

**Cascade/Domino Synthesis Strategy to Enrich Small
Molecule Collections with Skeletal diversity and
Molecular Complexity**

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DISSERTATION

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Erklärung/Declaration

Hiermit versichere ich an Eides statt, dass ich die vorliegende Arbeit selbständig und nur mit den angegebenen Hilfsmitteln angefertigt habe.

I hereby declare that I performed the work presented independently and did not use any other but the indicated aids.

Dortmund, July 2011

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Publications

Parts of the results reported in this dissertation have already been published in the following publications:

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1 Introduction

1.1 General

Small bioactive molecules are of always of great interest for any discovery research, be it drug discovery/medicinal chemistry research or a chemical biology/chemical genetics investigation ^[1]. As complementary method to genetic approaches, the use of small molecules as highly specific modulators (i.e., inhibitors or activators) of protein functions is a powerful approach which is frequently applied e.g. for the study of dynamic processes in cells. Due to the irreversible effects of genetic manipulations, such biological methods may be of limited use for this purpose ^[2]. For the success of chemical genetics/genomics-based research programs, efficient and rapid access to diverse sets of biologically relevant small molecules is mandatory ^[3]. Combinatorial chemistry and compound library synthesis along with developments in both solid- and solution-phase organic synthesis have emerged as important technologies to provide compound collections in an efficient manner. After an initial phase of development in which accessibility and size of compound collections gained a major share of attention, the 'quality' of compound libraries, in particular their resemblance to natural products structural features has become the key criterion in design and synthesis ^[4, 5]. Compound collections enriched in diversity, complexity and of biological relevance, the inherent characteristics of natural products, generally provide hits in biochemical and biological investigations with higher success rate than collections designed on the basis of chemical accessibility ^[6].

In the last six decades, synthetic organic chemistry has witnessed immense developments ^[7-8]. So much that, often the key question today in a target synthesis endeavor is not about what molecule to synthesize but how to make it more efficiently. However, *how to create bioactive molecules* remains in the realm of mysterious mother nature and chemists have to uncover a lot of truth to understand the natures

magic hands^[9,10]. Indeed, half of all therapeutic drugs, and an even greater proportion of narcotics, are based on natural compounds. However, the concerns for their feeble availability from natural resources by extraction and/or by expensive and inefficient semi-synthetic or synthetic means were always pushing the chemists especially in pharmaceutical industry to find alternatives to these secondary metabolites and therefore no surprise that a major decline in NP research has been around since early 1990s. However, the idea of accessing the large chemical space with combichem approaches combined with *in silico* methods though initially appeared very appealing for drug discovery, proved to be a false lead. The large numbers of compounds created through these efforts still represent only a fraction of the total number of compounds that could theoretically exist (in excess of 10^{60}) and could not provide any significant hit and lead structures^[11]. This period of 10-15 years also witnessed a steady decline in the output of new active substances or NCEs^[12]. It was being realized that combinatorial and NP chemistry should complement on a synergistic form to provide molecules with features of NPs and yet completely synthetic in nature^[13].

Targeting this synergistic approach to create molecules resembling natural products, chemists had developed synthesis concepts that could enrich a given compound collection with biological activities. Diversity oriented synthesis (DOS) and biology oriented synthesis (BIOS) have emerged as two guiding principles for the design and synthesis of compound collections for chemical biology and medicinal chemistry research. Among other less explored strategies include^[14, 15] “molecular editing” (Danishefsky)^[16], “libraries-from-libraries” (Houghten)^[17], function-oriented synthesis (FOS) by Wender^[18].

The non-focused nature of the concept *Diversity-oriented synthesis (DOS)* enables it to induce a vast range of physical and consequently biological properties to the library members and therefore can be useful to identify novel lead compounds^[18-20]. The goal of DOS is to discover the novel small molecules with appealing biological properties

and spanning new structure ^[14, 15].

1.2 Diversity Oriented Synthesis

Diversity oriented syntheses (DOS), as the name suggests is an approach to synthesize diverse molecular classes including natural products based molecules and spanning large areas of unexplored chemical space. To achieve that goal, DOS methods must be sufficiently robust and efficient to produce complex and diverse and natural product-like compounds combinatorial. DOS approach is therefore different to that of target-oriented synthesis (TOS), where often the target is one complex NP and chemistry is designed and developed with that focus only. TOS is thus a linear and convergent strategy, and follows a planned retrosynthesis which considers the logical breaking of complex molecule to the simpler substrates. DOS on the other hand targets the collections of structurally complex and diverse molecules from simple substrates ^[21-22]. DOS approach has thus developed a different divergent planning strategy termed as *forward synthetic analysis*. This planning involves and employs the complexity generating reactions of the relatively simple and easily accessible substrates in the direction of products (Fig. 1-1) ^[1, 14, 23].

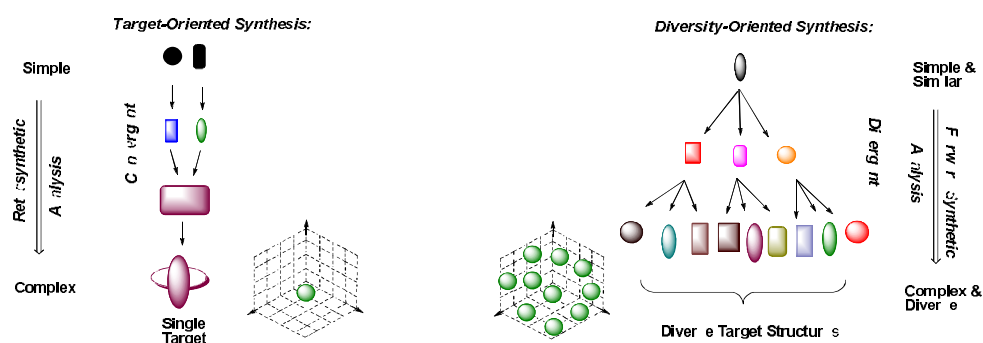


Figure. 1-1 **Comparison** of Target Oriented Synthesis and Diversity Oriented Synthesis

In order to gain quantity and quality of molecules by DOS, the molecules generated at one point of library synthesis should have functional sites that can be modified to yield more diverse structures that show a superior biological activity and selectivity characteristic. In this feature, DOS remarkably differs from TOS (Figure 1-2) ^[1, 14].

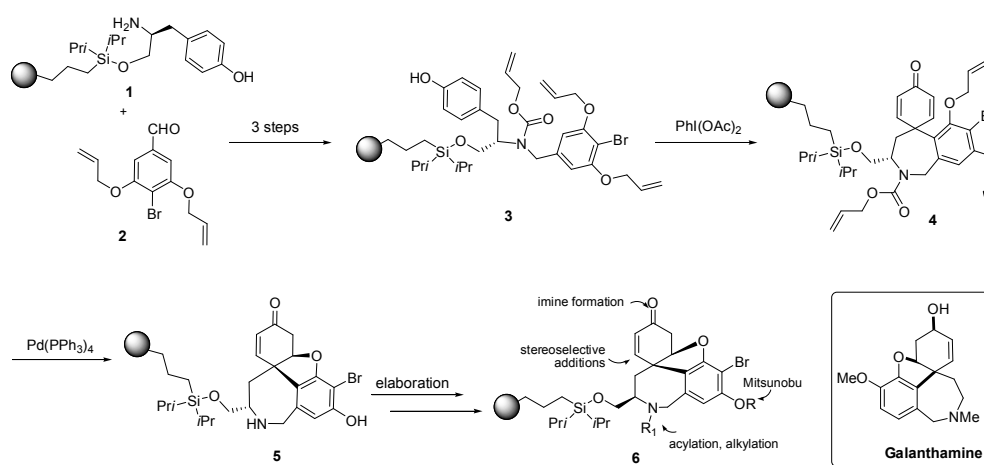
While TOS provides just a few analogues of a complex natural product,^[1, 14, 24, 25] DOS can maximize the structural complexity of every compound and consequently of the entire compound library^[26, 27].

DOS synthetic methods are branched and forked; they are schemed as mentioned before by using forward-synthetic analysis to design targets^[28]. The most significant feature of this ‘forward’ synthesis^[29] is the ability to propagate the functional and skeletal transformations to the next stages of the synthesis to cover large areas of chemical space^[30]. In the forward-synthetic strategy one target product is transformed into a collection of compounds by wide range of possible chemical transformations. Thus, in DOS a set of products are transformed into another set of new molecules by one common transformation on the common functionalities present in any set of molecules^[31].

1.3 Generating molecular complexity in DOS

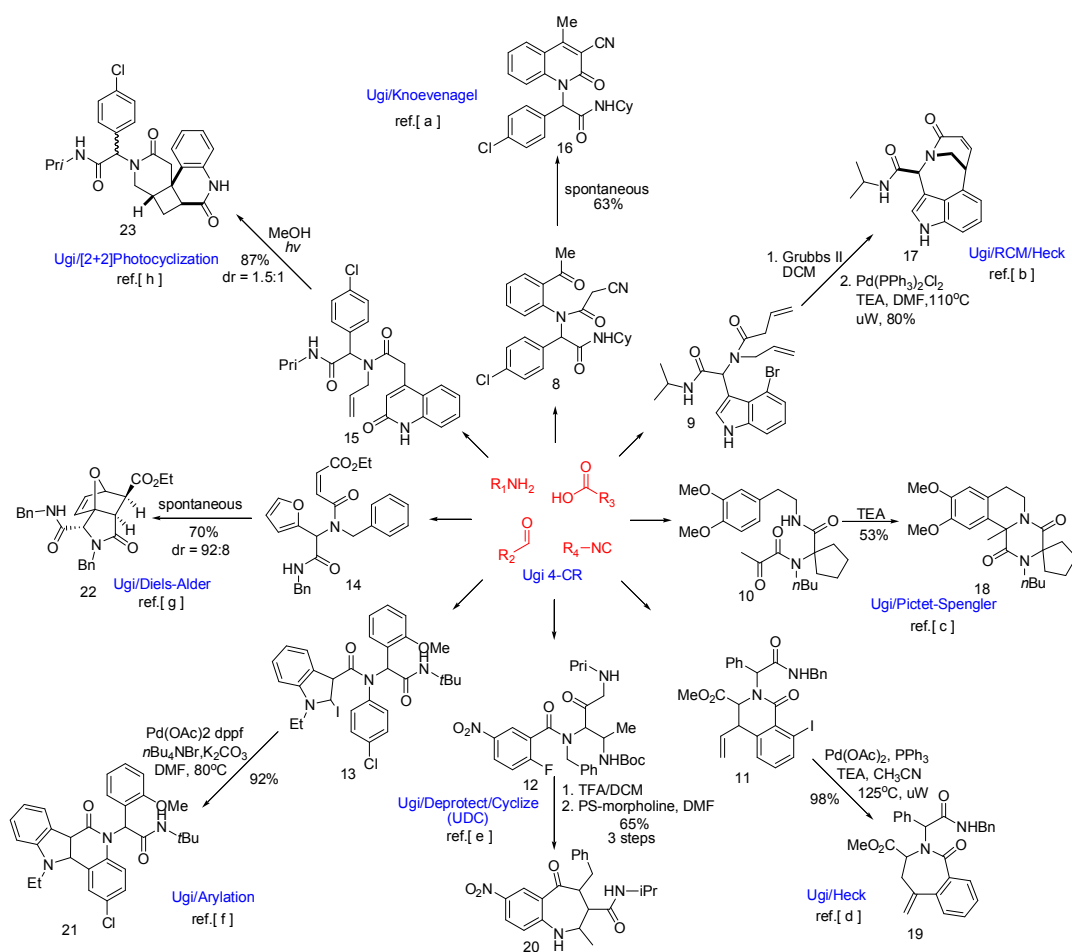
One of the features of NPs that possibly imparts the biological activity to this class of molecules in their relatively complex frameworks. Their continuous good record of providing hits and that too for difficult biological targets, e.g. to disrupt protein–protein interactions^[32-33] clearly suggest to induce their structural features to compound collections. It is thus an aim of DOS to prepare small molecules with complex molecular skeletons and in combination with forward-synthetic strategy to generate the compounds from simple to complex molecular scaffolds^[1, 14, 34, 35]. The structural complexity includes not only the ring- or architectural complexity but an overall three-dimensional complexity that includes diverse stereo-chemical properties^[36-38]. In order to enhance the efficiency of the whole DOS process in yielding diverse and complex molecules, the strategy should make the complex building blocks quickly (by not more than three to five steps) and if possible, without the use of protecting groups. For instance, Shair and co-workers synthesized a DOS based

library based on the natural product, galanthamine (Scheme. 1-1) commencing with imine formation by reaction of the aldehydes (2) and resin bound amine (1). A reductive amination and protecting-group adjustments later yielded 3. Treatment of the latter with $\text{PhI}(\text{OAc})_2$ afforded 4 which was transformed to 5 via Pd-mediated deprotection and spontaneous cyclization. Resin bound 5 was used as a template for generation of further diversity and complexity by means of different reactions (Scheme. 1-1). Finally cleavage of the products from the solid support yielded a galantamine-inspired library of ca. 2500 molecules [39].



Scheme 1-1: Galanthamine based compound library synthesis.

To efficiently generate complex molecules, multi-component, Domino or cascade reactions wherein more than one reaction happens consecutively and molecular complexity is rapidly built up, have been employed in the DOS processes [1, 14, 40, 41]. For instance, Martin and co-workers used the classic Ugi reaction to generate collection of complex scaffolds [42-44]. In the Ugi four component reaction (Ugi-4CR) each of its four components has the function, which can be used in subsequent transformations. Thus it can generate a number of cyclization manifolds. A graph showing diversity of some of the post-condensation cyclizations by the U-4CR is presented in (Scheme 1-2).



Scheme 1-2. An overview of the U-4CR post condensation cyclizations. (a) S. Marcaccini, R. Pepino, M. C. Pozo, S. Basurto, M. Garc_a- Valverde, T. Torroba, *Tetrahedron Lett.* **2004**, *45*, 3999 – 4001; (b) T. P. Ribelin, A. S. Judd, I. Akritopoulou-Zanze, R. F. Henry, J. L. Cross, D. N. Whittern, S. W. Djuric, *Org. Lett.* **2007**, *9*, 5119 – 5122; (c) L. El Kaim, M. Gageat, L. Gaultier, L. Grimaud, *Synlett* **2007**, 0500 – 0502; (d) V. Gracias, S. W. Djuric, *Tetrahedron Lett.* **2004**, *45*, 417 – 420; (e) P. Tempest, L. Pettus, V. Gore, C. Hulme, *Tetrahedron Lett.* **2003**, *44*, 1947 – 1950; (f) Z. Ma, Z. Xiang, T. Luo, K. Lu, Z. Xu, J. Chen, Z. Yang, *J. Comb. Chem.* **2006**, *8*, 696 – 704; (g) K. Paulvannan, *Tetrahedron Lett.* **1999**, *40*, 1851 – 1854; (h) I. Akritopoulou-Zanze, A. Whitehead, J. E. Waters, R. F. Henry, S. W. Djuric, *Org. Lett.* **2007**, *9*, 1299 – 1302.—Depicted by Martin's group^[34]

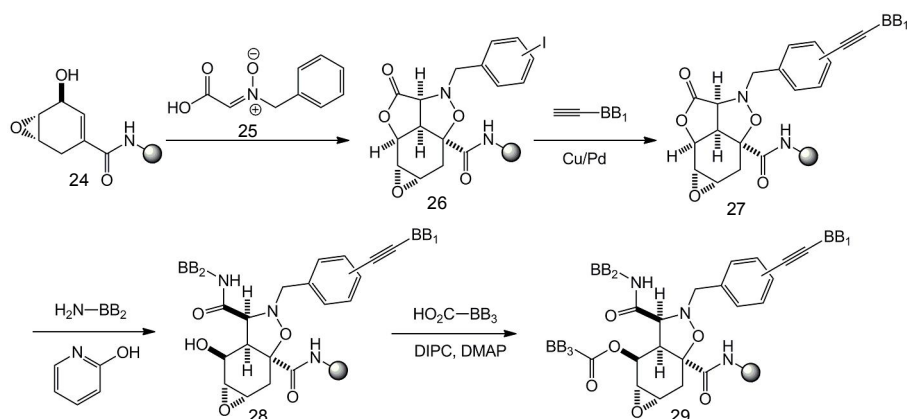
1.4 Generating Diversity in DOS (Similar→Diverse)

Structural diversity in a compound collection can be following ways; by a) generating diverse scaffolds or skeletons supporting functionalities that could further provide skeletal modification; b) incorporating elements of functional group diversity around the given cores structures; c) generating different stereoisomers to access different

binding patterns with protein targets (stereochemical diversity) ^[39]. To achieve these goals in DOS, the basic element in forward synthetic planning is the transformation of a collection of substrates into a collection of products by performing a number of common chemical transformations. The key to success in this strategy is the inherent reactivity of common sites available in all the substrates which not only transforms all of them to the products but also ensures their further possible common transformations by generating a new set of common reactive sites. ^[1, 14, 45].

1.4.1 Appendages diversity

The most feasible of all diversity generating possibilities is to cause 'Appendage diversity' and is the central diversity-generating process. It involves the use of coupling reactions to attach different appendages to a common molecular skeleton. If a molecular scaffold has multiple reactive sites with potential for orthogonal functionalization, then the split pool synthesis can be used to generate all possible combinations of appendages efficiently. This one-synthesis/one-skeleton approach has proven to be highly general and capable of generating hundreds, thousands, or even millions of distinct small molecules ^[39, 46]. For example, a complexity-generating, consecutive transesterification-cycloaddition sequence was used to generate, in one step, the tetracyclic skeleton **26** with potential for functionalization through a series of diversity-generating appending processes (Scheme 1-3) ^[46]. A Songashira coupling reaction was then used to append a collection of alkynes to the idolatory moiety of **26** and generated a collection of more diverse products **27**. The common lactones moiety **27** was transformed to a collection of new amide products **28**. Similarly, members of this new collection **28** share a common nucleophilic secondary hydroxyl group, thus making them all substrates for a third appending process i.e. coupling with a collection of carboxylic acid building blocks. This series of products-equals-substrates relationships made it possible to generate the complex arrangement of building blocks found in **29** in a highly efficient manner by using split pool synthesis.



Scheme 1-3. Appending processes in DOS

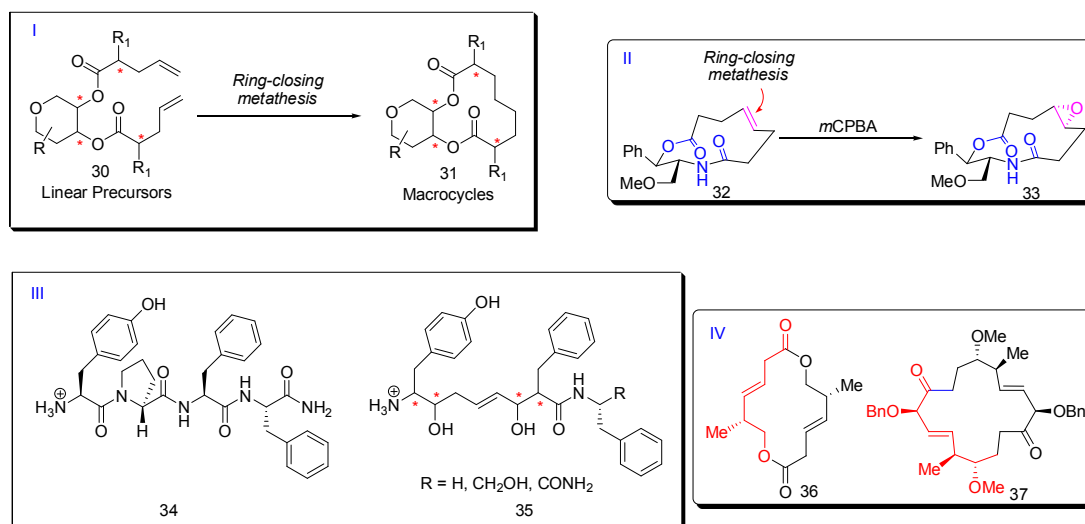
1.4.2 Stereochemical diversity

Stereochemical diversity provides diverse possible three dimensional and conformational possibilities of the elements in small molecules that interact with macromolecules. The best way to achieve this diversity is through reactions that proceed with enantio- or diastereoselectivity and are capable of generating all possible isomers in a selective manner. These collective asymmetric transformations of chiral substrates into products having enhanced stereochemical diversity require powerful reagents that can overcome any substrate bias and yield the highly diastereoselective product profiles ^[39, 47]. There are ample evidence to the fact that altering the relative stereochemistry of a given molecule can drastically change its overall shape, and consequently its biological profile and these calls for developments in asymmetric synthesis providing efficient access to all stereoisomers in a compound collection.

Some examples of stereochemically diverse library generation are shown in Scheme 1-4. A novel conformational restriction approach was used by Schrieber and co-workers to favor macrocyclization, via strategic placement of ester and amide functionalities in a linear precursor. The macrocyclization also provided further diversity points for structural modifications (Scheme 1-4, IV) ^[48]. Panek et al synthesized 14-, 16- and 22 member macrodiolides bearing up to six stereogenic centers (Scheme 1-4, IV) ^[49]. Oteras distannoxane transesterification catalysts were

employed to effect solution-phase cyclohomodimerization of ω -hydroxyesters. The products were obtained in high yields with limited trimer formation. Again, the products could be diversified further using substrate-controlled stereoselective reactions.

Verdine and co-workers used the concept of stereochemical variation and acyclic stereocontrol to generate non-peptides ligands for peptide receptors (Scheme 1-4. III) [50]. Inspired by an endogenous ligand for mu opioid receptor, endomorphin-2 (Scheme 1-4, III **34**) a stereodiverse collection of nonpeptide compounds **35**, was generated where the N-terminal tripeptide unit of **34** has been replaced by a nonpeptidic, stereodiverse unit incorporating a 1,5-enediol moiety. The dense array of stereocenters combined with the rigidifying olefin in **35** was intended to generate geometric diversity.



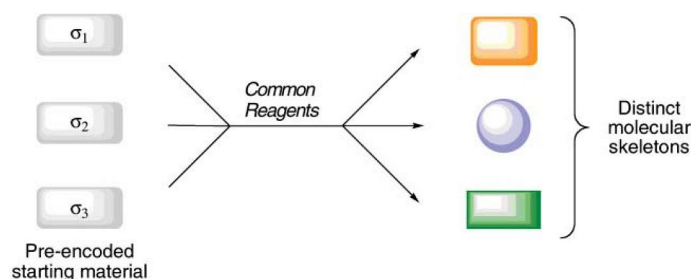
Scheme 1-4: Stereochemically diverse compound collections

1.4.3 Skeletal diversity

DOS pathways that yield collections of products with many distinct molecular frameworks are particularly effective at achieving a diverse display of chemical functionality in three dimensional spaces. There are, at present, two different strategies for planning DOS pathways that generate skeletal diversity. The first

strategy involves using different reagents to transform a common substrate with the potential for diverse reactivity into a collection of products having distinct molecular skeletons (Figure 1-3).^[1, 14, 51-56]

Substrate-based approach / folding process



Reagent-based approach / branching pathway

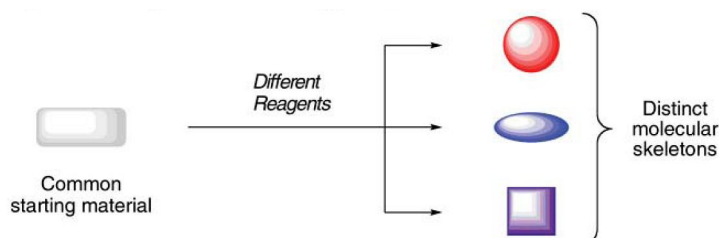
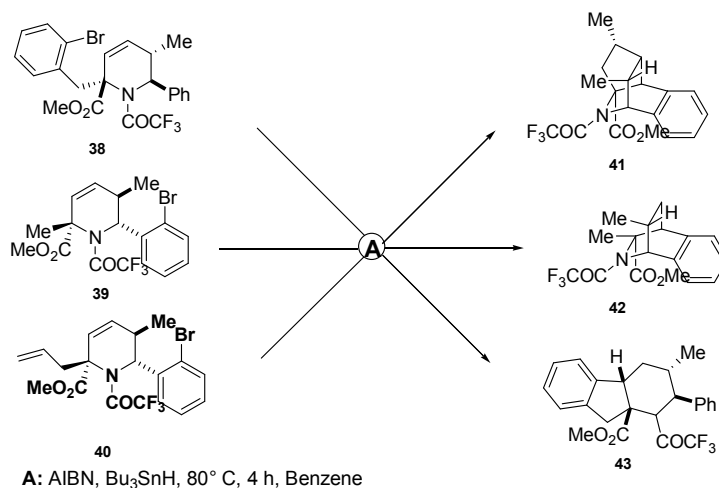


Figure 1-3. Two general approaches for planning synthesis pathways that generate skeletal diversity^[42].

a) The first approach is termed as ‘**folding pathway**’ and uses a common set of reaction conditions to transform a range of substrates into products with distinct and diverse molecular skeletons (Figure. 1-3). The substrates are encoded to ‘fold’ into the alternative scaffolds through strategically embodied functionalities, known as ‘ σ -elements’. Each σ -element thus dictates the formation of diverse molecular framework. In order to achieve the skeletal diversity efficiently and yielding wide range of distinct scaffolds, different precursors have been proposed to be explored for this cause, for instance, (1) the use of pluripotent functionality; (2) use of densely functionalized molecules and (3) the use of folding processes^[1, 14, 45].

Exploring the radical cyclizations Panek and Porco designed a folding approach to generate skeletal diversity (Scheme. 1-5) employing a set of tetrahydropyridines as substrates^[50]. The skeletons of the products **41-43** were pre-encoded in the substrates **38-40** by the location of the radical-initiating sites and the unsaturated groups. The

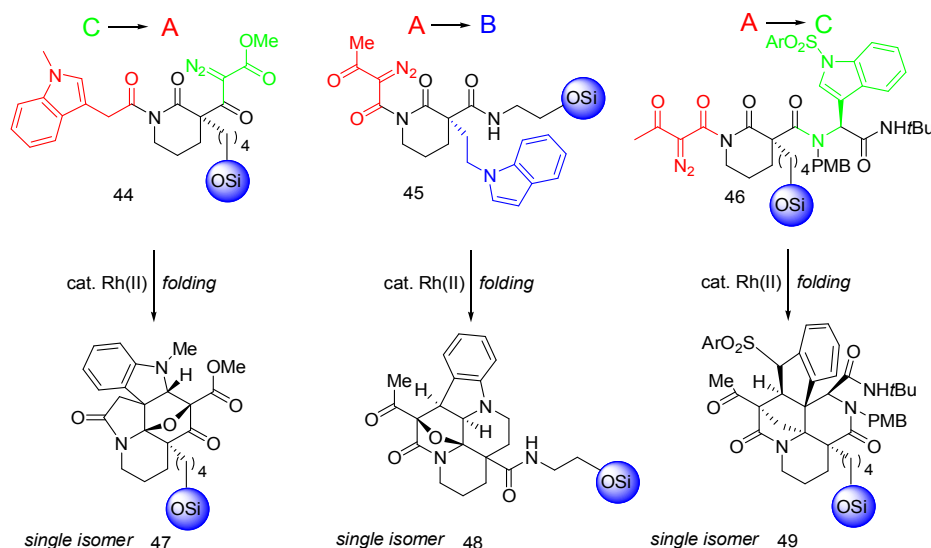
folding processes were triggered by treatment of the tetrahydropyridines **38-40** with tributyltin hydride and a substoichiometric amount of AIBN at 80°C. The bromine atom on the phenyl group was strategically placed in substrates in order to generate the site-specific radical and consequently selective cyclization reaction to yield a range of distinct polycyclic alkaloid like frameworks.



Scheme 1-5: Folding Pathways in DOS

Schreiber's group has developed a folding pathway by using multiple modes of intermolecular reactions in a systematic fashion to generate the indole alkaloid-like skeletons, which have elaborate substrates and a versatile scaffold (Scheme 1-6) [57]. A mode C→A reaction sequence using Schreiber's general protocol possessed *R*-diazoketocarbonyl and indole groups at sites C and A [58], respectively start with the installation of the alkyl linker on site B, via *C*-alkylation producing ester to be activate, the α -ketoester is installed on site C by a coupling reaction with a magnesium enolate [59]. Treatment of the *R*-diazo ketoester with a catalytic amount of rhodium(II) octanoate dimer in benzene at 80 °C results in the formation of a presumed carbonyl ylide intermediate that undergoes cycloaddition to afford hexacyclic **47** in 74% yield as a single isomer [58]. The pathway for the mode A→B, *C*-Alkylation that have an indole group at site B [60] and installing a linker having a terminal silyl ester, are treated with toluene to give *N*-acetoacetylated product which are converted into the α -diazoimide, then treated the α -diazoimide with rhodium (II) catalyst in benzene at 50 °C to generate hexacyclic **48** in good yield (74%) with

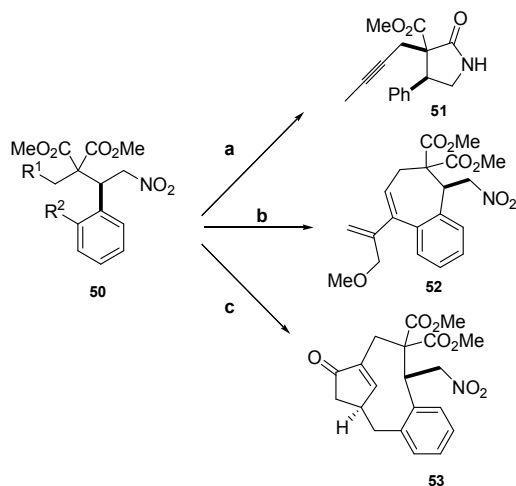
complete diastereoselectivity^[59, 61]. The pathway A → C is expected to provide an approach to generate diverse indole alkaloid-like compounds in only four steps, including a pair of complexity generating processes^[62], a Ugi four-component condensation reaction and a Rh-catalyzed tandem reaction.



Scheme 1-6. Folding strategy yielding a collection of products having diverse indole alkaloid-like skeletons—Depicted by Schreiber's group^[57]

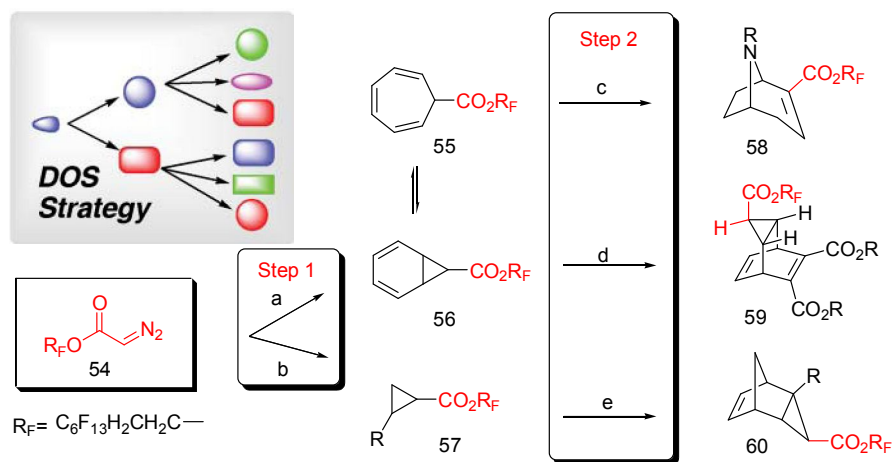
b) The **'branching pathway'** strategy involves the conversion of common precursors into a range of distinct molecular scaffolds (Figure. 1-3). This strategy is little more challenging and one needs to design the substrates which can be flexibly transformed into distinct molecular scaffolds. However, the synthesis of the molecules should remain combinatorial.

A branching pathway based on the chemistry of the Michael adducts **85** was developed by Porco (Scheme 1-7)^[62]. Reduction of the nitro group triggered lactamisation to yield γ -lactams such as **51**. In contrast, with appropriately positioned alkenyl and alkynyl substituent, cyclization via ring-closing metathesis or Pauson–Khand reaction was possible. With $R^1 = \text{allyl}$ and $R^2 = \text{C}\equiv\text{CCH}_2\text{OMe}$, enyne metathesis yielded the cyclic diene **52**. In contrast, with $R^1 = \text{C}\equiv\text{CH}$ and $R^2 = \text{allyl}$, a Pauson–Khand reaction allowed the remarkable bridged cyclopentenone **53** to be obtained.



Scheme 1-7: Porco's Branching Pathway; a) Zn, AcOH-THF, then Na₂CO₃ (aq.) [R₁ = C≡CMe, R₂ = H]; b) Grubb's 1st gen. cat., ethylene, MW, 150 W, 50° C, CH₂Cl₂ [R₁ = allyl, R₂ = C≡CMCH₂OMe]; c) Co₂(CO)₈, MW, 150 W, 80° C, CH₂Cl₂ [R₁ = C≡CH, R₂ = allyl].

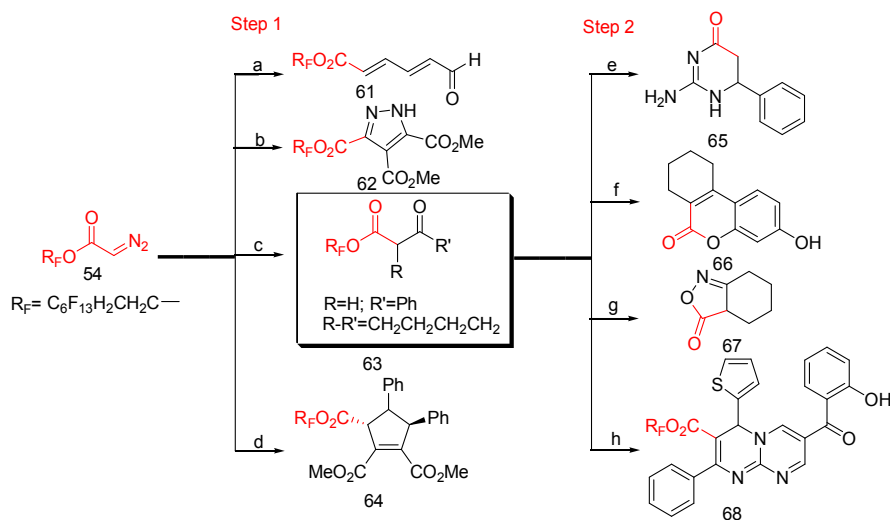
In another case of branching pathway approach inspired by the nature, Spring's et. al. used the fluororous tagged α -diazooacetate 'two-carbon' unit **54** as starting to create diverse scaffolds^[63]. The molecular complexity was generated in the second step of the synthesis as shown in Scheme 1-8 and Scheme 1-9 below^[64-66].



Scheme 1-8 Example of diversity-oriented synthesis with fluororous-tagged diazoacetate (1). (a) C₆H₆, Rh₂(O₂CCF₃)₄, 70%; (b) RCCH, Rh₂(OAc)₄, [BuCCH, 57%]; (c) RNH₂, NaOH then MeOH, H₂SO₄, [MeNH₂, 35%]; (d) dienophile [dimethyl acetylenedicarbonylate, 59%]; (e) C₅H₆, 92%.—Depicted by Spring's group^[58b]

Thus, in the first step of the DOS, multi-functional group **54** follows the following reactions to yield skeletally diverse molecules: (1) three member ring formation (shown in Scheme 1-8); (2) 1,3-dipolar cycloadditions (b and d, Scheme 1-8); and (3)

α -deprotonation and subsequent quenching with an electrophile and carbenoid formation (c, Scheme 1-8).

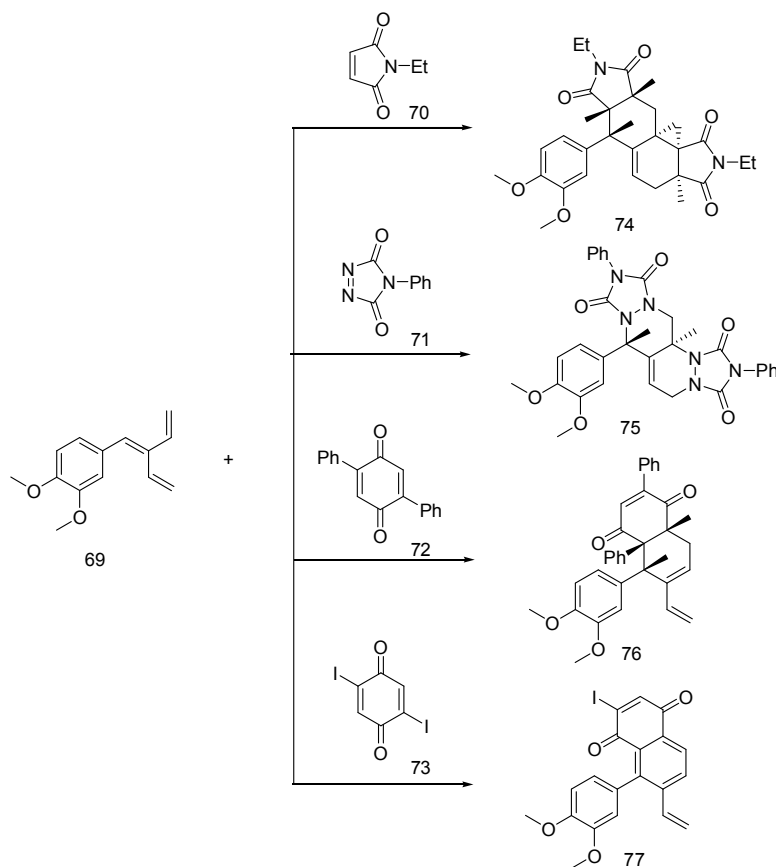


Scheme 1-9 Divergent reaction pathways lead to skeletal diversity. (a) $\text{Rh}_2(\text{OAc})_4$, furan, then I_2 , 60%(91%). (b) DMAD, 84% (88%). (c) LDA, RCOR_9 , then $\text{Rh}_2(\text{OAc})_4$; 8: 49%(90%); 9: 68%(97%). (d) PhCHO, PhNH₂, then DMAD, $\text{Rh}_2(\text{OAc})_4$, d.r. 5 : 20 : 1, 51%(80%). (e) Guanidine carbonate 62%(96%). (f) Resorcinol, H_2SO_4 , 74%(95%). (g) NH₂OH, 77%(89%). (h) Thiophene-2-carboxaldehyde, guanidine carbonate, then 3-formylchromone, 43%(98%). Yields and purity (in brackets) of the product example following generic purification using (reverse) fluoros SPE or precipitation shown. Purity determined by HPLC, LCMS or ¹H NMR. DMAD 5 dimethyl acetylenedicarboxylate.—Depicted by Spring's group^[63]

The divergent chemistry of the fluorous-tagged diazoacetate explained above thus, yielded 223 small molecules, which are divided into 30 discrete molecular frameworks with unique structural features (Scheme 1-4).

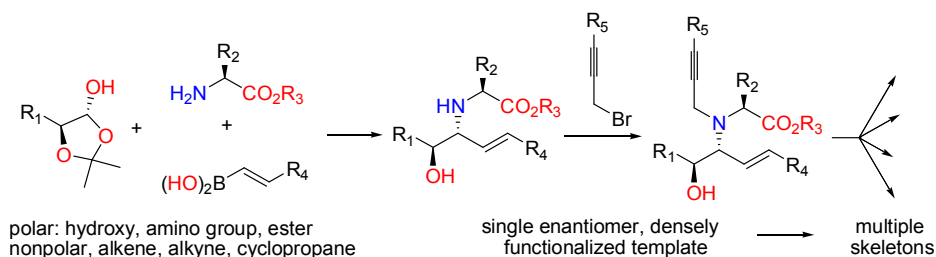
In a typical example of reagent-based approach, Fallis's group exploited the triene^[1, 67] **69** which due to characteristic functionalization of dienes undergo tandem Diels-Alder reactions with various dienophiles to generate diverse building blocks (Scheme 1-5)^[68]. Thus, the reaction of triene **69** with *N*-phenylmaleimide **70** and triazole **71** separately afford one Diels-Alder reaction *in situ* followed by another one with a second molecule of the dienophile **70** or **71** to give tetracyclic product (81%). In the same way, benzoquinone **72** or **73** are added to the starting compound triene **69** at 21 °C to yield the bicyclic skeletons in a single cycloaddition reaction and obtain functionalized cyclohexene derivatives.^[68] Thus, by using tandem cycloadditions

complex multicyclic skeletons were easily and efficiently built up.



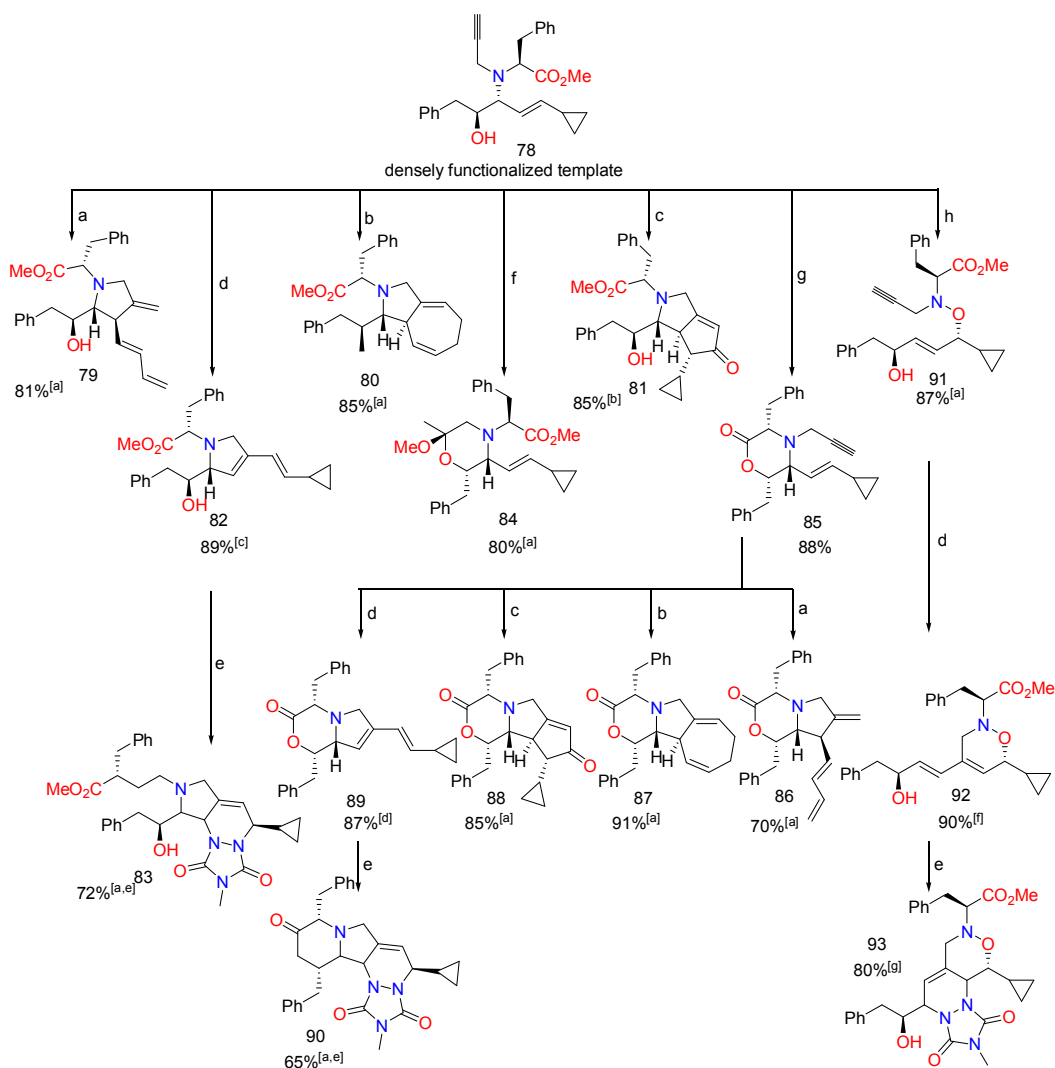
Scheme 1-10 DA reactions generate diverse compounds

Schreiber's group reported concise and efficient synthesis process, which used the succinct intermolecular cyclization reactions and densely functionalized amino alcohols^[14, 69]. The complete synthesis of a compound collection which has more than 15 different types of skeleton used only three to five steps. They used the Petasis three-component and boronic acid Mannich reactions, later an amine propargylation to generate β -amino alcohols. These compounds undertook polar (amino, hydroxy, ester) and nonpolar (alkene, alkyne, cyclopropane) functionalities to generate densely functionalized template, and then came to the skeletal diversification reactions (Scheme 1-11).



Scheme 1-11. The Petasis reaction followed by amine propargylation to yield β -amino alcohols.—Depicted by Schreiber's group^[69]

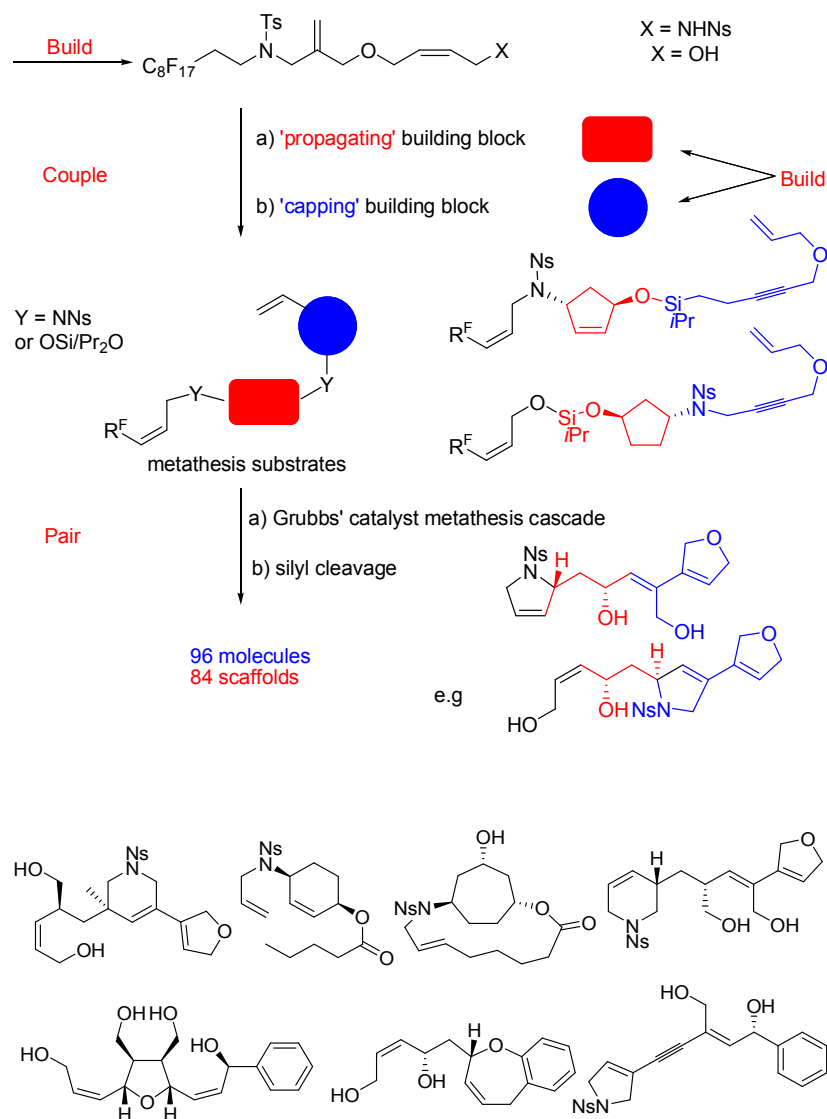
A series of skeletal diversification reactions with **78** (Scheme 1-12) were then explored. For instance, while the cycloisomerization catalyzed by $[\text{Pd}(\text{PPh}_3)_2(\text{OAc})_2]$ resulted in opening of the cyclopropyl ring to afford triene; cycloisomerization catalyzed by $[\text{CpRu}(\text{CH}_3\text{CN})_3\text{PF}_6]$ (Cp=cyclopentadienyl) resulted in a [5+2] reaction to afford cyclic diene. A Pauson–Khand reaction, in which the starting compound **78**, $[\text{Co}_2(\text{CO})_8]$ and trimethylamine N-oxide were mixed efficiently yielded azabicyclo-[3.3.0] ring-system diastereoselectively (>10:1 d.r.). Enyne metathesis of starting compound **91** using the Hoveyda–Grubbs catalyst provided diene, then followed Diels–Alder reaction with 4-methyl-1,2,4-triazolin-3,5-dione at room temperature to afford tricyclic building block **93**. Further reactions of selected skeletons generated a second generations of compounds. For example, the lactone **85** was subjected to the same reaction conditions as those for template **78** to well afford the corresponding bicyclic triene **86**, fused tricyclic [5+2] product **87**, fused tricyclic enone **88** and bicyclic diene **89**. Diene **89** was further converted into fused tetracyclic compound **90** by a Diels–Alder reaction using the same conditions. The transformations of lactone **85** also proceeded with high diastereoselectivity to generate each product as a single detectable diastereomer^[1, 69].



Scheme 1-12. a) $[\text{Pd}(\text{PPh}_3)_2(\text{OAc})_2]$ (10 mol%), benzene, 80°C ; b) $[\text{CpRu}(\text{CH}_3\text{CN})_3\text{PF}_6]$ (10 mol%), acetone, RT; c') $[\text{Co}_2(\text{CO})_8]$, trimethylamine Noxide, NH_4Cl (for conditions c), benzene, RT; d) Hoveyda–Grubbs second-generation catalyst (10 mol%), CH_2Cl_2 , reflux; e) 4-methyl-1,2,4-triazoline-3,5-dione, CH_2Cl_2 , RT; f) NaAuCl_4 (10 mol%), MeOH , RT; g) NaH , toluene, RT; h) mCPBA, THF, $-78-0^\circ\text{C}$. [a] Single diastereomer; [b] $>10:1$ d.r.; [c] trans/cis=6.7:1; [d] trans/cis=6.4:1; [e] from trans diene; [f] trans/cis=3:1; [g] combined yield from the trans and cis dienes. mCPBA=m-chloroperbenzoic acid.—Depicted by Schreiber's group ^[65]

Design of the common substrate which can be transformed into skeletally diverse molecules is obviously dictated by the nature of chemistry one plans to execute. An intelligent design can provide an easy access to numerous small molecular scaffolds in a very quick and efficient manner. One notable example is the preparation of a complex and highly diverse library by the group of Nelson ^[70] using ruthenium metathesis reactions as key transformations. This approach relies on the quick and efficient generation of simple scaffolds suitable for a series of cascading ring closing

and ring opening or ene-yne metathesis reactions (Scheme 1-13). The precursors consist of three parts, a constant fluorinated tag, to simplify the purification step using fluoruous solid-phase extraction; a propagating core of cyclic nature or containing alkynes, which allows the cascade propagation through ring-closing-ring-opening metathesis while the alkyne containing propagating unit allows for the propagation through ring-closing ene-yne metathesis cascade and a capping group, where the reaction sequences are initiated. With this approach, Nelson et al could generate more than 84 different molecular frameworks.



Scheme 1-13. Efficient generation of complexity using Grubbs ruthenium catalysts^[71].

1.5 Biology Oriented Synthesis (BIOS)

BIOS is another concept that leads to the synthesis planning and takes into account the biological relevance as a major prerequisite for design and synthesis of compound libraries^[72]. The core-structures of bioactive molecules like natural products or drugs form the basis for design of compound libraries. The concept of BIOS further exploits the evolutionary link between the protein and the natural products world. The typically targets for natural products and other bioactive molecules are the three-dimensional folds of proteins. These folds have been well conserved during and over the evolution than their underlying amino acid sequences.^[73] Similarly, the frameworks of different natural product classes exhibit a kind of conservatism. Thus, these two classes of molecules that often are ligand and receptors for each other do complement the elements of conservatism. On the basis of these facts, Waldmann et al developed the guidelines for compound library development and termed BIOS.^[72] Thus, the scaffolds of either natural products or medicinally important molecular classes are used as starting points for the design and synthesis of small focused libraries. In the first concept of BIOS i.e. “structural classification of natural products” (SCONP),^[74] a “natural product scaffold tree” was generated to correlate the scaffolds of natural products in a hierarchical manner thus allowing simplification of complex frameworks to simple ring systems that could be taken as starting points for the library synthesis (Figure 1-4)^[75].

