**114**, Scheme 30)**.**



Scheme 30: Trapping of the intermediate **35** to obtain hexacyclic indoloquinolizines **114**.

4.7.2. Preparation of the Disubstituted Chromone Dienes

Disubstituted dienes were synthesized using a different method than the procedure employed for the monosubstituted dienes described by Hangarge et al.[101] 3-formylchromones **18** were reacted with malonates **116** in water to undergo a Knoevenagel condensation (Scheme 31). The dienes were formed quantitatively and simple filtration of the compounds from the aqueous reaction mixture yielded the pure products that were used in the imino Diels-Alder reaction.

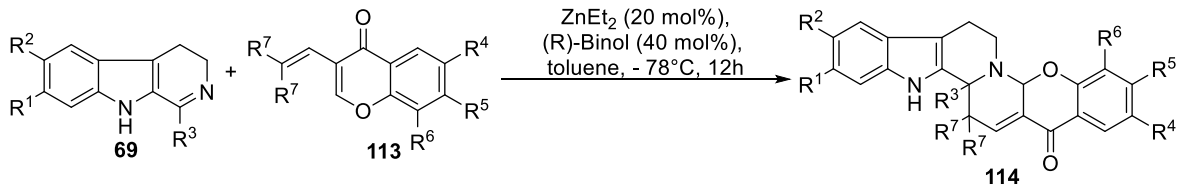


Scheme 31: Preparation of the disubstituted chromone dienes **113**.

4.7.3. Development and Scope of the Reaction

The disubstituted chromone dienes **113** underwent the asymmetric IEDIDA reaction with both tryptamine-derived imines **69** and the dihydroisoquinolines **94** to form hexacyclic indoloquinolizines **114** and pentacyclic pyridoisoquinolines **117**, in yields ranging from 64 to 85% respectively as a 1:1 mixture of two diastereoisomers (Table 20 and 21). The diastereoisomers could not be separated, as under the condition of purification by flash chromatography, the mixture underwent a retro-IEDIDA reaction catalysed by acidic silica gel that led to the recovery of up to 60% of the starting materials.

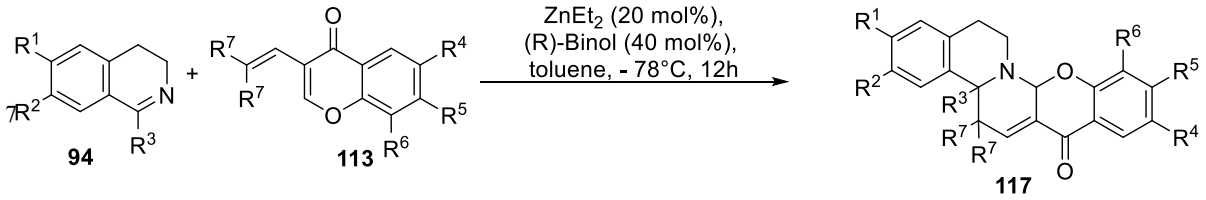
Table 20: Synthesis of the hexacyclic indoloquinolizines **114**



Product	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield[a] [%]
114a	H	H	H	H	H	H	CN	64
114b	H	H	H	H	H	H	CO_2Me	65
114c	H	OMe	Me	H	H	H	CN	81
114d	H	OMe	Me	H	H	H	CO_2Me	82

[a] isolated yields of the diastereoisomer mixture

Table 21 Synthesis of the pentacyclic pyridoisoquinolines **117**

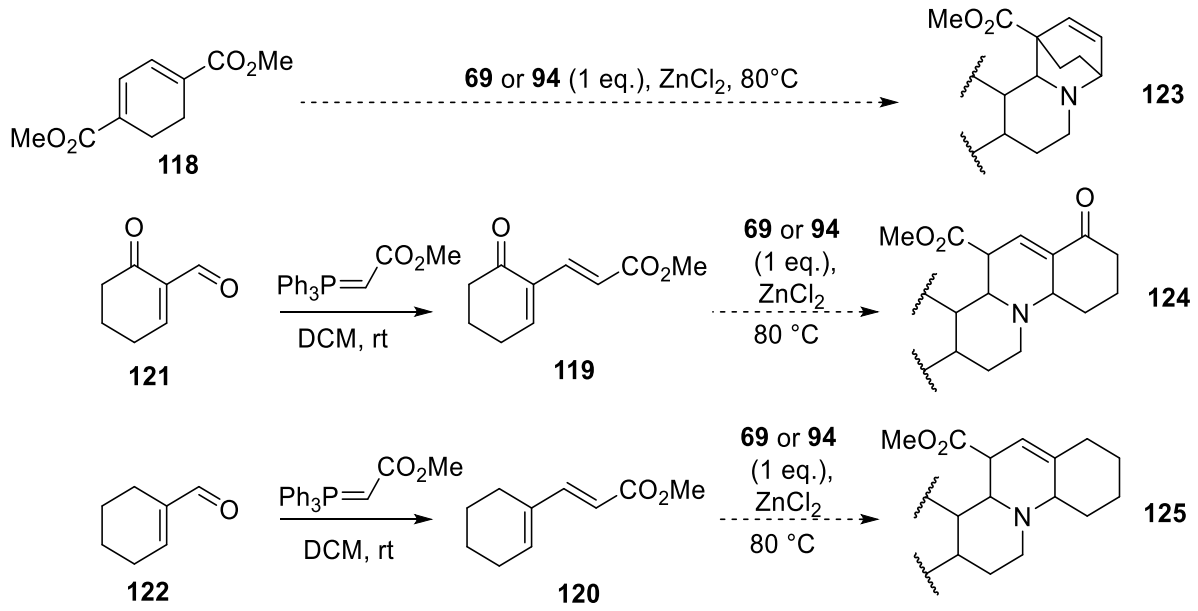


Product	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield[a] [%]
117a	H	H	H	H	H	H	CN	61
117b	H	H	H	H	H	H	CO_2Me	59
117c	H	OMe	Me	H	H	H	CN	68
117c	H	OMe	Me	H	H	H	CO_2Me	72

[a] isolated yields of the diastereoisomer mixture

4.8. Use of Other Dienes

In order to further explore the scope of the imino Diels-Alder reaction, the reaction was also attempted with other cyclic and non-cyclic dienes, in replacement for the chromone dienes. To this end, commercially available diene **118**, and dienes **119** and **120** obtained from the corresponding aldehydes following Wittig reaction with phosphoranylidenes, were subjected to the IEDIDA reaction with tryptimine **69a**, harmaline **69p**, and 3,4-dihydroisoquinoline **94a**, following the general procedure for the synthesis of racemic indoloquinolizines (20mol % of zinc chloride in DMSO at 80°C, Scheme 32). No conversion was observed after one week. The use of harsher conditions was also attempted by refluxing the substrates with 1 equivalent of zinc chloride in xylene, and only decomposition of the dienes was observed after 2 days.



Scheme 32: IEDIDA reaction of cyclic dienes **123-125**.

4.9. Summary of the Compound Collection Synthesis

The investigation of the scope of the enantioselective inverse electron demand imino-Diels-Alder reaction led to the synthesis of numerous ring-fused isoquinolines and quinolizines subclasses that are related to the natural product-inspired centrocountins **17** (Figure 18).

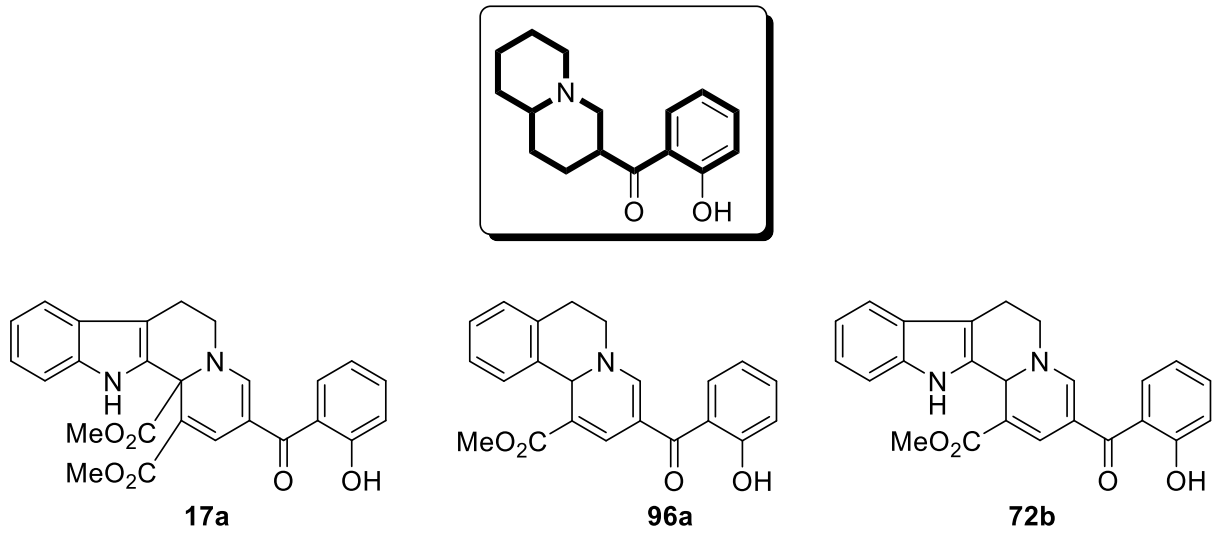


Figure 18: The common quinolizine core of the IEDIDA reaction and the principle hits **17a**, **96a** and **72b** developed in this work.

This further exploration led, among others, to the discovery of pyridoisoquinoline (*S*)-**96a** a mitotic modulator more potent than centrocountin-1 **17a** regarding its ability to influence the cell cycle in HeLa cells. However it seems that small modifications of the structure of the ring-fused quinolizines induces a substantial change in the activity of the compounds. The addition of a methyl group on the indole nitrogen leads to complete loss of the mitotis modulating activity. The depletion of one of the CH_2 groups in the C ring of the ring-fused quinolizines also leads to inactivity. On the other hand, the substitution patterns on the indole and the chromone aromatic rings is less significant important for the activity of the ring-fused quinolizines. The activity was consistently the highest in the absence of further substituents (Figure 19).

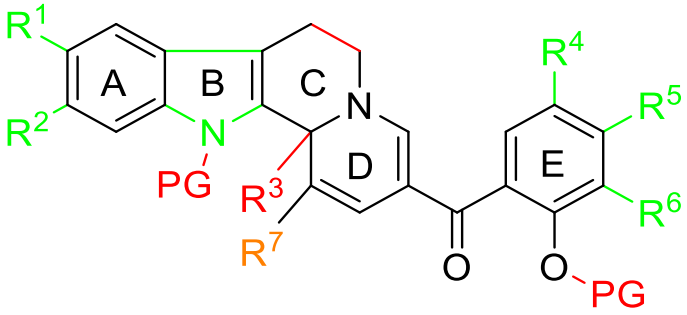


Figure 19: Structure activity relationship of the ring-fused quinolizines library toward mitotic modulation of HeLa cells. In red, the positions where substitution is not tolerated for the retention of the biological activity, green for tolerated substitution, orange for non conclusive.

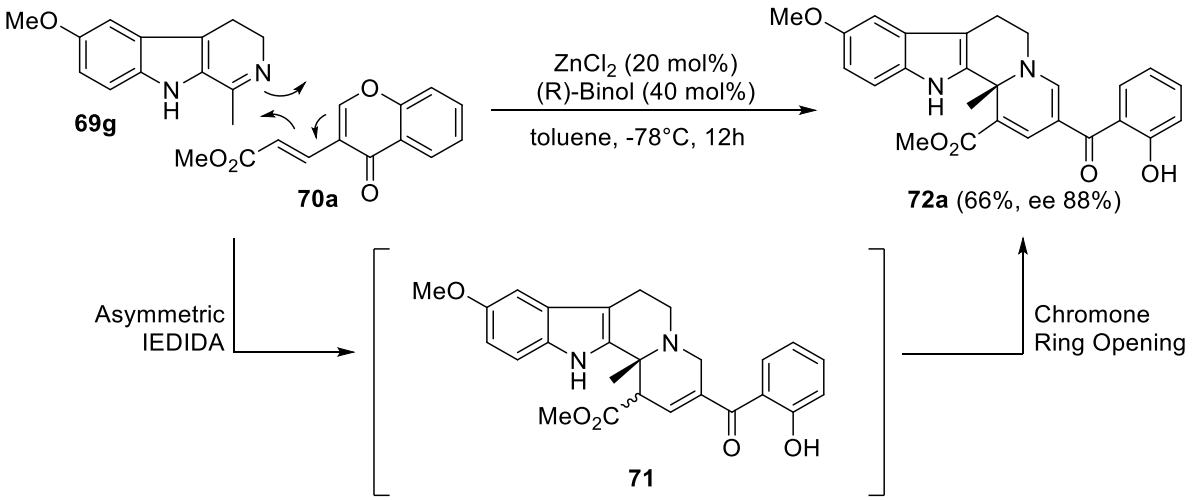
5. Summary

Natural product- inspired compound libraries are efficient tools for the discovery of compounds with interesting biological activities and may provide inspiration for medicinal chemistry research[102] The goal is the assembly in the most efficient and concise way of substances with a structural ressemblance to known natural products. The design of these analogues can also rely on the interaction of the substances with the corresponding biological target.[7,103,104]

In the syntheses of ring-fused quinolizines described in this work, the inspiration for the construction of the compound collection came from an interesting class of indole alkaloids displaying cytotoxic or anti-cancer activities, and particularly from the centrocountins, mitotic modulators that target centrosomal proteins. A unique 12-step organocatalysed cascade sequence yielded a small collection of centrocountins in a straightforward one-pot procedure from commercially available starting materials: 3-formylchromones, DMAD and tryptamines. Mechanistic investigations of the 12-step cascade reaction were carried out by trapping and characterizing intermediates as well as control experiments. These informations yielded in the development of new alternative cascade synthesis routes to indoloquinolizines and analogues, and overcame the limitations of the long cascade syntehsis established before.

Inspired from the last part of the cascade synthesis of the centrocountins, an inverse electron demand imino-Diels-Alder between cyclic imines and chromone dienes was developed to access new centrocountin analogues (Scheme 33), as well as, an enantioselective version of this reaction using a pre-formed zinc-Binol complex providing access to the

indoloquinolizines **72** and the pyridoisoquinolines **96**. Indeed, diethylzinc and (*R*)-Binol (*R*)-**80a** or (*R*)-dianthracenylbinol (*R*)-**80e** were dissolved under argon in dry toluene and stirred for 15 minutes. After the sequential addition of cyclic imine (synthesized by a Bischler-Napieralski reaction) **69** or **94** and chromone diene **70** (synthesized by a Wittig reaction) the mixture was allowed to react for 12 to 24h at -78°C in a sealed tube under Ar to yield after purification by flash chromatography the targeted quinolizines in yields up to 97% and ees up to 94%.



Scheme 33: Synthesis of indoloquinolizine **72a** by asymmetric IEDIDA reaction of cyclic imine **69g** with chromone diene **70a**.

These very encouraging results led to further expansion of the scope of the reaction and further construction of the centrocountin-based compound collection. New subclasses of compounds were synthesized by means of the IEDIDA reaction: various ring-fused quinolizines including pyridoisoquinolines **96**, dihydropyridoisoindole **111**, hexacyclic indoloquinolizines **114** and pentacyclic pyridoisoquinolines **117**, as well as internal indolopyridinium **87** and pyridoisoquinolinium **97** salts obtained by oxidation (Figure 20).

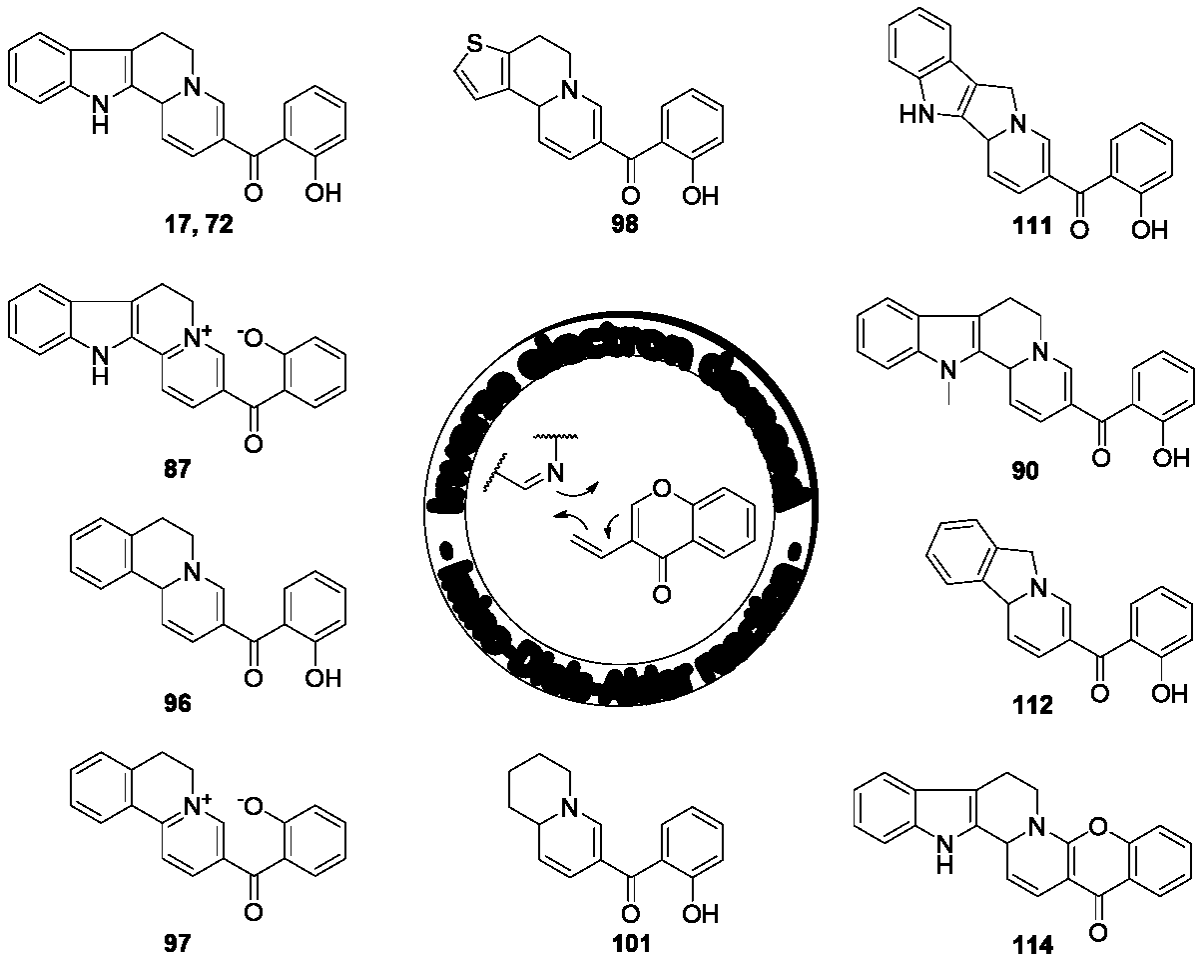


Figure 20: Representation of the diverse quinolizine subclasses synthesized by the inverse electron demand imino-Diels-Alder reaction.

Pyridoisoquinoline **96a** was identified as a potent mitotic modulator displaying the same phenotype (Figure 21) when exposed to HeLa cells as was observed for centrocountin-1 **17a**, but at lower concentrations. Treatment of cells with (S)-**96a** led to a higher count of mitotic cells at equivalent concentrations (mitotic ratio at 10 µM: 25% instead of 12%), and an effect on the cells was observable at lower concentration than for centrocountin-1 **17a** (IC_{50} : 4.7 ± 0.5 µM instead of 17.2 ± 2.4 µM). Furthermore, it was observed that only the (S)-**96a** enantiomer was active on HeLa cells, experiments carried out with (R)-**96a** rendered no activity at all.

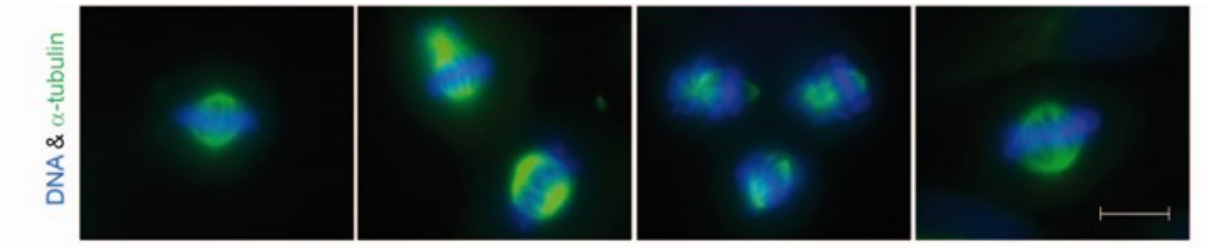


Figure 21: Images of mitotic HeLa cells under the influence of hit compound **96a**.

Further application of the inverse electron demand imino-Diels-Alder reaction can be easily imagined, for instance, using new cyclic dienes to replace the chromones, in order to find new compound classes which may be very different to centrocountins but still provide interesting molecules for chemical biology research.

5. Zusammenfassung

Die Synthese Naturstoffinspirierter Substanzsammlungen sind effiziente Werkzeuge für die Entdeckung neuer Verbindungen mit interessanten biologischen Aktivitäten, und möglicherweise zur Entdeckung neuer Leitstrukturen für die Wirkstoffentwicklung.[103] Ziel dieser Methode ist es, auf einfachem und elegantem Wege Substanzen mit strukturellen Ähnlichkeiten zu dem zugrundeliegenden Naturstoff zu synthetisieren.[7, 104-105]

Die in dieser Arbeit beschriebene Synthese anellierter Quinolizine wurde durch Indol-Alkaloide mit antitumor- und zytotoxischen Effekten inspiriert, insbesondere durch die Centrocountine, eine Klasse von Mitosemodulatoren, die zentrosomale Proteine addressieren.

Durch eine einzigartige organokatalysierte Kaskadenreaktion über 12 Stufen wurde eine kleine Sammlung von Centrocountinen in einem direkten Ein-Topf-Verfahren aus kommerziell erhältlichen 3-Formylchromonen, DMAD und diversen Tryptaminen erhalten. Die mechanistische Untersuchung dieser 12-Stufen-Kaskadenreaktion wurden Zwischenprodukte abgefangen. Diese Erkenntnisse ermöglichen einen neuen Zugang zu alternativen Kaskadenreaktionen zur Synthese von Indoloquinolizinen und deren Analoga, die die bisherigen Einschränkungen langer Kaskadenreaktionen überwinden.

Inspiriert vom letzten Teil der Kaskadenreaktion zur Synthese von Centrocountinen wurde eine enantioselektive Imino-Diels-Alder Reaktion mit inversem Elektronbedarf (IEBIDA) zwischen zyklischen Iminen und Chromondienen entwickelt um Zugang zu neuen Centrocountinanaloga zu erhalten (Abbildung 1), wie Indoloquinolizine **72** and

Pyridoisoquinoline **96**. Zu trockenem Toluol wurde Diethylzinc and (*R*)-Binol (*R*)-**80a** or (*R*)-dianthracenylbinol (*R*)-**80e** gegeben bei raum Temperatur unter Argon. Nach 15 Minuten, wurde zyklische Imin **69** oder **94** (synthetisiert durch eine Bischler-Napieralski reaktion) zugegeben, und die Reaktionsmischung wurde dann auf -78 °C gekühlt. Nach Zugabe von Chromone dien **70** (synthetisiert durch eine Wittig reaktion) wurde die Lösung weitere 12 bis 24 Stunde gerührt unter Argon und ergab nach Reinigung mittels Flash Chromatographie die gezielten quinolizine mit Ausbeute bis 97% und ees bis 94%.

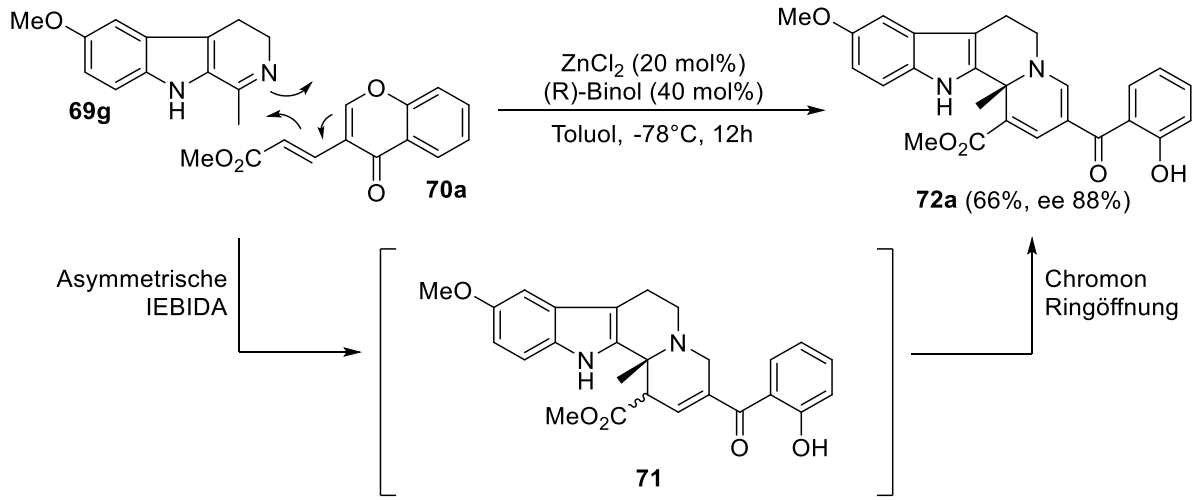


Abbildung 1: Synthese von Indoloquinolizin **72a** durch asymmetrische IEBIDA-Reaktion von zyklischen Imin **69g** mit Chromondien **70a**.

Diese ermutigenden Ergebnisse führten zur Erweiterung des Anwendungsbereiches der Reaktion und dem weiteren Ausbau der Centrocountin-inspirierten Substanzsammlung. Als neue Verbindungsunterklassen wurden mittels der IEBIDA Reaktion Pyridoisoquinoline **96**, Dihydropyridoisoindole **111**, hexazyklische Indoloquinolizine **114** und pentazyklische Pyridoisoquinoline **117**, sowie die Zwitterionen aus deren Oxidation, die Indolopyridiniumsalze **87** und Pyridoisoquinolinesalze **97** synthetisiert (Abbildung 2).

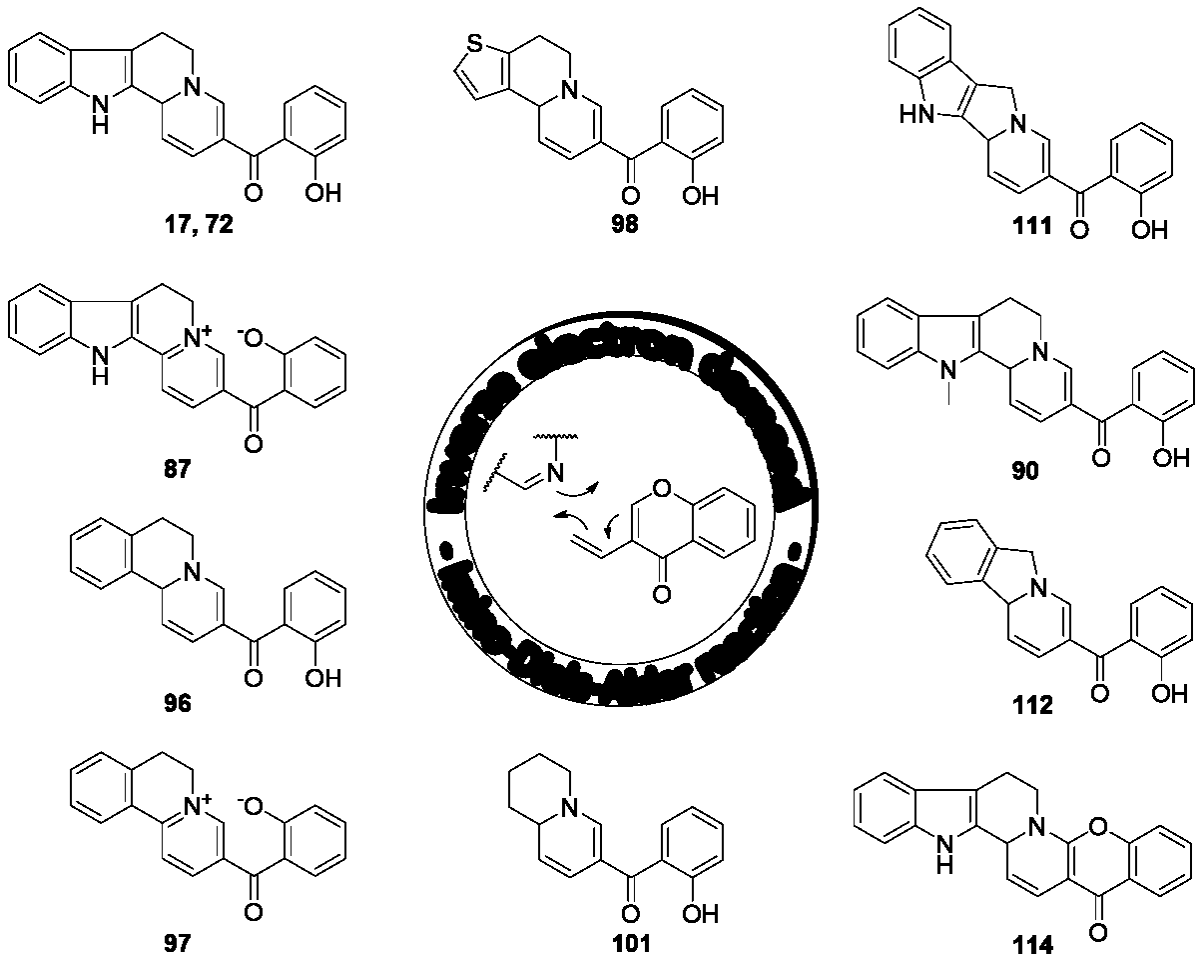
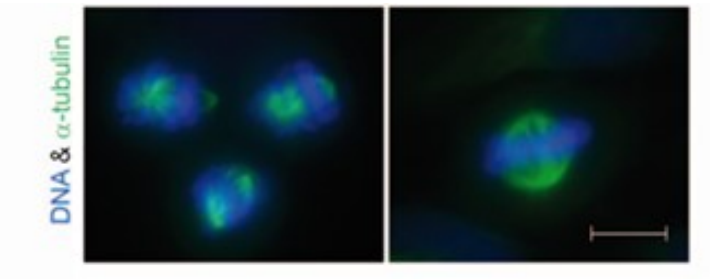


Abbildung 2: Darstellung von den diversen Quinolizines Unterklassen synthetisiert durch Imino-Diels-Alder Reaktion mit inversem Elektronbedarf.

Bei der biologischen Evaluierung wurde Pyridoisoquinolin **96a** als potenter Modulatorder Mitose identifiziert, der denselben Phänotyp wie Centrocountin-1 in Hela-Zellen induziert jedoch bereits bei niedrigeren Konzentrationen wirksam ist. Die Behandlung von Zellen mit *(S)*-**96a** ergab einen höheren Anteil mitotischer Zellen bei gleicher Substanzkonzentration (bei 10µM 25% statt 12%) in Vergleich zu Centrocountin-1, und der Effekt auf die Zellen war bereits bei niedrigeren Konzentrationen nachweisten (**17a,** IC_{50} : 4.7 ± 0.5 µM statt 17.2 ± 2.4 µM). Es wurde zudem beobachtet, dass nur das *(S)*-Enantiomer für die biologische Aktivität verantwortlich ist, das *(R)*-Enantiomer ist inaktiv.



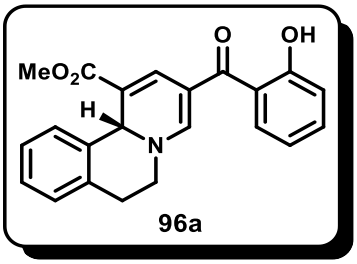


Abbildung 3: Bilder von den mitotischen HeLa-Zellen bei Behandlung mit **96a**.

Weitere Anwendungen der im Rahmen dieser Arbeit entwickelten Imino-Diels-Alder-Reaktion mit inversem Elektronbedarf sind aufgeregt und scheinen möglich. Zum Beispiel könnten die Chromondiene durch andere zyklische Diene ersetzt werden, um neue Substanzunterklassen zu entdecken, die sich strukturell von den originalen Centrocountinen unterscheiden, aber weiterhin biologische Aktivität aufweisen und somit neue interessante Substanzen für die Forschung im Bereich der chemischen Biologie darstellen.

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II. Abbreviations

Ac	Acyl
Ar	Aryl
AU	Arbitrary Units
Binol	1,1'-Bi-2-naphthol
Boc	*tert*-Butoxycarbonyl
CC1	Centrocountin-1
CD	Circular dichroism
$CDCl_3$	Deuterated chlroform
Crm1	Chromosomal region maintenance exportin 1
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
DAPI	4’,6-Diamidino-2-phenylindole
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAD	Dimethyl acetylenedicarboxylate
DMSO	Dimethylsulfoxide
DMSO-d_6	Deuterated dimethylsulfoxide
EDG	Electron donating group
ee	Enantiomeric excess
Eq.	Equivalents
ESI	Electrospray Ionisation
Et	Ethyl
Et_3N	Triethylamine
EWG	Electron withdrawing group
gHSQC	Gradient heteronuclear single quantum coherence
HOMO	Highest occupied molecular orbital
HPLC	High pressure liquid chromatography

HRMS	High resolution mass spectrometry
Hz	Hertz
IC_{50}	Half maximal inhibitory concentration
IEDIDA	Inverse-electron-demand imino-Diels-Alder
iPr	Iso-propyl
J	Coupling constant
LCMS	Liquid chromatography mass spectrometry
LUMO	Lowest unoccupied molecular orbital
Me	Methyl
MeCN	Acetonitrile
MW	Microwave irradiation
NMR	Nuclear magnetic resonance
Ph	Phenyl
Ref.	Reference
R_f	Retention factor
RT	Room temperature
SAR	Structure Activity Relationship
S_N	Nucleophilic substitution
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TLC	Thin layer chromatography

III. Experimental Part

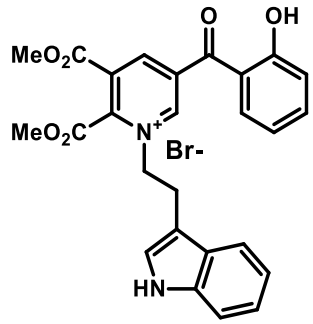
III.1. General

Unless otherwise noted, chemicals were obtained from Aldrich, Acros, TCI, or Alfa and were used without further purification. Reactions were carried out in standard glassware or a Radleys Carousel 12 parallel reactor using anhydrous solvents. ^{1}H and ^{13}C NMR spectroscopic data were recorded on a Varian Mercury VX 400 or Varian 500-inova 500 spectrometer at RT unless stated otherwise. NMR spectra were calibrated to the solvent signals of $CDCl_3$ or DMSO. Enantiomeric resolution was performed using a Dionex UltiMate 2000 HPLC with a 10mm Daicel IC column. HRMS-(FAB)-MS were taken on Finnigan MAT MS 70. HRMS-ESI were taken on an Accela HPLC-System (HPLC column 50/1 Hypersil GOLD 1.9 µm) with an LTQ Orbitrap mass spectrometer from Thermo Scientific. (ESI)-MS were measured by using an Agilent 1100 series binary pump together with a reversed-phase HPLC column (Macherey-Nagel). Optical rotation was measured using a Schmidt & Hänsch Polartronic polarimeter in cuvettes with a path length of 10 cm. CD-spectra were recorded on a J-815 CD-Spectrometer from Jasco. TLC was performed on Merck silica gel 60 F254 aluminum sheet. For flash chromatography silica gel from Baker (40-70 µm) was used. MPLC was performed using an Isco sq16 with pre-packed cartridges (30 µm, spherical silica gel) from Interchim were used.

III.2. Experimental Part for Chapter 2

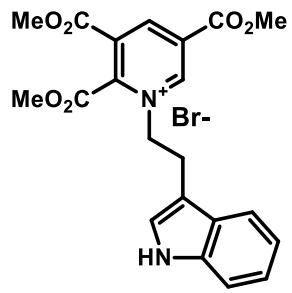
III.2.1. Synthesis of Pyridinium Salts 39-42

Compound **39:**



To a solution of the functionalized pyridine **40** (31.5 mg; 0.1 mmol; 1.0 eq) in dichloromethane (5 mL) was added 3-(2-bromoethyl)indole **41** (23.5 mg; 0.105 mmol; 1.05 eq) and Et_3N (15 µL; 0.11 mmol; 1.1 eq), and the solution was stirred at room temperature for 12h. Triethylamine and the solvent were removed under reduced pressure and the residue was dried in vacuo. TLC (cyclohexane/ethyl acetate, 2:4 v/v): R_F = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.60 (s, 1H), 10.97 (s, 1H), 9.04 (d, *J* = 2.0 Hz, 1H), 8.46 (d, *J* = 2.0 Hz, 1H), 7.64 – 7.56 (m, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.15 – 7.09 (m, 2H), 7.06 (s, 1H), 6.98 – 6.93 (m, 2H), 4.98 (t, *J* = 7.1 Hz, 2H), 4.04 (s, 3H), 3.97 (s, 3H), 3.32 ppm (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8, 168.2, 166.8, 164.6, 153.8, 151.3, 138.8, 136.4, 134.2, 133.1, 133.0, 127.8, 126.4, 122.7, 120.5, 119.7, 119.2, 118.8, 118.2, 112.6, 112.1, 111.2, 109.0, 53.6, 53.5, 27.6 ppm. HRMS (m/z): $[M]^+$ calcd for $C_{26}H_{23}N_2O_6$, 459.15506; found, 459.15492.

Compound **42:**



To a solution of the functionalized pyridine **43** (25.3 mg; 0.1 mmol; 1.0 eq) in DCM (5 mL) was added 3-(2-bromoethyl)indole **44** (23.5 mg; 0.105 mmol; 1.05 eq) and Et_3N (15 µL; 0.11 mmol; 1.1 eq), and the solution was stirred at room temperature for 12h. Triethylamine and

the solvent were removed under reduced pressure and the residue was dried under vacuum. TLC (cyclohexane/ethyl acetate, 2:4 v/v): R_F = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 9.19 (d, *J* = 1.9 Hz, 1H), 8.51 (d, *J* = 1.9 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.17 – 7.12 (m, 1H), 7.04 (s, 1H), 7.00 (m, 1H), 4.89 (t, *J* = 7.1 Hz, 2H), 4.03 (s, 3H), 4.02 (s, 3H), 3.98 (s,3H), 3.30 ppm (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 169.2, 166.2, 163.9, 144.8, 143.5, 138.5, 137.8, 136.2, 134.6, 126.1, 122.3, 120.4, 119.5, 118.4, 112.7, 111.4, 108.2, 57.0, 54.1, 54.0 ppm. HRMS (m/z): $[M]^+$ calcd for $C_{21}H_{21}N_2O_6$, 397.13941; found, 397.13975.

III.2.2. Synthesis of Indoloquinolizines 17

General procedures for the synthesis of indoloquinolizines

- Method Ia: General procedure for the cascade synthesis of indoloquinolizines using arylethylamines

A 3-formylchromone-derivative **18** (1.0 eq.) was dissolved in toluene (10 ml/mmol) by heating to 80°C. Acetylenedicarboxylate **19** (1.3 eq.) was added followed by triphenylphosphine (0.6 eq.). Monitoring by TLC (dichloromethane/methanol 100:1) showed completion typically after 5-10 minutes. Tryptamine-derivative **23** (1.1 eq.) was added. After the tryptamine had dissolved camphorsulfonic acid (1.5 eq.) was added. Monitoring by TLC (cyclohexane/ethyl acetate 60:40) showed that the reaction was complete after 5-30 minutes. The reaction mixture was directly subjected to column chromatography (30 g silica gel, cyclohexane/ethyl acetate 80:20). Removal of the solvent yielded the product as yellow solid. In case the purity was not sufficient the product was precipitated from methanol.

- Method Ib: General procedure for the cascade synthesis of indoloquinolizines using arylethylamine hydrochlorides:

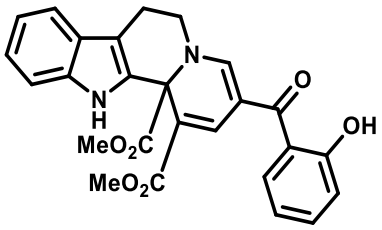
To a solution of tricyclic benzopyrone **22** (1.0 eq.) and substituted tryptamine hydrochloride **23** (1.05 eq.) in DMF (5 ml/mmol) was added triethylamine (1.1 eq.). After 30 minutes TLC (cyclohexane/ethyl acetate 3:2) showed that the starting material had been consumed. TFA (4 eq.) was added and after 30 minutes the formed intermediate could not be detected anymore in TLC (cyclohexane/ethyl acetate 3:2), the solution was diluted with ethyl acetate (30 ml/mmol) and washed with water (100 ml/ mmol), $NaHCO_3$ (satd. 50 ml/mmol) and brine

(50 ml/mmol), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was coevaporated with methylene chloride and dissolved in methanol (5 ml/mmol). After complete precipitation of the product the solvent was decanted and the product was washed with a small amount of methanol and dried in vacuo.

- Method II: General procedure for the aza-Diels-Alder synthesis

Tryptamine **23** (0.10 mmol; 1.0 eq.) was dissolved under argon in 5mL dry DMSO, and 3-formylchromone **18** (0.10 mmol; 1.0 eq.) and molecular sieves 4Å were added. The mixture was left at 80°C for 2h and monitored by TLC (Cyclohexane/EtOAc 2:1). The acetylenedicarboxylate **19** (1.2 eq.; 0.12 mmol) and dry $ZnCl_2$ (0.10 mmol; 1.0 eq) were added and the mixture was allowed to react for 12-24h at 80°C in a sealed tube under Ar. Disappearance of DMAD on TLC indicates complete reaction (cyclohexane/ethyl acetate 2:1). The reaction mixture is then diluted in 10 mL brine and extracted with 3x10mL DCM. The organic phase was dried over Na_2SO_4 evaporated to give a residue that is purified by flash chromatography as described in method Ia to yield a yellow solid, that can be recrystallized in methanol.

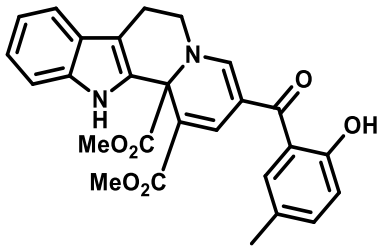
Compound **17a:**



Compound **17a** was synthesized according to method Ia. Yellow solid; m.p.: 237°C (decomposition); TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.43; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.25 (s, 1H), 9.05 (s, 1H), 7.92 (d, *J* = 1.5 Hz, 1H), 7.59 (d, *J* = 1.5 Hz, 1H), 7.45 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.16 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.05 (dd, *J* = 11.0, 3.9 Hz, 1H), 6.97 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.89 – 6.81 (m, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.73 (dd, *J* = 13.2, 5.0 Hz, 2H), 3.09 (ddd, *J* = 15.6, 12.0, 5.7 Hz, 1H), 2.98 (dd, *J* = 15.5, 3.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 170.0, 168.7, 161.3, 153.5, 136.3, 136.1, 134.5, 131.8, 130.4, 126.1, 123.0, 119.9, 119.9, 118.6, 118.4, 118.3, 113.4,

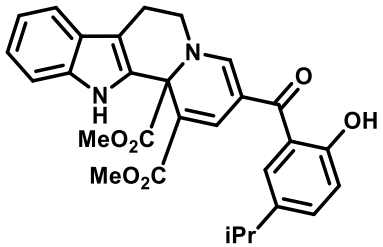
112.0, 108.2, 106.0, 68.0, 53.9, 52.6, 52.5, 23.2 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{26}H_{23}O_6N_2$, 459.15506; found, 459.15454.

Compound **17b:**



Compound **17b** was synthesized according to method Ia. Yellow solid; m.p.: 197°C; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (s, 1H), 9.03 (s, 1H), 7.93 (d, *J* = 1.4 Hz, 1H), 7.60 (d, *J* = 1.3 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.23 – 7.17 (m, 3H), 7.10 (dd, *J* = 11.0, 3.9 Hz, 1H), 6.94 – 6.85 (m, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.79 – 3.68 (m, 2H), 3.15 (ddd, *J* = 15.7, 11.9, 5.7 Hz, 1H), 2.93 (dd, *J* = 15.5, 3.6 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 170.2, 168.9, 159.1, 153.5, 136.5, 136.2, 135.5, 132.0, 130.4, 127.8, 126.1, 123.1, 120.0, 119.7, 118.4, 118.2, 113.4, 112.0, 108.2, 106.1, 68.1, 54.0, 52.7, 52.5, 23.4, 20.8 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{27}H_{25}O_6N_2$, 473.17071; found, 473.17010.

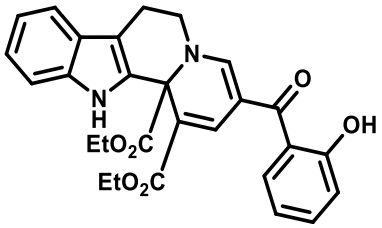
Compound **17c:**



Compound **17c** was synthesized according to method Ia. Yellow solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (s, 1H), 9.04 (s, 1H), 7.94 (d, *J* = 1.3 Hz, 1H), 7.66 (d, *J* = 1.2 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.27 – 7.21 (m, *J* = 14.6 Hz, 2H), 7.20 – 7.15 (m, 1H), 7.09 (dd, *J* = 11.1, 3.8 Hz, 1H), 6.90 (d, *J* = 9.1 Hz, 1H), 3.82 (s, 3H), 3.85 – 3.76 (m, *J* = 13.2 Hz, 1H), 3.79 (s, 3H), 3.70 (dd, *J* = 13.1, 5.3 Hz, 1H), 3.15 (ddd, *J* = 17.5, 12.0, 5.6 Hz, 1H), 2.93 (dd, *J* = 15.5, 3.8 Hz, 1H), 2.89 – 2.77 (m, 1H), 1.20 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 170.1, 168.8, 159.2, 153.7, 138.9,

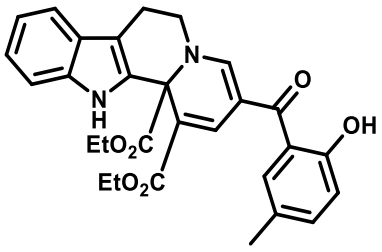
136.9, 136.1, 133.1, 132.0, 127.9, 126.1, 123.1, 120.0, 119.6, 118.4, 118.1, 112.9, 112.0, 108.2, 105.9, 68.1, 54.0, 52.6, 33.4, 27.1, 24.3, 24.3, 23.4 ppm HRMS (m/z): $[M+H]^+$ calcd for $C_{29}H_{29}O_6N_2$, 501.20201; found, 501.20134.