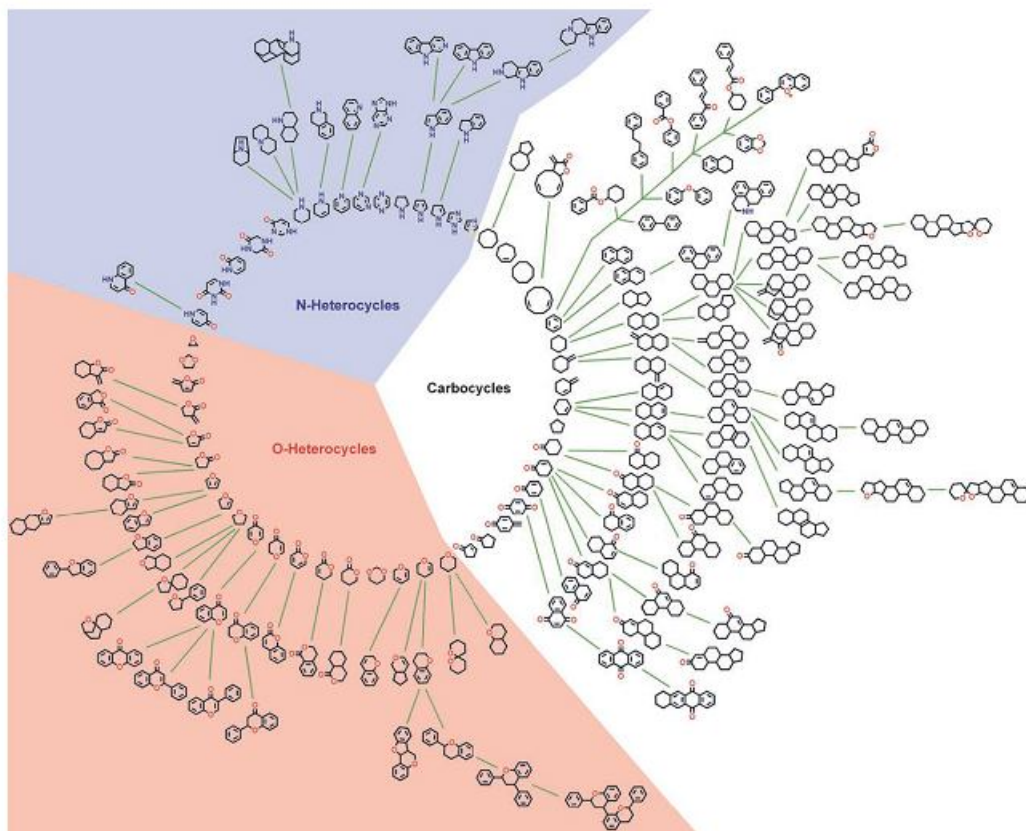
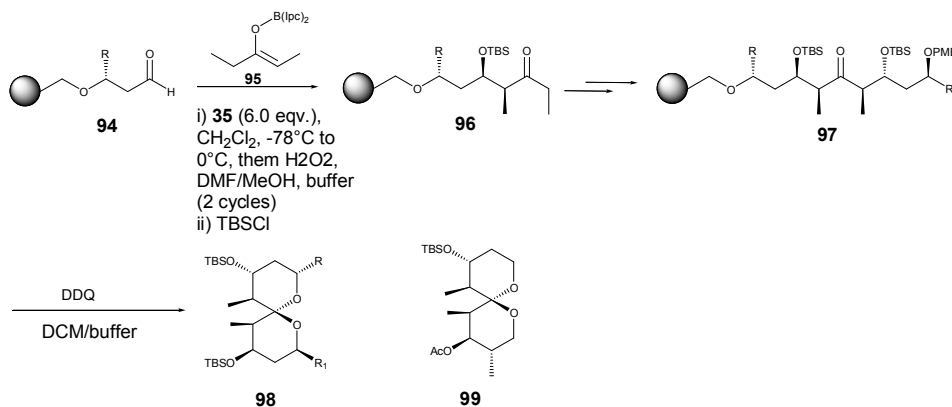


Figure 1-4: Tree-like graphical representation of natural-product scaffolds. For clarity, only scaffolds that cumulatively represent at least 0.2% of the natural products in the DNP are shown.

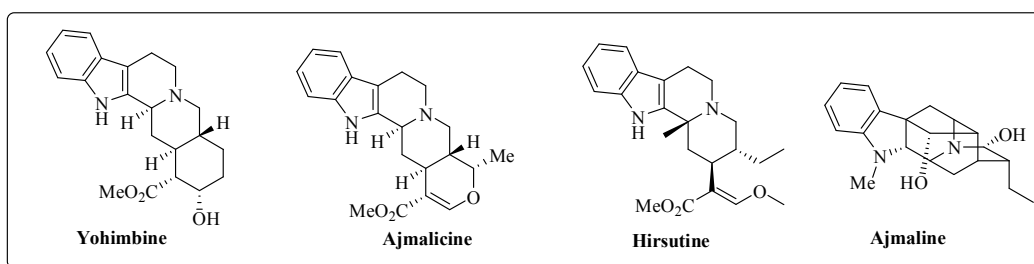
Thus, it would be of significant interest to find the structural motifs of natural products which could retain or improve the kind of biological activity of the parent natural product. For instance, Waldmann et al synthesized a compound library based on a simple spiroketal motif to determine if the spiroacetal moiety which is part of extraordinarily potent tubulin polymerization-inhibiting complex natural product spongistatins, could retain this bioactivity (Scheme 1-14).^[76]



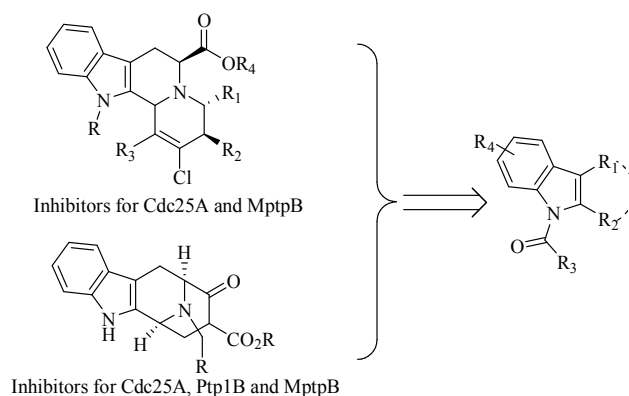
Scheme 1-14. Solid phase asymmetric synthesis of a spiroacetal collection.

An aldol reaction of the resin-bound aldehyde **94** with the preformed *Z*-boron enolate **95** provided the enantioenriched aldol adduct **96**. An *anti*-selective aldol reaction of an *E*-boron enolate (generated on the solid phase) with a set of aldehydes provided the protected bis (β -hydroxy) ketone **97**. Simultaneous removal of the PMB group and acetalization was performed by oxidative cleavage using DDQ, thereby releasing the spiroketals **98** from the resin.. Interestingly, compound **99** (Scheme 1-14) obtained from this collection was found to be an inhibitor of the phosphatases VHR and Ptp1b with IC₅₀ values of 6 and 39 μ M respectively and also could distort the correct organization of the tubulin network in a human carcinoma cell line.

Thus, BIOS may help identify structurally simpler starting points for library design and provide high hit rates in yielding desired inhibitor/activator molecules. In yet another example from the same group, structurally complex alkaloids – yohimbine and ajmalicine – were identified as inhibitors of the protein phosphatase Cdc25A. SCOMP analysis and brachiation simplification led to tetracyclic indolo[2,3-*a*]-quinolizidines. A library based on the indoloquinolizidine scaffold yielded two compounds with IC₅₀ values comparable to the natural products. By extending the screen to other phosphatases, structurally new inhibitors of the *Mycobacterium tuberculosis* phosphatase MptpB could be identified.^[77] In a similar manner, BIOS of a focused library of macroline analogs yielded several new inhibitors of the *Mycobacterium tuberculosis* phosphatase MptpB^[78]. Interestingly, further simplified compounds with three- and two-membered rings also yielded one inhibitor of Cdc25A with an IC₅₀ value similar to the value recorded for the pentacyclic molecule. The compound collection also contained inhibitors of protein tyrosine phosphatase 1B and MptpB including eight inhibitors with sub-micromolar IC₅₀ values.

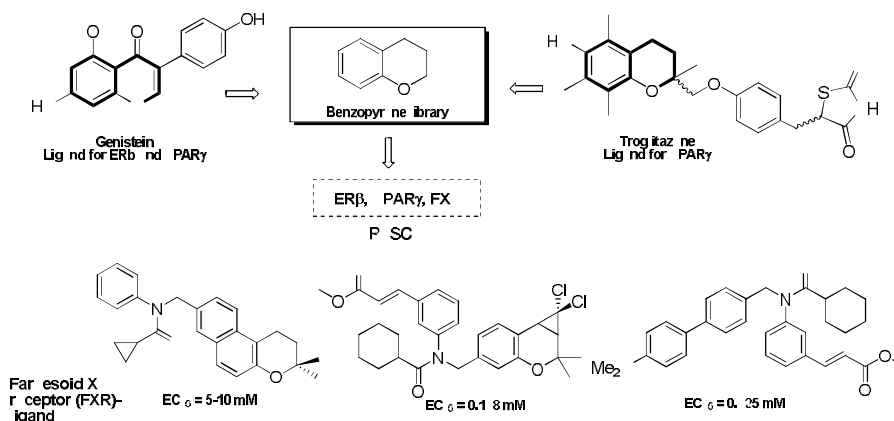


Natural products



Scheme 1-15. Natural product alkaloids inspired compound libraries.

In the second concept incorporated in BIOS i.e. “protein structure similarity clustering” (PSSC), the biological protein targets of small molecules are classified into clusters according to structural similarity in their ligand binding cores.^[79] The inhibitor of one of the proteins of such clusters could represent a class of potential inhibitors for all other proteins in that cluster. For instance, an example from a retrospective analysis of literature data using the PSSC concept would have suggested the development of ligands for the farnesoid X receptor.



Scheme 1-16. A BIOS approach to identify synthetic ligands for farnesoid X receptor.

The farnesoid X receptor is a member of the class of nuclear hormone receptors, which have key roles in development and homeostasis, as well as in many diseases like obesity, diabetes and cancer.^[80] The ligand sensing domain of the farnesoid X receptor was found to be structurally similar to the cores of the estrogen receptor β

(ER β)^[81] and the peroxisome proliferation-activated receptor γ (PPAR γ)^[82] This cluster of proteins exhibits a similar fold pattern but with less than 20% sequence similarities. The natural product genistein (Scheme 1-16) is an inhibitor for both the ER β and PPAR γ receptor.^[83] Also, troglitazone, a benzopyrane drug modulates the activity of the PPAR γ receptor.^[84] In a retrospective analysis, a BIOS approach would have taken the benzopyran scaffold which is common to both ligands as starting point for the library to identify farnesoid X inhibitors. The benzopyran library synthesized by Nicolaou *et al.* indeed yielded such ligands^[85] for the other members of this PSSC (Scheme 1-16)..

The BIOS approach thus not only provides simplified biologically relevant starting points for compound library synthesis but also opportunities for medicinal chemistry research by unraveling unprecedented classes of protein inhibitors. In another example dehydrodecalins were identified as potent inhibitors for 11 β HSDs. Glycyrrhetic acid (Figure 1-5), a structurally complex natural product is a ligand of the enzyme 11 β HSD1. On simplification by SCONP analysis, the parent structure of glycyrrhetic acid led to two decalin motifs as starting points for library synthesis. The critical decision for the right decalin scaffold as core structure was taken by considering a natural ligand for the Cdc25A protein which is a member of the protein cluster along with 11 β HSDs and AChE. Dysidiolide is a NP ligand for Cdc25A^[86] and also embody a dehydrodecalin motif and thus this scaffold was chosen as starting point for a collection of ca. 500 dehydrodecalins. These were synthesized using an asymmetric Robinson annulation as the key transformation^[87]. Biochemical screening of 162 compounds from this collection for inhibitory activity on 11 β HSD yielded 30 inhibitors with IC₅₀ values below 10 μ M; 4 of them even showed IC₅₀ values between 310 and 740 nM.

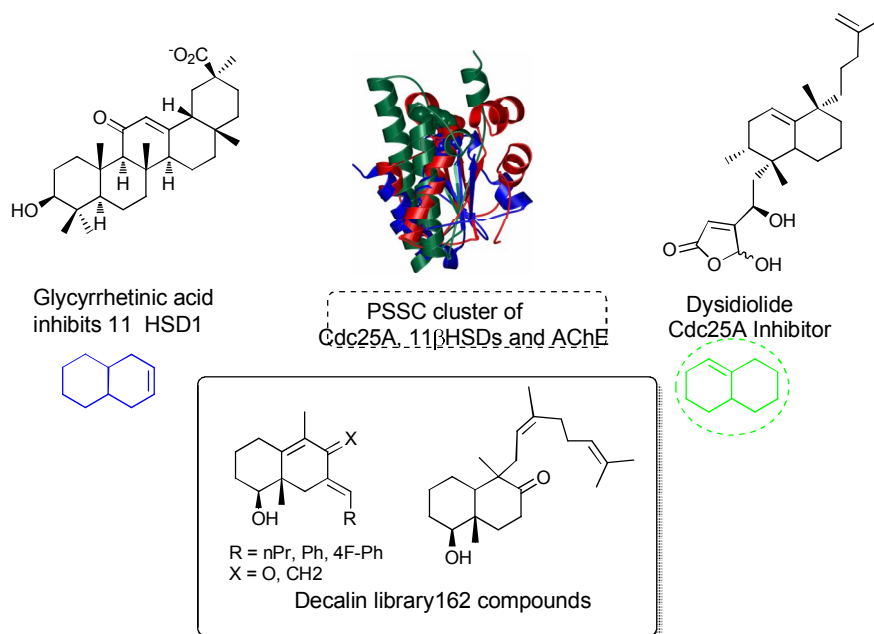


Figure 1-5. A BIOS approach to develop inhibitor classes for a cluster of proteins.

1.6 Summary and future perspectives

Progress in the biological sciences, in particular, the deciphering of the genomes of various organisms including man during the last decades has led to a steep increase in knowledge about basic biological processes as well as the factors leading to their misregulation and ultimately the establishment of disease. Small bioactive molecules can provide immensely important insights in chemical biology research, where they are used to perturb a given biological system followed by analysis of the difference between perturbed and non-perturbed state. In a drug discovery or medicinal chemistry research, small bioactive molecules as 'hit and lead compounds are prerequisites to progress them to the lead and development candidate stage in order to modify disease states. These two approaches differ from each other in their goals, although the initial steps and milestones to discover biologically active molecules are very similar. In both cases the chemist faces the same question as to which compounds to synthesize and use in biochemical or biological screen medium or high through-put screen? An answer to this question is not readily given and the selection is even made more complicated by the diverse criteria to be met in the subsequent

optimization steps. Given this uncertainty, one always desires to enrich the initial compound collections that undergo screening with biological activities in order to obtain certain number of starting hits which can be evolved into either chemical probes or drug candidates. Both DOS and BIOS are chemists' endeavors to enrich the collections with functional characteristics including biological activity.

In order to meet this goal, compound collections should incorporate both diversity and molecular complexity into their compound classes. That definitely calls for developing efficient synthesis strategies that can generate skeletally diverse and complex molecules rapidly and in a combinatorial fashion. In particular, synthesis planning should develop new complexity generating reactions that yield molecules embodying scaffolds of natural products in a concise and efficient manner.

1.7 The aim of this work

Recent years have witnessed chemists' endeavors targeting bioactive small molecules shaping up different hypothesis, for instance DOS and BIOS ^[89]. It would however be enlightening to understand the way nature targets bioactive regions of vast chemical space while creating diverse natural products ^[90]. Adapting similar strategies in compound library syntheses might enrich them with desired and interesting biological activities. In a prominent biosynthetic strategy, primary metabolites or derivatives would build up an intermediate scaffold which is later transformed into diverse secondary metabolites, often retaining the molecular framework of intermediate ^[91].

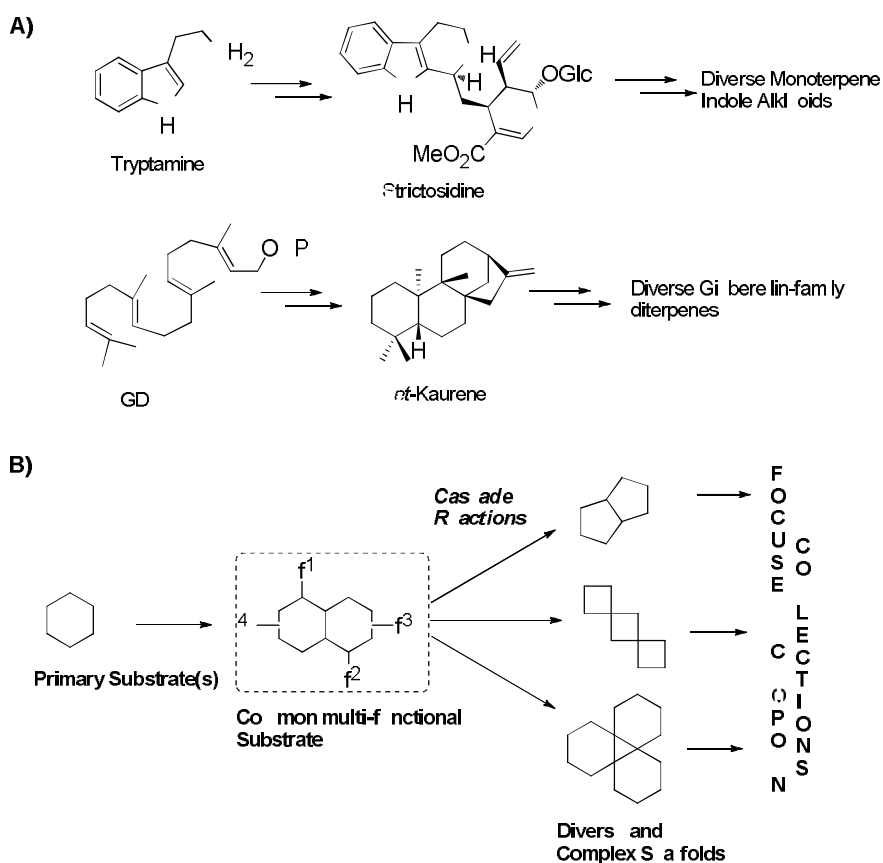


Figure 1-6 Biosynthetic and Cascade reaction strategies

Figure 1-6. A) Biosynthetic strategies leading to diverse secondary metabolites, B) Cascade reactions based strategy to transform a common multi-functional substrate into diverse scaffolds. For instance, in indole alkaloid biosynthesis^[92], tryptamine is converted into a template structure, Strictosidine, which is further transformed into a variety of monoterpene indole alkaloids (Figure 1-6, A). Similarly, in the Gibberellin biosynthesis pathway geranylgeranyl diphosphate (GGDP) is cyclized to form a template scaffold ent-kaurene, which undergoes skeletal and functional group transformations to at least 136 products with only few of them displaying biological activities (Figure 1-6, A).^[93] A different cyclization of GGPP catalyzed by taxadiene synthases forms another common intermediate taxadiene which later elaborates into taxol and related natural products^[94]. Nature, thus exploits branching pathway strategy in transforming the common intermediate into diverse and complex secondary metabolites to provide the required diversity in the secondary metabolites to achieve the desired biological activities^[90, 95]. On this inspiration, it could be

possible to design the common substrates decorated with required functional groups that can facilitate chemical transformations providing different scaffolds under different conditions. The better would be if these transformations happen in a one-pot strategy or in a domino reaction sequence fashion to yield complex and diverse molecular architectures.

Thus in our approach, which is based on branching pathway strategy and is termed as *branching cascades* for it exploits the cascade/domino reaction sequences, a common precursor follows different domino or cascade reaction sequences that are triggered by different reagents by exploiting diversely reactive multiple functionalities on the common substrates in our case (Figure 1-6, B). Every cascade reaction sequence could in principle lead to a different scaffold formation. The mode of triggering these cascades can be controlled by both adding non-addundant reagents that only activate and push a domino reaction. In this case, different intermolecular transformations would yield diverse molecules without addition in the overall molecular weight of the molecules. In the second approach, addition cascade triggering substrates could be employed that follow different cascade reaction owing to their diverse inherent chemical relativities and also add to the overall complexity of the final products. In the later case, therefore numerous variations in the inter- and intermolecular chemical transformations are possible and thereby far more skeletal diversity and complexity can be accessed. In addition, the branching cascade strategy would yield molecules that are already functionalized because out of much functionality in the common substrates only few would be exploited in every cascade reactions. Therefore, synthesis of analogues of the branching cascade products should be much easy and efficient and so should be the generation of focused compound collections.

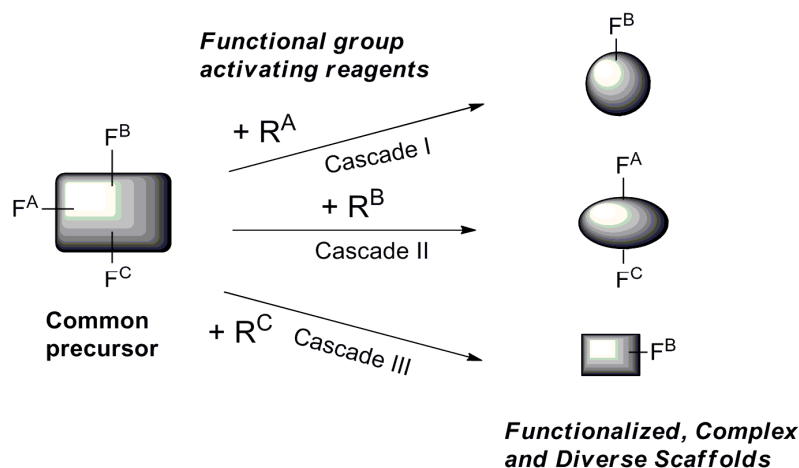
2. Reagent Controlled Branching Cascades

2.1 Introduction

The use of diverse sets of small molecules in chemical biology studies has led to many new insights into various biological phenomena ^[96-98]. For the development of compounds that help elucidate the mysteries of life processes, DOS and BIOS have proven to be useful approaches ^[99-101]. In both of these approaches, structural complexity and diversity is often generated by means of multi-step sequences employing skeletally-differentiating transformations on common precursors. Development of synthetic methods that allow rapid and systematic variation of molecular scaffolds has proven to be extremely challenging ^[99]. Not surprising, often it is impossible to avoid tedious and multistep synthesis to access different scaffold structures. Further, addition of functionalities and modifications thereof require more efforts with each and every synthetic step reducing the yield of the desired molecules. Targeting a cascade reaction sequence based concise synthesis strategy, we envisioned that branching cascade strategy could provide complex, diverse and functionalized scaffold structures and thereby small focused libraries in an efficient manner ^[100]. Substrates capable of entering cascade/domino reaction sequences must have diverse reactive sites, at which different chemical reactions can take place in a sequential manner. Therefore, a key to successful branching cascade strategy would require an elegant design of the common precursors. In the following section, the reagent controlled branching cascade strategy is detailed wherein a common precursor is activated by different reagents and thus pushed into different domino reaction sequences ^[101]. Every domino reaction sequence transforms the precursor into skeletally different scaffolds that comes out suitably functionalized.

The chemical functionalities on a common precursor (Figure 1-5) can be activated/modified in number of ways in order to trigger a cascade reaction sequence

that might include inter- and intermolecular transformations leading to a new complex scaffold. As depicted in the figure 2-1 below, different functionalities F^A , F^B or F^C on the common substrates can be modulated by different reagents R^A , R^B and R^C . A treatment with each reagent thus would trigger a cascade reaction wherein activation of one functional group pushes the reaction sequence involving other functional group(s) and leading to diverse scaffolds (Figure 2-1).



Reagent Controlled Branching Cascades

Figure 2-1: Reagents controlled branching cascades

2.2 Design and synthesis of Common Precursor

Appropriately substituted 3-chromanylidene- β -ketoesters (Figure 2-2) were envisioned as the key precursors for the establishment of new cascade or domino reaction sequences. If appropriately substituted with reactive functionalities that can be activated by different reagents, diverse inter- and intra-molecular chemical reactions would be plausible on these common substrates. The presence of reactive functionality (RF) along with an α,β -unsaturated moiety (blue), a vinylogous ester (grey), and a ketone (green) would bring numerous opportunities for performing different sequences of cascade reactions (Figure 2-2).

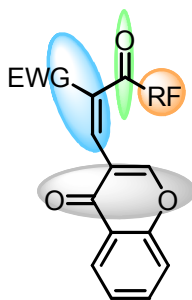


Figure 2-2: Substrate design for Branching Cascades; RF = reactive function, EWG = electron-withdrawing group.

Precisely, β -ketoesters **a1** with TBS protected group the common substrate **1** was planned. These compounds contain electrophilic centers, e.g. C2 and C10, where nucleophiles can attack, and also nucleophilic centers such as C4' and OH (after deprotection). Furthermore, the C3' ketone provides an entry into imine–enamine chemistry. Finally, the variable alkyl chain supports a terminal silylated alcohol. Thus, desilylating the alcohol at C7' could possibly induce the formation of six-membered hemiacetals. It was expected that different desilylating reagents might trigger different cascade reaction sequences and yield different molecules.

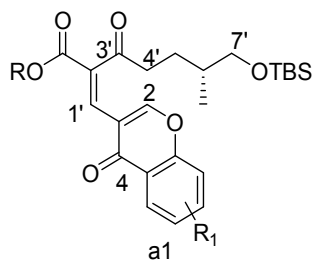
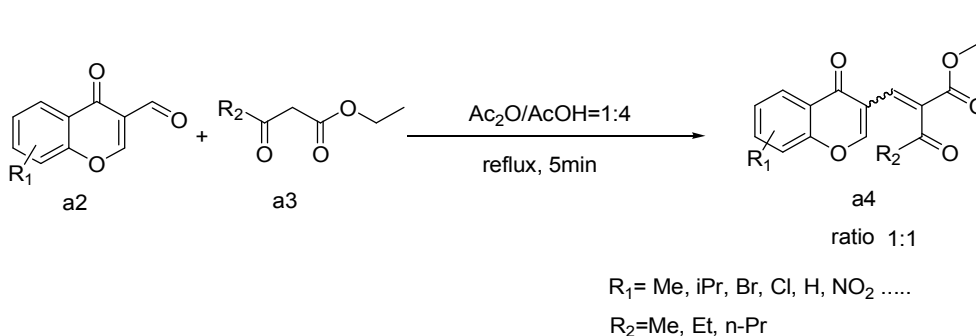


Figure 2-3: Common substrate for reagent controlled branching cascade.

Synthesis of **a1** and analogues commenced by condensing the substituted 3-formylchromones with ethyl 3-oxobutanoate in the acetic anhydride/acetic acid (Scheme 2-1). The reaction mixture was stirred in a preheated 145°C oil-bath under argon atmosphere which results in product formation within 5 minutes. After quenching the reaction mixture with water under argon, the mixture was kept for 2-3 hours when the suspending oil changed into transparent brown solution which was

extracted with ethyl acetate and dried over Na_2SO_4 . **A4** was formed as 1:1 mixture of E/Z-isomers, identified by two sets of peaks according to $^1\text{H-NMR}$ spectra. These two isomers were very difficult to isolate by silica gel column chromatographic purifications.



Scheme 2-1. Synthesis of chromen-methylene-anoate.

2.3 Reagent controlled branching cascades

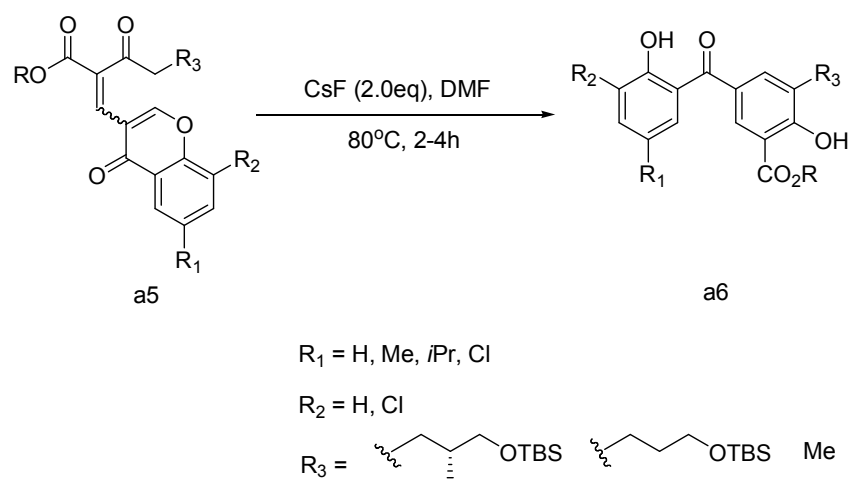
In order to induce a cascade reaction sequence on common substrates, it was planned to desilylate the alcohol by different desilylating reagent and determine if the formation of a possible hemiacetals or any other intermediate is followed by further reactions at the different electrophilic centers available in these molecules and result in transformation of common substrates into different ring systems.

2.3.1 Synthesis of functionalized phenols

Initially the standard desilylating reagent tetrabutylammoniumfluoride (TBAF) was employed. However to our disappointment the reaction led to a retro-aldol reaction, thereby hydrolyzing **a1** to form chromone and β -ketoesters.

In the next case, cesium fluoride as desilylating reagents was used. The common precursor beholds many electrophilic centers, especially highly electrophilic C2 (Figure 2-3), that can be easily attacked by nucleophiles. The chromanylidene

intermediates **a5** were treated with CsF in DMF at 80° C. Interestingly, the formation of substituted phenols **a6** was observed under these reaction conditions in moderate to good yields (Scheme 2-2). The reaction yields were much better using at least two equivalents of CsF. With these reaction conditions, differently substituted substrates **a5** were efficiently converted into the corresponding phenols **a6** in acceptable to good yields.



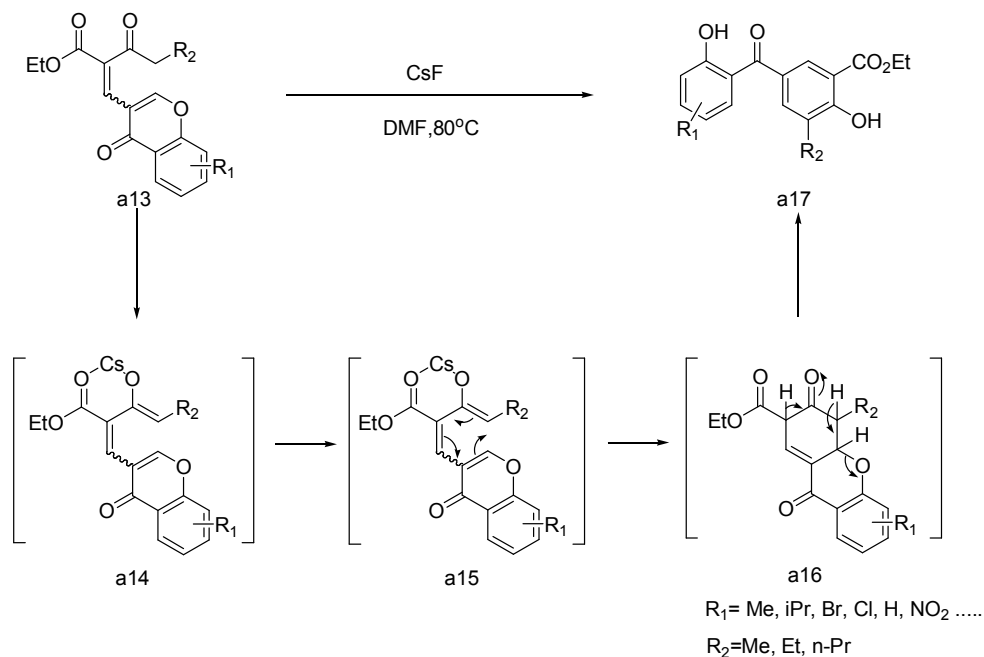
Scheme 2-2: Synthesis of functionalized phenols

COMPOUNDS	R ₁	R ₂	R ₃	R ₄	YIELD(%)
a7	iPr	H	H	Me	83%
a8	Me	H	H	Me	89%
a9	NO ₂	H	H	Me	81%
a10	F	H	NO ₂	Et	79%
a11	Cl	Me	H	Me	82%
a12	Br	H	H	Me	84%

Table 2-1 the results of functionalized phenols

Mechanistically, it is proposed that this cascade reaction sequence commences with the removal of the TBS group by CsF.

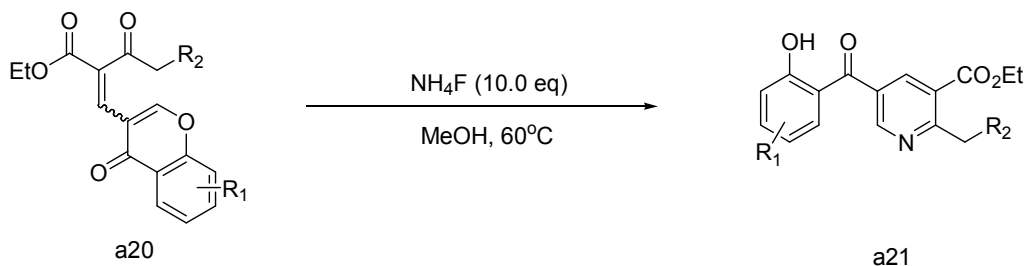
While the products lack the α -keto-CH₂ of the substrate **a15**, it is possible that a cesium enolate might have formed after desilylation reaction in this domino process and its addition C2 of the chromone ring generates the tricyclic intermediate **a16**. Isomerization and ring-opening of chromone would form **a17** that aromatize to generate the functionalized phenols **a17**.



Scheme 2-3. Domino synthesis of substituted phenols.

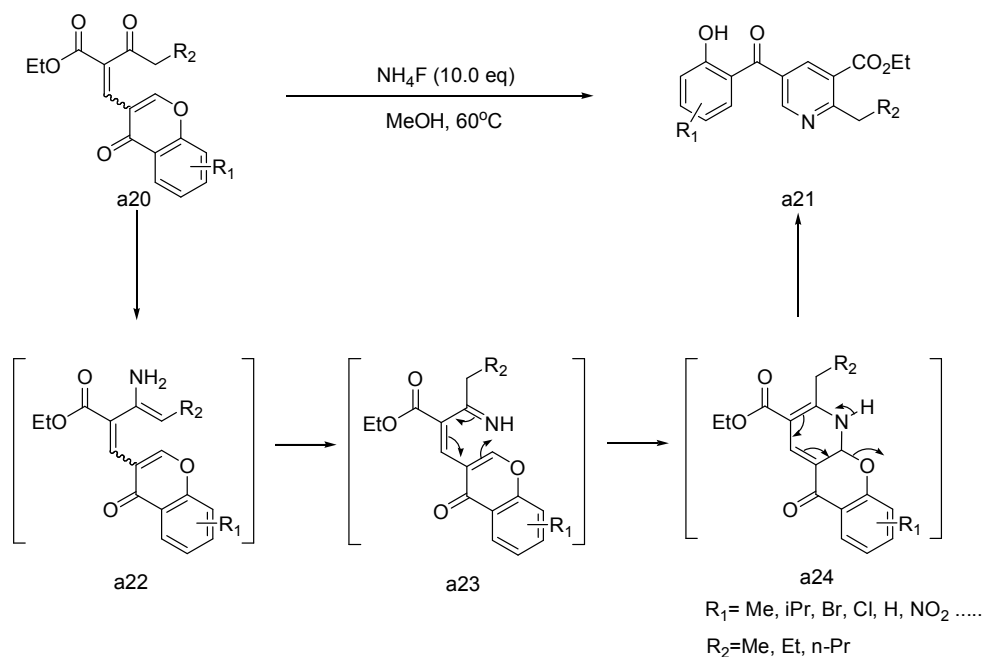
2.3.2 Synthesis of functionalized pyridines

In the second case, ammonium fluoride was employed as desilylating reagent at room temperature (Scheme 2-4). Interestingly, the reaction provided single products (TLC control) within an hour, which after purification (silica gel column chromatography) were identified by spectroscopic techniques (NMR, DEPT, HRMS) to be pyridines **a21** (Scheme 2-4). However, under these reaction conditions, the TBS ether remained intact. Extending the reaction time and raising the temperature (60 °C) led to clean removal of the protecting group (Scheme 2-4). Chromanylidene- β -ketoesters **a20** with short alkyl chains (R⁴ = Me or H) were also cleanly transformed to the corresponding substituted pyridines **a21** by means of this branching cascade (Scheme 2-4).



Scheme 2-4: synthesis of functionalized pyridines

Mechanistically, formation of the pyridine ring proceeded, most likely, by means of the initial conversion of e.g. β -ketoester **a20** into enamine **a22**, which then attacks the activated C-2 position in the chromone (**a23**, Scheme 2-5). Rearrangement was accompanied by opening of the chromone, and aromatization resulted in the formation of pyridine **a21**. Overall, this domino sequence provided high yields of substituted pyridines ^[102].

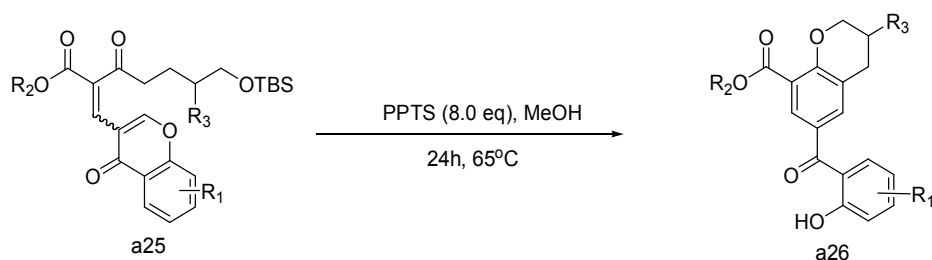


Scheme 2-5. Domino synthesis of substituted pyridine.

These two domino processes provided highly substituted phenols and pyridines, which could be further diversified for compound collection synthesis (Scheme 2-2 and Scheme 2-4).

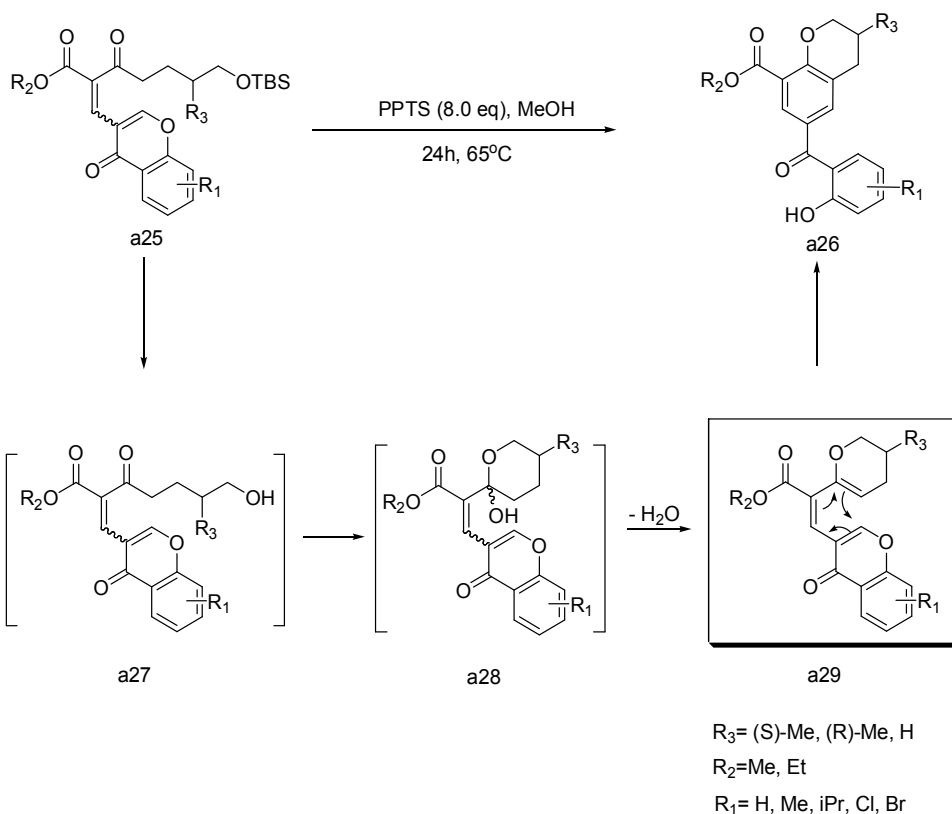
2.3.3 Synthesis of functionalized benzopyrans

One of the expected reaction pathway after desilylation of the TBS ether on common substrate was the formation of hemiacetal by addition of alcohol to ketone. However, in the two branching cascades described above, no reagent could induce this transformation. In order to realize this possibility that could lead to a different cascade reaction sequence, a desilylating reagent supporting the acetal formation reaction conditions is required. Based on this assumption, pyridinium para-toluene sulfonate (PPTS) was used as the desilylating reagent. Pleasingly, treatment of silyl ethers with PPTS in methanol at 65°C for 36 h led to the formation of benzopyrans (Scheme 2-6). During this reaction course, transesterification of the substrates was observed which could be successfully avoided by reducing the reaction time to 24 h.



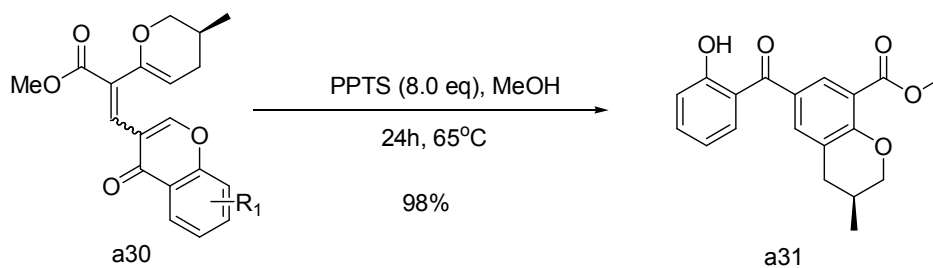
Scheme 2-6: Synthesis of functionalized benzopyrans

The PPTS controlled branching cascade operates by removal of the TBS group. The liberated alcohol cyclizes to generate the expected hemiacetal (Scheme 2-7). Removal of water molecule leads to the dihydropyran **a28**. An intermolecular cyclization followed by aromatization thus produces the benzopyrans **a29**. This domino sequence provided an obvious advantage on the reported multi-step synthesis of similar molecules ^[102].



Scheme 2-7. Domino synthesis of benzopyrans.

In order to have more insight into the reaction mechanism of this domino process, the reaction between building block **a25** and PPTS in methanol was stopped after 1 h, and the major product was quickly purified by flash column chromatography. We were pleased to find that this was not the final product—benzopyran but one of the expected intermediate i.e. chromanomethylidene- substituted dihydropyran **a30** (Scheme 2-8). Stirring the compound **a30** under the same reaction conditions—with PPTS in methanol at 65°C for 24 h, generated the corresponding benzopyran **a31** in almost quantitative yield was completely supporting the proposed cascade reaction mechanism in Scheme 2-8^[102].



Scheme 2-8. The reaction of dihydropyran to benzopyran.

In order to introduce hydrophobic alkyl chain which a stereoelement. The common substrates **a32** and **a33** were synthesis and employed in branching cascades. (Figure 2-4).

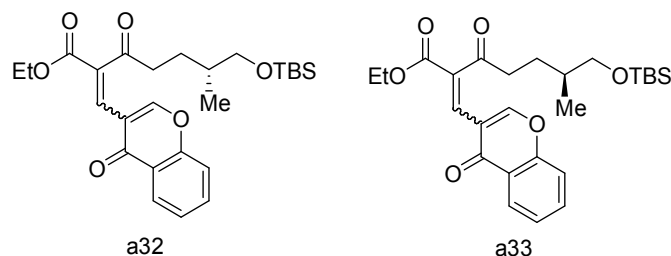
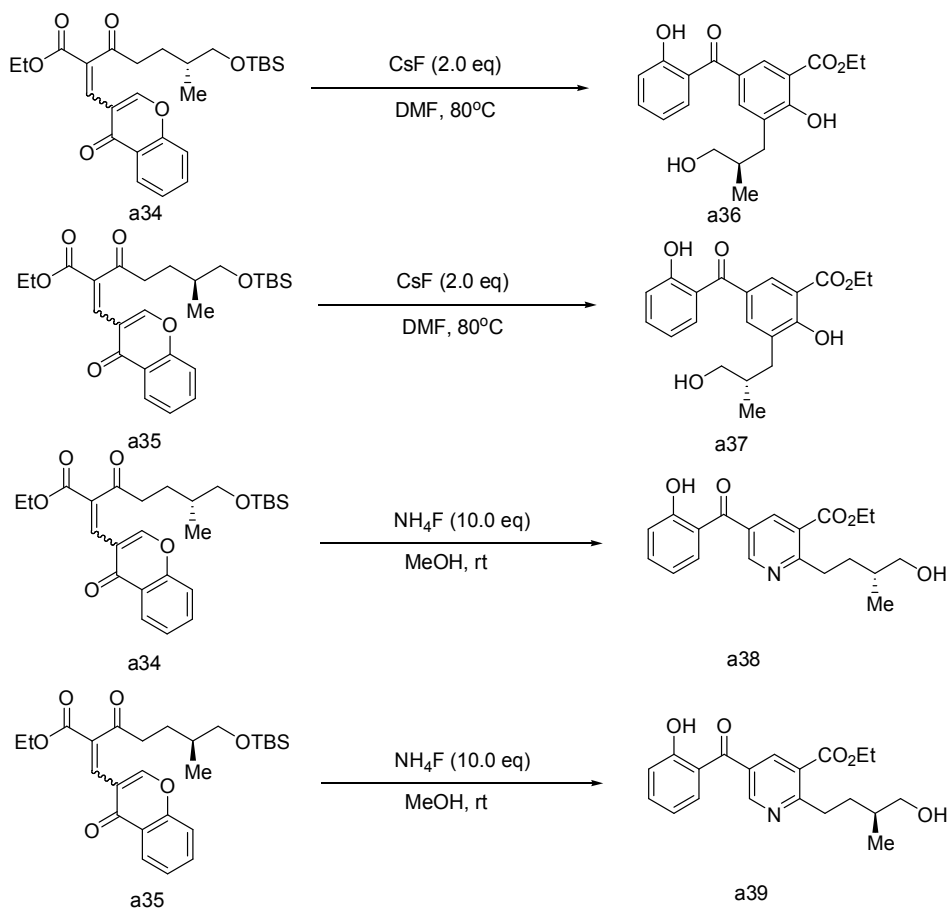


Figure 2-4. Silyl ester (offered by Francisca Martín Gálvez)

Indeed, expectedly and pleasingly, CsF and NH₄F induced their respective cascade reaction sequences. These substrates yield corresponding phenols and pyridine in good yield (Scheme 2-9).



Scheme 2-9. Silyl esters react with different reagents.

The hydrolysis of the ester groups with sodium hydroxide provided the corresponding carboxylic acids in good yields.

2.4 Functional group modification of the cascade products

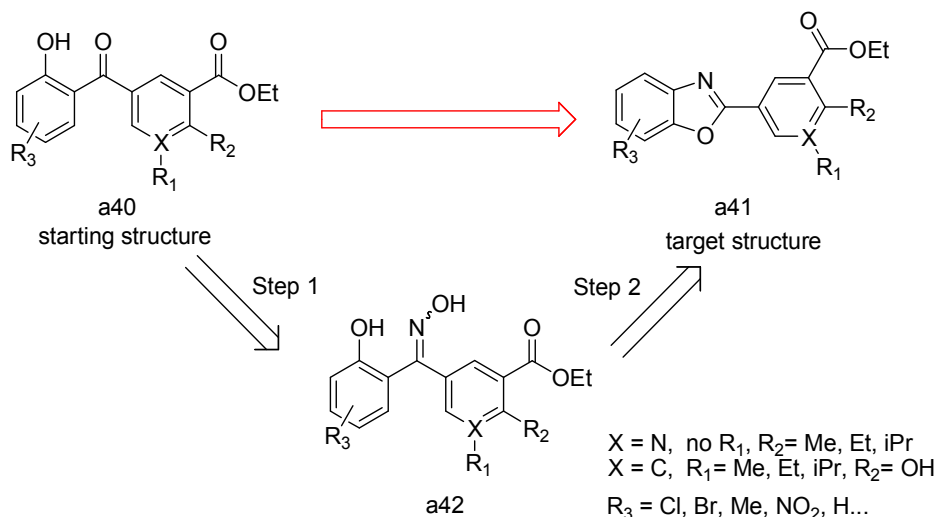
The reaction product obtained in above cascade sequences are well functionalized and therefore can be further modification to provide functional group diversity is the compound collection.

2.4.1 Synthesis of oximes, oxazole and isoxazole derivatives of pyridines and phenols

So as to combine the scaffold of the molecular architecture of the library with multiple biological properties and introduce special structure that were explored to add further diversity in three-dimension compounds space, synthesizing derivatives of building blocks are necessary. The structure of oximes, oxazole and isoxazole are similar with our building block and the building block can be easily converted into oxazole.

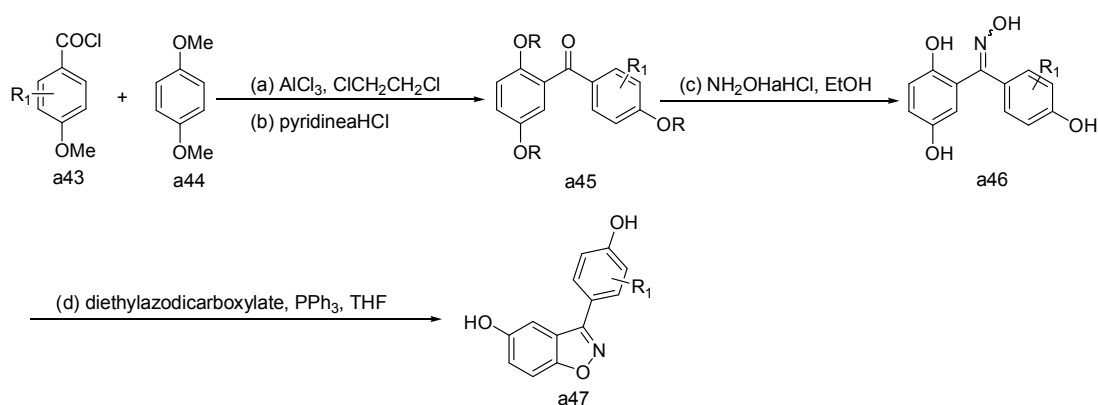
2.4.1.1 Synthesis of oximes

The presence of hydroxybenzoyl moiety in the cascade products, pyridines and phenols **a40**, suggest to covert the ketones to the corresponding oximes which can be transformed into the medicinally useful isoxazoles (Scheme 2-10) .



Scheme 2-11: Synthesis design the oxazole in our case.

A similar synthesis route from literature is presented in Scheme 2-11^[103]. In this case, benzophenone **a45** was prepared from benzoyl chloride **a43** and 1,4-dimethoxybenzene **a44** in the presence of aluminum chloride and 1,2-dichloroethane. The demethylation of benzophenone with pyridine hydrochloride at high temperatures (200 °C) produced benzophenone **a45**. This building was converted into benzisoxazole **a46** in two steps. First, oxime **a46** formation was accomplished with hydroxylamine in ethanol followed by dehydration of oxime **a46** under Mitsunobu condition—DIAD and PPh₃, yielded benzisoxazole **a47**.



Scheme 2-11: The synthesis of oxazole in literature

The corresponding oximes of the cascade products, pyridines and phenols were also of interest because they can modulate the bioactivity of the precursor ketones^[104-105].

For instance, it was proved that enones were easily converted into oximes and oxime hydrolysis was described as a substantial metabolic pathway. Oxime was regarded as useful prodrugs to develop more analogues (Figure 2-5) [106-107].

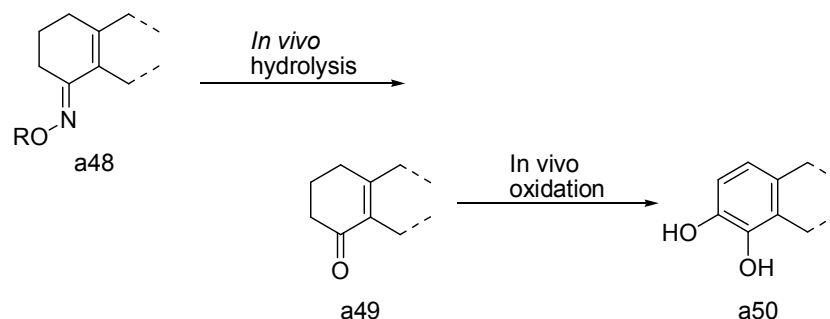
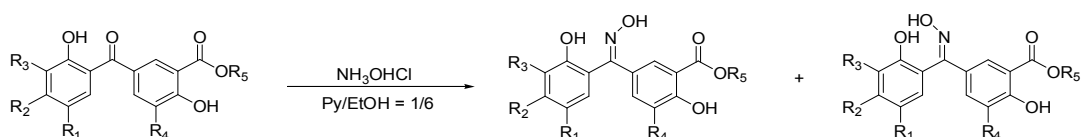


Figure 2-5. An oxime acting as a ‘cascade’ prodrug.—depicted by Wikström’s group. [107]

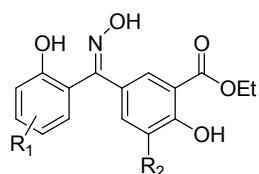
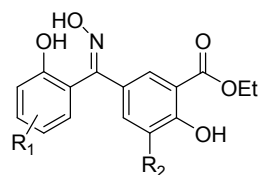
Thus, in order to access oxime formation of the phenols obtained in the branching cascade strategy, a mixture of hydroxyphenyl-benzoate, hydroxylamine hydrochloride (10.0 eq), pyridine (5 mL), and EtOH (30 mL) was heated to reflux. The solvent was removed under vacuum, after adding excess aqueous Na_2CO_3 , it was extracted with EtOAc. The organic layer was dried over MgSO_4 and concentrated to give a yellow solid. This solid was purified by column chromatography (30% EtOAc/hexane) to give two white solids in the 1:1 ratio. The two products appear very close on the TLC but could be purified by repeated chromatographic purifications (Table 2-2). These two products had the same molecular weight and the NMR spectra looked very similar, thus suggesting them to be the *E*- and *Z*- isomers of oximes (Figure 2-6). [103] Differently functionalized phenols were thus converted into their oximes in acceptable yields.



compounds	R_1	R_2	R_3	R_4	R_5	CONF.	Yield (%)
a51	Me	H	H	Me	Et	E	48%

a52	Me	H	H	Me	Me	Z	48%
a53	Br	H	H	Me	Et	E	47%
a54	Br	H	H	Me	Et	Z	47%
a55	i-Pr	H	H	Me	Et	Z	48%
a56	F	H	NO ₂	Me	Et	Z	45%
a57	NO ₂	H	H	Me	Et	E	47%
a58	NO ₂	H	H	Me	Et	Z	47%
a59	Cl	Me	H	Me	Et	E	47%
a60	Cl	Me	H	Me	Et	Z	47%
a61	H	H	H	Me	Et	E	49%
a62	Me	H	H	Me	Et	E	48%
a63	H	H	H	H	Et	E	48%
a64	H	H	H	H	Et	Z	48%
a65	Me	H	H	Et	Et	E	46%
a66	Br	H	H	Et	Et	E	47%
a67	Br	H	H	Et	Et	Z	47%
a68	H	H	H	Et	Et	E	48%
a69	H	H	H	Et	Et	Z	48%
a70	Cl	H	H	Me	Et	Z	44%
a71	H	H	H	Me	Me	E	49%
a72	H	H	H	Me	Me	Z	49%

Table 2-2: The synthesis of oxime.

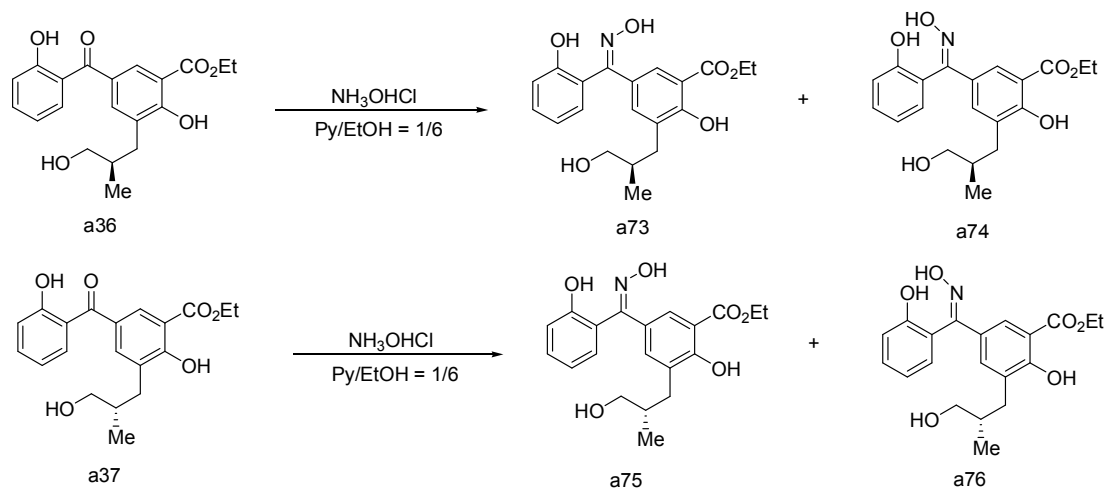

E

Z

 R₁ = Cl, Br, Me, NO₂, H...

 R₂ = Me, Et, iPr

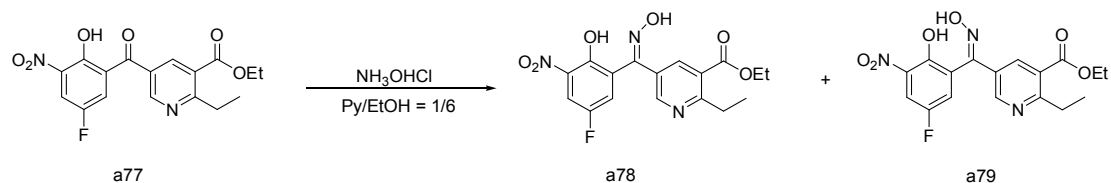
Figure 2-6. The isomer of oxime

Phenols with long alkyl chains i.e. **a36** and **a37** were also converted to their corresponding oximes under the optimized reaction conditions in good yields (Scheme 2-12).



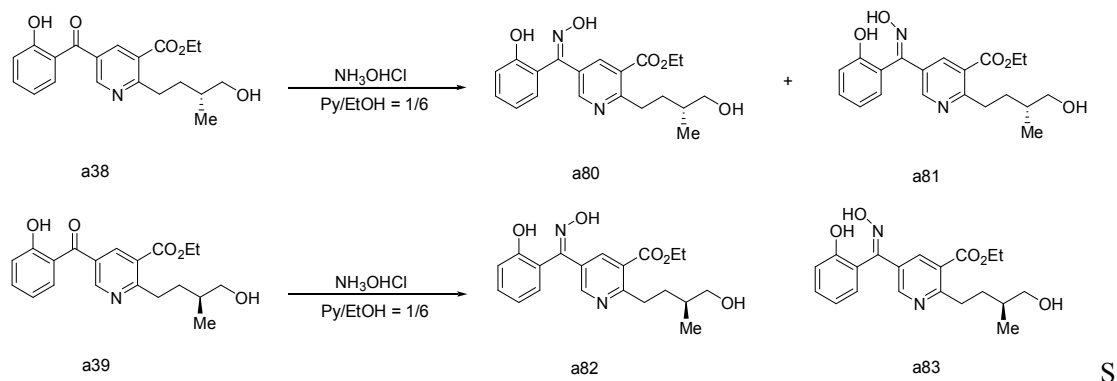
Scheme 2-12. The synthesis of oximes of phenols with longer alkyl chains.

In a similar fashion, the pyridines obtained from the branching cascade strategy were transformed into their corresponding oximes which were purified by column chromatography into E- and Z-isomers in good yields (Scheme 2-13).



Scheme 2-13. The synthesis of pyridine oxime.

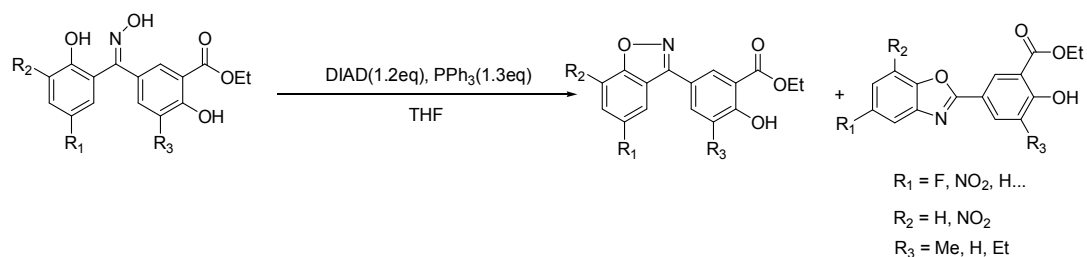
Pyridines with long alkyl chains were also successfully transformed into their oximes under the optimized reaction conditions (Scheme 2-14) in good yields.



cheme 2-14. The synthesis of isomeric oximes with pyridine building blocks.

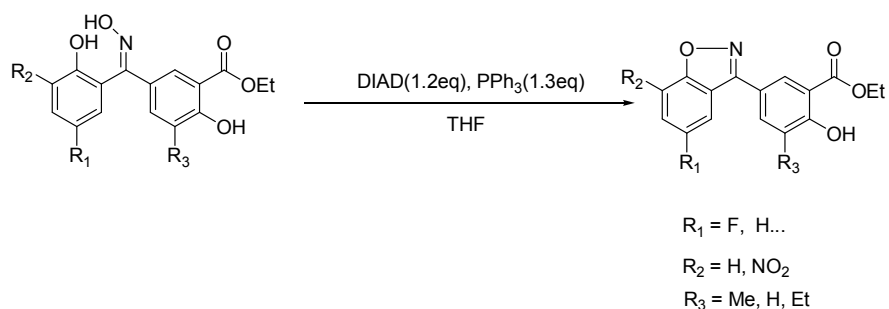
2.4.1.2 The synthesis of oxazole

As depicted in scheme 2-10, oximes can easily lead to isoxazoles. Therefore, both *E*- and *Z*-isomer of the oximes were separately exposed to Mitsunobu reaction conditions [108]. Thus, a mixture of oxime, DIAD (1.2eq) and PPh₃ (1.3eq) was added to a degassed THF solution and was stirred at room temperature for 3-6 h under argon atmosphere (Table 2-4, Table 2-5). The reaction of *E*-oxime produced two products—*isoxazole* **a90**, and *oxazoles* **a91**. However, the *Z*-oxime afforded only one product *oxazole* **a100**. The LC-MS spectra showed that these three products had the same molecule weights. These results are however, in good agreement with literature [108].



COMPOUNDS	R ₁	R ₂	R ₃	OXAZOLE(Y%)	ISOXAZOLE(Y%)
a90	F	NO ₂	Me	43%	
a91	F	NO ₂	Me		32%
a92	NO ₂	H	Me	45%	
a93	NO ₂	H	Me		35%

a94	H	H	Me	52%	
a95	H	H	Me		38%
a96	H	H	H	55%	
a97	H	H	H		39%
a98	Me	H	H	50%	
a99	Me	H	H		33%

 Table 2-4 Reaction of *E*-oximes to yield isoxazoles and oxazoles.


COMPOUNDS	R ₁	R ₂	R ₃	isoxazole
a91	F	NO ₂	Me	37%
a97	H	H	H	47%
a99	NO ₂	H	Me	39%

 Table 2-5 Reaction of *Z*-oximes to yield oxazoles

Thus, differently substituted phenolic oximes were converted into the isoxazoles and oxazoles to provide a focused compound collection.

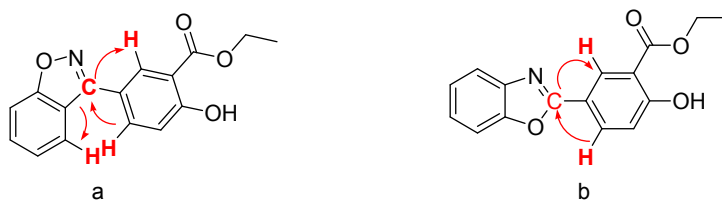
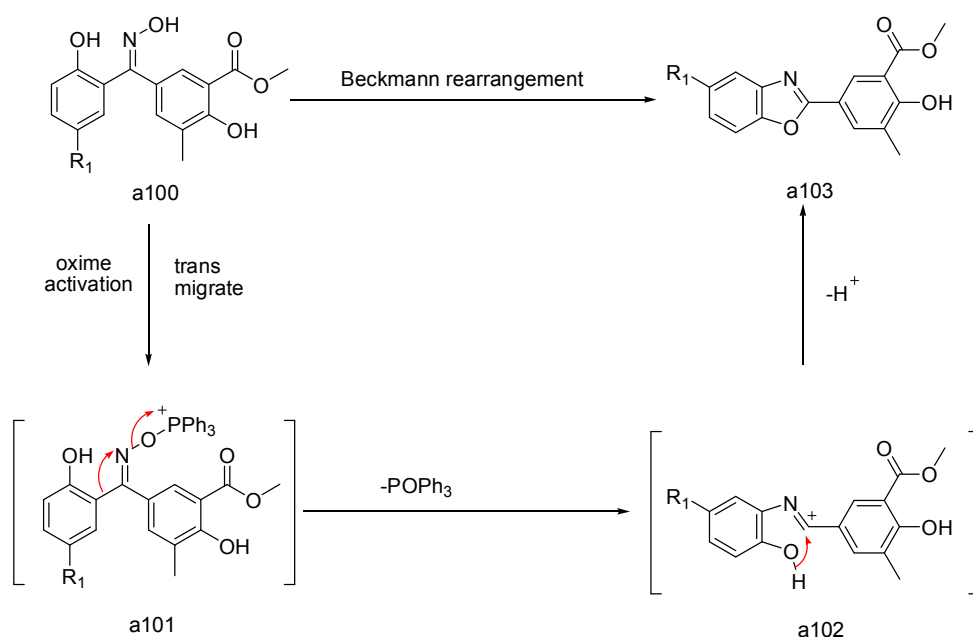


Figure 2-7. Identification of building blocks(a&b) by HMBC-NMR experiments.

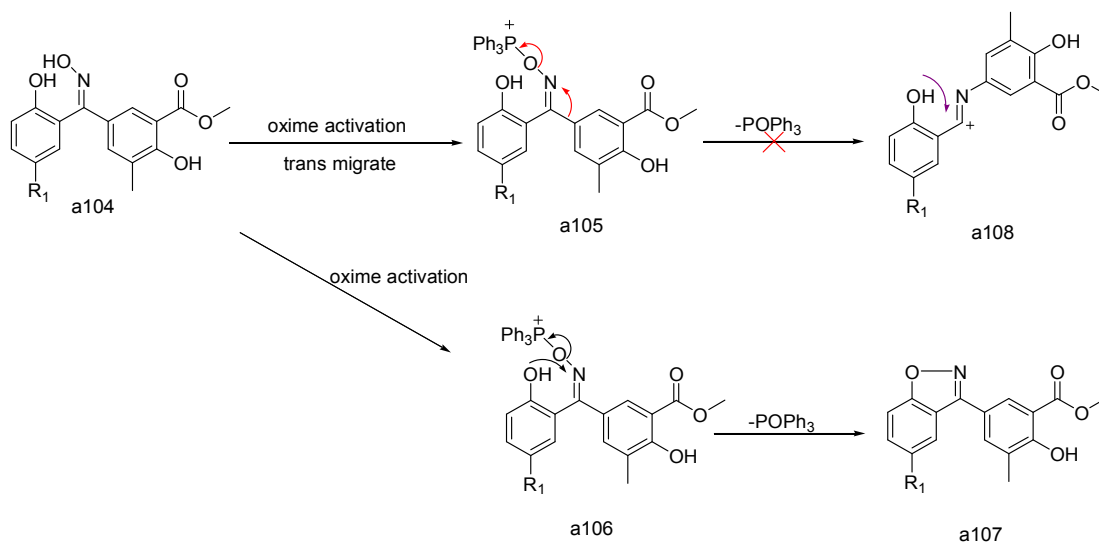
The generally accepted mechanism of the Backmann rearrangement follows protonation, etherification or esterification of the oximino hydroxyl group, then a

quasi three-member transition state is formed, in which the group *anti* to the hydroxyl migrates with synchronous lengthening of the N-O bond ^[109]. The departure of the leaving group is simultaneous accompanied with the [1,2]-shift of the anti group. The concept of a three-member transition state is involved in order to explain the observed retention of configuration of the migrating group and also the stereospecificity of the reaction ^[109]. If other nucleophiles (Nu^-) are present, they can intercept the reactive intermediates (both inter- or intra- molecularly) and several different imino-substituted derivatives can be formed. These facts demonstrate that, the transform of *N*-hydroxyl group of the oxime into a better leaving group is necessary ^[109].

In our case, we assume that the phosphine does activate the oxime by formation of intermediate **a107** supporting a leaving group that facilitates the migration of aryl moiety leading to **a108** wherein the intermolecular addition of phenol to carbenium cation formed provides the isoxazole. However, when *Z*-oxime **a104** had been activated by PPh_3 , the ethyl benzoate was transferred from the back of oxime to intermediate **a105** wherein the addition of phenol to form a four-member ring is not facilitated. Therefore, the intermediate **a106** may provide a nitrene type intermediate to which addition of phenol leads to formation of oxazoles **a107** (Scheme 2-15).



Scheme 2-15 The proposed mechanism of E-oxime

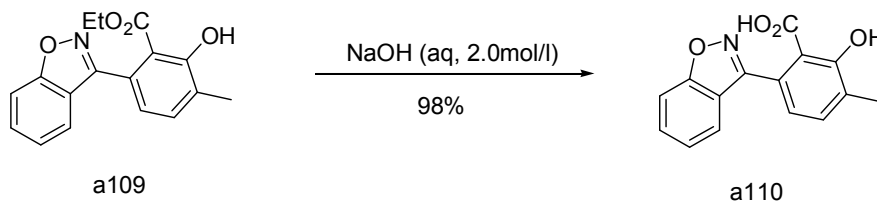


Scheme 2-16. The proposed mechanism of Z-oxime

2.4.2 The hydrolysis of compounds

2.4.2.1 The hydrolysis of isoxazole

Free acid was good resolvable in body and the ester was hydrolyzed to get free acid by using the solution of sodium hydroxide (Scheme 2-17). The reaction was nearly quantitative and only less starting compound remained.

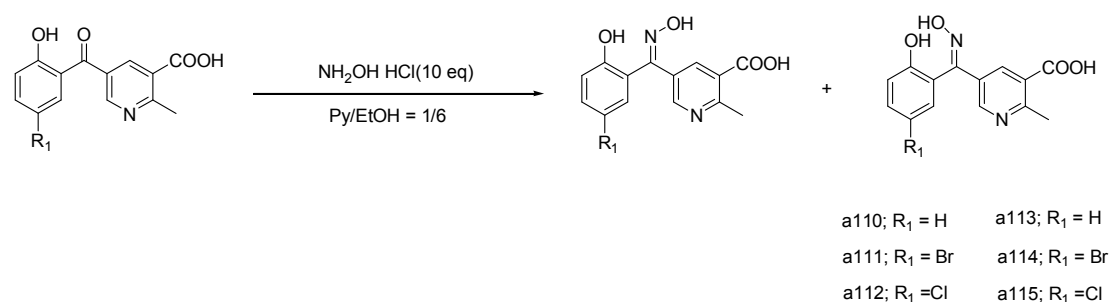


Scheme 2-17. Hydrolyzed the isoxazole

2.4.2.2 The hydrolysis of oxime

So as to develop the scaffold collection and to prove no effect with free acid under the

basic conditions, the free acid oximes with hydroxylamine were synthesized with good yields (Scheme2-18).

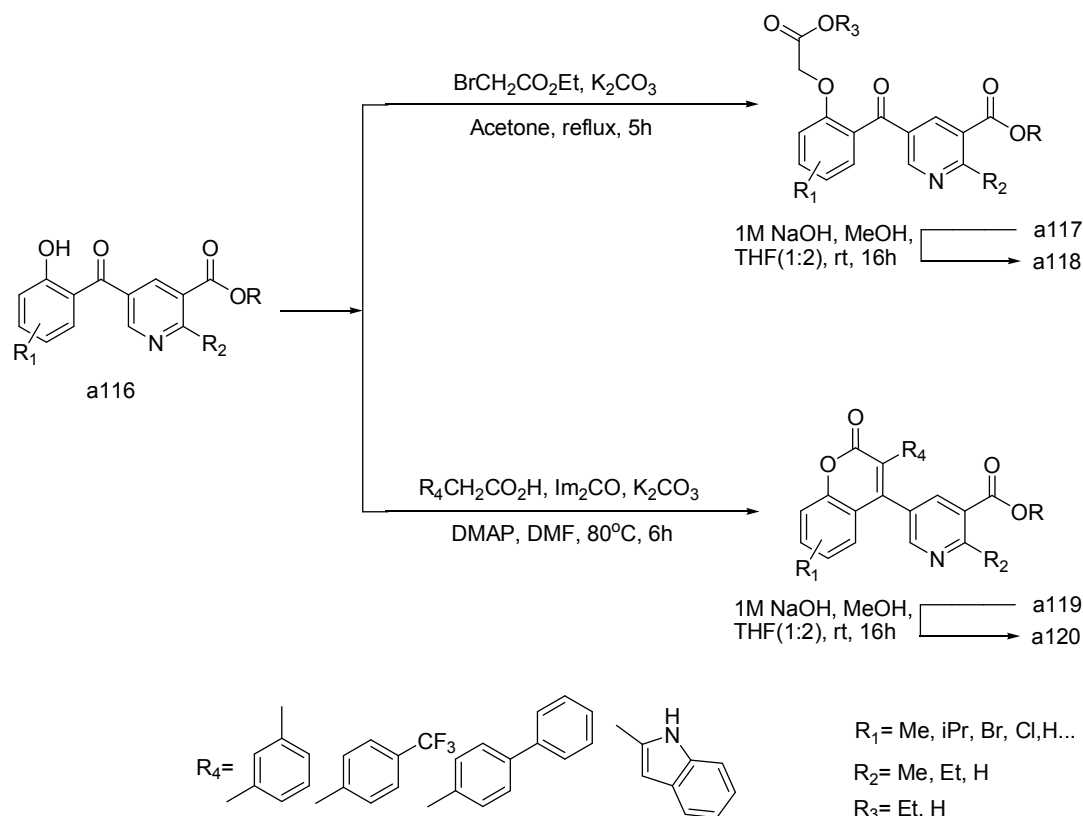


Compounds	R ₁	Yield E (%)	Yield Z (%)
a110	H	47%	
a111	H		42%
a112	Cl	45%	
a113	Cl		43%
a114	Br	44%	
a115	Br		42%

Scheme 2-18. The synthesis of free acid oxime

2.4.3 Other modifications of the phenol moiety in pyridines.

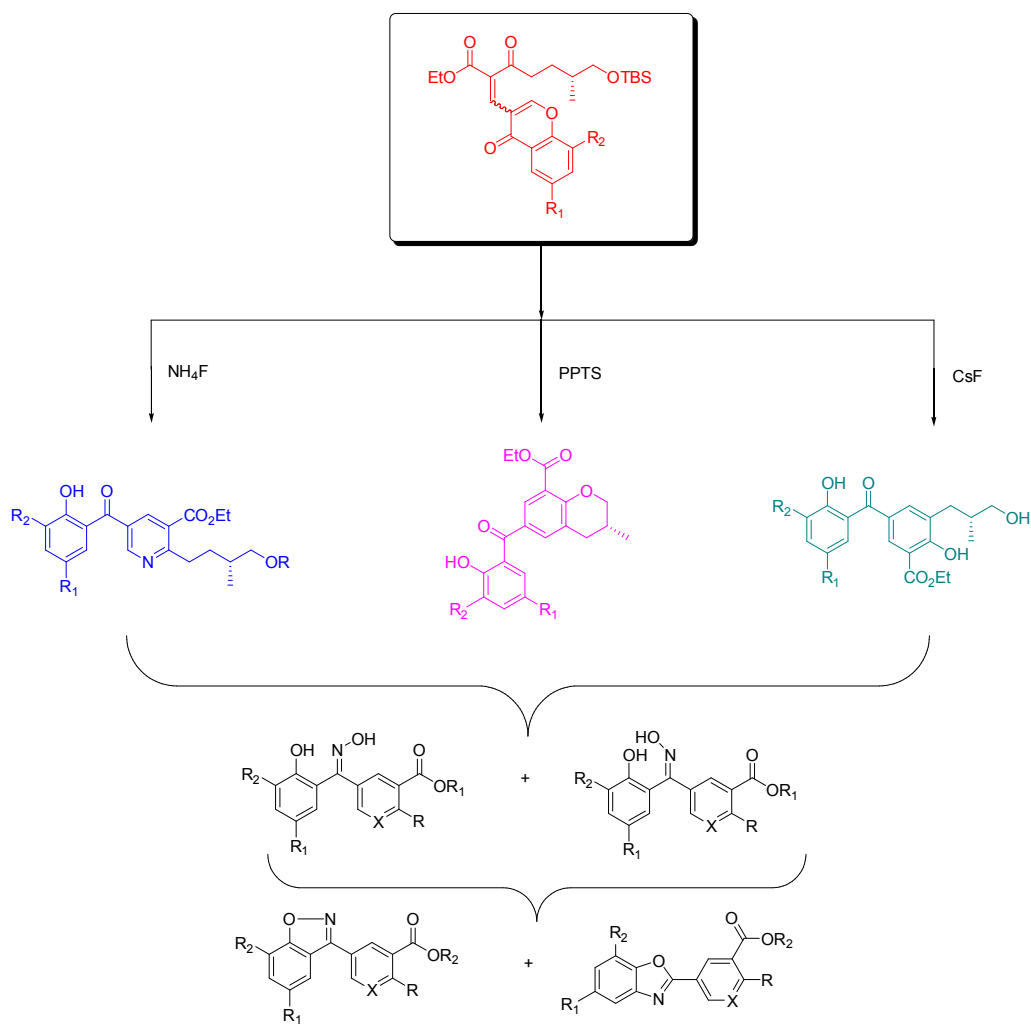
The reagents controlled domino reaction offered molecules with various functionalities, which could be explored to add further diversity to the compound collections^[102-104]. The phenol moiety in substituted pyridines was converted into intermediate esters by the treatment with bromoacetic acid esters under the basic conditions. Coumarin, as a “privileged” scaffold, showed multiple biological properties, especially anti-HIV and antibiotic activities^[111]. To combine our molecules with coumarin structure, the substituted pyridines were converted into the coumarin-substituted pyridine carboxylates by a one pot procedure with good yields (Scheme 2-18)^[102]. Alkylation with diverse acetic acids, which was treated with Im₂CO activation and base-mediated condensation, afforded the desired coumarin-substituted pyridine carboxylates^[102] (Scheme 2-18).



Scheme 2-18. Diversification of substituted pyridine molecules.

2.5 Summary

The branching cascade strategy leading to skeletal diversity can follow two pathways (Figure 1-3).^[42] One is reagent-based approach; another is substrate-based approach. The reagent-controlled branching cascade processes described in this chapter provide structurally-diverse functionalized molecules in a complementary manner. Diverse domino reaction sequences dictated by different cascade triggering reagents on the common chromonylidene precursors generated highly substituted and functionalized pyridines, phenols and benzoyprans which might be useful for chemical biology and medicinal chemistry research. The branching cascade products were further modified into oximes, oxazoles, isoxazoles and coumarins etc.



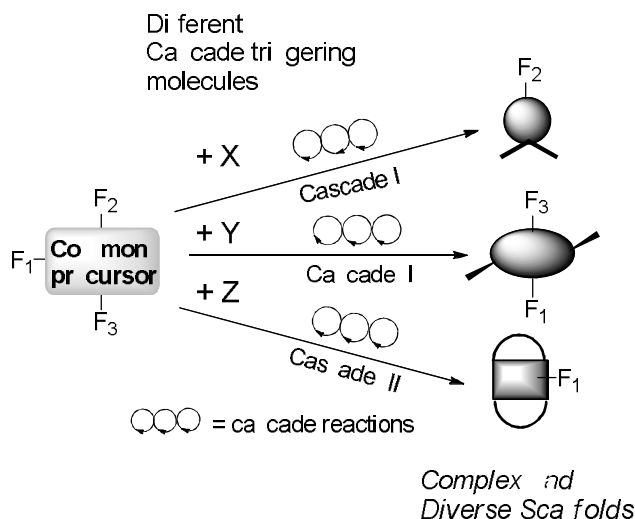
Scheme 2-19. Cascade reactions for skeletal diversity.

3. Substrate controlled branching cascades

3.1 Introduction

Small molecule libraries containing diverse and relatively complex molecules are required for drug discovery and chemical biology investigations. Compounds collection possessing skeletal or scaffold diversity can more effectively target bioactive regions of chemical space ^[4, 6, 14]. Natural products, for instance, represent the most diverse and complex compound library that exists in nature and have been a continuous source of interesting drug candidates and synthetic targets ^[4, 8]. Structural diversity, in particular, scaffold diversity and molecular complexity are thus two important criteria that enrich any compound collection in biological activity. Therefore, synthesis strategies targeting medium to large sized compound libraries based on diverse and relatively complex molecular architectures, including natural product-based molecular frameworks, offer great synthetic challenges to the art of organic syntheses ^[6, 14]. The previous chapter summarized exploring a reagent controlled branching cascade strategy wherein different reagents dictate and drive diverse reaction cascades to end up generating different scaffolds. However, after activation/modulation of a given functional moiety on the common substrate by a reagent, only intramolecular reactions of the common substrate would happen. Therefore, the scaffold diversity and the molecular complexity generated thereby would be very limited ^[112-115]. However, instead of reagents that only activate or induce a given cascade reaction sequence, if different substrates that can also trigger different cascade reaction sequences on a common substrate (just like different reagents could induce different cascade reactions depicted in previous chapter) are employed, it would not only generate the scaffold diversity in the ensuing products but also the resulting frameworks might be more complex owing to the addition of different sub-structures in intermolecular reactions. Thus, addition of molecules X, Y or Z to a common substrate might lead to more complex and diverse ring-systems or

scaffolds (Figure 3-1). This approach is termed as *substrate controlled branching cascades* and the following sections provide further details of this synthesis strategy [116-119].



Substrate Controlled Branching Cascades

Figure 3-1. Substrate controlled branching cascades.

3.2 Synthesis of a common multi-functionalized substrate

In the reagent controlled branching cascade strategy, only limited access to scaffold diversity is possible because of mostly intramolecular cascade reactions happening after the activation by the reagents [120]. That is why these transformations do not add to the overall molecular complexity. In order to access more complex and diverse scaffolds with the branching cascade strategy, it might be useful to add additional substrates that can trigger the cascade reactions and also add up to the common substrates to provide more complex molecules (Figure 3-2). The cascade triggering substrates can be chosen with the desired structural features so that more privileged and/or desired compound classes can be accessed [121]. However, this again would require the common multifunctionalized substrates which can accommodate a variety of cascade triggering substrates and end up with diverse scaffolds [122-124].

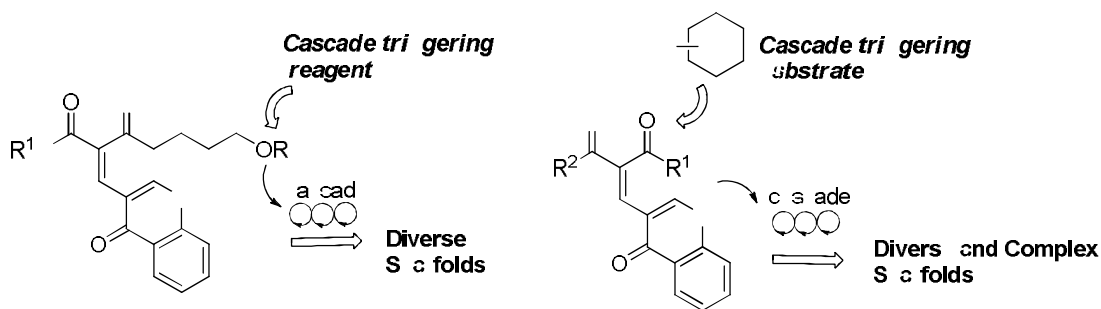
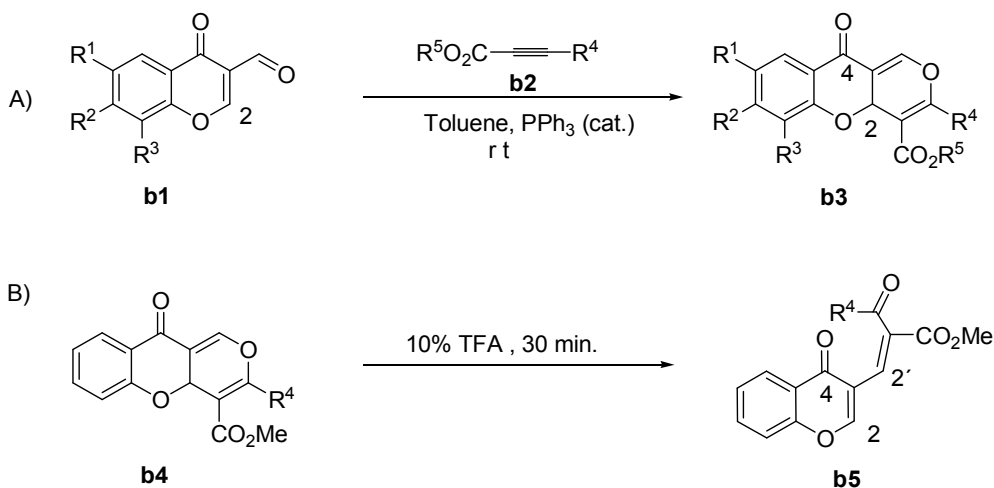


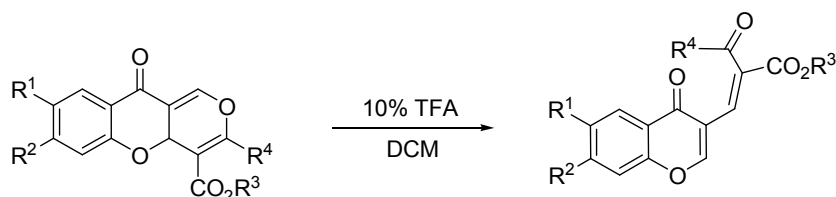
Figure 3-2 Scaffolds with the branching cascade strategy

Recently, a novel phosphine catalyzed [4+2] annulation reaction between 3-formylchromones (**b1**) and electron-deficient acetylene carboxylates (**b2**) was discovered. However, it was observed that tricyclic benzopyrones **b3** were not stable under acidic conditions and efficiently reorganize themselves to yield the corresponding chromone substituted α , β -unsaturated ketoesters or aldehydes (**b5**, Eq. B, Scheme 3-1). For instance, an overnight treatment of the pure adduct **b4** ($R^4 = \text{CO}_2\text{Me}$) with 1% trifluoroacetic acid (TFA) in dichloromethane at room temperature afforded dimethyl-2-oxo-3-[(4-oxo-4*H*-chromene-3-yl)methylene]succinate (**b5**, $R^4 = \text{CO}_2\text{Me}$) in 55% isolated yield.^[125] Being multi-functionalized, electron-deficient and highly conjugated, the chromone substituted ketoesters and aldehydes (**b5**) could prove excellent common precursors for the substrate controlled branching cascade strategy. In particular, they might undergo different cascade reactions with diverse nucleophilic substrates. To explore the potential of these interesting chromone olefines, their synthesis was further optimized.



Scheme 3-1. The reactions of substrates.

It was observed that increasing the concentration of TFA to 10% in dichloromethane led to completion of the reaction in half an hour yielding **b5** quantitatively. Although, $\text{BF}_3 \cdot \text{OEt}_2$ could complete the reaction within ten minutes with slightly reduced yield of **b5**, the milder reaction conditions with TFA for this transformation were preferred to use. The reaction produced the conjugated ketoesters decorated with a substituted benzopyrone moiety in excellent yields (Table 3-1, entries 1-7). Interestingly, when a tricyclic benzopyrone with only one ester moiety was treated with TFA, the conjugated aldehyde **b12** could be obtained in very good yield (entry 8, Table 3-1). Substrates **b13-b18** afforded the corresponding chromonyl acrylates **b13-b18** in acceptable yields (entries 9-14, Table 3-1). Moreover, employing the adduct **b19** supporting a phenyl group generated the corresponding phenyl ketone **b19** in good yield (entry 15, Table 3-1)^[125g].



Entry	compounds	R ¹	R ²	R ³	R ⁴	Yield (%)
1	b5	H	H	Me	CO ₂ Me	99
2	b6	Cl	H	Me	CO ₂ Me	94
3	b7	<i>i</i> Pr	H	Me	CO ₂ Me	98
4	b8	<i>i</i> Pr	H	Et	CO ₂ Et	98
5	b9	Me	H	Et	CO ₂ Et	91
6	b10	H	H	Et	CO ₂ Et	97
7	b11	Cl	H	Et	CO ₂ Et	91
8	b12	H	H	Me	H	87
9	b13	Cl	Me	Me	H	94
10	b14	Me	H	Me	H	92
11	b15	H	H	<i>t</i> Bu	H	98

12	b16	<i>i</i> Pr	H	Me	H	88
13	b17	Cl	H	Me	H	82
14	b18	Br	H	Me	H	83
15	b19	H	H	Et	Ph	89

Table 3-1. Rearrangement of the substrates: a, Reaction conditions; 10% TFA in dichloromethane, 30 minutes, room temp.; b, isolated yields after flash column chromatography.

The NMR spectra and LC-MS analysis clearly indicated the formation of a single isomer **b5-b19**. The configuration of the molecules **b5-b19** was identified with nOe NMR experiments. Selective irradiation of the aldehyde proton in **b17** led to enhancement of the signal for C1'-H and on irradiating the latter, a clear enhancement for the C2-H (and *vice versa*) was observed. Therefore, the *Z*-configuration of the molecule was established (Figure 3-3, A). Similar nOe effects were observed in the case of ketoester **b10**. While irradiation of C2-H in **b10** resulted in signal enhancement for C1'-H; the latter on irradiation led to the signal enhancement for C2-H besides a weak signal enhancement for the methylene(-OCH₂Me) proton of the conjugated ester (established by HMBC and HSQC NMR experiments) (Figure 3-3, B).^[125g] Thus, *E*-configuration was assigned to the ketoesters **b5-b11** (Figure 3-3, B).

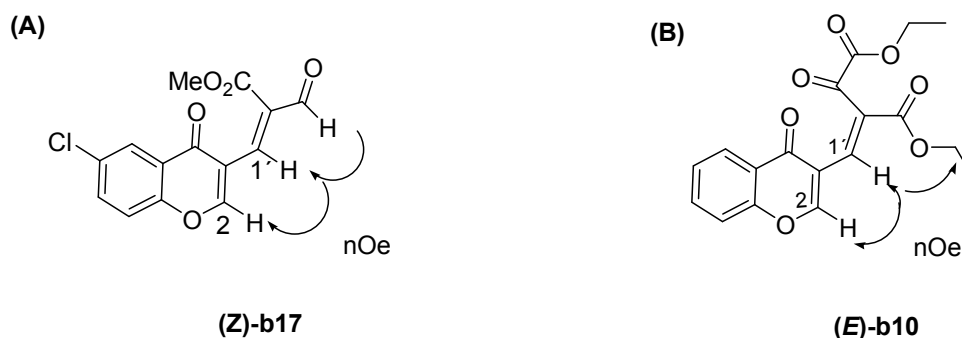


Figure 3-3. 1D nOe NMR of substrates.

Single crystal x-ray analysis of the ketoester-**b5** unambiguously proved the structure and assigned configuration (Figure 3-4).

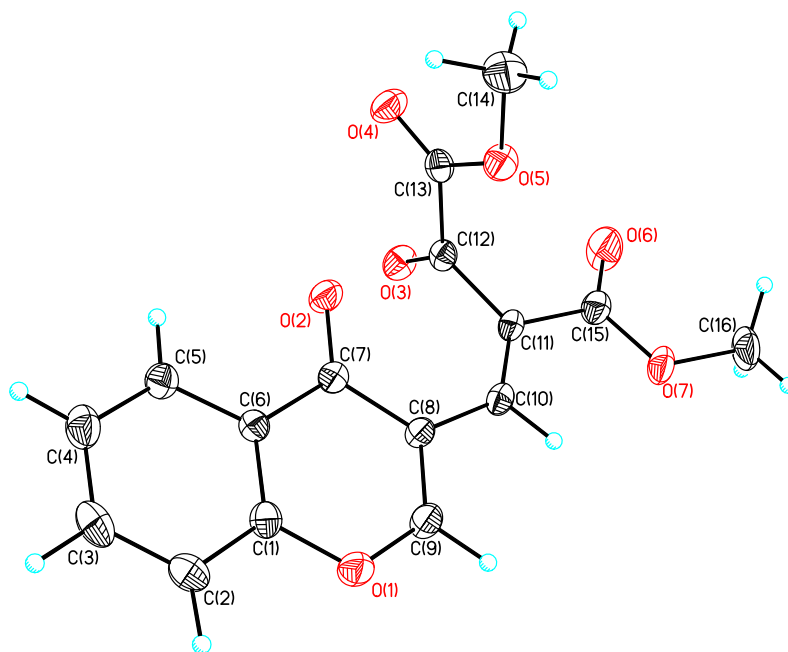
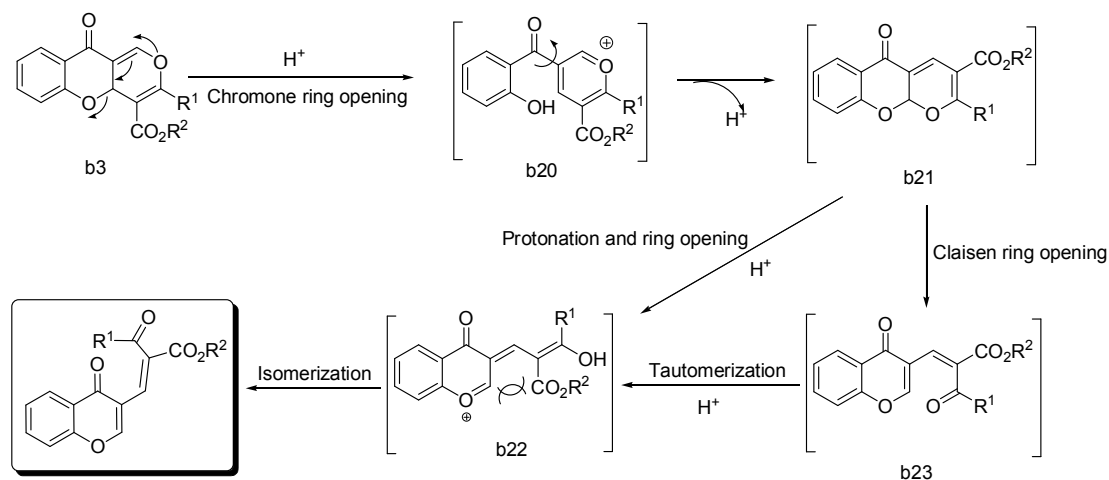


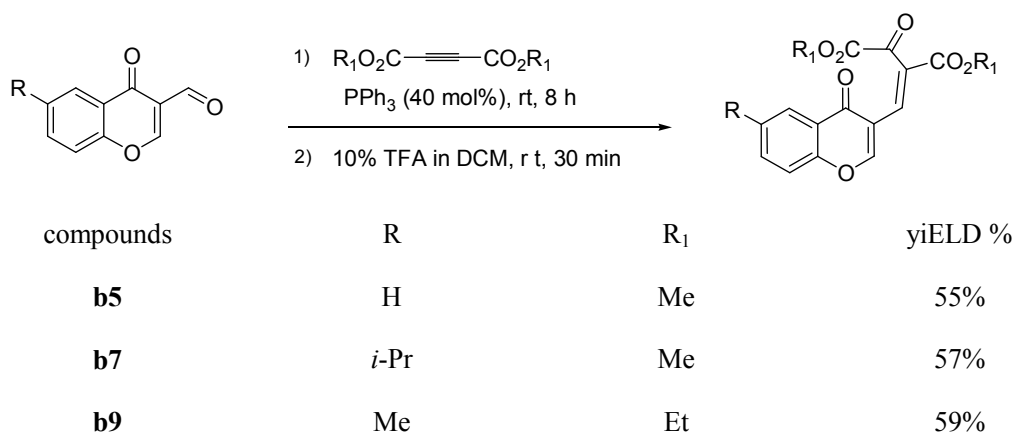
Figure 3-4. X-ray structure for **b5**

Mechanistically, the [4+2] adducts **b3** acted as push-pull system under acidic conditions. Facilitated by the formation of aromatic pyrilium cation, the chromone ring would open up to generate **b20** which underwent intermolecular addition of the phenol leading to cyclic alkyl vinyl ether **b21** formation. The vinyl-ether **b21** could undergo protonation and ring-opening of the dihydropyran ring forming an extended enol **b22** which tautomerized to the product **b5** after a single bond rotation to avoid the steric proximity of the ester functionality to the benzopyrone ring. Alternatively, the Claisen ring opening of **b21** would yield the isomer of product **b23** which could isomerize *via* acid-catalyzed automatism to **b22** before transforming to **b5** ^[125g] (Scheme 3-2).



Scheme 3-2. The mechanism of reactions.

In order to synthesize the products **b5-b19** directly from the commercially available chromone-3-aldehydes, a one pot—two step procedure was developed. In this process, 3-formylchromone was treated with dimethylacetylene-dicarboxylate (DMAD) and triphenylphosphine (PPh_3) to generate the [4+2] adduct **b5**. It was quenched by slow addition of a solution of 10% TFA in DCM at low temperature ($0-4^\circ\text{C}$) and stirring the solution at room temperature for three to four hours by using TLC to monitor the reaction (Table 3-2).


 Table 3-2. One pot synthesis of **b5**, **b7**, **b9** from commercially available 3-formylchromones.

By using this method, the separate purification of adducts **b3** could be avoided, however, the yields of the rearrangement products (**b5**, **b7**, **b9**) were obviously reduced (Table 3-2).

The significance of this methodology could be realized from the fact that other

possible routes to these molecules should be multistep and tedious considering the reactivity of 3-formylchromones ^[6, 14]. The reactive aldehyde and ketoester functionalities in the molecules (**b5**, **b7**, **b9**) would always compete with substrates in alternative routes ^[15]. Moreover, as compared to a possible Wittig olefination or an aldol condensation reaction of the chromone-3-aldehydes to yield **b5**, this protocol provides a completely atom economic, easy and efficient procedures to the interesting class of chromone substituted acrylates and succinates.

3.3 Substrate Controlled Branching Cascades

The dispersed electrophilicity of the common substrates **b5-16** provides ample opportunities to employ diverse and desired nucleophiles as cascades triggering substrates. To identify the cascade triggering nucleophiles that can provide interesting new scaffold structures in acceptable yields, a simple reaction screening of a set of twenty three diverse nucleophiles was planned (Figure 3-5). This set of nucleophiles contains mono- and bisnucleophilic substrates. In particular, it was of great interest to find whether and how bisnucleophiles could trap more than one electrophilic sites of the common precursor and provide complex ring-systems. The reaction screening batch, a set of 23 diverse nucleophiles that included 12 bisnucleophiles (*N-N*, *N-O*, *N-C* and *O-C* bis-nucleophiles), 7 mono-nucleophiles and 4 zwitterionic species (Figure 3-6) was used to observe the substrate conversions, product profile and reaction conditions etc. Screening was performed by using a Radley's Carousel Reaction Station with 12 reaction tubes under an argon atmosphere at room temperature. Mononucleophiles were screened as such in different concentrations (for HCl salts of hydroxylamines, an equimolar triethylamine was used), while most of the bisnucleophiles were screened for their reactions in the presence and absence of external base. After a quick aqueous work up, a LC-MS analysis of the crude reaction mixture was performed. Reactions with high conversions and relatively cleaner product profiles were then separately optimized (when required) for better results.

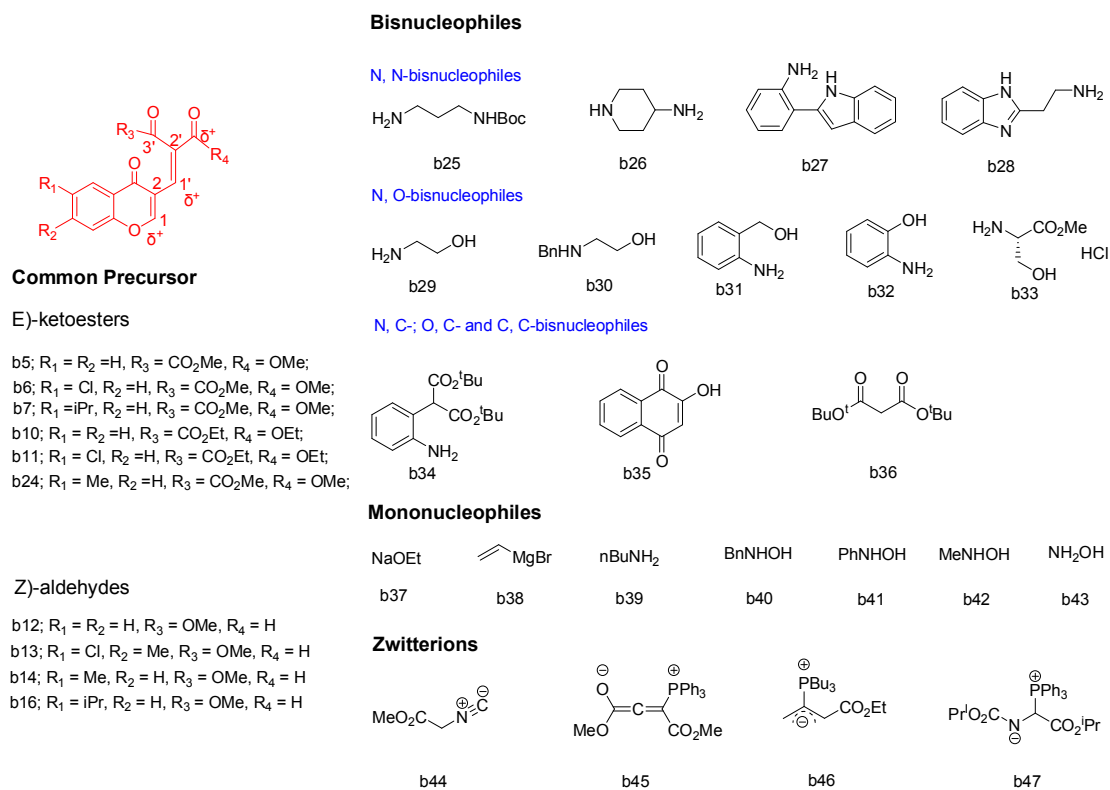


Figure 3-5. Cascade substrates and nucleophiles

A clear reactivity pattern of the nucleophiles towards common substrates was observed. Whereas many bis-nucleophiles reacted cleanly with 1-ketoesters, their corresponding reactions with aldehydes often yielded mixtures of products and with varying conversions. Among the attempted mono-nucleophiles and zwitterions, only a few performed well in the branching cascades, albeit displaying unbiased reactivity towards 1-ketoesters and 1-aldehydes. The unsuccessful cases included diaminoalkane **b25** and *t*-butylmalonate **b36** which yielded a complex mixture of products; amino alcohols **b29** and **b30** which displayed sluggish reactivity and their products too were showing decomposition during column chromatographic purifications; and *o*-aminophenol **b32** that did not yield any specific product consistently.

3.3.1 Scaffold diversity emerging from the branching cascades with bisnucleophiles

The electrophilicity of the common precursor could be transformed into diverse molecular frameworks with different bisnucleophiles. Interestingly, the screening results displayed that many of the bis-nucleophiles yielded the addition products with the common substrates. In most of the cases, there was no further optimization required and therefore products could be purified and analyzed for their structure elucidation. In cases yielding interesting scaffolds, further derivatives/analogues were prepared.

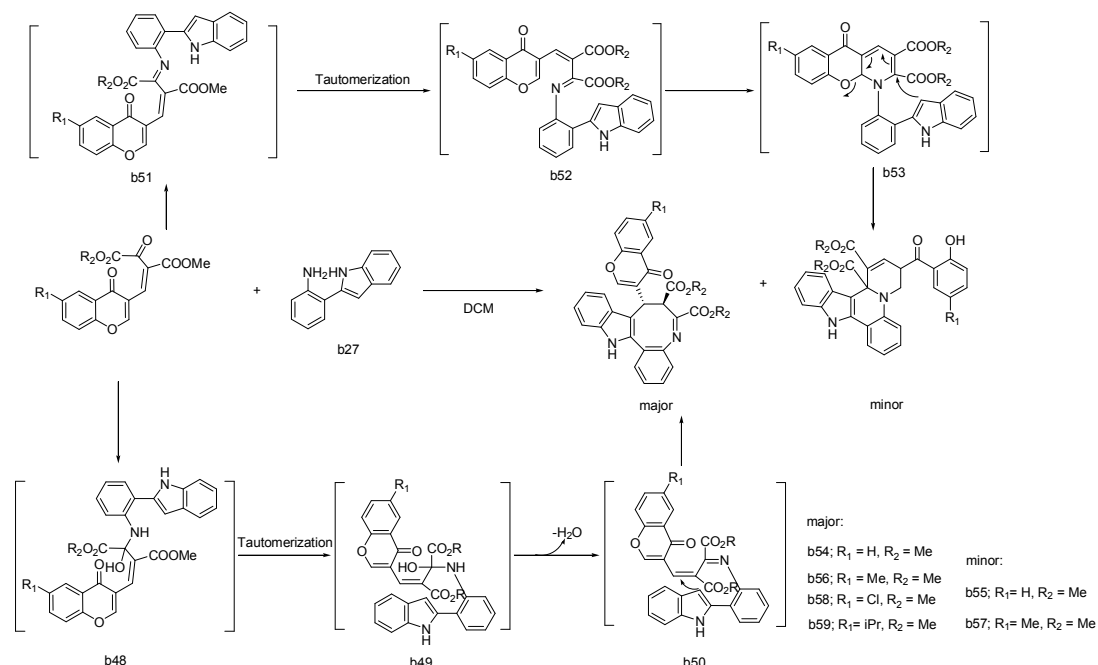
3.3.1.1 Branching cascades with N, N-Bisnucleophiles

The diaminoalkane **b25** provided a complex mixture of products, however, the amino alcohols **b29** and **b30** slowly reacted (conversions up to 50%) and their products decomposed during chromatographic purifications. In all three of these cases the formation of some amount of 3-formylchromones was observed, which were apparently the cleavage product of the precursor.

2-(2-Aminophenyl) indole **b27** proved to be an interesting cascade bisnucleophile and yielded a major and a minor products with different architecture (Scheme 3-3). Stirring a mixture of 1-ketoesters and **b27** in dichloromethane at room temperature led to the formation of novel chromone substituted benzo[2,3]azocino[4,5-b]indoles **b54** according to NMR spectrums. The azocine ring was easily characterized by the characteristic two doublets at δ 5.41 and δ 4.85 ($J = 12.0$) for the vicinal protons on the alpha carbon to the ester and the benzoylprone ring on the 8-member scaffold. This cascade reaction sequence, however, yielded a minor product with a different molecular architecture i.e. dihydroindolo-[3,2-c]-pyrido-[1,2-a]quinoline **b55**, **b57** in varying yields (Scheme 3-3). The structure of the minor product could easily be

assigned due the open chromone ring characterized by a H-bonded phenolic OH peak appearing at $\delta 11.20$ in ^1H NMR spectrum and corresponding carbonyl peak at 196.2 in ^{13}C NMR spectrum. Other ketoester precursors also yielded the azocines molecules in acceptable yields (Table 3-3) along with minor products.

Mechanistically, **b27** attacked the ketone first to form imine **b50** followed by a conjugated addition of C3-indole to yield the azocine **b54**, **b56**, **b58**, **b59**. In other case, the intermediate imine **b51** could also cyclize to yield tricyclic aminal **b53**. Addition of C3-indole to the tricyclic amine followed by chromone ring opening would then yield the minor product **b55**, **b57** (Scheme 3-3).

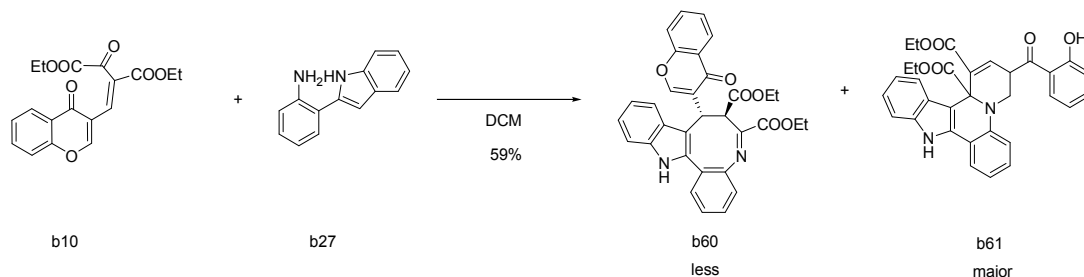


Scheme 3-3. Proposed mechanism of the reaction of common precursor-ketone ester with 2-(1H-indol-2-yl)-benzenamine **b27**.