Compound **17d:**



Compound **17d** was synthesized according to method Ia. Yellow solid; m.p.: 209 °C; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.44; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.26 (s, 1H), 9.11 (s, 1H), 7.93 (d, *J* = 1.5 Hz, 1H), 7.59 (d, *J* = 1.5 Hz, 1H), 7.50 – 7.37 (m, *J* = 15.6, 9.9, 7.4, 1.2 Hz, 3H), 7.33 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.18 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.00 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.85 (ddd, *J* = 7.8, 7.3, 1.2 Hz, 1H), 4.38 – 4.19 (m, 4H), 3.93 – 3.78 (m, 1H), 3.71 (dd, *J* = 13.2, 4.9 Hz, 1H), 3.15 (ddd, *J* = 15.5, 12.0, 5.6 Hz, 1H), 2.93 (dd, *J* = 15.5, 3.5 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 169.2, 168.3, 161.3, 153.6, 136.1, 135.8, 134.5, 131.9, 130.4, 126.1, 123.0, 120.0, 119.9, 118.6, 118.4, 118.3, 114.2, 112.0, 108.2, 106.1, 68.2, 63.2, 61.8, 52.4, 23.3, 14.5, 14.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{28}H_{27}O_6N_2$, 487.18636; found, 487.18574.

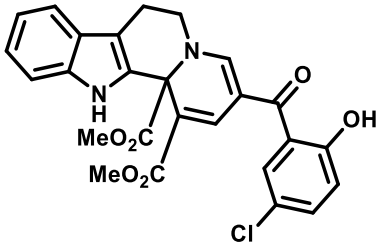
Compound **17e:**



Compound **17e** was synthesized according to method Ia. Yellow solid; m.p.: 208°C; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (s, 1H), 9.11 (s, 1H), 7.93 (d, *J* = 1.5 Hz, 1H), 7.61 (d, *J* = 1.5 Hz 1H), 7.47 (dd, *J* = 7.9, 0.5 Hz, 1H), 7.38 – 7.29 (m, 1H), 7.22 (s, 1H), 7.21 – 7.15 (m, 2H), 7.09 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H), 6.90 (d, *J* =

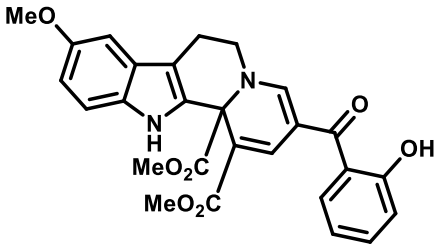
8.5 Hz, 1H), 4.38 – 4.21 (m, 4H), 3.92 – 3.81 (m, 1H), 3.72 (dd, *J* = 13.2, 5.3 Hz, 1H), 3.15 (ddd, *J* = 15.5, 12.0, 5.6 Hz, 1H), 2.93 (dd, *J* = 15.5, 3.7 Hz, 1H), 2.28 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 169.3, 168.4, 159.1, 153.6, 136.1, 136.0, 135.4, 132.1, 130.4, 127.7, 126.1, 123.0, 119.9, 119.7, 118.3, 118.2, 113.9, 112.0, 108.1, 106.1, 68.2, 63.2, 61.7, 52.4, 23.4, 20.8, 14.5, 14.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{29}H_{29}O_6N_2$, 501.20201; found,: 501.20133.

Compound **17f:**



Compound **17f** was synthesized according to method II. Yellow solid; m.p.: 232 °C (decomposition); TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 9.02 (s, 1H), 7.90 (d, *J* = 1.5 Hz, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 2.5 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.21 – 7.17 (m, 1H), 7.17 – 7.05 (m, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.81 – 3.73 (m, 2H), 3.16 (ddd, *J* = 15.6, 11.9, 5.8 Hz, 1H), 2.95 (dd, *J* = 15.6, 3.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6, 170.0, 168.7, 159.8, 153.6, 136.2, 135.8, 134.3, 131.7, 129.5, 126.0, 123.4, 123.2, 120.8, 120.0, 120.0, 118.4, 114.0, 112.0, 108.2, 105.8, 68.2, 54.1, 52.8, 52.7, 23.4 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{26}H_{22}O_6N_2Cl$, 493.11609; found, 493.11565.

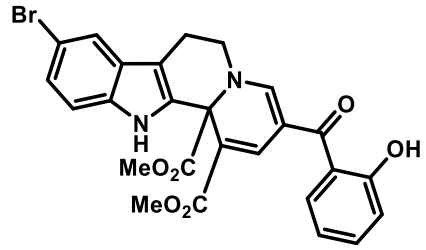
Compound **17g:**



Compound **17g** was synthesized according to method II. Yellow solid; m.p.: 163°C (decomposition); TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.26; 1H NMR (400 MHz, $CDCl_3$) δ 11.25 (s, 1H), 8.92 (s, 1H), 7.93 – 7.92 (m, 1H), 7.61 (d, *J* = 1.4 Hz, 1H), 7.46 – 7.36

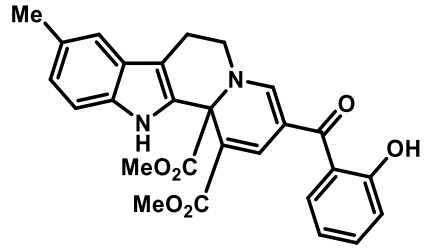
(m, 2H), 7.22 (s, 1H), 7.03 – 6.98 (m, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 6.88 – 6.81 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.80 – 3.67 (m, 2H), 3.12 (ddd, *J* = 15.6, 12.0, 5.7 Hz, 1H), 2.88 (dd, *J* = 15.4, 4.0 Hz, 1H); 13C NMR (126 MHz, $CDCl_3$) δ 192.1, 170.1, 168.8, 161.5, 154.5, 153.5, 136.3, 134.6, 132.5, 131.4, 130.4, 126.5, 120.0, 118.6, 118.5, 113.6, 113.3, 112.8, 107.9, 106.1, 100.4, 68.1, 56.2, 54.0, 52.7, 52.6, 23.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{27}H_{25}O_7N_2$, 489.16563; found, 489.16500.

Compound **17h:**



Compound **17h** was synthesized according to method Ib. Amorphous yellow solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.42; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.23 (s, 1H), 9.17 (s, 1H), 7.95 (d, *J* = 1.5 Hz, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.29 – 7.27 (m, 2H), 7.23 – 7.21 (m,1H), 7.02 – 7.00 (m, 1H), 6.85 – 6.89 (m 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.80 – 3.72 (m, 2H), 3.16 – 3.08 (m, 1H) 2.90 – 2.86 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 169.8, 168.6, 161.2, 153.2, 136.4, 134.8, 134.4, 130.1, 127.6, 125.7, 120.8, 119.7, 119.2, 118.5, 118.4, 118.3, 113.2, 112.9, 107.7, 106.0, 67.7, 53.8, 52.5, 52.1, 22.8 ppm; HRMS (ESI): calcd for $C_{26}H_{22}O_6N_2Br$ $[M+H^+]$: 537.06558, Found: 537.06527.

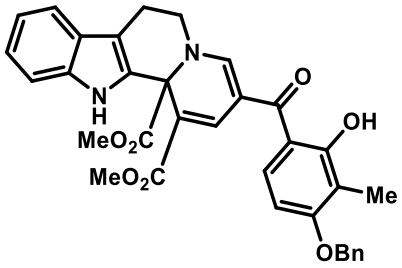
Compound **17i:**



Compound **17i** was synthesized according to method Ib. Amorphous yellow solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.27 (s, 1H), 8.94 (s, 1H), 7.96 (d, *J* = 1.5 Hz, 1H), 7.62 (d, *J* = 1.5 Hz, 1H), 7.45 (dd, *J* = 1.6, 7.8 Hz, 1H), 7.41 (td, *J* = 1.6, 7.8 Hz, 1H), 7.26 (m, 1H), 7.23 (m, 1H), 7.02 (m, 2H), 6.87 (t, *J* =7.8 Hz, 1H), 3.87

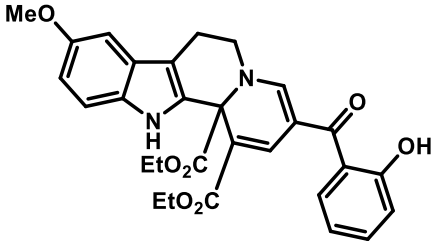
(s, 3H), 3.81 (s, 3H), 3.78-3.71 (m, 2H), 3.17-3-09 (m, 1H) 2.93-2-88 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.8, 169.9, 168.2, 161.1, 153.3, 136.0, 134.3, 131.6, 130.1, 129.0, 126.1, 124.4, 119.7, 118.4, 118.2, 117.7, 113.3, 111.4, 107.4, 105.8, 67.9, 53.6, 52.4, 52.3, 23.0, 21.4 ppm; HRMS (ESI): Calculated for $C_{27}H_{25}O_6N_2$ [M+H$^+$]: 473.17126, Found: 473.17160.

Compound **17j:**



Compound **17j** was synthesized according to method Ib Yellow solid; m.p. 230-235°C (decomposition); TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0,59; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.05 (s, 1H), 9.08 (s, 1H), 7.92 (d, *J* = 1.3 Hz, 1H), 7.56 (s, 1H), 7.49 – 7.31 (m, 8H), 7.21 (s, 1H), 7.12 (d, *J* = 7.1 Hz, 1H), 6.47 (d, *J* = 8.9 Hz, 1H), 5.15 (s, 2H), 3.86 (d, *J* = 5.6 Hz, 3H), 3.82 (s, 3H), 3.85 – 3.67 (m, 2H), 3.15 (ddd, *J* = 17.7, 12.1, 5.7 Hz, 1H), 2.93 (dd, *J* = 15.3, 3.7 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 170.2, 168.8, 161.6, 161.4, 152.8, 136.9, 136.9, 136.1, 131.9, 129.4, 128.8, 128.1, 127.2, 126.1, 123.0, 119.9, 118.3, 114.7, 113.7, 113.0, 111.9, 108.3, 106.2, 102.5, 70.2, 68.0, 53.9, 52.5, 52.3, 23.1, 8.2 ppm; HRMS (m/z): [M+H]$^+$ calcd for $C_{34}H_{31}O_7N_2$, 579.21258; found, 579.21214.

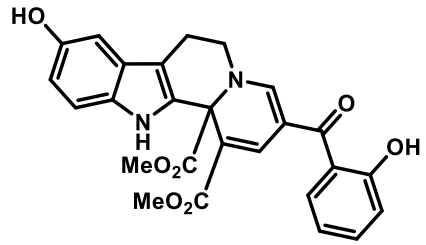
Compound **17k:**



Compound **17k** was synthesized according to method Ib. Yellow solid; m.p.: 212°C; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.25 (s, 1H), 8.98 (s, 1H), 7.92 (d, *J* = 1.5, 1H), 7.59 (d, *J* = 1.5, 1H), 7.43 (dd, *J* = 7.8, 1.6, 1H), 7.39 (ddd, *J* = 8.4, 7.3, 1.7, 1H), 7.22 (dd, *J* = 8.8, 0.5, 1H), 7.00 (dd, *J* = 8.4, 1.0, 1H), 6.89 (d, *J* = 2.4, 1H), 6.87 –

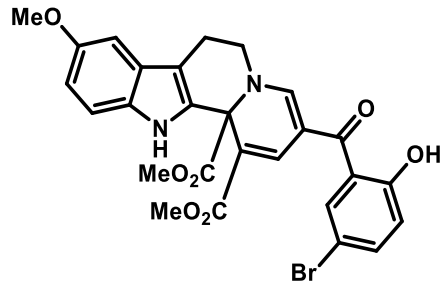
6.82 (m, 2H), 4.37 – 4.20 (m, 4H), 3.90 – 3.78 (m, 1H), 3.83 (s, 3H), 3.71 (dd, *J* = 13.2, 5.0, 1H), 3.11 (ddd, *J* = 15.5, 12.0, 5.7, 1H), 2.88 (dd, *J* = 15.4, 3.5, 1H), 1.34 (t, *J* = 7.1, 3H), 1.25 (t, *J* = 7.1, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 169.3, 168.3, 161.4, 154.4, 153.5, 135.7, 134.5, 132.7, 131.3, 130.4, 126.5, 120.1, 118.6, 118.4, 114.2, 113.1, 112.8, 107.9, 106.1, 100.3, 68.2, 63.2, 61.7, 56.1, 52.4, 23.4, 14.5, 14.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{29}H_{29}O_7N_2$, 517.19693; found, 517.19623.

Compound **17l:**



Compound **17l** was synthesized according to method Ib. Yellow solid; m.p.: 180 °C (decomposition); TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.25 ; 1H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.93 (s, 1H), 7.62 (s, 1H), 7.50 – 7.35 (m, 2H), 7.16 (d, *J* = 8.7 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.91 – 6.81 (m, 2H), 6.80 – 6.70 (m, 1H), 3.86 (d, *J* = 1.9 Hz, 3H), 3.82 (d, *J* = 1.9 Hz, 3H), 3.72 (ddd, *J* = 18.3, 12.4, 4.7 Hz, 2H), 3.09 – 2.94 (m, 1H), 2.78 (dd, *J* = 15.4, 3.7 Hz, 1H); 13C NMR (101 MHz, $CDCl_3$) δ 192.1, 170.1, 168.7, 161.3, 153.6, 149.9, 136.3, 134.6, 132.7, 131.4, 130.4, 126.8, 119.9, 118.7, 118.4, 113.4, 112.9, 112.6, 107.6, 106.0, 102.9, 68.0, 54.0, 52.6, 52.5, 23.1 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{26}H_{23}O_7N_2$, 475.14998; found, 475.14940.

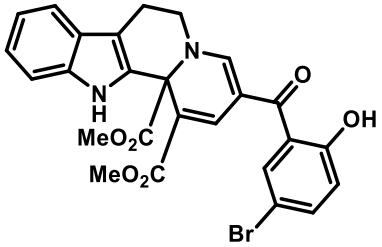
Compound **17m:**



Compound **17m** was synthesized according to method Ia. Yellow solid; m.p.: 197°C (decomposition); TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.28; ^{1}H NMR (400 MHz,

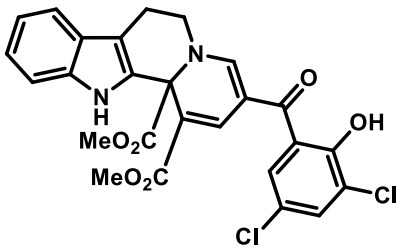
$CDCl_3$) δ 11.11 (s, 1H), 8.89 (s, 1H), 7.89 (d, *J* = 1.5 Hz, 1H), 7.60 (d, *J* = 1.5 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.46 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.88 (ddd, *J* = 11.2, 6.3, 1.9 Hz, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.81 – 3.72 (m, 2H), 3.13 (ddd, *J* = 15.5, 11.8, 5.8 Hz, 1H), 2.91 (dd, *J* = 15.5, 3.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 170.0, 168.7, 160.2, 154.5, 153.6, 137.1, 135.6, 132.4, 132.4, 131.3, 126.4, 121.4, 120.4, 114.1, 113.4, 112.8, 110.3, 107.8, 105.8, 100.2, 68.2, 56.1, 54.1, 52.8, 52.7, 23.4 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{27}H_{24}O_7N_2Br$, 567.07614; found, 567.07611.

Compound **17n:**



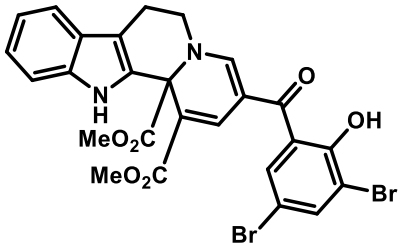
Compound **17n** was synthesized according to method Ia. Using the general procedure with 1.1 eq. 1-(*R*)-(-)-camphorsulfonic acid and 5 ml/mmol toluene. Yellow solid; m.p.: 220°C (decomposition); TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.37; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H), 9.02 (s, 1H), 7.90 (d, *J* = 1.4 Hz, 1H), 7.60 (d, *J* = 1.4 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.22 – 7.15 (m, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.81 – 3.72 (m, 2H), 3.25 – 3.08 (m, 1H), 2.95 (dd, *J* = 15.5, 3.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 170.0, 168.7, 160.2, 153.7, 137.1, 136.2, 135.7, 132.4, 131.7, 126.0, 123.2, 121.4, 120.4, 120.0, 118.4, 114.0, 112.0, 110.3, 108.2, 105.8, 68.2, 54.1, 52.8, 52.7, 23.4 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{26}H_{22}O_6N_2Br$, 537.06558; found, 537.06542.

Compound **17o:**



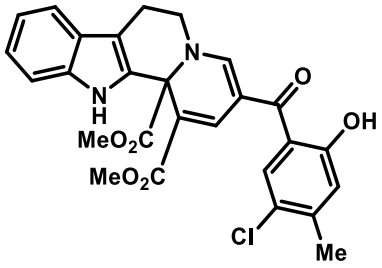
Compound **17o** was synthesized according to method Ia with 1.1 eq. 1-(*R*)-(-)-camphorsulfonic acid and 5 ml/mmol toluene. Yellow solid; m.p.: 238.2°C (decomposition); TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.59 (s, 1H), 9.01 (s, 1H), 7.88 (d, *J* = 1.5 Hz, 1H), 7.63 (d, *J* = 1.5 Hz, 1H), 7.53 – 7.43 (m, *J* = 7.1, 1.5 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 2.5 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.10 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H), 3.89 (s, 3H), 3.83 (d, *J* = 2.6 Hz, 3H), 3.81 (dd, *J* = 13.2, 5.2 Hz, 2H), 3.16 (ddd, *J* = 15.6, 11.9, 5.8 Hz, 1H), 2.96 (dd, *J* = 15.6, 3.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8, 169.9, 168.6, 155.7, 153.9, 136.2, 135.4, 134.0, 131.5, 128.0, 126.0, 124.0, 123.3, 123.2, 121.5, 120.1, 118.4, 114.2, 112.0, 108.2, 105.6, 68.3, 54.2, 52.9, 52.9, 23.4 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{26}H_{21}O_7N_2Cl_2$, 527.07712; found, 527.07684.

Compound **17p:**



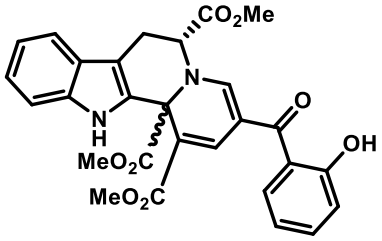
Compound **17p** was synthesized according to method Ia with 1.1 eq. 1-(*R*)-(-)-camphorsulfonic acid and 5 ml/mmol toluene. Yellow solid; m.p.: 131°C; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.75 (s, 1H), 9.01 (s, 1H), 7.88 (d, *J* = 1.6 Hz, 1H), 7.77 (d, *J* = 2.3 Hz, 1H), 7.63 (d, *J* = 1.5 Hz, 1H), 7.49 (d, *J* = 2.3 Hz, 1H), 7.47 (dd, *J* = 7.9, 0.6 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 3.88 (s, 3H), 3.82 (d, *J* = 2.8 Hz, 3H), 3.80 – 3.70 (m, 2H), 3.16 (ddd, *J* = 15.6, 11.8, 5.8 Hz, 1H), 2.96 (dd, *J* = 15.6, 3.5 Hz, 1H); 13C NMR (101 MHz, $CDCl_3$) δ 189.7, 169.9, 168.6, 157.0, 153.9, 139.5, 136.2, 135.4, 131.6, 131.5, 126.0, 123.3, 121.9, 120.1, 118.4, 114.2, 113.2, 112.0, 110.3, 108.2, 105.5, 68.3, 54.2, 52.9, 52.9, 23.4 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{26}H_{21}O_6N_2Br_2$, 614.97609; found, 614.97638.

Compound **17q:**



Compound **17q** was synthesized according to method Ia with 1.1 eq. 1-(*R*)-(-)-camphorsulfonic acid and 5 ml/mmol toluene. Yellow solid; m.p.: 245°C (decomposition); TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 9.06 (s, 1H), 7.94 (d, *J* = 1.4 Hz, 1H), 7.63 (d, *J* = 1.3 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.43 (s, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.27 – 7.19 (m, 1H), 7.18 – 7.10 (m, 1H), 6.92 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.85 – 3.75 (m, 2H), 3.20 (ddd, *J* = 15.8, 11.9, 5.8 Hz, 1H), 2.98 (dd, *J* = 15.5, 3.6 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6, 170.1, 168.8, 159.9, 153.4, 143.4, 136.2, 135.9, 131.8, 130.0, 126.1, 123.9, 123.1, 120.5, 120.0, 118.8, 118.4, 113.8, 112.0, 108.2, 105.8, 68.1, 54.1, 52.8, 52.6, 23.4, 20.8 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{27}H_{24}O_6N_2Cl$, 507.13174; found, 507.13130.

Compound **17r:**



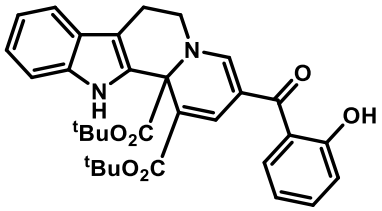
Compound **17r** was synthesized according to method Ia.

17r: Diastereomer 1: Yellow solid mp 202°C; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.37; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.36 (s, 1H), 9.31 (s, 1H), 7.90 (d, *J* = 1.4 Hz, 1H), 7.60 (d, *J* = 1.4 Hz, 1H), 7.57-7.55 (d, *J* = 7.8 Hz, 1H), 7.53-7.51 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.38-7.36 (d, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.04-7.01 (d, *J* = 7.8 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 4.52-4.50 (dd, *J* = 6.2, 1.0 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.67 (s, 3H), 3.58-3.53 (dd, *J* = 15.7, 1.0 Hz, 1H), 3.32-3-27 (dd, *J* = 15.7, 6.2 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 169.1, 168.5, 167.5, 161.4, 155.1, 136.1, 135.3, 134.7, 130.6,

128.2, 125.4, 123.0, 119.8, 119.6, 118.5, 118.3, 118.2, 116.6, 111.7, 108.3, 107.0, 66.2, 65.3, 53.3, 53.0, 52.3, 22.9 ppm; Calculated for $C_{28}H_{25}O_8N_2$ [M+H$^+$]: 517.16109, Found: 517.16119.

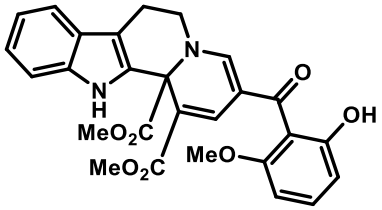
17r: Diastereomer 2: Yellow solid; mp 209°C; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.37; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.26 (s, 1H), 8.92 (s, 1H), 7.89 (d, *J* = 1.4 Hz, 1H), 7.64 (d, *J* = 1.4 Hz, 1H), 7.50-7.48 (d, *J* = 7.9 Hz, 1H), 7.47-7.45 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.40 (td, *J* = .8, 1.6 Hz, 1H), 7.36-7.34 (d, *J* = 7.9 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.01-6.99 (d, *J* = 7.8 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 4.57 (t, *J* = 7.6 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 3.32-3-30 (d, Hz, *J* =7.6 Hz, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 170.0, 168.4, 168.0, 161.4, 155.1, 136.2, 135.3, 134.7, 131.6, 130.4, 125.8, 123.0, 119.9, 119.4, 118.4, 118.3, 118.1, 114.9, 111.8, 108.2, 107.9, 68.9, 65.3, 54.0, 53.2, 52.6, 22.9 ppm; Calculated for $C_{28}H_{25}O_8N_2$ [M+H$^+$]: 517.16109, Found: 517.16129.

Compound **17s:**



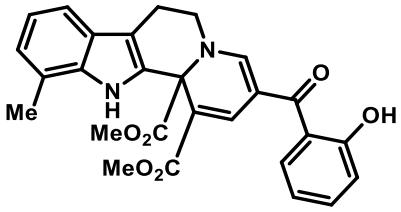
Compound **17s** was synthesized according to method Ia with 1.1 eq. 1-(*R*)-(-)-camphorsulfonic acid. Amorphous yellow solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.77; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.31 (s, 1H), 9.14 (s, 1H), 7.81 (d, *J* = 1.6 Hz, 1H), 7.60 (d, *J* = 1.5 Hz, 1H), 7.49 – 7.37 (m, 3H), 7.32 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.18 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.01 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.86 (ddd, *J* = 8.5, 7.6, 1.2 Hz, 1H), 3.88 (ddd, *J* = 16.5, 12.2, 4.4 Hz, 1H), 3.72 (dd, *J* = 13.1, 5.1 Hz, 1H), 3.15 (ddd, *J* = 15.4, 12.0, 5.6 Hz, 1H), 2.94 (dd, *J* = 15.5, 3.6 Hz, 1H), 1.58 (s, 9H), 1.48 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 191.9, 167.9, 161.3, 153.4, 136.1, 134.8, 134.4, 132.5, 130.3, 126.1, 122.7, 120.2, 119.7, 118.4, 118.3, 118.2, 116.1, 111.9, 107.8, 105.9, 83.8, 82.3, 69.1, 52.0, 28.4, 27.8, 23.3 ppm; HRMS (m/z): [M+H]$^+$ calcd for $C_{32}H_{35}O_6N_2$, 543,24896; found, 543,24858.

Compound **17t:**



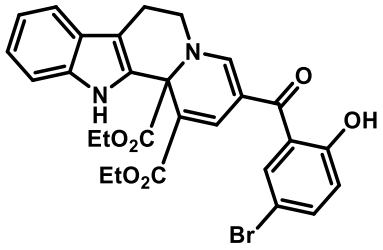
Compound **17t** was synthesized according to method Ia with 1.1 eq. 1-(*R*)-(-)-camphorsulfonic acid. Yellow solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.29; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.77 (s, 1H), 7.63 (s, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 6.45 (d, *J* = 8.3 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.83 – 3.68 (m, 2H), 3.74 (s, 3H), 3.24 – 3.06 (m, 1H), 2.94 (dd, *J* = 15.4, 4.1 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 189.3, 170.0, 169.0, 160.3, 158.2, 154.0, 137.3, 136.1, 133.5, 132.1, 126.1, 122.9, 119.8, 118.3, 112.4, 112.1, 111.9, 110.7, 108.1, 107.7, 102.8, 68.1, 55.8, 53.8, 52.5, 52.5, 23.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{27}H_{25}O_7N_2$, 489.16563; found, 489.16490.

Compound **17u:**



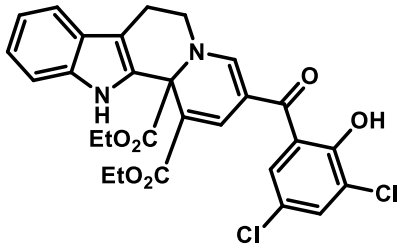
Compound **17u** was synthesized according to method Ib. Yellow solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.58; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.14 (s, 1H), 9.08 (s, 1H), 7.96 (d, *J* = 1.5 Hz, 1H), 7.63 (d, *J* = 1.4 Hz, 1H), 7.46 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.3, 1.6 Hz, 1H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.07 – 6.98 (m, 3H), 6.91 – 6.84 (m, 1H), 3.88 (s, 3H), 3.90 – 3.82 (m, 1H), 3.84 (s, 3H), 3.79 – 3.68 (m, 1H), 3.16 (ddd, *J* = 15.8, 12.1, 5.6 Hz, 1H), 2.93 (dd, *J* = 15.4, 4.1 Hz, 1H), 2.47 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 192.00, 170.00, 168.87, 161.36, 153.52, 136.33, 135.79, 134.52, 131.41, 130.36, 125.55, 123.50, 121.08, 120.15, 119.95, 118.58, 118.40, 115.95, 113.57, 108.69, 106.03, 68.07, 53.91, 52.62, 52.58, 23.31, 16.61; HRMS (m/z): $[M+H]^+$ calcd for $C_{27}H_{25}O_6N_2$, 473.17071; found, 473.17003.

Compound **17v:**



Compound **17v** was synthesized according to method Ia. Yellow solid; m.p.: 215°C; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.71; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.16 (s, 1H), 9.09 (s, 1H), 7.91 (d, *J* = 1.6 Hz, 1H), 7.62 (d, *J* = 1.6 Hz, 1H), 7.54 (d, *J* = 2.5 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.34 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.19 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.09 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 4.38 – 4.24 (m, 4H), 3.93 – 3.83 (m, 1H), 3.76 (dd, *J* = 13.5, 5.4 Hz, 1H), 3.22 – 3.10 (m, 1H), 2.95 (dd, *J* = 15.6, 3.6 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 169.1, 168.2, 160.3, 153.7, 137.0, 136.2, 135.4, 132.5, 131.8, 126.1, 123.1, 121.5, 120.4, 120.0, 118.4, 114.5, 112.0, 110.2, 108.2, 105.8, 68.4, 63.3, 61.8, 52.6, 23.4, 14.4, 14.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{28}H_{25}O_6N_2Br$, 565.09688; found, 565.09666.

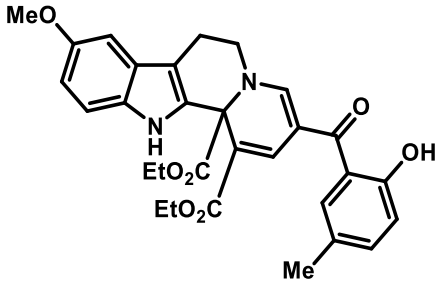
Compound **17w:**



Compound **17w** was synthesized according to method Ia. Amorphous yellow solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.72; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.65 (s, 1H), 9.09 (s, 1H), 7.88 (d, *J* = 1.6 Hz, 1H), 7.65 (d, *J* = 1.5 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.37 – 7.31 (m, *J* = 5.4 Hz, 2H), 7.19 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 4.42 – 4.20 (m, 4H), 3.95 – 3.82 (m, 1H), 3.77 (dd, *J* = 13.2, 5.0 Hz, 1H), 3.16 (ddd, *J* = 17.6, 12.0, 5.6 Hz, 1H), 2.96 (dd, *J* = 15.6, 3.6 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8, 169.0, 168.1, 155.7, 154.0, 136.2, 135.1, 133.9, 131.6, 128.0, 126.1, 124.0, 123.2, 123.1, 121.6, 120.0, 118.4, 114.7, 112.0, 108.2, 105.6, 68.4, 63.4, 61.9,

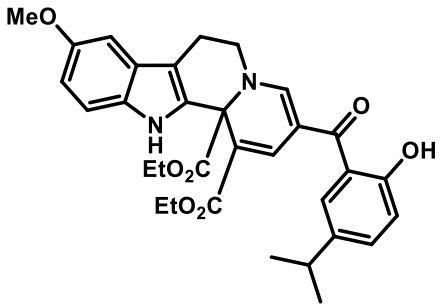
52.8, 23.4, 14.4, 14.2 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{28}H_{25}O_6N_2Cl_2$, 555.10842; found, 555.10811.

Compound **17x:**



Compound **17x** was synthesized according to method Ia. Yellow solid; m.p.: 228°C; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.56; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.01 (s, 1H), 8.97 (s, 1H), 7.92 (d, *J* = 1.5 Hz, 1H), 7.60 (d, *J* = 1.5 Hz, 1H), 7.24 – 7.19 (m, 3H), 6.92 – 6.88 (m, 2H), 6.84 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.34 – 4.23 (m, 4H), 3.89 – 3.80 (m, 1H), 3.83 (s, 3H), 3.71 (dd, *J* = 13.3, 5.1 Hz, 1H), 3.11 (ddd, *J* = 15.5, 12.1, 5.6 Hz, 1H), 2.89 (dd, *J* = 15.5, 3.8 Hz, 1H), 2.27 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 169.3, 168.4, 159.2, 154.4, 153.5, 136.0, 135.4, 132.8, 131.3, 130.4, 127.7, 126.5, 119.8, 118.2, 113.9, 113.1, 112.8, 107.8, 106.1, 100.3, 68.3, 63.2, 61.7, 56.1, 52.4, 23.4, 20.8, 14.5, 14.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{30}H_{31}O_7N_2$, 531.21258; found, 531.21189.

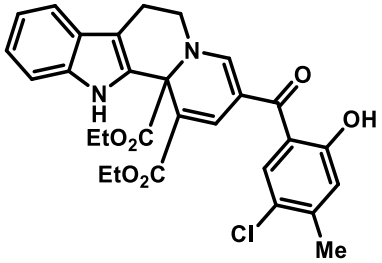
Compound **17y:**



Compound **17y** was synthesized according to method Ia. Amorphous yellow solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.63; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.05 (s, 1H), 8.95 (s, 1H), 7.89 (d, *J* = 1.5 Hz, 1H), 7.65 (d, *J* = 1.5 Hz, 1H), 7.21 (ddd, *J* = 8.8, 7.3, 3.1 Hz, 3H), 6.91 – 6.85 (m, 2H), 6.82 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.33 – 4.17 (m, 4H), 3.86 – 3.78 (m, 1H), 3.80 (s, 3H), 3.67 (dd, *J* = 13.2, 5.1, 1H), 3.10 (ddd, *J* = 15.3, 12.0, 5.6 Hz, 1H), 2.87 (dd, *J* = 15.8, 4.0

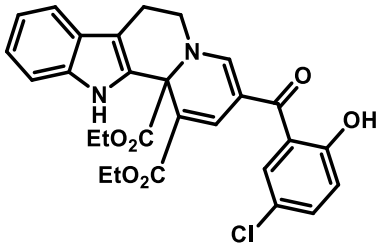
Hz, 1H), 2.83 – 2.77 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.23 – 1.17 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 169.2, 168.4, 159.3, 154.4, 153.6, 138.8, 136.2, 133.0, 132.9, 131.3, 127.9, 126.5, 119.7, 118.1, 113.5, 113.2, 112.8, 107.9, 105.9, 100.3, 68.3, 63.2, 61.7, 56.1, 52.4, 33.4, 24.4, 24.3, 23.4, 14.5, 14.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{32}H_{35}O_7N_2$, 559.24388; found, 559.24326.

Compound **17z:**



Compound **17z** was synthesized according to method Ia. Yellow solid; m.p.: 196°C; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.74; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 9.10 (s, 1H), 7.90 (d, *J* = 1.5 Hz, 1H), 7.60 (d, *J* = 1.5 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.41 (s, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.19 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.14 – 7.06 (m, 1H), 6.88 (d, *J* = 0.7 Hz, 1H), 4.38 – 4.22 (m, 4H), 3.93 – 3.80 (m, 1H), 3.74 (dd, *J* = 13.2, 4.9 Hz, 1H), 3.24 – 3.07 (m, 1H), 2.94 (dd, *J* = 15.5, 3.5 Hz, 1H), 2.35 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 169.2, 168.3, 159.9, 153.4, 143.3, 136.2, 135.5, 131.9, 130.0, 126.1, 123.8, 123.0, 120.5, 119.9, 118.9, 118.3, 114.3, 112.0, 108.2, 105.8, 68.3, 63.3, 61.8, 52.5, 23.4, 20.7, 14.4, 14.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{29}H_{28}O_6N_2Cl$, 535.16304; found, 535.16262.

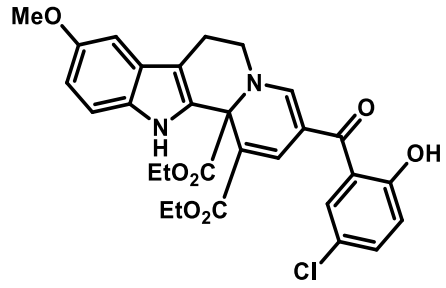
Compound **17aa:**



Compound **17aa** was synthesized according to method Ia. Yellow solid; m.p.: 216°C; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.71; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (s, 1H), 9.09 (s, 1H), 7.91 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 2.6

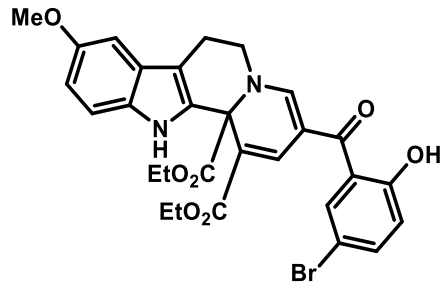
Hz, 1H), 7.35 – 7.34 (m, 1H), 7.32 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.19 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 4.42 – 4.21 (m, 4H), 3.95 – 3.81 (m, 1H), 3.76 (dd, *J* = 13.0, 5.2 Hz, 1H), 3.16 (ddd, *J* = 15.5, 12.1, 5.7 Hz, 1H), 2.95 (dd, *J* = 15.6, 3.5 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 169.1, 168.2, 159.8, 153.7, 136.2, 135.4, 134.2, 131.8, 129.5, 126.1, 123.3, 123.0, 120.9, 119.9 (2 C), 118.4, 114.5, 112.0, 108.2, 105.8, 68.3, 63.32, 61.8, 52.6, 23.4, 14.4, 14.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{28}H_{26}O_6N_2Cl$, 521.14739; found, 521.14689.

Compound **17ab:**



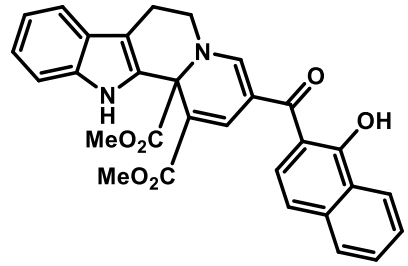
Compound **17ab** was synthesized according to method Ia. Yellow solid; m.p.: 230°C; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.62; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (s, 1H), 8.97 (s, 1H), 7.90 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 7.40 (d, *J* = 2.6 Hz, 1H), 7.33 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.39 – 4.21 (m, 4H), 3.93 – 3.80 (m, 1H), 3.83 (s, 3H), 3.75 (dd, *J* = 13.1, 5.3 Hz, 1H), 3.13 (ddd, *J* = 15.5, 12.0, 5.7 Hz, 1H), 2.91 (dd, *J* = 15.5, 3.6 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 169.1, 168.2, 159.8, 154.5, 153.6, 135.3, 134.2, 132.5, 131.4, 129.6, 126.5, 123.3, 120.9, 120.0, 114.6, 113.3, 112.8, 107.8, 105.8, 100.3, 68.4, 63.3, 61.8, 56.1, 52.6, 23.5, 14.4, 14.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{29}H_{28}O_7N_2Cl$, 551.15796; found, 551.15757.

Compound **17ac:**



Compound **17ac** was synthesized according to method Ia. Yellow solid; m.p.: 225°C; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.16 (s, 1H), 8.97 (s, 1H), 7.90 (d, *J* = 1.5 Hz, 1H), 7.62 (d, *J* = 1.5 Hz, 1H), 7.54 (d, *J* = 2.5 Hz, 1H), 7.47 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.24 – 7.22 (m, 1H), 6.92 – 6.87 (m, 2H), 6.85 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.40 – 4.20 (m, 4H), 3.92 – 3.80 (m, 1H), 3.83 (s, 3H), 3.75 (dd, *J* = 13.1, 5.1 Hz, 1H), 3.13 (ddd, *J* = 15.5, 12.0, 5.6 Hz, 1H), 2.91 (dd, *J* = 15.4, 3.7 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); 13C NMR (101 MHz, $CDCl_3$) δ 190.4, 169.1, 168.2, 160.3, 154.5, 153.7, 137.0, 135.3, 132.5, 132.5, 131.4, 126.5, 121.5, 120.4, 114.5, 113.3, 112.8, 110.2, 107.8, 105.8, 100.3, 68.4, 63.3, 61.9, 56.1, 52.7, 23.5, 14.5, 14.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{29}H_{28}O_7N_2Br$, 595.10744; found, 595.10736.

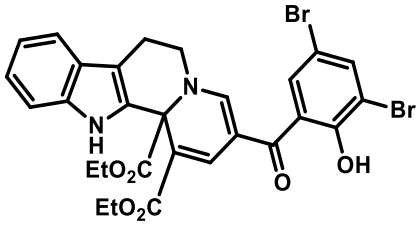
Compound **17ad:**



Compound **17ad** was synthesized according to method Ia. Amorphous yellow solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.57; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (s, 1H), 9.01 (s, 1H), 8.36 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.91 (d, *J* = 1.5 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.29 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.14 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.04 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 3.80 (s, 3H), 3.79 – 3.76 (m, 1H), 3.76 (s, 3H), 3.69 (dd, *J* = 13.3, 4.9 Hz, 1H), 3.11 (ddd, *J* = 15.6, 11.9, 5.7 Hz, 1H), 2.88 (dd, *J* = 15.5, 3.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4, 170.2, 168.8, 161.5, 153.3, 136.7, 136.7, 136.2, 131.9, 129.6, 127.5, 126.1, 126.0, 125.7,

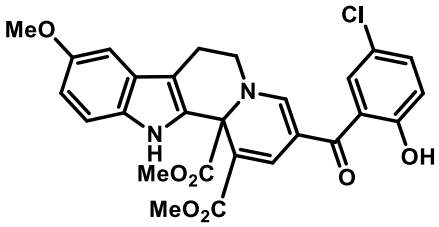
125.7, 124.3, 123.1, 119.9, 118.4, 117.8, 113.1, 112.8, 112.0, 108.3, 106.1, 68.1, 53.9, 52.7, 52.5, 23.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{30}H_{25}O_6N_2$, 509.17071; found, 509.17005.

Compound **17ae:**



Compound **17ae** was synthesized according to method II. Amorphous yellow solid; TLC (cyclohexane/ethyl acetate, 2:3 v/v): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.69 (s, 1H), 8.99 (s, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.75 (d, *J* = 2.5 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 2.5 Hz, 1H), 7.47 (dd, *J* = 7.9, 0.6 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 4.38 – 4.19 (m, 4H), 3.93 – 3.78 (m, 1H), 3.69 (dd, *J* = 13.0, 4.9 Hz, 1H), 3.15 (ddd, *J* = 15.5, 11.8, 5.6 Hz, 1H), 2.95 (dd, *J* = 15.5, 3.5 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); 13C NMR (101 MHz, $CDCl_3$) δ 189.5, 170.2, 168.7, 157.9, 153.0, 139.5, 136.3, 135.5, 131.8, 131.5, 126.5, 123.1, 121.8, 120.0, 118.4, 114.5, 113.2, 111.1, 110.0, 108.3, 105.2, 68.6, 63.0, 61.8, 52.6, 23.3, 14.5, 14.4 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{28}H_{25}Br_2N_2O_6$, 643.00739; found, 643.00765.

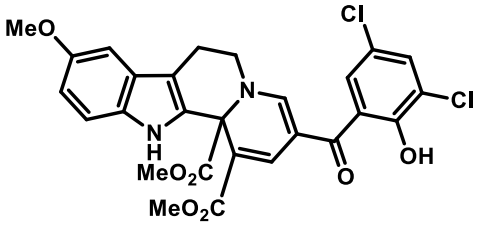
Compound **17af:**



Compound **17af** was synthesized according to method II. Amorphous yellow solid; TLC (cyclohexane/ethyl acetate, 2:3 v/v): R_F = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 9.03 (s, 1H), 7.85 (d, *J* = 1.5 Hz, 1H), 7.59 (d, *J* = 1.5 Hz, 1H), 7.52 (d, *J* = 2.3 Hz, 1H), 7.47 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 6.84 (ddd, *J* = 11.4, 6.0, 2.0 Hz, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.81 – 3.72 (m, 2H), 3.18 (ddd, *J* = 15.5, 11.4, 6.0 Hz, 1H), 2.95 (dd, *J* = 15.5, 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 169.9, 168.4, 162.0, 154.4, 152.0, 137.0, 135.5, 132.6, 132.4, 131.1, 126.3, 121.2, 119.9, 114.7, 113.6, 111.7, 110.2, 107.6, 106.1,

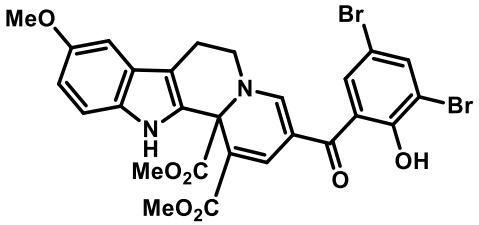
100.5, 68.4, 56.7, 54.2, 53.1, 52.5, 22.7 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{27}H_{24}ClN_2O_7$, 523.12666; found, 523.12963.

Compound **17ag:**



Compound **17ag** was synthesized according to method II. Amorphous yellow solid; TLC (cyclohexane/ethyl acetate, 2:3 v/v): R_F = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.01 (s, 1H), 8.90 (s, 1H), 7.89 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 1.6 Hz, 1H), 7.51 (d, *J* = 2.5 Hz, 1H), 7.42 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.90 – 6.84 (m, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.81 – 3.72 (m, 2H), 3.13 (ddd, *J* = 15.5, 11.8, 5.8 Hz, 1H), 2.91 (dd, *J* = 15.5, 3.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 170.1, 168.6, 160.3, 154.5, 154.3, 153.4, 137.2, 135.8, 134.7, 132.1, 131.3, 126.4, 118.7, 114.0, 112.4, 110.4, 107.1, 105.2, 99.9, 68.0, 57.0, 55.3, 54.2, 52.6, 52.4, 22.8 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{27}H_{23}Cl_2N_2O_7$, 557.08768; found, 557.08732.

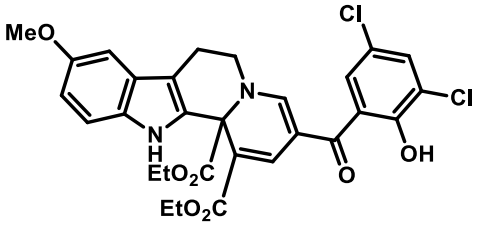
Compound **17ah:**



Compound **17ah** was synthesized according to method II. Amorphous yellow solid; TLC (cyclohexane/ethyl acetate, 2:3 v/v): R_F = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.16 (s, 1H), 8.91 (s, 1H), 7.88 (d, *J* = 1.5 Hz, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 7.52 (d, *J* = 2.5 Hz, 1H), 7.44 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 6.89 – 6.84 (m, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.81 – 3.72 (m, 2H), 3.13 (ddd, *J* = 15.5, 11.8, 5.8 Hz, 1H), 2.91 (dd, *J* = 15.5, 3.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8, 179.4, 169.7, 161.7, 154.3, 153.8, 153.0, 137.3, 135.7, 135.0, 132.4, 131.1, 126.9, 118.4, 114.3, 112.7, 110.1, 107.2, 105.9, 100.0, 67.9, 56.3, 55.0,

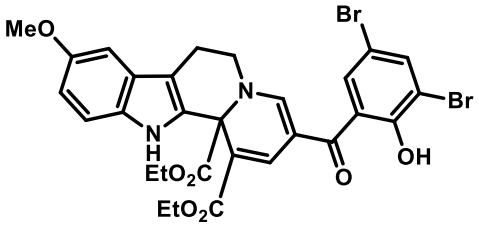
54.2, 52.6, 52.6, 22.9 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{27}H_{23}Br_2N_2O_7$, 644.98665; found, 644.98623.

Compound **17ai:**



Compound **17ai** was synthesized according to method II. Amorphous yellow solid; TLC (cyclohexane/ethyl acetate, 2:3 v/v): R_F = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (s, 1H), 8.89 (s, 1H), 7.90 (d, *J* = 1.4 Hz, 1H), 7.61 (d, *J* = 1.4 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.45 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.21 (d, *J* = 8.8Hz, 1H), 6.87 – 6.81 (m, 2H), 4.36 – 4.20 (m, 4H), 3.93 – 3.88 (m, 1H), 3.83 (s, 3H), 3.71 (dd, *J* = 13.0, 5.0 Hz, 1H), 3.18 (ddd, *J* = 15.7, 12.0, 5.6 Hz, 1H), 2.91 (dd, *J* = 15.7, 4.8 Hz, 1H), 1.37 (t, *J* = 6.9 Hz, 3H), 1.25 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0, 170.5, 169.0, 161.3, 154.2, 153.8, 153.0, 137.4, 135.6, 134.9, 132.4, 132.4, 131.3, 126.4, 118.4, 114.0, 112.9, 110.2, 107.7, 105.2, 100.6, 68.1, 63.1, 61.8, 58.3, 52.5, 23.3, 14.5, 14.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{29}H_{27}Cl_2N_2O_7$, 585.11898; found, 585.11914.