Compounds	R_1	R_2	major (%) / ratio	minor (%)
b54	H	Me	62% / 5:1	
b55	H	Me		31%
b56	Me	Me	65% / 2:1	
b57	Me	Me		30%
b58	iPr	Me	59%	
b59	Cl	Me	64%	

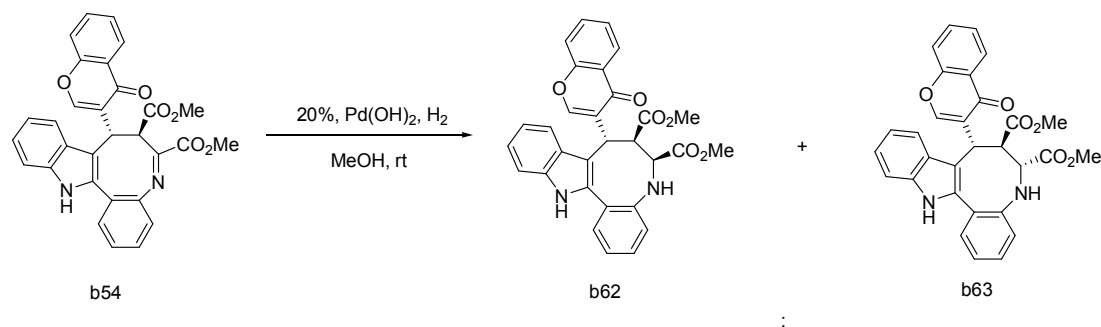
Table 3-3. The results of the reaction of common precursor with **b27**.

Interestingly, when a keto-ester substrate with ethyl esters (still bulkier) was employed in the reaction, the azocine molecule was formed as minor adduct while **b61** was formed as major product (Scheme 3-4).



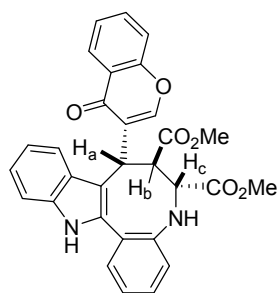
Scheme 3-4. The reaction of ketone ester **b10** with 2-(1H-indol-2-yl)benzenamine **b27**.

The eight membered imines are rare scaffolds and it was intriguing to examine and verify the structure of these cascade products. To this end, the imine moiety present in the azocine was reduced under Pd-catalyzed condition (Scheme 3-5). The reaction clearly confirmed that it was indeed an imine that was reduced to yield two diastereomeric amine molecules (ratio 1:1) whose structures were further corroborated by detailed spectroscopic analysis including NMR-gCOSY, NOESY, gHSQC and gHMBC (Figure 3-6).



Scheme 3-5. Reduction of the azocinimine

The spectrum of **b63** can clearly show the configuration of the reduce product.



b63

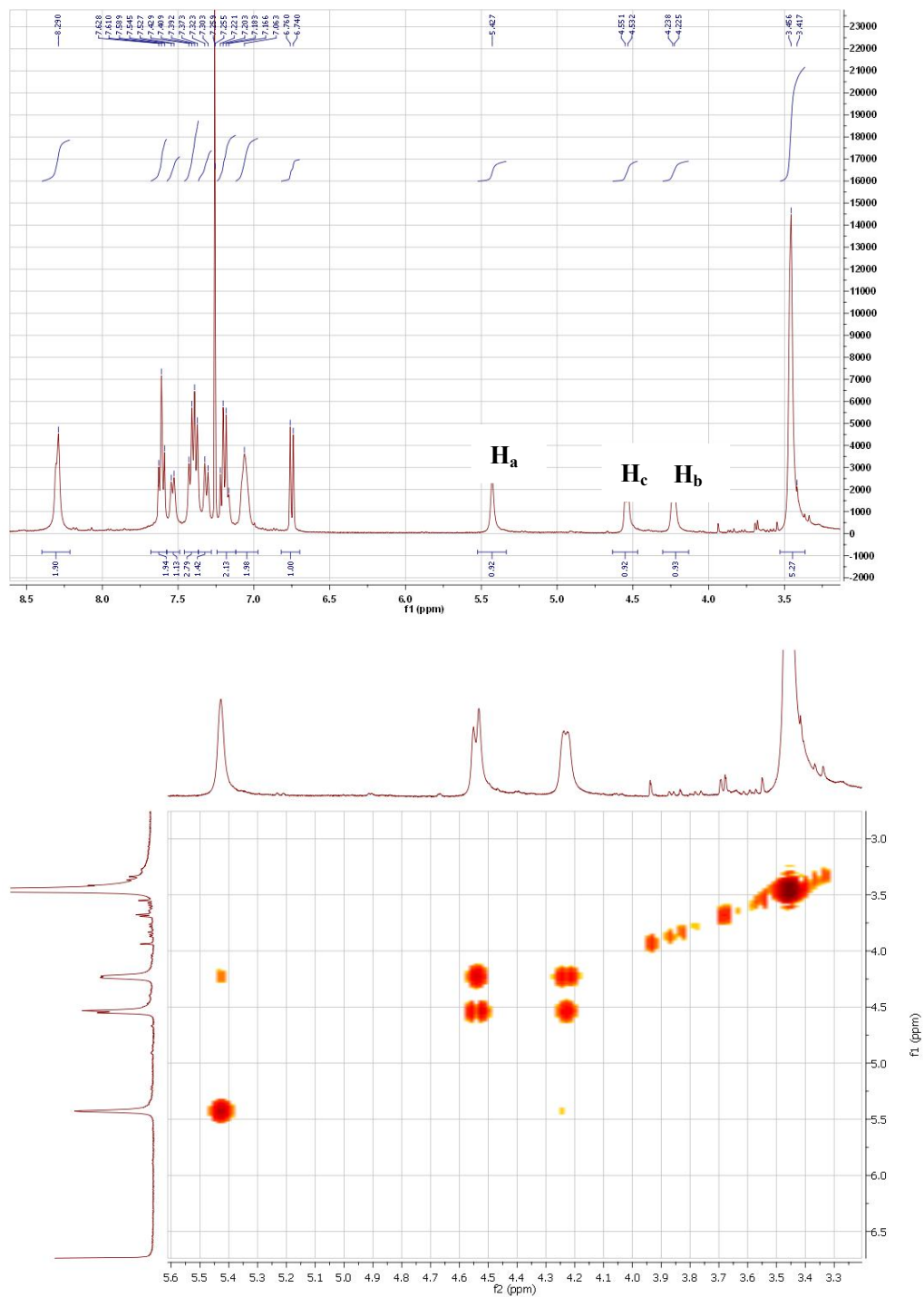
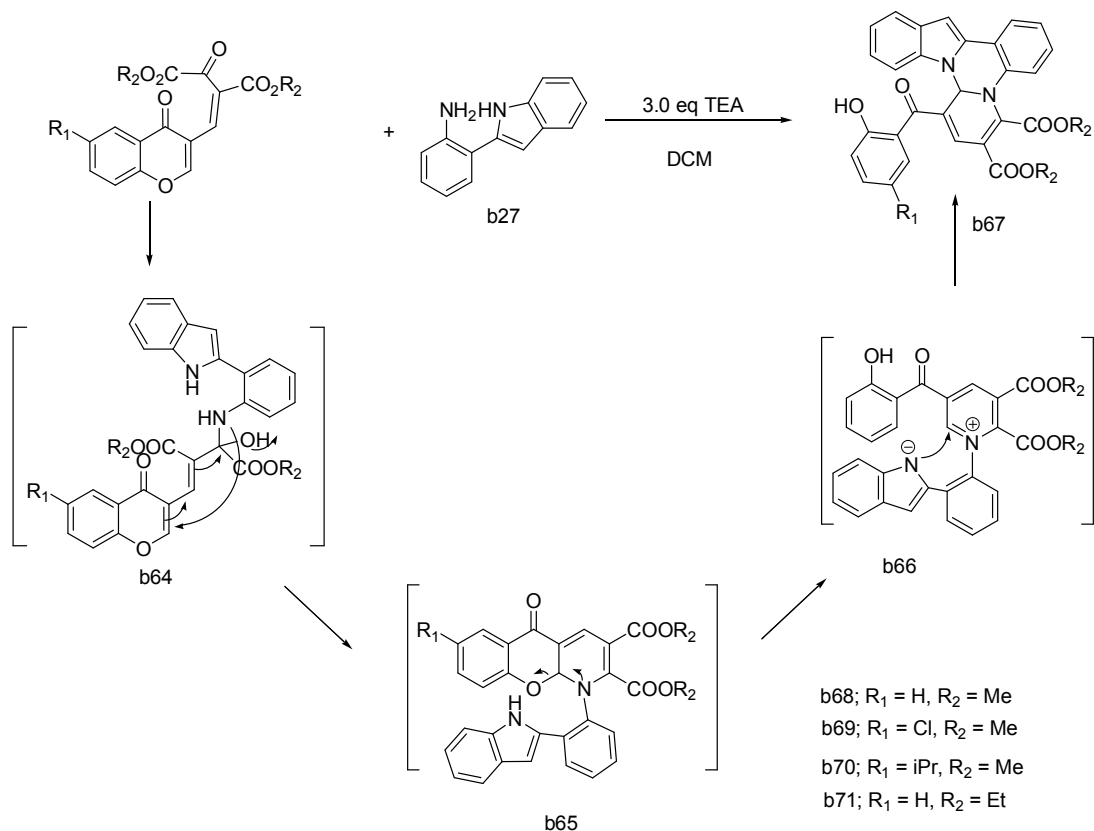


Figure 3-6 The NOESY spectrum of the product **b63**

One of the highlight of branching cascade methodology is that subtle changes in the reaction conditions could change the course of the reaction cascades and lead to different scaffold structure. The bis-nucleophile **b27** represents this example nicely. On the one hand, under neutral reaction conditions, it yielded two scaffolds i.e. azocines (**b54**, **b56**, **b58**, **b59**) and indolopyridoquinolines (**b55**, **b57**); on the other hand, under basic reaction conditions using excess of triethylamine, a completely different scaffold was formed as the only product in a clean reaction and in excellent yields (Scheme 3-6). Thus treating ketone esters with 2-(1*H*-indol-2-yl)benzenamine **b27** and three equivalents of triethylamine at room temperature in DCM led to the formation of **b68-71** as red solids which were purified by silica gel column chromatography in excellent yield (Table 3-4).

Mechanistically, under basic condition, the aniline undergoes a 1,2-addition fashion to yield aminal **b64**. The later forms the amide under basic condition which adds to chromone ring followed by removal of water to form **b65** intermediate. The pyridinim ring **b66** could easily be formed form **b65** that also yields an indole amide in **b66** that would prefer to add to the sterically less hindered pyridine site on **b66** to yield the cascade product **b67** (Scheme 3-6).

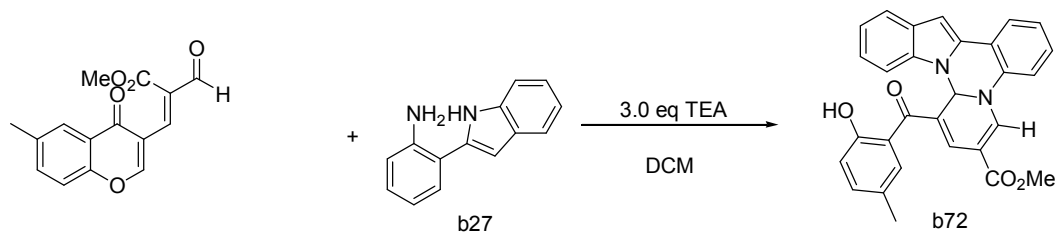


Scheme 3-6. The reaction of the common precursor-ketone ester with **b27** in base-TEA.

compounds	R ₁	R ₂	yield(%)
b68	H	Me	91%
b69	Cl	Me	86%
b70	iPr	Me	87%
b71	H	Et	88%

Table 3-4. The result of the common precursor with **b27** in basic conditions.

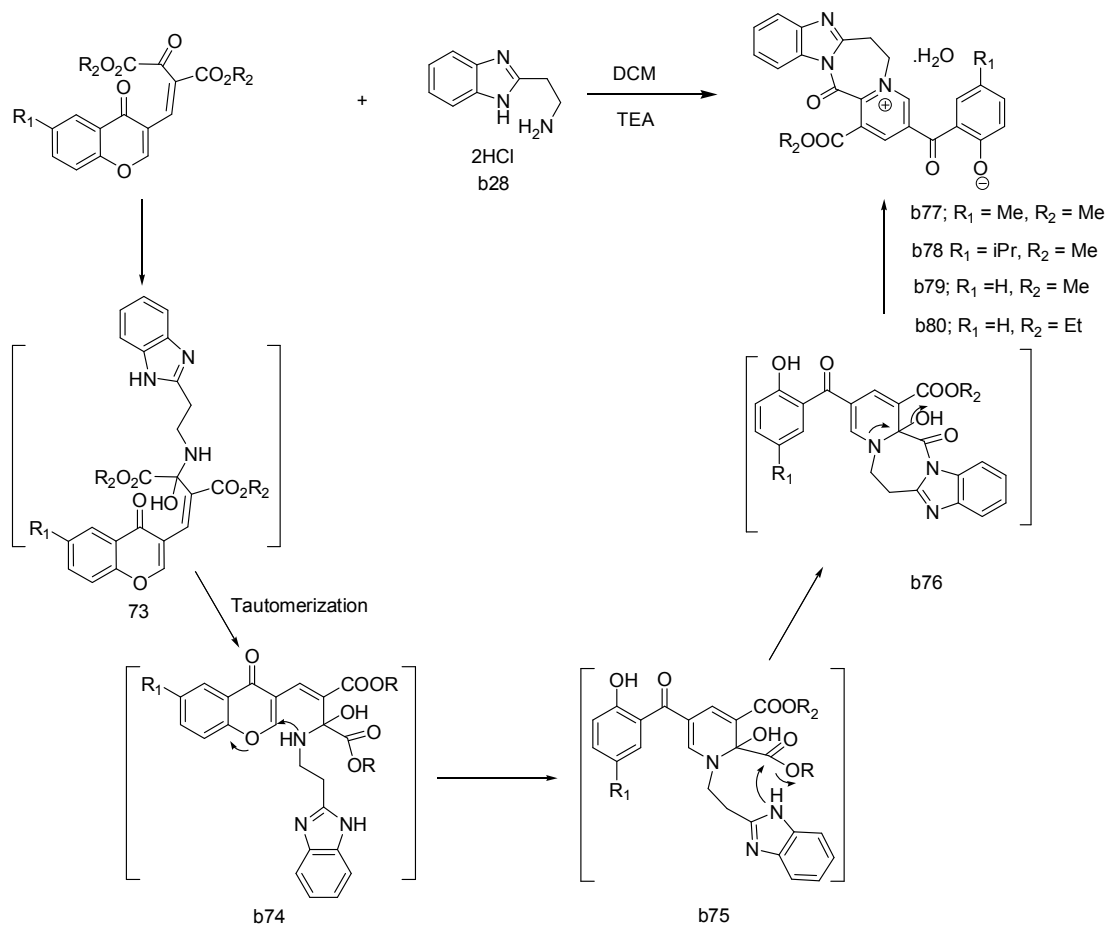
Encouraged by above results, this reaction was performed with ketone aldehyde **b14** under basic conditions. Pleasingly, the common aldehyde precursor also yielded the desired ring-system **b72** in good yield (71%). However, another product formed in the reaction could not be purified.



Scheme 3-7. The reaction of ketone aldehyde with 2-(1H-indol-2-yl)benzenamine **b27**.

2-(1*H*-benzo[d]imidazol-2-yl)ethanamine **b28**, another *N,N*-bisnucleophile, pleasingly transformed 1-ketoesters into novel internal pyridinium salts **b77-80** following yet another cascade reaction sequence. Complete spectroscopic analysis supported by palladium catalyzed hydrogenation of pyridinium internal salts to corresponding 1,2-dihydropyridines corroborated the structural assignments of these novel internal salts. Thus, treating a mixture of ketoester and triethylamine with the bis-nucleophile **b28** at room temperature till the consumption of ketoester (TLC) led to the formation of internal salts **b77-80** which was purified as white solids after silica gel column chromatography.

This cascade reaction sequence plausibly involved the formation of hemi-aminal **b74** wherein the attack of amine on to chromone ring leads to intermediate **b75**. Under basic conditions the benzimide group adds on to the keto-ester to form a seven member lactam ring. Dehydration facilitated by aromatization thus provides the internal salts (Scheme 3-8) in excellent yields (Table 3-5).

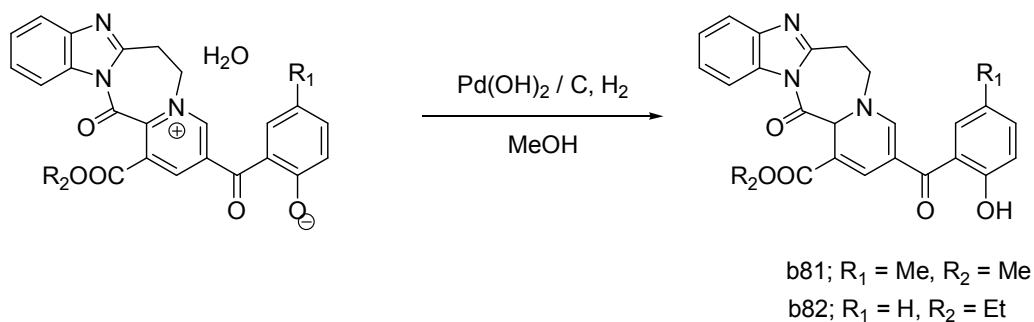


Scheme 3-8. The reaction of the common precursor-ketone ester with **b28** in base—TEA.

compound	R_1	R_2	yield(%)
b77	Me	Me	91%
b78	iPr	Me	82%
b79	H	Me	93%
b80	H	Et	88%

Table 3-5. The result of the reaction of common precursor with **b28** in basic conditions.

In order to verify the structure of these unprecedented novel internal salts, palladium catalyzed hydrogenation reaction was resorted to. The salt **b77** was treated with 0.1 equivalent of 20% Pd (OH)₂ / C dissolved in MeOH under the hydrogen atmosphere, and was stirred for more than two days (Scheme 3-9). Although it took quite long to reduce the pyridinium salt, only one product was formed which was purified by silica gel column chromatography and its spectral analysis revealed it to be 1,2-dihydropyridine **b81-82**.



Scheme 3-9. Reduction reaction of the salt.

NMR analysis of HMBC and NOESY spectrum of the dihydropyridine corroborated the assigned structure (Figure 3-7).

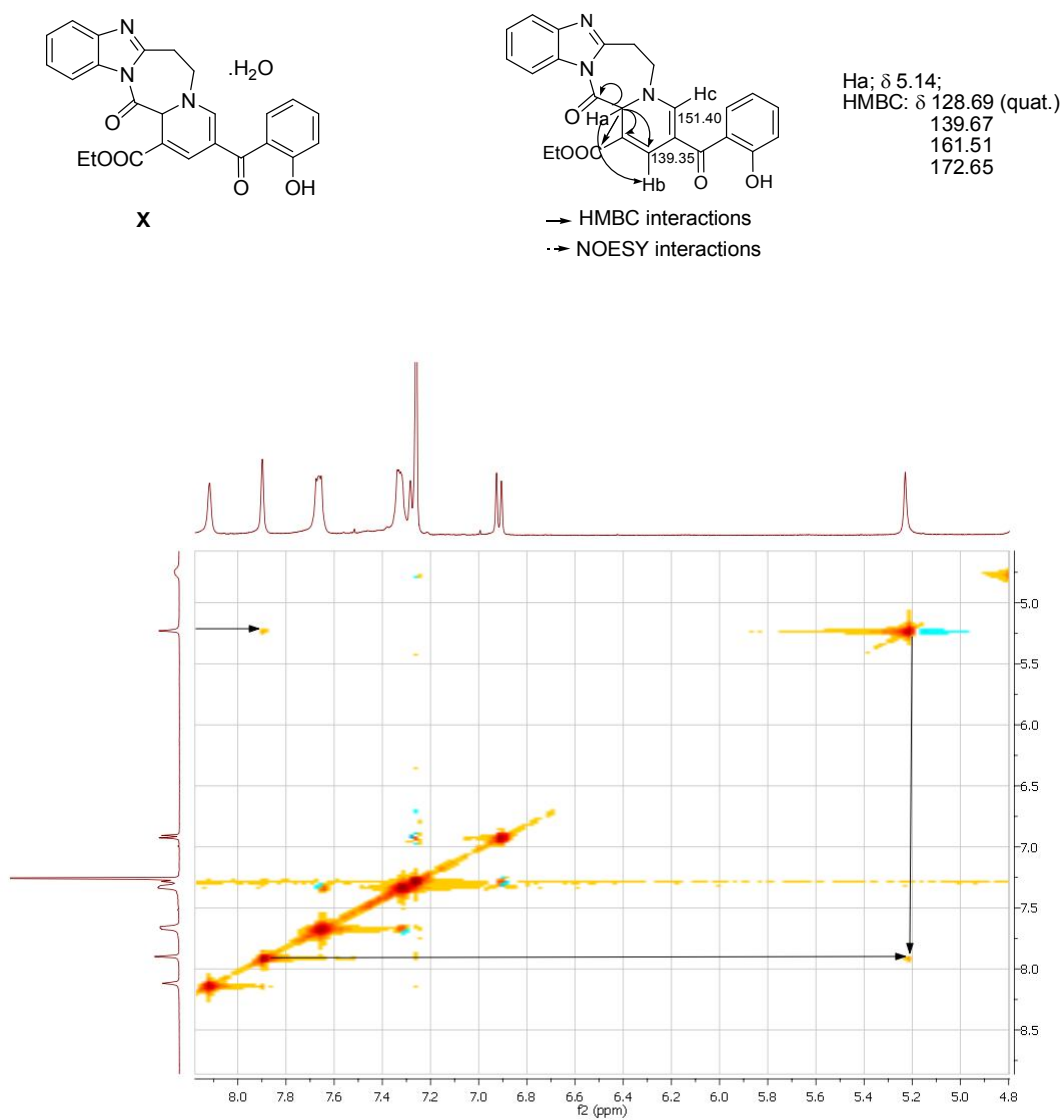
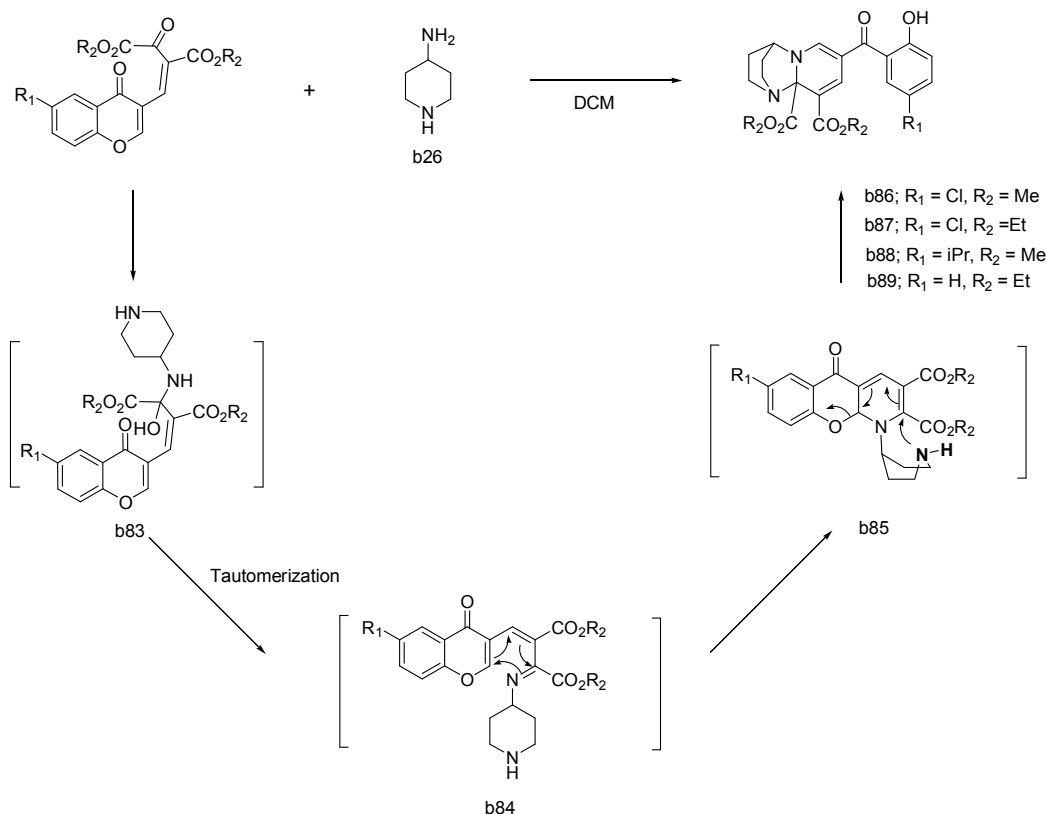


Figure 3-7. HMBC and NOESY of reduce product.

Another N,N-bisnucleophile, i.e. 4-aminopiperidine **b26**, worked very well in a cascade reaction sequence, and led to the formation of complex tetrahydro-1,4-ethanopyrido[1,2-a]pyrimidine ring-system **b86-89** in high yields (Scheme 3-10).



Scheme 3-10 The reaction of the common precursor with piperidin-4-amine **b26**.

compounds	R_1	R_2	yield(y)
b86	Cl	Me	87%
b87	Cl	Et	85%
b88	iPr	Me	86%
b89	Et	Et	91%

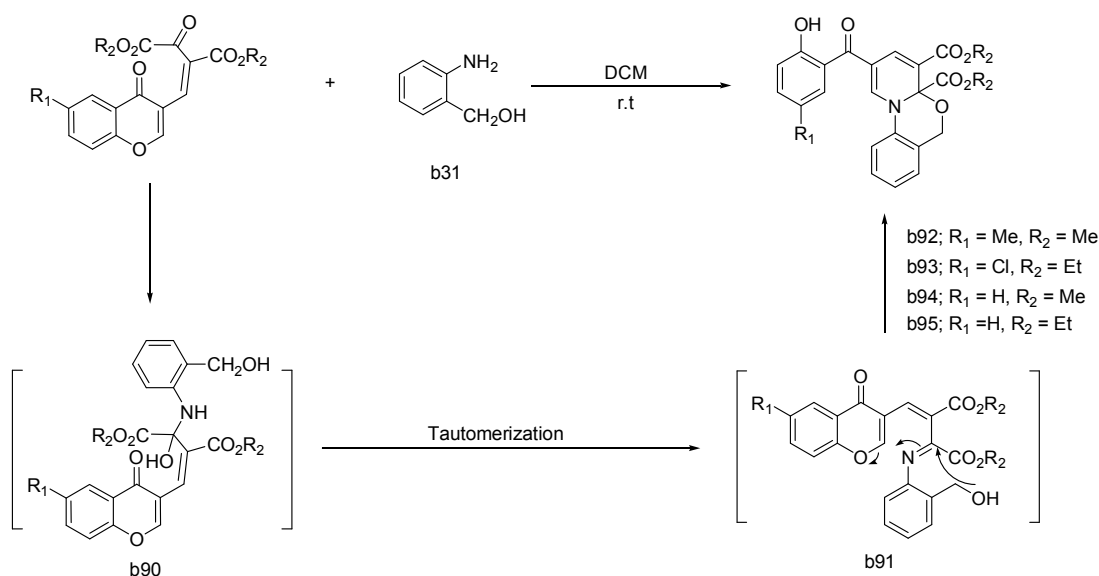
Table 3-6. The result of the reaction of common precursor with piperidin-4-amine **b26**.

3.3.1.2 Branching cascades with N, O-bisnucleophilies

Unlike **b30**, bisnucleophilic o-aminobenzyl alcohol **b31** afforded a clean reaction profile (TLC) leading to the formation of tricyclic oxazine **b92** in high yield (Table 3-7). The structure of the oxazines **b92** could be easily confirmed *via* spectroscopic

analysis. In particular, characteristic peaks in ^{13}C NMR for quaternary aminal carbon (108 ppm) and ketone moiety of the ring-opened chromone (193.7 ppm), and the appearance of an H-bond -OH signal in the ^1H -NMR spectrum at 11.5 ppm clearly supported the formation of oxazine **b92**. Apparently, two electrophilic sites C1 and C3 were attacked by the *bis*-nucleophile in the cascade reaction sequence.

Mechanistically, it is proposed that the ketone ester condensed with amine to form iminoester **b91**, which is attacked by the benzylic alcohol to yield an amine. Addition of amine to benzopyrone opens up the ring to yield the desired benoxazines in good yield.



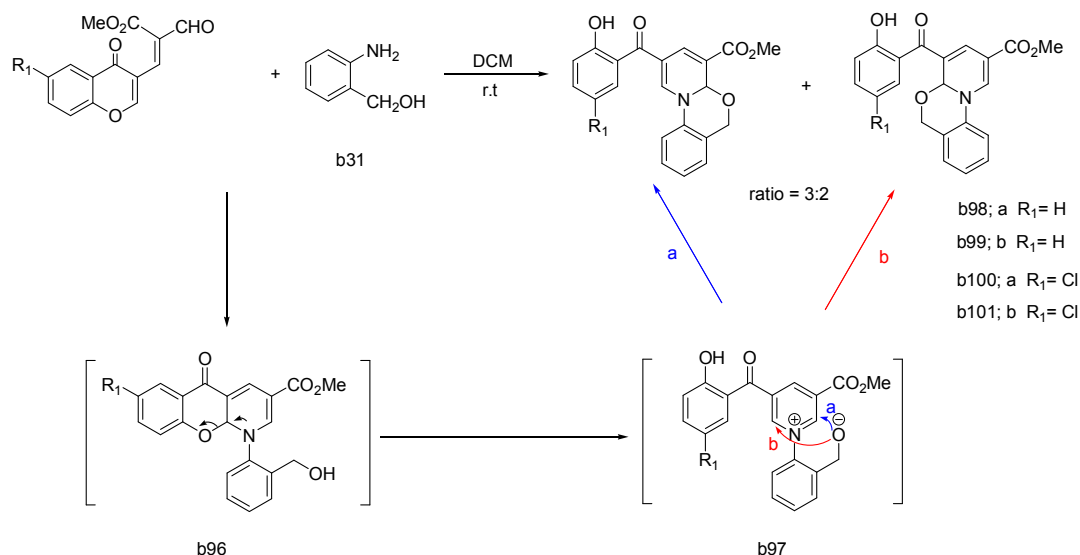
Scheme 3-11. The reaction of the common precursor-ketone ester with *o*-aminobenzyl alcohol **b31**.

compounds	R_1	R_2	yield(%)
b92	Me	Me	91%
b93	Cl	Et	90%
b94	H	Me	94%
b95	H	Et	89%

Table 3-7. The results of the reaction of common precursor with *o*-aminobenzyl alcohol **b31**.

In the same way, bisnucleophilic *o*-aminobenzyl alcohol **b31** was treated with aldehyde precursors that resulted in two products in good yield (Table 3-8). In this reaction, presumably the tricyclic intermediate **b96** leads to an internal pyridine salt

b97 that has two electrophilic sites available for addition of alkoxide. Therefore, addition of benzyl alcohol to either α -carbon of pyridine ring generate two benzoxazine rings (Scheme 3-12), which were quite difficult to isolate by column chromatograph. $^1\text{H-NMR}$ spectra of the mixture clearly revealed two sets of peaks in the ratio 3: 2.

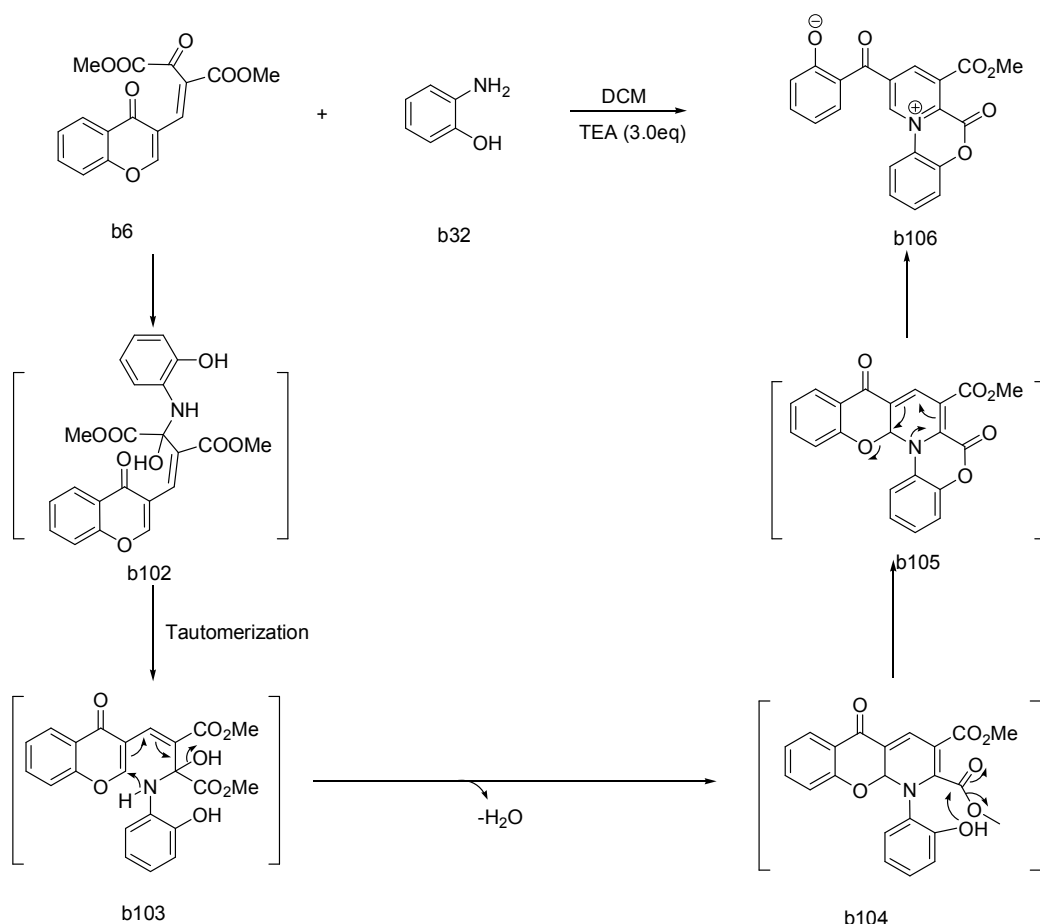


Scheme 3-12. The reaction of the common precursor aldehyde with *o*-aminobenzyl alcohol **b31**.

compounds	R_1	ratio	total yield (%)
b98	H	2/3	93%
b99	H	2/3	93%
b100	Cl	2/3	89%
b101	Cl	2/3	89%

Table 3-8. The results of the aldehyde with *o*-aminobenzyl alcohol **b31**.

2-aminophenol **b32** did not prove to be an interesting N, O-bisnucleophile because of different products formed in different attempts. Ketone ester **b6** was mixed with 2-aminophenol **b32** under basic conditions which resulted in the formation of many products judging from TLC and LC-MS. However a tricyclic lactone internal salt was isolated in very low yield (Scheme 3-13). Mechanistically, the ketoester **b6** condensed with aminophenol **b32** first to form aminal **b103** that cyclizes to yield **b104**. The lactone ring is formed by addition of phenol followed by chromone ring opening to yield the internal salt **b106** (Scheme 3-13).

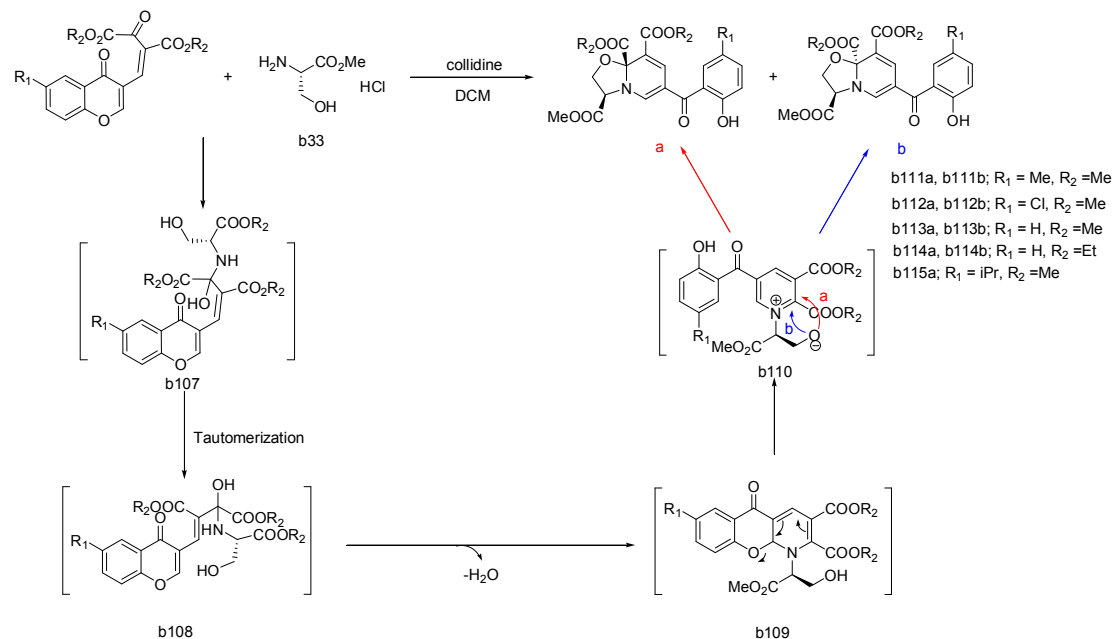


Scheme 3-13. The reaction of the common precursor **b6** with 2-aminophenol **b32**.

2-aminoethanol **b29** is a very simple bis-nucleophile and its reaction was attempted with the ketoester. However this led to the formation of many products which could not be purified. To avoid side reactions, Boc-protected 2-aminoethanol **b30** was resorted to. Addition of **b30** to ketoester changed the light yellow color of reaction mixture quickly to deep yellow; however, soon many products began to appear (TLC). Addition of 10% TFA to remove the protecting group Boc further messed up the reaction mixture and therefore, this transformation was not further pursued.

In order to incorporate stereogenic centers to the cascade products, L-serine methyl ester **b33** was used as *N,O*-bisnucleophile. However, under basic conditions— TEA, racemization was observed. So the TEA was replaced by the weak base collidine. In this cascade reaction two diastereomeric products were formed which could be purified carefully. However, the methods attempt to define their absolute

configuration by using different NMR technique failed. Crystallization attempts were also unsuccessful. It is assumed that dihydro-2H-oxazole[3.2.a]-pyridines are formed from the tricyclic intermediate **b108** (as in many others cases). Formation of two diastereoments also suggested that a flat pyridium salt **b110** might be involved (Scheme 3-14).



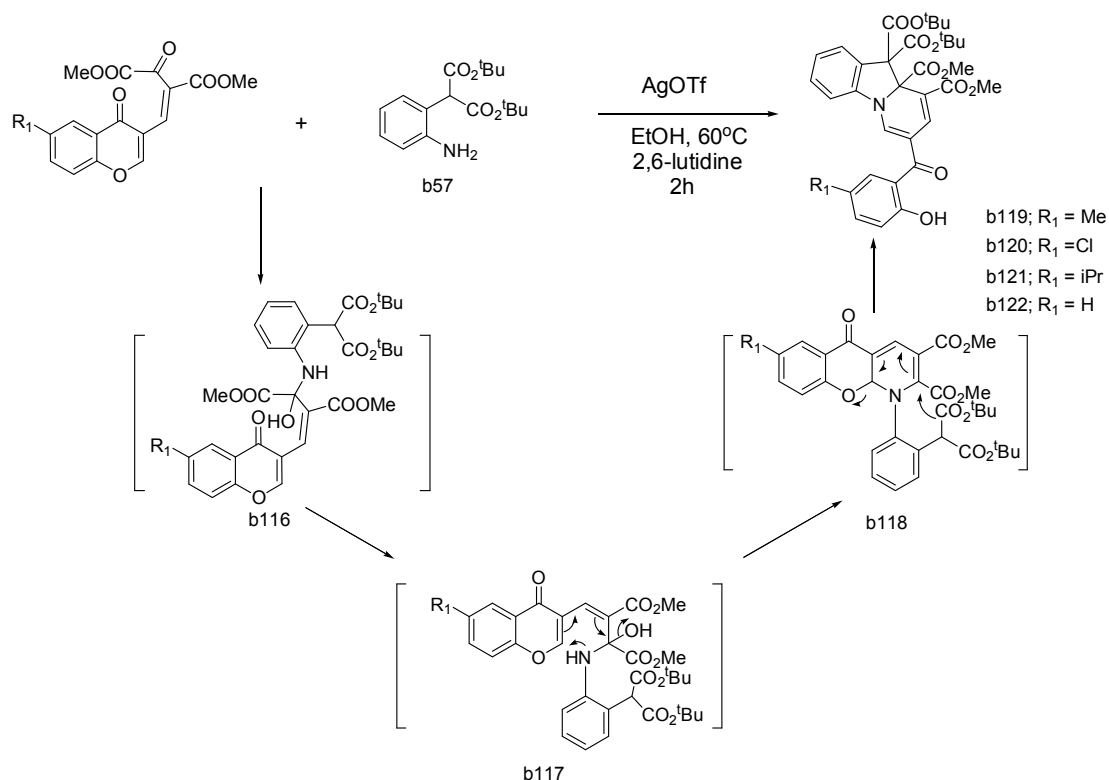
Scheme 3-18 The reaction of the common precursor-ketone ester with L-serine methyl ester **b56**

Compounds	R ₁	R ₂	Yield (%)
b111a	Me	Me	43%
b111b	Me	Me	46%
b112a	Cl	Me	44%
b112b	Cl	Me	45%
b113a	H	Me	41%
b113b	H	Me	41%
b114a	H	Et	45%
b114b	H	Et	43%
b115a	iPr	Me	47%

Table 3-9. The results of the reaction of common precursor-ketone ester with L-serine methyl ester **b33**.

3.3.1.3 Branching cascades with N, C; O, C; and C, C-bisnucleophilies

Among the other bisnucleophiles employed, two more bisnucleophiles that proved interesting cascade-triggering molecules in the branching-cascade strategy were the N,C- and O,C-bisnucleophiles **b57** and **b35**, respectively. Both of these nucleophiles displayed very sluggish reactivities in the initial screening and required further optimization of the reaction conditions. Interestingly, the use of di-*tert*-butyl-2-(2-aminophenyl)malonate (**b57**) led to the formation of benzoindolizine **b119-122** (Scheme 3-15): a scaffold that is part of many biologically active natural products. The use of silver triflate as a catalyst in ethanol at 60°C led to very good yields (Table 3-10) for this cascade reaction sequence (Schemes 3-15). Mechanistically, this cascade reaction too seems to form the tricyclic intermediate **b118** to which adds the di-*tert*-butyl-melonate nucleophile to yield the benzoindolizine scaffold (Scheme 3-15)^[126].

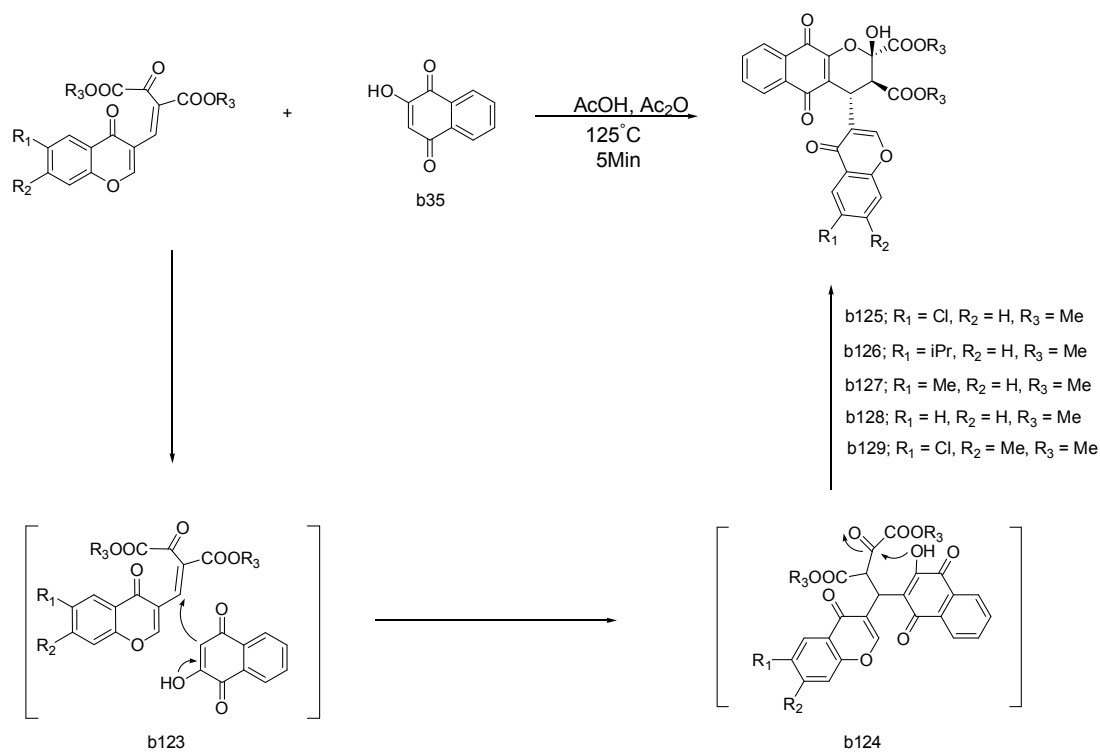
Scheme 3-15. The mechanism of the common precursor-ketone aldehyde with **b34**

Compounds	R ₁	Yield (%)
b119	Me	83%
b120	Cl	79%
b121	iPr	87%
b122	H	89%

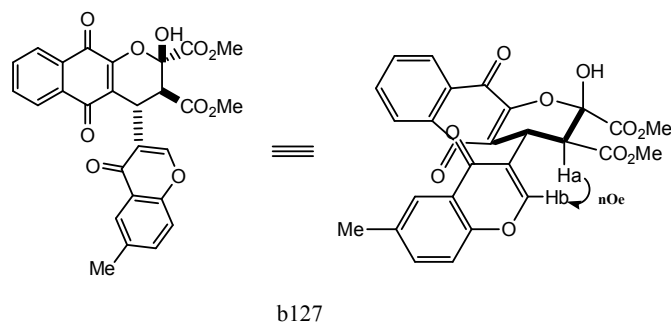
Table 3-10 The results of the common precursor with silver catalyzed

2-Hydroxynaphthalene-1,4-dione **b35**,^[127-128] a O,C-bisnucleophile beholds the naphthoquinone scaffold that exists in many biologically interesting natural products^[133]. Although **b35** did not show any promising reactivity in the initial screening, on tapping its potential to provide natural product based polycyclic quinones, in particular medicinally important pyranonaphthoquinones. Gratifyingly, the treatment of ketoester substrates **b11** with **b35** in the presence of acetic anhydride/acetic acid (1:3) at 150°C for a few minutes yielded chromone-substituted pyranonaphthoquinones **b125-129** in good yields with good diastereoselectivity (Scheme 3-16, Table 3-11). Although aldehyde substrates **b12** reacted well with **b35** under these conditions, the corresponding products were not stable enough and could not be purified.

A proposal for the plausible cascade reaction mechanism is depicted in Scheme 3-16. A conjugated addition of quinone enolate to the substrate ketoester would provide an intermediate **b124** after isomerization. The enolic hydroxyl group then adds to the ketone moiety to provide an anomericly stabilized and therefore stereoselective formation of pyranonaphthoquinone products (Scheme 3-16).


 Scheme 3-17. The mechanism of the common precursor-ketone ester with **b35**.

Compounds	R_1	R_2	R_3	yield(%)	Ratio
b125	Cl	H	Et	84%	5:1
b126	iPr	H	Me	85%	8:1
b127	Me	H	Me	88%	9:1
b128	H	H	Me	90%	9:1
b129	Cl	Me	Me	86%	9:1

 Table 3-11. The results of the common precursor with 2-hydroxynaphthalene-1,4-dione **b35**.


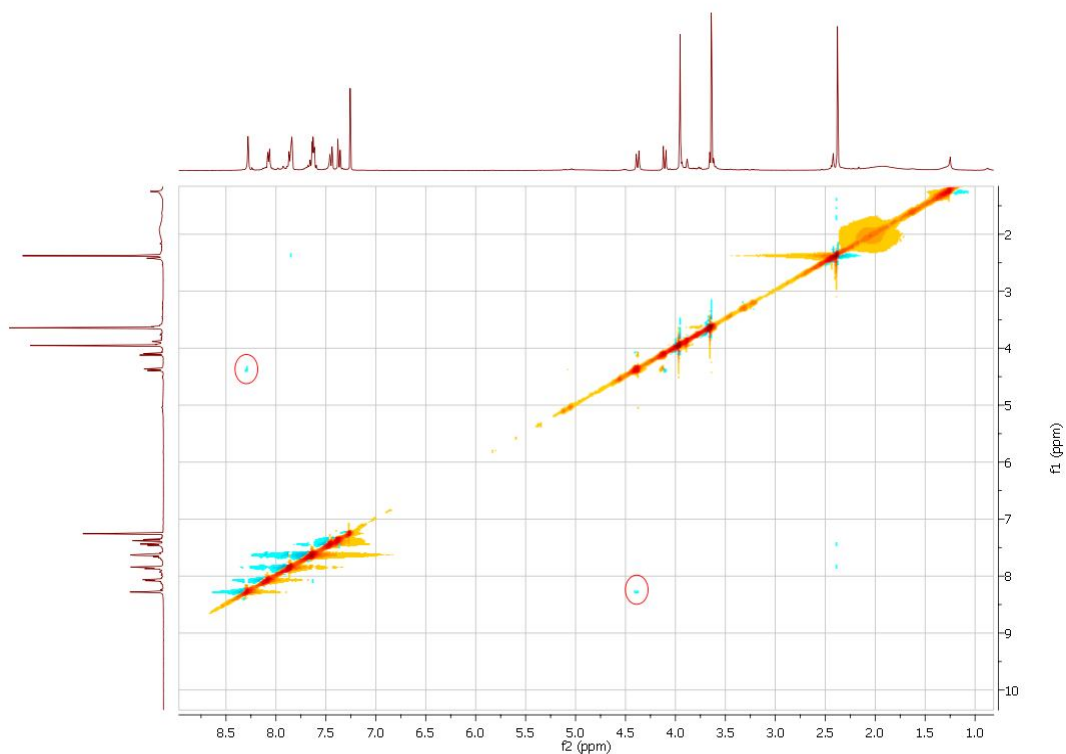


Figure 3-8 The NOESY spectrum of **b127**

The NOESY spectrum of **b127** shows the nOe interaction between the Ha and Hb which were assigned on the basis of ^1H - ^{13}C correlation spectrum. The diaxial coupling value ($J = 10.8$ Hz) for Ha with the vicinal benzylic proton further supports the predicted stereorelationship. The axial position of the hydroxyl group is due to the extra stabilization provided by the double anomeric effect in these acetals. ^[129]

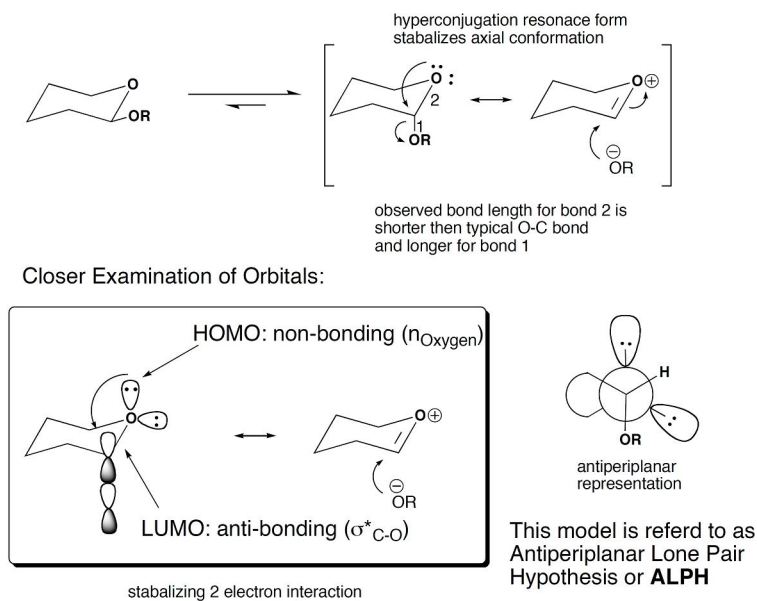


Figure 3-9. Most widely accepted explanation for the anomeric effect.

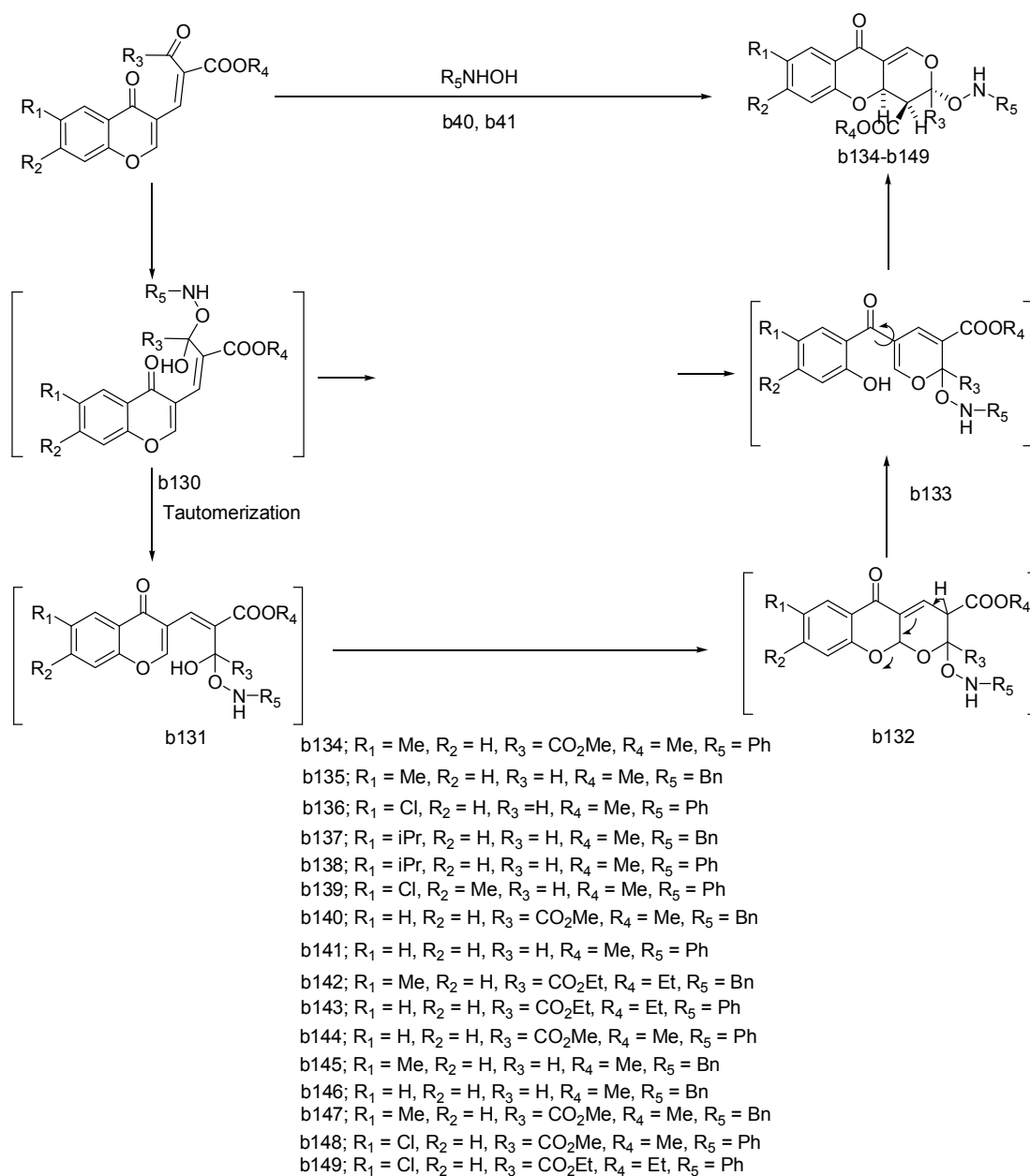
The anomeric stabilization is observed in this example, and a brief explanation is provided for this effect. The anomeric effect normally relates to the interaction between the orientation of the lone pair orbital on the endocyclic oxygen (Figure 3-9) and the exocyclic C-O sigma bond. In the case where the exocyclic oxygen is axial then there is an axially directed lone pair on the endocyclic oxygen that is in an antiperiplanar relationship to the exocyclic C-O bond and consequently is able, through the principle of maximum orbital overlap, to donate some electron density into the low energy C-O antibonding orbital ^[129]. The stabilization from the orbital interaction in the axial conformer can often be greater than the destabilization from steric clash with the axial hydrogen and the axial conformation can often be more stable than the equatorial conformation in these cases ^[129].

A C,C-bisnucleophilic di-tert-butyl malonate **b36** was also used in the reaction screening. Although, **b36** was completely consumed in the reaction (monitored by TLC and LC-MS), too many products were found which could not be purified by silica gel column chromatography.

3.3.2 Branching cascades with Mononucleophiles

It was very disappointing to realize that mononucleophiles **b37-40** yielded complex mixtures of inseparable products in the initial reaction screening. However, *N*-benzyl- and *N*-phenylhydroxylamines **b41** and **b42**, respectively, were found to be useful cascade-triggering substrates. These nucleophiles provided natural product related highly substituted tricyclic benzopyrones **b134-149** in excellent yields and with appreciable diastereoselectivity (Scheme 3-18). In this branching cascade, the hydroxylamines act as *O*-nucleophiles rather than *N*-nucleophiles and add to the keto or aldehyde group of the common substrate to give an intermediate **b131**, which

cyclizes to yield a cyclic acetal **b132**. Chromone ring opening leads to a dihydropyran **b133**, which undergoes intramolecular conjugated addition of the phenol to provide benzopyrones **b134-149**. The conjugate addition of the phenol in **b133** might occur preferentially *anti* to the initially added hydroxylamine for steric reasons and thus lead to the observed stereoselectivity in the formation of anomerically stabilized benzopyrone acetals **b134-149** (Scheme 3-18). The structure and relative configuration of products are corroborated by the results of comprehensive NMR spectroscopic studies.



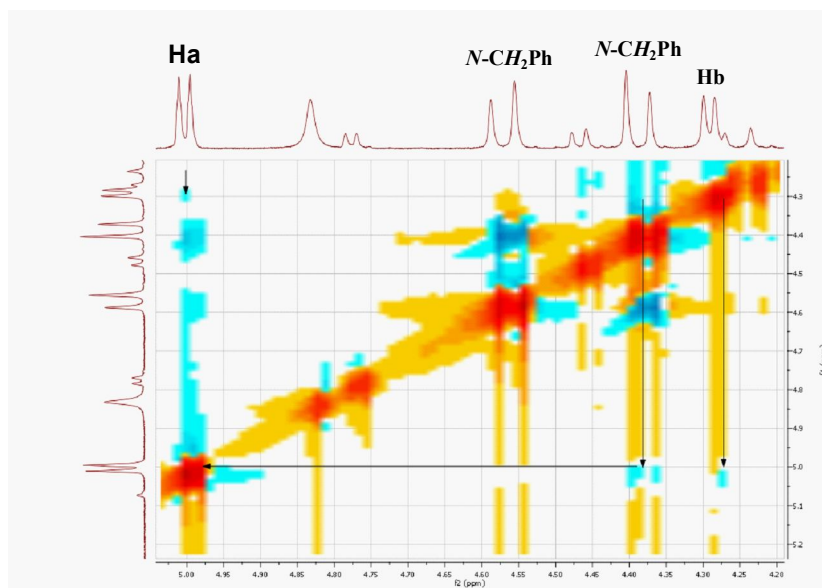
Scheme 3-17 The mechanism of the common precursor-ketone ester and aldehyde with

N-hydroxybenzenamine **b40** and N-hydroxy(phenyl)methanamine **b41**;

Compounds	R ₁	R ₂	R ₃	R ₄	R ₅	ratio	yield
b134	Me	H	CO ₂ Me	Me	Ph	84/16	93%
b135	Me	H	H	Me	Bn	91/9	87%
b136	Cl	H	CO ₂ Et	Et	Ph	84/16	90%
b137	iPr	H	H	Me	Bn	88/12	86%
b138	iPr	H	H	Me	Ph	85/15	88%
b139	Cl	Me	H	Me	Ph	81/19	89%
b140	H	H	CO ₂ Me	Me	Bn	90/10	94%
b141	H	H	H	Me	Ph	82/18	88%
b142	H	H	CO ₂ Et	Et	Bn	87/13	91%
b143	H	H	CO ₂ Et	Et	Ph	87/13	93%
b144	H	H	CO ₂ Me	Me	Ph	82/18	95%
b145	Me	H	H	Me	Bn	81/19	88%
b146	H	H	H	Me	Bn	88/12	89%
b147	Me	H	CO ₂ Me	Me	Bn	86/14	94%
b148	Cl	H	CO ₂ Me	Me	Ph	85/15	92%
b149	Cl	H	CO ₂ Et	Et	Ph	86/14	88%

Table 3-12. The results of the common precursor-ketone ester and aldehyde with N-hydroxybenzenamine **b40** and N-hydroxy(phenyl)methanamine **b41**.

The relative stereochemistry of the tricyclic benzopyrones was confirmed by NOESY, gHSQC, gHMBC etc (Figure 3-10). The observed anomeric effects might be more pronounced in these systems due to the special structure of the spirocycle and might contribute to the unexpected stability of these systems ^[130].



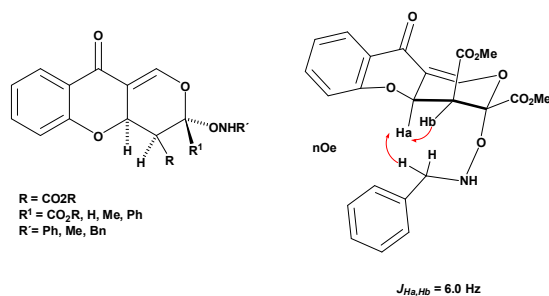
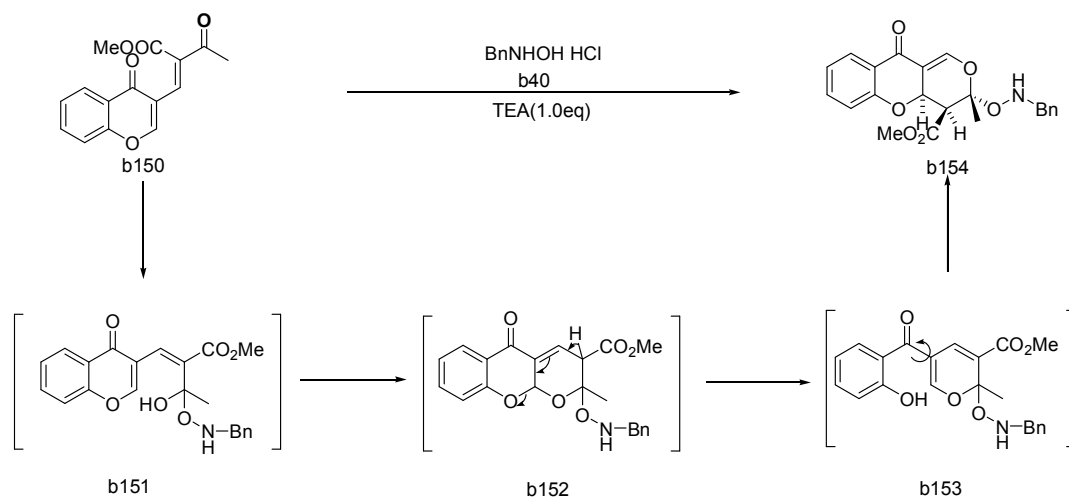
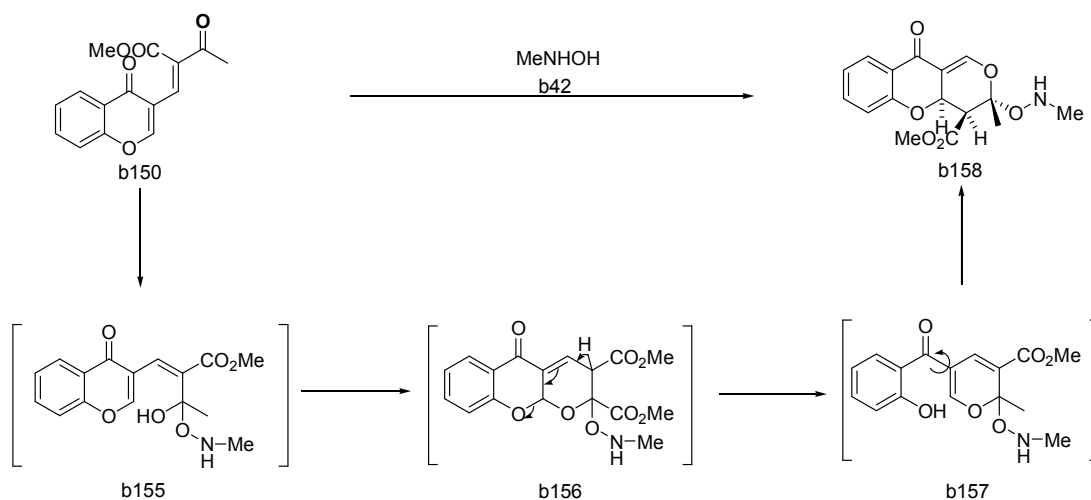


Figure 3-10 Double anomeric stability function

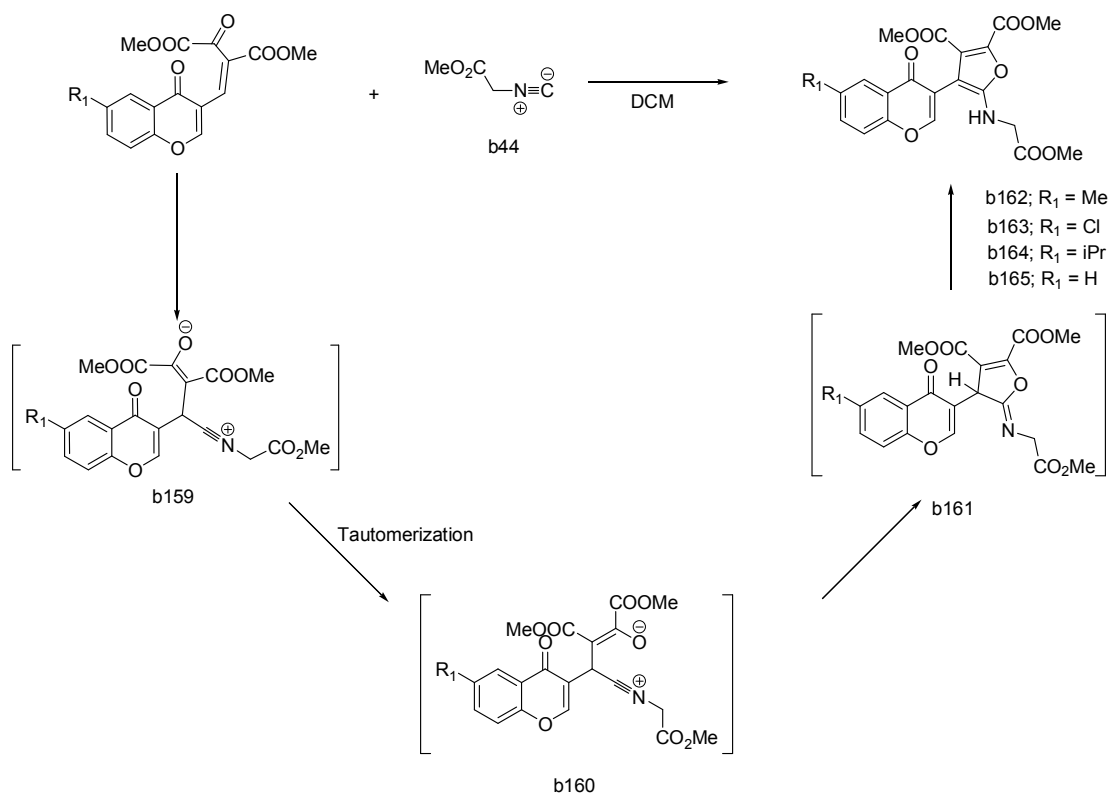
An analogue of ketone ester **b150** supporting methyl ketone instead of keto-ester, was treated with N-hydroxybenzylamine **b40** and N-methylhydroxylamine **b42** under the same reaction conditions. Pleasingly, this led to the formation of corresponding tricyclic benzoyprones **b154** and **b158** respectively in good yield (Scheme 3-18, Scheme 3-19).


 Scheme 3-18. The mechanism of the ketone **b154** with N-hydroxybenzylamine **b40**.

 Scheme 3-19. The mechanism of ketone **b158** and N-hydroxymethylamine **b42**.

Other mono-nucleophilic reactants like sodium ethoxide, vinylmagnesium bromide, hydroxyamino, and butan-1-amine could not provide appreciable product profiles and resulted in formation of complex mixture of many products including trans-esterified and hydrolyzed products. Therefore these reactions were not further optimized.

3.3.3 Branching cascades with Zwitterions

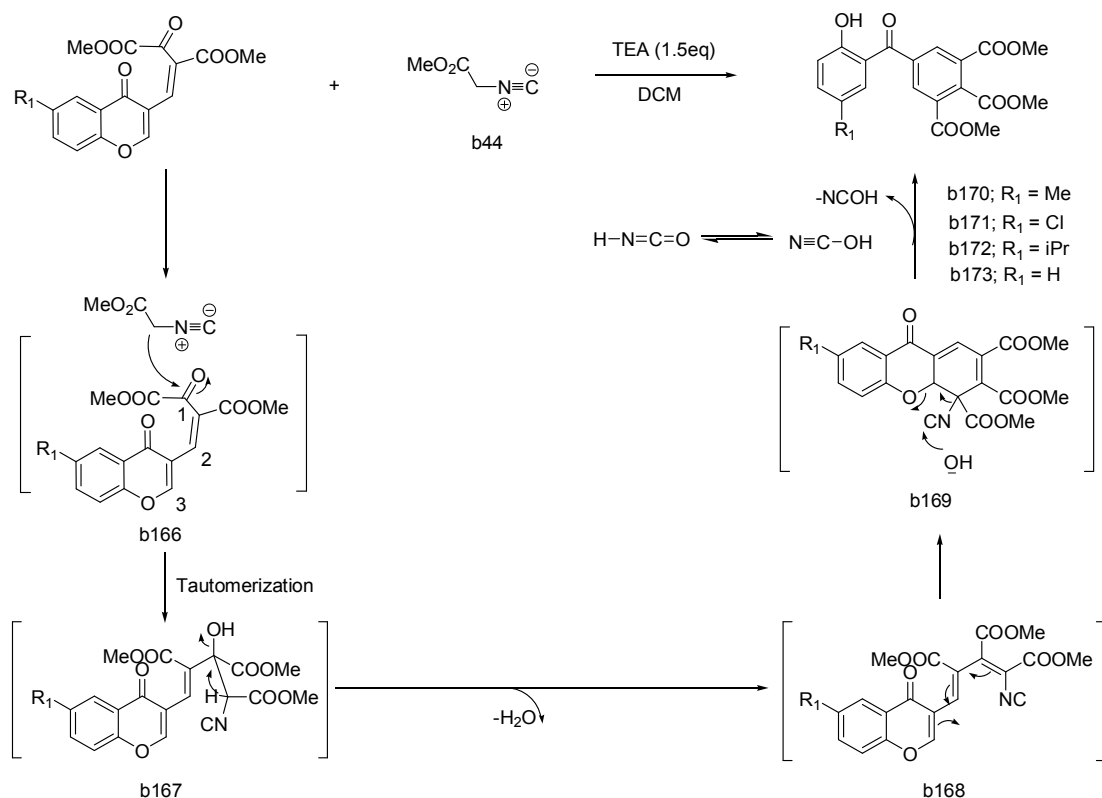
In the reaction screening, some zwitterionic species were intentionally added that could act as both simple nucleophiles or as dipoles for plausible dipolar annulations. Among the zwitterions attempted in the branching cascades strategy, **b45** did not react at all and the allene derived zwitterion **b46** was too slow to yield traces of an unidentified product. Zwitterion **b44** i.e. methyl isocyanoacetate though reacted nicely with both aldehydes and ketoester substrates and yielded another flavonoid based benzopyrone molecules supporting substituted furan ring (**b162-165**, Scheme 3-20). An initial conjugated addition of **b44** on to the C1' of **1** leads to formation of oxanion **b160** was assumed which adds on to the iminium cation in the proximity to provide **b161**. Isomerization/aromatization of **b161** provides the final products **b162-165** in this branching cascade (Scheme 3-20) in excellent yields (Table 3-13).

Scheme 3-21. The mechanism of the common precursor-ketone ester with **b44**.

Compounds	R ₁	yield(%)
b162	Me	94%
b163	Cl	91%
b164	iPr	93%
b165	H	95%

Table 3-13. The results of the common precursor with methyl 2-isocyanoacetate **b44**.

Interestingly, when the common precursor-ketone ester was traded with **b44** in the presence of triethylamine, the results were totally different yielding highly electron-deficient benzenes **b170-173** (Scheme 3-22) in excellent yields (Table 3-14). It is proposed that under basic condition, the anion of the **b44** adds to the keto group of the ketoester moiety to form **b166** which might also exist in the form of **b167**. The later leads to the *s-cis* conformation (**b168**) followed by 6π cyclization leading to **b169** where decyanation occurs providing highly substituted and electron-deficient benzophenones (Scheme 3-21 and Table 3-14) ^[131].



Scheme 3-21. The mechanism of the common precursor-ketone ester with methyl 2-isocyanoacetate **b44** under basic conditions.

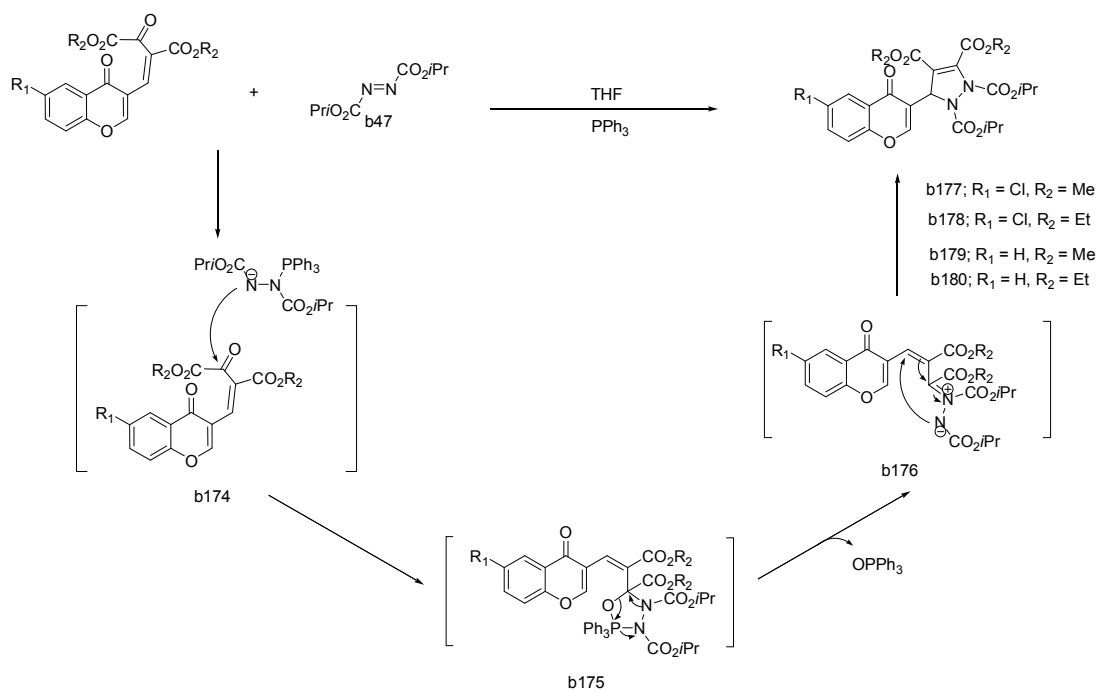
Compounds	R_1	yield(%)
b170	Me	93%
b171	Cl	89%
b172	iPr	91%
b173	H	94%

Table 3-14. The results of the common precursor with methyl 2-isocyanoacetate **b44** under basic conditions.

Huisgen's zwitterions (**b47**, Figure 3-5) had been well explored on various aldehydes and ketones including chalcones. Based on their reported reactivity pattern, it was intriguing to find how they behave with the highly conjugated common substrates of the branching cascades. Precisely, the effort was to see if the expected intermediate **b176** that is formed by addition of **b47** to ketones, would follow a 1,4-addition or a possible yet rare 1,6-addition. Thus, a mixture of ketoester, dimethyldiazodicarboxylate (DIAD) and triphenylphosphine was stirred overnight at room temperature in dichloromethane when all of the ketoester was consumed. Column chromatographic purification of the crude reaction mixture provided the

expected chromone substituted pyrazole as the major product. Differently substituted common substrates yielded the pyrazoles **b177-180** in very good yields (Scheme 3-22 and Table 3-15, Figure 3-11). Nevertheless, a pyrazole substitution on to the privileged chromone moiety brings structural features of the flavonoid natural products and might enrich the collection in interesting and related biological activities.

Mechanistically, the zwitterion **b174** is formed after the addition of triphenylphosphine to DIAD and it adds to the ketone moiety to form the cyclic structure **b175**. The later removes the triphenylphosphine oxide to form the critical intermediate **b176** which follows the 1,4-addition to yield the pyrazoles (Scheme 3-22).



Scheme 3-22. The mechanism of the common precursor-ketone ester with DIAD

Compounds	R ₁	R ₂	yield(%)
b177	Cl	Me	86%
b178	Cl	Et	84%
b179	H	Me	91%
b180	H	Et	89%

Table 3-15. The results of the common precursor-ketone ester with DIAD.

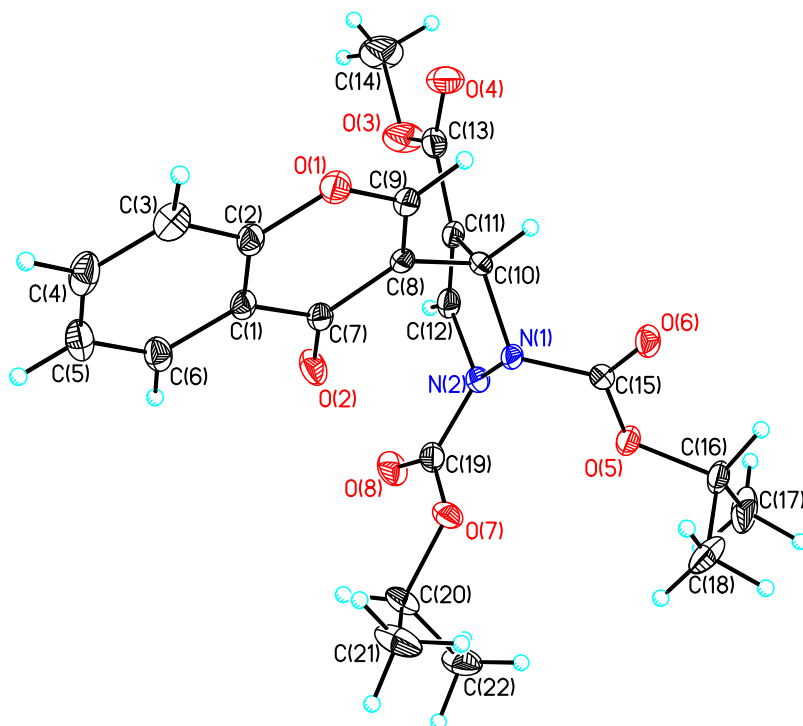
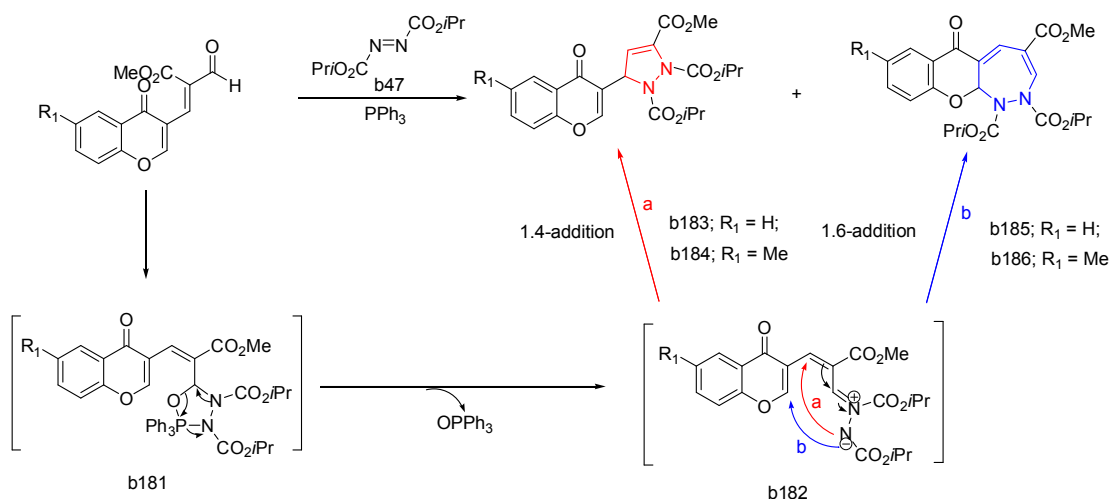


Figure 3-11 X-ray structure of **b179**

In all these cases, therefore the major reaction pathway the intermediate **b176** follow is the 1,4-addition. However, in cases of aldehydes, minor products could be isolated (**b185-186**) that appear to be the 1,6-addition products, along with the expected pyrazoles as major products **b183-184** (Table 3-16). Different spatial arrangement of the functional groups in the case of ketoesters and aldehydes i.e. different configurations might be playing a role in providing small amount of chromonodiazepines. It is obvious that in case of aldehydes the intermediate **b182** is more proximal to the chromone ring than in ketoesters (Scheme 3-23).

Scheme 3-23. The mechanism of the common precursor aldehyde with DIAD **b47**

Compounds	R ₁	Yield (%)
b183	H	86%
b184	H	13%
b185	Me	73%
b186	Me	11%

Table 3-16. The results of the common precursor aldehyde with DIAD **b47**.

3.4 Summary

In the substrate controlled branching cascades, diverse chosen cascade triggering substrates can push different cascade reactions and incorporate their molecular complexity to the overall architectures that result from these reactions. Therefore, not only diverse scaffolds result from these efforts but also relatively more complex scaffolds are generated. The methodology also provides access to new unprecedented structures and chemical transformations of broader use and applications in general organic synthesis. The examples provided above clearly demonstrate these observations, wherein fourteen different nucleophiles provided seventeen complex and functionalized scaffolds following ten different cascade reaction sequences. A very important point in this branching cascade strategy is to have suitable multifunctionalized common precursors which can facilitate numerous reaction cascades and entertain diverse addition substrates to yield skeletally diverse focused compound collections. In the presented strategy diverse nucleophiles i.e.

bisnucleophiles, mono-nucleophiles and zwitterions were employed on a common substrate that has largely dispersed electrophilicity. These contrasting features along with inherent hard and soft nucleophilicities of the additional substrates helped direct different cascade reactions and as a consequence result in different scaffold structures. The strategy is particularly suitable to address the synthesis of natural product inspired compound collections wherein diverse and complex natural product-based motifs are desired but in efficient and quick manner. Because branching cascade design employs easily accessible common substrates that are ring-transformed efficiently, this strategy is highly amenable to generate diverse focused compound collections.

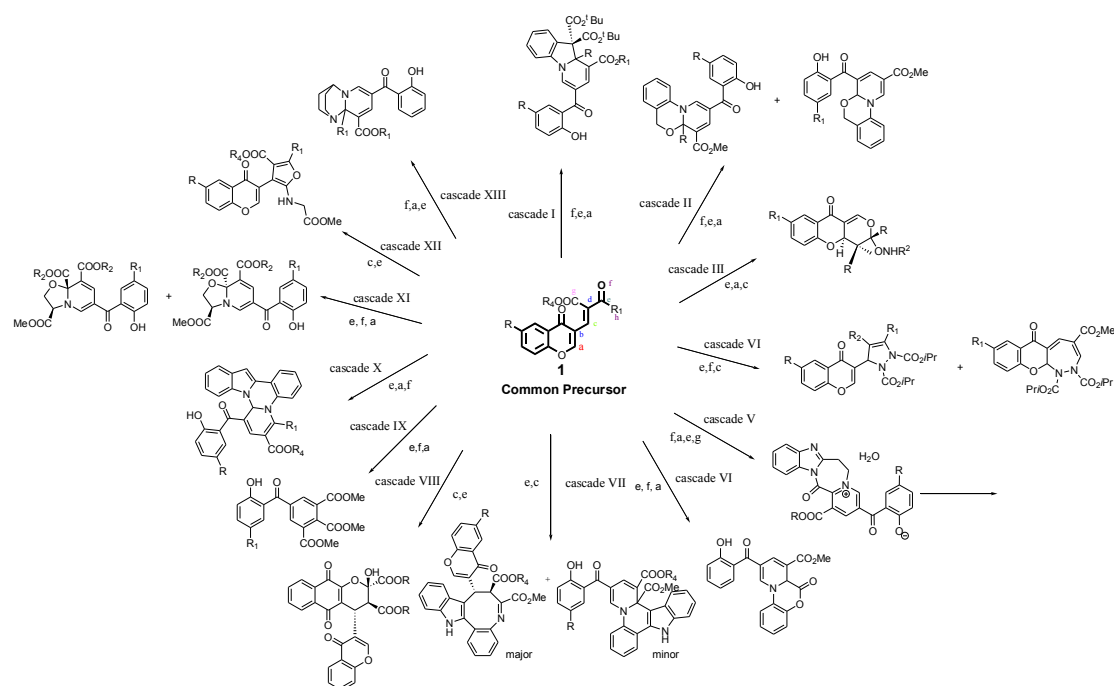


Figure 3-10. Substrate control branching cascades.

4. Summary

4.1 Summary(English)

The dilemma of any organic chemist in this era of highly interdisciplinary research, in particular when comes to explore small molecules for chemical genetics and chemical biology research, is that what kind of small molecules should be made? Different strategies therefore have emerged in the last decade covering different areas of vast chemical space. While on the one hand, diversity oriented synthesis (DOS) has emerged as a powerful combinatorial tool to cover largely unbiased chemical space, biology oriented synthesis (BIOS) focuses on the biologically relevant scaffold structures and tends to generate natural product inspired libraries. However, most of the compound collection synthesis strategies follow multi-step syntheses wherein typically a scaffold is generated in few steps followed by the modification or incorporation of functional groups that can help generate a sufficient number of molecules in a collection. Synthesis strategies that can provide easy, concise and efficient access to diverse sets of scaffold structures are very demanding and challenging to develop. Cascade or domino reaction sequences, where multiple reactions occur consecutively in a one-pot protocol could provide efficient access to compound collection synthesis.

In the work presented in this thesis, a cascade reaction based synthesis strategy termed “branching cascades” was developed. Based on the branching pathways of DOS, in this strategy, a common substrate enters diverse scale reaction sequences, which are triggered either by activating reagents or by additional substrates and each cascade or domino reaction sequence yields diverse and complex scaffold structures (Figure 4-1). The scaffolds emerging from this strategy are already suitably functionalized for further functional group manipulation that provides the desired number of complex

small molecules. Therefore, the most important aspect of this strategy is to design the common, multi-functionalized precursor which can support and facilitate diverse cascade reaction sequences.

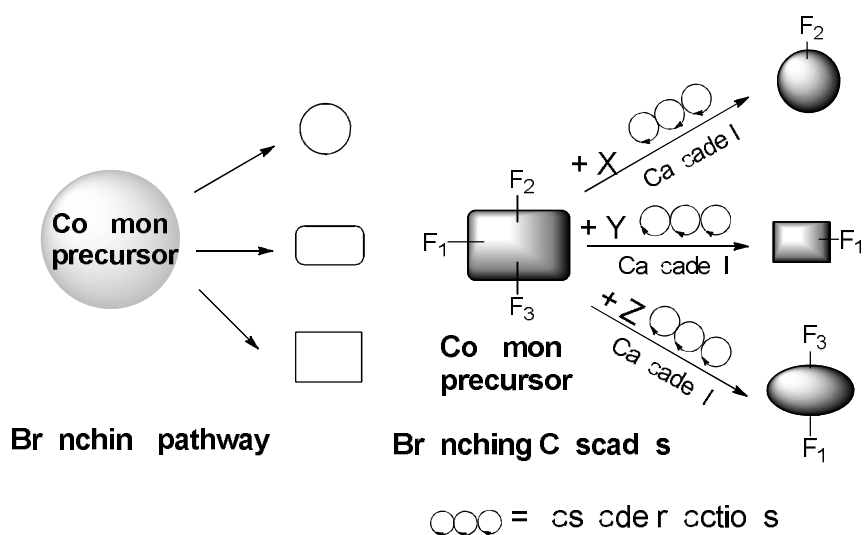


Figure 4-1. Branching Cascades

In the second chapter of this thesis, the common substrate was designed to have different reactive sites along with a TBS protected alkyl ether handle. A branching cascade strategy was developed wherein diverse cascade reactions were triggered by different desilylating reagents. Thus, different reagents, i.e. ammonium fluoride, cesium fluoride and PPTS triggered different cascade reaction sequences and yielded a compound collection of highly substituted pyridines, benzophenones and benzopyran scaffolds. The resulting diverse collections were already decorated with functional groups that can be easily modified to make further small libraries. Thus, this strategy provides an easy access to libraries from a library. In this regard, a collection of benzoximes and benzoxazoles and isoxazoles was efficiently generated (Figure 4-2).

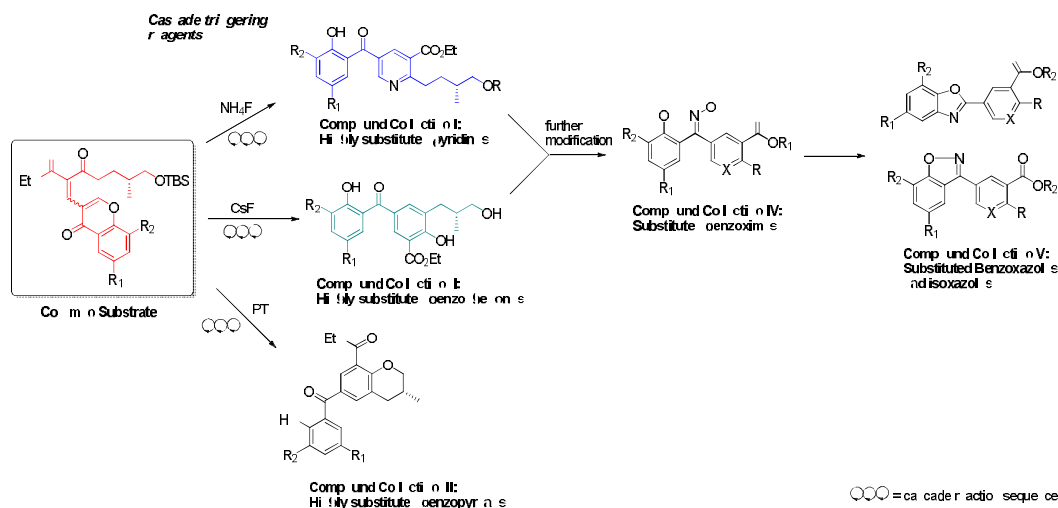


Figure 4-2. Reagent controlled branching cascades.

The third chapter of this thesis explains the substrate controlled branching cascade strategy, wherein instead of reagents, different additional substrates are employed as cascade reaction triggers. This approach is more interesting and useful, because one can choose the substrates with sub-structures that should be incorporated into the resulting scaffolds. Thus, the resulting collection would have both scaffold diversity and enriched molecular complexity. It was good evident from the results presented in this chapter. A common substrate with multiple electrophilic centers was used with a group of twenty three diverse nucleophiles, which include mono- and bis-nucleophiles and nucleophilic zwitterionic species. Fourteen nucleophiles provided sufficiently clean reaction profiles and afford seventeen diverse and complex ring-systems including some unprecedented molecular frameworks (Figure 4-3). There were ten different cascade reaction pathways that were followed by these substrates on the common substrates. While one can choose the cascade triggering substrates with the desired sub-structures, this strategy is particularly useful for generating natural product inspired compound collection as depicted in Figure 3. In addition, there were novel scaffold structures generated that could be of further interest from a medicinal chemistry point of view. Moreover, this strategy also revealed novel chemical transformations, for instance, hydroxylamines acted as *O*-nucleophiles rather than *N*-nucleophiles in delivering natural product based tricyclic benzopyrones. Further,

subtle changes in reaction conditions changed the course of the reaction completely to a different cascade sequence. For instance, methyl isocyanoacetate under neutral reaction conditions provided furan substituted benzopyrones. However, in the presence of triethylamine, a completely different reaction course was adopted leading to benzophenones (Figure 4-3).

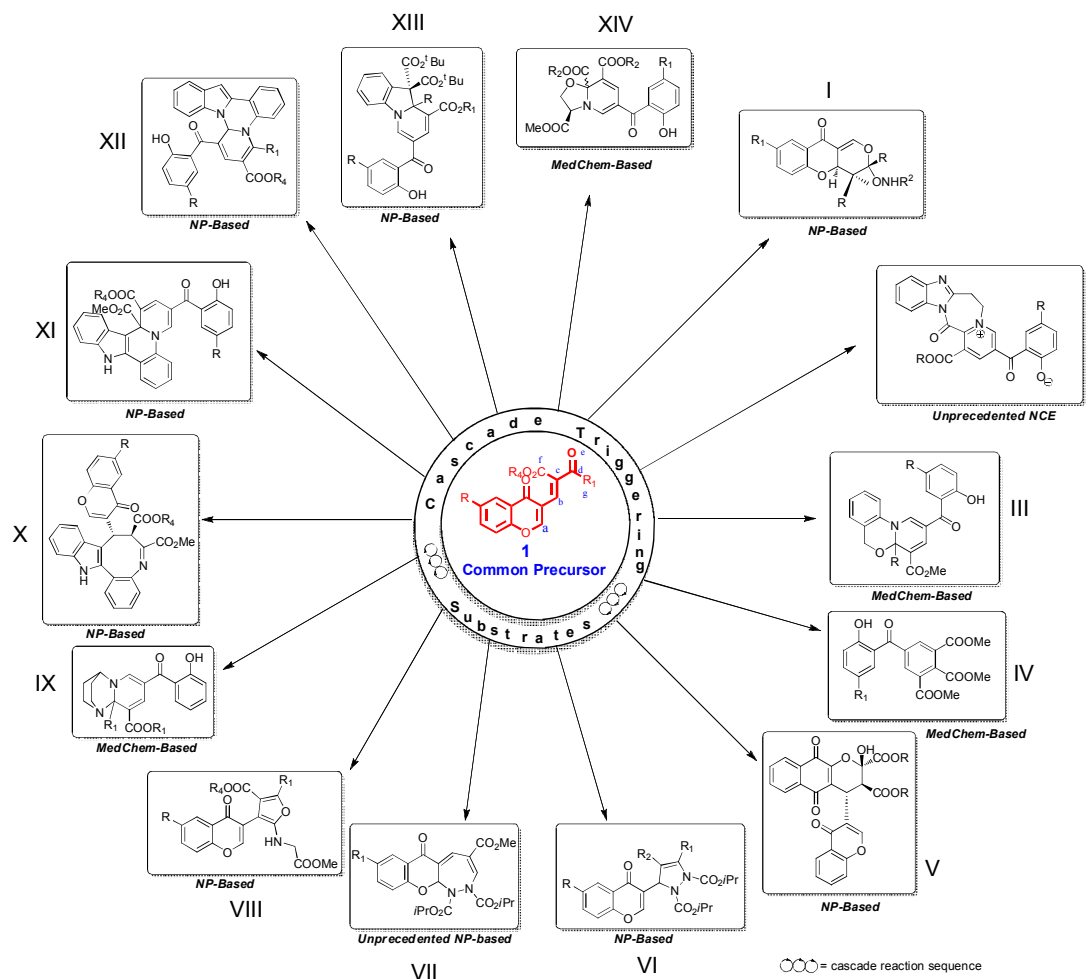


Figure 4-3 Triggering substrates cascade.

While the branching cascade design employs easily accessible common substrates that are ring-transformed efficiently, this strategy is highly amenable to generate diverse focused compound collections.

4.2. Zusammenfassung (German)

Die interdisziplinären Gebiete der Chemischen Genetik und der Chemischen Biologie stellen einen organischen Chemiker stets vor die Herausforderung ein geeignetes Grundgerüst für die Synthese von biologisch aktiven Molekülen zu finden und eine entsprechend effiziente Syntheseroute zu etablieren. Mehrere Strategien wurden diesbezüglich in den letzten Jahren entwickelt. Während sich die diversitätsorientierte Synthese (DOS) als kombinatorische Prozedur, auf eine möglichst große Diversität bezüglich der zu synthetisierenden Verbindungen fokussiert, zielt die biologisch orientierte Synthese (BIOS) auf Verbindungen ab, die bereits biologisch validierte Grundgerüste enthalten und generiert somit naturstoffinspirierte Substanzbibliotheken. Die Synthese der meisten Substanzbibliotheken basiert häufig auf mehreren Syntheseschritten, wobei ein Grundgerüst synthetisiert und derivatisiert werden muss. Synthesestrategien, die möglichst schnell und in hohen Ausbeuten eine Vielzahl an neuen Verbindungen generieren können, sind hierbei von besonderem Interesse. In dieser Hinsicht bieten Kaskaden- und Dominoreaktionen, besonders als "Eintopfreaktionen", einen effizienten und raschen Zugang zu Substanzbibliotheken.

In dieser Arbeit wurde eine Kaskadenreaktion basierte Strategie entwickelt und angewendet. Basierend auf dem DOS-Prinzip, wird in dieser Strategie eine herkömmliche Substanz mit weiteren Edukten in Domino- oder Kaskadenreaktionen umgesetzt und dabei eine große Anzahl an komplexen Molekülen synthetisiert (Abb. 1). Die hierbei entstandenen Grundgerüste sind bereits mit funktionellen Gruppen für weitere chemische Modifikationen ausgerüstet, um eine komplexe Substanzbibliothek zu etablieren. Der wichtigste Aspekt hierbei ist das Design und die Synthese einer geeigneten Ausgangsverbindungen, die für die Kaskadenreaktion effizient eingesetzt werden kann.

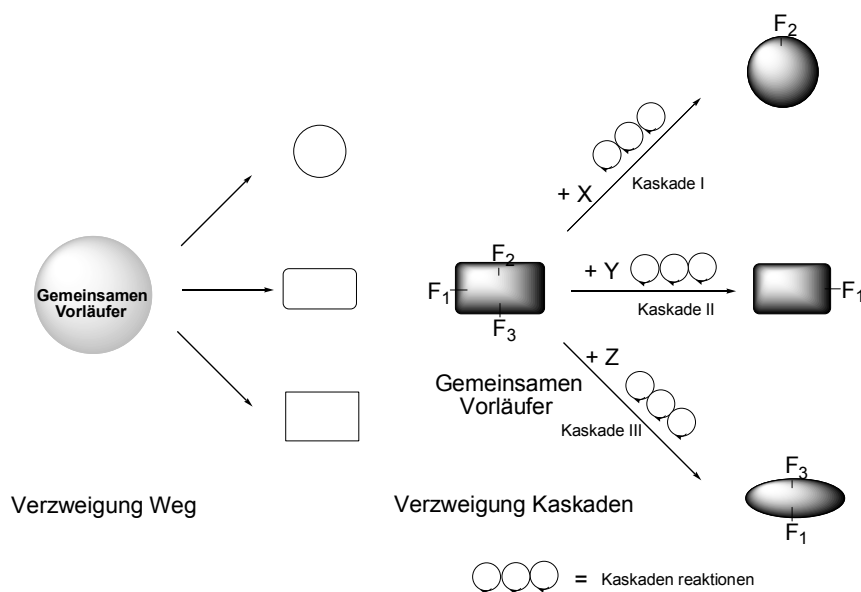


Abbildung 1. Branching Cascades

Im zweiten Teil dieser Arbeit wird eine Substratklasse mit verschiedenen Reaktionszentren und TBS-geschützten Alkylether-Seitenketten etabliert, die einen Ausgangspunkt für Kaskadenreaktionen darstellt. Die Kaskadenreaktionen werden hierbei mit verschiedenen Desilylierungsreagenzien gestartet. Der Einsatz von verschiedenen Reagenzien, wie zum Beispiel Ammoniumfluorid, Cäsiumfluorid oder PPTS, führten zu einer Substanzbibliothek von substituierten Pyridinen, Benzophenonen und Benzopyranen. Die resultierenden Grundgerüste waren bereits entsprechend mit funktionellen Gruppen ausgestattet, so dass weitere Bibliotheken aus dieser Ursprungsbibliothek generiert werden konnten. Hierdurch konnten Substanzkollektionen basierend auf Benzoxim-, Benzoxazol und Isoxazolgrundgerüsten dargestellt werden. (Abb.2)

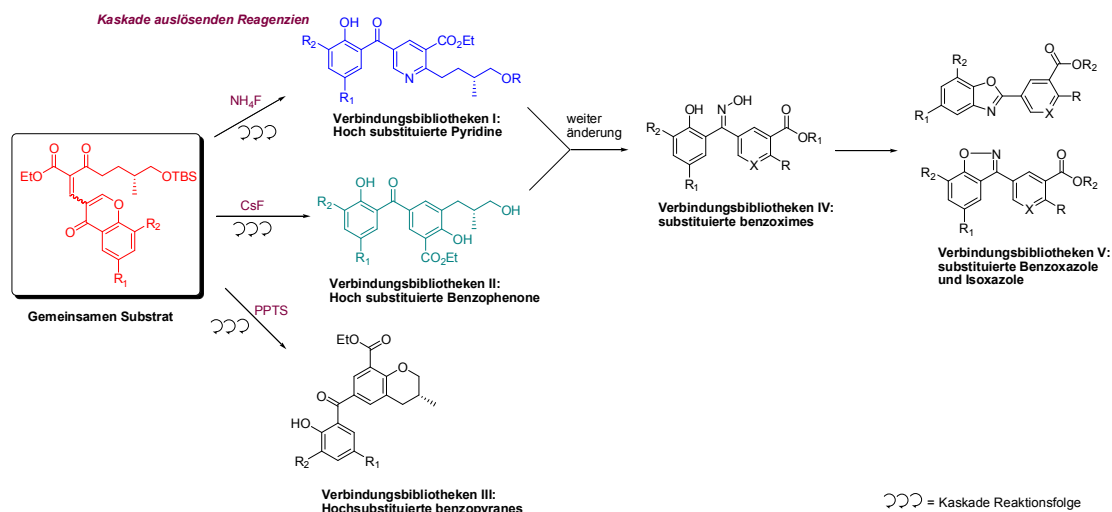


Abbildung 2. Reagenz kontrolliert Verzweigung Kaskaden.

Das dritte Kapitel erklärt eine Substrat kontrollierte verzweigte Kaskadenstrategie, in der anstatt eines Reagenzes, verschiedene zusätzliche Substrate als Auslöser fungieren. Dieser Ansatz ist interessanter und nützlicher, weil man Substrate mit speziellen Substrukturen in das Gerüst mit einbauen kann. So besitzt die resultierende Substanzkollektion sowohl eine strukturelle Vielfalt als auch eine gesteigerte molekulare Komplexität, was aus den Ergebnissen dieses Kapitels klar hervorgeht. Es wurde ein gemeinsames Substrat mit mehreren elektrophilen Zentren mit einer Charge von 23 verschiedenen Nucleophilen umgesetzt, welche Mono- und Bis-Nucleophile und nucleophile-zwitterionische Spezies umfassten. Vierzehn Nucleophile zeigten ein sauberes Reaktionsprofil und ermöglichten 17 vielfältige und komplexe Ringsysteme einschließlich einiger noch nie gezeigter molekularer Gerüste (abb3).

Darüber hinaus konnten neue Molekül-Gerüste erzeugt werden, die von weiterem Interesse für die Medizinische Chemie sein könnten. Zusätzlich konnte durch diese Strategie neu chemische Umwandlungen aufgezeigt werden, zum Beispiel Hydroxylamine, welche bei der Bereitstellung von trizyklischen Benzopyronen eher als O- und nicht als N-Nucleophile fungieren. Darüber hinaus zeigte sich, dass kleine Änderungen der Reaktionsbedingungen zu komplett unterschiedlichen Kaskadensequenz führen können. Zum Beispiel führen Reaktionen der

Isocyanoacetate unter neutralen Bedingungen zu Furan substituierten Benzopyronen. Aber in Gegenwart von Triethylamin wurde eine komplett andere Reaktionsfolge beobachtet, bei der diese zu Benzophenonen umgewandelt wurden (Abb 3).

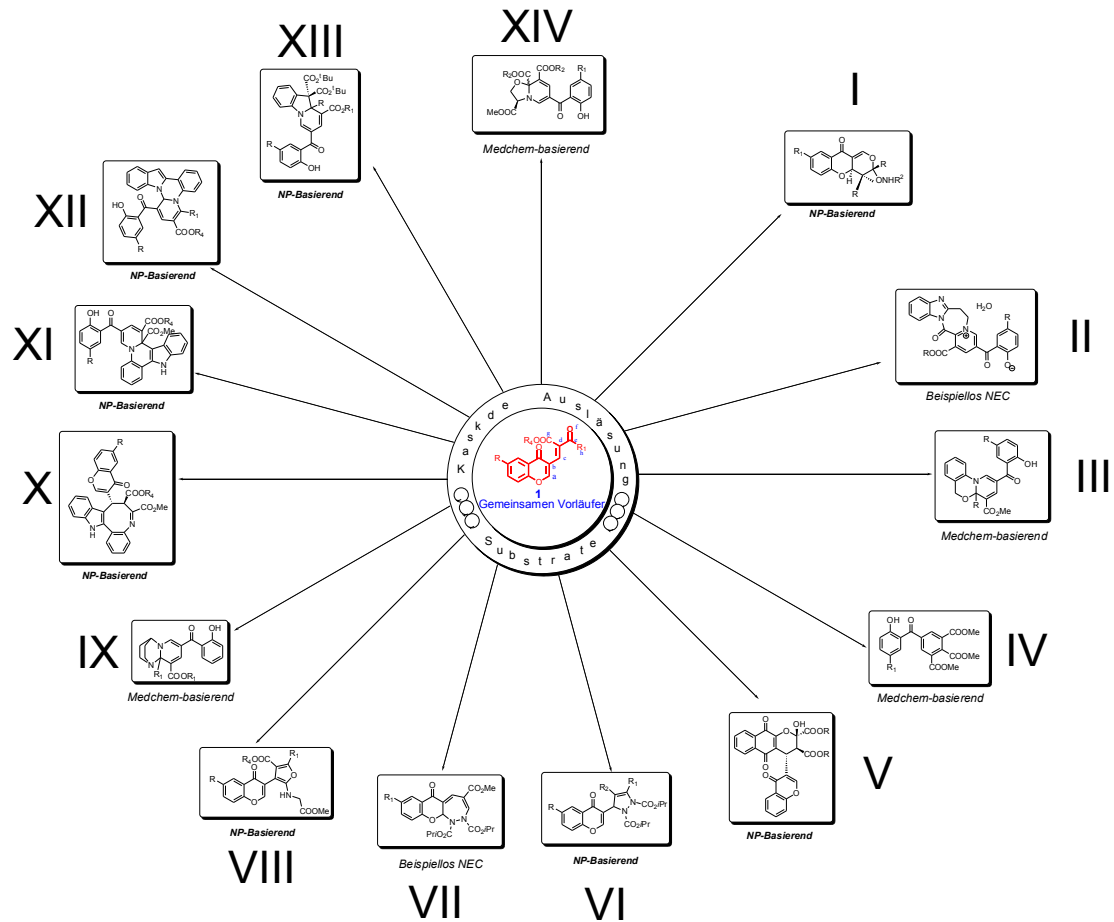


Abbildung 3 Triggering Substrate Kaskade.

Während das verzweigte Kaskaden-Design leicht zugängliche Substrate einsetzt, welche leicht zum Ringschluss neigen, ist diese Strategie sehr gut geeignet um diverse Substanzkolektionen zu generieren.

5. Experimental section

5.1 General methods

Silica gel flash liquid chromatography:

Purifications were performed using silica gel from J. T. Baker or Merck (particle size 40-60 μ m) under approximately 0.5 bar pressure.