Compound **17aj:**

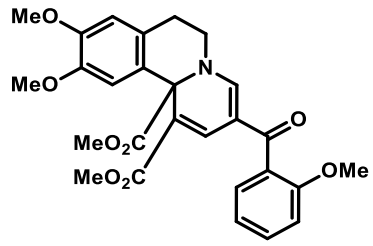


Compound **17aj** was synthesized according to method II. Amorphous yellow solid; TLC (cyclohexane/ethyl acetate, 2:3 v/v): R_F = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 8.87 (s, 1H), 7.88 (d, *J* = 1.5 Hz, 1H), 7.58 (d, *J* = 1.5 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.45 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.22 (d, *J* = 8.8Hz, 1H), 6.88 – 6.80 (m, 2H), 4.34 – 4.19 (m, 4H), 3.93 – 3.78 (m, 1H), 3.82 (s, 3H), 3.71 (dd, *J* = 13.2, 5.3 Hz, 1H), 3.15 (ddd, *J* = 15.5, 12.0, 5.3 Hz, 1H), 2.93 (dd, *J* = 15.5, 3.7 Hz, 1H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 172.6, 168.4, 162.2, 155.0, 154.5, 153.1, 137.6, 135.9, 134.4, 132.4, 132.3,

131.4, 126.4, 118.6, 114.6, 112.8, 110.3, 107.3, 105.2, 99.8, 68.0, 63.4, 61.7, 58.6, 52.1, 23.3, 15.2, 14.8 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{29}H_{27}Br_2N_2O_7$, 673.01795; found, 673.01823.

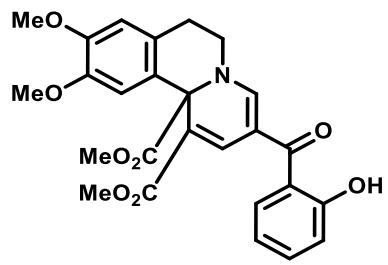
III.2.3. Synthesis of Benzoquinolizines 47 and Imidazoquinolizines 49

Compound **47a**:



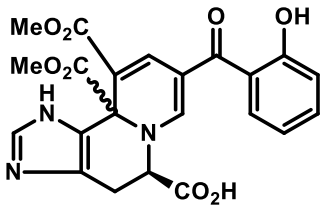
Compound **47a** was synthesized according to method Ib, dopamine hydrochloride **30a** (63 mg; 0.33 mol; 1.05 eq.), tricyclic benzopyrone **5a** (100 mg; 0.32 mmol; 1.00 eq.), DIPEA (204 mg; 1.58 mmol; 5.00 eq.) and trifluoroacetic acid (36 mg; 0.32 mmol; 1.05 eq.) were combined in DMF (3 ml). After aqueous workup, extraction with ethyl acetate and drying over magnesium sulfate the crude product was taken up in acetone (3 ml). To this solution were added potassium carbonate (219 mg; 1.58 mmol; 5.0 eq.), and dimethyl sulfate (199 mg; 1.58 mmol; 5.0 eq.). The mixture was subjected to microwave irradiation (120°C; 20 minutes). After washing with ammonium acetate solution and brine, and drying over magnesium sulfate the crude product was purified by HPLC (Nucleosil np column, isohexane/ (methylene chloride/ethanol 100:2) 9:1 to 0:1). The product (52 mg; 0.11 mmol; 35%) was obtained as amorphous yellow solid. TLC (dichloromethane/methanol, 95:5 v/v): RF = 0.58; 1H-NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.42 – 7.32 (m, 2H), 7.22 (d, *J* = 7.4 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.68 (s, 1H), 6.56 (s, 1H), 3.85 (s, 3H), 3.80 (d, *J* = 0.7 Hz, 6H), 3.78 (s, 3H), 3.75 (s, 3H), 3.69 – 3.58 (m, 2H), 3.16 – 3.03 (m, 1H), 2.86 (dd, *J* = 16.5, 3.3 Hz, 1H) ppm; HRMS (m/z): [M+H]+ calcd for $C_{27}H_{28}O_8N$, 494.18094; found, 494.18028.

Compound **47b:**



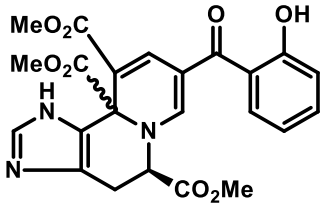
Compound **47b** was synthesized according to method Ia. TLC (dichloromethane/methanol, 95:5 v/v): R_F = 0.58; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.43 – 7.32 (m, 2H), 7.21 (d, *J* = 7.3 Hz, 1H), 6.97 (t, *J* = 7.3 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.67 (s, 1H), 6.57 (s, 1H), 3.80 (s, 6H), 3.78 (s, 3H), 3.75 (s, 3H), 3.69 – 3.58 (m, 2H), 3.16 – 3.03 (m, 1H), 2.86 (dd, *J* = 16.5, 3.3 Hz, 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 192.5, 173.4, 167.0, 163.5, 151.1, 148.2, 147.4, 135.2, 134.5, 131.1, 131.1, 129.0, 126.4, 122.7, 122.0, 118.4, 115.7, 114.9, 112.0, 81.7, 56.4, 56.4, 52.2, 52.1, 49.5, 29.7 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{26}H_{26}O_8N$, 479.15802; found, 479.15762.

Compound **49a:**



Compound **49a** was synthesized according to method Ib. Amorphous yellow solid; TLC (ethyl acetate): R_F = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.30 (s, 1H), 7.95 (d, *J* = 1.8 Hz, 1H), 7.56 (s, 1H), 7.43 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.11 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.05 – 6.99 (m, 1H), 6.86 – 6.81 (m, 1H), 4.09 (t, *J* =7.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.45 (dd, *J* = 13.2, 5.0Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 175.2, 169,2, 168.1, 161.5, 153.2, 138.2, 134.3, 134.0, 132.8, 132.4, 120.0, 118.0, 117.6, 108.0, 106.3, 65.9, 53.1, 51.4, 50.0, 49.9, 24.5 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{22}H_{20}N_3O_8$, 454.12449; found, 454.12487.

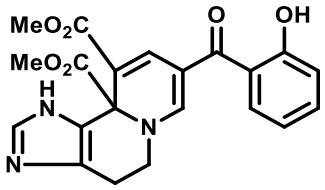
Compound **49b:**



Compound **49b** was synthesized according to method Ib. Amorphous yellow solid; TLC (ethyl acetate): R_F = 0.32; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (s, 1H), 7.91 (d, *J* = 1.5 Hz, 1H), 7.56 (s, 1H), 7.44 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.16 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.08 (dd, *J* = 11.6, 4.1 Hz, 1H), 6.86 – 6.83 (m, 1H), 4.11 (dd, *J* = 15.6, 12.0, 1H), 3.88 (s, 3H), 3.87 (s,

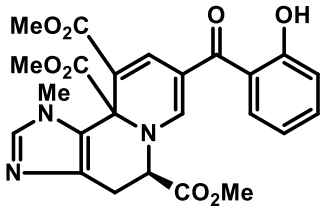
3H), 3.76 (s, 3H), 3.74 – 3.71 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.9, 174.0, 171.2, 167.8, 161.5, 153.7, 136.0, 134.9, 134.7, 131.4, 130.2, 120.5, 120.5, 118.4, 118.2, 108.1, 106.4, 69.4, 58.1, 52.5, 52.5, 51.9, 41.3 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{23}H_{22}N_3O_8$, 468.14014; found, 468.14236.

Compound **49c:**



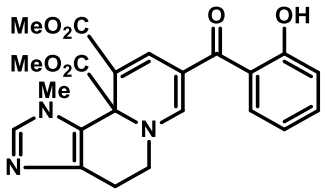
Compound **49c** was synthesized according to method Ia. Amorphous yellow solid; TLC (ethyl acetate): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 7.85 (d, *J* = 2.0 Hz, 1H), 7.52 (s, 1H), 7.43 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.39 – 7.35 (m, 1H), 7.16 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.02 (dd, *J* = 11.5, 4.9 Hz, 1H), 6.86 – 6.79 (m, 1H), 3.92 (s, 3H), 3.90-3.86 (m, 4H), 3.48 (dd, *J* = 13.2, 5.0, 2H), 3.13 (ddd, *J* = 15.4, 12.2, 6.0 Hz, 1H), 2.98 (dd, *J* = 15.4, 4.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7, 171.2, 168.9, 161.5, 153.3, 135.9, 134.7, 134.3, 131.9, 130.3, 119.6, 119.6, 118.8, 118.3, 107.9, 106.2, 68.2, 54.0, 52.8, 52.8, 23.0 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{21}H_{20}N_3O_6$, 410.13466; found, 410.13501.

Compound **49d:**



Compound **49d** was synthesized according to method Ia. Amorphous yellow solid; TLC (ethyl acetate): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.30 (s, 1H), 7.91 (d, *J* = 1.5 Hz, 1H), 7.55 (s, 1H), 7.44 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.15 (dd, *J* = 8.0, 7.1 Hz, 1H), 7.08 (dd, *J* = 12.0, 4.1 Hz, 1H), 6.86 – 6.83 (m, 1H), 4.54 (s, 3H), 4.10 (dd, *J* = 15.6, 12.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.77 (s, 3H), 3.52 (dd, *J* = 13.2, 5.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 173.3, 170.1, 167.8, 160.8, 153.6, 136.0, 134.7, 134.6, 131.9, 130.6, 120.0, 120.0, 118.7, 118.5, 108.0, 105.9, 68.2, 60.2, 54.3, 53.0, 52.9, 52.0, 23.6 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{24}H_{24}N_3O_8$, 482.15579; found, 482.15556.

Compound **49e:**



Compound **49e** was synthesized according to method Ia. Amorphous yellow solid; TLC (cyclohexane/ethyl acetate, 2:3 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 7.85 (d, *J* = 2.1 Hz, 1H), 7.53 (s, 1H), 7.44 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.16 (dd, *J* = 8.3, 7.0 Hz, 1H), 7.04 (dd, *J* = 11.7, 5.0 Hz, 1H), 6.84 – 6.79 (m, 1H), 4.47 (s, 3H), 3.92 (s, 3H), 3.91-3.88 (m, 4H), 3.43 (dd, *J* = 13.2, 5.1, 2H), 3.11 (ddd, *J* = 15.0, 12.5, 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8, 171.6, 168.9, 161.0, 153.6, 136.1, 134.9, 134.5, 131.6, 130.3, 119.8, 119.8, 118.5, 118.3, 108.4, 106.1, 67.7, 59.8, 53.6, 52.4, 52.4, 23.0 ppm; HRMS (m/z): $[M+H]^+$ calcd for $C_{22}H_{21}N_3O_8$, 424.15031; found, 424.15023.

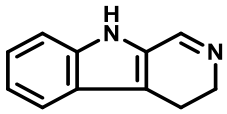
III.3. Experimental Part for Chapter 3

III.3.1. Synthesis of the Cyclic Imines 69

- General procedure for the preparation of non-α substituted imines:

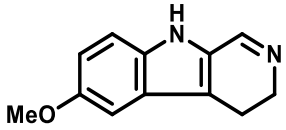
A solution of 0.125 mol of tryptamine **23** in ethyl formate (150 mL) was refluxed for 6h. After evaporating the excess solvent in vacuum, the residue was dissolved in dry dichloromethane and POCl3 (11 mL, 0.132 mol) was added dropwise in ice-bath. The mixture was stirred for 2h. After evaporating the excess solvent, the residue was dissolved in water, and washed with ether. The pH of the aqueous layer was asjusted by ammonium hydroxide to pH 10. The, the solution was extracted with dichloromethane, washed with brine and drier over sodium sulfate. The crude imines **69** were obtained by evaporating the solvent in vacuum followed by recrystallization from ethyl acetate.

Compound **69a:**



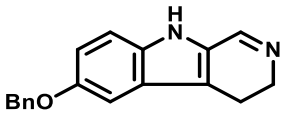
Compound **69a** was synthesized according to the general procedure for non-α substituted imines. Dark red amorphous solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.32 (s, 1H), 8.36 (s, 1H), 7.56 (d, *J* = 7.7Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 3.78 (t, *J* = 8.8 Hz, 2H), 2.80 (t, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.6, 136.7, 128.4, 124.8, 123.7, 119.7, 119.6, 113.8, 112.5, 48.1, 18.7 ppm; HRMS: Calcd for $C_{11}H_{11}N_2$ $[M+H]^+$: 171.09174, Found: 171.09209.

Compound **69b:**



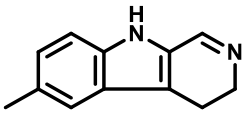
Compound **69b** was synthesized according to the general procedure for non-α substituted imines. Dark red amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 6.93 (s, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 3.83 – 3.77 (m, 5H), 2.80 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.7, 151.6, 136.6, 128.4, 124.7, 123.7, 119.7, 113.7, 112.5, 56.0, 48.2, 18.6 ppm; HRMS: Calcd for $C_{12}H_{13}N_2O$ $[M+H]^+$: 200.09471, Found: 200.09592.

Compound **69c:**



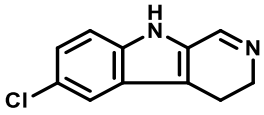
Compound **69c** was synthesized according to the general procedure for non-α substituted imines. Dark red amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.40-7.26 (m, 6H), 7.00-6.93 (m, 2H), 4.96 (s, 2H), 3.74 (t, *J* = 8.5 Hz, 2H), 2.75 (t, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 152.2, 137.4, 132.7, 128.5, 127.9, 127.6, 125.5, 116.3, 115.5, 113.1, 112.2, 102.3, 70.8, 48.3, 19.2 ppm; HRMS: Calcd for $C_{18}H_{17}N_2O$ $[M+H]^+$: 278.14191, Found: 278.14202.

Compound **69d:**



Compound **69d** was synthesized according to the general procedure for non-α substituted imines. Dark red amorphous solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.41 (s, 1H), 8.34 (s, 1H), 7.35 (s, 1H), 7.24 (d, *J* = 6.4 Hz, 1H), 7.08 (d, *J* = 6.4 Hz, 1H), 3.70 (t, *J* = 8.6 Hz, 2H), 2.84 (t, *J* = 8.6 Hz, 2H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.5, 136.7, 128.3, 124.8, 123.7, 128.6, 120.6, 118.8, 113.5, 48.0, 22.0, 18.9 ppm; HRMS: Calcd for $C_{12}H_{13}N_2$ $[M+H]^+$: 185.10732, Found: 185.10720.

Compound **69e:**

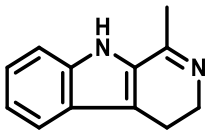


Compound **69e** was synthesized according to the general procedure for non-α substituted imines. Dark red amorphous solid: R_F = 0.35; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 (s, 1H), 8.33 (s, 1H), 7.64 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 3.67 (t, *J* = 8.6 Hz, 2H), 2.81 (t, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.4, 136.6, 128.3, 124.7, 122.1, 119.9, 119.5, 113.8, 110.3, 48.2, 18.8 ppm; HRMS: Calcd for $C_{11}H_{10}N_2$ $[M+H]^+$: 205.05270, Found: 205.05276.

- General procedure for the preparation of α substituted imines:

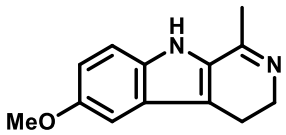
Tryptamine **23** (5.0 mmol) was dissolved in dichloromethane (20 mL) at 0 °C and triethylamine (10.0 mmol, 2 eq., 0.67 mL) and the acyl chlroide **76** (6.0 mmol) were added to the solution. The mixture was stirred for 2h. After evaporating the excess solvent in vacuum, the residue was dissolved in dry dichloromethane and POCl3 (11 mL, 0.132 mol) was added dropwise in ice-bath. The mixture was stirred for 2h. After evaporating the excess solvent, the residue was dissolved in water, and washed with ether. The pH of the aqueous layer was asjusted by ammonium hydroxide to pH 10. The, the solution was extracted with dichloromethane, washed with brine and drier over sodium sulfate. The crude imines **69** were obtained by evaporating the solvent in vacuum followed by recrystallization from ethyl acetate.

Compound **69f:**



Compound **69f** was synthesized according to the general procedure for α substituted imines. Dark red amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 3.87 (t, *J* = 8.4 Hz, 2H), 2.87 (t, *J* = 8.8 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.1, 136.8, 129.1, 125.5, 124.5, 120.3, 120.0, 116.6, 112.1, 48.1, 22.0, 19.4 ppm; HRMS: Calcd for $C_{12}H_{13}N_2$ $[M+H]^+$: 185.10732, Found: 185.10744.

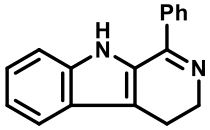
Compound **69g:**



Compound **69g** was synthesized according to the general procedure for α substituted imines. Dark red amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.29 (d, *J* = 8.3 Hz, 1H), 6.97 (s, 1H), 6.93 (d, *J* = 8.43 Hz, 1H), 3.74 (m, 5H), 2.86 (t, *J* = 8.2 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.0, 154.4, 136.7, 129.1, 124.5, 122.5, 119.3, 113.6, 112.0,

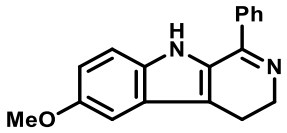
56.1, 48.1, 22.1, 19.4 ppm; HRMS: Calcd for $C_{13}H_{15}N_2O$ $[M+H]^+$: 215.11789, Found: 215.11791.

Compound **69h:**



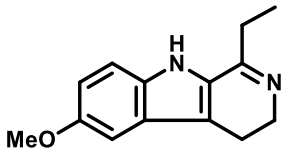
Compound **69h** was synthesized according to the general procedure for α substituted imines. Dark red amorphous solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 7.78 – 7.75 (m, 2H), 7.63 – 7.45 (m, 5H), 7.21 – 7.18 (m, 1H), 7.10 – 7.07 (m, 1H), 3.98 (t, *J* = 8.2 Hz, 2H), 2.86 (t, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.4, 137.6, 136.5, 129.9, 128.8, 127.8, 124.6, 120.4, 119.9, 117.9, 111.9, 48.8, 19.2 ppm; HRMS: Calcd for $C_{17}H_{15}N_2$ $[M+H]^+$: 247.12297, Found: 247.12311.

Compound **69i:**



Compound **69i** was synthesized according to the general procedure for α substituted imines. Dark red amorphous solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.26 – 7.14 (m, 5H), 6.97 (s, 1H), 6.93 (d, *J* = 8.43 Hz, 1H), 3.74 (m, 5H), 2.86 (t, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.4, 153.2, 137.6, 136.5, 129.9, 128.8, 124.6, 119.9, 117.9, 111.9, 113.8, 112.7, 56.1, 48.8, 19.2 ppm; HRMS: Calcd for $C_{18}H_{17}N_2O$ $[M+H]^+$: 277.13354, Found: 277.13333.

Compound **69j:**

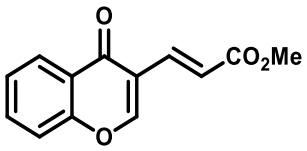


Compound **69j** was synthesized according to the general procedure for α substituted imines. Dark red amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.62 – 7.43 (m, 3H), 3.90 (t, *J* = 8.4 Hz, 2H), 3.87 (s, 3H), 2.87 (t, *J* = 8.4 Hz, 2H), 2.71 (q, *J* = 7.4 Hz, 2H), 1.29 (t, *J*, = 7.4

Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.7, 136.6, 128.6, 125.6, 124.4, 120.3, 120.0, 118.0, 116.8, 111.9, 48.2, 28.4, 19.3, 10.9 ppm; HRMS: Calcd for $C_{14}H_{17}N_2O$ $[M+H]^+$: 229.13354, Found: 229.13367.

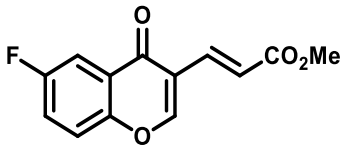
III.3.2. Synthesis of the Chromone Dienes 70

Compound **70a:**



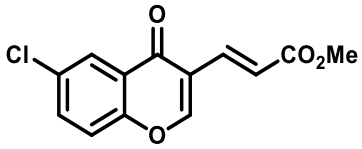
Compound **70a** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.09 (s, 1H), 7.67 (td, *J* = 7.2, 1.6 Hz, 1H), 7.37 (d, *J* = 15.6 Hz, 1H), 7.26 (d, *J* = 15.6 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 168.0, 157.6, 155.7, 135.8, 134.2, 126.5, 126.0, 124.4, 121.9, 119.5, 118.3, 51.8 ppm; HRMS: Calcd for $C_{13}H_{10}O_4Na$ $[M+Na]^+$: 253.04712, Found: 253.04793.

Compound **70b:**



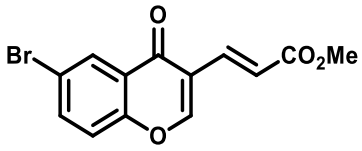
Compound **70b** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.73 – 7.69 (m, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 11.8 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 166.7, 160.0, 153.7, 148.7, 134.8, 131.4, 127.0, 124.6, 124.4, 121.2, 118.0, 52.0 ppm; HRMS: Calcd for $C_{13}H_{10}O_4F$ $[M+H]^+$: 249.05576, Found: 249.05563.

Compound **70c:**



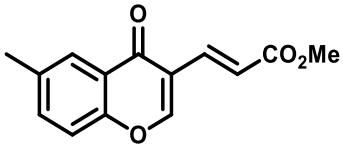
Compound **70c** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 12.1 Hz, 1H), 7.01 (d, *J* = 12.1 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 166.8, 160.2, 153.7, 148.9, 135.8, 131.5, 127.4, 124.8, 120.9, 119.3, 118.1, 52.1 ppm; HRMS: Calcd for $C_{13}H_{10}O_4Cl$ $[M+H]^+$: 265.02621, Found: 265.02644.

Compound **70d:**



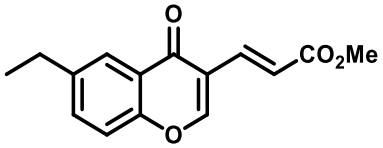
Compound **70d** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 12.3 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H) 7.01 (d, *J* = 12.3 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 166.8, 156.2, 148.9, 135.8, 134.5, 126.2, 124.5, 121.3, 120.9, 118.1, 114.7, 52.1 ppm; HRMS: Calcd for $C_{13}H_{10}O_4Br$ $[M+H]^+$: 308.97570, Found: 308.97549.

Compound **70e:**



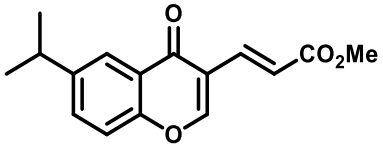
Compound **70e** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 8.0, 1.8 Hz, 1H), 8.08 (s, 1H), 7.74 (td, *J* = 7.2, 1.8 Hz, 1H), 7.51 (q, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 14.6 Hz, 1H), 7.24 (d, *J* = 14.6 Hz, 1H), 3.79 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 168.4, 156.2, 154.8, 135.9, 134.2, 126.4, 125.8, 124.3, 122.0, 119.6, 118.7, 52.4, 21.6 ppm; HRMS: Calcd for $C_{14}H_{13}O_4$ $[M+H]^+$: 245.08084, Found: 245.08066.

Compound **70f:**



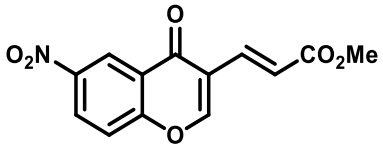
Compound **70f** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.09 (s, 1H), 7.70 (td, *J* = 7.2, 1.8 Hz, 1H), 7.52 (q, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 14.3 Hz, 1H), 7.26 (d, *J* = 14.3 Hz, 1H), 3.78 (s, 3H), 2.72 (q, *J* = 8.0 Hz, 2H), 1.91 (t, *J* = 8.0 Hz; 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 167.1, 156.7, 154.0, 138.7, 134.2, 126.5, 125.7, 124.1, 119.9, 119.3, 118.7, 52.3, 28.4, 14.6 ppm; HRMS: Calcd for $C_{15}H_{15}O_4$ $[M+H]^+$: 259.09649, Found: 259.09629.

Compound **70g:**



Compound **70g** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 8.0, 1.9 Hz, 1H), 8.11 (s, 1H), 7.71 (td, *J* = 7.3, 1.8 Hz, 1H), 7.47 (q, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 13.0 Hz, 1H), 7.19 (d, *J* = 13.0 Hz, 1H), 3.80 (s, 3H), 2.90 (q, *J* = 6.8 Hz, 1H), 1.25 (d, *J* = 6.8 Hz; 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 167.0, 156.4, 154.1, 137.9, 134.1, 128.1, 125.6, 123.9, 120.2, 119.1, 118.8, 52.3, 35.6, 22.4, 22.4 ppm; HRMS: Calcd for $C_{16}H_{17}O_4$ $[M+H]^+$: 273.11214, Found: 273.11200.

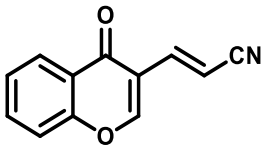
Compound **70h:**



Compound **70h** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 7.75 (t, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 12.0 Hz, 1H),

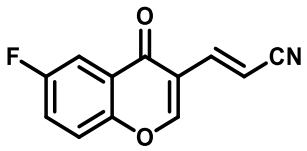
6.98 (d, *J* = 11.9 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 166.7, 160.1, 153.5, 142.1, 135.7, 131.8, 125.3, 124.7, 120.7, 121.3, 118.1, 52.1 ppm; HRMS: Calcd for $C_{13}H_{10}O_6N$ $[M+H]^+$: 276.05026, Found: 276.05009.

Compound **70i:**



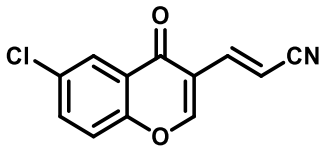
Compound **70i** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.07 (s, 1H), 7.75 – 7.72 (m, 1H), 7.52 – 7.48 (m, 2H), 7.13 (d, *J* = 17.1 Hz, 1H), 7.01 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 158.1, 155.6, 141.7, 134.7, 126.5, 126.4, 124.3, 118.6, 118.4, 113.4, 101.7 ppm; HRMS: Calcd for $C_{12}H_8O_2N$ $[M+H]^+$: 198.05495, Found: 198.05508.

Compound **70j:**



Compound **70j** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.35 (d, *J* = 15.8 Hz, 1H), 6.94 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 159.7, 153.8, 148.7, 131.3, 127.1, 124.6, 124.4, 121.2, 119.8, 113.8, 101.9 ppm; HRMS: Calcd for $C_{12}H_7O_2NF$ $[M+H]^+$: 216.04553, Found: 216.04538.

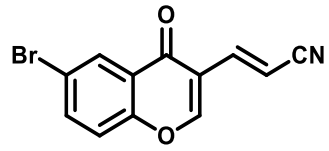
Compound **70k:**



Compound **70k** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.05

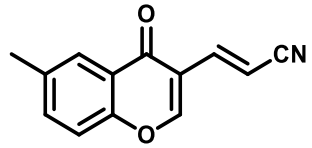
(d, *J* = 8.4 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 12.0 Hz, 1H), 6.99 (d, *J* = 12.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 160.2, 153.7, 148.9, 135.8, 131.5, 127.4, 124.8, 120.9, 119.3, 113.6, 101.8 ppm; HRMS: Calcd for $C_{12}H_7O_2NCl$ $[M+H]^+$: 232.01598, Found: 232.01605.

Compound **70l:**



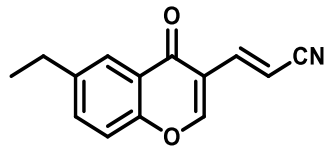
Compound **70l** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.82 (t, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 12.5 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H) 7.00 (d, *J* = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 156.3, 148.8, 135.4, 134.3, 126.2, 124.5, 121.7, 119.9, 114.6, 113.9, 101.4 ppm; HRMS: Calcd for $C_{12}H_7O_2NBr$ $[M+H]^+$: 275.96547, Found: 275.96548.

Compound **70m:**



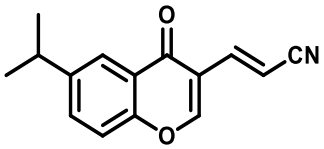
Compound **70m** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 7.9, 1.9 Hz, 1H), 8.13 (s, 1H), 7.67 (td, *J* = 7.4, 1.9 Hz, 1H), 7.52 (q, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 14.6 Hz, 1H), 7.21 (d, *J* = 14.6 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 156.2, 154.7, 135.9, 134.3, 126.4, 124.2, 122.0, 119.7, 118.4, 112.1, 101.7, 21.6 ppm; HRMS: Calcd for $C_{13}H_{10}O_2N$ $[M+H]^+$: 212.07060, Found: 212.07071.

Compound **70n:**



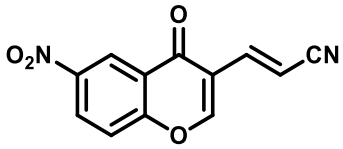
Compound **70n** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 7.9, 2.1 Hz, 1H), 8.07 (s, 1H), 7.73 (td, *J* = 7.2, 2.0 Hz, 1H), 7.50 (q, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 14.7 Hz, 1H), 7.25 (d, *J* = 14.7 Hz, 1H), 2.72 (q, *J* = 8.0 Hz, 2H), 1.91 (t, *J* = 8.0 Hz; 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 167.1, 156.7, 154.0, 138.7, 134.2, 126.5, 124.1, 119.9, 119.3, 118.7, 113.4, 28.4, 14.6 ppm; HRMS: Calcd for $C_{14}H_{12}O_2N$ $[M+H]^+$: 226.08626, Found: 226.08603.

Compound **70o:**



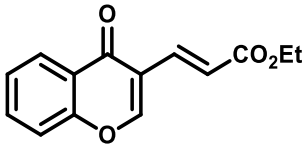
Compound **70o** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 7.6, 1.8 Hz, 1H), 8.09 (s, 1H), 7.69 (td, *J* = 7.6, 1.8 Hz, 1H), 7.45 (q, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 12.9 Hz, 1H), 7.21 (d, *J* = 12.9 Hz, 1H), 2.91 (q, *J* = 6.8 Hz, 1H), 1.27 (d, *J* = 6.8 Hz; 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 156.4, 154.1, 137.9, 134.1, 128.1, 125.7, 123.9, 120.2, 119.1, 118.8, 113.7, 35.6, 22.4, 22.3 ppm; HRMS: Calcd for $C_{15}H_{14}O_2N$ $[M+H]^+$: 240.10191, Found: 240.10184.

Compound **70p:**



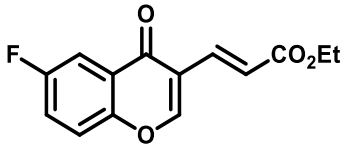
Compound **70p** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 12.7 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H) 7.00 (d, *J* = 12.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 156.3, 148.6, 135.3, 134.4, 130.1, 126.3, 124.5, 119.9, 114.7, 113.9, 101.3 ppm; HRMS: Calcd for $C_{12}H_7O_4N_2$ $[M+H]^+$: 243.04003, Found: 243.03991.

Compound **70q:**



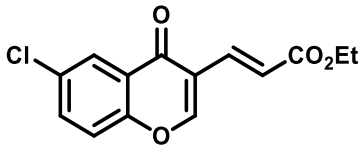
Compound **70q** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.12 (s, 1H), 7.72 – 7.69 (m, 1H), 7.49 – 7.44 (m, 2H), 7.42 (d, *J* = 16.0 Hz, 1H), 7.29 (d, *J* = 16.3 Hz, 1H), 4.26 (q, *J* = 6.9 Hz, 2H), 1.33 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 167.5, 157.5, 155.7, 135.5, 134.2, 126.5, 126.0, 124.4, 122.4, 119.6, 118.3, 60.7, 14.5 ppm; HRMS: Calcd for $C_{14}H_{13}O_4$ $[M+H]^+$: 245.08084, Found: 245.08088.

Compound **70r:**



Compound **70r** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 12.0 Hz, 1H), 4.26 (q, *J* = 7.0 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 166.7, 160.0, 153.7, 148.7, 134.8, 131.4, 127.0, 124.6, 124.4, 120.9, 118.0, 60.8, 14.4 ppm; HRMS: Calcd for $C_{14}H_{12}O_4F$ $[M+H]^+$: 263.07141, Found: 263.07137.

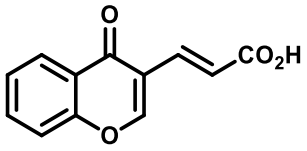
Compound **70s:**



Compound **70s** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.08 (d, *J* = 8.3 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 12.0 Hz, 1H), 7.01 (d, *J* = 12.0 Hz, 1H), 4.28 (q, *J* = 6.9 Hz, 2H), 1.37 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz,

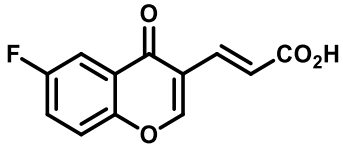
$CDCl_3$): δ 175.4, 166.9, 160.0, 153.7, 148.9, 135.7, 131.4, 127.4, 124.7, 124.1, 121.0, 118.1, 61.0, 14.5 ppm; HRMS: Calcd for $C_{14}H_{12}O_4Cl$ $[M+H]^+$: 279.04186, Found: 279.04169.

Compound **70t:**



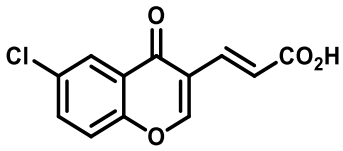
Compound **70t** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.41 (s, 1H), 8.88 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.83 (t, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.2, 164.0, 159.1, 156.8, 148.4, 137.1, 128.8, 126.2, 123.7, 122.7, 121.4, 118.7 ppm; HRMS: Calcd for $C_{12}H_8O_4Na$ $[M+Na]^+$: 239.03148, Found: 239.03140.

Compound **70u:**



Compound **70u** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.49 (s, 1H), 8.92 (s, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.84 (t, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 9.0 Hz, 1H), 7.03 (d, *J* = 10.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.1, 164.9, 159.3, 154.0, 148.1, 135.2, 131.0, 128.4, 124.9, 124.2, 121.7, 121.1, 118.1 ppm; HRMS: Calcd for $C_{13}H_7O_4FNa$ $[M+Na]^+$: 257.02206, Found: 257.02198.

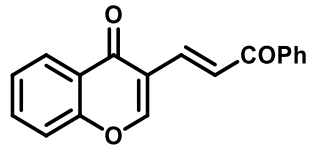
Compound **70v:**



Compound **70v** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.51 (s, 1H),

8.91 (s, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.83 (t, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 10.2 Hz, 1H), 7.01 (d, *J* = 10.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.4, 164.8, 160.1, 153.8, 148.3, 135.1, 130.7, 128.4, 124.8, 124.5, 121.9, 121.2, 118.1 ppm; HRMS: Calcd for $C_{13}H_7O_4ClNa$ $[M+Na]^+$: 273.99251, Found: 273.99261.

Compound **70w:**



Compound **70w** was synthesized according to the general procedure. White solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 16.4 Hz, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 8.21 (s, 1H), 8.11 (d, *J* = 7.4 Hz, 2H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.52–7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.8, 176.5, 159.1, 155.7, 138.1, 135.5, 134.3, 133.2, 128.9, 128.8, 126.5, 126.2, 126.0, 124.5, 119.9, 118.4 ppm; HRMS: Calcd for $C_{18}H_{13}O_3$ $[M+H]^+$: 277.08592, Found: 277.08571.

III.3.3. Synthesis of the Indoloquinolizines 72

General procedure for the racemic synthesis of ring-fused quinolizines:

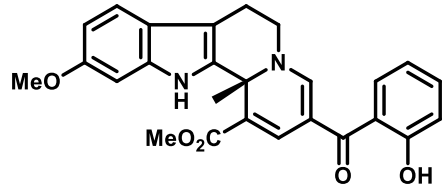
The cyclic imine (0.10 mmol; 1.0 eq.) was dissolved under argon in 5mL dry DMSO, and dry $ZnCl_2$ (0.10 mmol; 1.0 eq) was added and stirred for 5min. Chromone diene **70** (0.10 mmol; 1.0 eq.) was added and the reaction mixture was allowed to react for 1h at 80°C in a sealed tube under Ar. Disappearance of the chromone on TLC indicates complete reaction (cyclohexane/ethyl acetate 1:1). The reaction mixture is then diluted in 10 mL brine and extracted with 3x10mL DCM. The organic phase was dried over Na_2SO_4 evaporated to give a residue that is purified by flash chromatography to yield the ring-fused quinolizines as colorful solids.

General procedure for the asymmetric imino-Diels-Alder synthesis of ring-fused quinolizines:

$ZnEt_2$ (0.01 mmol; 20 mol%) and (R)-Binol (R)-**80a** or (R)-dianthracenylbinol (R)-**80e** (0.02 mmol; 40 mol%) were dissolved under argon in 5mL dry toluene and stirred for 15 minutes,

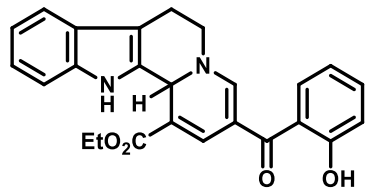
then the cyclic imine (0.05 mmol; 1.0 eq) was added to the reaction mixture which is subsequently cooled to -78°C. Chromone diene **70** (0.10 mmol; 1.0 eq.) was added and the reaction mixture was allowed to react for 12-24h at -78°C in a sealed tube under Ar. Disappearance of the chromone on TLC indicates complete reaction (cyclohexane/ethyl acetate 1:1). The reaction mixture is then evaporated to give a residue that is purified by flash chromatography to yield the ring-fused quinolizines as colorful solids.

Compound **72a:**



Compound **72a** was synthesized according to the general procedures. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.21 (s, 1H), 8.72 (s, 1H), 7.80 (s, 1H), 7.74 (s, 1H), 7.44 – 7.31 (m, 3H), 7.23 – 7.16 (m, 1H), 6.97 – 6.85 (m, 3H), 3.91 (dd, *J* = 12.3, 6.3 Hz, 1H), 3.87 (s, 3H), 3.68 (td, *J* = 12.4, 6.3 Hz, 1H), 3.61 (s, 3H), 3.53 (s, 3H), 3.16 (dd, *J* = 13.8, 3.2 Hz, 1H), 3.02 (dd, *J* = 13.8, 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6, 164.5, 164.2, 150.8, 135.8, 135.1, 132.5, 131.7, 131.5, 127.7, 123.4, 121.5, 120.4, 119.6, 117.4, 116.5, 116.0, 113.2, 111.7, 104.2, 70.2, 67.7, 55.4, 49.8, 24.3, 22.6 ppm; HRMS: Calcd for $C_{26}H_{25}O_4N_2$ $[M+H]^+$: 445.17580, Found: 445.17561; $[\alpha]_D^{20}$ -8.4 ° (c 0.002 in ethanol).

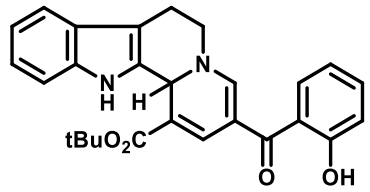
Compound **72b:**



Compound **72b** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 9.73 (s, 1H), 7.78 (s, 1H), 7.70 (s, 1H), 7.34 – 7.27 (m, 2H), 7.18 – 7.10 (m, 3H), 7.03 – 6.99 (m, 1H), 6.90 – 6.84 (m, 2H), 6.31 (s, 1H), 4.15 – 4.10 (m, 3H), 3.50 – 3.46 (m, 1H), 3.05 – 2.97 (m, 1H), 2.88 – 2.83 (m, 1H), 1.32 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.3, 170.8, 155.0, 153.7, 136.1, 134.3, 132.1, 131.5, 131.3, 129.3, 125.8, 125.6,

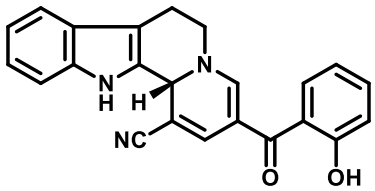
121.2, 119.0, 117.9, 116.2, 112.3, 111.6, 106.7, 106.1, 67.1, 61.2, 49.8, 22.4, 16.2 ppm; HRMS: Calcd for $C_{25}H_{23}O_4N_2$ $[M+H]^+$: 415.16523, Found: 415.16511

Compound **72c:**



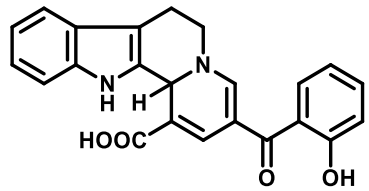
Compound **72c** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 9.74 (s, 1H), 7.79 (s, 1H), 7.69 (s, 1H), 7.33 – 7.28 (m, 2H), 7.17 – 7.10 (m, 3H), 7.04 – 6.98 (m, 1H), 6.91 – 6.84 (m, 2H), 6.31 (s, 1H), 4.02 – 3.99 (m, 1H), 3.49 – 3.44 (m, 1H), 3.04 – 2.97 (m, 1H), 2.89 – 2.83 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.3, 170.9, 155.0, 153.7, 136.1, 134.3, 132.1, 131.5, 131.4, 129.3, 125.8, 125.6, 121.2, 119.0, 117.9, 116.2, 112.3, 111.6, 106.7, 106.1, 81.5, 67.1, 49.8, 28.8, 21.6 ppm; HRMS: Calcd for $C_{27}H_{27}O_4N_2$ $[M+H]^+$: 443.19653, Found: 449.19670.

Compound **72d:**



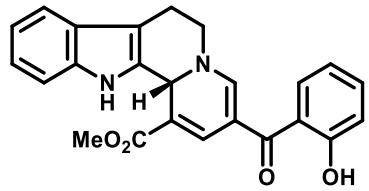
Compound **72d** was synthesized according to the general procedures. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) 11.31 (s, 1H), 9.14 (s, 1H), 7.81 (s, 1H), 7.60 (s, 1H), 7.48 – 7.40 (m, 3H), 7.25 – 7.18 (m, 1H), 7.33 – 7.31 (m, 1H), 7.09 – 7.00 (m, 2H), 6.86 (m, 1H), 6.29 (s, 1H), 3.83 – 3.79 (m, 1H), 3.20 – 3.13 (m, 1H), 2.96 – 2.91 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9, 153.4, 136.1, 134.8, 132.5, 130.3, 126.1, 122.7, 120.2, 119.7, 118.4, 118.3, 118.2, 118.1, 116.1, 111.9, 107.8, 105.9, 83.8, 82.3, 69.1, 52.0, 23.4 ppm; HRMS: Calcd for $C_{23}H_{18}O_2N_3$ $[M+H]^+$: 368.13935, Found: 368.13932; $[\alpha]_D^{20}$ -7.4 ° (c 0.002 in ethanol).

Compound **72e:**



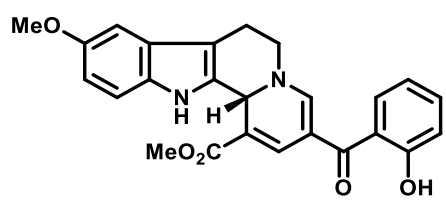
Compound **72e** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H), 11.22 (s, 1H), 9.74 (s, 1H), 7.74 (s, 1H), 7.68 (s, 1H), 7.33 – 7.27 (m, 2H), 7.17 – 7.10 (m, 3H), 7.05 – 7.00 (m, 1H), 6.91 – 6.84 (m, 2H), 6.31 (s, 1H), 4.16 – 4.11 (m, 1H), 3.49 – 3.45 (m, 1H), 3.03 – 2.96 (m, 1H), 2.86 – 2.82 (m, 1H) ; ^{13}C NMR (101 MHz, DMSO-d_6) δ 188.3, 173.1, 155.3, 153.7, 136.2, 132.1, 132.0, 131.5, 131.3, 129.3, 125.7, 125.5, 121.1, 119.0, 118.0, 116.3, 112.3, 111.6, 106.8, 106.1, 67.0, 49.8, 22.1 ppm; HRMS: Calcd for $C_{23}H_{19}O_4N_2$ $[M+Na]^+$: 409.11588, Found: 4019.11574.

Compound **72f:**



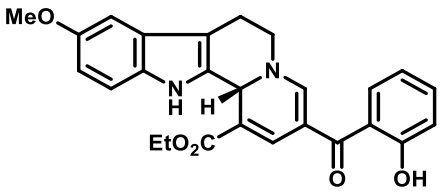
Compound **72f** was synthesized according to the general procedures. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 9.76 (s, 1H), 7.75 (s, 1H), 7.70 (s, 1H), 7.32 – 7.27 (m, 2H), 7.18 – 7.10 (m, 3H), 7.03 – 7.00 (m, 1H), 6.90 – 6.84 (m, 2H), 6.30 (s, 1H), 4.15 – 4.11 (m, 1H), 3.72 (s, 3H), 3.51 – 3.48 (m, 1H), 3.03 – 2.97 (m, 1H), 2.86 – 2.82 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 188.5, 170.1, 155.2, 153.9, 136.2, 134.4, 132.1, 131.6, 131.4, 129.3, 125.8, 125.7, 121.2, 119.0, 117.9, 116.3, 112.3, 111.6, 106.8, 106.1, 67.1, 53.5, 50.0, 49.8, 22.4 ppm; HRMS: Calcd for $C_{24}H_{21}O_4N_2$ $[M+H]^+$: 401.14958, Found: 401.14950; $[\alpha]_D^{20}$ -8.1 ° (c 0.002 in ethanol).

Compound **72g:**



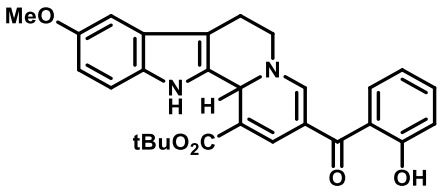
Compound **72g** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.35 (s, 1H), 8.60 (s, 1H), 7.83 (s, 1H), 7.70 (s, 1H), 7.45 – 7.32 (m, 3H), 7.23 – 7.17 (m, 1H), 6.93 – 6.85 (m, 3H), 6.28 (s, 1H), 3.91 – 3.87 (m, 4H), 3.68 – 3.60 (m, 4H), 3.14 (dd, *J* = 14.0, 3.2 Hz, 1H), 2.93 (dd, *J* = 14.0, 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 165.0, 164.5, 150.7, 135.8, 135.1, 132.4, 131.5, 131.3, 127.6, 123.4, 121.6, 120.4, 119.5, 117.3, 116.5, 116.2, 113.2, 111.8, 104.2, 70.4, 67.8, 55.4, 50.0, 22.7 ppm; HRMS: Calcd for $C_{25}H_{23}O_5N_2$ $[M+H]^+$: 431.16015, Found: 431.16007.

Compound **72h:**



Compound **72h** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 8.79 (s, 1H), 7.80 (s, 1H), 7.72 (s, 1H), 7.44 – 7.32 (m, 4H), 7.23 – 7.18 (m, 3H), 5.99 (s, 1H), 4.02 (q, *J* = 7.6 Hz, 2H), 3.91 – 3.87 (m, 4H), 3.68 – 3.60 (m, 1H), 3.13 (dd, *J* = 13.6, 3.1 Hz, 1H), 3.00 (dd, *J* = 13.7, 3.1 Hz, 1H), 1.48 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 165.2, 164.5, 150.6, 135.8, 135.2, 132.4, 131.5, 131.1, 127.4, 123.4, 121.7, 120.3, 119.6, 117.3, 116.6, 116.2, 114.2, 111.7, 104.2, 70.3, 67.7, 61.7, 50.2, 22.6, 14.2 ppm; HRMS: Calcd for $C_{26}H_{25}O_5N_2$ $[M+H]^+$: 445.17580, Found: 445.17593.

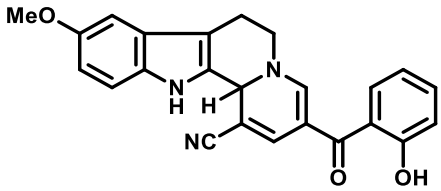
Compound **72i:**



Compound **72i** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.25 (s, 1H), 8.91 (s, 1H), 7.93 – 7.90 (m, 1H), 7.61 (d, *J* = 1.4 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.22 (s, 1H), 7.03 – 6.99 (m, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.88 – 6.80 (m, 2H), 6.01 (s, 1H), 3.81 – 3.67

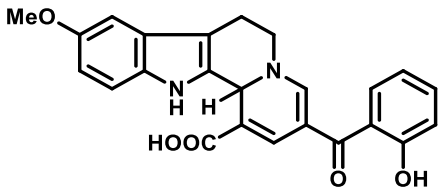
(m, 5H), 3.12 (ddd, *J* = 15.6, 12.0, 5.7 Hz, 1H), 2.88 (dd, *J* = 15.4, 4.0 Hz, 1H), 1.48 (s, 9H); 13C NMR (126 MHz, $CDCl_3$) δ 192.1, 168.8, 161.5, 154.5, 153.5, 136.3, 134.6, 132.5, 131.4, 130.4, 126.5, 120.0, 118.6, 118.5, 113.6, 113.3, 112.8, 107.9, 106.1, 100.4, 82.3, 68.1, 54.0, 52.7, 29.3, 29.3, 29.2, 21.7 ppm; HRMS: Calcd for $C_{28}H_{29}O_5N_2$ $[M+H]^+$: 473.20710, Found: 473.20688.

Compound **72j:**



Compound **72j** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 8.75 (s, 1H), 7.80 (s, 1H), 7.72 (s, 1H), 7.46 – 7.33 (m, 3H), 7.23 – 7.16 (m, 1H), 6.96 – 6.87 (m, 3H), 6.01 (s, 1H), 3.91 – 3.86 (m, 1H), 3.75 (s, 3H), 3.67 – 3.61 (m, 1H), 3.13 (dd, *J* = 13.9, 3.0 Hz, 1H), 2.98 (dd, *J* = 13.9, 3.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 164.2, 150.6, 135.7, 135.0, 132.3, 131.7, 131.4, 127.6, 123.4, 121.5, 120.4, 119.7, 117.4, 117.3, 116.6, 116.2, 113.4, 111.8, 104.6, 70.5, 67.9, 52.4, 22.5 ppm; HRMS: Calcd for $C_{24}H_{20}O_3N_3$ $[M+H]^+$: 398.14992, Found: 398.14974.

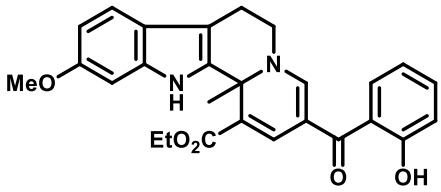
Compound **72k:**



Compound **72k** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H), 11.09 (s, 1H), 8.93 (s, 1H), 7.84 (s, 1H), 7.72 (s, 1H), 7.46 – 7.34 (m, 3H), 7.23 – 7.17 (m, 1H), 6.95 – 6.87 (m, 3H), 6.17 (s, 1H), 3.91 – 3.86 (m, 4H), 3.68 – 3.63 (m, 1H), 3.12 (dd, *J* = 13.9, 3.2 Hz, 1H), 2.97 (dd, *J* = 13.9, 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0, 173.7, 164.4, 150.9, 135.5, 135.4, 133.0, 131.4, 131.3, 127.7, 123.4, 121.5, 120.7, 119.9,

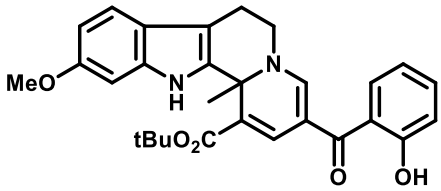
117.4, 116.3, 116.2, 113.2, 111.7, 104.0, 70.7, 67.7, 52.9, 22.3 ppm; HRMS: Calcd for $C_{24}H_{21}O_5N_2$ $[M+Na]^+$: 439.12644, Found: 439.12657.

Compound **72l:**



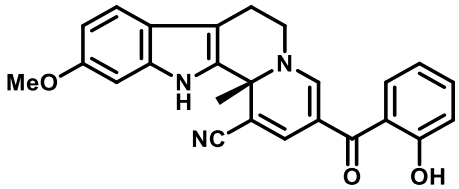
Compound **72l** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 8.73 (s, 1H), 7.81 (s, 1H), 7.73 (s, 1H), 7.47 – 7.32 (m, 4H), 7.24 – 7.18 (m, 3H), 4.14 (q, *J* = 6.7 Hz, 2H), 3.90 (dd, *J* = 12.3, 6.3 Hz, 1H), 3.77 (s, 3H), 3.66 (td, *J* = 12.0, 6.2 Hz, 1H), 3.53 (s, 3H), 3.14 (dd, *J* = 13.8, 3.3 Hz, 1H), 2.98 (dd, *J* = 13.8, 3.3 Hz, 1H), 1.44 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 164.0, 163.7, 150.7, 135.6, 135.1, 132.5, 131.7, 131.5, 127.6, 123.4, 121.5, 120.3, 119.9, 119.7, 117.1, 116.4, 113.0, 111.9, 104.1, 70.5, 67.6, 62.7, 55.9, 24.3, 22.6, 14.9 ppm; HRMS: Calcd for $C_{27}H_{27}O_5N_2$ $[M+H]^+$: 459.19145, Found: 459.19115.

Compound **72m:**



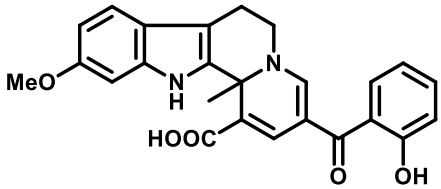
Compound **72m** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.14 (s, 1H), 8.92 (s, 1H), 7.82 (s, 1H), 7.72 (s, 1H), 7.48 – 7.32 (m, 4H), 7.23 – 7.18 (m, 3H), 3.93 (dd, *J* = 12.7, 6.5 Hz, 1H), 3.79 (s, 3H), 3.65 (td, *J* = 12.1, 6.3 Hz, 1H), 3.51 (s, 3H), 3.12 – 3.08 (m, 1H), 2.97 (dd, *J* = 13.9, 3.2 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.7, 165.3, 163.4, 151.2, 135.2, 135.1, 132.7, 131.8, 131.4, 128.0, 123.5, 121.4, 120.4, 119.7, 119.5, 118.0, 116.4, 113.2, 111.8, 104.0, 81.2, 70.2, 67.6, 55.8, 29.1, 24.4, 22.6 ppm; HRMS: Calcd for $C_{29}H_{31}O_5N_2$ $[M+H]^+$: 498.22275, Found: 498.22268.

Compound **72n:**



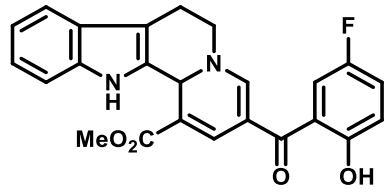
Compound **72n** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.26 (s, 1H), 9.12 (s, 1H), 7.94 (s, 1H), 7.62 (s, 1H), 7.47 – 7.44 (m, 2H), 7.30 – 7.23 (m, 3H), 6.99 – 6.91 (m, 2H), 3.86 (s, 3H), 3.81 – 3.74 (m, 2H), 3.64 (s, 3H), 3.16 – 3.07 (m, 1H), 2.91 – 2.86 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 161.3, 153.0, 136.5, 134.7, 134.4, 130.0, 127.5, 125.8, 120.8, 119.6, 119.1, 118.5, 118.4, 118.2, 116.8, 113.5, 112.7, 107.6, 106.2, 67.0, 53.2, 52.4, 26.9, 22.8 ppm; HRMS: Calcd for $C_{25}H_{22}O_3N_3$ $[M+H]^+$: 412.16557, Found: 412.16550; $[\alpha]_D^{20}$ -7.9 ° (c 0.002 in ethanol).

Compound **72o:**



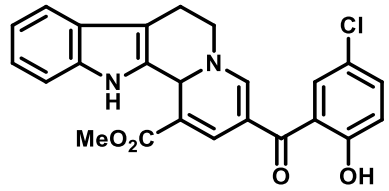
Compound **72o** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H), 11.24 (s, 1H), 8.85 (s, 1H), 7.79 (s, 1H), 7.73 (s, 1H), 7.46 – 7.34 (m, 3H), 7.23 – 7.17 (m, 1H), 6.95 – 6.87 (m, 3H), 3.93 (dd, *J* = 12.4, 6.4 Hz, 1H), 3.88 (s, 3H), 3.69 (td, *J* = 12.3, 6.3 Hz, 1H), 3.56 (s, 3H), 3.14 (dd, *J* = 13.4, 3.2 Hz, 1H), 3.00 (dd, *J* = 13.4, 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0, 173.4, 164.7, 151.2, 135.7, 135.0, 132.6, 131.8, 131.7, 127.7, 123.3, 121.5, 120.3, 119.7, 117.4, 116.0, 115.8, 113.9, 111.6, 104.1, 70.2, 67.8, 52.1, 24.4, 22.4 ppm; HRMS: Calcd for $C_{25}H_{23}O_5N_2$ $[M+Na]^+$: 453.14209, Found: 453.14187.

Compound **72p:**



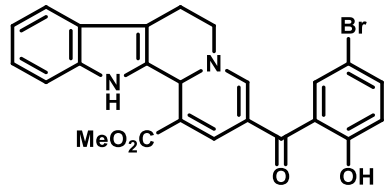
Compound **72p** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 9.02 (s, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.30 (m, 3H), 7.22 – 7.12 (m, 2H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.00 (s, 1H), 3.83 – 3.75 (m, 5H), 3.20 (m, 1H), 2.99 (dd, *J* = 14.0, 4.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 167.2, 159.5, 153.4, 136.2, 135.1, 134.3, 131.6, 129.6, 125.9, 122.3, 121.2, 120.9, 120.1, 119.7, 118.3, 114.6, 112.0, 108.2, 105.9, 68.4, 52.6, 50.6, 23.6 ppm; HRMS: Calcd for $C_{24}H_{20}O_4N_2F$ $[M+H]^+$: 419.14016, Found: 419.13999.

Compound **72q:**



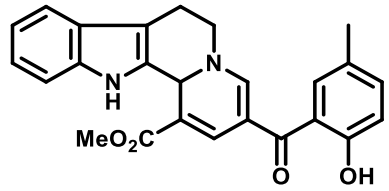
Compound **72q** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 8.99 (s, 1H), 7.92 (d, *J* = 1.5 Hz, 1H), 7.59 (d, *J* = 1.5 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.22 – 7.12 (m, 2H), 6.98 (d, *J* = 8.7 Hz, 1H), 6.02 (s, 1H), 3.83 – 3.73 (m, 5H), 3.16 (m, 1H), 2.97 (dd, *J* = 15.6, 3.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 168.9, 159.7, 153.6, 136.2, 135.6, 134.3, 131.6, 129.5, 125.9, 122.4, 121.2, 120.8, 120.0, 119.7, 118.3, 114.5, 112.0, 108.3, 105.8, 68.4, 52.7, 50.6, 23.4 ppm; HRMS: Calcd for $C_{24}H_{20}O_4N_2Cl$ $[M+H]^+$: 435.11061, Found: 435.11066.

Compound **72r:**



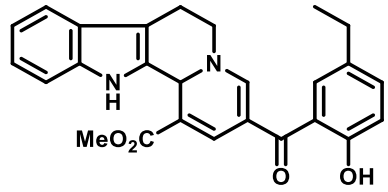
Compound **72r** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 9.02 (s, 1H), 7.95 (d, *J* = 1.5 Hz, 1H), 7.50 (d, *J* = 1.5 Hz, 1H), 7.42 – 7.31 (m, 4H), 7.22 – 7.12 (m, 2H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.00 (s, 1H), 3.80 – 3.70 (m, 5H), 3.14 (m, 1H), 2.98 (dd, *J* = 15.5, 3.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6, 168.3, 159.4, 154.0, 136.2, 135.4, 134.3, 131.1, 129.5, 125.8, 122.6, 121.0, 120.7, 120.0, 119.7, 118.4, 114.6, 112.0, 108.7, 105.8, 68.4, 52.6, 50.6, 23.2 ppm; HRMS: Calcd for $C_{24}H_{20}O_4N_2Br$ $[M+H]^+$: 479.06010, Found: 479.05979.

Compound **72s:**



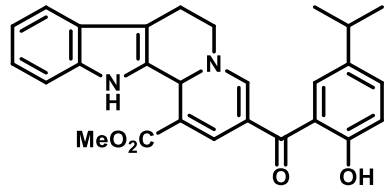
Compound **72s** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 9.02 (s, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.20 – 7.10 (m, 4H), 6.94 – 6.90 (m, 1H), 6.01 (s, 1H), 3.86 (s, 3H), 3.79 – 3.68 (m, 2H), 3.15 (ddd, *J* = 15.7, 11.9, 5.7, 9.9 Hz, 1H), 2.93 (dd, *J* = 15.5, 3.6 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 169.0, 159.2, 153.4, 136.7, 136.0, 135.4, 132.5, 130.2, 127.7, 126.0, 123.1, 120.4, 119.6, 118.4, 118.2, 113.4, 112.0, 108.5, 106.1, 68.0, 54.2, 52.7, 23.6, 20.5 ppm; HRMS: Calcd for $C_{25}H_{23}O_4N_2$ $[M+H]^+$: 415.16523, Found: 415.16504.

Compound **72t:**



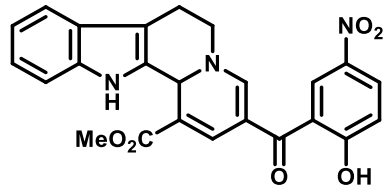
Compound **72t** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 9.03 (s, 1H), 7.92 (d, *J* = 2.3 Hz, 1H), 7.60 (d, *J* = 2.4 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.20 – 7.12 (m, 4H), 6.95 – 6.91 (m, 1H), 6.00 (s, 1H), 3.84 (s, 3H), 3.78 – 3.71 (m, 2H), 3.17 – 3.14 (m, 1H), 2.93 – 2.87 (m, 1H), 2.72 (q, *J* = 8.0 Hz, 2H), 1.31 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 169.4, 159.3, 153.5, 136.7, 136.0, 135.3, 132.5, 130.2, 127.8, 126.0, 123.2, 120.5, 119.5, 118.4, 118.2, 113.3, 111.7, 108.4, 106.0, 67.9, 54.3, 52.7, 27.1, 23.5, 14.7 ppm; HRMS: Calcd for $C_{26}H_{25}O_4N_2$ $[M+H]^+$: 429.18088, Found: 429.18057.

Compound **72u:**



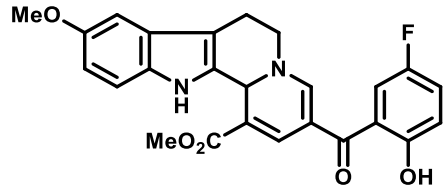
Compound **72u** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (s, 1H), 9.03 (s, 1H), 7.92 (d, *J* = 1.8 Hz, 1H), 7.67 (d, *J* = 1.8 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.27 - 7.16 (m, 3H), 7.09 (m, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 5.97 (s, 1H), 3.85 – 3.76 (m, 4H), 3.65 (dd, *J* = 13.1, 5.3 Hz, 1H), 3.15 – 3.19 (m, 1H), 2.96 (dd, *J* = 14.9, 4.0 Hz, 1H), 2.87 – 2.79 (m, 1H), 1.31 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 168.7, 159.4, 154.0, 138.7, 136.8, 136.6, 133.4, 132.2, 127.8, 126.1, 123.1, 120.4, 119.6, 118.7, 118.1, 112.9, 112.3, 108.2, 105.9, 68.4, 53.2, 33.7, 27.1, 24.2, 24.1, 23.2 ppm; HRMS: Calcd for $C_{27}H_{27}O_4N_2$ $[M+H]^+$: 443.19653, Found: 443.19626).

Compound **72v:**



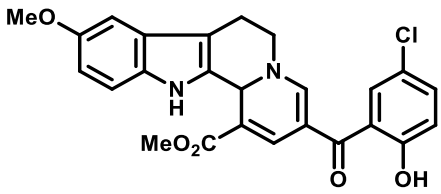
Compound **72v** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 8.99 (s, 1H), 7.87 (d, *J* = 2.7 Hz, 1H), 7.68 (d, *J* = 2.7 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.32 (m, 3H), 7.22 – 7.13 (m, 2H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.03 (s, 1H), 3.83 – 3.76 (m, 5H), 3.19 (m, 1H), 2.98 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 167.4, 159.7, 153.1, 136.4, 134.9, 134.3, 131.8, 129.6, 125.7, 122.4, 121.3, 121.0, 120.1, 119.7, 118.2, 114.7, 112.3, 108.2, 105.9, 68.7, 52.4, 50.4, 23.7 ppm; HRMS: Calcd for $C_{24}H_{20}O_6N_3$ $[M+H]^+$: 446.13466, Found: 446.13438.

Compound **72w:**



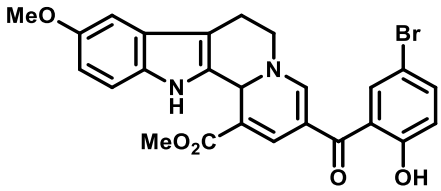
Compound **72w** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (s, 1H), 8.99 (s, 1H), 7.78 (d, *J* = 2.0 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.29 (d, *J* = 8.6 Hz, 1H), 6.92 – 6.88 (m, 3H), 6.00 (s, 1H), 3.85 (s, 3H), 3.81 - 3.74 (m, 5H), 3.15 – 3.11 (m, 1H), 2.93 (dd, *J* = 15.7, 3.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 168.4, 160.0, 154.4, 153.6, 137.2, 135.7, 132.8, 132.0, 131.2, 126.5, 121.6, 120.7, 114.3, 113.2, 112.7, 110.1, 107.8, 105.6, 100.1, 68.7, 55.1, 53.0, 52.1, 23.4 ppm; HRMS: Calcd for $C_{25}H_{22}O_5N_2F$ $[M+H]^+$: 449.15073, Found: 449.15047.

Compound **72x:**



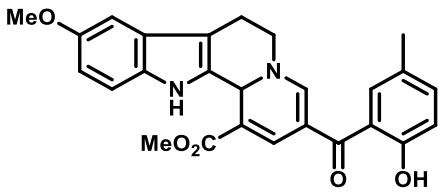
Compound **72x** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.05 (s, 1H), 9.02 (s, 1H), 7.83 (d, *J* = 1.7 Hz, 1H), 7.58 (d, *J* = 1.7 Hz, 1H), 7.51 (d, *J* = 2.3 Hz, 1H), 7.49 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 6.84 – 6.80 (m, 3H), 6.04 (s, 1H), 3.88 (s, 3H), 3.81 – 3.72 (m, 5H), 3.21 (ddd, *J* = 15.7, 11.4, 6.1 Hz, 1H), 2.98 (dd, *J* = 15.7, 3.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 169.7, 162.1, 154.4, 152.5, 137.0, 135.9, 132.6, 132.1, 131.0, 126.3, 121.4, 119.9, 114.7, 113.6, 111.7, 110.2, 107.6, 106.1, 100.9, 68.3, 56.6, 53.1, 52.7, 22.4 ppm; HRMS: Calcd for $C_{25}H_{22}O_5N_2Cl$ $[M+H]^+$: 465.12118, Found: 465.12098.

Compound **72y:**



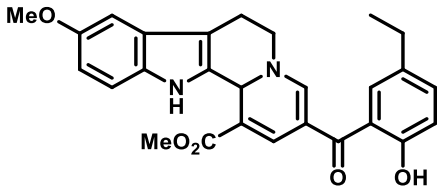
Compound **72y** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.16 (s, 1H), 8.93 (s, 1H), 7.87 (d, *J* = 1.9 Hz, 1H), 7.60 (d, *J* = 1.5 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.25 (d, *J* = 8.7 Hz, 1H), 6.97 – 6.90 (m, 3H), 6.01 (s, 1H), 3.86 (s, 3H), 3.81 – 3.72 (m, 5H), 3.15 – 3.11 (m, 1H), 2.94 (dd, *J* = 15.8, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 168.9, 160.2, 154.3, 153.6, 137.1, 135.7, 132.9, 132.7, 131.1, 126.4, 121.6, 120.4, 113.8, 113.1, 112.5, 110.1, 107.7, 105.6, 100.2, 68.5, 55.0, 53.1, 52.2, 23.8 ppm; HRMS: Calcd for $C_{25}H_{22}O_5N_2Br$ $[M+H]^+$: 509.07066, Found: 509.07085.

Compound **72z:**



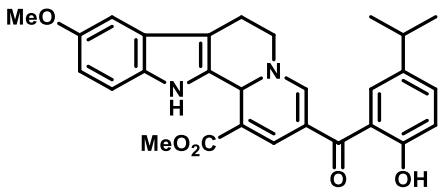
Compound **72z** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.01 (s, 1H), 8.97 (s, 1H), 7.93 (d, *J* = 1.5 Hz, 1H), 7.60 (d, *J* = 1.6 Hz, 1H), 7.24 – 7.19 (m, 3H), 6.92 – 6.88 (m, 2H), 6.85 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.98 (s, 1H), 3.89 – 3.80 (m, 4H), 3.78 (s, 3H), 3.71 (dd, *J* = 13.3, 5.1 Hz, 1H), 3.11 (ddd, *J* = 15.5, 12.1, 5.5 Hz, 1H), 2.89 (dd, *J* = 15.5, 3.7 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 169.3, 168.4, 159.2, 154.4, 153.5, 136.0, 135.4, 132.8, 131.3, 130.4, 127.7, 126.5, 119.8, 118.2, 113.9, 113.1, 112.8, 107.8, 100.3, 68.3, 56.1, 52.8, 52.4, 23.6, 21.2 ppm; HRMS: Calcd for $C_{26}H_{25}O_5N_2$ $[M+H]^+$: 445.17580, Found: 445.17575.

Compound **72aa:**



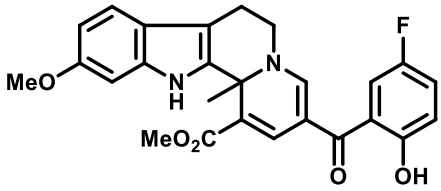
Compound **72aa** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (s, 1H), 8.99 (s, 1H), 7.91 (d, *J* = 1.5 Hz, 1H), 7.60 (d, *J* = 1.5 Hz, 1H), 7.23 – 7.18 (m, 3H), 6.93 – 6.87 (m, 3H), 5.99 (s, 1H), 3.89 – 3.82 (m, 4H), 3.77 (s, 3H), 3.70 (dd, *J* = 13.2, 5.2 Hz, 1H), 3.09 (ddd, *J* = 15.6, 12.0, 5.2 Hz, 1H), 2.92 – 2.87 (m, 3H), 1.32 (t , *J* = 7.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.1, 169.4, 168.4, 159.5, 154.4, 153.6, 136.0, 135.5, 132.7, 131.2, 130.4, 127.7, 126.5, 119.8, 118.2, 113.9, 113.1, 112.8, 107.8, 100.3, 68.0, 56.1, 52.8, 52.5, 28.3, 23.5, 17.3 ppm; HRMS: Calcd for $C_{27}H_{27}O_5N_2$ $[M+H]^+$: 459.19145, Found: 459.19137.

Compound **72ab:**



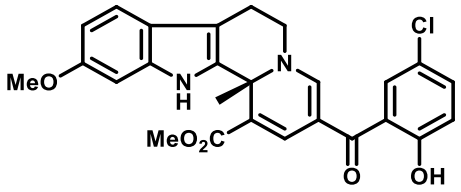
Compound **72ab** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 8.95 (s, 1H), 7.89 (d, *J* = 1.6 Hz, 1H), 7.57 (d, *J* = 1.5 Hz, 1H), 7.26 – 7.20 (m, 3H), 6.92 – 6.82 (m, 3H), 6.03 (s, 1H), 3.89 – 3.80 (m, 4H), 3.78 (s, 3H), 3.70 (dd, *J* = 13.4, 5.0 Hz, 1H), 3.17 – 3.13 (m, 1H), 2.95 – 2.90 (m, 2H), 1.31 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 169.3, 168.4, 159.2, 154.4, 153.5, 136.0, 135.4, 132.8, 131.3, 130.4, 127.7, 126.5, 119.8, 118.2, 113.9, 113.1, 107.8, 106.1, 100.3, 68.3, 56.1, 52.8, 52.4, 34.1, 23.6, 21.8, 21.7 ppm; HRMS: Calcd for $C_{28}H_{29}O_5N_2$ $[M+H]^+$: 437.20710, Found: 437.20687.

Compound **72ac:**



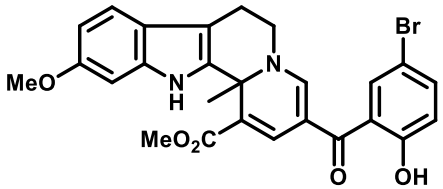
Compound **72ac** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H), 8.99 (s, 1H), 7.87 (s, 1H), 7.63 (s, 1 H), 7.51 (s, 1H), 7.36 – 7.31 (m, 2H), 7.26 – 7.22 (m, 2H), 6.98 (d, *J* = 9.0 Hz, 1H), 3.88 (s, 3H), 3.81 (m, 4H), 3.53 – 3.46 (m, 4H), 3.22 – 3.17 (m, 1H), 3.01 (dd, *J* = 15.3, 3.0 Hz, 1H); 13C NMR (101 MHz, $CDCl_3$) δ 191.2, 176.8, 159.7, 153.5, 136.0, 135.8, 134.3, 131.7, 129.3, 126.0, 123.5, 123.1, 120.7, 120.2, 119.0, 118.4, 115.1, 112.0, 108.2, 105.7, 68.1, 54.2, 52.8, 52.6, 23.8, 22.4 ppm; HRMS: Calcd for $C_{26}H_{24}O_5N_2F$ $[M+H]^+$: 463.16638, Found: 463.16611.

Compound **72ad:**



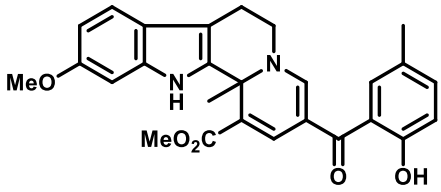
Compound **72ad** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.23 (s, 1H), 9.03 (s, 1H), 7.91 (s, 1H), 7.62 (s, 1 H), 7.58 (s, 1H), 7.37 – 7.30 (m, 2H), 7.20 – 7.14 (m, 2H), 6.95 (d, *J* = 8.7 Hz, 1H), 3.87 (s, 3H), 3.84 – 3.80 (m, 4H), 3.54 – 3.46 (m, 4H), 3.22 – 3.16 (m, 1H), 2.95 ppm (dd, *J* = 15.6, 3.4 Hz, 1H); 13C NMR (101 MHz, $CDCl_3$) δ 190.5, 170.1, 159.8, 153.5, 136.1, 135.8, 134.2, 131.7, 129.4, 126.0, 123.4, 123.1, 120.8, 120.0, 119.1, 118.4, 114.0, 112.1, 108.2, 105.8, 68.1, 54.3, 52.8, 52.6, 23.7, 22.5 ppm; HRMS: Calcd for $C_{26}H_{24}O_5N_2Cl$ $[M+H]^+$: 479.13683, Found: 479.13677; $[\alpha]_D^{20}$ -8.8 ° (c 0.002 in ethanol).

Compound **72ae:**



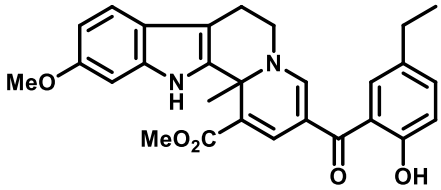
Compound **72ae** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.23 (s, 1H), 9.03 (s, 1H), 7.91 (s, 1H), 7.62 (s, 1 H), 7.58 (s, 1H), 7.37 – 7.30 (m, 2H), 7.20 – 7.14 (m, 2H), 6.95 (d, *J* = 8.7 Hz, 1H), 3.87 (s, 3H), 3.82 – 3.78 (m, 4H), 3.54 – 3.46 (m, 4H), 3.22 – 3.16 (m, 1H), 2.95 ppm (dd, *J* = 15.6, 3.4 Hz, 1H); 13C NMR (101 MHz, $CDCl_3$) δ 190.5, 170.1, 159.8, 153.5, 136.1, 135.8, 134.2, 131.7, 129.4, 126.0, 123.4, 123.1, 120.8, 120.0, 119.1, 118.4, 114.0, 112.1, 108.2, 105.8, 68.1, 54.3, 52.8, 52.6, 23.7, 22.5 ppm; HRMS: Calcd for $C_{26}H_{24}O_5N_2Br$ $[M+H]^+$: 523.08631, Found: 523.08614.

Compound **72af:**



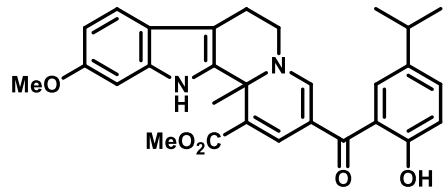
Compound **72af** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (s, 1H), 9.02 (s, 1H), 7.91 (s, 1H), 7.58 (s, 1H), 7.46 – 7.39 (m, 2H), 7.27 – 7.23 (m, 2H), 7.04 (m, 1H), 6.89 (t, *J* =7.8 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.69 – 3.64 (m, 2H), 3.39 (s, 3H), 3.18 – 3.13 (m, 1H) 2.93 – 2.87 (m, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 169.9, 168.2, 161.1, 153.2, 136.8, 134.2, 131.8, 129.2, 126.2, 124.7, 119.6, 118.4, 118.2, 117.6, 113.3, 111.4, 107.7, 105.7, 70.0, 67.9, 53.6, 52.5, 52.3, 23.1, 22.7, 21.5 ppm; HRMS: Calcd for $C_{27}H_{27}O_5N_2$ $[M+H]^+$: 459.19145, Found: 459.19139; $[\alpha]_D^{20}$ -10.1 ° (c 0.002 in ethanol).

Compound **72ag:**



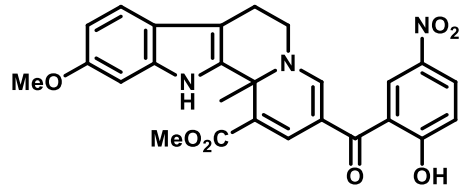
Compound **72ag** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 9.01 (s, 1H), 7.92 (s, 1H), 7.59 (s, 1H), 7.46 – 7.40 (m, 2H), 7.28 – 7.23 (m, 2H), 7.04 – 7.01 (m, 1H), 6.92 (t, *J* =7.8 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.69 – 3.64 (m, 2H), 3.49 (s, 3H), 3.18 – 3.12 (m, 1H) 2.92 – 2.87 (m, 1H), 2.79 (q, *J* = 7.9 Hz, 2H), 1.32 (t , *J* = 7.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 169.9, 165.2, 161.0, 153.2, 136.9, 134.3, 131.7, 129.2, 126.1, 124.7, 119.6, 118.3, 118.2, 117.6, 113.4, 111.4, 107.8, 105.7, 69.9, 67.8, 53.7, 52.5, 52.2, 28.1, 23.3, 22.8, 17.1 ppm; HRMS: Calcd for $C_{28}H_{29}O_5N_2$ $[M+H]^+$: 473.20710, Found: 473.20685.

Compound **72ah:**



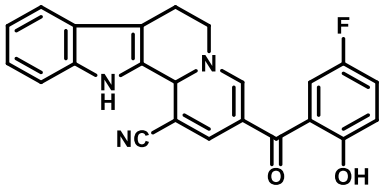
Compound **72ah** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (s, 1H), 8.99 (s, 1H), 7.87 (s, 1H), 7.59 (s, 1H), 7.26 – 7.19 (m, 3H), 6.92 – 6.84 (m, 3H), 3.88 – 3.80 (m, 4H), 3.77 – 3.72 (m, 4H), 3.55 (s, 3H), 3.18 – 3.13 (m, 1H), 2.93 – 2.87 (m, 2H), 1.31 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 169.5, 168.3, 159.4, 154.3, 153.6, 136.1, 135.5, 132.7, 131.2, 130.6, 127.8, 126.4, 119.7, 118.4, 113.8, 113.2, 107.7, 106.3, 100.3, 68.3, 56.2, 52.6, 52.1, 34.0, 27.5, 23.8, 21.7, 21.4 ppm; HRMS: Calcd for $C_{29}H_{31}O_5N_2$ $[M+H]^+$: 487.22275, Found: 487.22255.

Compound **72ai:**



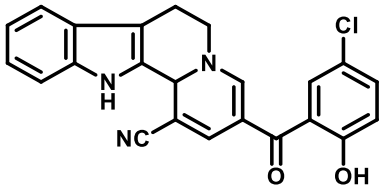
Compound **72ai** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 9.00 (s, 1H), 7.88 (d, *J* = 3.0 Hz, 1H), 7.70 (d, *J* = 3.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.23 – 7.12 (m, 2H), 6.99 – 6.93 (d, *J* = 8.0 Hz, 1H), 3.84 – 3.75 (m, 8H), 3.61 (s, 3H), 3.29 – 3.26 (m, 1H), 2.95 – 2.90 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8, 166.4, 160.7, 153.2, 136.4, 135.9, 134.3, 131.6, 129.5, 125.4, 122.4, 121.2, 121.0, 120.0, 119.9, 118.1, 114.7, 112.4, 110.2, 108.2, 68.7, 54.0, 52.4, 52.3, 50.3, 23.4 ppm; HRMS: Calcd for $C_{26}H_{24}O_7N_3$ $[M+H]^+$: 490.16088, Found: 490.16084.

Compound **72aj:**



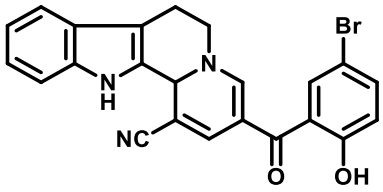
Compound **72aj** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 8.97 (s, 1H), 7.93 (d, *J* = 1.5 Hz, 1H), 7.60 (d, *J* = 1.5 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.39 – 7.30 (m, 3H), 7.25 – 7.19 (m, 1H), 7.17 – 7.10 (m, 1H), 6.00 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 3.80 – 3.73 (m, 2H), 3.16 (dd, *J* = 15.6, 12.0 Hz, 1H), 2.98 (dd, *J* = 15.6, 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 159.7, 153.6, 136.3, 135.8, 134.4, 131.7, 129.6, 126.0, 123.3, 123.2, 120.7, 121.0, 120.0, 118.2, 115.3, 114.1, 112.0, 108.1, 105.7, 68.2, 54.1, 23.4 ppm; HRMS: Calcd for $C_{23}H_{17}O_2N_3F$ $[M+H]^+$: 386.12993, Found: 386.12981.

Compound **72ak:**



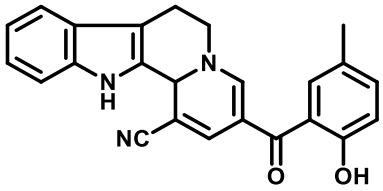
Compound **72ak** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 8.97 (s, 1H), 7.93 (d, *J* = 1.5 Hz, 1H), 7.60 (d, *J* = 1.5 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.39 – 7.30 (m, 3H), 7.25 – 7.19 (m, 1H), 7.17 – 7.10 (m, 1H), 6.00 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 3.80 – 3.73 (m, 2H), 3.16 (dd, *J* = 15.6, 12.0 Hz, 1H), 2.98 (dd, *J* = 15.6, 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 159.7, 153.6, 136.3, 135.8, 134.4, 131.7, 129.6, 126.0, 123.3, 123.2, 120.7, 121.0, 120.0, 118.2, 115.3, 114.1, 112.0, 108.1, 105.7, 68.2, 54.1, 23.4 ppm; HRMS: Calcd for $C_{23}H_{17}O_2N_3$ $[M+H]^+$: 402.10038, Found: 402.10005.

Compound **72al:**



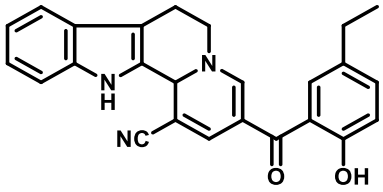
Compound **72al** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 8.97 (s, 1H), 7.93 (d, *J* = 1.5 Hz, 1H), 7.60 (d, *J* = 1.5 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.39 – 7.30 (m, 3H), 7.25 – 7.19 (m, 1H), 7.17 – 7.10 (m, 1H), 6.00 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 3.80 – 3.73 (m, 2H), 3.16 (dd, *J* = 15.6, 12.0 Hz, 1H), 2.98 (dd, *J* = 15.6, 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 159.7, 153.6, 136.3, 135.8, 134.4, 131.7, 129.6, 126.0, 123.3, 123.2, 120.7, 121.0, 120.0, 118.2, 115.3, 114.1, 112.0, 108.1, 105.7, 68.2, 54.1, 23.4 ppm; HRMS: Calcd for $C_{23}H_{17}O_2N_3Br$ $[M+H]^+$: 446.04987, Found: 446.04961.

Compound **72am:**



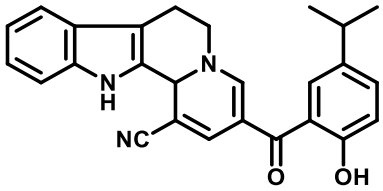
Compound **72am** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (s, 1H), 9.01 (s, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 1.7 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.13 (m, 4H), 6.94 – 6.90 (m, 1H), 6.00 (s, 1H), 3.83 – 3.77 (m, 2H), 3.18 (dd, *J* = 15.8, 3.7 Hz, 1H), 2.95 (dd, *J* = 15.7, 3.6 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 160.2, 153.7, 136.4, 136.1, 135.4, 132.3, 130.5, 127.9, 126.0, 123.4, 120.3, 119.5, 118.3, 118.2, 113.7, 112.1, 111.5, 108.4, 106.2, 68.0, 53.7, 23.6, 21.0 ppm; HRMS: Calcd for $C_{24}H_{20}O_2N_3$ $[M+H]^+$: 382.15500, Found: 382.15467.

Compound **72an:**



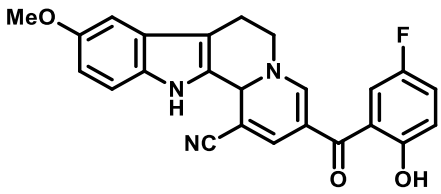
Compound **72an** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (s, 1H), 9.00 (s, 1H), 7.90 (d, *J* = 2.0 Hz, 1H), 7.60 (d, *J* = 1.8 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.24 – 7.15 (m, 4H), 6.98 – 6.94 (m, 1H), 6.01 (s, 1H), 3.80 – 3.73 (m , 2H), 3.17 (dd, *J* = 15.8, 3.8 Hz, 1H), 2.96 (dd, *J* = 15.7, 3.8 Hz, 1H), 2.79 (q, *J* = 7.9 Hz, 2H), 1.32 (t , *J* = 7.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 160.3, 153.8, 136.4, 136.1, 135.7, 132.1, 130.5, 127.8, 126.0, 123.3, 120.4, 119.5, 118.2, 118.1, 113.8, 112.0, 111.6, 108.7, 106.2, 68.4, 53.4, 27.5, 23.3, 17.5 ppm; HRMS: Calcd for $C_{25}H_{22}O_2N_3$ $[M+H]^+$: 396.17065, Found: 396.17044.

Compound **72ao:**



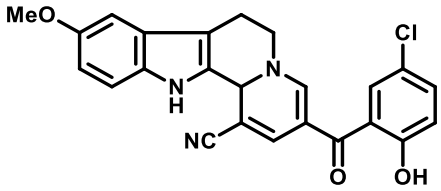
Compound **72ao** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (s, 1H), 8.99 (s, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.60 (d, *J* = 1.7 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.23 – 7.14 (m, 4H), 6.95 – 6.90 (m, 1H), 5.99 (s, 1H), 3.84 – 3.78 (m, 2H), 3.19 (dd, *J* = 15.6, 3.8 Hz, 1H), 2.96 – 2.91 (m, 2H), 1.31 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 160.2, 153.7, 136.4, 136.1, 135.4, 132.3, 130.5, 127.9, 126.0, 123.4, 120.3, 119.5, 118.3, 118.2, 113.7, 112.1, 111.5, 108.4, 106.2, 68.0, 34.0, 27.5, 23.7, 21.4 ppm; HRMS: Calcd for $C_{26}H_{24}O_2N_3$ $[M+H]^+$: 410.18630 Found: 410.18604.

Compound **72ap:**



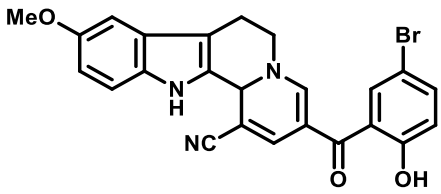
Compound **72ap** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 8.95 (s, 1H), 7.85 (d, *J* = 3.5 Hz, 1H), 7.59 – 7.53 (m, 3H), 7.31 (d, *J* = 7.7 Hz, 1H), 6.97 (ddd, *J* = 12.0, 8.0, 2.4 Hz, 3H), 5.95 (s, 1H), 3.81 – 3.72 (m, 5H), 3.15 – 3.11 (m, 1H), 2.98 (dd, *J* = 14.9, 3.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.7, 160.3, 154.3, 153.4, 137.0, 135.7, 132.8, 132.7, 131.0, 126.4, 121.8, 120.4, 113.8, 113.0, 112.5, 111.8, 110.1, 107.6, 105.6, 102.4, 68.9, 53.8, 52.1, 23.9 ppm; HRMS: Calcd for $C_{24}H_{19}O_3N_3F$ $[M+H]^+$: 416.14050, Found: 416.14021.

Compound **72aq:**



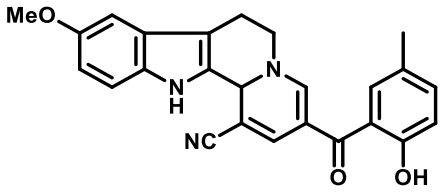
Compound **72aq** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (s, 1H), 9.01 (s, 1H), 7.89 (d, *J* = 3.6 Hz, 1H), 7.54 – 7.48 (m, 3H), 7.25 (d, *J* = 6.7 Hz, 1H), 7.02 – 6.96 (m, 3H), 6.04 (s, 1H), 3.82 – 3.71 (m, 5H), 3.15 – 3.10 (m, 1H), 3.02 (dd, *J* = 13.8, 4.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 160.8, 156.1, 151.4, 137.5, 135.7, 132.6, 132.4, 131.5, 126.3, 121.7, 120.4, 113.9, 113.0, 112.4, 111.8, 110.2, 107.5, 105.6, 102.7, 68.9, 53.7, 52.0, 23.8 ppm; HRMS: Calcd for $C_{24}H_{19}O_3N_3Cl$ $[M+H]^+$: 432.11095, Found: 432.11060.

Compound **72ar:**



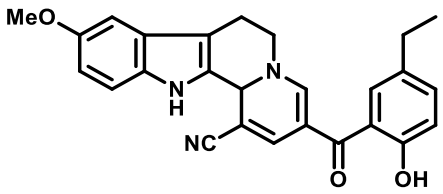
Compound **72ar** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.06 (s, 1H), 8.99 (s, 1H), 7.87 (d, *J* = 3.7 Hz, 1H), 7.56 – 7.49 (m, 3H), 7.24 (d, *J* = 6.7 Hz, 1H), 7.00 – 6.94 (m, 3H), 5.98 (s, 1H), 3.81 – 3.73 (m, 5H), 3.16 – 3.12 (m, 1H), 3.02 – 2.98 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 160.7, 156.6, 151.1, 137.7, 135.7, 132.6, 132.5, 131.1, 126.0, 121.7, 120.4, 113.8, 113.0, 112.7, 111.8, 110.3, 107.5, 105.7, 102.8, 68.9, 53.6, 52.4, 23.8 ppm; HRMS: Calcd for $C_{24}H_{19}O_3N_3Cl$ $[M+H]^+$: 476.06043, Found: 476.06029.

Compound **72as:**



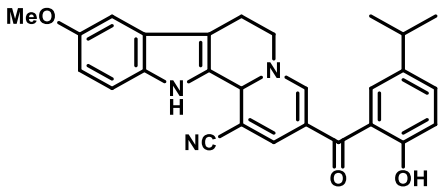
Compound **72as** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 9.04 (s, 1H), 7.88 (s, 1H), 7.57 (s, 1H), 7.47 – 7.40 (m, 2H), 7.27 – 7.23 (m, 2H), 7.02 (m, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 6.00 (s, 1H), 3.87 (s, 3H), 3.69 – 3.64 (m, 2H), 3.17 – 3.12 (m, 1H), 2.93 – 2.89 (m, 1H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.4, 168.3, 161.4, 153.2, 136.5, 134.3, 131.8, 129.4, 126.4, 124.8, 119.5, 118.5, 118.0, 117.5, 113.7, 111.4, 111.1, 107.5, 105.8, 67.8, 53.4, 52.3, 22.7, 21.7 ppm; HRMS: Calcd for $C_{25}H_{22}O_3N_3$ $[M+H]^+$: 412.16557, Found: 412.16551.

Compound **72at:**



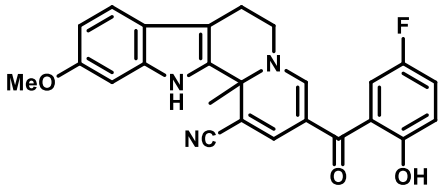
Compound **72at** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 9.02 (s, 1H), 7.90 (s, 1H), 7.56 (s, 1H), 7.46 – 7.41 (m, 2H), 7.26 – 7.23 (m, 2H), 7.04 – 6.96 (m, 2H), 5.99 (s, 1H), 3.85 (s, 3H), 3.67 – 3.63 (m, 2H), 3.17 – 3.12 (m, 1H), 2.90 – 2.86 (m, 1H), 2.77 (q, *J* = 7.8 Hz, 2H), 1.38 (t , *J* = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 165.4, 161.2, 153.7, 136.7, 134.2, 131.5, 129.5, 126.2, 124.6, 119.7, 118.5, 118.2, 117.4, 113.7, 111.7, 111.3, 107.7, 105.7, 100.8, 67.9, 53.3, 52.2, 28.2, 22.6, 17.1 ppm; HRMS: Calcd for $C_{26}H_{24}O_3N_3$ $[M+H]^+$: 426.18122, Found: 426.18100.