Nuclear magnetic resonance spectroscopy (NMR):

^1H - and ^{13}C -NMR spectra were recorded using a Varian Mercury 400 spectrometer (400MHz) $^1(\text{H})$ and 100.6MHz (^{13}C). Chemical shifts are expressed in parts per million (ppm) from internal deuterated solvent standard (CDCl_3 : $\delta \text{H} = 7.26$ ppm, $\delta \text{C} = 77.0$ ppm; CD_3OD : $\delta \text{H} = 4.84$ ppm, $\delta \text{C} = 49.05$ ppm; DMSO : $\delta \text{H} = 2.50$ ppm, $\delta \text{C} = 39.43$ ppm; CD_3CN : $\delta \text{H} = 1.94$ ppm, $\delta \text{H} = 1.24$ ppm). Coupling constants (J) are given in Hertz (Hz) and the following notations indicate the multiplicity of the signals: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), m (multiplet), br (broad signal).

Mass spectrometry (ESI-MS and FAB-HR/LR):

Electrospray mass spectrometric analyses (ESI-MS) were performed on a Finnigan LCQ spectrometer. Fast atom bombardment (FAB) mass spectra were recorded on a Finnigan MAT MS 70 spectrometer, using *m*-nitrobenzylalcohol as matrix. Calculated masses were obtained using the software ChemDraw Ultra (CambridgeSoft Corporation) or Xcalibur.

Reversed-phase liquid chromatography – electrospray ionization mass

spectrometry (LC-MS):

LC-MS measurements were carried out on a Hewlett Packard HPLC 1100/Finnigan LCQ mass spectrometer system using Nucleodur C18 Gravity, Nucleosyl 100-5 C18 Nautilus (Macherey-Nagel) or Jupiter C4 (Phenomenex) columns and detection at 215 and 254 nm.

Method A: Positive linear gradients of solvent B (0.1% formic acid in acetonitrile) and solvent A (0.1% formic acid in water) were used at 1mL/min flow rate.

Method B: Negative linear gradients of solvent B (10mM NH₄OH in acetonitrile) and solvent A (10mM NH₄OH in water) were used at 1mL/min flow rate.

Method C: Positive linear gradients of solvent B (0.1% formic acid and 5% THF in methanol) and solvent A (0.1% formic acid in water) were used at 1mL/min flow rate.

Method D: Negative linear gradients of solvent B (10mM NH₄OH and 5% THF in methanol) and solvent A (10mM NH₄OH in water) were used at 1mL/min flow rate.

Analytical reversed-phase high performance liquid chromatography (an. HPLC):

Analyses were performed on a Varian prostar system using CC 125/4 Nucleodur C18 Gravity 3 mm and CC 125/4 Nucleodur C4 Gravity columns (Macherey-Nagel), autosampler prostar 410 and UV/Vis detector with Varian prostar 335. Linear gradients were used at 1mL/min flow rate (A: water, B: acetonitrile, C: 2% TFA in water).

Preparative reverse-phase high performance liquid chromatography (prep HPLC):

Purification of compounds was performed on an Varian Prostar system using VP 250/21 Nucleodur C4 Gravity 5 mm column (Macherey-Nagel), fraction collector

prostar 701 and detection at 220 ~ 240 nm with UV/V is prostar 340. Linear gradients of solvent A (water) and solvent B (acetonitrile) were used at 20mL/min flow rate.

Thin layer chromatography (TLC):

TLC was carried out on Merck precoated silica gel plates (60F-254) using ultraviolet light irradiation at 254 nm and 360 nm or the following solutions as developing agents: *Staining solution A*: molybdotophosphoric acid (25g) and cerium (IV) sulfate (10g) in concentrated sulfuric acid (60mL) and water (to 1000mL);

Staining solution B: (for detection of free amino groups): ninhydrin (300mg) in ethanol (100mL) and acetic acid (3mL).

Staining solution C: KMnO_4 (1g), K_2CO_3 (6.6g), 5% NaOH solution (1.7mL) in H_2O (to 100mL).

Gas chromatography – mass spectrometry (GC-MS):

Spectra were obtained from a Hewlett Packard 6890 GC system coupled to a Hewlett Packard 5973 Mass Selective Detector. A HP 5TA capillary column (0.33 μm x 25m x 0.2mm) and helium flow rate of 2mL/min were used.

Method A: temperature gradient: 0min (100°C) → 1min (100°C) → 6min (300°C) → 12min (300°C).

Method B: temperature gradient: 0min (50°C) → 2min (50°C) → 8min (300°C) → 12min (300°C).

Optical rotation:

Optical rotations were measured in a Schmidt + Haensch Polartronic HH8 polarimeter at 589 nm. Concentrations are given in g/100mL solvent.

FT-IR:

Fourier transform infrared spectroscopy (FT-IR) spectra were measured in Bruker vector 22 with a diffuse reflectance head A527 from Spectra Tech (KBr as matrix) and a Bruker tensor 27 spectrometer with transmission and attenuated total reflection (ATR) and coupled with infrared microscope from Spectra Tech (neat). The following notations indicate the intensity of the absorption bands: s = strong, m = middle, w = weak, b = broad.

Melting Point:

Melting points were measured in Büchi melting point B-540 with open capillary (uncorrected).

5.2 Abbreviations

Ac	acetyl (CH ₃ CO)
Aq	aqueous
Ar	aromatic
Bn	benzyl (PhCH ₂)
Bu	butyl
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N</i> -dicyclohexyl carbodiimide
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	<i>N,N</i> -dimethylamino pyridine
DMF	<i>N,N</i> -dimethyl formamide
DMSO	<i>N,N</i> -dimethyl sulfoxide
ee	enantiomeric excess
EI	electron impact
eq	stoichiometric equivalent

Et	ethyl (CH ₃ CH ₂)
FAB	fast atom bombardment
GC-MS	gas chromatography-mass spectroscopy
h	hour
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
<i>i</i> -Pr	iso-propyl
LC-MS	liquid chromatography-mass spectroscopy
Me	methyl (CH ₃)
Min	minute
mmol	milimole
NBS	<i>N</i> -bromosuccinimide
<i>n</i> -Bu	normal butyl (CH ₃ CH ₂ CH ₂ CH ₂)
NMR	nuclear magnetic resonance
Ph	phenyl (C ₆ H ₅)
ppm	parts per million
Py	pyridine
<i>R_f</i>	retention factor
r.t.	room temperature
TBAF	tetrabutylammonium fluoride
<i>t</i> -Bu	<i>tert</i> -butyl [(CH ₃) ₃ C]
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
<i>t_R</i>	retention time
TS	transition state
[α] ²⁰ _D	specific optical rotation

5.3 Solvents and Reagents

The reagents were purchased from Acros Chimica, Aldrich, Fluka, Merck,

Novabiochem, Riedel de Haen, Roth. Deionized water was obtained using a Millipore Q-plus System.

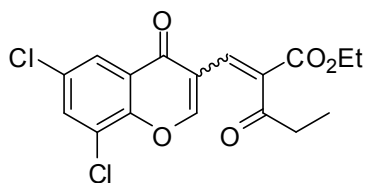
Solvents and reagents purification.

Dichloromethane, acetonitrile, 2,6-lutidine, DIPEA and triethylamine were refluxed and distilled from CaH_2 under argon and stored with KOH. Acetonitrile was stored with molecular sieves 4Å. Ethanol was refluxed with Mg and I_2 under argon and distilled, then stored with molecular sieves 4Å. Other anhydrous solvents like diethylether, DMF, MeOH, toluene and pyridine were directly purchased from Fluka. Triphenylphosphine (PPh_3) was recrystallized from ethanol. Acetic anhydride was redistilled.

5.4 Experimental: chapter 2 (Reagent Controlled Branching Cascades)

5.4.1 Synthesis of common substrates

General procedure: A solution of 3-chroman (1mmol, 1.0eq) and 3-oxopentanoate (1.0mmol, 1.0eq) was stirred at a preheating oilbath to reflux for 5min in 10mL $\text{Ac}_2\text{O}/\text{AcOH}=1/4$. 10ml of water was added to black reaction mixture at room temperature. Ac_2O and AcOH were removed under vacuum and the crude reaction mixture was added 10ml water and extracted with EtOAc (15mlX4). The organic layer was combined and washed with brine (15mlX2). The organic layer was dried with anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by flash column chromatography (eluent: petroleum ether/ethyl acetate 10/1) to give white solid product.



Chemical Formula: $C_{17}H_{14}Cl_2O_5$

Exact Mass: 368,0218

Molecular Weight: 369,1961

a4;

White solid;

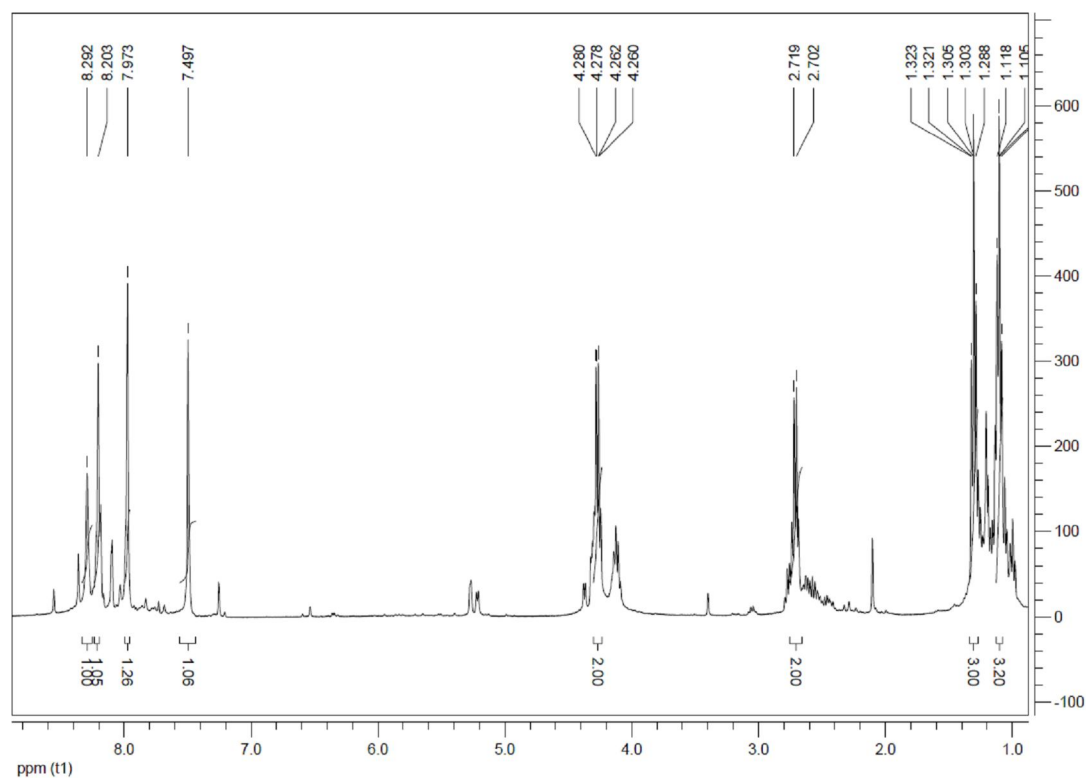
M.P.: 151°C;

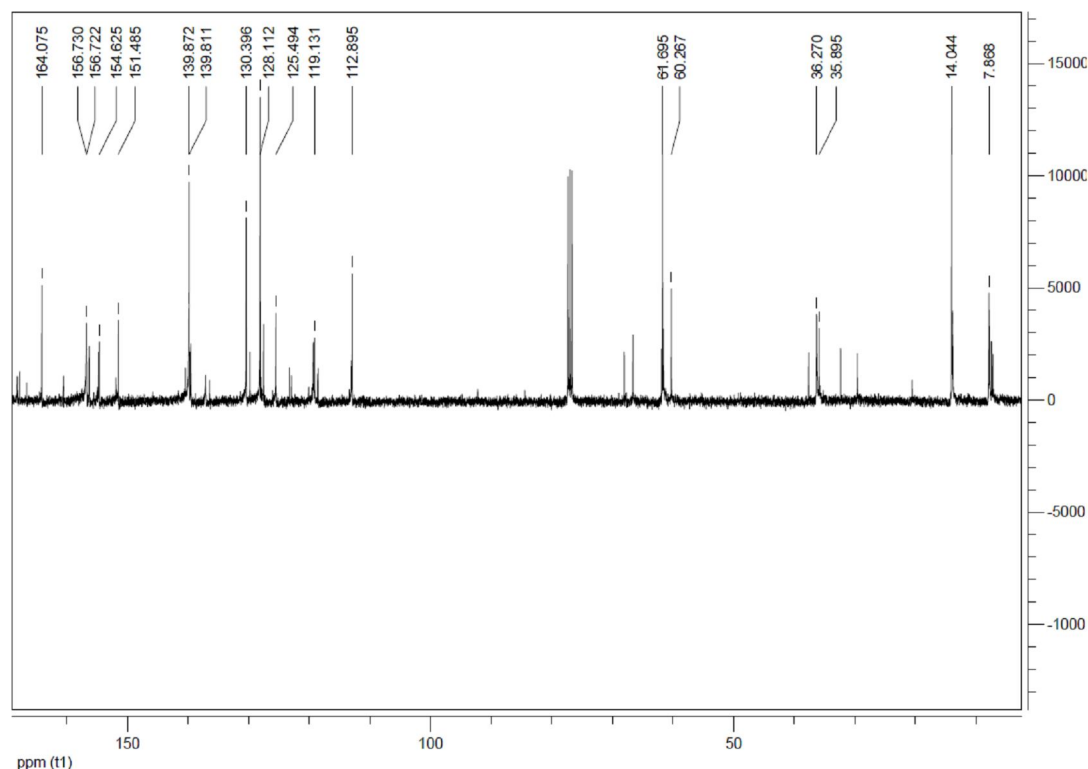
TLC: $R_f = 0.45$ cyclohexane/ethyl acetate (4:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 8.20 (s, 2H), 7.97 (s, 1H), 7.50 (s, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 2.71 (q, $J = 7.2$ Hz, 2H), 1.31 (t, $J = 7.2$ Hz, 3H), 1.10 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 164.1, 156.73, 156.72, 154.6, 151.5, 139.9, 139.8, 130.4, 128.1, 125.5, 119.1, 112.9, 61.7, 36.3, 14.0, 7.9;

HRMS (ESI): Calculated for $C_{17}H_{14}Cl_2O_5$ [$M+H^+$]: 620.2488, Found: 620.2487.

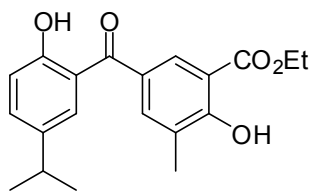




5.4.2 General procedure for cascade synthesis of functional phenols (E:Z= 1:1)

A solution of 3-chromanylidene- β -ketoesters (a4, 1mmol, 1.0eq) and cesium fluorin (2mmol, 2.0eq) was stirred at a preheating 80°C oilbath for 5-20min in 10mL DMF. 10ml of water was added to black reaction mixture at room temperature. DMF was removed under vacuum and the crude reaction mixture was added 10ml water and extracted with EtOAc (15mlX4). The organic layer was combined and washed with brine (15mlX3). The organic layer was dried with anhydrous Na₂SO₄ and evaporated to dryness. The residue was purified by flash column chromatography (eluent: petroleum ether/ethyl acetate 20/1) to give white solid product.

Ethyl 2-hydroxy-5-(2-hydroxy-5-isopropylbenzoyl)-3-methylbenzoate



Chemical Formula: C₂₀H₂₂O₅

Exact Mass: 342,1467

Molecular Weight: 342,3857

a7;

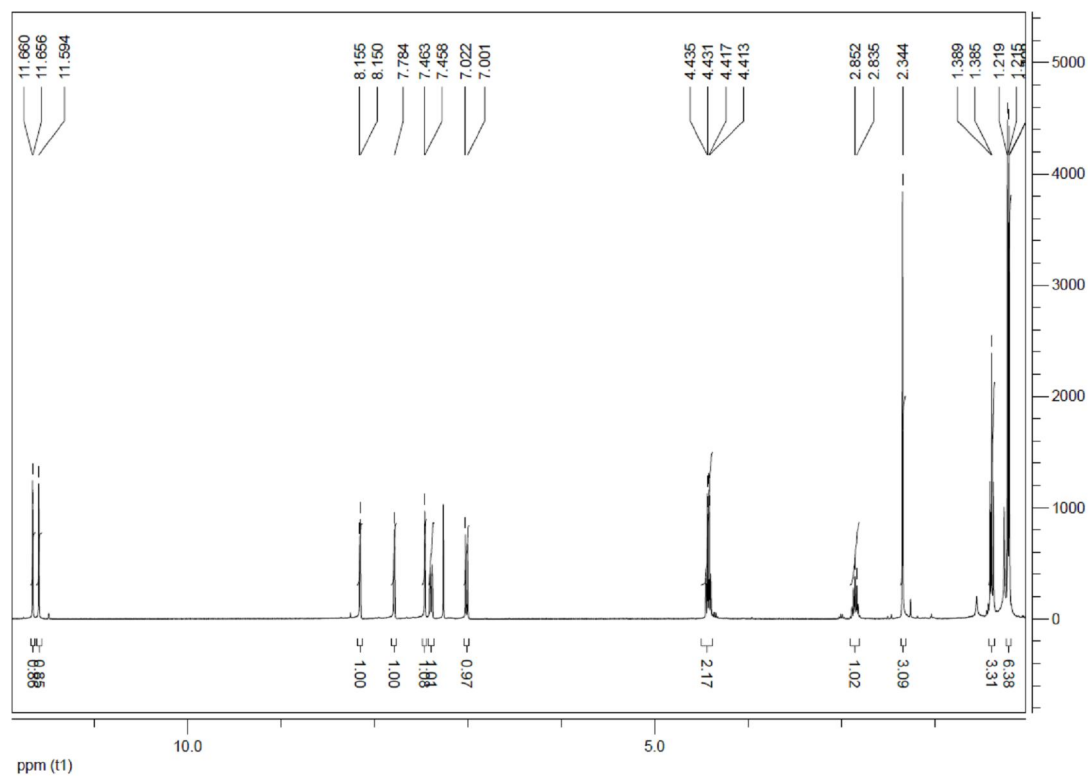
White solid;

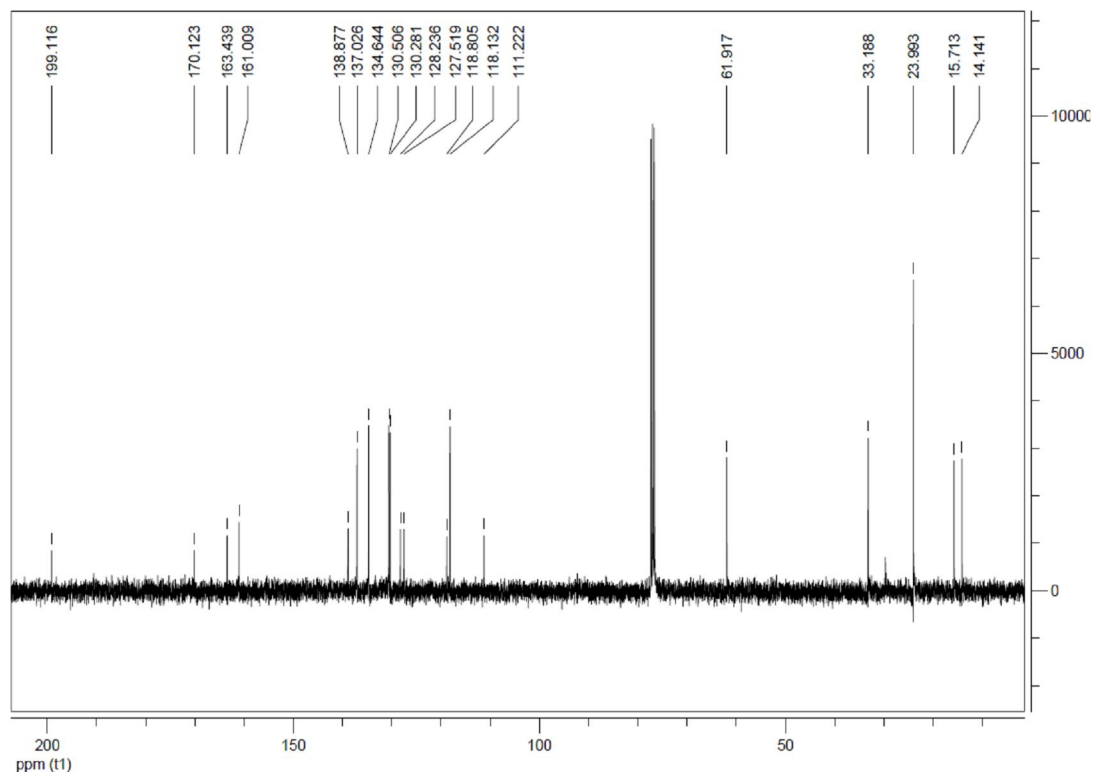
M.P.: 137°C;

TLC: R_f = 0.35 cyclohexane/ethyl acetate (10:1);

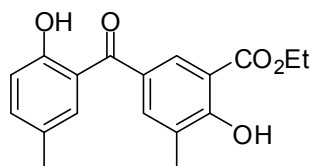
¹H NMR (400 MHz, CDCl₃): δ 11.66 (s, 1H), 11.59 (s, 1H), 8.15 (s, 1H), 7.78 (s, 1H), 7.46 (s, 1H), 7.39(d, *J* = 8.8 Hz, 1H), 7.01(d, *J* = 8.8 Hz, 1H), 4.42(q, *J* = 7.2 Hz, 2H), 2.85(m, *J* = 6.8 Hz, 1H), 2.34 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.21(d, *J* = 6.8 Hz, 6H);

¹³C NMR (100 MHz, CDCl₃): δ 199.1, 170.1, 163.4, 161.0, 138.9, 137.0, 134.6, 130.5, 130.3, 128.2, 127.5, 118.8, 118.1, 111.2, 61.9, 33.2, 24.0, 15.7, 14.1;





Ethyl 2-hydroxy-5-(2-hydroxy-5-methylbenzoyl)-3-methylbenzoate



Chemical Formula: $C_{18}H_{18}O_5$
 Exact Mass: 314,1154
 Molecular Weight: 314,3325

a8;

White solid;

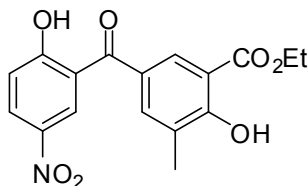
M.P.: 141-142°C;

TLC: $R_f = 0.35$ cyclohexane/ethyl acetate (10:1);

1H NMR (400 MHz, $CDCl_3$): δ 11.68 (s, 1H), 11.57 (s, 1H), 8.13 (s, 1H), 7.71 (s, 1H), 7.37 (s, 1H), 7.32(d, $J = 8.0$ Hz, 1H), 6.98(d, $J = 8.0$ Hz, 1H), 4.43(q, $J = 7.2$ Hz, 2H), 2.34(s, 3H), 2.28 (s, 3H), 1.40 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.4, 170.1, 163.3, 160.9, 137.0, 136.8, 132.8, 130.1, 128.4, 127.8, 127.3, 118.9, 118.2, 61.9, 20.5, 15.8, 14.2;

Ethyl 2-hydroxy-5-(2-hydroxy-5-nitrobenzoyl)-3-methylbenzoate



Chemical Formula: C₁₇H₁₅NO₇

Exact Mass: 345,0849

Molecular Weight: 345,3035

a9;

White solid;

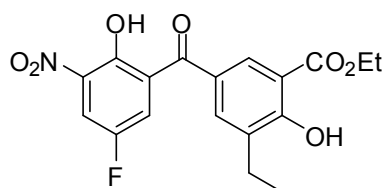
M.P.: 133-134°C;

TLC: R_f = 0.35 cyclohexane/ethyl acetate (5:1);

¹H NMR (400 MHz, CDCl₃): δ 12.56 (s, 1H), 11.72 (s, 1H), 8.61 (d, *J* = 2.4 Hz, 1H), 8.38 (d, *J* = 8.8 Hz, 1H), 8.16(d, *J* = 2.4 Hz, 1H), 7.76 (s, 1H), 7.18(d, *J* = 8.8 Hz, 1H), 4.45(q, *J* = 7.2 Hz, 2H), 2.35(s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 198.0, 169.8, 167.8, 164.3, 139.4, 136.6, 130.6, 130.5, 130.4, 129.0, 128.3, 126.7, 119.5, 118.0, 111.8, 62.2, 15.8, 14.1;

Ethyl 3-ethyl-5-(5-fluoro-2-hydroxy-3-nitrobenzoyl)-2-hydroxybenzoate



Chemical Formula: C₁₈H₁₆FNO₇

Exact Mass: 377,0911

Molecular Weight: 377,3205

a10;

White solid;

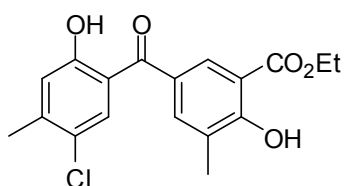
M.P.: 142-143°C;

TLC: R_f = 0.435 cyclohexane/ethyl acetate (10:1);

¹H NMR (400 MHz, CDCl₃): δ 8.37 (s, 1H), 8.13-8.08 (m, 2H), 7.43 (s, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 2.72 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 197.1, 172.4, 166.3, 163.9, 158.9, 156.4, 144.6, 136.9, 129.0, 126.5, 119.0, 117.4, 61.8, 32.5, 13.9, 7.7;

Ethyl 5-(5-chloro-2-hydroxy-4-methylbenzoyl)-2-hydroxy-3-methylbenzoate



Chemical Formula: C₁₈H₁₇ClO₅

Exact Mass: 348,0765

Molecular Weight: 348,7776

a11;

White solid;

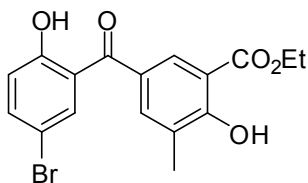
M.P.: 146-145°C;

TLC: R_f = 0.35 cyclohexane/ethyl acetate (10:1);

¹H NMR (400 MHz, CDCl₃): δ 11.78 (s, 1H), 11.60 (s, 1H), 8.11 (s, 1H), 7.70 (s, 1H), 7.56 (s, 1H), 6.97 (s, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 2.34 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 170.0, 163.5, 161.4, 145.3, 136.6, 132.4, 130.0, 127.8, 127.6, 126.0, 120.5, 62.0, 20.8, 15.8, 14.2;

Ethyl 5-(5-bromo-2-hydroxybenzoyl)-2-hydroxy-3-methylbenzoate



Chemical Formula: C₁₇H₁₅BrO₅

Exact Mass: 378,0103

Molecular Weight: 379,2020

a12;

White solid;

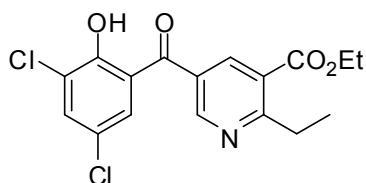
M.P.: 137-138°C;

TLC: R_f = 0.35 cyclohexane/ethyl acetate (10:1);

¹H NMR (400 MHz, CDCl₃): δ 11.76 (s, 1H), 11.63 (s, 1H), 8.12 (s, 1H), 7.72 (s, 1H), 7.58(d, *J* = 8.8 Hz, 1H), 7.00(d, *J* = 8.8 Hz, 1H), 4.45(q, *J* = 7.2 Hz, 2H), 2.35 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 198.2, 170.0, 163.7, 161.9, 138.6, 136.6, 135.0, 130.3, 127.8, 120.5, 111.7, 110.2, 109.8, 62.1, 15.8, 14.2;

Ethyl 5-(3,5-dichloro-2-hydroxybenzoyl)-2-ethylnicotinate



Chemical Formula: C₁₇H₁₅Cl₂NO₄

Exact Mass: 367,0378

Molecular Weight: 368,2113

White solid;

M.P.: 157-158°C;

TLC: R_f = 0.35 cyclohexane/ethyl acetate (10:1);

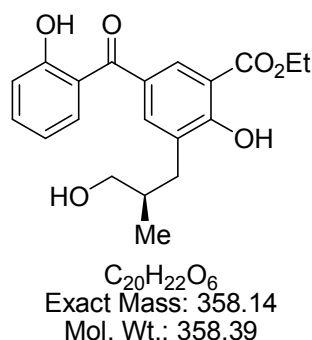
¹H NMR (400 MHz, CDCl₃): δ 12.21 (s, 1H), 8.86 (s, 1H), 8.40 (s, 1H), 7.88 (s, 1H), 7.58 (s, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.23 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 197.1, 168.7, 165.4, 158.7, 151.2, 142.1, 139.1, 133.9,

129.9, 125.8, 120.5, 113.7, 110.7, 62.0, 30.5, 14.2, 13.6;

To a solution of chromonylidene- β -ketoester (45.9 mg, 0.097 mmol, 1.0eq) in DMF (8 ml) was added Cesium fluoride (29.5 mg, 0.194 mmol, 2.0 eq.) at 80°C and the reaction mixture was stirred for 2h (TLC-control) at 80°C. The DMF was removed in *vacuo*, water was added, and the mixture was extracted with EtOAc (3 \times 20ml). The combined organic phases were dried over anhydrous NaSO₄, filtered and evaporated to give the crude phenol. The residue was purified by column chromatography.

(R)-Ethyl 2-hydroxy-3-(3-hydroxy-2-methylpropyl)-5-(2-hydroxybenzoyl)-benzoate



a36;

White solid;

M.P.: 165-167°C;

TLC: R_f = 0.40 ethyl acetate /methanol (20:1);

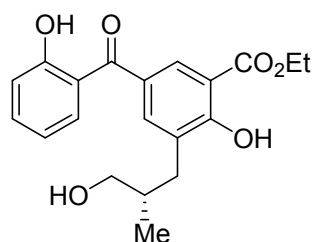
¹H NMR (400 MHz, CDCl₃): δ 11.86 (s, 1H), 11.78 (s, 1H), 8.17 (s, 1H), 7.69 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 3.47 (t, J = 6.0 Hz, 2H), 2.87 (q, J = 7.2 Hz, 1H), 2.61 (q, J = 7.2 Hz, 1H), 2.07-2.02 (m, 1H), 1.41 (t, J = 7.2 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 170.2, 163.1, 137.6, 136.2, 133.0, 132.98, 132.93, 130.4, 129.4, 128.6, 119.1, 118.7, 118.5, 112.0, 66.8, 62.2, 36.3, 32.8, 16.7, 14.2;

HRMS (ESI): Calculated for C₂₀H₂₃O₆ [M+H⁺]: 359.1489, Found: 359.1490;

Optical rotation: $[\alpha]_D^{25}$ = -4.4 °(C = 0.16, MeOH).

(S)-ethyl 2-hydroxy-3-(3-hydroxy-2-methylpropyl)-5-(2-hydroxybenzoyl)benzoate



$C_{20}H_{22}O_6$
Exact Mass: 358.14
Mol. Wt.: 358.39

a37;

White solid;

M.P.: 154-157°C;

TLC: $R_f = 0.40$ ethyl acetate /methanol (20:1);

1H NMR (400 MHz, $CDCl_3$): δ 11.87 (s, 1H), 11.78 (s, 1H), 8.17 (s, 1H), 7.70 (s, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.08 (d, $J = 8.0$ Hz, 1H), 6.90 (d, $J = 8.0$ Hz, 1H), 4.44 (q, $J = 7.2$ Hz, 2H), 3.52-3.44 (m, 2H), 2.88 (q, $J = 7.2$ Hz, 1H), 2.61 (q, $J = 7.2$ Hz, 1H), 2.09-2.03 (m, 1H), 1.41 (t, $J = 7.2$ Hz, 3H), 0.98 (d, $J = 6.8$ Hz, 3H);

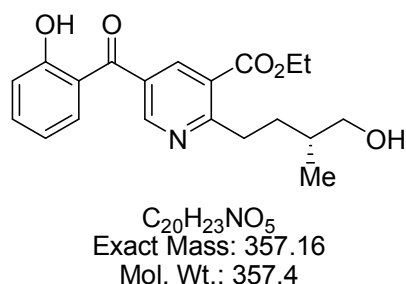
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 163.1, 137.6, 136.2, 133.0, 130.4, 129.5, 128.6, 118.7, 118.5, 114.17, 114.16, 112.0, 109.8, 66.8, 62.2, 36.3, 32.8, 16.7, 14.2;

HRMS (ESI): Calculated for $C_{20}H_{23}O_6$ [$M+H^+$]: 359.1489, Found: 359.1490;

Optical rotation: $[\alpha]_D^{25} = 6.2$ (C = 1.51, $CHCl_3$).

To a solution of chromonylidene- β -ketoester (45.9 mg, 0.097 mmol) in MeOH (5 ml) was added ammonium fluoride (35.9 mg, 0.97 mmol, 10.0 eq.) at room temperature and the reaction mixture was stirred for 6h (TLC-control) at 60°C. The methanol was removed in *vacuo*, water was added, and the mixture was extracted with EtOAc (3 \times 20ml). The combined organic phases were dried over anhydrous $NaSO_4$, filtered and evaporated to give the crude pyridine. The residue was purified by column chromatography.

(R)-ethyl 2-(4-hydroxy-3-methylbutyl)-5-(2-hydroxybenzoyl)nicotinate



a38;

White solid;

M.P.: 181-183°C;

TLC: R_f = 0.36 ethyl acetate /methanol (20:1);

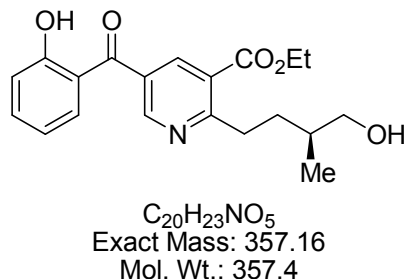
1H NMR (400 MHz, $CDCl_3$): δ 10.70 (s, 1H), 8.89 (s, 1H), 8.49 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 4.39 (q, J = 7.2 Hz, 2H), 3.52-3.39 (m, 2H), 3.35-3.22 (m, 2H), 1.89-1.84 (m, 2H), 1.55-1.51 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.514, 166.505, 163.3, 157.5, 140.0, 137.3, 132.8, 126.2, 119.31, 119.28, 118.9, 68.2, 62.0, 36.2, 33.5, 26.0, 16.6, 14.2;

HRMS (ESI): Calculated for $C_{20}H_{24}O_5N$ [$M+H^+$]: 358.1649., Found: 358.1650;

Optical rotation: $[\alpha]_D^{25} = -6.7$ (C = 1.56, DMSO).

(S)-Ethyl 2-(4-hydroxy-3-methylbutyl)-5-(2-hydroxybenzoyl)nicotinate



a39;

white solid;

M.P.: 158-160°C;

TLC: R_f = 0.36 ethyl acetate /methanol (20:1);

^1H NMR (400 MHz, CDCl_3): δ 10.60 (s, 1H), 8.91 (s, 1H), 8.61 (s, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.45 (d, J = 7.2 Hz, 1H), 7.08 (d, J = 7.2 Hz, 1H), 6.91 (d, J = 7.2 Hz, 1H), 4.41 (q, J = 7.2 Hz, 2H), 3.52-3.41 (m, 2H), 3.38-3.32 (m, 2H), 1.90-1.74 (m, 2H), 1.58-1.52 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H);

HRMS (ESI): Calculated for $\text{C}_{20}\text{H}_{24}\text{O}_5\text{N}$ [$\text{M}+\text{H}^+$]: 358.1649., Found: 358.1649;

Optical rotation: $[\alpha]_D^{25} = 4.5$ (C = 0.98, DMSO)

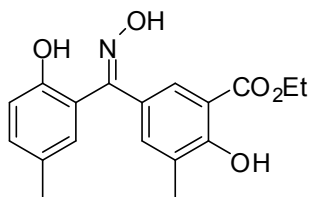
5.4.3 Synthesis of diverse oxime from cascade

5.4.3.1 General synthesis procedure products

Bisaryl ketone (1mmol) and hydroxylamine hydrochloride (10mmol, 10eq) were dissolved in a solution of pyridine/ethanol = 1/6 (10ml) and the solution was heated to reflux for overnight. 10ml water was added to the reaction mixture at the room temperature. The solvent was evaporated under vacuum to yield a concentrated solution. 10ml water was added to this crude mixture and extracted with EtOAc (15mlX4), The organic layers were combined; washed with brine (15ml) and dried over anhydrous Na_2SO_4 . After evaporating the solution in vacuum, the residue was purified by flash chromatography (eluent: petroleum ether/ethyl acetate 20/1) to give white solid oximes as E and Z-isomers

The structures of E and Z-isomers were confirmed by the followed Mitsunobu reactions. The structure of E-oxime got two products—*isoxazole* and *oxazole*, and the structure of Z-oxime only got one product—*isoxazole*.

(E)-ethyl-2-hydroxy-5-((2-hydroxy-5-methylphenyl)(hydroxyimino)methyl)-3-methyl benzoate



Chemical Formula: $C_{18}H_{19}NO_5$
 Exact Mass: 329,1263
 Molecular Weight: 329,3472

a51;

White solid;

M.P.: 171-173°C;

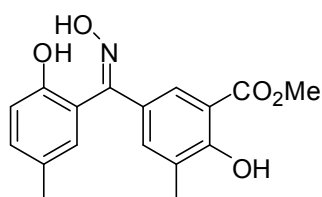
TLC: $R_f = 0.36$ cyclohexane/ethyl acetate (10 :1);

1H NMR (400 MHz, $CDCl_3$): δ 11.30 (s, 1H), 7.75 (s, 1H), 7.23 (s, 1H), 7.03 (d, $J = 8.0$ Hz, 1H), 6.87(d, $J = 8.0$ Hz, 1H), 6.59 (s, 1H), 4.36(q, $J = 7.2$ Hz, 2H), 2.29 (s, 3H), 2.11 (s, 3H), 1.35 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 160.7, 155.7, 136.1, 131.9, 130.6, 128.2, 127.7, 127.3, 118.2, 117.0, 112.0, 61.7, 20.5, 15.8, 14.2;

HRMS (ESI): Calculated for $C_{18}H_{20}O_5N$ [$M+H^+$]: 330.1336, Found: 330.1337.

(Z)-methyl-2-hydroxy-5-((2-hydroxy-5-methylphenyl)(hydroxyimino)methyl)-3-methylbenzoate



Chemical Formula: $C_{17}H_{17}NO_5$
 Exact Mass: 315,1107
 Molecular Weight: 315,3206

a52;

White solid;

M.P.: 1193-195°C;

TLC: $R_f = 0.37$ cyclohexane/ethyl acetate (10:1);

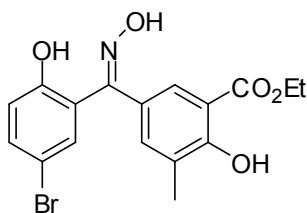
1H NMR (400 MHz, $CDCl_3$): δ 11.24 (s, 1H), 7.69 (s, 1H), 7.29 (s, 1H), 7.08 (d, $J = 8.0$ Hz, 1H), 6.93(d, $J = 8.0$ Hz, 1H), 6.63(s, 1H), 3.94(s, 3H), 2.33(s, 3H), 2.15(s,

3H);

¹³C NMR (100 MHz, CDCl₃): δ 170.6, 160.7, 155.8, 136.3, 132.1, 130.6, 128.2, 127.9, 127.5, 118.2, 117.0, 111.7, 112.0, 52.5, 20.5, 15.8;

HRMS (ESI): Calculated for C₁₇H₁₈O₅N [M+H⁺]: 316.1180, Found: 316.1181;

(E)-ethyl-5-((5-bromo-2-hydroxyphenyl)(hydroxyimino)methyl)-2-hydroxy-3-methyl benzoate



Chemical Formula: C₁₇H₁₆BrNO₅

Exact Mass: 393,0212

Molecular Weight: 394,2166

a53;

White solid;

M.P.: 155-157°C;

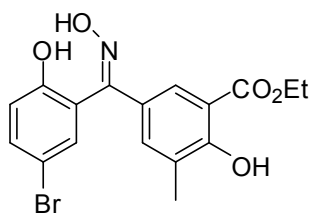
TLC: R_f = 0.38 cyclohexane/ethyl acetate (10:1);

¹H NMR (400 MHz, CDCl₃): δ 11.30 (s, 1H), 7.59 (s, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 6.89 (s, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 170.1, 161.0, 157.2, 135.9, 133.9, 132.7, 132.6, 127.7, 120.3, 120.1, 119.1, 112.1, 110.8, 61.8, 15.8, 14.2;

HRMS (ESI): Calculated for C₁₇H₁₇BrO₅N [M+H⁺]: 394.0285, 396.0264, Found: 394.0280, 396.0258

(Z)-ethyl-5-((5-bromo-2-hydroxyphenyl)(hydroxyimino)methyl)-2-hydroxy-3-methyl benzoate



Chemical Formula: $C_{17}H_{16}BrNO_5$

Exact Mass: 393,0212

Molecular Weight: 394,2166

a54;

White solid;

M.P.: 171-174°C;

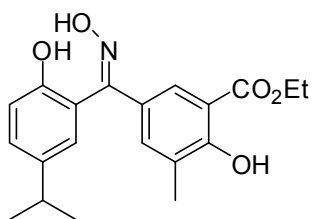
TLC: $R_f = 0.37$ cyclohexane/ethyl acetate (10:1);

1H NMR (400 MHz, $CDCl_3$): δ 11.37 (s, 1H), 7.66 (t, $J = 2.4$ Hz, 1H), 7.35 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.95 (d, $J = 2.4$ Hz, 1H), 6.91 (d, $J = 8.8$ Hz, 1H), 4.41 (q, $J = 7.2$ Hz, 2H), 2.33 (s, 3H), 1.40 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 162.2, 156.4, 136.1, 135.1, 134.1, 133.2, 132.9, 128.3, 127.8, 121.1, 120.9, 119.3, 62.0, 15.9, 14.5;

HRMS (ESI): Calculated for $C_{17}H_{17}BrO_5N$ [$M+H^+$]: 394.0285, 396.0264 Found: 394.0279, 396.0254.

(Z)-ethyl-2-hydroxy-5-((2-hydroxy-5-isopropylphenyl)(hydroxyimino)methyl)-3-methylbenzoate



Chemical Formula: $C_{20}H_{23}NO_5$

Exact Mass: 357,1576

Molecular Weight: 357,4003

a55;

White solid;

M.P.: 143-144°C;

TLC: $R_f = 0.35$ cyclohexane/ethyl acetate (10:1);

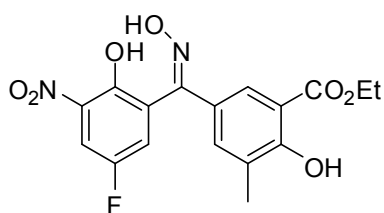
1H NMR (400 MHz, $CDCl_3$): δ 11.36 (s, 1H), 7.73 (s, 1H), 7.34 (s, 1H), 7.15 (d, $J =$

8.4 Hz, 1H), 6.96 (d, $J = 8.4$ Hz, 1H), 6.73 (s, 1H), 4.41(q, $J = 7.2$ Hz, 2H), 2.72(m, $J = 7.2$ Hz, 1H), 2.33(s, 3H), 1.38(t, $J = 7.2$ Hz, 3H), 1.10(d, $J = 7.2$ Hz, 6H);

^{13}C NMR (100 MHz, CDCl_3): δ 170.3, 161.1, 160.7, 155.9, 139.4, 136.5, 129.0, 128.4, 128.1, 127.1, 120.9, 118.1, 117.0, 111.8, 61.7, 33.1, 24.0, 15.8, 14.1;

HRMS (ESI): Calculated for $\text{C}_{20}\text{H}_{24}\text{O}_5\text{N}$ [$\text{M}+\text{H}^+$]: 358.1649, Found: 358.1652;

(Z)-ethyl-5-((5-fluoro-2-hydroxy-3-nitrophenyl)(hydroxyimino)methyl)-2-hydroxy-3-methylbenzoate



Chemical Formula: $\text{C}_{17}\text{H}_{15}\text{FN}_2\text{O}_7$
 Exact Mass: 378,0863
 Molecular Weight: 378,3086

a56;

Yellow solid;

M.P.: 165-167°C;

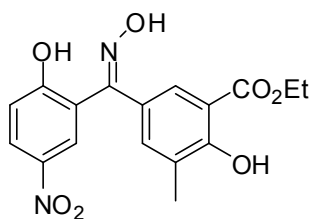
TLC: $R_f = 0.33$ cyclohexane/ethyl acetate (10:1);

^1H NMR (400 MHz, CDCl_3): δ 11.26 (s, 1H), 10.48 (s, 1H), 7.89 (d, $J = 7.2$ Hz, 1H), 7.71(s, 1H), 7.41 (s, 1H), 7.26 (d, $J = 7.2$ Hz, 1H), 4.32(q, $J = 7.2$ Hz, 2H), 2.19 (s, 3H), 1.30 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 170.1, 161.7, 160.7, 155.9, 139.4, 134.0, 133.9, 127.6, 126.2, 126.1, 126.0, 112.0, 111.8, 111.5, 61.7, 15.8, 14.1;

HRMS (ESI): Calculated for $\text{C}_{17}\text{H}_{16}\text{FO}_7\text{N}_2$ [$\text{M}+\text{H}^+$]: 379.0936, Found: 379.0937.

(E)-ethyl-2-hydroxy-5-((2-hydroxy-5-nitrophenyl)(hydroxyimino)methyl)-3-methylbenzoate



Chemical Formula: $C_{17}H_{16}N_2O_7$

Exact Mass: 360,0958

Molecular Weight: 360,3181

a57;

White solid;

M.P.: 191-192°C;

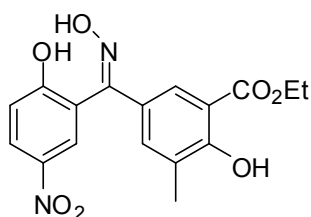
TLC: $R_f = 0.39$ cyclohexane/ethyl acetate (10:1);

1H NMR (400 MHz, $CDCl_3$): δ 11.42 (s, 1H), 8.17 (d, $J = 9.2$ Hz, 1H), 7.87 (s, 1H), 7.69 (s, 1H), 7.28 (s, 1H), 7.10 (d, $J = 9.2$ Hz, 1H), 4.42 (q, $J = 7.2$ Hz, 2H), 2.34 (s, 3H), 1.38 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 161.4, 156.5, 149.7, 135.83, 135.75, 128.1, 127.8, 126.74, 126.71, 118.0, 117.9, 107.1, 61.9, 15.9, 14.1;

HRMS (ESI): Calculated for $C_{17}H_{17}O_7N_2$ [$M+H^+$]: 361.1030, Found: 361.1031;

(Z)-ethyl-2-hydroxy-5-((2-hydroxy-5-nitrophenyl)(hydroxyimino)methyl)-3-methylbenzoate



Chemical Formula: $C_{17}H_{16}N_2O_7$

Exact Mass: 360,0958

Molecular Weight: 360,3181

a58;

White solid;

M.P.: 177-179°C;

TLC: $R_f = 0.38$ cyclohexane/ethyl acetate (10:1);

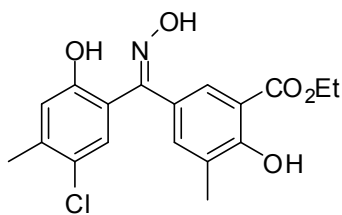
1H NMR (400 MHz, MD_3OD): δ 8.17 (dd, $J = 9.2, 2.8$ Hz, 1H), 7.97 (d, $J = 2.8$ Hz, 1H), 7.71 (d, $J = 2.8$ Hz, 1H), 7.55-7.54 (m, 1H), 7.01 (d, $J = 9.2$ Hz, 1H), 4.33 (q, $J =$

7.2 Hz, 2H), 2.19 (s, 3H), 1.30 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 171.6, 162.1, 153.4, 141.6, 135.2, 127.8, 127.6, 127.1, 122.9, 117.0, 112.8, 62.7, 15.8, 14.4;

HRMS (ESI): Calculated for $\text{C}_{17}\text{H}_{17}\text{O}_7\text{N}_2$ [$\text{M}+\text{H}^+$]: 361.1030, Found: 361.1031;

(E)-ethyl-5-((5-chloro-2-hydroxy-4-methylphenyl)(hydroxyimino)methyl)-2-hydroxy-3-methylbenzoate



Chemical Formula: $\text{C}_{18}\text{H}_{18}\text{ClNO}_5$

Exact Mass: 363,0874

Molecular Weight: 363,7922

a59;

White solid;

M.P.: 193-194°C;

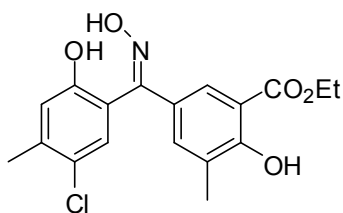
TLC: $R_f = 0.33$ cyclohexane/ethyl acetate (10:1);

^1H NMR (400 MHz, CDCl_3): δ 11.36 (s, 1H), 7.67 (s, 1H), 7.19 (s, 1H), 6.90 (s, 1H), 6.80(s, 1H), 4.41(q, $J = 7.2$ Hz, 2H), 2.33 (s, 6H), 1.40 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 170.2, 168.0, 156.4, 139.5, 135.9, 130.1, 127.7, 127.6, 119.4, 117.7, 112.1, 109.8, 97.1, 61.8, 20.1, 15.8, 14.2;

HRMS (ESI): Calculated for $\text{C}_{18}\text{H}_{19}\text{ClO}_5\text{N}$ [$\text{M}+\text{H}^+$]: 364.0946, 366.0917. Found: 364.0948, 366.0917.

(Z)-ethyl-5-((5-chloro-2-hydroxy-4-methylphenyl)(hydroxyimino)methyl)-2-hydroxy-3-methylbenzoate



Chemical Formula: $C_{18}H_{18}ClNO_5$

Exact Mass: 363,0874

Molecular Weight: 363,7922

a60;

White solid;

M.P.: 181-183°C;

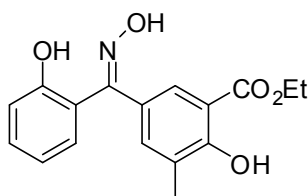
TLC: $R_f = 0.32$ cyclohexane/ethyl acetate (10:1);

1H NMR (400 MHz, $CDCl_3$): δ 11.36 (s, 1H), 7.67 (s, 1H), 7.26 (s, 1H), 6.90 (s, 1H), 6.80 (s, 1H), 4.42 (q, $J = 7.2$ Hz, 2H), 2.33 (s, 6H), 1.40 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 160.9, 160.5, 156.4, 139.5, 135.9, 130.1, 127.6, 124.3, 120.4, 119.4, 112.1, 61.8, 20.1, 15.8, 14.2;

HRMS (ESI): Calculated for $C_{18}H_{19}ClO_5N$ [$M+H^+$]: 364.0948, 366.0919, Found: 364.0946, 366.0917;

(E)-ethyl 2-hydroxy-5-((hydroxyimino)(2-hydroxyphenyl)methyl)-3-methylbenzoate



Chemical Formula: $C_{17}H_{17}NO_5$

Exact Mass: 315,1107

Molecular Weight: 315,3206

a61;

White solid;

M.P.: 171-174°C;

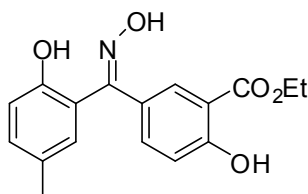
TLC: $R_f = 0.37$ cyclohexane/ethyl acetate (10:1);

1H NMR (400 MHz, $CDCl_3$): δ 11.35 (s, 1H), 7.71 (s, 1H), 7.30 (s, 1H), 7.27 (d, $J = 8.4$ Hz, 1H), 7.02 (d, $J = 8.4$ Hz, 1H), 6.90 (dd, $J = 8.0, 1.6$ Hz, 1H), 6.79 (dt, $J = 8.0, 1.2$ Hz, 1H), 4.40 (q, $J = 7.2$ Hz, 2H), 2.33 (s, 3H), 1.39 (t, $J = 7.2$ Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 170.3, 160.7, 157.8, 136.2, 131.1, 130.6, 127.7, 127.3, 121.0, 119.1, 118.7, 117.1, 111.9, 61.7, 15.8, 14.1;

HRMS (ESI): Calculated for C₁₇H₁₈O₅N [M+H⁺]: 316.1180, Found: 316.1180.

(E)-ethyl 2-hydroxy-5-((2-hydroxy-5-methylphenyl)(hydroxyimino)methyl)benzoate



Chemical Formula: C₁₇H₁₇NO₅
 Exact Mass: 315,1107
 Molecular Weight: 315,3206

a62;

White solid;

M.P.: 168-170°C;

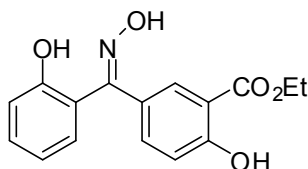
TLC: R_f = 0.37 cyclohexane/ethyl acetate (10:1);

¹H NMR (400 MHz, CDCl₃): δ 11.08 (s, 1H), 7.85 (d, *J* = 2.0 Hz, 1H), 7.43 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.36 (s, 1H), 7.30-7.26 (m, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.02 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.87 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.78 (dt, *J* = 8.0, 1.2 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 2.17 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 169.8, 162.2, 161.0, 158.1, 135.9, 131.2, 130.6, 121.7, 119.0, 118.4, 117.9, 117.3, 112.7, 108.8, 61.8, 30.9, 14.1;

HRMS (ESI): Calculated for C₁₇H₁₈O₅N [M+H⁺]: 316.1338, Found: 316.1336;

(E)-ethyl 2-hydroxy-5-((hydroxyimino)(2-hydroxyphenyl)methyl)benzoate



Chemical Formula: C₁₆H₁₅NO₅
 Exact Mass: 301,0950
 Molecular Weight: 301,2940

a63;

White solid;

M.P.: 177-178°C;

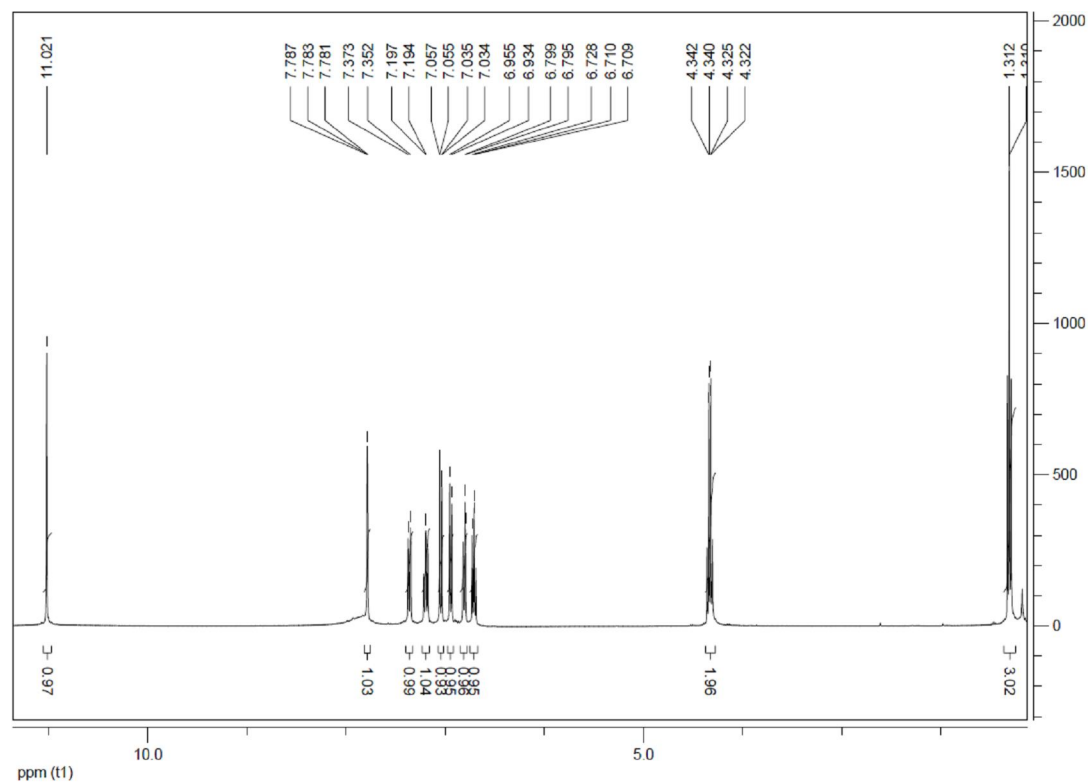
TLC: $R_f = 0.38$ cyclohexane/ethyl acetate (10:1);

^1H NMR (400 MHz, CDCl_3): δ 11.02 (s, 1H), 7.78 (d, $J = 2.4$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.19 (t, $J = 8.4$ Hz, 1H), 7.04 (d, $J = 8.4$ Hz, 1H), 6.94 (d, $J = 8.4$ Hz, 1H), 6.80 (d, $J = 7.6$ Hz, 1H), 6.71 (t, $J = 7.6$ Hz, 1H), 4.33 (q, $J = 7.2$ Hz, 2H), 1.31 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 169.8, 162.2, 160.8, 157.8, 135.9, 131.1, 130.5, 130.4, 121.7, 119.2, 118.5, 117.9, 117.2, 112.7, 61.8, 14.1;

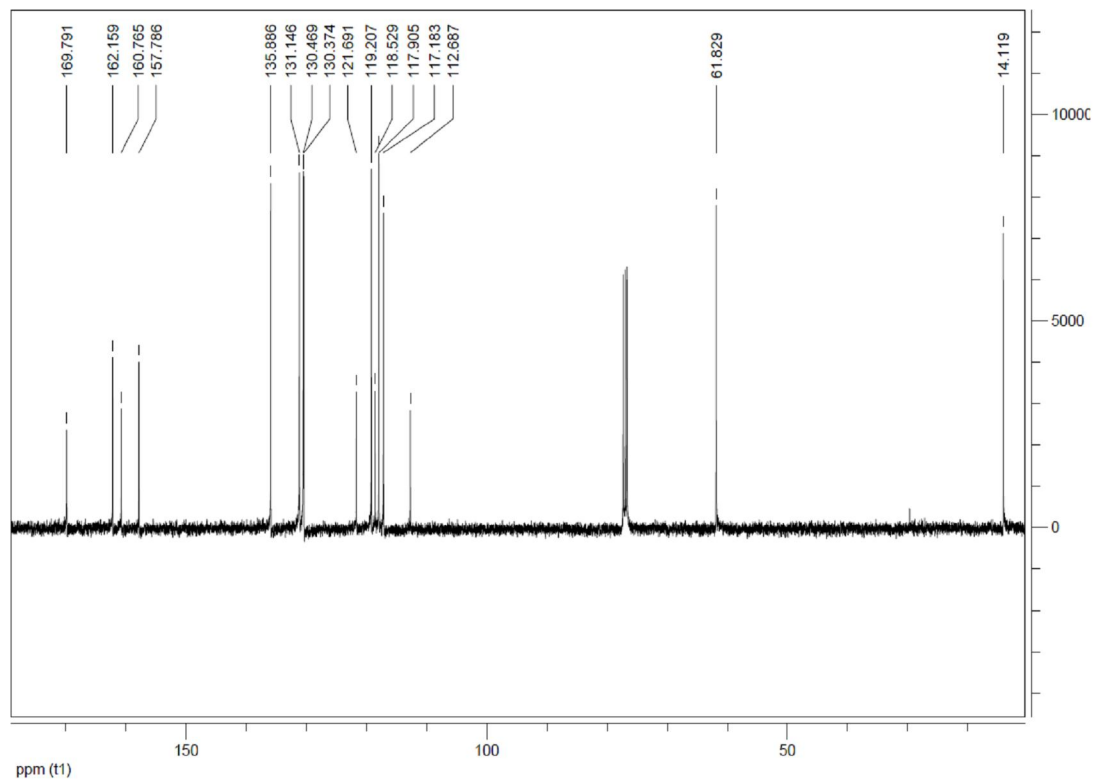
HRMS (ESI): Calculated for $\text{C}_{16}\text{H}_{16}\text{O}_5\text{N}$ [$\text{M}+\text{H}^+$]: 302.1023, Found: 302.1024;

a63 H spectrum;

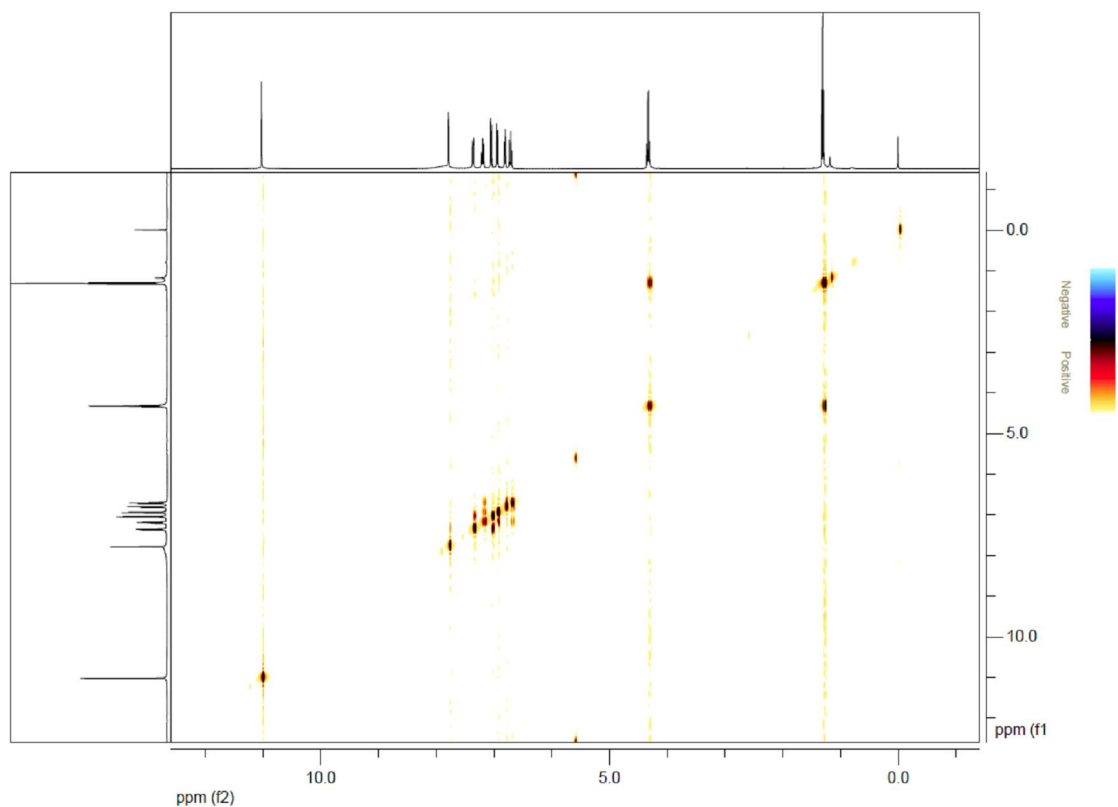


a63 C spectrum;

Experimental section

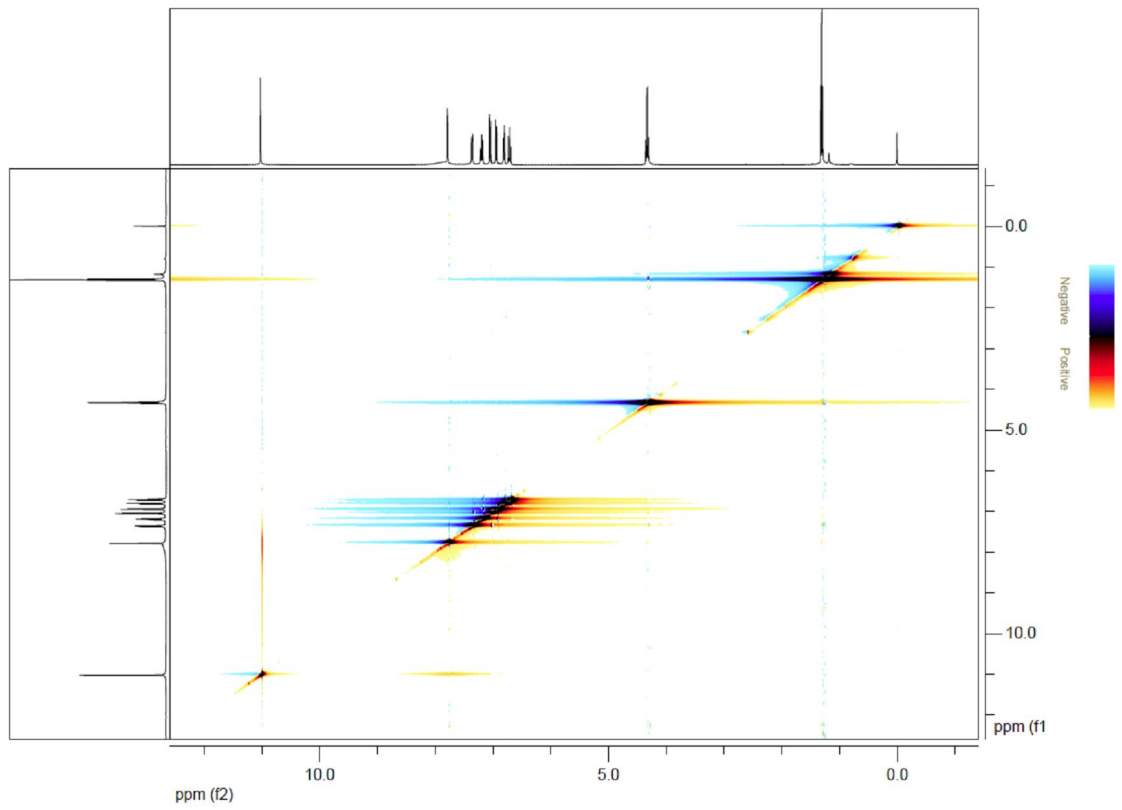


a63 gcosy spectrum;

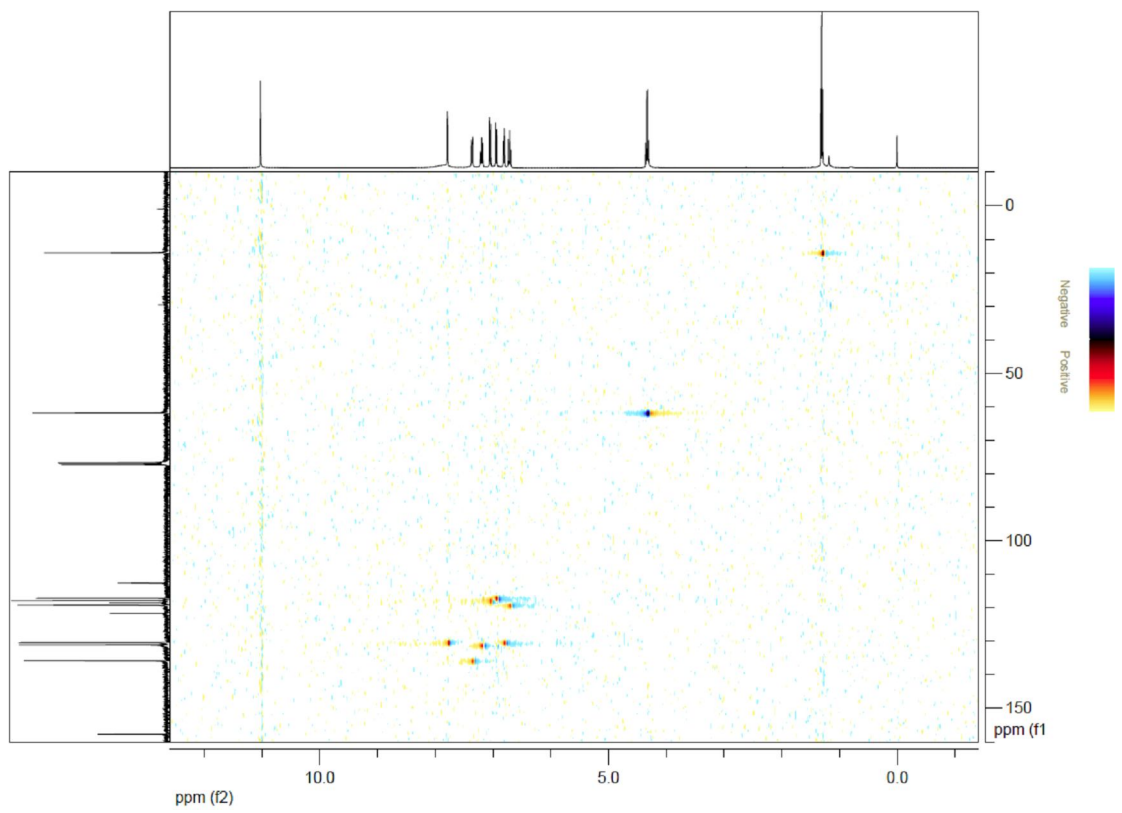


a63 noesy spectrum;

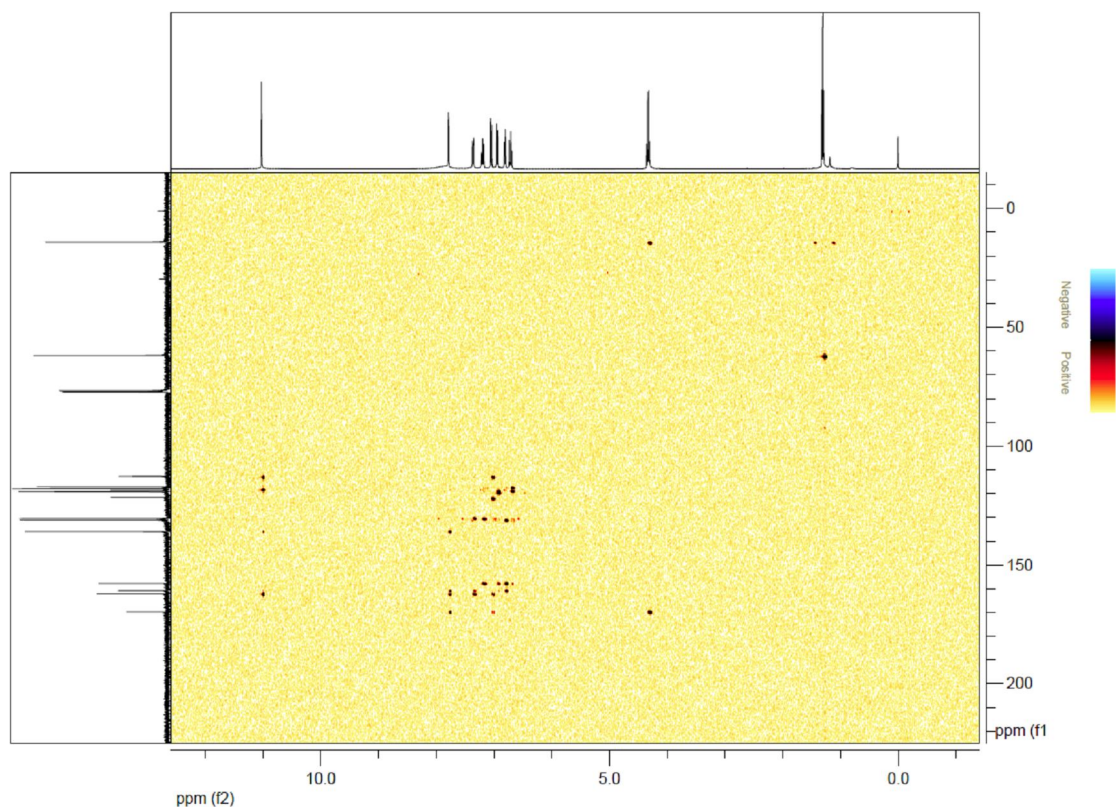
Experimental section



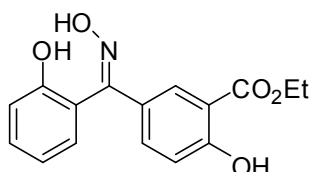
a63 ghsqc spectrum;



a63 ghmbc spectrum;



(Z)-ethyl 2-hydroxy-5-((hydroxyimino)(2-hydroxyphenyl)methyl)benzoate



Chemical Formula: $C_{16}H_{15}NO_5$
Exact Mass: 301,0950
Molecular Weight: 301,2940

a64;

White solid;

M.P.: 164-165°C;

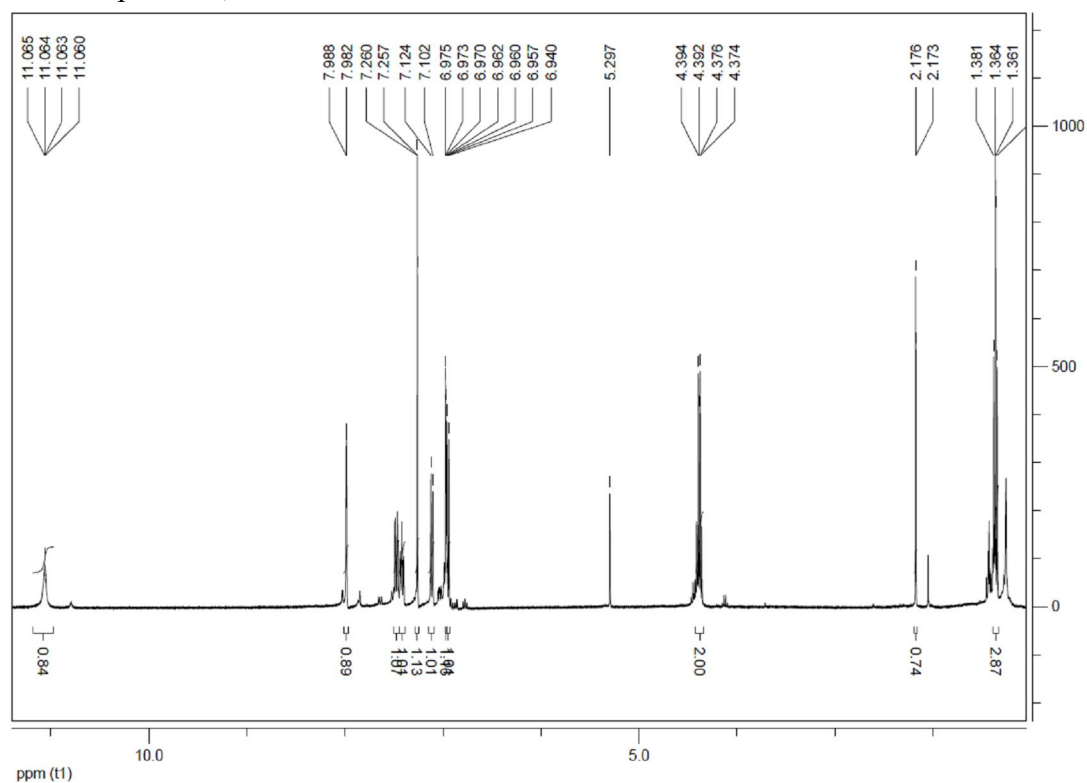
TLC: $R_f = 0.37$ cyclohexane/ethyl acetate (10:1);

1H NMR (400 MHz, $CDCl_3$): δ 11.06 (s, 1H), 7.98 (d, $J = 2.4$ Hz, 1H), 7.47 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.42 (dt, $J = 8.4, 2.4$ Hz, 1H), 7.26 (s, 1H), 7.11 (d, $J = 8.4$ Hz, 1H), 6.97 (s, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 4.39 (q, $J = 7.2$ Hz, 2H), 1.36 (t, $J = 7.2$ Hz, 3H);

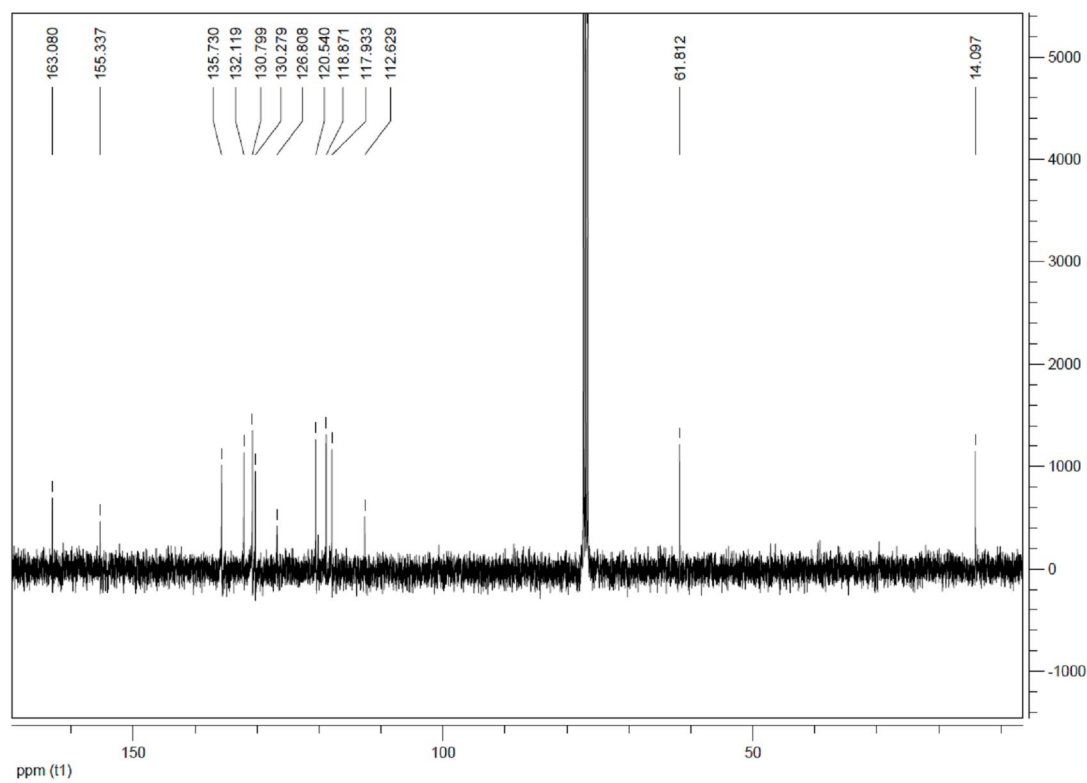
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 163.1, 155.3, 135.7, 132.1, 130.9, 130.8, 130.3, 126.8, 120.5, 120.1, 118.9, 117.9, 112.6, 61.8, 14.1;

HRMS (ESI): Calculated for C₁₆H₁₆O₅N [M+H⁺]: 302.1023, Found: 302.1025;

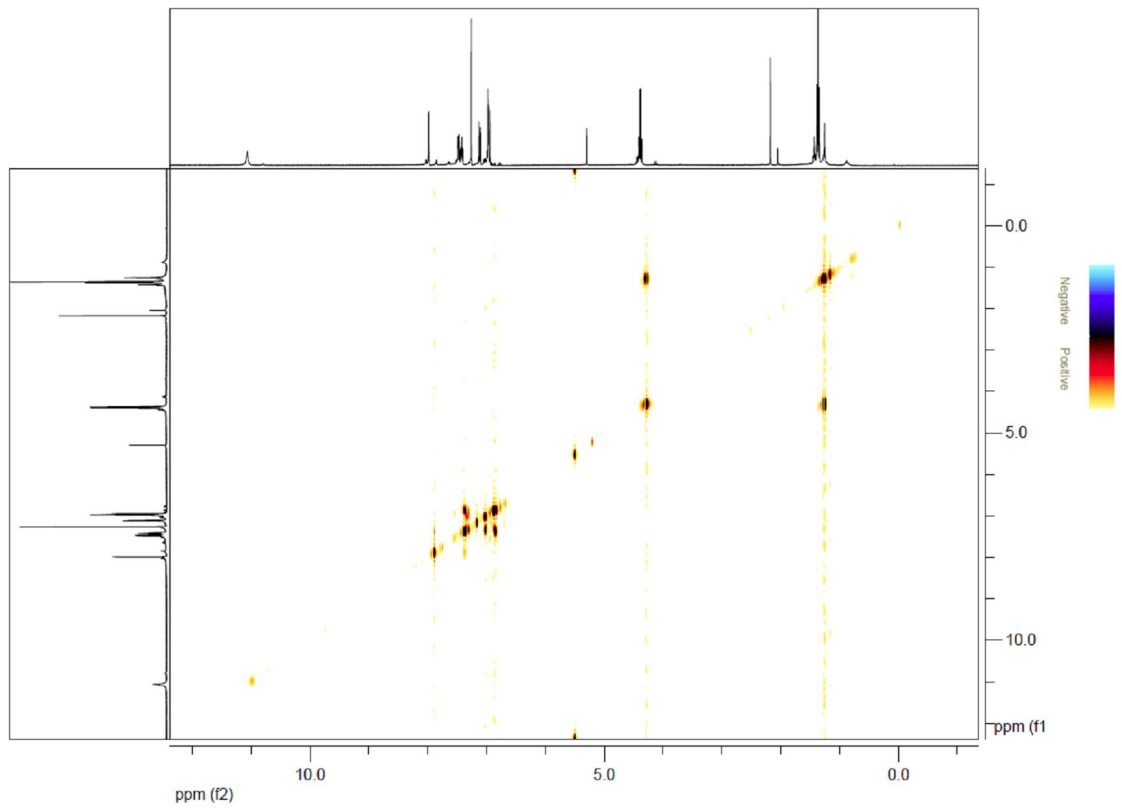
a64 ¹H spectrum;



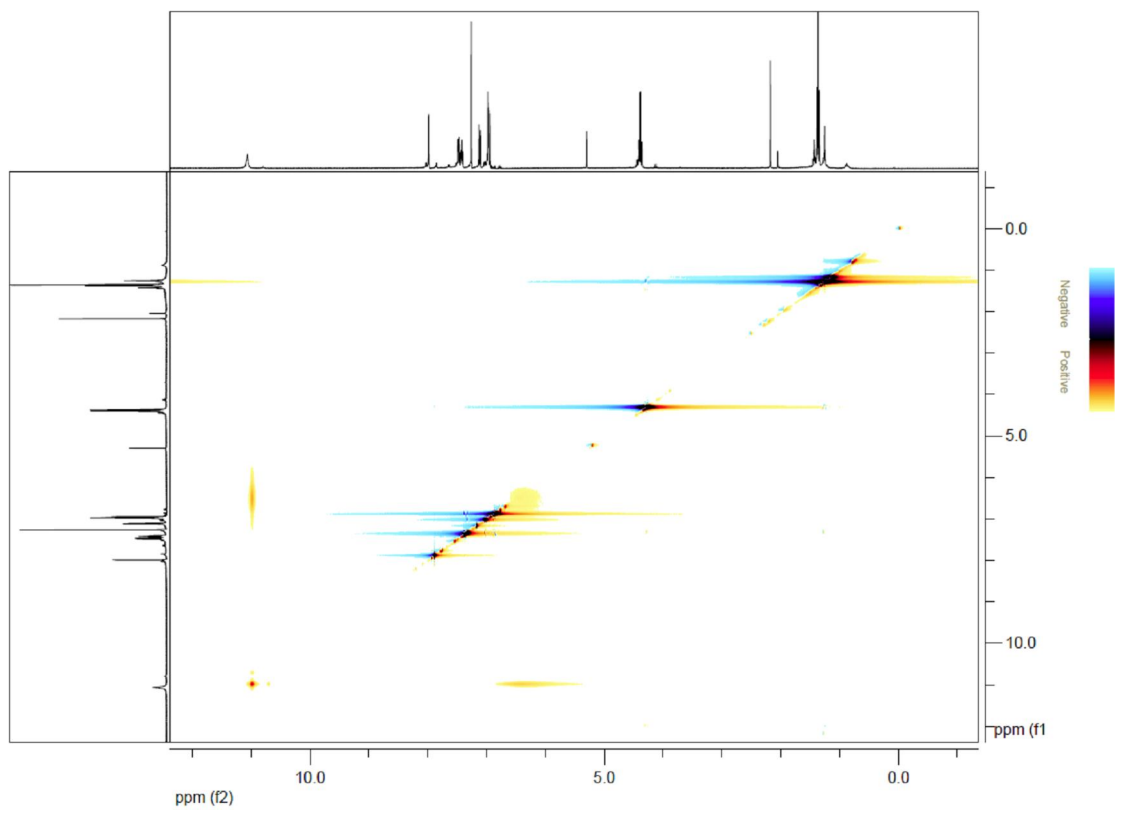
a64 ¹³C spectrum;



a64 gcosy spectrum

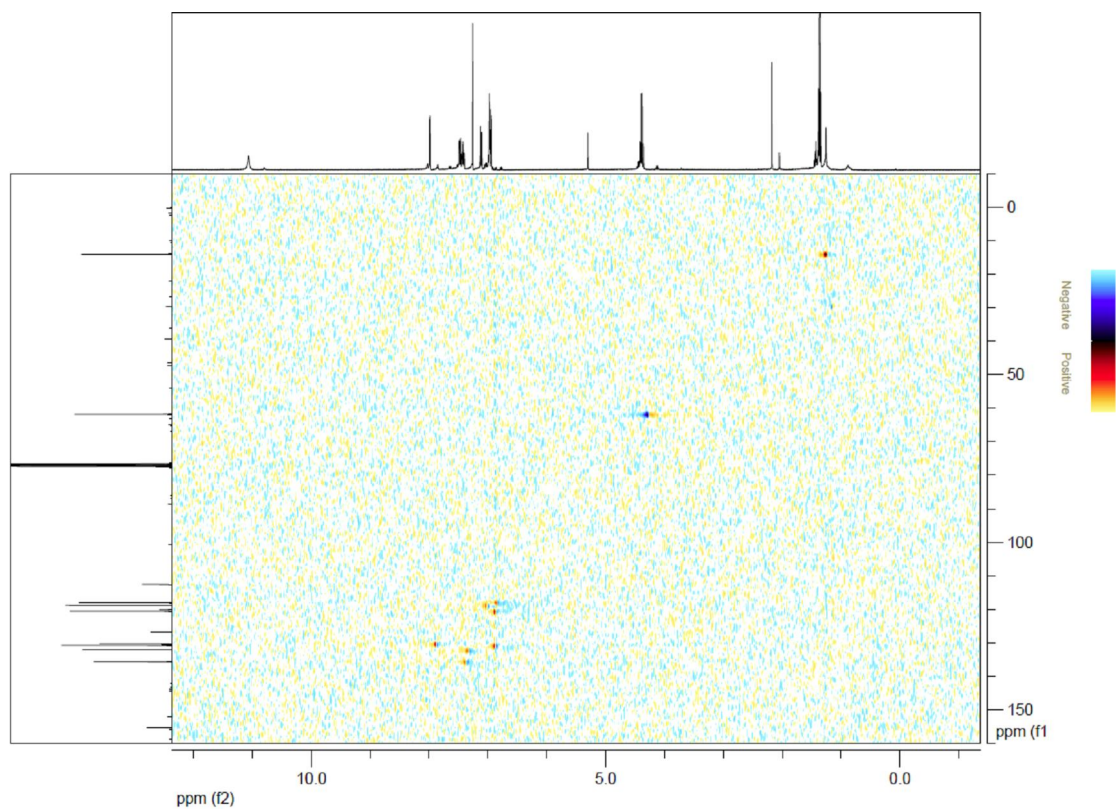


a64 noesy spectrum

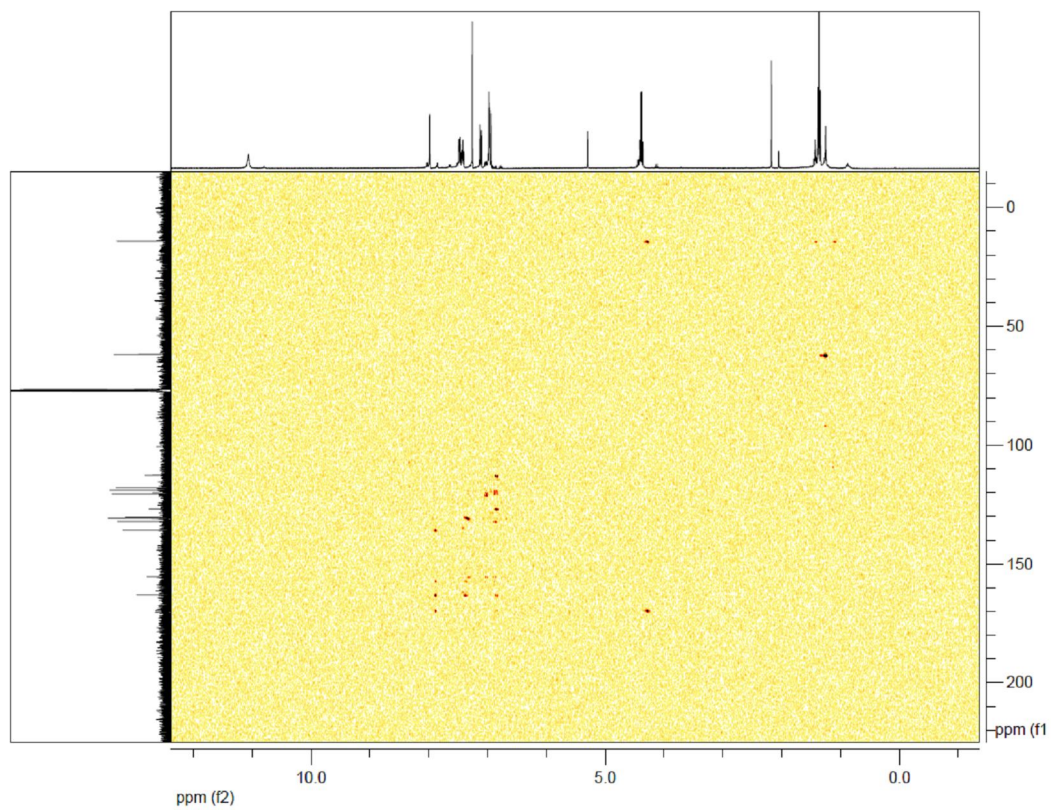


a64 ghsqc spectrum

Experimental section

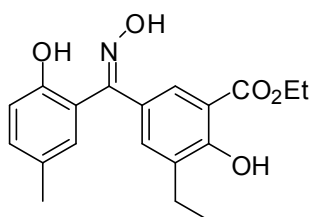


a64 ghnbc spectrum



(E)-ethyl-3-ethyl-2-hydroxy-5-((2-hydroxy-5-methylphenyl)(hydroxyimino)methyl)b

enzoate



Chemical Formula: C₁₉H₂₁NO₅

Exact Mass: 343,1420

Molecular Weight: 343,3737

a65;

White solid;

M.P.: 164-166°C;

TLC: R_f = 0.37 cyclohexane/ethyl acetate (10:1);

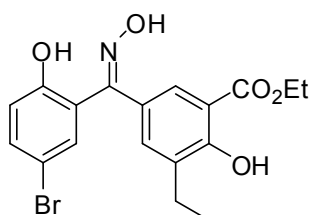
¹H NMR (400 MHz, CDCl₃): δ 11.37 (s, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.29 (d, *J* = 2.0 Hz, 1H), 7.26 (s, 1H), 7.08 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 2.76 (q, *J* = 7.2 Hz, 2H), 2.16 (s, 3H), 1.39(t, *J* = 7.2 Hz, 3H), 1.26(t, *J* = 7.2 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 170.4, 161.3, 160.4, 155.7, 134.6, 133.0, 131.8, 130.6, 128.1, 127.7, 121.1, 118.2, 117.0, 112.0, 61.7, 22.8, 20.5, 13.5;

HRMS (ESI): Calculated for C₁₉H₂₂O₅N [M+H⁺]: 344.1495, Found: 344.1496;

(E)-ethyl-5-((5-bromo-2-hydroxyphenyl)(hydroxyimino)methyl)-3-ethyl-2-hydroxybenzoate

nzoate



Chemical Formula: C₁₈H₁₈BrNO₅

Exact Mass: 407,0368

Molecular Weight: 408,2432

a66;

Yellow solid;

M.P.: 181-182°C;

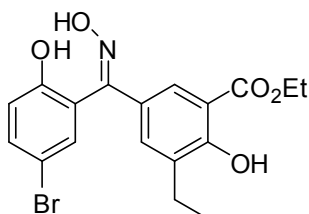
TLC: R_f = 0.39 cyclohexane/ethyl acetate (10:1);

¹H NMR (400 MHz, CDCl₃): δ 11.39 (s, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.35 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.27 (s, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 2.75 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 170.2, 160.7, 160.5, 157.2, 134.4, 133.8, 133.4, 132.7, 127.7, 120.4, 120.2, 119.1, 112.2, 110.8, 61.8, 22.8, 14.2, 13.5;

HRMS (ESI): Calculated for C₁₈H₁₉BrO₅N [M+H⁺]: 408.0441, 410.0421; Found: 408.0440, 410.0419;

(Z)-ethyl-5-((5-bromo-2-hydroxyphenyl)(hydroxyimino)methyl)-3-ethyl-2-hydroxybenzoate



Chemical Formula: C₁₈H₁₈BrNO₅
Exact Mass: 407,0368
Molecular Weight: 408,2432

a67;

Yellow solid;

M.P.: 177-179°C;

TLC: R_f = 0.38 cyclohexane/ethyl acetate (10:1);

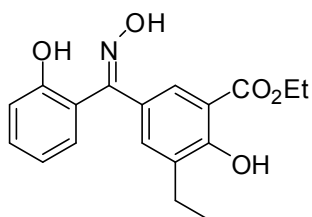
¹H NMR (400 MHz, CDCl₃): δ 11.40 (s, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.35 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 2.74 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 170.2, 160.7, 157.2, 137.3, 134.4, 133.9, 133.4, 132.7, 129.1, 127.9, 127.7, 120.7, 120.3, 120.1, 119.1, 112.2, 110.8, 61.8, 22.8, 14.2, 13.5;

HRMS (ESI): Calculated for C₁₈H₁₉BrO₅N [M+H⁺]: 408.0441, 410.0421; Found: 408.0438, 410.0417;

(E)-ethyl 3-ethyl-2-hydroxy-5-((hydroxyimino)(2-hydroxyphenyl)methyl)benzoate

(a68)



Chemical Formula: C₁₈H₁₉NO₅

Exact Mass: 329,1263

Molecular Weight: 329,3472

a68;

White solid;

M.P.: 178-180°C;

TLC: R_f = 0.0,37 cyclohexane/ethyl acetate (10:1);

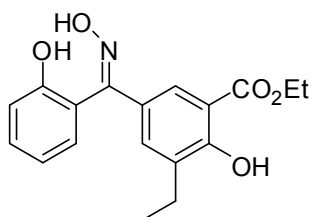
¹H NMR (400 MHz, CDCl₃): δ 11.39 (s, 1H), 8.33 (bs, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.33 (d, *J* = 2.0 Hz, 1H), 7.28 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.93 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.81 (t, *J* = 8.0 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 2.76 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.27(t, *J* = 7.2 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 170.3, 161.0, 160.4, 157.7, 134.6, 133.0, 131.0, 130.5, 127.7, 121.1, 119.2, 118.7, 117.1, 111.9, 61.7, 22.7, 14.1, 13.5;

HRMS (ESI): Calculated for C₁₈H₂₀O₅N [M+H⁺]: 330.1336, Found: 330.1338;

(Z)-ethyl 3-ethyl-2-hydroxy-5-((hydroxyimino)(2-hydroxyphenyl)methyl)benzoate

(a69)



Chemical Formula: C₁₈H₁₉NO₅

Exact Mass: 329,1263

Molecular Weight: 329,3472

a69;

White solid;

M.P.: 161-163°C;

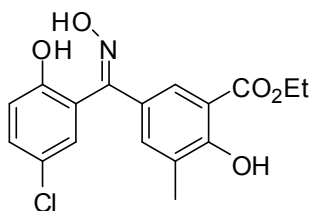
TLC: R_f = 0.36 cyclohexane/ethyl acetate (10:1);

^1H NMR (400 MHz, CDCl_3): δ 11.34 (s, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.42 (dt, J = 8.0, 2.4 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.26 (s, 1H), 6.99-6.96 (m, 1H), 6.94 (t, J = 8.0 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 2.62 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.15(t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 170.2, 161.4, 155.7, 134.6, 133.1, 132.2, 131.1, 128.1, 125.9, 120.4, 120.2, 119.0, 111.9, 61.7, 22.8, 14.1, 13.6;

HRMS (ESI): Calculated for $\text{C}_{18}\text{H}_{20}\text{O}_5\text{N}$ [$\text{M}+\text{H}^+$]: 6330.1336, Found: 330.1339;

(Z)-ethyl-5-((5-chloro-2-hydroxyphenyl)(hydroxyimino)methyl)-2-hydroxy-3-methyl benzoate



Chemical Formula: $\text{C}_{17}\text{H}_{16}\text{ClNO}_5$
 Exact Mass: 349,0717
 Molecular Weight: 349,7656

a70;

Yellow solid;

M.P.: 170-172°C;

TLC: R_f = 0.36 cyclohexane/ethyl acetate (10:1);

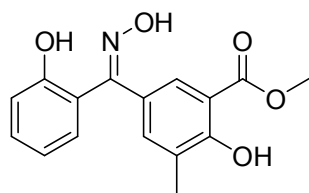
^1H NMR (400 MHz, CDCl_3): δ 11.24 (s, 1H), 7.29 (s, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.63(s, 1H), 3.94 (s, 3H), 2.33 (s, 3H), 2.16 (s, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 170.7, 161.1, 160.6, 155.7, 136.3, 131.9, 130.5, 128.2, 127.8, 127.3, 121.2, 118.2, 116.9, 111.7, 52.4, 20.5, 15.8;

HRMS (ESI): Calculated for $\text{C}_{17}\text{H}_{17}\text{O}_5\text{ClN}$ [$\text{M}+\text{H}^+$]: 350.0797, Found: 350.0793.

(E)-methyl 2-hydroxy-5-((hydroxyimino)(2-hydroxyphenyl)methyl)-3-methylben-

zoate



$C_{16}H_{15}NO_5$
Exact Mass: 301.1
Mol. Wt.: 301.29

a71;

White solid;

M.P.: 172-173°C;

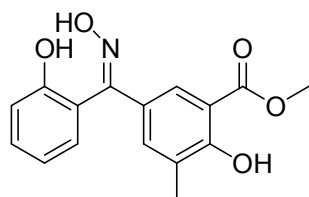
TLC: R_f = 0.30 ethyl acetate/MeOH (5:1);

1H NMR (400 MHz, DMSO): δ 7.45 (s, 1H), 7.24 (s, 1H), 7.04 (t, J = 8.0 Hz, 1H), 6.75-6.70 (m, 2H), 6.58 (t, J = 8.0 Hz, 1H), 3.70(s, 3H), 2.04 (s, 3H);

^{13}C NMR (100 MHz, DMSO): δ 169.9, 159.1, 157.2, 136.7, 130.3, 129.9, 127.7, 126.1, 122.6, 120.0, 118.8, 116.5, 111.3, 53.7, 15.4;

HRMS (ESI): Calculated for $C_{16}H_{15}O_5N$ [$M+H^+$]: 302.1023, Found: 302.1023;

(Z)-methyl 2-hydroxy-5-((hydroxyimino)(2-hydroxyphenyl)methyl)-3-methylbenzoate



$C_{16}H_{15}NO_5$
Exact Mass: 301.1
Mol. Wt.: 301.29

a72;

White solid;

M.P.: 177-178°C;

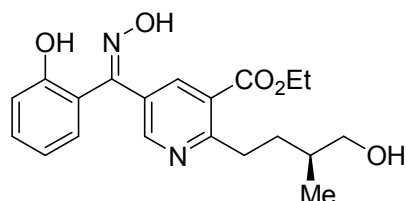
TLC: R_f = 0.31 ethyl acetate/MeOH (5:1);

1H NMR (400 MHz, DMSO): δ 7.47-7.46 (m, 2H), 7.13 (t, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.81-6.74 (m, 2H), 3.73(s, 3H), 2.07 (s, 3H);

^{13}C NMR (100 MHz, DMSO): δ 169.9, 159.2, 154.2, 152.6, 133.7, 129.8, 129.6, 127.5, 126.0, 125.3, 120.7, 118.8, 115.8, 111.2, 52.7, 15.6;

HRMS (ESI): Calculated for $\text{C}_{15}\text{H}_{15}\text{O}_4\text{N}_2$ [$\text{M}+\text{H}^+$]: 302.1023, Found: 302.1023;

(S,E)-ethyl-2-(4-hydroxy-3-methylbutyl)-5-((hydroxyimino)(2-hydroxyphenyl)methyl)nicotinate



$\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_5$
Exact Mass: 372.17
Mol. Wt.: 372.41

a73;

White solid;

M.P.: 188-190°C;

TLC: R_f = 0.40 ethyl acetate /methanol (20:1);

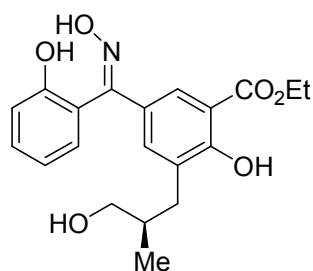
^1H NMR (400 MHz, CDCl_3): δ 10.82 (bs, 1H), 9.21 (bs, 1H), 8.63 (s, 1H), 8.23 (s, 1H), 7.30-7.28 (m, 1H), 6.02 (d, J = 8.0 Hz, 1H), 6.80-6.74 (m, 2H), 4.39 (q, J = 7.2 Hz, 2H), 3.66-3.55 (m, 2H), 3.33-3.29 (m, 2H), 1.93-1.83 (m, 2H), 1.77-1.71 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 163.9, 158.0, 157.3, 150.6, 139.9, 131.4, 129.8, 125.6, 125.2, 119.3, 117.8, 117.5, 109.8, 67.2, 62.0, 35.7, 33.5, 32.9, 16.8, 14.2;

HRMS (ESI): Calculated for $\text{C}_{20}\text{H}_{25}\text{O}_5\text{N}_2$ [$\text{M}+\text{H}^+$]: 373.1758, Found: 373.1759;

Optical rotation: $[\alpha]_D^{25} = 5.1$ (C = 0.23, MeOH).

(S,E)-ethyl-2-hydroxy-3-(3-hydroxy-2-methylpropyl)-5-((hydroxyimino)(2-hydroxyphenyl)methyl)benzoate



$C_{20}H_{23}NO_6$
 Exact Mass: 373.15
 Mol. Wt.: 373.4

a74;

White solid;

M.P.: 177-179°C;

TLC: $R_f = 0.35$ ethyl acetate /methanol (20:1);

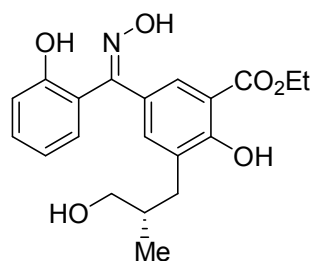
1H NMR (400 MHz, $CDCl_3$): δ 11.49 (s, 1H), 7.67 (d, $J = 2.0$ Hz, 1H), 7.23-7.20 (m, 2H), 6.95 (d, $J = 8.0$ Hz, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 6.70 (t, $J = 8.0$ Hz, 1H), 4.33 (q, $J = 7.2$ Hz, 2H), 3.45-3.36 (m, 2H), 2.77 (q, $J = 2.8$ Hz, 1H), 2.56 (q, $J = 2.8$ Hz, 1H), 2.00-1.93 (m, 1H), 1.31 (t, $J = 7.2$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 161.0, 160.3, 158.1, 146.5, 137.1, 131.1, 130.5, 129.3, 128.3, 121.3, 119.0, 117.3, 112.3, 66.8, 61.9, 36.3, 32.6, 16.7, 14.1;

HRMS (ESI): Calculated for $C_{20}H_{24}NO_6$ [$M+H^+$]: 374.1598, Found: 374.1602;

Optical rotation: $[\alpha]_D^{25} = -4.0$ (C = 0.31, MeOH).

(R,Z)-ethyl-2-hydroxy-3-(3-hydroxy-2-methylpropyl)-5-((hydroxyimino)(2-hydroxyphenyl)methyl)benzoate



$C_{20}H_{23}NO_6$
 Exact Mass: 373.15
 Mol. Wt.: 373.4

a75;

White solid;

M.P.: 166-168°C;

TLC: R_f = 0.35 ethyl acetate /methol (20:1);

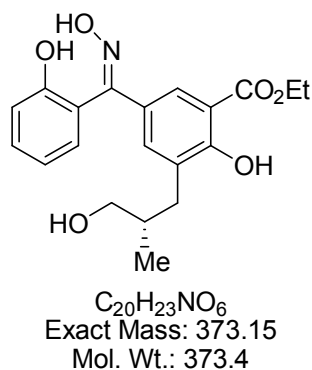
^1H NMR (400 MHz, CDCl_3): δ 10.66 (bs, 1H), 8.57 (s, 1H), 8.14 (s, 1H), 7.26-7.22 (m, 1H), 6.98 (dd, J = 8.0,2.0 Hz, 1H), 6.76-6.71 (m, 2H), 4.33 (q, J = 7.2 Hz, 2H), 3.58-3.50 (m, 2H), 3.26-3.21 (m, 2H), 1.85-1.77 (m, 2H), 1.70-1.66 (m, 1H), 1.32 (t, J = 7.2 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 163.39, 163.38, 157.2, 150.1, 150.0, 133.8, 132.3, 130.7, 129.2, 129.1, 128.0, 127.9, 118.4, 116.7, 66.4, 61.0, 34.8, 32.0, 16.0, 13.4;

HRMS (ESI): Calculated for $\text{C}_{20}\text{H}_{23}\text{O}_6$ [$\text{M}+\text{H}^+$]: 374.1598, Found: 374.1600;

Optical rotation: $[\alpha]_D^{25} = 4.0$ °(C = 0.17, MeOH).

(R,E)-ethyl-2-(4-hydroxy-3-methylbutyl)-5-((hydroxyimino)(2-hydroxyphenyl)methyl)nicotinate



a76;

White solid;

M.P.: 155-156°C;

TLC: R_f = 0.40 ethyl acetate /methol (20:1);

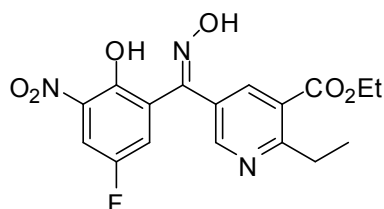
^1H NMR (400 MHz, CDCl_3): δ 10.86 (bs, 1H), 9.70 (bs, 1H), 8.57 (s, 1H), 8.15 (s, 1H), 7.22-7.20 (m, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.73-6.70 (m, 2H), 4.31 (q, J = 7.2 Hz, 2H), 3.58-3.48 (m, 2H), 3.25-3.20 (m, 2H), 1.86-1.74 (m, 2H), 1.68-1.63 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 165.7, 164.0, 158.0, 157.2, 151.8, 139.7, 131.3, 129.8, 125.5, 125.2, 119.3, 117.9, 117.4, 62.2, 61.9, 35.6, 33.6, 32.9, 16.8,14.2;

HRMS (ESI): Calculated for C₂₀H₂₅O₅N₂ [M+H⁺]: 373.1758, Found: 373.1762;

Optical rotation: [α]_D²⁵ = -4.6 °(C = 0.21, MeOH).