Compound **72au:**



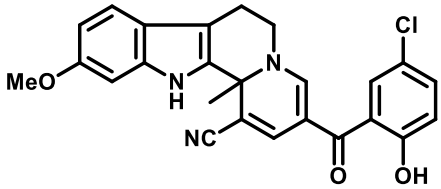
Compound **72au** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 9.04 (s, 1H), 7.87 (s, 1H), 7.63 (s, 1H), 7.25 – 7.20 (m, 3H), 6.97 – 6.92 (m, 3H), 6.00 (s, 1H), 3.86 – 3.80 (m, 4H), 3.78 – 3.72 (m, 1H), 3.18 – 3.12 (m, 1H), 2.93 – 2.87 (m, 2H), 1.37 (d, *J* = 7.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4, 168.0, 159.6, 154.2, 153.7, 136.0, 135.7, 132.8, 131.2, 130.6, 127.5, 126.4, 119.6, 118.3, 113.1, 113.2, 111.7, 107.5, 106.0, 100.3, 68.4, 53.6, 52.1, 34.0, 27.6, 21.8, 21.4 ppm; HRMS: Calcd for $C_{27}H_{26}O_3N_3$ $[M+H]^+$: 440.19687, Found: 440.19658.

Compound **72av:**



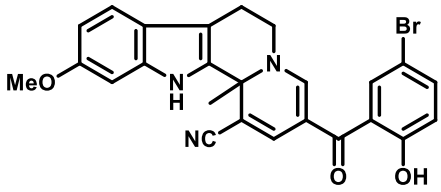
Compound **72av** was synthesized according to racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 8.99 (s, 1H), 7.90 (s, 1H), 7.67 (s, 1 H), 7.59 (s, 1H), 7.36 – 7.30 (m, 2H), 7.20 – 7.13 (m, 2H), 7.01 (d, *J* = 8.5 Hz, 1H), 3.78 – 3.74 (m, 4H), 3.55 – 3.47 (m, 4H), 3.23 – 3.17 (m, 1H), 2.98 (dd, *J* = 15.7, 4.4 Hz, 1H); 13C NMR (101 MHz, $CDCl_3$) δ 190.1, 157.9, 153.3, 136.0, 135.9, 134.2, 131.9, 129.4, 126.3, 123.4, 123.0, 120.8, 120.2, 119.1, 118.3, 114.0, 113.2, 112.0, 108.2, 105.9, 68.1, 54.4, 53.1, 23.6, 22.3 ppm; HRMS: Calcd for $C_{25}H_{21}O_3N_3F$ $[M+H]^+$: 430.15615, Found: 430.15586.

Compound **72aw:**



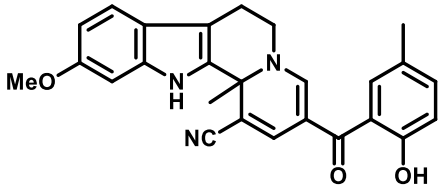
Compound **72aw** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 9.00 (s, 1H), 7.87 (s, 1H), 7.64 (s, 1 H), 7.51 (s, 1H), 7.36 – 7.30 (m, 2H), 7.26 – 7.22 (m, 2H), 6.98 (d, *J* = 8.9 Hz, 1H), 3.76 – 3.72 (m, 4H), 3.54 – 3.47 (m, 4H), 3.23 – 3.17 (m, 1H), 2.98 (dd, *J* = 15.2, 3.2 Hz, 1H); 13C NMR (101 MHz, $CDCl_3$) δ 190.7, 158.4, 153.7, 136.0, 135.7, 134.3, 131.7, 129.4, 126.0, 123.7, 123.0, 120.7, 120.4, 119.0, 118.4, 115.4, 113.7, 112.0, 108.7, 105.7, 68.0, 54.2, 53.5, 24.7, 22.7 ppm; HRMS: Calcd for $C_{25}H_{21}O_3N_3Cl$ $[M+H]^+$: 446.12660, Found: 446.12635.

Compound **72ax:**



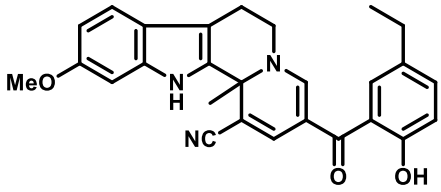
Compound **72ax** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 9.02 (s, 1H), 7.86 (s, 1H), 7.67 (s, 1 H), 7.50 (s, 1H), 7.35 – 7.30 (m, 2H), 7.26 – 7.21 (m, 2H), 7.01 (d, *J* = 8.7 Hz, 1H), 3.75 – 3.70 (m, 4H), 3.55 – 3.50 (m, 4H), 3.23 - 3.18 (m, 1H), 2.96 – 2.91 (m, 1H); 13C NMR (101 MHz, $CDCl_3$) δ 192.1, 158.3, 153.8, 136.2, 135.7, 134.1, 131.5, 129.3, 126.1, 123.4, 123.0, 120.8, 120.7, 119.1, 118.2, 115.3, 113.8, 112.0, 108.6, 105.7, 68.1, 54.3, 53.6, 24.8, 22.6 ppm; HRMS: Calcd for $C_{25}H_{21}O_3N_3Br$ $[M+H]^+$: 490.07608, Found: 490.07589.

Compound **72ay:**



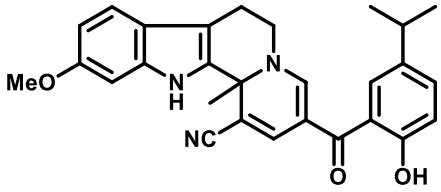
Compound **72ay** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.26 (s, 1H), 9.00 (s, 1H), 7.89 (s, 1H), 7.57 (s, 1H), 7.47 – 7.40 (m, 2H), 7.28 – 7.23 (m, 2H), 7.03 (m, 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 3.87 (s, 3H), 3.69 – 3.64 (m, 2H), 3.38 (s, 3H), 3.18 – 3.12 (m, 1H), 2.94 – 2.89 (m, 1H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 168.1, 161.4, 153.0, 136.7, 134.2, 131.8, 129.3, 126.2, 124.7, 119.5, 118.4, 118.1, 117.6, 113.0, 111.5, 111.4, 107.7, 105.8, 100.8, 67.8, 53.0, 52.8, 52.3, 22.7, 21.4 ppm; HRMS: Calcd for $C_{26}H_{24}O_3N_3$ $[M+H]^+$: 426.18122, Found: 426.18097.

Compound **72az:**



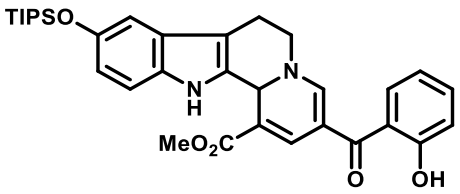
Compound **72az** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.23 (s, 1H), 8.99 (s, 1H), 7.90 (s, 1H), 7.57 (s, 1H), 7.46 – 7.41 (m, 2H), 7.27 – 7.23 (m, 2H), 7.04 – 7.00 (m, 1H), 6.93 (t, *J* =7.9 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.68 – 3.63 (m, 2H), 3.17 – 3.12 (m, 1H) 2.92 – 2.87 (m, 1H), 2.78 (q, *J* = 8.0 Hz, 2H), 1.34 (t , *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 165.2, 161.2, 153.2, 136.8, 134.2, 131.7, 129.5, 126.1, 124.8, 119.7, 118.3, 118.1, 117.5, 114.5, 113.3, 111.4, 107.7, 105.7, 100.5, 67.7, 53.3, 52.4, 52.1, 28.0, 22.7, 17.0 ppm; HRMS: Calcd for $C_{27}H_{26}O_3N_3$ $[M+H]^+$: 440.19687, Found: 440.19649.

Compound **72ba:**



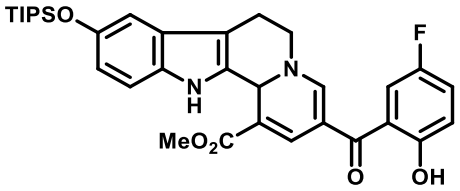
Compound **72ba** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 9.00 (s, 1H), 7.86 (s, 1H), 7.62 (s, 1H), 7.26 – 7.20 (m, 3H), 6.93 – 6.86 (m, 3H), 3.87 – 3.80 (m, 4H), 3.78 – 3.73 (m, 1H), 3.57 (s, 3H), 3.18 – 3.13 (m, 1H), 2.94 – 2.87 (m, 2H), 1.34 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 168.2, 159.7, 154.1, 153.6, 136.0, 135.5, 132.8, 131.3, 130.6, 127.6, 126.4, 119.7, 118.3, 114.5, 113.7, 113.2, 107.6, 106.2, 100.5, 100.3, 68.4, 52.6, 52.2, 33.2, 25.4, 23.3 ppm; HRMS: Calcd for $C_{28}H_{28}O_3N_3$ $[M+H]^+$: 454.21252, Found: 454.21239.

Compound **72bb:**



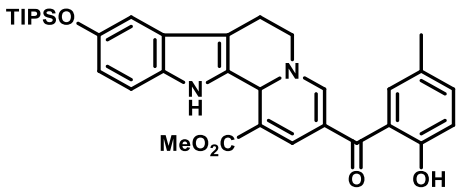
Compound **72bb** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 8.72 (s, 1H), 7.80 (s, 1H), 7.68 (s, 1H), 7.46 – 7.32 (m, 4H), 7.26 – 7.17 (m, 3H), 6.00 (s, 1H), 3.91 – 3.86 (m, 1H), 3.67 – 3.59 (m, 4H), 3.12 (dd, *J* = 13.8, 4.0 Hz, 1H), 2.99 (dd, *J* = 12.0, 3.8 Hz, 1H), 1.47 – 1.43 (m, 3H), 1.02 – 0.95 (d, *J* = 6.4 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1, 165.9, 164.3, 150.6, 135.9, 135.2, 132.3, 131.8, 131.5, 127.1, 123.2, 121.4, 120.3, 119.4, 117.3, 116.7, 116.2, 113.2, 111.0, 104.1, 70.4, 67.7, 55.3, 50.7, 26.3, 26.2, 22.7, 18.0, 17.9 ppm; HRMS: Calcd for $C_{33}H_{41}O_5N_2Si$ $[M+H]^+$: 573.27793, Found: 573.27765.

Compound **72bc:**



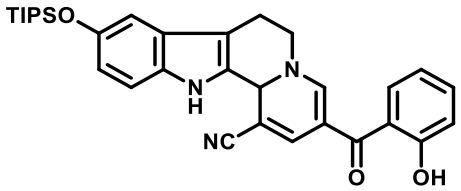
Compound **72bc** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 9.04 (s, 1H), 7.91 (d, *J* = 2.1 Hz, 1H), 7.66 (d, *J* = 2.2 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.22 – 7.13 (m, 2H), 7.00 – 6.94 (m, 1H), 5.98 (s, 1H), 3.82 – 3.75 (m, 5H), 3.21 – 3.17 (m, 1H), 3.01 (dd, *J* = 13.9, 4.0 Hz, 1H), 1.47 – 1.43 (m, 3H), 0.99 (d, *J* = 6.4 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.0, 167.5, 159.3, 154.0, 136.1, 135.6, 134.2, 131.7, 129.6, 125.9, 122.4, 121.0, 120.8, 120.1, 119.7, 118.4, 114.6, 112.6, 108.1, 105.9, 68.3, 55.3, 50.9, 26.2, 26.1, 23.5, 18.0, 17.9 ppm; HRMS: Calcd for $C_{33}H_{40}O_5N_2Si$ $[M+H]^+$: 591.26850, Found: 591.26813.

Compound **72bd:**



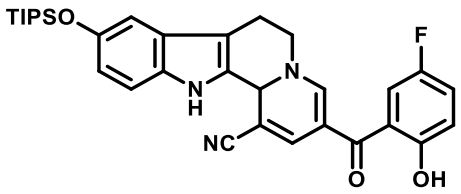
Compound **72bd** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 8.99 (s, 1H), 7.93 (d, *J* = 2.2 Hz, 1H), 7.69 (d, *J* = 2.1 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.23 – 7.13 (m, 2H), 6.99 – 6.93 (m, 1H), 6.00 (s, 1H), 3.83 – 3.75 (m, 5H), 3.20 – 3.16 (m, 1H), 3.00 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.46 (s, 3H), 1.47 – 1.42 (m, 3H), 1.04 (d, *J* = 6.5 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 167.0, 160.0, 153.9, 136.2, 135.4, 134.2, 130.4, 129.7, 123.6, 122.4, 121.1, 120.7, 120.1, 119.0, 118.4, 113.5, 112.5, 108.3, 105.4, 69.1, 55.4, 50.8, 26.2, 26.1, 23.7, 22.2, 18.0, 17.9 ppm; HRMS: Calcd for $C_{34}H_{43}O_5N_2Si$ $[M+H]^+$: 597.29358, Found: 597.29319.

Compound **72be:**



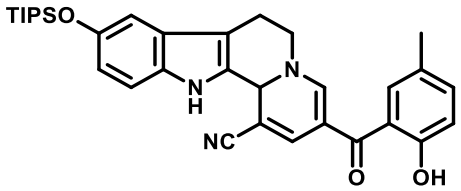
Compound **72be** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 9.00 (s, 1H), 7.84 (s, 1H), 7.71 (s, 1H), 7.42 – 7.30 (m, 4H), 7.23 – 7.17 (m, 3H), 5.99 (s, 1H), 3.89 – 3.84 (m, 1H), 3.67 – 3.61 (m, 1H), 3.10 (dd, *J* = 14.0, 3.0 Hz, 1H), 2.96 (dd, *J* = 14.0, 3.0 Hz, 1H), 1.47 – 1.42 (m, 3H), 1.01 (d, *J* = 6.4 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 163.4, 153.4, 135.8, 132.2, 131.7, 131.5, 127.5, 123.4, 121.7, 120.6, 119.5, 118.9, 117.3, 117.2, 116.6, 116.3, 113.4, 111.7, 104.6, 70.2, 68.0, 52.4, 26.2, 26.1, 22.6, 18.0, 17.9 ppm; HRMS: Calcd for $C_{32}H_{38}O_3N_3Si$ $[M+H]^+$: 540.26770, Found: 540.26749.

Compound **72bf:**



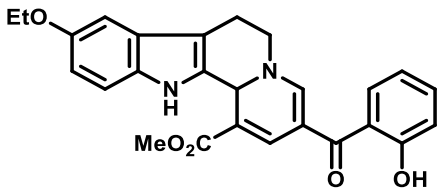
Compound **72bf** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.14 (s, 1H), 9.02 (s, 1H), 7.89 (d, *J* = 2.2 Hz, 1H), 7.68 (d, *J* = 2.2 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.23 – 7.13 (m, 2H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.00 (s, 1H), 3.82 – 3.75 (m, 2H), 3.21 – 3.16 (m, 1H), 2.99 (dd, *J* = 13.8, 4.0 Hz, 1H), 1.47 – 1.42 (m, 3H), 1.00 (d, *J* = 6.3 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 167.6, 159.2, 154.8, 136.2, 135.4, 134.2, 131.8, 129.6, 125.8, 122.4, 121.2, 120.8, 120.0, 119.7, 118.9, 114.3, 112.5, 108.3, 105.8, 68.3, 51.2, 26.2, 26.1, 23.4, 18.0, 17.9 ppm; HRMS: Calcd for $C_{32}H_{37}O_3N_3Si$ $[M+H]^+$: 558.25827, Found: 558.25804.

Compound **72bg:**



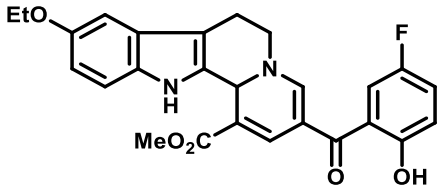
Compound **72bg** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 8.99 (s, 1H), 7.88 (d, *J* = 2.2 Hz, 1H), 7.68 (d, *J* = 2.2 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.23 – 7.13 (m, 2H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.04 (s, 1H), 3.80 – 3.74 (m, 2H), 3.22 – 3.16 (m, 1H), 3.02 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.46 (s, 3H), 1.47 – 1.41 (m, 3H), 1.02 (d, *J* = 6.4 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.5, 166.4, 159.3, 154.3, 136.7, 135.2, 131.8, 129.4, 125.7, 122.4, 121.6, 120.8, 120.4, 120.1, 119.7, 118.7, 115.0, 112.7, 108.1, 105.7, 68.3, 50.9, 26.2, 26.1, 23.5, 22.5, 18.0, 17.9 ppm; HRMS: Calcd for $C_{33}H_{40}O_3N_3$ $[M+H]^+$: 554.28335, Found: 554.28311.

Compound **72bh:**



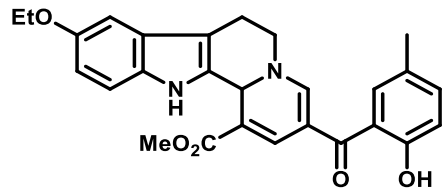
Compound **72bh** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 8.79 (s, 1H), 7.84 (s, 1H), 7.71 (s, 1H), 7.45 – 7.31 (m, 3H), 7.23 – 7.17 (m, 1H), 6.94 – 6.85 (m, 3H), 6.08 (s, 1H), 4.04 (q, *J* = 7.9 Hz, 2H), 3.91 – 3.86 (m, 1H), 3.68 – 3.61 (m, 4H), 3.12 (dd, *J* = 14.0, 3.0 Hz, 1H), 2.94 (dd, *J* = 14.0, 3.0 Hz, 1H), 1.37 (t, *J* = 7.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 167.2, 164.4, 150.7, 135.9, 135.0, 132.4, 131.5, 131.4, 127.5, 123.4, 121.7, 120.5, 119.3, 117.3, 116.4, 116.2, 113.2, 111.7, 104.2, 70.4, 67.7, 54.4, 50.8, 22.4, 14.7 ppm; HRMS: Calcd for $C_{26}H_{25}O_5N_2$ $[M+H]^+$: 445.17580, Found: 445.17547.

Compound **72bi:**



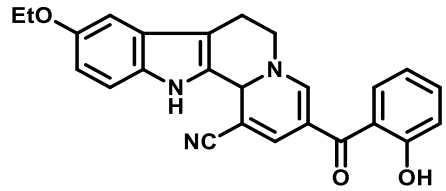
Compound **72bi** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.14 (s, 1H), 9.0 (s, 1H), 7.79 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.28 (d, *J* = 8.6 Hz, 1H), 6.92 – 6.88 (m, 3H), 6.02 (s, 1H), 4.03 (q, *J* = 8.0 Hz, 2H), 3.81 - 3.75 (m, 5H), 3.16 – 3.11 (m, 1H), 2.95 (dd, *J* = 15.8, 3.8 Hz, 1H), 1.38 (t, *J* = 7.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 168.5, 160.0, 154.3, 153.6, 137.4, 135.7, 132.7, 132.1, 131.1, 126.4, 121.6, 120.8, 114.3, 113.7, 112.6, 110.4, 107.8, 105.7, 100.4, 70.1, 68.9, 53.2, 52.1, 23.3, 14.5 ppm; HRMS: Calcd for $C_{26}H_{24}O_5N_2F$ $[M+H]^+$: 463.16638, Found: 463.16651.

Compound **72bj:**



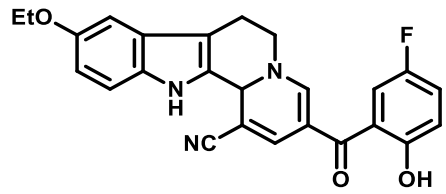
Compound **72bj** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 8.99 (s, 1H), 7.92 (d, *J* = 1.6 Hz, 1H), 7.63 (d, *J* = 1.6 Hz, 1H), 7.24 – 7.18 (m, 3H), 6.93 – 6.85 (m, 3H), 6.01 (s, 1H), 4.05 (q, *J* = 7.9 Hz, 2H), 3.85 – 3.80 (m, 4H), 3.70 (dd, *J* = 13.5, 5.1 Hz, 1H), 3.10 (ddd, *J* = 15.3, 12.3, 5.6 Hz, 1H), 2.90 (dd, *J* = 15.3, 3.7 Hz, 1H), 2.31 (s, 3H), 1.37 (t, *J* = 7.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1, 168.4, 166.4, 158.7, 154.2, 153.4, 136.3, 135.7, 132.8, 131.4, 130.4, 127.8, 126.5, 119.6, 118.2, 113.4, 113.1, 112.7, 107.8, 100.8, 70.2, 68.3, 52.7, 52.4, 23.7, 21.2, 14.8 ppm; HRMS: Calcd for $C_{27}H_{27}O_5N_2$ $[M+H]^+$: 459.19145, Found: 459.19111.

Compound **72bk:**



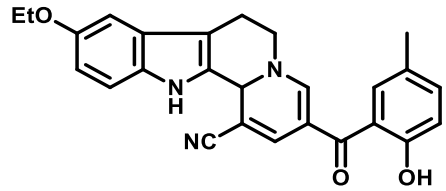
Compound **72bk** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 8.89 (s, 1H), 7.82 (s, 1H), 7.73 (s, 1H), 7.46 – 7.33 (m, 3H), 7.23 – 7.16 (m, 1H), 6.96 – 6.88 (m, 3H), 6.02 (s, 1H), 4.04 (q, *J* = 8.0 Hz, 2H), 3.90 – 3.86 (m, 1H), 3.67 – 3.62 (m, 1H), 3.12 – 3.08 (m, 1H), 2.99 (dd, *J* = 14.0, 3.0 Hz, 1H), 1.38 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.5, 164.1, 150.9, 135.6, 135.1, 132.3, 131.4, 131.2, 127.5, 123.4, 121.7, 120.4, 119.6, 117.4, 117.2, 116.6, 116.2, 113.4, 111.7, 104.6, 70.3, 67.7, 51.2, 22.4, 14.9 ppm; HRMS: Calcd for $C_{25}H_{22}O_3N_3$ $[M+H]^+$: 412.16557, Found: 412.16519.

Compound **72bl:**



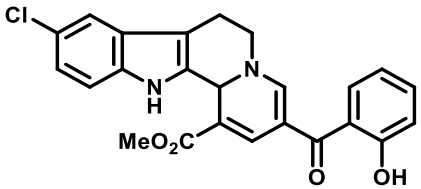
Compound **72bl** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 8.99 (s, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.25 – 7.19 (m, 1H), 7.16 – 7.10 (m, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 5.99 (s, 1H), 4.04 (q, *J* = 7.9 Hz, 2H), 3.81 – 3.75 (m, 2H), 3.18 – 3.14 (m, 1H), 2.97 (dd, *J* = 15.8, 7.5 Hz, 1H), 1.36 (t, *J* = 7.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 159.9, 153.5, 136.4, 135.8, 134.4, 131.6, 129.6, 126.4, 123.3, 123.1, 121.7, 121.4, 120.0, 118.3, 115.2, 114.2, 112.9, 108.1, 105.9, 70.1, 68.8, 52.4, 23.2, 14.7 ppm; HRMS: Calcd for $C_{25}H_{21}O_3N_3F$ $[M+H]^+$: 430.15615, Found: 430.15598.

Compound **72bm:**



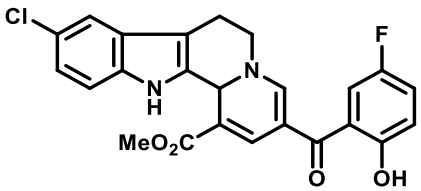
Compound **72bm** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 9.02 (s, 1H), 7.86 (s, 1H), 7.58 (s, 1H), 7.47 – 7.39 (m, 2H), 7.27 – 7.20 (m, 2H), 7.02 – 6.95 (m, 2H), 6.01 (s, 1H), 4.07 (q, *J* = 8.0 Hz, 2H), 3.69 – 3.64 (m, 2H), 3.17 – 3.12 (m, 1H), 2.93 – 2.88 (m, 1H), 2.51 (s, 3H), 1.39 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 167.2, 161.9, 153.3, 136.7, 134.3, 131.7, 129.4, 126.0, 124.8, 119.6, 118.4, 118.0, 117.8, 113.7, 111.3, 111.1, 107.2, 105.8, 69.9, 68.2, 52.6, 23.7, 21.3, 14.6 ppm; HRMS: Calcd for $C_{26}H_{24}O_3N_3$ $[M+H]^+$: 426.18122, Found: 426.18104.

Compound **72bn:**



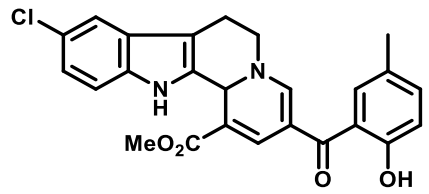
Compound **72bn** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (s, 1H), 9.07 (s, 1H), 7.94 (d, *J* = 1.7 Hz, 1H), 7.61 (d, *J* = 1.7 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.29 – 7.23 (m, 3H), 7.02 – 7.00 (m, 1H), 6.89 – 6.85 (m 1H), 6.01 (s, 1H), 3.81 – 3.72 (m, 5H), 3.16 – 3.07 (m, 1H), 2.90 – 2.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.8, 168.5, 161.1, 153.2, 136.4, 134.9, 134.7, 130.1, 127.5, 125.7, 120.7, 119.7, 119.2, 118.4, 118.3, 118.2, 113.1, 112.7, 107.6, 106.0, 67.6, 53.8, 52.7, 22.4 ppm; HRMS: Calcd for $C_{24}H_{20}O_4N_2Cl$ $[M+H]^+$: 435.11061, Found: 435.11037.

Compound **72bo:**



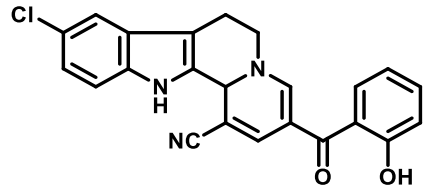
Compound **72bo** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 8.99 (s, 1H), 7.88 (d, *J* = 1.5 Hz, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 7.54 (d, *J* = 2.5 Hz, 1H), 7.45 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 6.93 – 6.89 (m, 3H), 6.02 (s, 1H), 3.82 (s, 3H), 3.81 – 3.74 (m, 2H), 3.12 (ddd, *J* = 15.6, 11.6, 5.8 Hz, 1H), 2.90 (dd, *J* = 15.6, 3.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0, 168.6, 160.2, 154.3, 153.2, 137.0, 135.5, 132.4, 132.3, 131.2, 126.4, 121.5, 120.4, 114.0, 113.7, 112.8, 110.2, 107.8, 105.6, 100.2, 68.1, 53.5, 52.8, 23.3 ppm; HRMS: Calcd for $C_{24}H_{19}O_4N_2F$ $[M+H]^+$: 453.10119, Found: 453.10111.

Compound **72bp:**



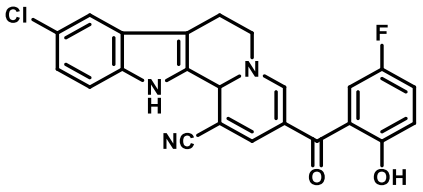
Compound **72bp** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 11.09 (s, 1H), 8.98 (s, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.53 (d, *J* = 2.5 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.22 (d, *J* = 8.7 Hz, 1H), 6.93 – 6.88 (m, 3H), 6.01 (s, 1H), 3.82 – 3.74 (m, 5H), 3.15 – 3.10 (m, 1H), 2.93 (dd, *J* = 15.7, 3.4 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.0, 168.4, 166.5, 158.8, 154.2, 153.3, 136.3, 135.8, 132.6, 131.5, 130.4, 127.9, 126.5, 119.5, 118.2, 113.7, 113.2, 112.5, 107.8, 100.7, 69.8, 52.6, 52.4, 23.6, 21.5 ppm; HRMS: Calcd for $C_{25}H_{22}O_4N_2Cl$ $[M+H]^+$: 449.12626, Found: 449.12626.

Compound **72bq:**



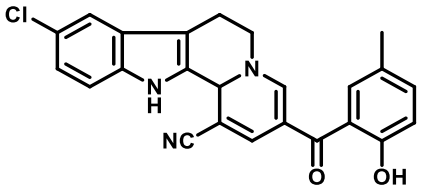
Compound **72bq** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 9.04 (s, 1H), 7.93 (d, *J* = 1.8 Hz, 1H), 7.59 (d, *J* = 1.8 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.29 – 7.22 (m, 3H), 7.02 – 6.97 (m, 2H), 6.01 (s, 1H), 3.81 – 3.75 (m, 2H), 3.15 – 3.09 (m, 1H), 2.91 – 2.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.4, 161.0, 153.2, 136.7, 134.7, 134.6, 130.1, 127.4, 125.7, 120.7, 119.8, 119.2, 118.4, 118.0, 116.9, 114.0, 113.7, 112.4, 107.6, 106.4, 67.9, 52.6, 22.8 ppm; HRMS: Calcd for $C_{23}H_{17}O_2N_3Cl$ $[M+H]^+$: 402.10038, Found: 402.10014.

Compound **72br:**



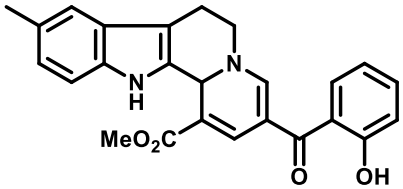
Compound **72br** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 8.97 (s, 1H), 7.85 (d, *J* = 1.7 Hz, 1H), 7.60 (d, *J* = 1.7 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.47 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.27 (d, *J* = 8.9 Hz, 1H), 6.98 – 6.93 (m, 3H), 6.04 (s, 1H), 3.81 – 3.74 (m, 2H), 3.15 (ddd, *J* = 15.7, 11.4, 6.0 Hz, 1H), 2.94 (dd, *J* = 15.8, 3.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 160.2, 154.3, 153.6, 137.2, 135.6, 132.7, 132.4, 131.3, 126.3, 121.4, 120.4, 114.4, 114.0, 113.4, 112.7, 110.3, 107.6, 105.8, 100.1, 69.0, 52.9, 23.6 ppm; HRMS: Calcd for $C_{23}H_{16}O_2N_3ClF$ $[M+H]^+$: 420.09096, Found: 420.09081.

Compound **72bs:**



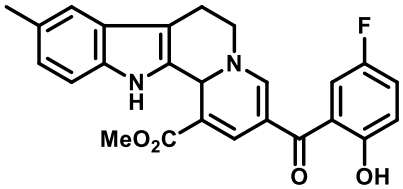
Compound **72bs** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.15 (s, 1H), 8.99 (s, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.51 (d, *J* = 2.5 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.28 (d, *J* = 8.7 Hz, 1H), 6.98 – 6.93 (m, 3H), 6.01 (s, 1H), 3.81 – 3.75 (m, 2H), 3.18 – 3.13 (m, 1H), 2.97 (dd, *J* = 15.4, 3.2 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 161.4, 154.7, 153.5, 137.7, 135.5, 132.6, 132.7, 131.2, 126.4, 121.5, 120.2, 114.7, 114.0, 113.1, 112.7, 110.9, 107.6, 105.7, 100.1, 70.0, 52.4, 23.7, 21.9 ppm; HRMS: Calcd for $C_{24}H_{19}O_2N_3Cl$ $[M+H]^+$: 416.11603, Found: 416.11571.

Compound **72bt:**



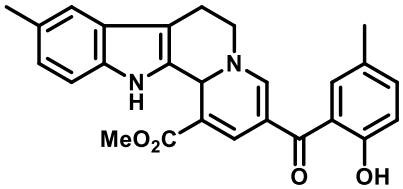
Compound **72bt** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 9.01 (s, 1H), 7.95 (d, *J* = 1.9 Hz, 1H), 7.60 (d, *J* = 1.9 Hz, 1H), 7.42 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.41 (td, *J* = 7.8, 1.6 Hz, 1H), 7.26 – 7.23 (m, 2H), 7.03 – 6.98 (m, 2H), 6.90 (t, *J* =7.9 Hz, 1H), 5.99 (s, 1H), 3.81 (s, 3H), 3.78 – 3.71 (m, 2H), 3.17 – 3.09 (m, 1H), 2.93 – 2.88 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 168.2, 161.2, 153.4, 136.7, 134.2, 131.4, 130.0, 129.1, 126.1, 124.5, 119.8, 118.4, 118.3, 116.9, 113.3, 111.5, 109.8, 107.3, 105.8, 67.8, 52.7, 51.9, 23.1, 21.7 ppm; HRMS: Calcd for $C_{25}H_{23}O_4N_2$ $[M+H]^+$: 415.16523, Found: 415.16523.

Compound **72bu:**



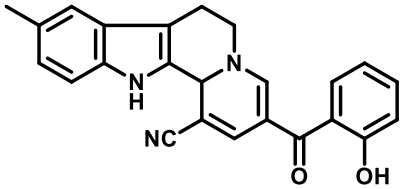
Compound **72bu** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (s, 1H), 9.02 (s, 1H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.55 (d, *J* = 2.6 Hz, 1H), 7.46 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 1H), 6.94 – 6.89 (m, 3H), 6.00 (s, 1H), 3.81 – 3.74 (m, 5H), 3.14 (ddd, *J* = 15.8, 11.5, 5.6 Hz, 1H), 2.95 (dd, *J* = 15.8, 3.5 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 168.7, 161.3, 154.5, 153.0, 138.2, 135.6, 132.5, 132.0, 131.3, 126.5, 121.5, 120.7, 114.4, 113.8, 112.9, 110.2, 107.6, 105.5, 100.7, 68.4, 53.7, 52.7, 26.4, 23.5 ppm; HRMS: Calcd for $C_{25}H_{22}O_4N_2F$ $[M+H]^+$: 433.15581, Found: 433.15569.

Compound **72bv:**



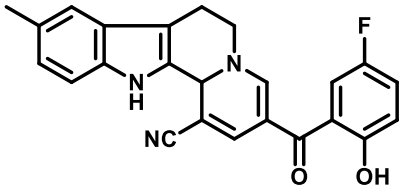
Compound **72bv** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 8.99 (s, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.56 (d, *J* = 2.2 Hz, 1H), 7.43 – 7.38 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.95 – 6.89 (m, 3H), 6.03 (s, 1H), 3.81 – 3.74 (m, 5H), 3.12 – 3.07 (m, 1H), 2.99 – 2.94 (m, 1H), 2.54 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 168.6, 161.1, 154.9, 153.2, 138.2, 135.5, 132.9, 131.9, 131.3, 126.4, 121.5, 120.6, 114.9, 113.8, 112.8, 110.2, 107.5, 105.5, 100.6, 68.4, 53.5, 52.7, 26.2, 24.1, 23.9 ppm; HRMS: Calcd for $C_{26}H_{25}O_4N_2$ $[M+H]^+$: 429.18088, Found: 429.18059.

Compound **72bw:**



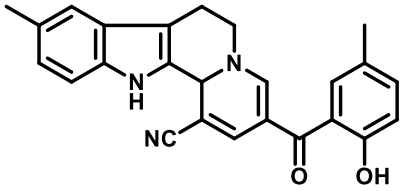
Compound **72bw** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 8.99 (s, 1H), 7.90 (d, *J* = 1.9 Hz, 1H), 7.61 (d, *J* = 1.8 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.22 – 7.15 (m, 4H), 6.94 – 6.91 (m, 1H), 6.03 (s, 1H), 3.78 (dd, *J* = 15.7, 3.7 Hz , 2H), 3.24 (dd, *J* = 15.7, 3.7 Hz, 1H), 3.00 (dd, *J* = 15.6, 3.5 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5, 160.7, 153.9, 136.4, 136.2, 135.4, 132.4, 130.6, 127.9, 126.4, 123.4, 120.2, 119.5, 118.4, 118.2, 113.9, 112.2, 111.4, 108.4, 106.7, 68.2, 53.6, 23.6, 21.7 ppm; HRMS: Calcd for $C_{24}H_{20}O_2N_3$ $[M+H]^+$: 382.15500, Found: 382.15476.

Compound **72bx:**



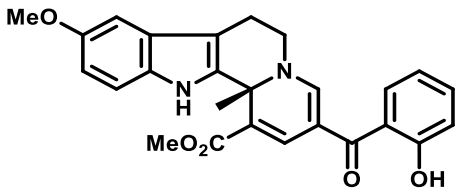
Compound **72bx** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (s, 1H), 8.99 (s, 1H), 7.86 (d, *J* = 1.8 Hz, 1H), 7.61 (d, *J* = 1.8 Hz, 1H), 7.54 (d, *J* = 2.5 Hz, 1H), 7.48 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 6.97 – 6.92 (m, 3H), 6.03 (s, 1H), 3.80 – 3.75 (m, 2H), 3.16 (ddd, *J* = 15.6, 11.4, 6.0 Hz, 1H), 2.93 (dd, *J* = 15.6, 3.3 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 160.4, 154.2, 137.2, 135.4, 132.7, 132.5, 131.2, 126.3, 121.3, 120.2, 114.3, 114.0, 113.2, 112.7, 110.1, 109.8, 107.6, 105.7, 100.1, 69.7, 54.6, 52.5, 23.8 ppm; HRMS: Calcd for $C_{24}H_{19}O_2N_3F$ $[M+H]^+$: 400.14558, Found: 400.14517.

Compound **72by:**



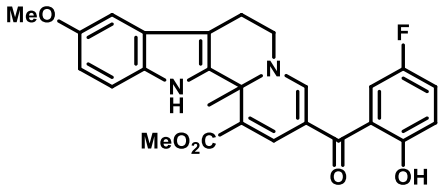
Compound **72by** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (s, 1H), 9.02 (s, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.55 (d, *J* = 2.2 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.26 – 7.22 (m, 1H), 6.97 – 6.90 (m, 3H), 6.02 (s, 1H), 3.80 – 3.75 (m, 2H), 3.18 – 3.13 (m, 1H), 2.96 – 2.91 (m, 1H), 2.53 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 161.2, 153.8, 137.5, 135.3, 132.9, 132.8, 131.2, 126.3, 121.4, 120.2, 114.4, 114.0, 113.9, 112.6, 110.5, 109.6, 107.6, 105.8, 100.4, 69.8, 54.5, 52.5, 24.6, 23.7 ppm; HRMS: Calcd for $C_{25}H_{22}O_2N_3$ $[M+H]^+$: 396.17065, Found: 396.17033.

Compound **72bz:**



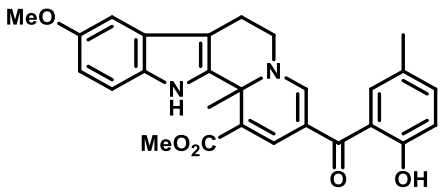
Compound **72bz** was synthesized according to the general procedures. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 8.95 (s, 1H), 7.96 (d, *J* = 1.7Hz, 1H), 7.63 (d, *J* = 1.7 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.25 – 7.21 (m, 2H), 7.03 – 6.98 (m, 2H), 6.88 (t, *J* =7.8 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.78 – 3.70 (m, 2H), 3.47 (s, 3H), 3.18 – 3.11 (m, 1H), 2.91 – 2.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.5, 170.2, 168.5, 161.4, 153.2, 136.3, 134.5, 131.8, 130.1, 129.2, 126.3, 124.6, 119.9, 118.6, 118.4, 117.9, 113.5, 111.6, 107.6, 106.0, 68.1, 53.9, 52.6, 52.5, 23.2, 21.6 ppm; HRMS: Calcd for $C_{26}H_{24}O_5N_2$ $[M+H]^+$: 445.17580, Found: 445.17577; $[\alpha]_D^{20}$ -8.6 ° (c 0.002 in ethanol).

Compound **72ca:**



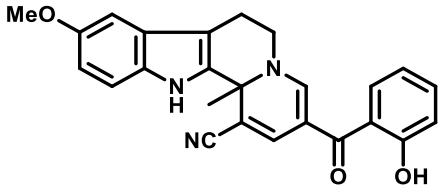
Compound **72ca** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 8.99 (s, 1H), 7.81 (s, 1H), 7.62 (s, 1 H), 7.58 (s, 1H), 7.37 – 7.30 (m, 2H), 7.26 – 7.21 (m, 2H), 6.97 (d, *J* = 8.9 Hz, 1H), 3.74 – 3.69 (m, 7H), 3.53 – 3.47 (m, 4H), 3.22 – 3.17 (m, 1H), 3.02 – 2.98 (m, 1H); 13C NMR (101 MHz, $CDCl_3$) δ 189.4, 160.2, 153.6, 136.4, 135.8, 134.2, 131.7, 129.3, 126.0, 123.7, 123.1, 120.7, 120.3, 119.0, 118.3, 115.4, 113.8, 112.4, 108.8, 105.7, 68.0, 54.3, 53.4, 24.7, 24.6, 22.4 ppm; HRMS: Calcd for $C_{26}H_{24}O_5N_2F$ $[M+H]^+$: 463.16638, Found: 463.16614.

Compound **72cb:**



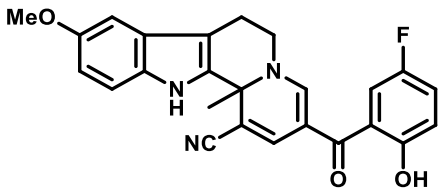
Compound **72cb** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 9.00 (s, 1H), 7.83 (s, 1H), 7.61 (s, 1 H), 7.55 (s, 1H), 7.37 – 7.31 (m, 2H), 7.26 – 7.20 (m, 2H), 6.98 (d, *J* = 8.8 Hz, 1H), 3.76 – 3.71 (m, 7H), 3.53 – 3.46 (m, 4H), 3.22 – 3.16 (m, 1H), 3.00 – 2.96 (m, 1H), 2.54 (s, 3H); 13C NMR (101 MHz, $CDCl_3$) δ 190.1, 163.4, 153.8, 137.2, 135.8, 134.3, 131.6, 129.3, 126.2, 123.8, 123.5, 120.7, 120.4, 118.9, 118.4, 115.2, 113.8, 112.3, 108.7, 105.7, 68.2, 54.4, 53.2, 24.6, 24.5, 23.2, 22.7 ppm; HRMS: Calcd for $C_{27}H_{27}O_5N_2$ $[M+H]^+$: 459.19145, Found: 459.19111.

Compound **72cc:**



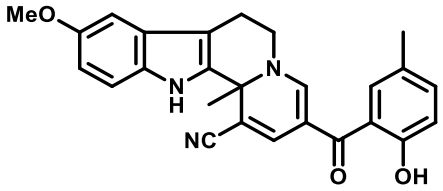
Compound **72cc** was synthesized according to the general procedures. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.23 (s, 1H), 9.17 (s, 1H), 7.95 (d, *J* = 1.5 Hz, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.29 – 7.27 (m, 2H), 7.23 – 7.21 (m, 1H), 7.02 – 7.00 (m, 1H), 6.89 – 6.85 (m 1H), 3.87 (s, 3H), 3.80 – 3.70 (m, 5H), 3.16 – 3.08 (m, 1H), 2.90 – 2.86 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 161.4, 153.4, 136.6, 134.7, 134.6, 130.3, 127.8, 125.8, 120.8, 119.9, 118.6, 118.5, 118.4, 116.9, 113.4, 113.2, 112.9, 107.9, 106.1, 70.0, 54.1, 52.4, 26.9, 23.0 ppm; HRMS: Calcd for $C_{25}H_{22}O_3N_3$ $[M+H]^+$: 412.16557, Found: 412.16552; $[\alpha]_D^{20}$ -9.5 ° (c 0.002 in ethanol).

Compound **72cd:**



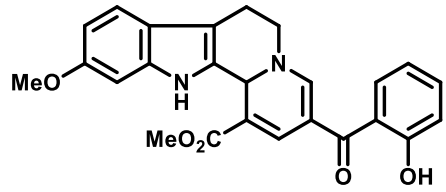
Compound **72cd** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 9.01 (s, 1H), 7.83 (s, 1H), 7.64 (s, 1 H), 7.57 (s, 1H), 7.37 – 7.31 (m, 2H), 7.27 – 7.21 (m, 2H), 7.00 – 6.96 (m, 1H), 3.75 – 3.70 (m, 4H), 3.53 – 3.47 (m, 4H), 3.23 – 3.17 (m, 1H), 3.03 – 2.98 (m, 1H); 13C NMR (101 MHz, $CDCl_3$) δ 189.7, 153.5, 136.7, 135.8, 134.3, 131.6, 129.3, 126.2, 123.6, 123.1, 120.9, 120.3, 119.0, 118.7, 115.4, 114.3, 113.5, 112.4, 108.9, 105.0, 69.1, 53.3, 24.7, 24.6, 22.7 ppm; HRMS: Calcd for $C_{25}H_{21}O_3N_3F$ $[M+H]^+$: 430.15615, Found: 430.15590.

Compound **72ce:**



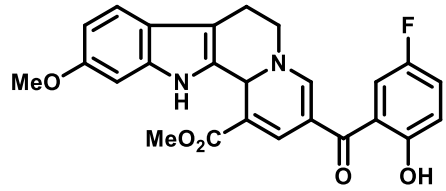
Compound **72ce** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 9.02 (s, 1H), 7.82 (s, 1H), 7.61 (s, 1 H), 7.53 (s, 1H), 7.37 – 7.30 (m, 2H), 7.26 – 7.21 (m, 2H), 6.98 (d, J = 8.9 Hz, 1H), 3.76 – 3.71 (m, 4H), 3.53 – 3.47 (m, 4H), 3.22 – 3.16 (m, 1H), 3.00 – 2.95 (m, 1H), 2.53 (s, 3H); 13C NMR (101 MHz, $CDCl_3$) δ 189.9, 154.2, 136.9, 135.6, 134.3, 131.6, 129.5, 126.2, 123.9, 123.5, 120.8, 120.4, 119.0, 118.4, 115.5, 115.7, 113.8, 112.5, 108.7, 105.8, 68.7, 53.2, 24.6, 24.5, 23.7, 22.8 ppm; HRMS: Calcd for $C_{26}H_{24}O_3N_3$ $[M+H]^+$: 426.18122, Found: 426.18098.

Compound **72cf:**



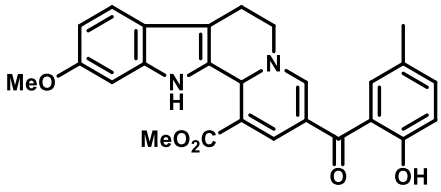
Compound **72cf** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (s, 1H), 9.74 (s, 1H), 7.74 (s, 1H), 7.68 (s, 1H), 7.33 – 7.27 (m, 2H), 7.17 – 7.10 (m, 3H), 7.05 – 7.00 (m, 1H), 6.91 – 6.84 (m, 2H), 6.01 (s, 1H), 3.78 – 3.73 (m, 4H), 3.49 – 3.45 (m, 1H), 3.03 – 2.96 (m, 1H), 2.86 – 2.82 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 188.3, 173.1, 155.3, 153.7, 136.2, 132.1, 132.0, 131.3, 129.3, 125.7, 125.5, 121.1, 119.0, 118.0, 116.3, 112.3, 111.6, 110.7, 106.8, 106.1, 67.0, 52.1, 51.8, 51.7, 22.1 ppm; HRMS: Calcd for $C_{25}H_{24}O_5N_2$ $[M+H]^+$: 431.16015, Found: 431.15979.

Compound **72cg:**



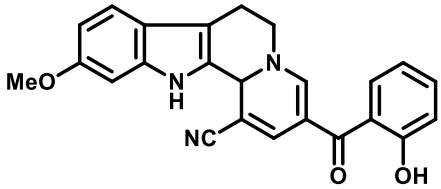
Compound **72cg** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 9.04 (s, 1H), 7.88 (s, 1H), 7.64 (s, 1 H), 7.53 (s, 1H), 7.37 – 7.31 (m, 2H), 7.26 – 7.22 (m, 2H), 6.99 – 6.95 (m, 1H), 6.01 (s, 1H), 3.89 (s, 3H), 3.82 (m, 4H), 3.55 – 3.48 (m, 1H), 3.23 – 3.17 (m, 1H), 2.98 (dd, J = 15.2, 3.0 Hz, 1H); 13C NMR (101 MHz, $CDCl_3$) δ 190.7, 176.9, 159.5, 153.3, 136.2, 135.9, 134.1, 131.6, 129.4, 126.2, 123.9, 123.2, 120.5, 120.0, 119.9, 118.3, 115.1, 112.7, 108.3, 105.5, 68.2, 54.3, 52.8, 52.6, 22.7 ppm; HRMS: Calcd for $C_{25}H_{22}O_5N_2F$ $[M+H]^+$: 449.15073, Found: 449.15047.

Compound **72ch:**



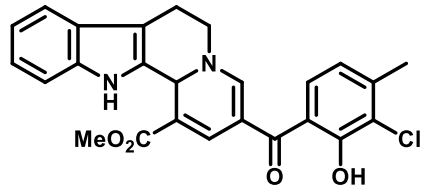
Compound **72ch** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 9.01 (s, 1H), 7.93 (s, 1H), 7.63 (s, 1H), 7.49 – 7.38 (m, 2H), 7.28 – 7.23 (m, 2H), 7.01 (m, 1H), 6.88 (t, *J* = 8.0 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.68 – 3.63 (m, 2H), 3.20 – 3.15 (m, 1H) 2.93 – 2.87 (m, 1H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 170.2, 167.4, 161.7, 153.3, 136.5, 134.9, 131.4, 129.7, 126.1, 124.6, 119.5, 118.7, 118.5, 117.4, 113.5, 111.3, 107.8, 105.8, 69.9, 67.8, 53.8, 52.3, 22.7, 21.9 ppm; HRMS: Calcd for $C_{26}H_{25}O_5N_2$ $[M+H]^+$: 445.17580, Found: 445.17559.

Compound **72ci:**



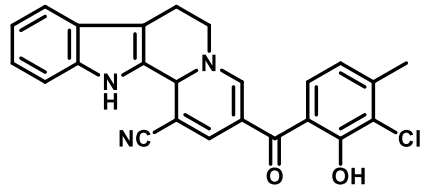
Compound **72ci** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 9.72 (s, 1H), 7.73 (s, 1H), 7.65 (s, 1H), 7.30 – 7.23 (m, 2H), 7.18 – 7.10 (m, 3H), 7.04– 7.00 (m, 1H), 6.91 – 6.87 (m, 2H), 5.98 (s, 1H), 3.77 – 3.73 (m, 4H), 3.51 – 3.47 (m, 1H), 3.03 – 2.98 (m, 1H), 2.85 – 2.80 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 190.5, 165.2, 153.8, 136.7, 132.8, 132.0, 131.4 129.5, 125.8, 125.5, 121.9, 119.0, 118.5, 116.2, 116.0, 112.7, 111.5, 110.9, 106.7, 106.2, 67.2, 51.7, 51.6, 22.8 ppm; HRMS: Calcd for $C_{24}H_{20}O_3N_3$ $[M+H]^+$: 398.14992, Found: 398.14961.

Compound **72cj:**



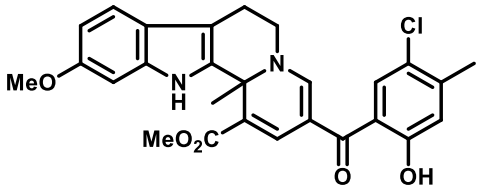
Compound **72cj** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (s, 1H), 9.22 (s, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.43 (s, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.27 – 7.19 (m, 1H), 7.18 – 7.10 (m, 1H), 6.92 (s, 1H), 6.07 (s, 1H), 3.85 – 3.79 (m, 5H), 3.23 – 3.18 (m, 1H), 3.02 – 2.97 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 171.4, 159.7, 153.4, 143.0, 136.6, 135.8, 131.8, 130.0, 126.3, 123.7, 123.1, 120.6, 120.1, 118.8, 113.7, 112.4, 111.0, 108.2, 105.7, 68.1, 53.7, 52.7, 23.2, 21.1 ppm; HRMS: Calcd for $C_{25}H_{22}O_4N_2Cl$ $[M+H]^+$: 449.12626, Found: 449.12640.

Compound **72ck:**



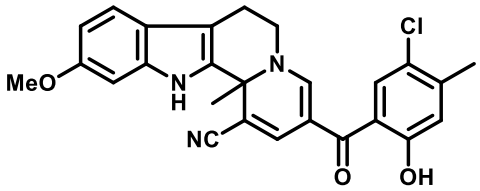
Compound **72ck** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 9.18 (s, 1H), 7.92 (d, *J* = 1.9 Hz, 1H), 7.64 (d, *J* = 1.9 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.47 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.16 – 7.12 (m, 1H), 6.95 (s, 1H), 6.04 (s, 1H), 3.82 – 3.78 (m, 2H), 3.21 (ddd, *J* = 14.0, 10.9, 6.0 Hz, 1H), 2.95 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 159.9, 153.4, 143.7, 136.2, 135.7, 131.6, 130.1, 126.4, 123.9, 123.1, 120.5, 120.1, 118.9, 113.7, 112.3, 111.2, 111.1, 108.9, 104.3, 67.4, 52.9, 24.2, 21.4 ppm; HRMS: Calcd for $C_{24}H_{19}O_2N_3Cl$ $[M+H]^+$: 416.11603, Found: 416.11597.

Compound **72cl:**



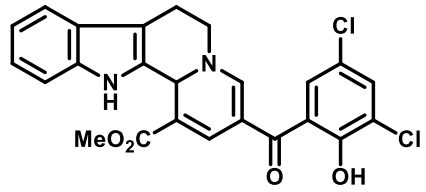
Compound **72cl** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.23 (s, 1H), 9.03 (s, 1H), 7.88 (d, *J* = 2.0 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.42 – 7.37 (d, *J* = 8.3 Hz, 1H), 7.27 – 7.21 (m, 2H), 6.92 (s, 1H), 3.86 – 3.75 (m, 8H), 3.69 (s, 3H), 3.24 (ddd, *J* = 15.7, 11.6, 5.9 Hz, 1H), 2.96 (dd, *J* = 15.7, 3.4 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 170.3, 159.9, 153.5, 143.4, 136.4, 135.9, 131.7, 129.7, 126.1, 123.8, 123.1, 120.5, 120.1, 118.8, 118.3, 114.7, 112.0, 108.1, 105.8, 68.2, 54.0, 53.2, 52.3, 28.1, 23.5, 20.4 ppm; HRMS: Calcd for $C_{27}H_{26}O_5N_2Cl$ $[M+H]^+$: 493.15248, Found: 493.15211.

Compound **72cm:**



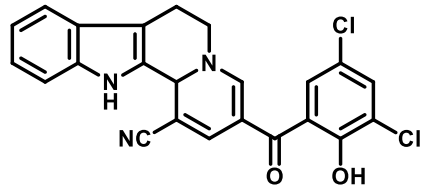
Compound **72cm** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.84 (s, 1H), 9.05 (s, 1H), 7.87 (d, *J* = 1.8 Hz, 1H), 7.56 (s, 1H), 7.49 – 7.31 (m, 3H), 7.21 (s, 1H), 6.63 (d, *J* = 7.9 Hz, 1H), 3.72 (s, 3H), 3.65 – 3.57 (m, 5H), 3.18 (ddd, *J* = 17.7, 12.0, 5.6 Hz, 1H), 2.98 (dd, *J* = 15.2, 4.0 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.4, 160.4, 153.7, 136.7, 135.8, 134.3, 132.1, 130.3, 129.7, 126.4, 123.2, 120.8, 119.7, 119.1, 118.9, 113.5, 114.2, 112.2, 108.7, 105.8, 68.2, 54.3, 53.3, 25.7, 23.6, 22.5 ppm; HRMS: Calcd for $C_{26}H_{23}O_3N_3Cl$ $[M+H]^+$: 460.14225, Found: 460.14214.

Compound **72cn:**



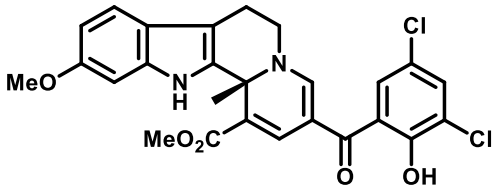
Compound **72cn** was synthesized according to the racemic general procedure.Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.85 (s, 1H), 9.06 (s, 1H), 7.87 (d, *J* = 1.8 Hz, 1H), 7.78 (d, *J* = 2.0 Hz, 1H), 7.64 (d, *J* = 1.7 Hz, 1H), 7.49 – 7.47 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.18 – 7.12 (m, 2H), 6.00 (s, 1H), 3.80 – 3.72 (m, 5H), 3.19 (ddd, *J* = 15.6, 11.9, 5.9 Hz, 1H), 2.98 (m, 1H); 13C NMR (101 MHz, $CDCl_3$) δ 189.4, 168.8, 157.2, 153.8, 139.6, 136.1, 135.4, 131.6, 131.4, 126.7, 123.3, 121.8, 120.1, 118.4, 114.2, 113.1, 112.0, 110.0, 108.2, 105.7, 68.3, 53.8, 52.1, 23.3 ppm; HRMS: Calcd for $C_{24}H_{19}O_4N_2Cl_2$ $[M+H]^+$: 469.07164, Found: 469.07133.

Compound **72co:**



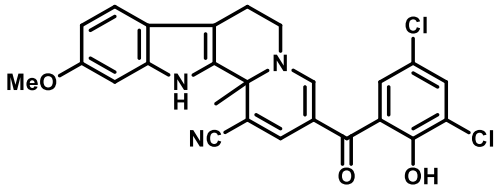
Compound **72co** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (s, 1H), 9.01 (s, 1H), 7.88 (d, *J* = 1.5 Hz, 1H), 7.64 (d, *J* = 1.5 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 2.5 Hz, 1H), 7.20 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.13 (ddd, *J* = 7.9, 7.1 Hz, 1H), 5.98 (s, 1H), 3.76 (dd, *J* = 13.4, 5.0 Hz, 2H), 3.21 (ddd, *J* = 14.0, 10.9, 6.0 Hz, 1H), 2.95 (dd, *J* = 14.0, 5.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 155.9, 153.8, 136.1, 135.4, 133.9, 131.5, 128.4, 126.3, 124.0, 123.2, 123.1, 121.6, 120.0, 118.4, 114.3, 113.5, 112.1, 108.2, 105.7, 68.1, 53.0, 23.5 ppm; HRMS: Calcd for $C_{23}H_{16}O_2N_3Cl_2$ $[M+H]^+$: 436.06141, Found: 436.06104.

Compound **72cp:**



Compound **72cp** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 8.99 (s, 1H), 7.89 (s, 1H), 7.65 (s, 1H), 7.58 (s, 1H), 7.42 – 7.31 (m, 3H), 7.04 (d, *J* = 8.7 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.52 – 3.44 (m, 5H), 3.31 – 3.23 (m, 1H), 3.00 – 2.97 ppm (m, 1H); 13C NMR (101 MHz, $CDCl_3$) δ 189.9, 170.4, 159.8, 153.6, 136.2, 135.9, 134.2, 132.1, 131.1, 129.7, 126.2, 123.2, 120.8, 120.0, 119.7, 118.5, 114.2, 112.2, 108.5, 105.9, 68.2, 54.5, 52.8, 52.7, 23.3, 22.4 ppm; HRMS: Calcd for $C_{26}H_{23}O_5N_2Cl_2$ $[M+H]^+$: 513.09785, Found: 513.09781; $[\alpha]_D^{20}$ -6.7 ° (c 0.002 in ethanol).

Compound **72cq:**



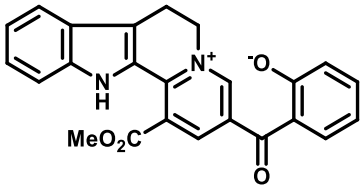
Compound **72cq** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 9.01 (s, 1H), 7.87 (s, 1H), 7.66 (s, 1H), 7.57 (s, 1H), 7.42 – 7.31 (m, 3H), 7.07 (d, *J* = 8.6 Hz, 1 H), 3.69 (s, 3H), 3.51 – 3.43 (m, 5H), 3.20 (ddd, *J* = 13.9, 10.9, 5.7 Hz, 1H), 2.89 (ddd, *J* = 13.9, 11.0, 5.7 Hz, 1H); 13C NMR (101 MHz, $CDCl_3$) δ 189.9, 160.2, 153.7, 136.7, 135.9, 134.3, 132.1, 130.4, 129.7, 126.3, 123.1, 120.8, 119.9, 119.2, 118.6, 114.2, 113.7, 112.3, 108.6, 105.9, 68.2, 54.4, 53.0, 23.7, 22.3 ppm; HRMS: Calcd for $C_{25}H_{20}O_3N_3Cl_2$ $[M+H]^+$: 480.08762, Found: 480.08771.

III.4. Experimental Part for Chapter 4

III.4.1. Synthesis of the Indolopyridiniums **87**

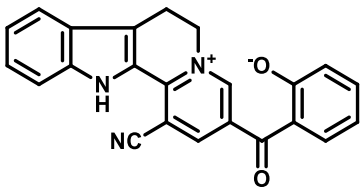
The cyclic imine (0.10 mmol; 1.0 eq.) was dissolved under argon in 5mL dry DMSO, and dry $ZnCl_2$ (0.10 mmol; 1.0 eq) was added and stirred for 5min. Chromone diene **70** (0.10 mmol; 1.0 eq.) was added and the reaction mixture was allowed to react for 24h at 80°C in a sealed tube under Ar. The reaction mixture is then diluted in 10 mL brine and extracted with 3x10mL DCM. The organic phase was dried over Na_2SO_4 evaporated to give a residue that is purified by flash chromatography to yield the indolopyridiniums as red amorphous solids.

Compound **87a:**



Compound **87a** was synthesized according to the general procedure. Red amorphous solid; TLC (ethyl acetate): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.03 (s, 1H), 9.44 (s, 1H), 9.08 (s, 1H), 7.74 (s, 1H), 7.46 – 7.30 (m, 4H), 7.27 – 7.20 (m, 3H), 5.21 (t, *J* = 9.5 Hz, 2H), 3.95 – 3.90 (m, 3H), 3.43 (t, *J* = 9.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8, 165.5, 164.6, 153.7, 150.9, 138.2, 135.4, 132.3, 131.5, 131.4, 127.6, 123.7, 122.0, 121.6, 120.4, 119.5, 117.3, 116.8, 113.2, 111.4, 104.9, 70.7, 60.2, 22.6 ppm; HRMS: Calcd for $C_{24}H_{19}O_4N_2$ $[M+H]^+$: 399.13393, Found: 399.13385.

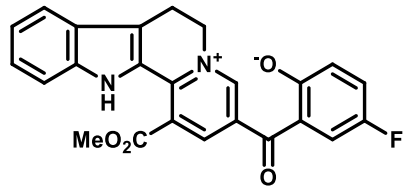
Compound **87b:**



Compound **87b** was synthesized according to the general procedure. Red amorphous solid; TLC (ethyl acetate): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.96 (s, 1H), 9.45 (s, 1H), 9.07 (s, 1H), 7.75 (s, 1H), 7.48 – 7.32 (m, 4H), 7.26 – 7.20 (m, 3H), 5.18 (t, *J* = 9.6 Hz, 2H), 3.41 (t, *J* = 9.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8, 165.5, 153.6, 150.9, 138.3, 135.4, 132.2, 131.5,

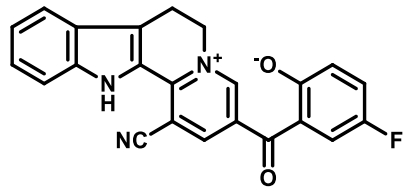
131.4, 127.7, 124.0, 123.6, 122.0, 121.5, 120.4, 119.4, 117.3, 116.8, 113.1, 111.4, 104.8, 65.2, 22.5 ppm; HRMS: Calcd for $C_{23}H_{16}O_4N_3$ $[M+H]^+$: 366.12370, Found: 366.12375.

Compound **87c:**



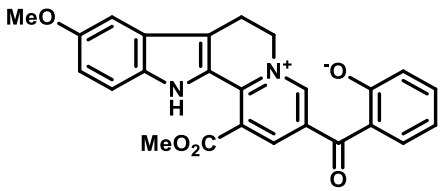
Compound **87c** was synthesized according to the general procedure. Red amorphous solid; TLC (ethyl acetate): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.18 (s, 1H), 9.02 (s, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.30 (m, 3H), 7.22 – 7.12 (m, 2H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.00 (s, 1H), 3.83 – 3.75 (m, 5H), 3.20 (m, 1H), 2.99 (dd, *J* = 14.0, 4.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 167.2, 159.5, 153.4, 136.2, 135.1, 134.3, 131.6, 129.6, 125.9, 122.3, 121.2, 120.9, 120.1, 119.7, 118.3, 114.6, 112.0, 108.2, 105.9, 68.4, 52.6, 50.6, 23.6 ppm; HRMS: Calcd for $C_{24}H_{17}O_4N_2F$ $[M+H]^+$: 417.12451, Found: 417.12441.

Compound **87d:**



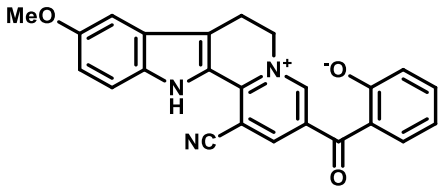
Compound **87d** was synthesized according to the general procedure. Red amorphous solid; TLC (ethyl acetate): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.10 (s, 1H), 8.97 (s, 1H), 7.93 (d, *J* = 1.5 Hz, 1H), 7.60 (d, *J* = 1.5 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.39 – 7.30 (m, 3H), 7.25 – 7.19 (m, 1H), 7.17 – 7.10 (m, 1H), 6.00 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 3.80 – 3.73 (m, 2H), 3.16 (dd, *J* = 15.6, 12.0 Hz, 1H), 2.98 (dd, *J* = 15.6, 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 159.7, 153.6, 136.3, 135.8, 134.4, 131.7, 129.6, 126.0, 123.3, 123.2, 120.7, 121.0, 120.0, 118.2, 115.3, 114.1, 112.0, 108.1, 105.7, 68.2, 54.1, 23.4 ppm; HRMS: Calcd for $C_{23}H_{14}O_2N_3F$ $[M+H]^+$: 384.11428, Found: 384.11429.

Compound **87e:**



Compound **87e** was synthesized according to the general procedure. Red amorphous solid; TLC (ethyl acetate): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.03 (s, 1H), 9.37 (s, 1H), 9.09 (s, 1H), 7.74 (s, 1H), 7.56 (dd, *J* = 12.3, 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.02 – 6.92 (m, 2H), 5.11 (t, *J* = 9.3Hz, 2H), 4.15 (m, 3H), 3.88 (m, 3H), 3.46 (t, *J* = 9.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 165.0, 164.7, 153.4, 150.8, 138.2, 135.8, 135.0, 132.4, 131.5, 131.7, 127.6, 123.5, 121.6, 120.4, 119.6, 117.3, 116.7, 113.2, 111.7, 104.5, 70.3, 60.3, 50.2, 22.4 ppm; HRMS: Calcd for $C_{25}H_{21}O_5N_2$ $[M+H]^+$: 429.14450, Found: 429.14466.

Compound **87f:**



Compound **87f** was synthesized according to the general procedure. Red amorphous solid; TLC (ethyl acetate): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.96 (s, 1H), 9.45 (s, 1H), 9.07 (s, 1H), 7.75 (s, 1H), 7.48 – 7.32 (m, 4H), 7.26 – 7.20 (m, 3H), 5.18 (t, *J* = 9.6 Hz, 2H), 3.91 (t, *J* = 9.5 Hz, 2H), 3.41 (t, *J* = 9.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8, 165.5, 153.6, 150.9, 138.3, 135.4, 132.2, 131.5, 131.4, 127.7, 124.0, 123.6, 122.0, 121.5, 120.4, 119.4, 117.3, 116.8, 115.2, 113.1, 111.4, 104.8, 65.2, 22.5 ppm; HRMS: Calcd for $C_{24}H_{18}O_3N_3$ $[M+H]^+$: 396.13427, Found: 396.13401.

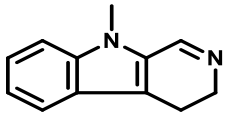
III.4.2. Synthesis of the Methyl-protected Indoloquinolizines 90

Synthesis of methyl-protected imines 88 and 89

To a suspension of sodium hydride (28.2 mmol) in anhydrous DMF (20 mL) was added dropwise with stirring at -10 °C under argon a solution of compound **69a** (16.7 mmol) in DMF (10 mL). The mixture was stirred for 1 h at -10 °C and then cooled to -60 °C before dropwise addition of a solution of methyl tosylate (18.4 mmol) in DMF (10 mL). Stirring was maintained

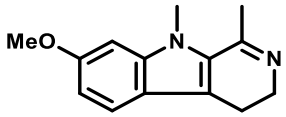
for 2 h at -60 °C and methanol (5 mL), water (5 mL) and saturated aqueous sodium chloride (250 mL) were added successively. The solution was extracted with dichloromethane (3×75 mL), the organic extracts were combined, washed with water (30 mL) and dried over sodium sulfate. The solvents were removed under reduced pressure, the residue was taken up in dichloromethane and the solution was filtered through a pad of silica gel. Evaporation of the filtrate afforded compound 11 which was crystallized in ethyl acetate–95% ethanol.

Compound **88:**



Compound **88** was synthesized according to the general procedure for Me-protected imines. Dark red amorphous solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 7.52 (d, *J* = 7.8Hz, 1H), 7.39 (d, *J* = 8.9 Hz, 1H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 3.81 (t, *J* = 8.8 Hz, 2H), 3.19 (s, 3H), 2.82 (t, *J* = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.4, 136.8, 128.2, 124.7, 123.6, 120.0, 119.3, 113.7, 112.5, 48.0, 34.7, 18.8 ppm; HRMS: Calcd for $C_{12}H_{13}N_2$ $[M+H]^+$: 185.10732, Found: 185.10710.

Compound **89:**

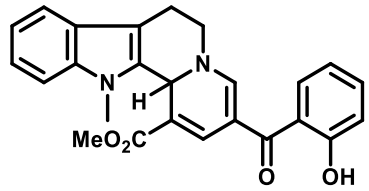


Compound **89** was synthesized according to the general procedure for Me-protected imines. Dark red amorphous solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (d, *J* = 8.4 Hz, 1H), 7.04 (s, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 3.79 – 3.71 (m, 5H), 3.24 (s, 3H), 2.84 (t, *J* = 8.0 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.0, 154.4, 136.7, 129.1, 124.5, 122.5, 119.3, 113.6, 112.0, 56.1, 48.1, 35.0, 22.1, 19.4 ppm; HRMS: Calcd for $C_{14}H_{17}N_2O$ $[M+H]^+$: 229.13354, Found: 229.13307.

Synthesis of methyl-protected indoloquinolizines 90

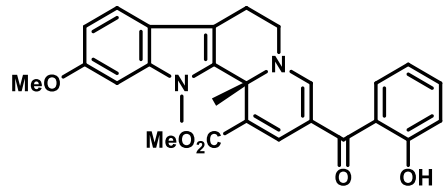
Indoloquinolizines **90** were synthesized following the general procedure for the synthesis of indoloquinolizines **72**.

Compound **90a:**



Compound **90a** was synthesized according to the general procedures. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.33 (s, 1H), 7.87 (s, 1H), 7.67 (s, 1H), 7.48 – 7.30 (m, 4H), 7.14 – 7.08 (m, 4H), 6.32 (s, 1H), 3.85 (s, 3H), 3.81 – 3.78 (m, 1H), 3.65 – 3.58 (m, 4H), 3.20 – 3.16 (m, 1H), 2.96 – 2.91 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 167.0, 164.6, 149.7, 136.7, 136.1, 133.5, 131.6, 130.9, 127.5, 121.8, 121.5, 120.7, 120.2, 117.4, 116.6, 116.0, 113.2, 112.1, 108.2, 67.4, 54.2, 50.1, 27.1, 23.4 ppm; HRMS: Calcd for $C_{25}H_{23}O_4N_2$ $[M+H]^+$: 415.16523, Found: 415.16520.

Compound **90b:**



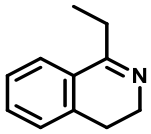
Compound **90b** was synthesized according to the general procedures. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.28 (s, 1H), 7.89 (s, 1H), 7.67 (s, 1H), 7.47 – 7.40 (m, 2H), 7.30 – 7.25 (m, 2H), 7.01 – 6.96 (m, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.77 – 3.70 (m, 5H), 3.51 (s, 3H), 3.16 – 3.10 (m, 1H) 2.93 – 2.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 169.7, 168.2, 161.0, 153.3, 135.9, 134.2, 131.6, 130.1, 129.1, 126.3, 124.4, 119.7, 118.5, 118.2, 117.6, 113.3, 111.3, 107.4, 105.9, 68.0, 53.7, 52.4, 52.0, 33.7, 23.7, 21.9 ppm; HRMS: Calcd for $C_{27}H_{27}O_5N_2$ $[M+H]^+$: 459.19145, Found: 459.19137; $[\alpha]_D^{20}$ -8.6 ° (c 0.002 in ethanol).

III.4.3. Synthesis of the Benzoquinolizines 96 and Benzopyridiniums 97

Synthesis of 3,4-dihydroisoquinolines 94

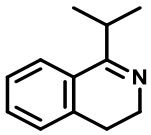
The 3,4-dihydroisoquinolines **94** were synthesized following the same general procedure as for the tryptamine derived imines **69**.

Compound **94a:**



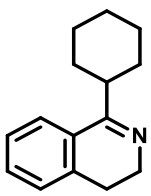
Compound **94a** was synthesized according to the general procedure for α substituted imines. Yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.2 Hz, 1H), 7.35 – 7.26 (m, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 3.66 (t, *J* = 7.2 Hz, 2H), 2.75 (q, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 137.8, 130.2, 129.0, 127.5, 126.8, 124.8, 46.8, 28.7, 26.1, 11.2 ppm; HRMS: Calcd for $C_{11}H_{14}N$ $[M+H]^+$: 160.11208, Found: 160.11199.

Compound **94b:**



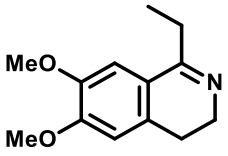
Compound **94b** was synthesized according to the general procedure for α substituted imines. Yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.2 Hz, 1H), 7.34–7.27 (m, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 3.66 (t, *J* = 7.4 Hz, 2H), 3.31 – 3.21 (m, 1H), 2.64 (t, *J* = 7.4 Hz, 2H), 1.20 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 138.2, 130.0, 128.8, 127.5, 126.7, 124.6, 46.8, 31.6, 26.3, 20.7 ppm; HRMS: Calcd for $C_{12}H_{16}N$ $[M+H]^+$: 174.12773, Found: 174.12781.

Compound **94c:**



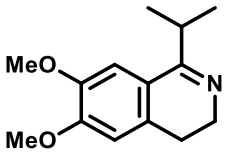
Compound **94c** was synthesized according to the general procedure for α substituted imines. Yellow amorphous solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 5.7 Hz, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 9.66 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.59 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.49 (d, *J* = 5.7 Hz; 1H), 3.57 (tt, *J* = 11.6, 3.2 Hz, 1H), 2.04 – 1.91 (m, 4H), 1.88 – 1.75 (m, 3H), 1.54 (qt, *J* = 12.5, 3.1 Hz, 2H), 1.40 (qt, *J* = 12.7, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.9, 142.1, 136.6, 129.7, 127.7, 127.0, 126.5, 124.9, 119.1, 41.7, 32.8, 27.1, 26.4 ppm; HRMS: Calcd for $C_{15}H_{20}N$ $[M+H]^+$: 214.15903, Found: 214.15894.

Compound **94d:**



Compound **94d** was synthesized according to the general procedure for α substituted imines. Yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.67 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.61 (t, *J* = 7.6 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.75 (q, *J* = 7.2 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 150.8, 147.4, 131.1, 122.4, 110.2, 109.0, 56.2, 55.9, 46.9, 25.7, 23.4 ppm; HRMS: Calcd for $C_{13}H_{18}O_2N$ $[M+H]^+$: 220.13321, Found: 220.13335.

Compound **94e:**



Compound **94e** was synthesized according to the general procedure for α substituted imines. Yellow amorphous solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.04 (s, 1H), 6.70 (s, 1H), 3.92 (s, 6H), 3.66 – 3.61 (m, 2H), 3.20 – 3.17 (m, 1H), 2.61 – 2.56 (q, *J* = 6.7 Hz, 2H), 1.21 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.9, 150.6, 147.5, 132.2, 121.8, 110.5, 108.7, 56.4, 56.1, 47.1, 32.0, 26.2, 21.0 ppm; HRMS: Calcd for $C_{14}H_{20}O_2N$ $[M+H]^+$: 234.14886, Found: 234.14895.

Synthesis of Benzoquinolizines 96

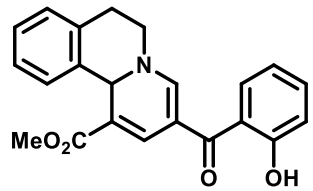
- **General procedure for the racemic synthesis of ring-fused quinolizines:**

The cyclic imine (0.10 mmol; 1.0 eq.) was dissolved under argon in 5mL dry DMSO, and dry $ZnCl_2$ (0.10 mmol; 1.0 eq) was added and stirred for 5min. Chromone diene **70** (0.10 mmol; 1.0 eq.) was added and the reaction mixture was allowed to react for 12-24h at 80°C in a sealed tube under Ar. Disappearance of the chromone on TLC indicates complete reaction (cyclohexane/ethyl acetate 1:1). The reaction mixture is then diluted in 10 mL brine and extracted with 3x10mL DCM. The organic phase was dried over Na_2SO_4 evaporated to give a residue that is purified by flash chromatography to yield the ring-fused quinolizines as colorful solids.

- **General procedure for the asymmetric imino-Diels-Alder synthesis of ring-fused quinolizines:**

$ZnEt_2$ (0.01 mmol; 20 mol%) and (R)-Binol (R)-**80a** or (R)-dianthracenylbinol (R)-**80e** (0.02 mmol; 40 mol%) were dissolved under argon in 5mL dry toluene and stirred for 15 minutes, then the cyclic imine (0.05 mmol; 1.0 eq) was added to the reaction mixture which is subsequently cooled to -78°C. Chromone diene **70** (0.10 mmol; 1.0 eq.) was added and the reaction mixture was allowed to react for 12-24h at -78°C in a sealed tube under Ar. Disappearance of the chromone on TLC indicates complete reaction (cyclohexane/ethyl acetate 1:1). The reaction mixture is then evaporated to give a residue that is purified by flash chromatography to yield the ring-fused quinolizines as colorful solids.

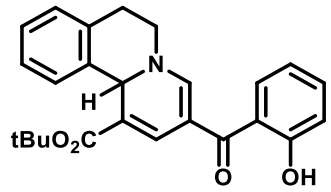
Compound **96a:**



Compound **96a** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 7.94 (s, 1H), 7.64 (s, 1H), 7.53 – 7.51 (m, 1H), 7.40 – 7.16 (m, 6H), 6.97 – 6.90 (m, 1H), 5.49 (s, 1H), 3.86 – 3.77 (m, 5H), 3.19 (dd, J = 13.9, 4.0 Hz, 1H), 2.97 (dd, J = 14.0, 4.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6, 168.8, 159.9, 143.4, 136.2, 136.0, 135.9, 131.8, 130.0,

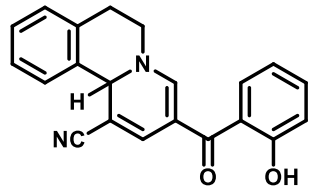
126.1, 123.9, 120.5, 120.0, 118.8, 118.4, 113.8, 112.0, 108.2, 68.1, 54.0, 45.2, 23.3 ppm; HRMS: Calcd for $C_{22}H_{20}O_4N$ $[M+H]^+$: 362.13868, Found: 362.13867.

Compound **96c:**



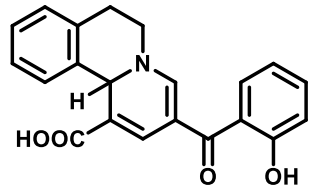
Compound **96c** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (s, 1H), 7.99 (s, 1H), 7.65 (s, 1H), 7.54 – 7.50 (m, 1H), 7.39 – 7.20 (m, 6H), 6.97 – 6.93 (m, 1H), 5.79 (s, 1H), 3.86 – 3.80 (m, 2H), 3.20 (dd, J = 14.0, 3.9 Hz, 1H), 2.98 (dd, J = 14.0, 3.9 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.9, 163.8, 160.0, 143.7, 136.3, 136.0, 135.7, 131.9, 130.2, 126.3, 123.7, 120.5, 120.2, 118.8, 118.3, 113.8, 112.4, 108.2, 81.0, 68.1, 45.2, 28.8, 28.7, 23.2 ppm; HRMS: Calcd for $C_{25}H_{26}O_4N$ $[M+H]^+$: 404.18563, Found: 404.18541.

Compound **96d:**



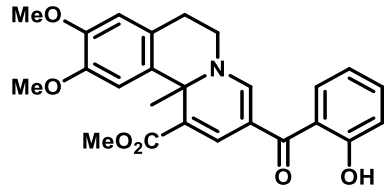
Compound **96d** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 9.04 (s, 1H), 7.84 (s, 1H), 7.63 (s, 1H), 7.48 – 7.41 (m, 3H), 7.25 – 7.19 (m, 1H), 7.33 – 7.30 (m, 1H), 7.08 – 7.00 (m, 3H), 6.09 (s, 1H), 3.85 – 3.79 (m, 2H), 3.20 – 3.13 (m, 1H), 2.96 – 2.91 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9, 153.4, 138.4, 136.1, 134.8, 132.5, 130.3, 127.4, 127.0, 126.1, 122.7, 120.2, 118.4, 118.1, 116.1, 105.9, 83.8, 82.3, 69.1, 52.0, 23.4 ppm; HRMS: Calcd for $C_{21}H_{17}O_2N_2$ $[M+H]^+$: 329.12845, Found: 329.12811.

Compound **96e:**



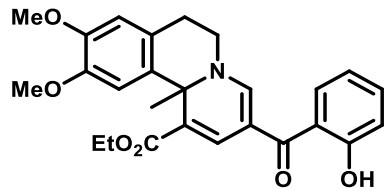
Compound **96e** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.18 (s, 1H), 11.12 (s, 1H), 9.79 (s, 1H), 7.73 (s, 1H), 7.67 (s, 1H), 7.34 – 7.27 (m, 2H), 7.19 – 7.12 (m, 2H), 7.05 – 7.01 (m, 1H), 6.94 – 6.88 (m, 2H), 6.11 (s, 1H), 4.06 – 4.02 (m, 1H), 3.50 – 3.45 (m, 1H), 3.03 – 2.95 (m, 1H), 2.91 – 2.87 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.4, 173.1, 155.3, 153.8, 136.4, 132.4, 132.2, 132.0, 131.7, 129.3, 127.8, 125.7, 125.5, 124.2, 116.4, 112.7, 111.8, 106.1, 67.9, 49.8, 22.5 ppm; HRMS: Calcd for $C_{21}H_{18}O_4N$ $[M+H]^+$: 348.12303, Found: 348.12274.

Compound **96f:**



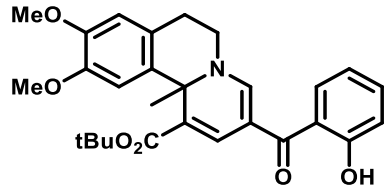
Compound **96f** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 7.89 (s, 1H), 7.72 (s, 1H), 7.46 – 7.42 (m, 2H), 7.20 – 7.13 (m, 2H), 6.99 (s, 1H), 6.88 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.58 (s, 3H), 3.52 – 3.46 (m, 1H), 3.43 – 3.36 (m, 4H); 2.96 – 2.88 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 170.0, 166.0, 158.9, 145.2, 135.1, 132.8, 131.6, 131.1, 128.7, 127.5, 127.3, 123.1, 121.4, 119.5, 116.7, 116.0, 111.2, 105.1, 69.9, 56.3, 56.2, 52.4, 49.8, 24.2 ppm; HRMS: Calcd for $C_{25}H_{26}O_6N$ $[M+H]^+$: 436.17546, Found: 436.17519.

Compound **96g:**



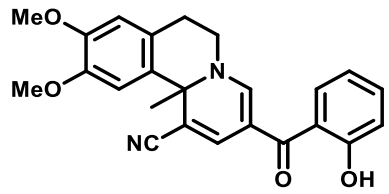
Compound **96g** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.23 (s, 1H), 7.88 (s, 1H), 7.71 (s, 1H), 7.47 – 7.42 (m, 2H), 7.20 – 7.12 (m, 2H), 7.00 (s, 1H), 6.89 (s, 1H), 4.06 (q, *J* = 7.8 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.46 – 3.38 (m, 5H), 2.95 – 2.89 (m, 2H), 1.30 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 169.9, 166.2, 158.8, 145.3, 135.0, 132.7, 131.6, 131.2, 128.7, 127.6, 127.3, 123.7, 121.5, 119.5, 116.8, 116.1, 111.4, 105.0, 69.9, 61.8, 56.3, 56.2, 49.7, 24.2, 15.0 ppm; HRMS: Calcd for $C_{26}H_{28}O_6N$ $[M+H]^+$: 450.19111, Found: 450.19098.

Compound **96h:**



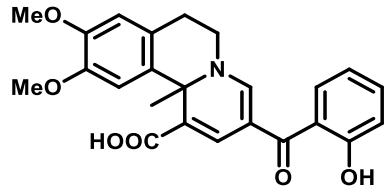
Compound **96h** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 7.88 (s, 1H), 7.74 (s, 1H), 7.47 – 7.42 (m, 2H), 7.22 – 7.14 (m, 2H), 6.98 (s, 1H), 6.88 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.53 – 3.46 (m, 1H), 3.43 – 3.37 (m, 4H), 2.97 – 2.90 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 170.5, 166.4, 158.8, 145.2, 135.2, 132.7, 131.5, 131.1, 128.6, 127.5, 127.0, 123.1, 121.6, 119.6, 116.7, 116.1, 111.2, 105.9, 81.6, 70.1, 56.4, 56.3, 49.7, 28.9, 24.3 ppm; HRMS: Calcd for $C_{28}H_{32}O_6N$ $[M+H]^+$: 478.22241, Found: 478.22237.

Compound **96i:**



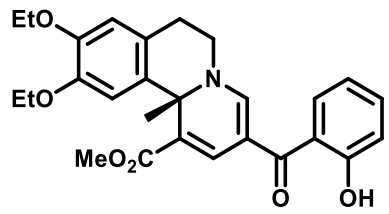
Compound **96i** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 7.89 (s, 1H), 7.75 (s, 1H), 7.48 – 7.41 (m, 2H), 7.22 – 7.16 (m, 2H), 7.00 (s, 1H), 6.91 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.52 – 3.45 (m, 1H), 3.41 – 3.37 (m, 4H), 2.93 – 2.87 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 166.7, 158.8, 145.2, 135.1, 132.8, 131.7, 131.0, 128.7, 127.4, 127.2, 123.2, 121.7, 119.8, 117.7, 116.8, 113.2, 111.7, 104.2, 69.8, 56.3, 56.3, 49.7, 24.3 ppm; HRMS: Calcd for $C_{24}H_{23}O_4N_2$ $[M+H]^+$: 403.16523, Found: 403.16497.

Compound **96j:**



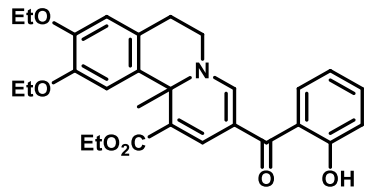
Compound **96j** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.04 (s, 1H), 11.27 (s, 1H), 7.90 (s, 1H), 7.74 (s, 1H), 7.47 – 7.41 (m, 2H), 7.22 – 7.17 (m, 2H), 7.02 (s, 1H), 6.93 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.50 – 3.44 (m, 1H), 3.40 – 3.35 (m, 4H), 2.94 – 2.88 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 172.4, 166.7, 158.0, 145.1, 135.1, 132.7, 131.7, 131.1, 128.7, 127.8, 127.3, 123.2, 121.4, 119.8, 116.7, 114.7, 111.3, 104.2, 69.9, 56.3, 56.2, 49.6, 24.7 ppm; HRMS: Calcd for $C_{24}H_{24}O_6N$ $[M+H]^+$: 422.15981, Found: 422.15958.

Compound **96k:**



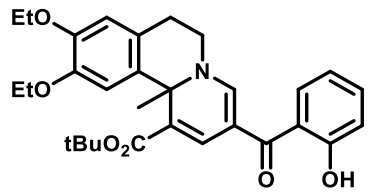
Compound **96k** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.25 (s, 1H), 7.90 (s, 1H), 7.73 (s, 1H), 7.47 – 7.42 (m, 2H), 7.20 – 7.14 (m, 2H), 7.00 (s, 1H), 6.89 (s, 1H), 4.02 – 3.94 (m, 4H), 3.58 (s, 3H), 3.52 – 3.47 (m, 1H), 3.41 – 3.35 (m, 4H), 2.97 – 2.90 (m, 2H), 1.55 – 1.48 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 170.1, 164.5, 158.8, 135.3, 135.0, 132.1, 131.7, 131.0, 128.6, 127.5, 127.3, 123.4, 121.4, 119.5, 116.1, 111.2, 104.6, 70.4, 67.9, 61.3, 61.2, 52.2, 49.7, 24.0, 15.3, 15.2 ppm; HRMS: Calcd for $C_{27}H_{30}O_6N$ $[M+H]^+$: 464.20676, Found: 464.20671; $[\alpha]_D^{20}$ -14.8 ° (c 0.002 in ethanol).

Compound **96l:**



Compound **96l** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 7.90 (s, 1H), 7.73 (s, 1H), 7.47 – 7.41 (m, 2H), 7.22 – 7.18 (m, 2H), 7.01 (s, 1H), 6.89 (s, 1H), 4.04 – 3.94 (m, 6H), 3.53 – 3.47 (m, 1H), 3.41 – 3.37 (m, 4H), 2.95 – 2.91 (m, 2H), 1.55 – 1.43 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 170.2, 164.1, 158.9, 135.5, 134.8, 132.0, 131.7, 131.2, 128.5, 127.5, 127.2, 123.4, 121.5, 119.5, 116.7, 111.2, 104.9, 70.5, 67.8, 61.6, 61.3, 61.2, 49.8, 24.4, 15.9, 15.3, 15.2 ppm; HRMS: Calcd for $C_{28}H_{32}O_6N$ $[M+H]^+$: 478.22241, Found: 478.22223.

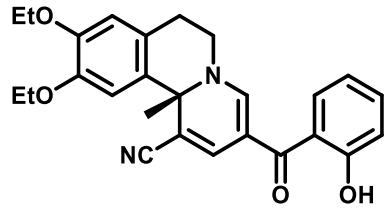
Compound **96m:**



Compound **96m** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 7.89 (s, 1H), 7.74 (s, 1H), 7.49 – 7.44 (m, 2H), 7.19 – 7.14 (m, 2H), 7.03 (s, 1H), 6.91 (s, 1H), 4.02 – 3.94 (m, 4H), 3.53 – 3.47 (m, 1H), 3.41 – 3.36 (m, 4H), 2.96 – 2.90

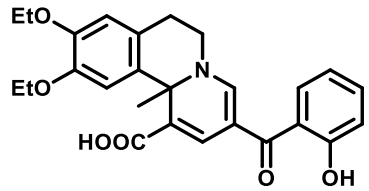
(m, 2H), 1.55 – 1.42 (m, 15H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.9, 170.4, 164.6, 158.8, 135.7, 135.4, 132.1, 131.9, 131.2, 128.6, 127.4, 127.3, 123.7, 121.4, 119.6, 116.2, 111.2, 104.5, 70.0, 81.1, 67.8, 61.3, 61.2, 49.6, 24.2, 15.3, 15.2, 14.7 ppm; HRMS: Calcd for $C_{30}H_{36}O_6N$ $[M+H]^+$: 506.25371, Found: 506.25344.

Compound **96n:**



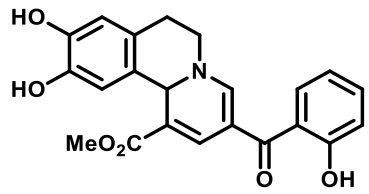
Compound **96n** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 7.94 (s, 1H), 7.73 (s, 1H), 7.49 – 7.43 (m, 2H), 7.20 – 7.15 (m, 2H), 6.98 (s, 1H), 6.90 (s, 1H), 4.03 – 3.94 (m, 4H), 3.58 – 3.45 (m, 1H), 3.40 – 3.34 (m, 4H); 2.95 – 2.89 (m, 2H), 1.54 – 1.47 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.5, 164.7, 159.0, 135.3, 135.1, 132.2, 131.8, 131.0, 128.6, 127.6, 127.3, 123.4, 121.5, 119.5, 118.6, 116.2, 111.5, 104.6, 69.9, 67.7, 56.3, 56.1, 49.6, 24.2, 15.1, 14.9 ppm; HRMS: Calcd for $C_{26}H_{27}O_4N_2$ $[M+H]^+$: 431.19653, Found: 431.19647; $[\alpha]_D^{20}$ -14.2 ° (c 0.002 in ethanol).

Compound **96o:**



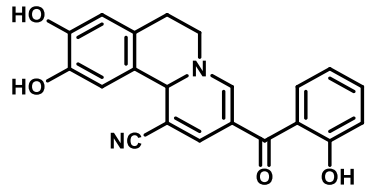
Compound **96o** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.04 (s, 1H), 11.13 (s, 1H), 7.93 (s, 1H), 7.74 (s, 1H), 7.48 – 7.41 (m, 2H), 7.23 – 7.16 (m, 2H), 7.00 (s, 1H), 6.88 (s, 1H), 4.03 – 3.94 (m, 4H), 3.55 – 3.49 (m, 1H), 3.44 – 3.39 (m, 4H), 2.96 – 2.90 (m, 2H), 1.54 – 1.48 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6, 174.3, 162.5, 158.9, 135.2, 135.1, 131.9, 131.4, 131.2, 128.4, 128.0, 127.9, 123.5, 121.4, 119.6, 116.1, 111.0, 104.6, 69.9, 67.8, 61.3, 61.2, 49.6, 24.7, 15.2, 15.2 ppm; HRMS: Calcd for $C_{26}H_{28}O_6N$ $[M+H]^+$: 450.19111, Found: 450.19087.

Compound **96p:**



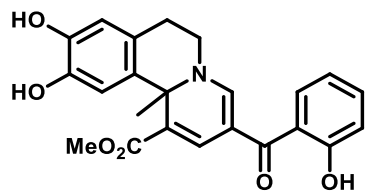
Compound **96p** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.97 (s, 1H), 9.57 (br s, 2H), 7.88 (s, 1H), 7.74 (s, 1H), 7.47 – 7.41 (m, 2H), 7.20 – 7.13 (m, 2H), 6.98 (s, 1H), 6.88 (s, 1H), 6.03 (s, 1H), 3.83 (s, 3H), 3.52 – 3.46 (m, 1H), 3.42 – 3.36 (m, 1H), 2.97 – 2.90 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 169.7, 164.4, 159.2, 145.2, 145.0, 136.3, 134.7, 131.5, 128.6, 127.6, 127.3, 123.3, 121.3, 119.5, 116.7, 111.6, 104.8, 70.5, 57.8, 52.3, 24.0 ppm; HRMS: Calcd for $C_{22}H_{20}O_6N$ $[M+H]^+$: 394.12851, Found: 394.12833.

Compound **96q:**



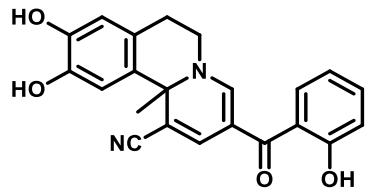
Compound **96q** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.83 (s, 1H), 7.95 (s, 1H), 7.72 (s, 1H), 7.48 – 7.41 (m, 2H), 7.20 – 7.13 (m, 2H), 6.99 (s, 1H), 6.89 (s, 1H), 3.60 – 3.54 (m, 1H), 3.41 – 3.35 (m, 1H); 2.93 – 2.88 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.9, 164.8, 159.4, 145.3, 145.1, 136.7, 131.2, 131.1, 128.7, 127.6, 127.3, 123.9, 121.4, 119.4, 118.9, 116.1, 110.6, 104.8, 70.3, 52.9, 24.4 ppm; HRMS: Calcd for $C_{21}H_{16}O_4N_2$ $[M+H]^+$: 361.11828, Found: 361.11801.

Compound **96r:**



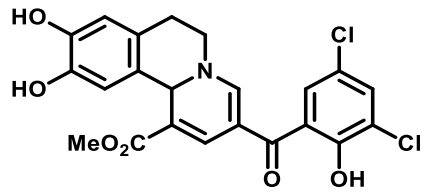
Compound **96r** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.98 (s, 1H), 9.53 (br s, 2H), 7.88 (s, 1H), 7.73 (s, 1H), 7.46 – 7.42 (m, 2H), 7.20 – 7.13 (m, 2H), 6.98 (s, 1H), 6.87 (s, 1H), 3.57 (s, 3H), 3.52 – 3.46 (m, 1H), 3.43 – 3.35 (m, 4H); 2.96 – 2.89 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.9, 170.7, 166.5, 158.7, 145.2, 145.1, 137.2, 134.6, 131.2, 128.8, 127.5, 123.1, 121.5, 119.4, 116.6, 116.2, 111.7, 105.2, 69.9, 53.4, 52.3, 49.7, 24.4 ppm; HRMS: Calcd for $C_{23}H_{22}O_6N$ $[M+H]^+$: 408.14416, Found: 408.14442.

Compound **96s:**



Compound **96s** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (s, 1H), 9.57 (br s, 2H), 7.90 (s, 1H), 7.73 (s, 1H), 7.48 – 7.41 (m, 2H), 7.23 – 7.16 (m, 2H), 7.01 (s, 1H), 6.92 (s, 1H), 3.52 – 3.46 (m, 1H), 3.40 – 3.36 (m, 4H), 2.92 – 2.87 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 166.8, 158.9, 145.4, 145.3, 132.7, 131.5, 128.6, 127.3, 127.0, 124.5, 121.9, 119.7, 117.0, 116.9, 113.5, 111.8, 104.5, 70.0, 49.9, 47.1, 24.7 ppm; HRMS: Calcd for $C_{22}H_{19}O_4N_2$ $[M+H]^+$: 375.13393, Found: 375.13402.

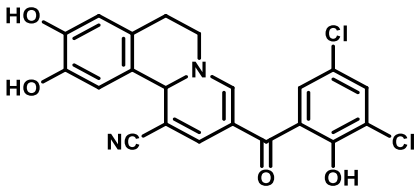
Compound **96t:**



Compound **96t** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (s, 1H), 9.54 (br s, 2H), 7.86 (s, 1H), 7.72 (s, 1H), 7.63 (s, 1H), 7.28 (s, 1H), 6.99 (s, 1H), 6.88 (s, 1H), 5.99, (s, 1H), 3.59 (s, 3H), 3.55 – 3.50 (m, 1H), 3.42 – 3.37 (m, 1H), 2.94 – 2.87 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.2, 170.5, 164.7, 156.3, 144.2, 144.0, 137.3, 134.6,

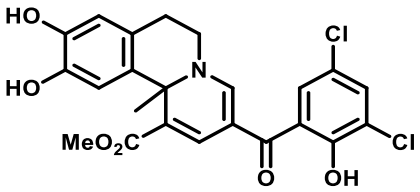
131.9, 128.5, 127.5, 127.2, 123.2, 121.5, 119.7, 116.3, 111.4, 104.7, 70.2, 67.8, 51.2, 24.0 ppm; HRMS: Calcd for $C_{22}H_{18}O_6NCl_2$ $[M+H]^+$: 462.05057, Found: 462.05024.

Compound **96u:**



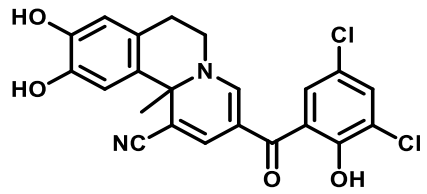
Compound **96u** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.87 (s, 1H), 9.54 (br s, 2H), 7.83 (s, 1H), 7.73 (s, 1H), 7.58 (s, 1H), 7.29 (s, 1H), 6.98 (s, 1H), 6.88 (s, 1H), 6.01 (s, 1H), 3.51 – 3.47 (m, 1H), 3.41 – 3.35 (m, 1H); 2.90 – 2.81 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 164.2, 158.7, 145.4, 145.3, 137.2, 131.1, 130.4, 128.5, 127.7, 127.3, 123.5, 121.5, 119.7, 117.3, 116.0, 111.5, 104.2, 70.7, 49.8, 24.7 ppm; HRMS: Calcd for $C_{21}H_{15}O_4N_2Cl_2$ $[M+H]^+$: 429.04304, Found: 429.04281.

Compound **96v:**



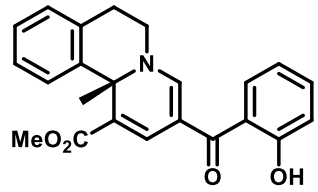
Compound **96v** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H), 9.57 (br s, 2H), 7.83 (s, 1H), 7.74 (s, 1H), 7.63 (s, 1H), 7.28 (s, 1H), 7.02 (s, 1H), 6.88 (s, 1H), 3.57 (s, 3H), 3.53 – 3.48 (m, 1H), 3.40 – 3.34 (m, 4H), 2.93 – 2.87 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 168.7, 164.9, 158.6, 146.0, 145.9, 137.3, 131.6, 131.2, 128.4, 127.5, 127.2, 123.1, 121.7, 119.6, 116.2, 111.2, 104.8, 71.0, 53.8, 52.1, 49.6, 24.7 ppm; HRMS: Calcd for $C_{23}H_{20}O_6NCl_2$ $[M+H]^+$: 476.06622, Found: 476.06593.

Compound **96w:**



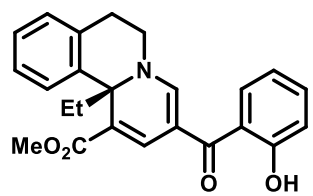
Compound **96w** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.05 (s, 1H), 9.56 (br s, 2H), 7.81 (s, 1H), 7.72 (s, 1H), 7.63 (s, 1H), 7.26 (s, 1H), 6.98 (s, 1H), 6.89 (s, 1H), 3.51 – 3.46 (m, 1H), 3.40 – 3.36 (m, 4H); 2.93 – 2.85 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.7, 164.7, 158.5, 145.0, 144.8, 138.8, 133.9, 132.0, 128.7, 127.6, 127.3, 123.0, 121.7, 119.6, 117.2, 116.1, 111.4, 104.7, 68.7, 51.7, 49.9, 24.5 ppm; HRMS: Calcd for $C_{22}H_{17}O_4N_2Cl_2$ $[M+H]^+$: 443.05599, Found: 443.05563.

Compound **96x:**



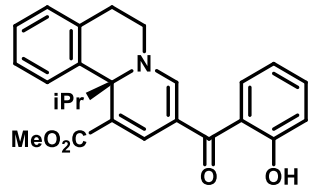
Compound **96x** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H), 7.90 (s, 1H), 7.60 (s, 1H), 7.53 (m, 1H), 7.48- – 7.45 (m, 2H), 7.36 – 7.34 (m, 1H), 7.22 – 7.18 (m, 2H), 7.12 – 7.08 (m, 1H), 6.89 – 6.87 (m, 1H), 3.88 (s, 3H), 3.82 – 3.73 (m, 2H), 3.49 (s, 3H), 3.20 – 3.15 (m, 1H), 2.97 – 2.93 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 168.7, 160.3, 153.7, 136.2, 135.8, 132.4, 131.7, 126.0, 123.2, 121.4, 120.0, 118.4, 114.0, 112.0, 110.3, 108.2, 105.8, 68.2, 54.1, 52.8, 26.2, 23.4 ppm; HRMS: Calcd for $C_{23}H_{22}O_4N$ $[M+H]^+$: 376.15433, Found: 376.15427; $[\alpha]_D^{20}$ -14.1° (c 0.002 in ethanol).

Compound **96y:**



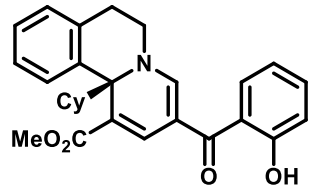
Compound **96y** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (s, 1H), 8.02 (s, 1H), 7.54 (s, 1H), 7.44 – 7.38 (m, 2H), 7.25 (d, *J* = 6.5 Hz, 1H), 7.17 – 7.11 (m, 3H), 7.01 – 6.95 (m, 2H), 3.85 – 3.79 (m, 1H), 3.74 – 3.68 (m, 1H), 3.67 (s, 3H), 3.30 (q, *J* = 7.5 Hz, 2H), 3.18 (dd, *J* = 14.1, 4.0 Hz, 1H), 2.97 (dd, *J* = 14.0, 4.0 Hz, 1H), 1.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 167.5, 164.1, 149.6, 136.8, 136.0, 135.9, 134.2, 133.5, 130.9, 121.9, 120.7, 120.5, 117.6, 116.7, 116.2, 111.2, 108.5, 68.7, 54.7, 49.5, 26.6, 25.0, 14.6 ppm; HRMS: Calcd for $C_{24}H_{24}O_4N$ $[M+H]^+$: 390.16998, Found: 390.16994; $[\alpha]_D^{20}$ -15.6 ° (c 0.002 in ethanol).

Compound **96z:**



Compound **96z** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (s, 1H), 7.99 (s, 1H), 7.54 (s, 1H), 7.42 – 7.31 (m, 2H), 7.20 – 7.09 (m, 4H), 6.98 – 6.93 (m, 2H), 3.84 – 3.78 (m, 1H), 3.73 – 3.68 (m, 4H), 3.18 – 3.13 (m, 1H), 2.93 – 2.87 (m, 2H); 1.59 (d, J = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 168.0, 164.0, 149.6, 136.9, 136.4, 136.1, 134.5, 133.2, 130.8, 124.3, 121.7, 120.9, 120.2, 117.5, 116.5, 116.2, 111.1, 108.7, 68.5, 55.1, 49.5, 38.3, 25.1, 16.3 ppm; HRMS: Calcd for $C_{25}H_{26}O_4N$ $[M+H]^+$: 404.18563, Found: 404.18562; $[\alpha]_D^{20}$ -18.3 ° (c 0.002 in ethanol).

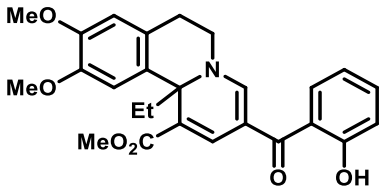
Compound **96aa:**



Compound **96aa** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.32 (s, 1H), 7.91 (s, 1H), 7.59 (s, 1H), 7.42 – 7.35 (m, 2H), 7.20 – 7.11 (m, 4H), 6.99 – 6.93 (m, 2H),

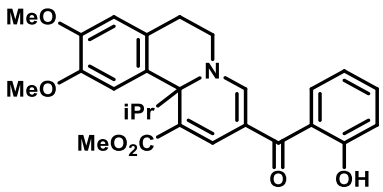
3.78 – 3.72 (m, 2H), 3.61 (s, 3H), 3.16 – 3.11 (m, 1H), 2.94 – 2.87 (m, 1H); 2.10 – 1.69 (m, 11H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 167.9, 164.1, 149.6, 136.7, 136.1, 135.9, 134.0, 133.4, 130.9, 124.3, 120.9, 120.4, 117.6, 116.7, 116.3, 111.4, 108.8, 68.9, 54.5, 49.7, 42.1, 26.8, 26.7, 26.6, 26.2, 26.0, 25.0 ppm; HRMS: Calcd for $C_{28}H_{30}O_4N$ $[M+H]^+$: 444.21693, Found: 444.21688; $[\alpha]_D^{20}$ -19.2 ° (c 0.002 in ethanol).

Compound **96ab:**



Compound **96ab** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 7.87 (s, 1H), 7.71 (s, 1H), 7.46 - 7.41 (m, 2H), 7.21 - 7.13 (m, 2H), 6.98 (s, 1H), 6.88 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.59 (s, 3H), 3.52 – 3.47 (m, 1H), 3.43 – 3.37 (m, 1H), 3.33 (q, *J* = 7.8 Hz, 2H), 3.16 (dd, *J* = 13.9, 4.0 Hz, 1H), 2.97 (dd, *J* = 13.9, 4.0 Hz, 1H), 1.96 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 171.2, 166.1, 158.4, 145.1, 135.1, 132.7, 131.7, 131.0, 128.7, 127.4, 127.3, 123.0, 121.5, 119.5, 116.8, 116.1, 111.3, 105.0, 69.9, 56.4, 56.2, 52.5, 24.4, 24.1, 14.1 ppm; HRMS: Calcd for $C_{26}H_{28}O_6N$ $[M+H]^+$: 450.19111, Found: 450.19096.

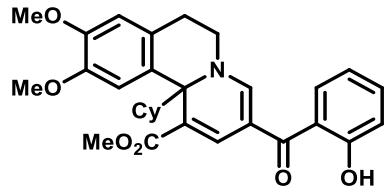
Compound **96ac:**



Compound **96ac** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 7.88 (s, 1H), 7.70 (s, 1H), 7.45 – 7.40 (m, 2H), 7.20 – 7.12 (m, 2H), 6.98 (s, 1H), 6.87 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.60 (s, 3H), 3.52 – 3.47 (m, 1H), 3.43 – 3.37 (m, 1H), 3.16 (dd, *J* = 13.9, 4.0 Hz, 1H), 2.94 – 2.86 (m, 2H); 1.65 (d, J = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 171.2, 166.1, 158.4, 145.1, 135.1, 132.7, 131.7, 131.0, 128.7, 127.4,

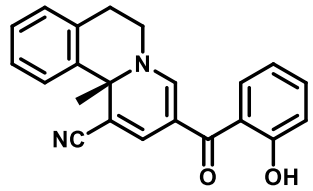
127.3, 123.0, 121.5, 119.5, 116.8, 116.1, 111.3, 105.0, 69.9, 56.4, 56.2, 52.5, 24.4, 24.1, 14.1 ppm; HRMS: Calcd for $C_{27}H_{30}O_6N$ $[M+H]^+$: 464.20676, Found: 464.20689.

Compound **96ad:**



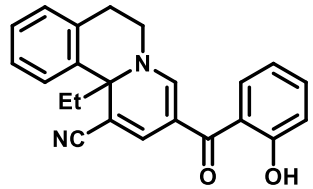
Compound **96ad** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 7.90 (s, 1H), 7.62 (s, 1H), 7.41 – 7.34 (m, 2H), 7.23 (d, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.90 (s, 1H), 6.87 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.69 – 3.58 (m, 5H), 3.15 – 3.09 (m, 1H), 2.90 – 2.84 (m, 1H), 2.11 - 1.78 (m, 11H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2, 171.2, 166.1, 149.8, 146.3, 146.1, 135.8, 134.0, 133.0, 130.9, 124.2, 120.9, 120.6, 118.0, 116.9, 116.3, 111.0, 108.2, 68.7, 56.1, 55.7, 52.0, 49.6, 42.1, 26.8, 26.6, 26.5, 26.1, 26.0, 24.3 ppm; HRMS: Calcd for $C_{30}H_{34}O_6N$ $[M+H]^+$: 504.23806, Found: 504.23789.

Compound **96ae:**



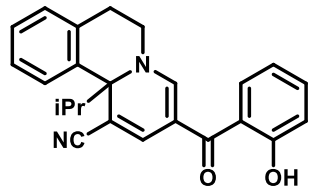
Compound **96ae** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (s, 1H), 7.91 (s, 1H), 7.57 (s, 1H), 7.41 – 7.35 (m, 2H), 7.19 – 7.06 (m, 4H), 6.98 – 6.94 (m, 2H), 3.80 – 3.74 (m, 1H), 3.72 (td, *J* = 14.1, 5.6 Hz, 1H), 3.64 (s, 3H), 3.24 (dd, *J* = 14.2, 4.1 Hz, 1H), 3.00 (dd, *J* = 14.2, 4.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.8, 164.7, 149.5, 136.7, 136.3, 136.0, 134.0, 133.5, 130.8, 124.3, 121.8, 120.9, 120.5, 117.5, 116.8, 116.1, 111.4, 108.8, 66.6, 55.0, 49.5, 25.3 ppm; HRMS: Calcd for $C_{22}H_{19}O_2N_2$ $[M+H]^+$: 343.14420, Found: 343.14417; $[\alpha]_D^{20}$ -13.2 ° (c 0.002 in ethanol).

Compound **96af:**



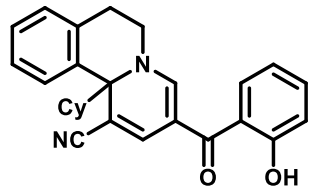
Compound **96af** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 7.94 (s, 1H), 7.56 (s, 1H), 7.45 – 7.38 (m, 2H), 7.23 (d, *J* = 7.0 Hz, 1H), 7.16 – 7.10 (m, 3H), 7.00 – 6.95 (m, 2H), 3.84 – 3.78 (m, 1H), 3.73 – 3.68 (m, 1H), 3.32 (q, *J* = 7.7 Hz, 2H), 3.17 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.98 (dd, *J* = 14.0, 4.0 Hz, 1H), 1.93 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 167.5, 164.1, 149.6, 136.8, 136.0, 135.9, 134.2, 133.5, 130.9, 121.9, 120.7, 120.5, 117.6, 116.7, 116.2, 111.2, 108.5, 68.7, 49.5, 26.6, 25.0, 14.6 ppm; HRMS: Calcd for $C_{23}H_{21}O_2N_2$ $[M+H]^+$: 357.15975, Found: 357.15953.

Compound **96ag:**



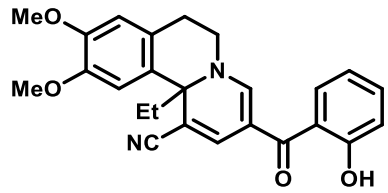
Compound **96ag** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (s, 1H), 8.03 (s, 1H), 7.57 (s, 1H), 7.41 – 7.31 (m, 2H), 7.19 – 7.07 (m, 4H), 6.98 – 6.91 (m, 2H), 3.84 – 3.78 (m, 1H), 3.73 – 3.67 (m, 1H), 3.17 – 3.13 (m, 1H), 2.94 – 2.87 (m, 2H), 1.61 (d, J = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7, 164.3, 149.4, 136.7, 136.8, 136.2, 134.3, 133.4, 130.7, 124.4, 121.6, 120.8, 120.0, 117.4, 116.7, 116.1, 114.0, 111.0, 108.6, 68.7, 49.4, 38.8, 25.2, 16.3 ppm; HRMS: Calcd for $C_{24}H_{23}O_2N_2$ $[M+H]^+$: 371.17540, Found: 371.17513.

Compound **96ah:**



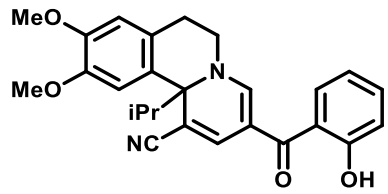
Compound **96ah** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 7.92 (s, 1H), 7.58 (s, 1H), 7.42 – 7.34 (m, 2H), 7.19 – 7.09 (m, 4H), 6.99 – 6.92 (m, 2H), 3.78 – 3.73 (m, 2H), 3.15 – 3.11 (m, 1H), 2.95 – 2.89 (m, 1H); 2.10 – 1.71 (m, 11H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1, 166.2, 149.7, 136.7, 136.0, 135.9, 134.4, 133.0, 130.8, 124.3, 120.9, 120.3, 117.6, 116.7, 116.2, 115.5, 111.4, 108.7, 68.9, 49.9, 42.3, 26.7, 26.6, 26.5, 26.2, 26.0, 24.9 ppm; HRMS: Calcd for $C_{27}H_{27}O_2N_2$ $[M+H]^+$: 411.20670, Found: 411.20641.

Compound **96ai:**



Compound **96ai** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 7.86 (s, 1H), 7.70 (s, 1H), 7.47 – 7.41 (m, 2H), 7.21 – 7.13 (m, 2H), 6.98 (s, 1H), 6.88 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.53 – 3.47 (m, 1H), 3.42 – 3.37 (m, 1H), 3.34 (q, J = 7.8 Hz, 2H), 3.12 (dd, J = 13.9, 4.0 Hz, 1H), 2.98 (dd, J = 13.9, 4.0 Hz, 1H), 1.99 (t, J = 7.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 166.1, 158.9, 145.2, 135.2, 132.0, 131.7, 131.1, 128.6, 127.4, 127.2, 123.0, 121.6, 119.5, 116.7, 116.2, 116.1, 111.4, 104.9, 69.8, 56.7, 56.6, 24.3, 24.1, 14.0 ppm; HRMS: Calcd for $C_{25}H_{25}O_4N_2$ $[M+H]^+$: 417.18088, Found: 417.18067.

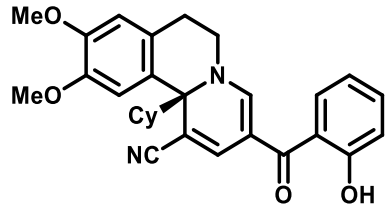
Compound **96aj:**



Compound **96aj** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 7.87 (s, 1H), 7.74 (s, 1H), 7.45 – 7.39 (m, 2H), 7.20 – 7.13 (m, 2H), 6.98 (s, 1H), 6.88 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.51 – 3.47 (m, 1H), 3.43 – 3.37 (m, 1H), 3.18

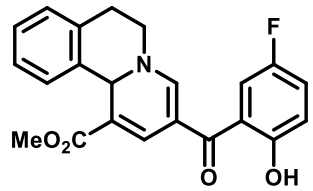
(dd, *J* = 14.0, 4.0 Hz, 1H), 2.94 - 2.87 (m, 2H); 1.66 (d, J = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 166.1, 158.3, 145.1, 135.9, 132.7, 131.6, 131.0, 128.8, 127.4, 127.2, 123.0, 121.7, 119.5, 116.7, 116.1, 111.2, 105.3, 70.0, 56.3, 56.2, 55.3, 24.2, 24.1, 14.4 ppm; HRMS: Calcd for $C_{26}H_{26}O_4N_2$ $[M+H]^+$: 431.19653, Found: 431.19647.

Compound **96ak:**



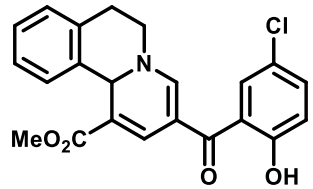
Compound **96ak** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.14 (s, 1H), 7.91 (s, 1H), 7.61 (s, 1H), 7.40 – 7.32 (m, 2H), 7.22 (d, *J* = 7.4 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.91 (s, 1H), 6.89 (s, 1H), 3.80 (d, 6H), 3.69 – 3.58 (m, 2H), 3.16 – 3.03 (m, 1H), 2.89 – 2.83 (m, 1H), 2.12-1.71 (m, 11H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 164.0, 149.7, 146.5, 146.1, 135.7, 134.0, 133.2, 130.9, 124.1, 120.9, 120.5, 118.1, 117.6, 116.5, 116.2, 111.1, 108.7, 68.5, 56.0, 55.8, 49.6, 42.2, 26.8, 26.7, 26.5, 26.2, 26.1, 24.2 ppm; HRMS: Calcd for $C_{29}H_{31}O_4N_2$ $[M+H]^+$: 471.22783, Found: 471.22780; $[\alpha]_D^{20}$ -17.4 ° (c 0.002 in ethanol).

Compound **96al:**



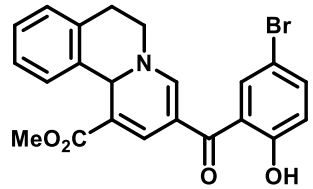
Compound **96al** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.41 – 7.32 (m, 3H), 7.22 – 7.13 (m, 2H), 6.99 – 6.95 (d, *J* = 8.3 Hz, 1H), 5.99 (s, 1H), 3.82 – 3.74 (m, 5H), 3.22 – 3.18 (m, 1H), 2.97 (dd, *J* = 13.9, 3.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 167.2, 159.6, 153.4, 138.4, 136.2, 135.6, 134.3, 131.7, 129.8, 127.4, 125.8, 122.4, 120.8, 120.4, 114.7, 112.2, 105.9, 68.7, 52.7, 50.6, 23.4 ppm; HRMS: Calcd for $C_{22}H_{19}O_4NF$ $[M+H]^+$: 380.12926, Found: 380.12898.

Compound **96am:**



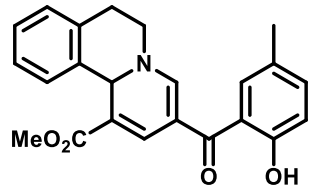
Compound **96am** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (s, 1H), 7.94 (d, *J* = 1.9 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.39 – 7.31 (m, 3H), 7.21 – 7.14 (m, 2H), 6.98 - 6.95 (d, *J* = 8.2 Hz, 1H), 6.03 (s, 1H), 3.83 – 3.77 (m, 5H), 3.23 – 3.19 (m, 1H), 2.95 (dd, *J* = 14.1, 3.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 167.8, 159.8, 153.6, 138.4, 136.3, 135.6, 134.1, 131.7, 129.7, 127.2, 125.9, 122.4, 120.7, 120.3, 114.3, 112.1, 105.9, 68.6, 52.6, 50.8, 23.7 ppm; HRMS: Calcd for $C_{22}H_{19}O_4NCl$ $[M+H]^+$: 396.09971, Found: 396.09949.

Compound **96an:**



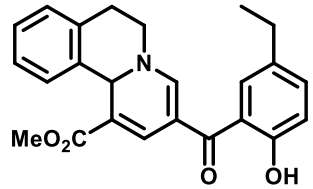
Compound **96an** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.16 (s, 1H), 7.94 (d, *J* = 1.9 Hz, 1H), 7.66 (d, *J* = 1.9 Hz, 1H), 7.47 – 7.42 (m, 4H), 7.23 – 7.15 (m, 2H), 7.01 - 6.97 (d, *J* = 8.2 Hz, 1H), 6.00 (s, 1H), 3.83 – 3.76 (m, 5H), 3.23 – 3.18 (m, 1H), 2.96 (dd, *J* = 14.0, 4.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0, 167.4, 159.4, 153.2, 138.3, 136.7, 135.6, 134.1, 131.8, 129.8, 127.5, 125.8, 122.7, 120.9, 120.7, 114.6, 112.2, 105.6, 68.8, 52.5, 50.6, 23.1 ppm; HRMS: Calcd for $C_{22}H_{19}O_4NBr$ $[M+H]^+$: 440.04920, Found: 440.04904.

Compound **96ao:**



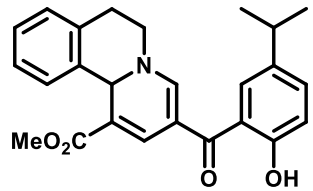
Compound **96ao** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.14 (s, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.20 – 7.14 (m, 2H), 6.99 – 6.95 (d, *J* = 8.1 Hz, 1H), 6.00 (s, 1H), 3.82 – 3.75 (m, 5H), 3.22 – 3.17 (m, 1H), 3.00 (dd, *J* = 13.9, 3.9 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 167.7, 159.9, 153.5, 138.4, 136.3, 135.6, 134.2, 131.8, 129.6, 127.2, 125.5, 122.4, 121.0, 120.3, 114.2, 112.1, 105.8, 68.7, 52.6, 50.5, 24.6, 23.7 ppm; HRMS: Calcd for $C_{23}H_{22}O_4N$ $[M+H]^+$: 376.15433, Found: 376.15412.

Compound **96ap:**



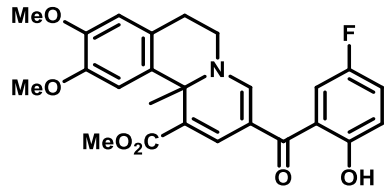
Compound **96ap** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.62 (d, *J* = 2.4 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.30 (m, 3H), 7.21 – 7.14 (m, 2H), 6.98 – 6.94 (d, *J* = 8.0 Hz, 1H), 6.04 (s, 1H), 3.81 – 3.74 (m, 5H), 3.23 – 3.17 (m, 1H), 2.94 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.71 (q, *J* = 8.1 Hz, 2H), 1.34 (t, *J* = 8.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0, 167.9, 159.4, 153.7, 138.5, 136.6, 135.3, 134.1, 131.9, 129.5, 127.3, 125.6, 122.9, 121.2, 120.2, 114.9, 112.0, 107.4, 68.9, 52.4, 50.1, 28.3, 23.7, 15.1 ppm; HRMS: Calcd for $C_{24}H_{24}O_4N$ $[M+H]^+$: 390.16998, Found: 390.16967.

Compound **96aq:**



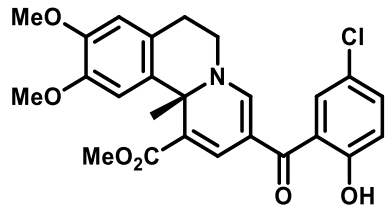
Compound **96aq** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.30 (m, 3H), 7.20 – 7.14 (m, 2H), 6.98 – 6.93 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 1H), 3.80 – 3.74 (m, 5H), 3.23 – 3.16 (m, 1H), 2.96 (dd, *J* = 13.8, 4.1 Hz, 1H), 2.80 (t, *J* = 7.0 Hz, 1H), 1.30 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 167.8, 159.3, 153.8, 138.4, 136.7, 135.3, 134.2, 131.8, 129.5, 127.4, 125.6, 123.2, 120.9, 120.2, 114.7, 112.5, 107.3, 69.2, 52.3, 50.2, 33.1, 23.6, 23.2 ppm; HRMS: Calcd for $C_{25}H_{26}O_4N$ $[M+H]^+$: 404.18563, Found: 404.18537.

Compound **96ar:**



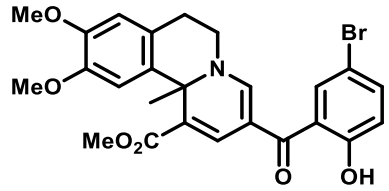
Compound **96ar** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 7.88 (s, 1H), 7.51 (s, 1H), 7.43 (s, 1H), 7.30 (d, *J* = 5.0 Hz, 1H), 7.10 (d, *J* = 5.2 Hz, 1H), 6.92 (s, 1H), 6.89 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.69 – 3.63 (m, 4H), 3.51 – 3.46 (m, 4H), 3.13 – 3.07 (m, 1H), 2.87 – 2.83 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.7, 171.2, 165.4, 149.5, 146.0, 145.8, 135.6, 134.2, 133.2, 130.8, 128.2, 124.1, 120.4, 118.0, 116.3, 116.2, 111.1, 108.4, 68.6, 55.6, 51.2, 49.2, 25.3, 24.1 ppm; HRMS: Calcd for $C_{25}H_{25}O_6NF$ $[M+H]^+$: 454.16604, Found: 455.16571.

Compound **96as:**



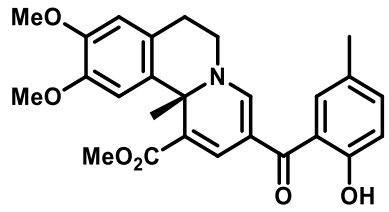
Compound **96as** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.30 (s, 1H), 7.90 (s, 1H), 7.59 (s, 1H), 7.46 (s, 1H), 7.30 (d, *J* = 5.9 Hz, 1H), 7.03 (d, *J* = 5.9 Hz, 1H), 6.90 (s, 1H), 6.85 (s, 1H), 3.82 (d, 6H), 3.68 – 3.61 (m, 4H), 3.52 – 3.46 (m, 5H), 3.14 – 3.09 (m, 1H), 2.89 – 2.85 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.7, 170.4, 165.4, 149.5, 146.0, 145.9, 135.7, 134.1, 133.3, 130.6, 128.2, 124.1, 120.8, 117.5, 116.6, 116.1, 111.1, 108.6, 68.7, 55.7, 51.3, 49.3, 25.0, 24.1 ppm; HRMS: Calcd for $C_{24}H_{26}O_6NCl$ $[M+H]^+$: 470.13649, Found: 470.13643; $[\alpha]_D^{20}$ -9.8 ° (c 0.002 in ethanol).

Compound **96at:**



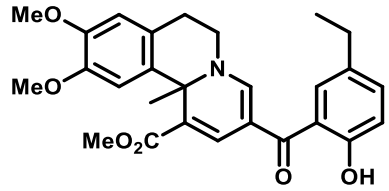
Compound **96at** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 7.89 (s, 1H), 7.62 (s, 1H), 7.45 (s, 1H), 7.31 (d, *J* = 6.0 Hz, 1H), 7.04 (d, *J* = 6.0 Hz, 1H), 6.92 (s, 1H), 6.89 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.70 – 3.63 (m, 4H), 3.51 – 3.45 (m, 4H), 3.13 – 3.09 (m, 1H), 2.88 – 2.84 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 170.7, 165.5, 149.6, 146.0, 145.7, 135.5, 134.1, 133.2, 130.7, 128.2, 124.2, 120.7, 117.6, 116.4, 116.1, 111.1, 108.5, 68.6, 55.7, 51.3, 51.2, 49.3, 25.3, 24.2 ppm; HRMS: Calcd for $C_{25}H_{25}O_6NBr$ $[M+H]^+$: 514.085098, Found: 514.08574.

Compound **96au:**



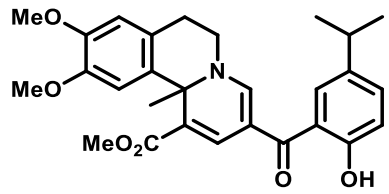
Compound **96au** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.26 (s, 1H), 7.89 (s, 1H), 7.60 (s, 1H), 7.45 (s, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.91 (s, 1H), 6.86 (s, 1H), 3.80 (d, 6H), 3.68 – 3.61 (m, 4H), 3.50 – 3.44 (m, 4H), 3.15 – 3.09 (m, 1H), 2.89 – 2.82 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1, 169.5, 164.4, 149.4, 146.1, 146.0, 135.7, 134.0, 133.2, 130.7, 124.1, 120.7, 120.4, 117.5, 116.5, 116.1, 111.7, 108.6, 68.6, 56.1, 55.8, 51.2, 49.4, 25.0, 24.5, 21.3 ppm; HRMS: Calcd for $C_{26}H_{28}O_6N$ $[M+H]^+$: 450.19111, Found: 450.19103; $[\alpha]_D^{20}$ -12.9 ° (c 0.002 in ethanol).

Compound **96av:**



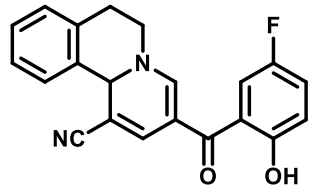
Compound **96av** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 7.91 (s, 1H), 7.61 (s, 1H), 7.47 (s, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 6.98 - 6.95 (m, 2H), 6.88 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.66 – 3.62 (m, 4H), 3.51 – 3.45 (m, 4H), 3.15 – 3.10 (m, 1H), 2.87 – 2.83 (m, 1H), 2.72 (q, *J* = 8.0 Hz, 2H), 1.31 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 170.3, 164.8, 149.2, 146.1, 145.9, 135.7, 134.2, 133.1, 130.6, 124.4, 120.8, 120.4, 117.4, 116.6, 116.2, 111.7, 108.8, 68.6, 56.2, 55.7, 51.2, 49.5, 29.2, 25.3, 21.4, 15.0 ppm; HRMS: Calcd for $C_{27}H_{30}O_6N$ $[M+H]^+$: 464.20676, Found: 464.20651.

Compound **96aw:**



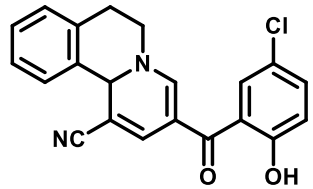
Compound **96aw** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 7.90 (s, 1H), 7.62 (s, 1H), 7.48 (s, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 6.99 – 6.94 (m, 2H), 6.89 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.65 – 3.61 (m, 4H), 3.50 – 3.45 (m, 4H), 3.16 – 3.11 (m, 1H), 2.87 – 2.81 (m, 2H), 1.22 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 170.1, 164.9, 149.3, 146.2, 145.8, 135.7, 134.3, 133.1, 130.7, 124.5, 120.6, 120.5, 117.3, 116.8, 116.2, 111.6, 108.4, 68.6, 56.1, 55.8, 51.2, 49.6, 34.0, 30.7, 25.2, 21.2 ppm; HRMS: Calcd for $C_{28}H_{32}O_6N$ $[M+H]^+$: 478.22241, Found: 478.22217.

Compound **96ax:**



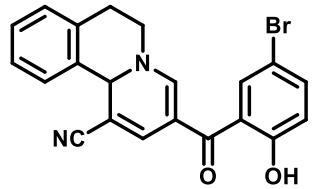
Compound **96ax** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H), 7.89 (d, *J* = 2.7 Hz, 1H), 7.64 (d, *J* = 2.7 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.39 – 7.33 (m, 3H), 7.20 – 7.15 (m, 2H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.04 (s, 1H), 3.81 – 3.74 (m, 2H), 3.19 – 3.13 (m, 1H), 2.94 (dd, *J* = 14.1, 3.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 159.7, 153.5, 138.5, 136.3, 135.7, 134.2, 131.9, 129.6, 127.3, 125.5, 122.7, 121.0, 120.2, 114.3, 113.6, 112.1, 106.0, 69.2, 52.1, 24.2 ppm; HRMS: Calcd for $C_{21}H_{16}O_2N_2F$ $[M+H]^+$: 347.11903, Found: 347.11869.

Compound **96ay:**



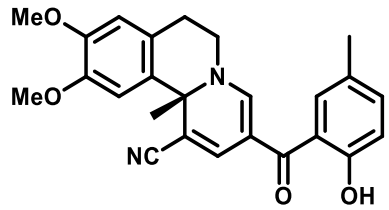
Compound **96ay** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (s, 1H), 7.93 (d, *J* = 2.3 Hz, 1H), 7.71 (d, *J* = 2.4 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.29 (m, 3H), 7.22 – 7.17 (m, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 5.98 (s, 1H), 3.80 – 3.75 (m, 2H), 3.18 – 3.13 (m, 1H), 3.00 (dd, *J* = 13.7, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 160.2, 153.7, 138.4, 136.2, 135.7, 134.5, 131.9, 129.9, 127.3, 125.3, 122.7, 121.0, 120.8, 114.3, 113.7, 112.1, 105.4, 69.1, 52.3, 24.3 ppm; HRMS: Calcd for $C_{21}H_{16}O_2N_2Cl$ $[M+H]^+$: 363.08948, Found: 363.08911.

Compound **96az:**



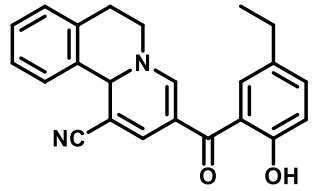
Compound **96az** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.05 (s, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.29 (m, 3H), 7.23 – 7.17 (m, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.03 (s, 1H), 3.82 – 3.76 (m, 2H), 3.19 – 3.14 (m, 1H), 2.99 (dd, *J* = 13.8, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 159.8, 153.9, 138.6, 136.2, 135.5, 134.4, 131.9, 129.8, 127.8, 125.6, 122.4, 121.2, 120.7, 114.2, 113.7, 112.3, 105.7, 69.8, 52.4, 24.4 ppm; HRMS: Calcd for $C_{21}H_{16}O_2N_2Br$ $[M+H]^+$: 407.03897, Found: 407.03861.

Compound **96ba:**



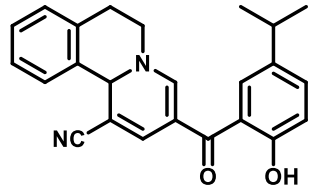
Compound **96ba** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 7.88 (s, 1H), 7.60 (s, 1H), 7.44 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 8.0 Hz, 1H), 6.92 (s, 1H), 6.87 (s, 1H), 3.82 (d, 6H), 3.67 – 3.59 (m, 1H), 3.49 – 3.43 (m, 4H), 3.16 – 3.10 (m, 1H), 2.89 – 2.83 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 164.5, 150.1, 146.5, 146.2, 135.5, 134.9, 133.1, 130.6, 124.2, 120.6, 120.5, 118.1, 117.6, 116.4, 116.1, 111.1, 108.5, 68.4, 56.2, 55.7, 49.6, 25.1, 24.6, 22.0 ppm; HRMS: Calcd for $C_{25}H_{25}O_4N_2$ $[M+H]^+$: 417.18088, Found: 417.18086; $[\alpha]_D^{20}$ -13.4 ° (c 0.002 in ethanol).

Compound **96bb:**



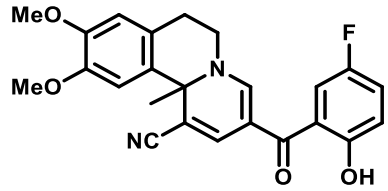
Compound **96bb** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.37 – 7.31 (m, 3H), 7.22 – 7.16 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 5.99 (s, 1H), 3.80 – 3.75 (m, 2H), 3.23 – 3.19 (m, 1H), 2.99 (dd, *J* = 14.1, 4.0 Hz, 1H), 2.74 (q, *J* = 8.0 Hz, 2H), 1.33 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.4, 160.2, 153.6, 138.7, 136.2, 135.8, 134.1, 131.9, 129.6, 127.3, 125.4, 122.4, 122.1, 120.9, 114.3, 113.4, 112.1, 105.9, 68.8, 51.0, 28.5, 24.6, 15.1 ppm; HRMS: Calcd for $C_{23}H_{21}O_2N_2$ $[M+H]^+$: 357.15975, Found: 357.15949.

Compound **96bc:**



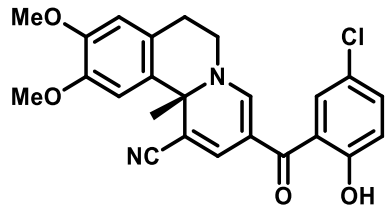
Compound **96bc** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.37 – 7.31 (m, 3H), 7.19 – 7.14 (m, 2H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.03 (s, 1H), 3.81 – 3.74 (m, 2H), 3.23 – 3.15 (m, 1H), 2.98 (dd, *J* = 14.0, 4.1 Hz, 1H), 2.82 (t, *J* = 7.0 Hz, 1H), 1.33 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 159.3, 153.5, 138.3, 136.6, 135.4, 134.1, 131.9, 129.6, 127.3, 125.6, 123.1, 122.0, 120.4, 114.7, 113.6, 112.4, 107.4, 69.0, 50.3, 33.4, 23.5, 23.1 ppm; HRMS: Calcd for $C_{24}H_{23}O_2N_2$ $[M+H]^+$: 371.17540, Found: 371.17517.

Compound **96bd:**



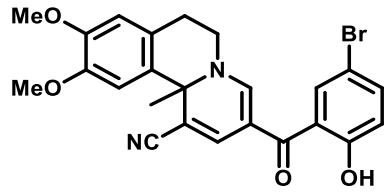
Compound **96bd** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 7.85 (s, 1H), 7.56 (s, 1H), 7.43 (s, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.97 (s, 1H), 6.90 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.64 – 3.59 (m, 1H), 3.50 – 3.46 (m, 4H), 3.17 – 3.12 (m, 1H), 2.89 – 2.84 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 164.5, 150.3, 146.5, 146.3, 135.6, 134.9, 133.1, 130.6, 127.1, 124.3, 120.4, 120.2, 118.1, 116.4, 116.2, 111.4, 108.6, 68.4, 56.7, 55.8, 49.4, 24.7, 24.3 ppm; HRMS: Calcd for $C_{24}H_{22}O_4N_2F$ $[M+H]^+$: 421.15581, Found: 421.15559.

Compound **96be:**



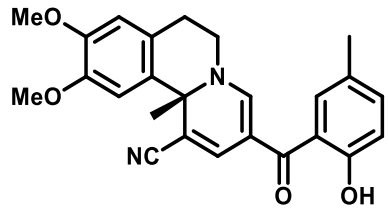
Compound **96be** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 7.87 (s, 1H), 7.58 (s, 1H), 7.42 (s, 1H), 7.21 (d, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.93 (s, 1H), 6.88 (s, 1H), 3.78 (d, 6H), 3.66 – 3.59 (m, 1H), 3.49 – 3.44 (m, 4H), 3.16 – 3.11 (m, 1H), 2.90 – 2.85 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 164.4, 150.2, 146.4, 146.3, 135.6, 134.8, 133.0, 130.7, 127.1, 124.1, 120.5, 120.3, 118.2, 116.5, 116.1, 111.4, 108.5, 68.4, 56.3, 55.9, 49.3, 24.9, 24.2 ppm; HRMS: Calcd for $C_{24}H_{22}O_4N_2Cl$ $[M+H]^+$: 437.12626, Found: 437.12623; $[\alpha]_D^{20}$ -8.6 ° (c 0.002 in ethanol).

Compound **96bf:**



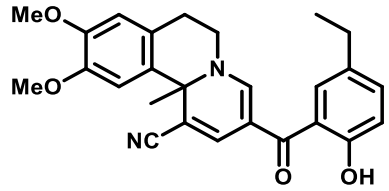
Compound **96bf** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 7.88 (s, 1H), 7.57 (s, 1H), 7.41 (s, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.90 (s, 1H), 6.87 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.66 – 3.60 (m, 1H), 3.5 – 3.46 (m, 4H), 3.14 – 3.10 (m, 1H), 2.90 – 2.86 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 165.2, 150.3, 146.6, 146.0, 135.5, 134.8, 133.0, 130.8, 127.1, 124.2, 120.5, 120.2, 118.1, 116.4, 116.0, 111.4, 108.6, 68.4, 56.7, 55.7, 49.2, 24.9, 24.3 ppm; HRMS: Calcd for $C_{24}H_{22}O_4N_2Br$ $[M+H]^+$: 481.07575, Found: 481.07548.

Compound **96bg:**



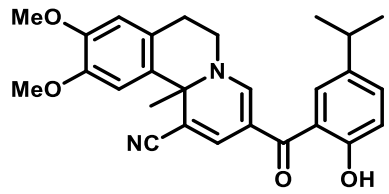
Compound **96bg** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 7.88 (s, 1H), 7.60 (s, 1H), 7.44 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 8.0 Hz, 1H), 6.92 (s, 1H), 6.87 (s, 1H), 3.82 (d, 6H), 3.67 – 3.59 (m, 1H), 3.49 – 3.43 (m, 4H), 3.16 – 3.10 (m, 1H), 2.89 – 2.83 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 164.5, 150.1, 146.5, 146.2, 135.5, 134.9, 133.1, 130.6, 124.2, 120.6, 120.5, 118.1, 117.6, 116.4, 116.1, 111.1, 108.5, 68.4, 56.2, 55.7, 49.6, 25.1, 24.6, 22.0 ppm; HRMS: Calcd for $C_{25}H_{25}O_4N_2$ $[M+H]^+$: 417.18088, Found: 417.18086; $[\alpha]_D^{20}$ -13.4 ° (c 0.002 in ethanol).

Compound **96bh:**



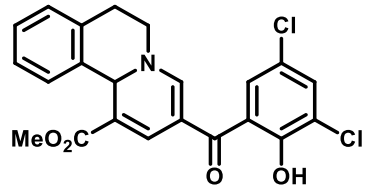
Compound **96bh** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (s, 1H), 7.90 (s, 1H), 7.63 (s, 1H), 7.45 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 6.98 (t, *J* = 8.0 Hz, 1H), 6.93 (s, 1H), 6.85 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.66 – 3.62 (m, 1H), 3.49 – 3.44 (m, 4H), 3.15 – 3.10 (m, 1H), 2.90 – 2.85 (m, 1H), 2.72 (q, *J* = 8.0 Hz, 2H), 1.31 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 164.6, 150.0, 146.7, 146.1, 135.4, 134.8, 133.0, 130.7, 124.1, 120.5, 120.4, 118.0, 117.5, 116.3, 116.0, 111.1, 108.7, 68.4, 56.0, 55.6, 49.5, 28.0, 25.2, 24.6, 14.9 ppm; HRMS: Calcd for $C_{26}H_{27}O_4N_2$ $[M+H]^+$: 431.19653, Found: 431.19619.

Compound **96bi:**



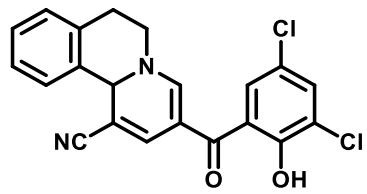
Compound **96bi** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (s, 1H), 7.90 (s, 1H), 7.63 (s, 1H), 7.45 (s, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 6.98 (t, *J* = 8.0 Hz, 1H), 6.91 (s, 1H), 6.88 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.65 – 3.60 (m, 1H), 3.50 – 3.44 (m, 4H), 3.16 – 3.11 (m, 1H), 2.87 – 2.81 (m, 2H), 1.22 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.0, 166.2, 150.0, 146.7, 146.2, 135.6, 134.9, 133.2, 130.5, 124.3, 120.7, 120.4, 118.1, 117.7, 116.4, 116.2, 111.1, 108.6, 68.5, 56.3, 49.7, 33.2, 25.1, 24.8, 23.2, 22.1 ppm; HRMS: Calcd for $C_{27}H_{29}O_4N_2$ $[M+H]^+$: 445.21218, Found: 445.21197.

Compound **96bj:**



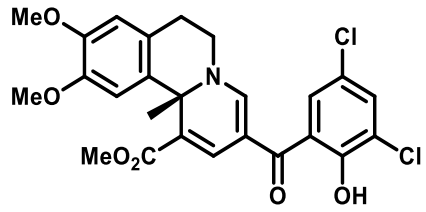
Compound **96bj** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.95 (s, 1H), 7.87 (s, 1H), 7.74 (s, 1H), 7.63 (s, 1H), 7.28 – 7.22 (m, 3H), 7.01 (s, 1H), 6.88 (s, 1H), 6.12 (s, 1H), 3.58 (s, 3H), 3.53 – 3.49 (m, 1H), 3.42 – 3.35 (m, 1H), 2.94 – 2.89 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 170.5, 164.7, 158.8, 135.4, 135.1, 132.1, 131.8, 131.5, 128.5, 127.4, 127.3, 123.4, 119.4, 116.0, 111.2, 104.7, 70.3, 67.8, 54.1, 52.2, 24.0 ppm; HRMS: Calcd for $C_{22}H_{18}O_4NCl_2$ $[M+H]^+$: 430.06074, Found: 430.06036.

Compound **96bk:**



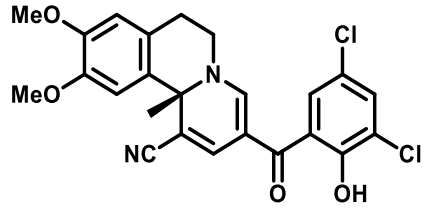
Compound **96bk** was synthesized according to the racemic general procedure. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.81 (s, 1H), 7.88 (s, 1H), 7.75 (s, 1H), 7.63 (s, 1H), 7.29 (s, 1H), 7.00 (s, 1H), 6.88 (s, 1H), 6.14 (s, 1H), 3.54 – 3.50 (m, 1H), 3.42 – 3.37 (m, 1H), 2.95 – 2.89 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 164.7, 158.8, 135.4, 135.1, 132.1, 131.8, 131.5, 128.5, 127.4, 127.3, 123.4, 121.2, 119.4, 116.0, 114.2, 111.2, 104.7, 70.3, 67.8, 52.2, 25.1 ppm; HRMS: Calcd for $C_{21}H_{15}O_2N_2Cl_2$ $[M+H]^+$: 397.05051, Found: 397.05023.

Compound **96bl:**



Compound **96bl** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (s, 1H), 7.85 (s, 1H), 7.73 (s, 1H), 7.62 (s, 1H), 7.29 (s, 1H), 7.00 (s, 1H), 6.89 (s, 1H), 3.74 (s ,3H), 3.73 (s, 3H), 3.58 (s, 3H), 3.52 – 3.48 (m, 1H), 3.42 – 3.34 (m, 4H), 2.94 – 2.83 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 170.1, 164.5, 158.8, 135.3, 135.0, 132.1, 131.7, 131.0, 128.6, 127.5, 127.3, 123.4, 121.4, 119.5, 116.1, 111.2, 104.6, 70.4, 67.9, 56.3, 56.2, 52.2, 49.7, 24.0 ppm; HRMS: Calcd for $C_{25}H_{243}O_6N$ $[M+H]^+$: 504.09752, Found: 504.09747; $[\alpha]_D^{20}$ -13.8 ° (c 0.002 in ethanol).

Compound **96bm:**



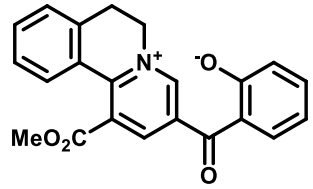
Compound **96bm** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.04 (s, 1H), 7.82 (s, 1H), 7.74 (s, 1H), 7.60 (s, 1H), 7.27 (s, 1H), 6.97 (s, 1H), 6.88 (s, 1H), 3.75 (s ,3H), 3.74 (s, 3H), 3.51 – 3.47 (m, 1H), 3.41 – 3.36 (m, 4H); 2.93 – 2.81 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 164.1, 158.6, 135.4, 135.0, 132.4, 131.6, 131.1, 128.5, 127.5, 127.3,

123.4, 121.5, 119.5, 117.4, 116.0, 111.2, 104.2, 70.3, 67.8, 56.4, 56.3, 49.7, 24.5 ppm; HRMS: Calcd for $C_{24}H_{21}O_4N_2$ $[M+H]^+$: 471.08729, Found: 471.08726; $[\alpha]_D^{20}$ -13.4 ° (c 0.002 in ethanol).

Synthesis of Benzopyridinium 97

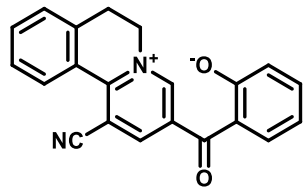
The benzopyridinium **97** were synthesized following the standard procedure for the synthesis of indolopyridiniums **87**.

Compound **97a:**



Compound **97a** was synthesized according to the general procedure. Red amorphous solid; TLC (ethyl acetate): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.97 (s, 1H), 9.42 (s, 1H), 9.08 (s, 1H), 7.74 (s, 1H), 7.40 – 7.16 (m, 5H), 6.94 – 6.90 (m, 1H), 5.22 (t, J = 9.0 Hz, 2H), 3.94 (s, 3H), 3.46 (t, J = 9.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8, 165.4, 164.6, 153.8, 150.9, 138.1, 135.4, 132.3, 131.3, 127.6, 122.2, 121.6, 120.4, 119.4, 118.4, 117.3, 113.1, 111.4, 104.9, 70.7, 60.2, 22.6 ppm; HRMS: Calcd for $C_{22}H_{18}O_4N$ $[M+H]^+$: 360.12303, Found: 360.12298.

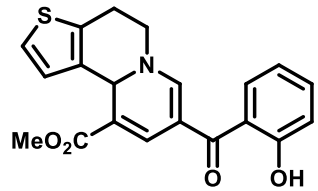
Compound **97b:**



Compound **97b** was synthesized according to the general procedure. Red amorphous solid; TLC (ethyl acetate): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.96 (s, 1H), 9.42 (s, 1H), 9.07 (s, 1H), 7.75 (s, 1H), 7.39 – 7.18 (m, 6H), 5.18 (t, *J* = 9.1 Hz, 2H), 3.41 (t, *J* = 9.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 165.3, 153.6, 150.9, 136.4, 135.4, 132.2, 131.7, 127.7, 123.5, 122.0, 121.5, 120.3, 119.4, 118.2, 117.4, 113.1, 111.4, 104.7, 65.2, 22.4 ppm; HRMS: Calcd for $C_{21}H_{15}O_2N_2$ $[M+H]^+$: 327.11280, Found: 327.11247.

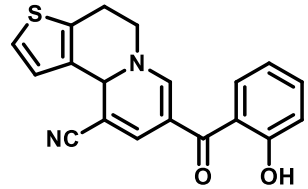
III.4.4. Synthesis of Ring-Fused Quinolizines 98-101

Compound **98a:**



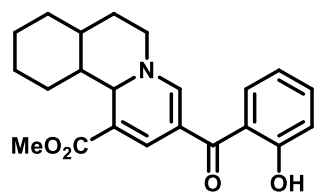
Compound **98a** was synthesized according to the racemic general procedure. Orange amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) 11.72 (s, 1H), 8.10 (s, 1H), 7.74 – 7.66 (m, 2H), 7.53 – 7.48 (m, 2H), 7.32 (s, 1H), 7.05 – 6.99 (m, 2H), 6.10 (s, 1H), 3.72 (s, 3H), 3.14 – 3.10 (m, 2H), 3.02 – 2.97 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8, 169.9, 168.5, 153.9, 136.2, 135.4, 134.0, 131.5, 128.0, 126.0, 124.0, 123.3, 123.2, 121.5, 120.1, 118.4, 68.3, 54.2, 52.9, 23.4 ppm; HRMS: Calcd for $C_{20}H_{18}O_4NS$ $[M+H]^+$: 368.09511, Found: 368.09509.

Compound **98b:**



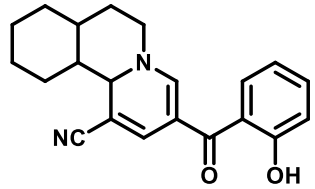
Compound **98b** was synthesized according to the racemic general procedure. Orange amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) 11.74 (s, 1H), 8.08 (s, 1H), 7.75 – 7.66 (m, 2H), 7.52 – 7.46 (m, 2H), 7.33 (s, 1H), 7.06 – 6.99 (m, 2H), 6.15 (s, 1H), 3.18 – 3.11 (m, 2H), 3.04 – 2.96 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 163.6, 152.6, 134.9, 134.8, 132.7, 131.6, 131.3, 126.7, 124.9, 124.2, 122.2, 121.4, 120.0, 118.7, 115.4, 70.0, 52.3, 25.0 ppm; HRMS: Calcd for $C_{19}H_{15}O_2N_2S$ $[M+H]^+$: 335.08487, Found: 335.08481.

Compound **99a:**



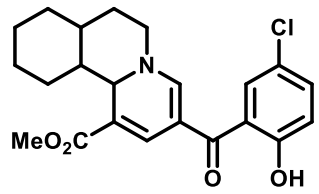
Compound **12a** was synthesized according to the racemic general procedure. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.59 (s, 1H), 7.91 (s, 1H), 7.52 – 7.42 (m, 3H), 7.27 (s, 1H), 6.96 (m, 1H), 5.11 (m, 1H), 3.61 (s, 3H), 2.94 – 2.86 (m, 2H), 1.63 – 1.31 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 169.2, 163.9, 151.5, 137.2, 130.8, 126.5, 122.2, 121.0, 118.2, 117.4, 115.6, 110.2, 62.1, 49.0, 37.6, 37.0, 32.4, 28.6, 26.4, 26.0, 25.5 ppm; HRMS: Calcd for $C_{22}H_{26}O_4N$ $[M+H]^+$: 368.18563, Found: 368.18561.

Compound **99b:**



Compound **99b** was synthesized according to the racemic general procedure. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.51 (s, 1H), 7.93 (s, 1H), 7.53 – 7.44 (m, 3H), 7.28 (s, 1H), 6.95 (m, 1H), 5.04 (m, 1H), 2.96 – 2.89 (m, 2H), 1.64 – 1.34 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 163.8, 151.2, 135.9, 130.1, 126.5, 122.7, 121.9, 120.0, 118.8, 117.4, 115.4, 110.1, 60.6, 37.7, 37.5, 32.4, 28.3, 27.0, 26.4, 25.2 ppm; HRMS: Calcd for $C_{21}H_{23}O_2N_2$ $[M+H]^+$: 335.17540, Found: 335.17536.

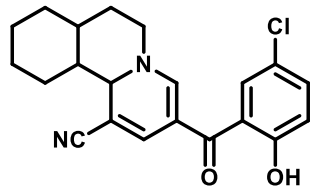
Compound **99c**:



Compound **99c** was synthesized according to the racemic general procedure. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.43 (s, 1H), 8.07 (s, 1H), 7.49 – 7.43 (m, 2H), 7.24 (s, 1H), 6.99 (d, J = 6.8 Hz, 1H), 5.14 (m, 1H), 3.55 (s, 3H), 2.91 – 2.86 (m, 2H), 1.58 – 1.32 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 169.6, 163.4, 151.4, 138.0, 137.0, 129.5, 126.4, 121.8, 118.0, 117.0, 115.4, 110.5,

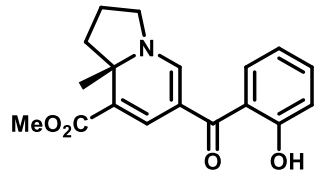
59.8, 49.1, 37.3. 37.0, 32.2, 28.6, 27.2, 26.8, 25.1 ppm; HRMS: Calcd for $C_{22}H_{25}O_4NCl$ $[M+H]^+$: 402.14666, Found: 402.14662.

Compound **99d:**



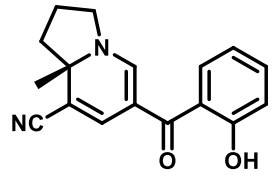
Compound **99d** was synthesized according to the general procedures. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (s, 1H), 8.05 (s, 1H), 7.48 – 7.42 (m, 2H), 7.26 (s, 1H), 7.01 (d, J = 7.0 Hz, 1H), 5.01 (m, 1H), 2.92 – 2.87 (m, 2H), 1.60 – 1.34 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 162.1, 153.7, 136.4, 130.1, 126.8, 122.2, 121.5, 120.1, 118.9, 117.8, 115.6, 110.3, 60.4, 38.0, 37.0, 32.9, 28.2, 27.3, 26.7, 25.5 ppm; HRMS: Calcd for $C_{21}H_{22}O_2N_2Cl$ $[M+H]^+$: 369.13643, Found: 369.13637.

Compound **100a:**



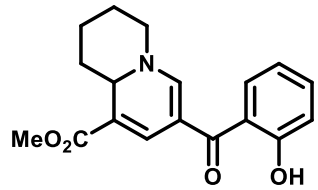
Compound **100a** was synthesized according to the general procedures. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.53 (s, 1H), 7.94 (s, 1H), 7.61 (s, 1H), 7.49 – 7.41 (m, 3H), 7.25 (s, 1H), 3.42 (s, 3H), 2.65 – 2.59 (m, 2H), 1.96 (s, 3H), 1.64 – 1.56 (m, 2H), 1.50 – 1.44 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.6, 170.1, 163.9, 153.6, 140.0, 137.1, 128.9, 126.4, 122.3, 121.0, 118.4, 115.9, 69.1, 53.1, 50.6, 44.9, 26.4, 22.1 ppm; HRMS: Calcd for $C_{18}H_{20}O_4N$ $[M+H]^+$: 314.13868, Found: 314.13687; $[\alpha]_D^{20}$ -18.8 ° (c 0.002 in ethanol).

Compound **100b:**



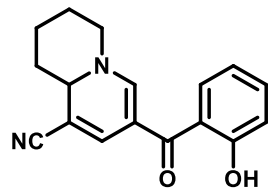
Compound **13b** was synthesized according to the general procedures. Red amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.49 (s, 1H), 7.92 (s, 1H), 7.47 – 7.40 (m, 3H), 7.24 (s, 1H), 7.02 – 6.99 (m, 1H), 2.63 – 2.60 (m, 2H), 2.00 (m, 3H), 1.66 – 1.59 (m, 2H), 1.51 – 1.46 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.0, 163.4, 153.2, 140.3, 137.6, 128.4, 126.6, 122.3, 121.0, 118.6, 117.3, 116.0, 69.2, 50.5, 44.8, 26.3, 22.5 ppm; HRMS: Calcd for $C_{17}H_{17}O_2N_2$ $[M+H]^+$: 281.12845, Found: 281.12842; $[\alpha]_D^{20}$ -19.4 ° (c 0.002 in ethanol).

Compound **101a:**



Compound **101a** was synthesized according to the racemic general procedure. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 7.98 (s, 1H), 7.50 – 7.41 (m, 3H), 7.31 (s, 1H), 7.02 (d, J = 6.9 Hz, 1H), 4.99 (m, 1H), 3.41 (s, 3H), 2.76 – 2.71 (m, 2H), 1.63 – 1.55 (m, 3H), 1.50 – 1.43 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 168.2, 163.5, 149.9, 137.6, 130.7, 127.3, 122.6, 121.9, 119.2, 115.6, 110.3, 61.3, 53.6, 50.1, 29.4, 26.3, 22.2 ppm; HRMS: Calcd for $C_{18}H_{20}O_4N$ $[M+H]^+$: 314.13868, Found: 314.13865.

Compound **101b:**

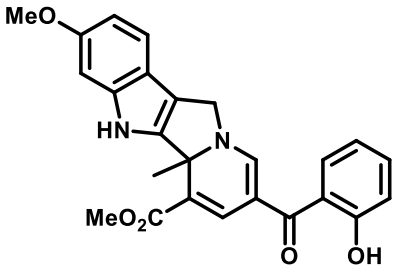


Compound **101b** was synthesized according to the racemic general procedure. Yellow amorphous solid; TLC (cyclohexane/ethyl acetate, 1:1 v/v): R_F = 0.40; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 11.15 (s, 1H), 7.98 (s, 1H), 7.49 – 7.42 (m, 3H), 7.29 (s, 1H), 7.01 (d, J = 7.1 Hz, 1H), 4.97 (m, 1H), 2.77 – 2.72 (m, 2H), 1.63 – 1.56 (m, 3H), 1.51 – 1.43 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6, 163.9, 150.1, 137.5, 130.4, 127.6, 122.5, 121.8, 119.4, 117.8, 115.4, 109.8, 61.7, 50.0, 29.6, 26.7, 22.6 ppm; HRMS: Calcd for $C_{17}H_{17}O_2N_2$ $[M+H]^+$: 281.12845, Found: 281.12840.

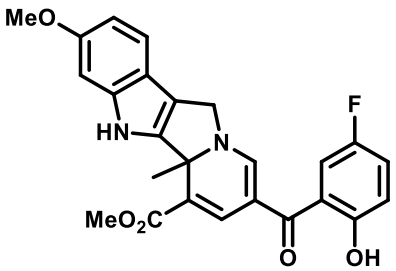
III.4.5. Synthesis of Indoloindolizines 111 and Dihydropyridoisoindoles 112

Compound **111a:**



Compound **111a** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 8.89 (s, 1H), 7.79 (s, 1H), 7.71 (s, 1H), 7.50 – 7.36 (m, 4H), 7.24 – 7.18 (m, 3H), 4.24 (s, 1H), 4.15 (s, 1H), 3.84 (s, 3H), 3.65 (s, 3H), 3.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.7, 167.2, 150.9, 135.8, 135.1, 132.5, 131.9, 131.3, 127.5, 127.0, 123.4, 121.8, 120.4, 119.5, 118.4, 117.5, 117.0, 115.2, 110.7, 99.2, 70.2, 68.4, 56.3, 55.1, 26.8 ppm; HRMS: Calcd for $C_{25}H_{23}O_5N_2$ $[M+H]^+$: 431.16015, Found: 431.16999.

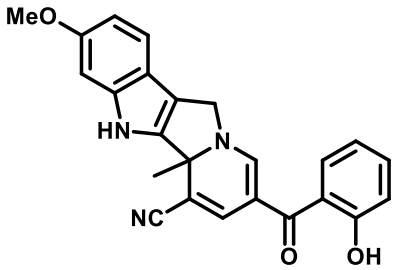
Compound **111b:**



Compound **111b** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 9.02 (s, 1H), 7.87 (s, 1H), 7.61 – 7.57 (m, 2H), 7.37 – 7.30 (m, 2H), 7.20 – 7.14 (m, 2H), 6.97 (d, *J* = 8.6 Hz, 1H), 4.30 (s, 1H), 4,22 (s, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.54 (s, 3H); 13C

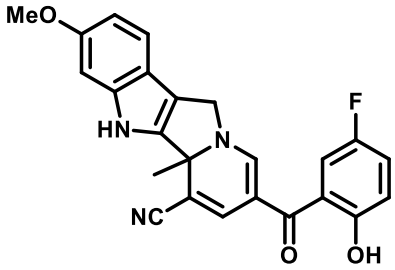
NMR (101 MHz, $CDCl_3$) δ 190.5, 170.1, 159.8, 153.5, 136.1, 135.8, 134.2, 131.7, 129.4, 126.0, 123.4, 123.1, 120.8, 120.0, 119.1, 118.4, 114.0, 112.1, 108.2, 105.8, 68.1, 58.7, 54.3, 52.8, 24.5 ppm; HRMS: Calcd for $C_{25}H_{22}O_5N_2F$ $[M+H]^+$: 449.15073, Found: 449.15044.

Compound **111c:**



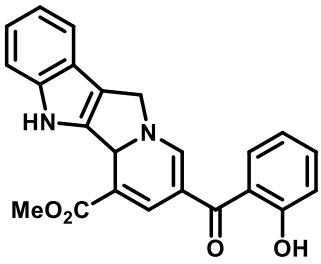
Compound **111c** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.14 (s, 1H), 9.01 (s, 1H), 7.94 (s, 1H), 7.62 (s, 1H), 7.47 – 7.41 (m, 2H), 7.30 – 7.23 (m, 3H), 6.99 – 6.92 (m, 2H), 4.30 (s, 1H), 4.23 (s, 1H), 3.87 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 161.3, 153.0, 136.5, 134.7, 134.4, 130.0, 127.5, 125.8, 120.8, 119.6, 119.1, 118.5, 118.4, 118.2, 116.8, 113.5, 112.7, 107.6, 106.2, 67.0, 59.1, 53.2, 22.8 ppm; HRMS: Calcd for $C_{24}H_{20}O_3N_3$ $[M+H]^+$: 398.14992, Found: 398.14971.

Compound **111d:**



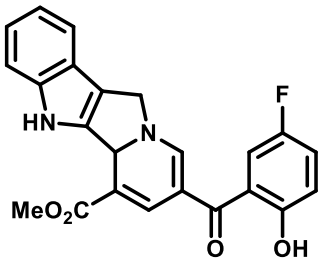
Compound **111d** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 9.03 (s, 1H), 7.94 (s, 1H), 7.68 (s, 1 H), 7.57 (s, 1H), 7.37 – 7.30 (m, 2H), 7.24 – 7.17 (m, 2H), 7.00 (d, *J* = 8.4 Hz, 1H), 4.31 (s, 1H), 4.23 (s, 1H), 3.78 (m, 3H), 3.74 (s, 3H); 13C NMR (101 MHz, $CDCl_3$) δ 190.0, 157.9, 153.4, 138.0, 135.7, 134.2, 129.5, 126.3, 125.0, 123.4, 123.1, 122.8, 120.2, 119.2, 118.7, 114.0, 113.7, 112.0, 108.3, 105.9, 68.3, 58.1, 54.5, 22.8 ppm; HRMS: Calcd for $C_{24}H_{19}O_3N_3F$ $[M+H]^+$: 416.14050, Found: 416.14011.

Compound **111e:**



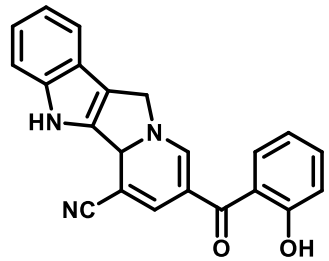
Compound **111e** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 9.06 (s, 1H), 7.75 (s, 1H), 7.70 (s, 1H), 7.32 – 7.28 (m, 2H), 7.18 – 7.11 (m, 3H), 7.04 – 6.99 (m, 1H), 6.90 – 6.85 (m, 2H), 6.13 (s, 1H), 4.30 (s, 1H), 4.22 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 188.7, 170.2, 155.3, 153.9, 136.2, 134.3, 133.0, 132.1, 131.4, 129.7, 125.8, 124.0, 121.1, 119.9, 119.0, 117.9, 116.2, 111.6, 106.8, 106.0, 67.4, 59.0, 52.3 ppm; HRMS: Calcd for $C_{23}H_{19}O_4N_2$ $[M+H]^+$: 387.13393, Found: 387.13367.

Compound **111f:**



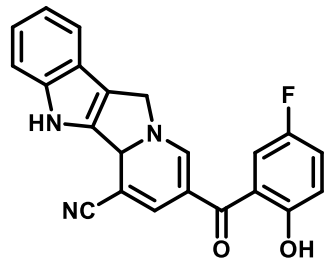
Compound **111f** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 9.07 (s, 1H), 7.92 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.39 – 7.30 (m, 3H), 7.23 – 7.12 (m, 2H), 6.97 (d, J = 8.4 Hz, 1H), 6.07 (s, 1H), 4.30 (s, 1H), 4.22 (s, 1H), 3.77 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 167.2, 159.6, 153.4, 136.1, 135.1, 134.3, 131.6, 130.2, 129.6, 125.7, 122.3, 121.2, 120.7, 119.6, 118.3, 114.6, 112.0, 108.1, 105.9, 68.3, 52.7, 50.6 ppm; HRMS: Calcd for $C_{23}H_{18}O_4N_2F$ $[M+H]^+$: 405.12451, Found: 405.12437.

Compound **111g:**



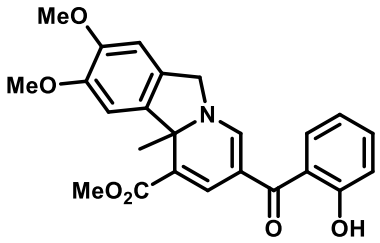
Compound **111g** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H), 9.04 (s, 1H), 7.94 (d, *J* = 1.5 Hz, 1H), 7.62 (d, *J* = 1.5 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.09 – 7.01 (m, 2H), 6.94 (m, 1H), 6.02 (s, 1H), 4.34 (s, 1H), 4.26 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.0, 153.3, 136.0, 134.9, 132.4, 130.3, 126.2, 122.7, 121.4, 119.6, 118.4, 117.9, 117.4, 117.0, 116.1, 114.0, 113.7, 108.8, 106.9, 105.0, 82.2, 59.1 ppm; HRMS: Calcd for $C_{22}H_{16}O_2N_3$ $[M+H]^+$: 354.12370, Found: 354.12349.

Compound **111h:**



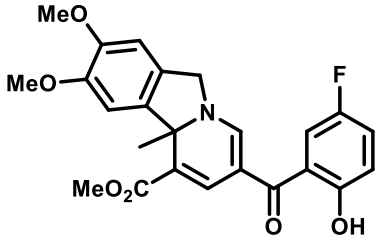
Compound **111h** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 9.04 (s, 1H), 7.95 (d, *J* = 1.7 Hz, 1H), 7.63 (d, *J* = 1.7 Hz, 1H), 7.46 (d, *J* = 8.9 Hz, 1H), 7.39 – 7.31 (m, 4H), 7.25 – 7.17 (m, 2H), 5.99 (s, 1H), 4.31 (s, 1H), 4.21 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 153.6, 136.4, 135.8, 134.4, 131.8, 129.6, 128.0, 126.4, 125.0, 123.2, 120.7, 121.0, 120.7, 119.7, 118.3, 114.1, 112.2, 108.1, 105.8, 68.2, 54.0 ppm; HRMS: Calcd for $C_{22}H_{15}O_3N_3F$ $[M+H]^+$: 372.11428, Found: 372.11402.

Compound **112a:**



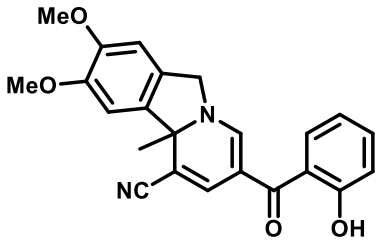
Compound **112a** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 7.91 (s, 1H), 7.70 (s, 1H), 7.46 – 7.39 (m, 2H), 7.22 – 7.14 (m, 2H), 6.98 (s, 1H), 6.88 (s, 1H), 4.32 (s, 1H), 4.21 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.58 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 170.0, 166.0, 158.9, 145.2, 135.1, 132.8, 131.6, 131.1, 128.7, 127.5, 123.1, 121.4, 119.5, 116.7, 116.0, 111.2, 105.1, 69.9, 56.3, 56.2, 52.4, 49.8, 24.2; HRMS: Calcd for $C_{24}H_{24}O_6N$ $[M+H]^+$: 422.15981, Found: 422.15971.

Compound **112b:**



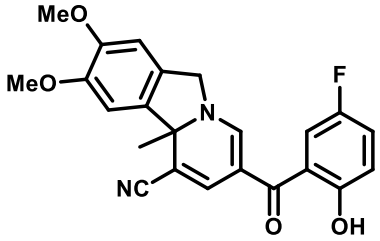
Compound **112b** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 7.91 (s, 1H), 7.58 (s, 1H), 7.45 (s, 1H), 7.32 (d, J = 6.0 Hz, 1H), 7.13 (d, J = 6.0 Hz, 1H), 6.90 (s, 1H), 6.85 (s, 1H), 4.29 (s, 1H), 4.20 (s, 1H), 3.82 (d, 6H), 3.78 (s, 3H), 3.52 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.6, 169.7, 165.4, 149.7, 146.0, 145.7, 138.0, 135.7, 134.2, 130.6, 128.2, 123.2, 122.1, 120.8, 117.5, 116.6, 111.1, 108.6, 68.7, 60.1, 58.7, 54.3, 54.2, 24.1 ppm; HRMS: Calcd for $C_{24}H_{23}O_6NF$ $[M+H]^+$: 440.15039, Found: 440.15012.

Compound **112c:**



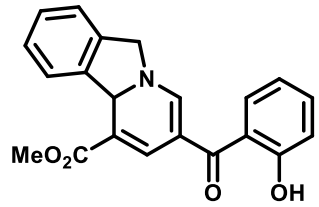
Compound **112c** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 7.87 (s, 1H), 7.64 (s, 1H), 7.44 (s, 1H), 7.21 – 7.03 (m, 3H), 6.93 (s, 1H), 6.87 (s, 1H), 4.31 (s, 1H), 4.22 (s, 1H), 3.82 (d, 6H), 3.49 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 164.5, 150.2, 146.5, 146.2, 138.7, 134.9, 133.1, 130.4, 124.2, 120.5, 118.2, 118.0, 117.6, 116.5, 113.2, 111.1, 108.5, 68.6, 56.2, 56.0, 55.7, 24.6 ppm; HRMS: Calcd for $C_{23}H_{21}O_4N_2$ $[M+H]^+$: 389.14958, Found: 389.14921.

Compound **112d:**



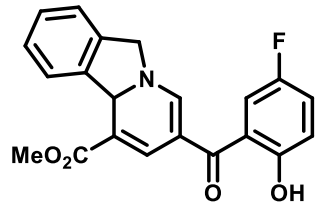
Compound **112d** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (s, 1H), 7.90 (s, 1H), 7.57 (s, 1H), 7.43 (s, 1H), 7.20 (d, J = 7.8 Hz, 1H), 7.07 (d, J = 7.8 Hz, 1H), 6.91 (s, 1H), 6.87 (s, 1H), 4.29 (s, 1H), 4.21 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 164.4, 150.8, 146.3, 146.0, 135.6, 134.9, 133.1, 131.2, 130.6, 127.1, 124.4, 122.6, 120.5, 118.4, 116.5, 111.4, 108.6, 68.4, 60.4, 55.7, 55.6, 24.1 ppm; HRMS: Calcd for $C_{23}H_{20}O_4N_2F$ $[M+H]^+$: 407.14016, Found: 407.14003.

Compound **112e:**



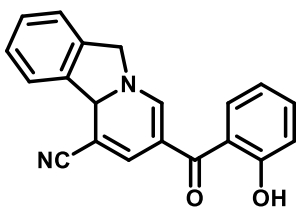
Compound **112e** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 7.92 (s, 1H), 7.63 (s, 1H), 7.54 – 7.51 (m, 1H), 7.39 – 7.18 (m, 6H), 6.94 – 6.90 (m, 1H), 5.47 (s, 1H), 4.30 (s, 1H), 4.23 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.4, 168.7, 159.8, 143.4, 136.3, 136.0, 133.5, 131.7, 130.0, 128.4, 126.2, 123.9, 120.1, 118.7, 113.8, 112.7, 108.3, 107.2, 68.2, 59.8, 52.5 ppm; HRMS: Calcd for $C_{21}H_{18}O_4N$ $[M+H]^+$: 348.12303, Found: 348.12289.

Compound **112f:**



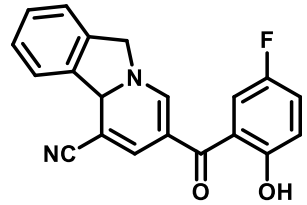
Compound **112f** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.43 – 7.32 (m, 4H), 7.23 – 7.13 (m, 2H), 6.99 – 6.94 (d, J = 7.9 Hz, 1H), 6.04 (s, 1H), 4.32 (s, 1H), 4.22 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.0, 167.5, 159.5, 153.7, 138.3, 136.7, 135.7, 134.0, 133.0, 129.7, 127.6, 126.0, 122.3, 121.0, 120.3, 114.8, 112.3, 105.8, 69.9, 60.1, 52.5 ppm; HRMS: Calcd for $C_{21}H_{17}O_4NF$ $[M+H]^+$: 366.11361, Found: 366.11347.

Compound **112g:**



Compound **112g** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.15 (s, 1H), 7.91 (s, 1H), 7.64 (s, 1H), 7.54 – 7.50 (m, 1H), 7.37 – 7.19 (m, 6H), 6.95 – 6.91 (m, 1H), 5.62 (s, 1H), 4.32 (s, 1H), 4.24 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 159.6, 144.0, 136.7, 135.7, 135.6, 133.4, 131.2, 130.0, 128.3, 126.5, 124.0, 120.2, 118.6, 113.9, 112.8, 108.2, 107.1, 68.7, 59.7 ppm; HRMS: Calcd for $C_{20}H_{14}O_2N_2$ $[M+H]^+$: 315.11280, Found: 315.11296.

Compound **112h:**

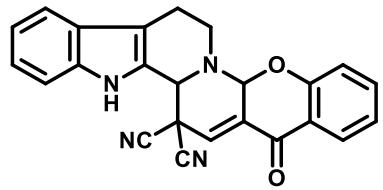


Compound **112h** was synthesized according to the asymmetric Diels-Alder procedure. Red solid; TLC (cyclohexane/ethyl acetate, 3:2 v/v): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (s, 1H), 7.95 (d, *J* = 2.1 Hz, 1H), 7.68 (d, *J* = 2.1 Hz, 1H), 7.42 – 7.31 (m, 4H), 7.23 – 7.13 (m, 2H), 7.00 – 6.95 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 1H), 4.31 (s, 1H), 4.22 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 159.3, 153.8, 138.3, 136.4, 135.4, 134.7, 133.1, 129.2, 126.4, 126.2, 122.4, 121.7, 120.0, 118.7, 114.5, 112.5, 105.7, 69.7, 59.9 ppm; HRMS: Calcd for $C_{20}H_{14}O_2N_2F$ $[M+H]^+$: 333.10338, Found: 333.10310.

III.4.6. Synthesis of Ring Closed Quinolizines 114 and 117

Ring-closed quinolizines **114** and **117** were synthesized following the standard procedure of asymmetric Diels-Alder reaction.

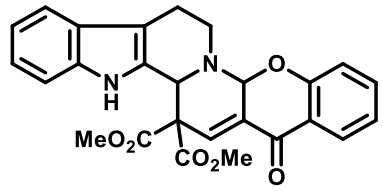
Compound **114a:**



Compound **114a** was synthesized according to the asymmetric general procedure. orange amorphous solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.50 (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 7.94 – 7.90 (m, 1H), 7.49 – 7.41 (m, 3H), 7.29 – 7.20

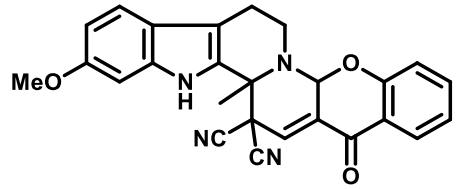
(m, 3H), 7.04 – 6.96 (m, 2H), 6.03 – 5.97 (m, 1H), 5.53 – 5.49 (m, 1H), 3.80 – 3.74 (m, 2H), 3.15 – 3.08 (m, 1H), 2.91 – 2.86 (m, 1H); HRMS: Calcd for $C_{24}H_{17}O_2N_4$ $[M+H]^+$: 393.13460, Found: 393.13443.

Compound **114b:**



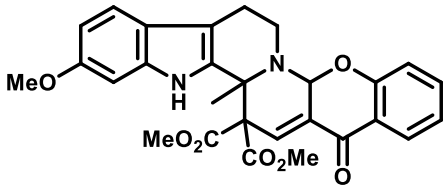
Compound **114b** was synthesized according to the asymmetric general procedure. orange amorphous solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.50 (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.13 (s, 1H), 7.95 – 7.91 (m, 1H), 7.48 – 7.40 (m, 3H), 7.28 – 7.20 (m, 3H), 7.06 – 6.95 (m, 2H), 6.04 – 5.96 (m, 1H), 5.55 – 5.49 (m, 1H), 3.80 – 3.73 (m, 8H), 3.15 – 3.09 (m, 1H), 2.91 - 2.86 (m, 1H); HRMS: Calcd for $C_{26}H_{23}O_6N_2$ $[M+H]^+$: 459.15506, Found: 459.15471.

Compound **114c:**



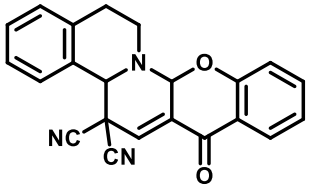
Compound **114c** was synthesized according to the asymmetric general procedure. orange amorphous solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.50 (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 7.94 – 7.91 (m, 1H), 7.60 – 7.55 (m, 1H), 7.47 – 7.41 (m, 2H), 7.29 – 7.20 (m, 2H), 7.02 – 6.98 (m, 1H), 6.89 – 6.84 (m, 1H), 5.55 – 5.50 (m, 1H), 3.86 (s, 3H), 3.80 – 3.74 (m, 5H), 3.16 – 3.09 (m, 1H), 2.91 – 2.88 (m, 1H); HRMS: Calcd for $C_{26}H_{21}O_3N_4$ $[M+H]^+$: 437.16082, Found: 437.16058.

Compound **114d:**



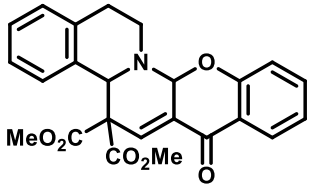
Compound **114d** was synthesized according to the asymmetric general procedure. orange amorphous solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.50 (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (s, 1H), 7.93 – 7.89 (m, 1H), 7.61 – 7.58 (m, 1H), 7.47 – 7.42 (m, 2H), 7.30 – 7.22 (m, 3H), 7.02 – 6.97 (m, 1H), 6.89 – 6.84 (m, 1H), 3.86 (s, 3H), 3.80 – 3.74 (m, 8H), 3.17 – 3.10 (m, 4H), 2.91 – 2.86 (m, 1H); HRMS: Calcd for $C_{28}H_{27}O_7N_2$ $[M+H]^+$: 503.18128, Found: 503.18102.

Compound **117a:**



Compound **117a** was synthesized according to the asymmetric general procedure. orange amorphous solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.50 (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 – 7.88 (m, 1H), 7.58 – 7.54 (m, 1H), 7.39 – 7.20 (m, 5H), 7.02 – 6.98 (m, 1H), 6.89 – 6.83 (m 1H), 6.04 – 5.95 (m, 1H), 3.85 – 3.79 (m, 2H), 3.15 – 3.09 (m, 1H), 2.90 – 2.86 (m, 1H); HRMS: Calcd for $C_{22}H_{16}O_2N_3$ $[M+H]^+$: 354.12370, Found: 354.12339.

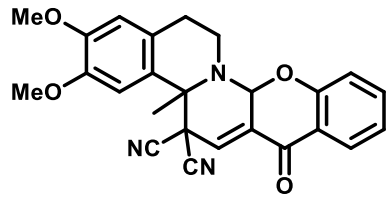
Compound **117b:**



Compound **117b** was synthesized according to the asymmetric general procedure. orange amorphous solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.50 (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (m, 1H), 7.59 (m, 1H), 7.37 – 7.18 (m, 6H), 7.03 – 6.98 (m, 1H),

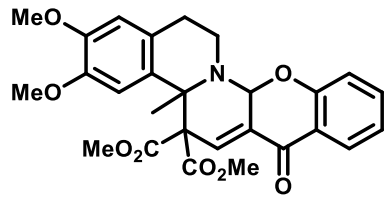
6.88 – 6.83 (m, 1H), 6.05 – 5.98 (m, 1H), 3.87 – 3.79 (m, 8H), 3.15 – 3.08 (m, 1H), 2.91 – 2.86 (m, 1H); HRMS: Calcd for $C_{24}H_{22}O_6N$ $[M+H]^+$: 420.14416, Found: 420.14402.

Compound **117c:**



Compound **117c** was synthesized according to the asymmetric general procedure. orange amorphous solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.50 (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (m, 1H), 7.69 – 7.64 (m, 1H), 7.58 – 7.53 (m, 1H), 7.47 – 7.42 (m, 2H), 7.29 – 7.21 (m, 1H), 7.02 – 6.97 (m, 1H), 6.81 – 6.74 (m 1H), 3.89 (s, 6H), 3.80 – 3.72 (m, 5H), 3.16 – 3.08 (m, 1H), 2.91 – 2.86 (m, 1H); HRMS: Calcd for $C_{25}H_{21}O_4N_3$ $[M+H]^+$: 428.16048, Found: 428.16014.

Compound **117d:**



Compound **117d** was synthesized according to the asymmetric general procedure. orange amorphous solid; TLC (cyclohexane/ethyl acetate, 2:1 v/v): R_F = 0.50 (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (m, 1H), 7.70 – 7.63 (m, 1H), 7.59 – 7.53 (m, 1H), 7.47 – 7.43 (m, 2H), 7.27 – 7.21 (m, 1H), 7.01 – 6.95 (m, 1H), 6.81 – 6.75 (m 1H), 3.93 – 3.87 (m, 12H), 3.81 – 3.74 (m, 5H), 3.16 – 3.09 (m, 1H), 2.93 – 2.87 (m, 1H); HRMS: Calcd for $C_{27}H_{28}O_6N$ $[M+H]^+$: 494.18094, Found: 494.18072.

IV. Curriculum Vitae

Vincent Eschenbrenner-Lux

Birth: April 11th, 1988 in Strasbourg (France)

Education:

07/2010 – 07/2014 PhD Thesis under the supervision of Prof. Dr. Herbert Waldmann and Dr. Kamal Kumar, at the Max Planck Institute for Molecular Physiology, Dortmund (Germany).

09/2008 – 06/2010 Master of Science in Chemistry and Biology, with distinction, University of Strasbourg (UdS, France).

02/2010 – 06/2010 Master Thesis at the Institute of Chemical Research of Catalonia (ICIQ, Tarragona, Spain), on "Total Synthesis of Epiquinamide" under the supervision of Prof. Dr. Kilian Muñiz.

09/2006 – 06/2008 Bachelor in Cellular and Molecular Biology, with distinction, UdS.

09/2005 – 06/2008 Bachelor in Chemistry, with distinction, UdS.

Work Experience:

06/2011 – 07/2013 Chemistry Teacher, at the Hochbegabteförderung e.V., Bochum (Germany). Teaching general chemistry to teenagers as extracurricular activity.

08/2008 – 01/2010 Research Internship at the Laboratory of Homogenous Catalysis and Molecular Synthesis. CNRS, Strasbourg (France).

Scientific Publications:

1) The Asymmetric Hetero Diels-Alder Reaction in the Synthesis of Biologically Relevant Compounds; V. Eschenbrenner-Lux, K. Kumar, H. Waldmann; *Angew. Chem. Int. Ed.* **2014**, 53, DOI: 10.1002/anie.201404094R1.

2) Enantioselective Inverse-Electron-Demand Imino-Diels-Alder Reaction; V. Eschenbrenner-Lux, P. Küchler, S. Ziegler, K. Kumar, H. Waldmann; *Angew. Chem. Int. Ed.* **2014**, 53, 2134-2137. Highlighted in: *Synfacts* **2014**, 10(5), 496.

3) Domino Reactions in Library Synthesis, V. Eschenbrenner-Lux, H. Waldmann, K. Kumar; *Domino Reactions: Concepts for Efficient Organic Synthesis*, *Wiley* **2014**, 497-521.

4) Cascade Syntheses Route to the Centrocountins; V. Eschenbrenner-Lux, H. Dückert, V. Khedkar, H. Bruss, H. Waldmann, K. Kumar; *Chem. Eur. J.* **2013**, 19(7), 2294-2304. (Selected for cover picture)

5) Substituted Indolo[2,3-a]quinolizines; V. Eschenbrenner, H. Dückert, V. Pries, V. Khedkar, H. Bruss, S. Menninger, S. Ziegler, K. Kumar, H. Waldmann; *U.S. Pat. Appl.* **2012**, US 20120316195A1.

Conferences:

20 - 25.07.2014	Gordon Research Conference: Natural Products. Poster presentation of: A
Andover, NH, U.S.A.	Natural Product Inspired Ring-fused Quinolizine Compound Collection Provides Mitotic Modulators. *Scholarship awarded by the Deutscher Akademischer Austauschdienst (DAAD Kongressreisenstipendium).*
24 - 27.06.2014	15th Tetrahedron Symposium: Challenges in Bioorganic and Organic
London, U.K.	Medicinal Chemistry. Poster presentation of: Enantioselective Inverse Electron Demand Imino-Diels-Alder Reaction Provides Potent Mitotic Modulators

Dortmund, Juni 2014

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Finally, I would like to express all my gratitude to my family, especially my mother, for their constant support provided during these four years in Germany.

VI. Eidesstattliche Erklärung

Ich versichere hiermit, dass ich die vorliegende Dissertation selbstständig und ohne unzulässige fremde Hilfe erbracht habe. Ich habe keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, sowie wörtliche und sinngemäße Zitate kenntlich gemacht.

Dortmund, 24.06.2014 Vincent Eschenbrenner-Lux

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Ort, Datum Unterschrift