(E)-ethyl-2-ethyl-5-((5-fluoro-2-hydroxy-3-nitrophenyl)(hydroxyimino)methyl)nicotinate



Chemical Formula: C₁₇H₁₆FN₃O₆

Exact Mass: 377,1023

Molecular Weight: 377,3238

a78;

White solid;

M.P.: 181-183°C;

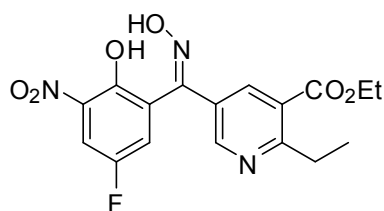
TLC: R_f = 0.12 cyclohexane/ethyl acetate (10:1);

¹H NMR (400 MHz, CDCl₃): δ 11.29 (bs, 1H), 8.77 (s, 1H), 8.26 (s, 1H), 7.81-7.79 (m, 1H), 7.29-7.26 (m, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 3.25 (q, *J* = 7.2 Hz, 2H), 1.41-1.33 (m, 6H);

¹³C NMR (100 MHz, CDCl₃): δ 165.8, 165.1, 151.8, 151.0, 149.8, 139.2, 135.4, 125.8, 125.0, 124.4, 124.2, 113.1, 112.8, 61.9, 30.1, 14.2, 14.0;

HRMS (ESI): Calculated for C₁₇H₁₇FO₆N₃ [M+H⁺]: 378.1096, Found: 378.1097;

(Z)-ethyl-2-ethyl-5-((5-fluoro-2-hydroxy-3-nitrophenyl)(hydroxyimino)methyl)nicotinate



Chemical Formula: C₁₇H₁₆FN₃O₆

Exact Mass: 377,1023

Molecular Weight: 377,3238

a79;

White solid;

M.P.: 167-169°C;

TLC: R_f = 0.11 cyclohexane/ethyl acetate (10:1);

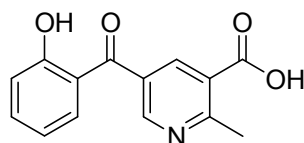
¹H NMR (400 MHz, CDCl₃): δ 10.53 (bs, 1H), 8.77 (s, 1H), 8.25 (s, 1H), 7.99-7.97 (m, 1H), 7.39-7.37 (m, 1H), 4.39 (q, J = 7.2 Hz, 2H), 3.20-3.18 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H), 1.31 (q, J = 7.2 Hz, 3H);

HRMS (ESI): Calculated for C₁₇H₁₇FO₆N₃ [M+H⁺]: 378.1096, Found: 378.1103;

5.4.3.2 The hydrolysis of ester

To a solution of ester in THF/MeOH 2:1 (v/v) was added 2N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (2 × 20ml). The combined organic phases were dried over anhydrous MgSO₄, filtered and evaporated to give the crude acid. The residue was purified by column chromatography.

5-(2-hydroxybenzoyl)-2-methylnicotinic acid



C₁₄H₁₁NO₄
Exact Mass: 257.07
Mol. Wt.: 257.24

White solid,

M.P.: 164-166°C;

TLC: R_f = 0.34 EtOAc/MeOH (5:3);

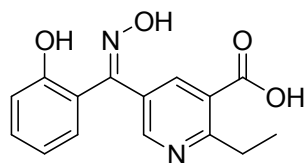
¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) = 10.52 (br s, 1H), 8.83 (d, J = 2.2 Hz, 1H), 8.36 (d, J = 2.2 Hz, 1H), 7.52-7.38 (m, 2H), 6.98 (m, 2H), 2.80 (s, 3H);

¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) = 194.7, 167.0, 162.4, 156.8, 151.3, 138.4,

133.9, 130.7, 130.5, 125.6, 124.0, 119.4, 116.8, 24.6;

HRMS (ESI): Calculated for $C_{14}H_{12}NO_4[M+H^+]$:258.07608;Found 258.07605

(E)-2-ethyl-5-((hydroxyimino)(2-hydroxyphenyl)methyl)nicotinic acid



$C_{15}H_{14}N_2O_4$
Exact Mass: 286.1
Mol. Wt.: 286.28

White solid;

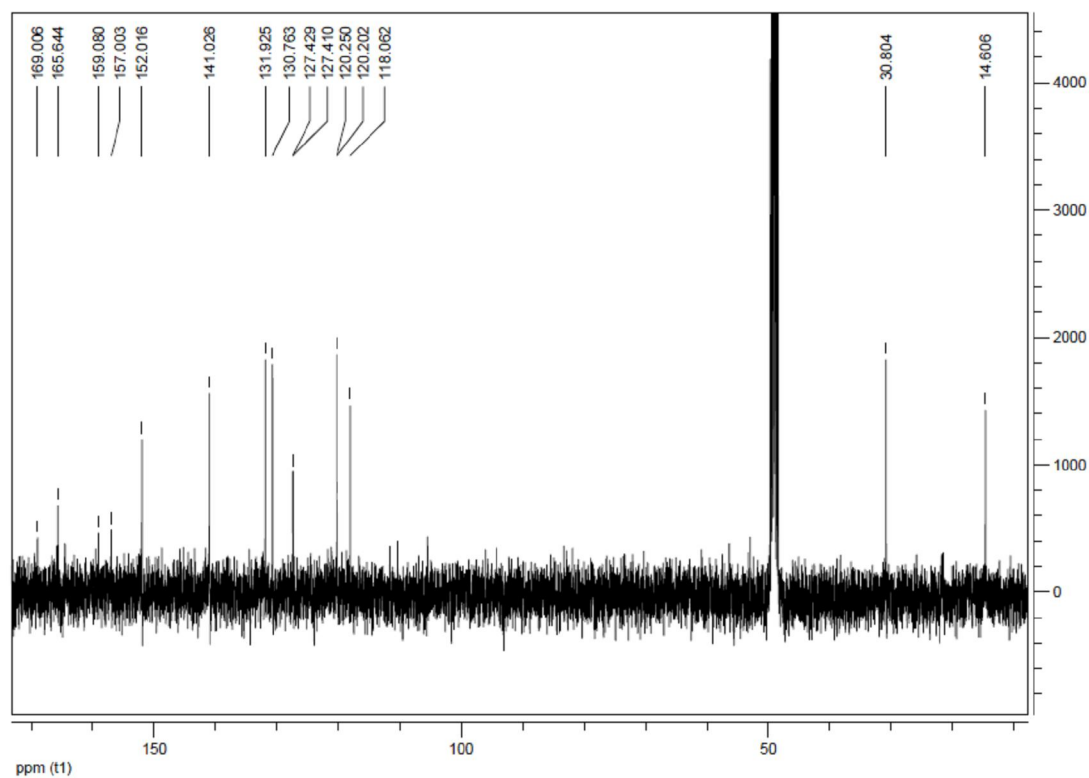
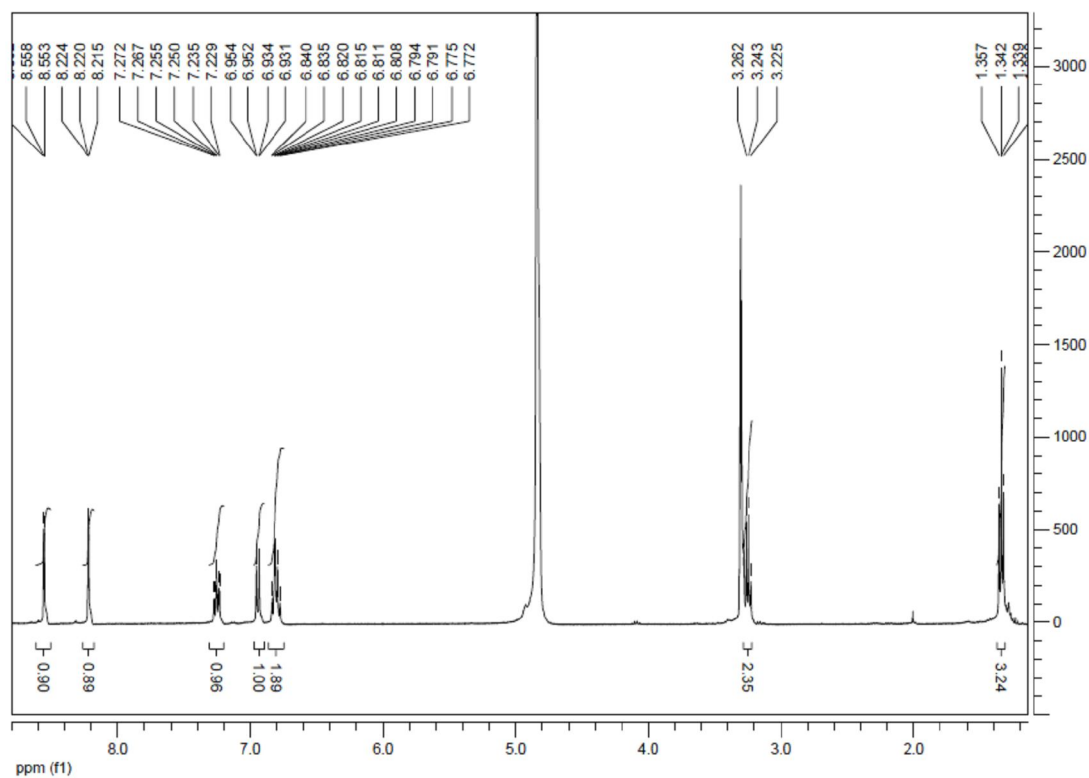
M.P.: 181-182°C;

TLC: $R_f = 0.29$ ethyl acetate/MeOH (5:1);

1H NMR (400 MHz, MeOD): δ 8.56 (d, $J = 3.6$ Hz, 1H), 8.22 (d, $J = 3.6$ Hz, 1H), 7.25 (dt, $J = 8.0, 2.0$ Hz, 1H), 6.94 (d, $J = 8.0$ Hz, 1H), 6.84-6.78 (m, 2H), 3.24 (q, $J = 7.2$ Hz, 2H), 1.34 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, MeOD): δ ; 169.0, 165.6, 159.1, 157.0, 152.0, 141.0, 131.9, 130.8, 127.43, 127.41, 120.3, 120.2, 118.6, 30.8, 14.6;

HRMS (ESI): Calculated for $C_{15}H_{15}O_4N_2[M+H^+]$: 287.1027, Found: 287.1026;



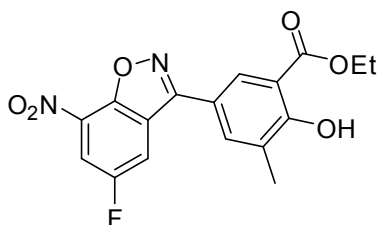
5.4.4 Synthesis of oxazoles and isoxazoles from oximes

General Procedure: To the solution of anhydrous THF (15ml) E-oxime (1.0mmol,

1.0eq) was added DIAD (1.2mmol, 1.2eq) and PPh₃ (1.5mmol, 1.5eq) at room temperature under argon atmosphere. The colour of solution turned from straw yellow to yellow. The reaction mixture was stirred for 2-4 hours when oxime was consumed (TLC using cyclohexane/ethyl acetate (10:1) as eluent). The reaction mixture was added 10ml water to quench the reaction. THF was evaporated and 10ml water was added to residue that was extracted with EtOAc (15mlX4). Organic layers were combined and washed with brine (15ml) and dried over anhydrous Na₂SO₄. The residue was purified by flash chromatography (eluent: petroleum ether/ethyl acetate 20/1) to give two yellow solid products.

General Procedure: To the solution of anhydrous THF (15ml) Z-oxime (1.0mmol, 1.0eq) was added DIAD (1.2mmol, 1.2eq) and PPh₃ (1.5mmol, 1.5eq) at room temperature under argon atmosphere. The colour of solution turned from straw yellow to yellow. The reaction mixture was stirred for 2-4 hours when oxime was consumed (TLC using cyclohexane/ethyl acetate (10:1) as eluent). The reaction mixture was added 10ml water to quench the reaction. THF was evaporated and 10ml water was added to residue that was extracted with EtOAc (15mlX4). Organic layers were combined and washed with brine (15ml) and dried over anhydrous Na₂SO₄. The residue was purified by flash chromatography (eluent: petroleum ether/ethyl acetate 20/1) to give one yellow solid product.

Ethyl 5-(5-fluoro-7-nitrobenzo[d]isoxazol-3-yl)-2-hydroxy-3-methylbenzoate



Chemical Formula: C₁₇H₁₃FN₂O₆
Exact Mass: 360,0758
Molecular Weight: 360,2933

a91;

Yellow solid;

M.P.: 137.2°C;

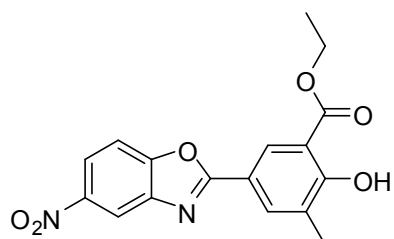
TLC: R_f = 0.46 cyclohexane/ethyl acetate (10:1);

^1H NMR (400 MHz, CDCl_3): δ 11.65 (s, 1H), 8.62 (d, J = 2.4 Hz, 1H), 8.19 (d, J = 2.4 Hz, 1H), 7.81 (dd, J = 9.2, 2.4 Hz, 1H), 7.67 (dd, J = 7.6, 2.4 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 2.32 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 169.9, 164.0, 159.8, 157.1, 135.2, 128.6, 128.5, 115.8, 113.1, 112.9, 112.6, 108.3, 108.0, 62.2, 15.7, 14.2;

HRMS (ESI): Calculated for $\text{C}_{17}\text{H}_{14}\text{O}_6\text{N}_2$ [$\text{M}+\text{H}^+$]: 361.0830, Found: 361.0832;

Ethyl 2-hydroxy-3-methyl-5-(5-nitrobenzo[d]oxazol-2-yl)benzoate



Chemical Formula: $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_6$

Exact Mass: 342,0852

Molecular Weight: 342,3029

a92;

White solid;

M.P.: 157-159°C;

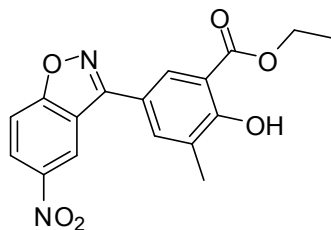
TLC: R_f = 0.43 cyclohexane/ethyl acetate (10:1);

^1H NMR (400 MHz, CDCl_3): δ 11.63 (s, 1H), 8.59 (t, J = 2.4 Hz, 2H), 8.28 (dd, J = 8.8, 2.4 Hz, 1H), 8.19 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 4.49 (q, J = 7.2 Hz, 2H), 2.36 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 169.9, 165.5, 163.6, 154.2, 145.4, 142.7, 135.0, 128.3, 128.1, 120.8, 116.3, 115.8, 112.4, 110.5, 62.1, 15.7, 14.3;

HRMS (ESI): Calculated for $\text{C}_{17}\text{H}_{15}\text{O}_6\text{N}_2$ [$\text{M}+\text{H}^+$]: 343.0926, Found: 343.0927.

Ethyl 2-hydroxy-3-methyl-5-(5-nitrobenzo[d]isoxazol-3-yl)benzoate



Chemical Formula: $C_{17}H_{14}N_2O_6$

Exact Mass: 342,0852

Molecular Weight: 342,3029

a93;

White solid;

M.P.: 174-176°C;

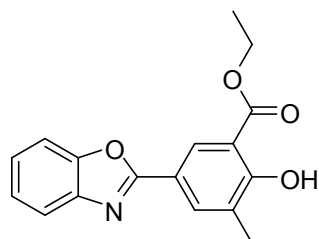
TLC: $R_f = 0.42$ cyclohexane/ethyl acetate (10:1);

1H NMR (400 MHz, $CDCl_3$): δ 11.64 (s, 1H), 8.60 (t, $J = 2.8$ Hz, 2H), 8.29 (dd, $J = 8.8, 2.4$ Hz, 1H), 8.21-8.20 (m, 1H), 7.65(d, $J = 8.8$ Hz, 1H), 4.49(d, $J = 7.2$ Hz, 1H), 2.37(s, 3H), 1.49(t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 165.5, 163.6, 154.2, 142.7, 135.0, 128.3, 128.1, 120.8, 116.3, 115.8, 112.5, 110.5, 62.1, 15.7, 14.3;

HRMS (ESI): Calculated for $C_{17}H_{14}N_2O_6$ [$M+H^+$]: 343.0925, Found: 343.0924;

Ethyl 5-(benzo[d]oxazol-2-yl)-2-hydroxy-3-methylbenzoate



Chemical Formula: $C_{17}H_{15}NO_4$

Exact Mass: 297,1001

Molecular Weight: 297,3053

a94;

White solid;

M.P.: 147-149°C;

TLC: $R_f = 0.41$ cyclohexane/ethyl acetate (10:1);

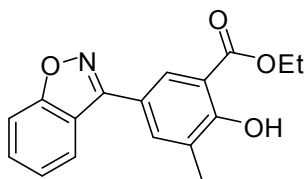
1H NMR (400 MHz, $CDCl_3$): δ 11.04 (s, 1H), 8.60 (d, $J = 2.4$ Hz, 1H), 8.22-8.21 (m,

1H), 7.58-7.55 (m, 1H), 7.35-7.32 (m, 1H), 4.07(q, $J = 7.2$ Hz, 2H), 2.36(s, 3H), 1.48(t, $J = 7.2$ Hz, 3H); .

^{13}C NMR (100 MHz, CDCl_3): δ 170.2, 162.8, 150.7, 42.1, 134.8, 127.9, 127.4, 124.8, 124.5, 119.7, 117.6, 112.3, 110.4, 61.9, 15.7, 14.3;

HRMS (ESI): Calculated for $\text{C}_{17}\text{H}_{16}\text{O}_4\text{N}$ [$\text{M}+\text{H}^+$]: 298.1075, Found: 298.1074;

Ethyl 5-(benzo[d]isoxazol-3-yl)-2-hydroxy-3-methylbenzoate



Chemical Formula: $\text{C}_{17}\text{H}_{15}\text{NO}_4$
 Exact Mass: 297,1001
 Molecular Weight: 297,3053

a95;

White solid;

M.P.: 138-139°C;

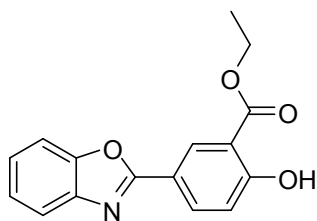
TLC: $R_f = 0.40$ cyclohexane/ethyl acetate (10:1);

^1H NMR (400 MHz, CDCl_3): δ 11.32 (s, 1H), 8.27 (d, $J = 1.6$ Hz, 1H), 7.88 (s, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.57 (t, $J = 8.0$ Hz, 1H), 7.54 (t, $J = 8.0$ Hz, 1H), 7.33 (t, $J = 8.0$ Hz, 1H), 4.40(q, $J = 7.2$ Hz, 2H), 2.31(s, 3H), 1.38(t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 161.7, 135.4, 129.8, 128.0, 127.3, 123.8, 122.1, 120.4, 119.3, 112.4, 110.2, 61.8, 15.8, 14.2;

HRMS (ESI): Calculated for $\text{C}_{17}\text{H}_{16}\text{O}_4\text{N}$ [$\text{M}+\text{H}^+$]: 298.1074, Found: 298.1074;

Ethyl 5-(benzo[d]oxazol-2-yl)-2-hydroxybenzoate



Chemical Formula: $C_{16}H_{13}NO_4$

Exact Mass: 283,0845

Molecular Weight: 283,2787

a96;

White solid;

M.P.: 157-159°C;

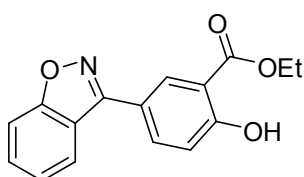
TLC: $R_f = 0.44$ cyclohexane/ethyl acetate (10:1);

1H NMR (400 MHz, $CDCl_3$): δ 11.13 (s, 1H), 8.50 (d, $J = 2.4$ Hz, 1H), 8.07 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.90 (d, $J = 8.0$ Hz, 1H), 7.65 (t, $J = 8.4$ Hz, 1H), 7.61 (t, $J = 8.4$ Hz, 1H), 7.40 (t, $J = 8.0$ Hz, 1H), 7.17 (t, $J = 8.4$ Hz, 1H), 4.48 (q, $J = 7.2$ Hz, 2H), 1.46 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 163.9, 163.1, 156.2, 134.9, 129.8, 123.9, 121.9, 120.3, 120.1, 118.6, 113.2, 110.3, 61.9, 14.2;

HRMS (ESI): Calculated for $C_{16}H_{14}O_4N$ [$M+H^+$]: 284.0917, Found: 284.0917;

Ethyl 5-(benzo[d]isoxazol-3-yl)-2-hydroxybenzoate



Chemical Formula: $C_{16}H_{13}NO_4$

Exact Mass: 283,0845

Molecular Weight: 283,2787

a97;

White solid;

M.P.: 183-184°C;

TLC: $R_f = 0.43$ cyclohexane/ethyl acetate (10:1);

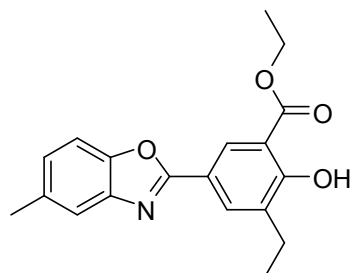
1H NMR (400 MHz, $CDCl_3$): δ 11.24 (s, 1H), 8.67-8.64 (m, 1H), 8.25 (d, $J = 8.8$ Hz, 1H), 7.70 (d, $J = 8.8$ Hz, 1H), 7.52-7.48 (m, 1H), 7.31-7.28 (m, 2H), 7.06 (t, $J = 8.8$

Hz, 1H), 4.43(q, $J = 7.2$ Hz, 2H), 1.45(t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 169.6, 164.0, 162.0, 150.5, 142.0, 134.3, 129.7, 124.8, 124.5, 119.6, 118.3, 112.9, 110.3, 61.9, 14.2;

HRMS (ESI): Calculated for $\text{C}_{16}\text{H}_{14}\text{O}_4\text{N}$ [$\text{M}+\text{H}^+$]: 284.0917, Found: 284.0918;

Ethyl 3-ethyl-2-hydroxy-5-(5-methylbenzo[d]oxazol-2-yl)benzoate



Chemical Formula: $\text{C}_{19}\text{H}_{19}\text{NO}_4$
 Exact Mass: 325,1314
 Molecular Weight: 325,3585

a98;

White solid;

M.P.: 169-170°C;

TLC: $R_f = 0.40$ cyclohexane/ethyl acetate (10:1);

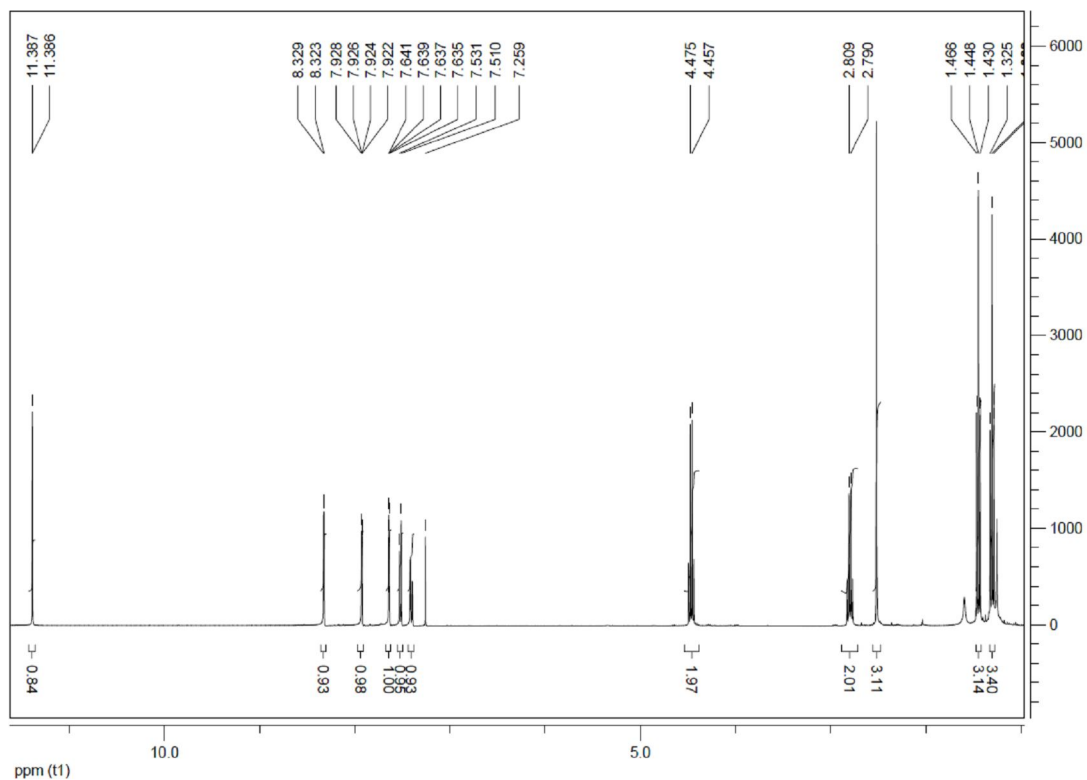
^1H NMR (400 MHz, CDCl_3): δ 11.39 (s, 1H), 8.33 (d, $J = 2.4$ Hz, 1H), 7.93-7.92 (m, 1H), 7.64-7.63 (m, 1H), 7.52 (d, $J = 8.4$ Hz, 1H), 7.40 (dd, $J = 8.4, 1.6$ Hz, 1H), 4.46 (q, $J = 7.2$ Hz, 2H), 2.80 (q, $J = 7.2$ Hz, 2H), 2.52 (s, 3H), 1.45 (t, $J = 7.2$ Hz, 3H), 1.31(t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 170.3, 162.5, 161.3, 125.1, 133.8, 133.7, 133.5, 131.3, 127.2, 121.2, 120.6, 119.6, 112.4, 109.7, 61.8, 22.9, 21.3, 14.2, 13.7;

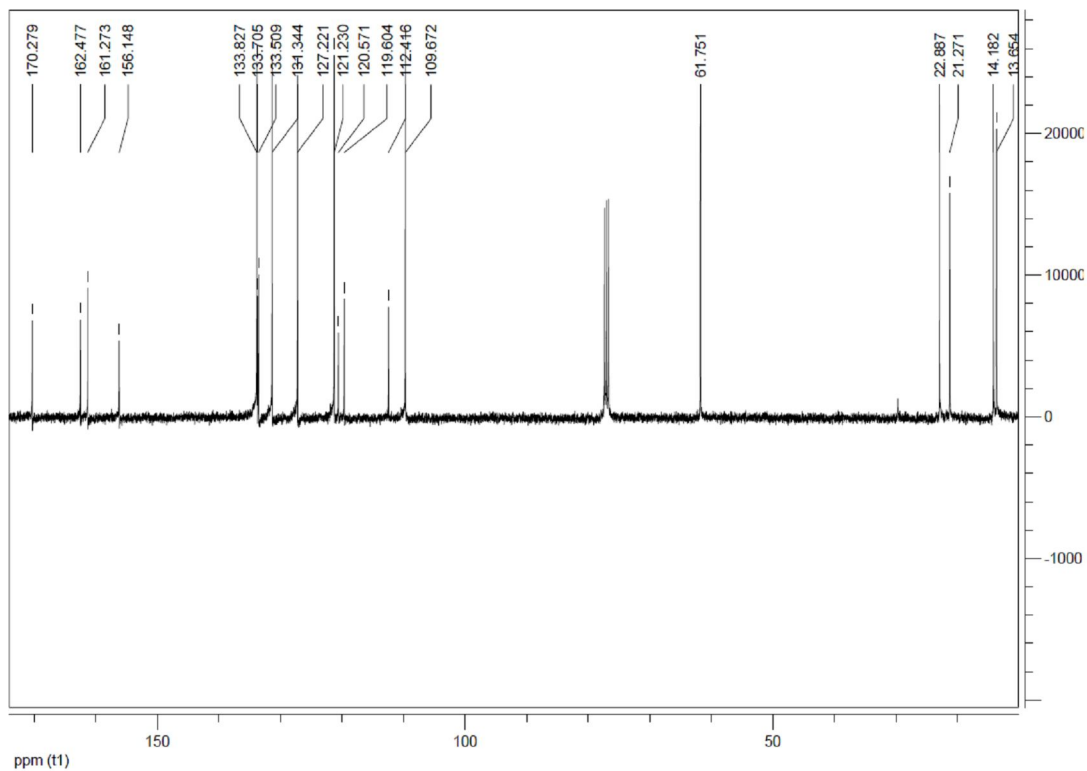
HRMS (ESI): Calculated for $\text{C}_{19}\text{H}_{20}\text{O}_4\text{N}$ [$\text{M}+\text{H}^+$]: 326.1387, Found: 326.1388;

a98 ^1H spectrum;

Experimental section

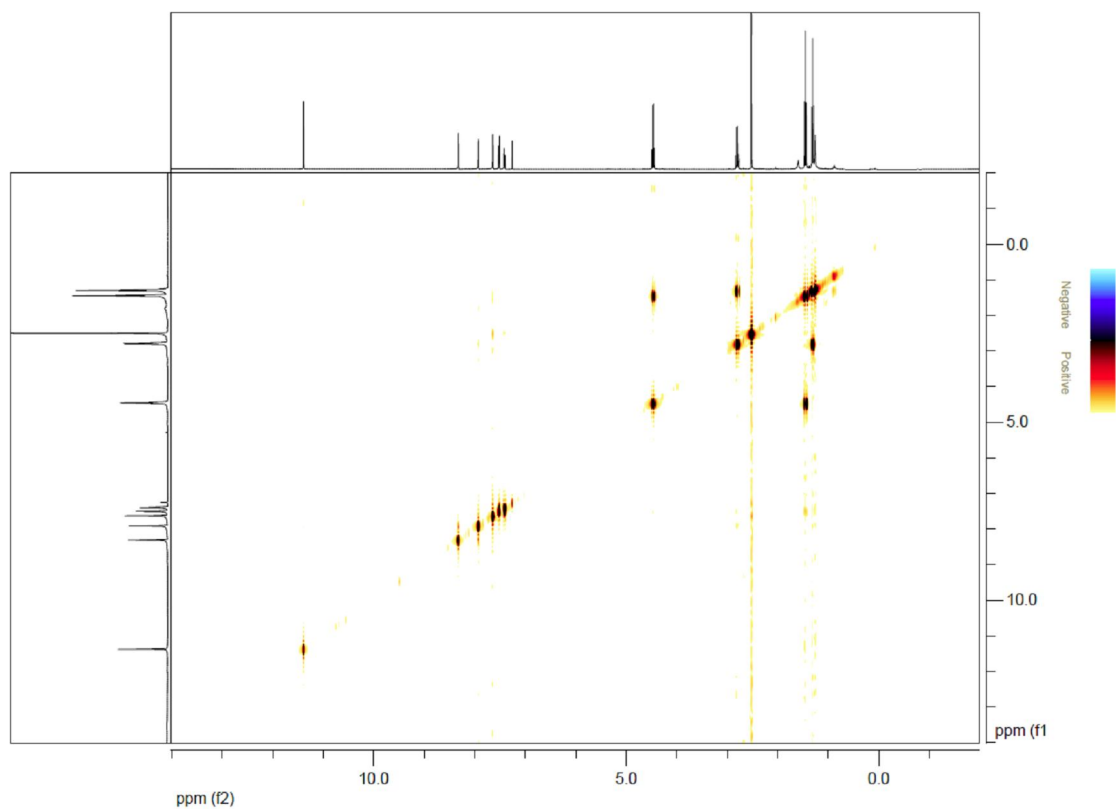


a98 ¹³C spectrum;

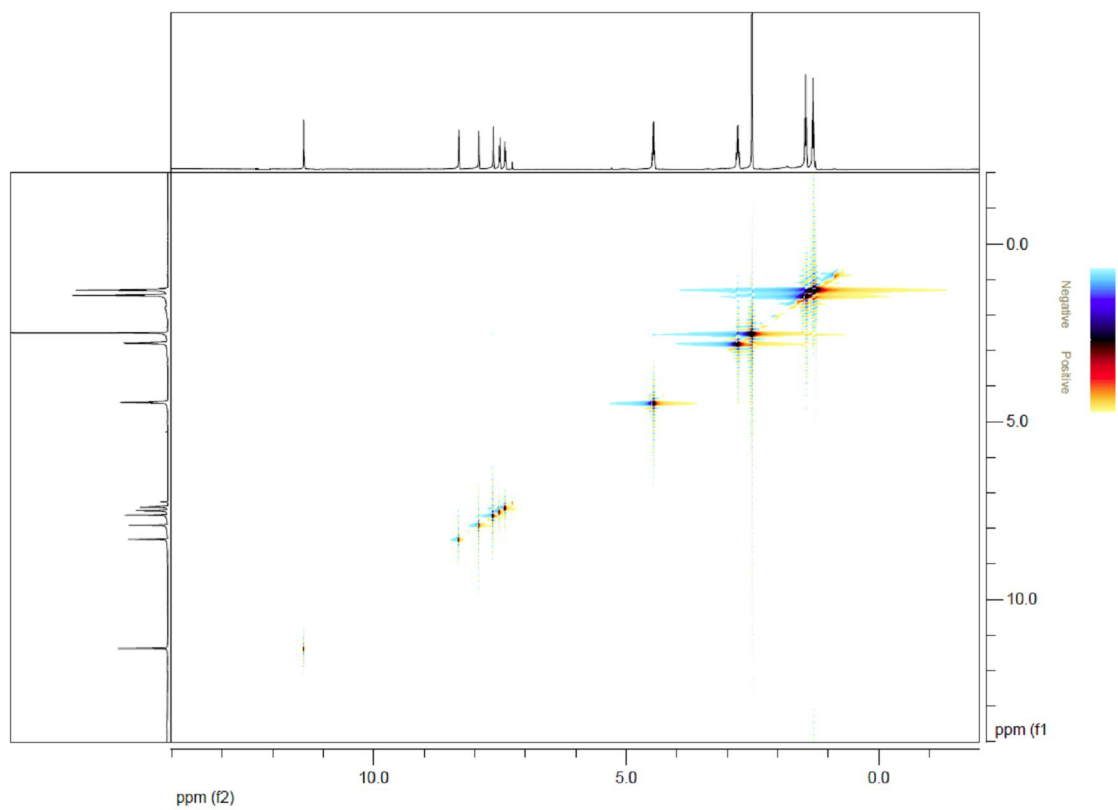


a98 gcosy spectrum;

Experimental section

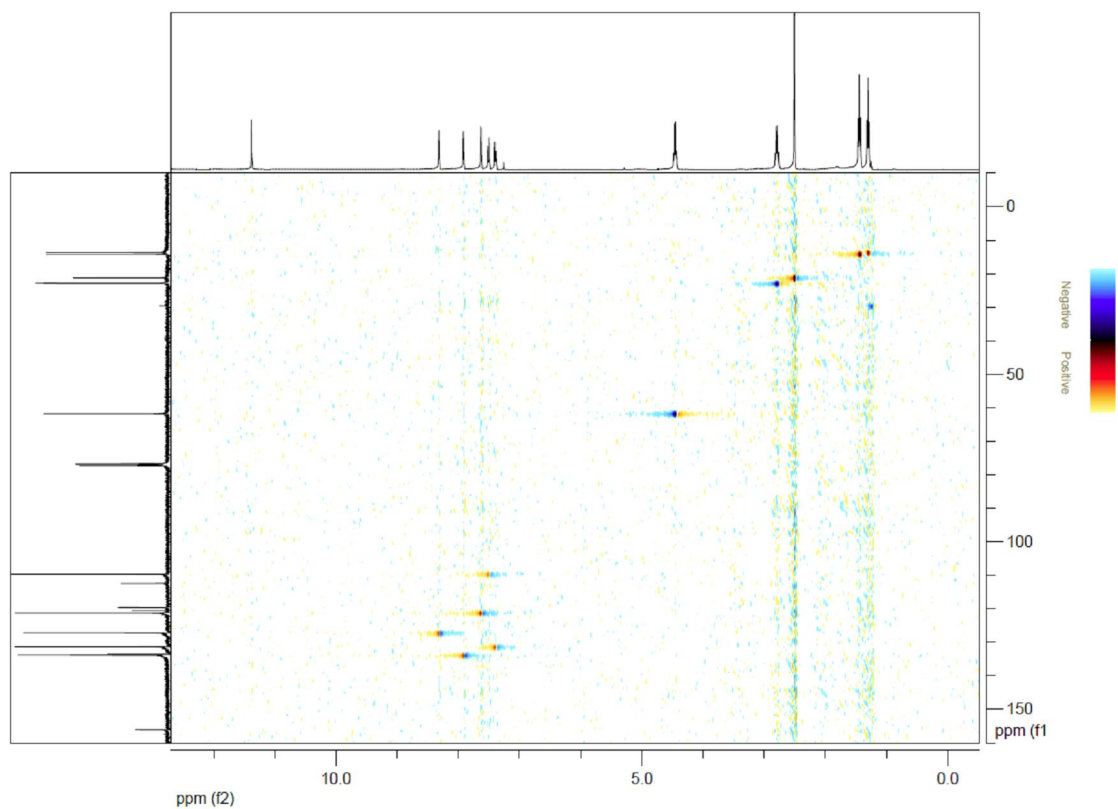


a98 noesy spectrum;

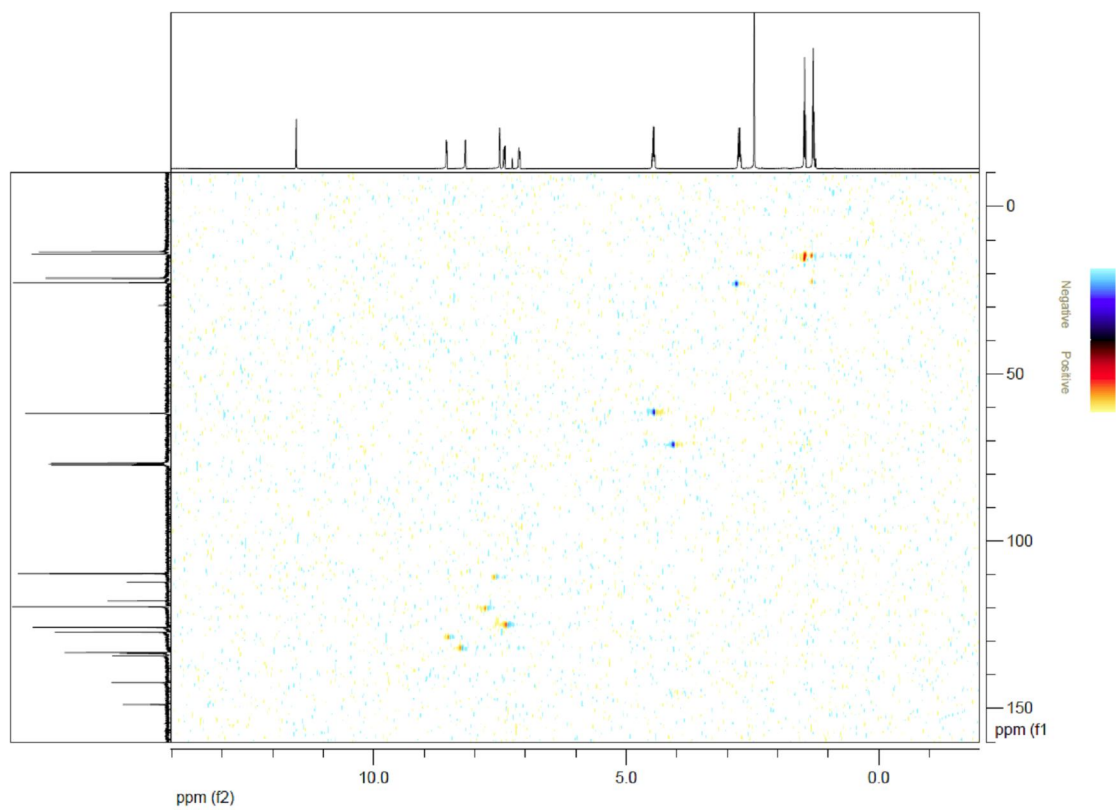


a98 ghsqc spectrum;

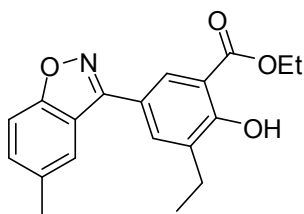
Experimental section



a98 ghmbc spectrum;



Ethyl 3-ethyl-2-hydroxy-5-(5-methylbenzo[d]isoxazol-3-yl)benzoate



Chemical Formula: C₁₉H₁₉NO₄

Exact Mass: 325,1314

Molecular Weight: 325,3585

a99;

White solid;

M.P.: 159-161°C;

TLC: R_f = 0.41 cyclohexane/ethyl acetate (10:1);

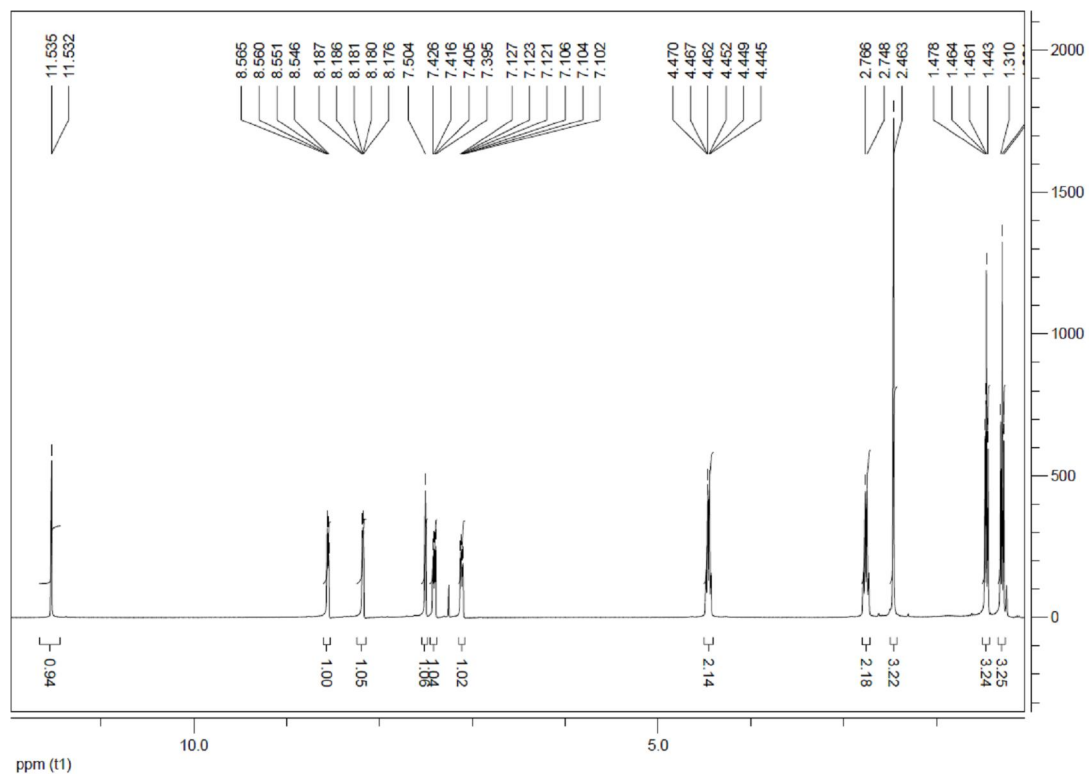
¹H NMR (400 MHz, CDCl₃): δ 11.53 (s, 1H), 8.56 (dd, *J* = 5.6, 2.0 Hz, 1H), 8.19-8.18 (m, 1H), 7.50 (s, 1H), 7.41 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.11 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 2.75 (q, *J* = 7.2 Hz, 2H), 2.46 (s, 3H), 1.46 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 170.2, 162.4, 148.9, 142.3, 134.3, 133.6, 133.3, 127.3, 125.8, 119.6, 117.9, 112.3, 109.7, 61.9, 22.8, 21.5, 14.3, 13.6;

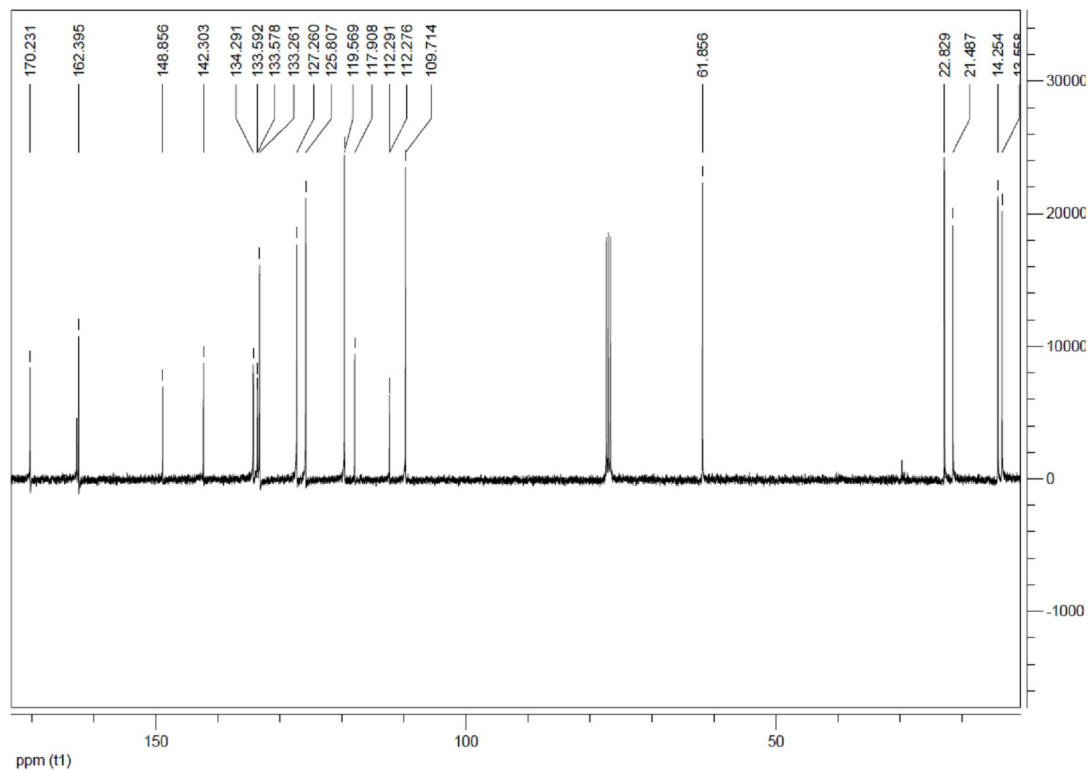
HRMS (ESI): Calculated for C₁₉H₂₀O₄N [M+H⁺]: 326.1387, Found: 326.1387;

a99 ¹H spectrum;

Experimental section

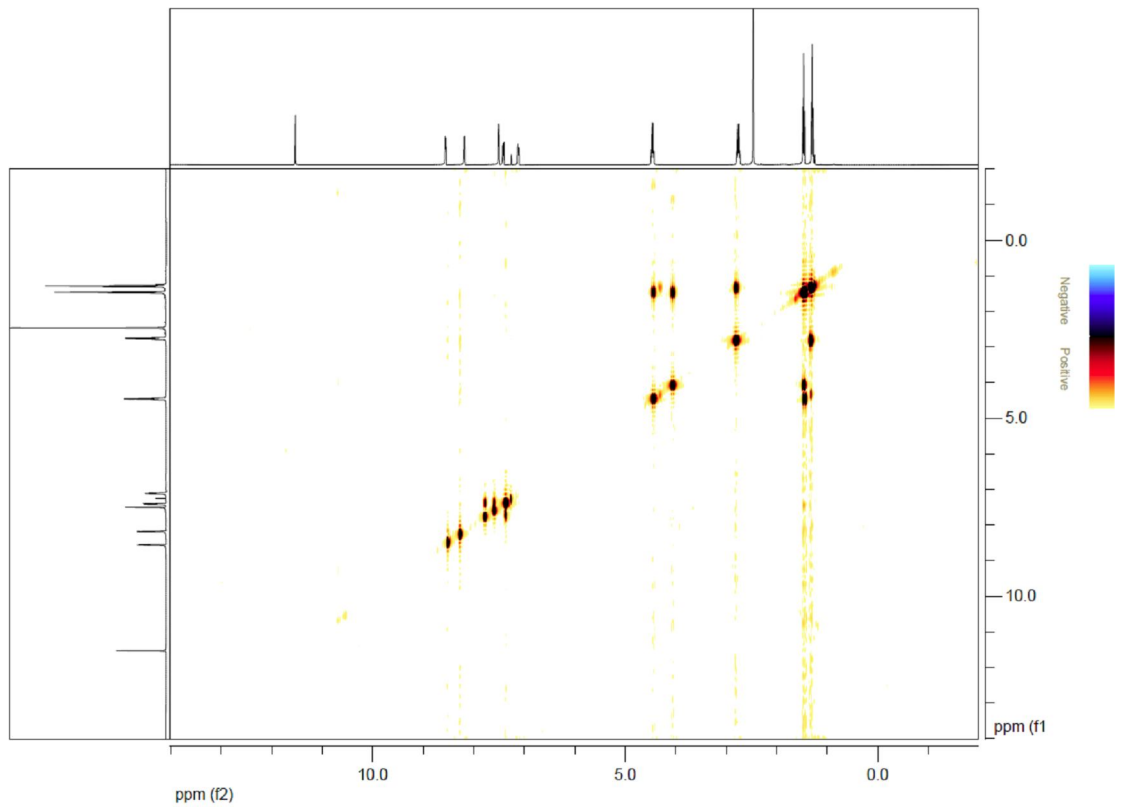


a99 ¹³C spectrum;

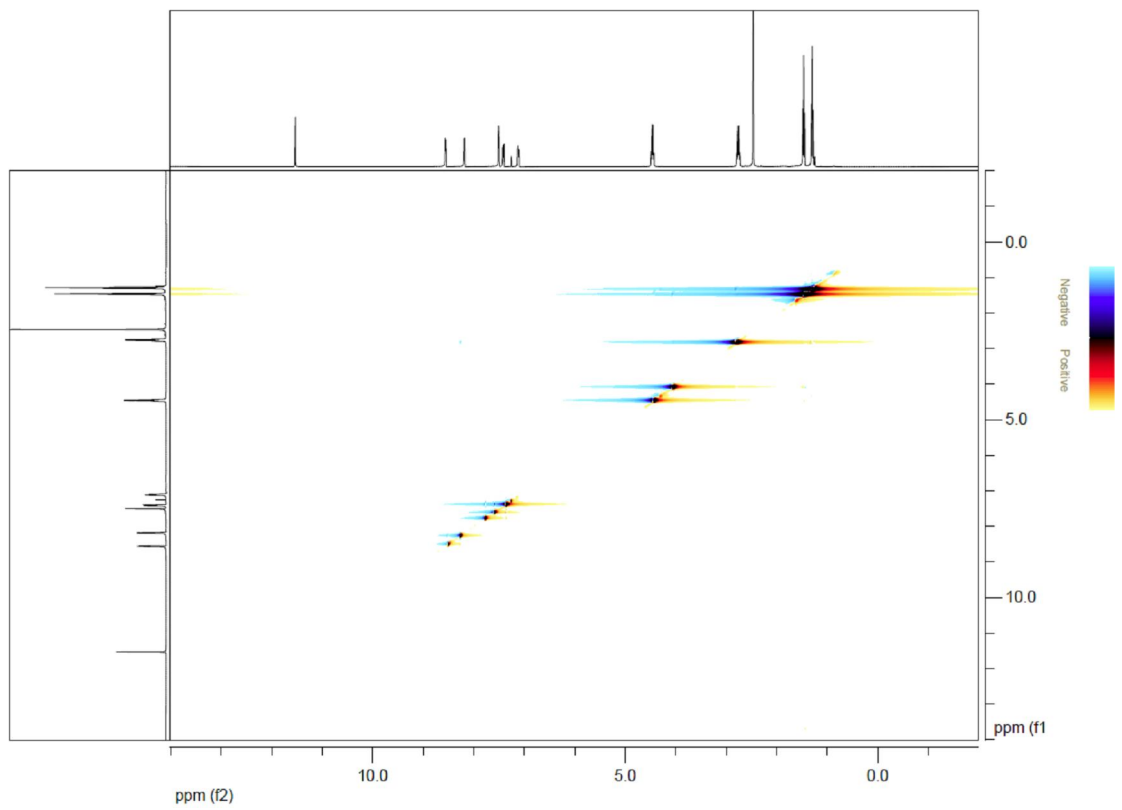


a99 gcosy spectrum;

Experimental section

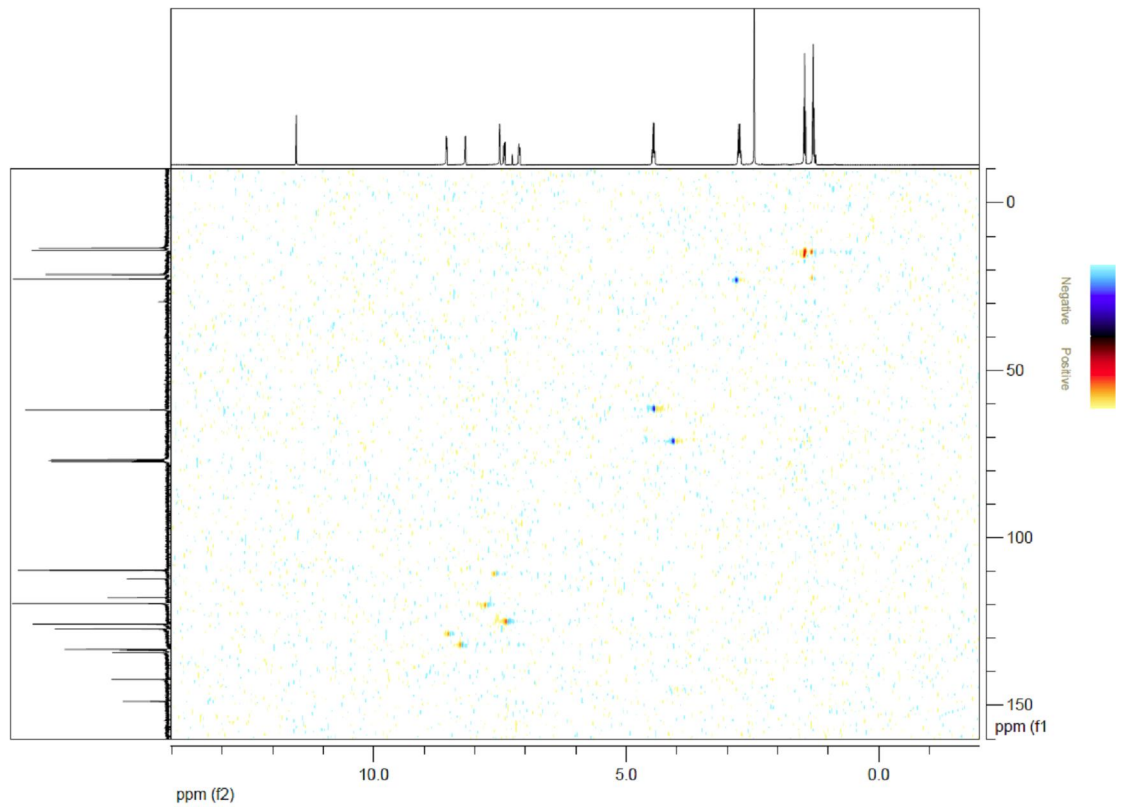


a99 noesy spectrum;

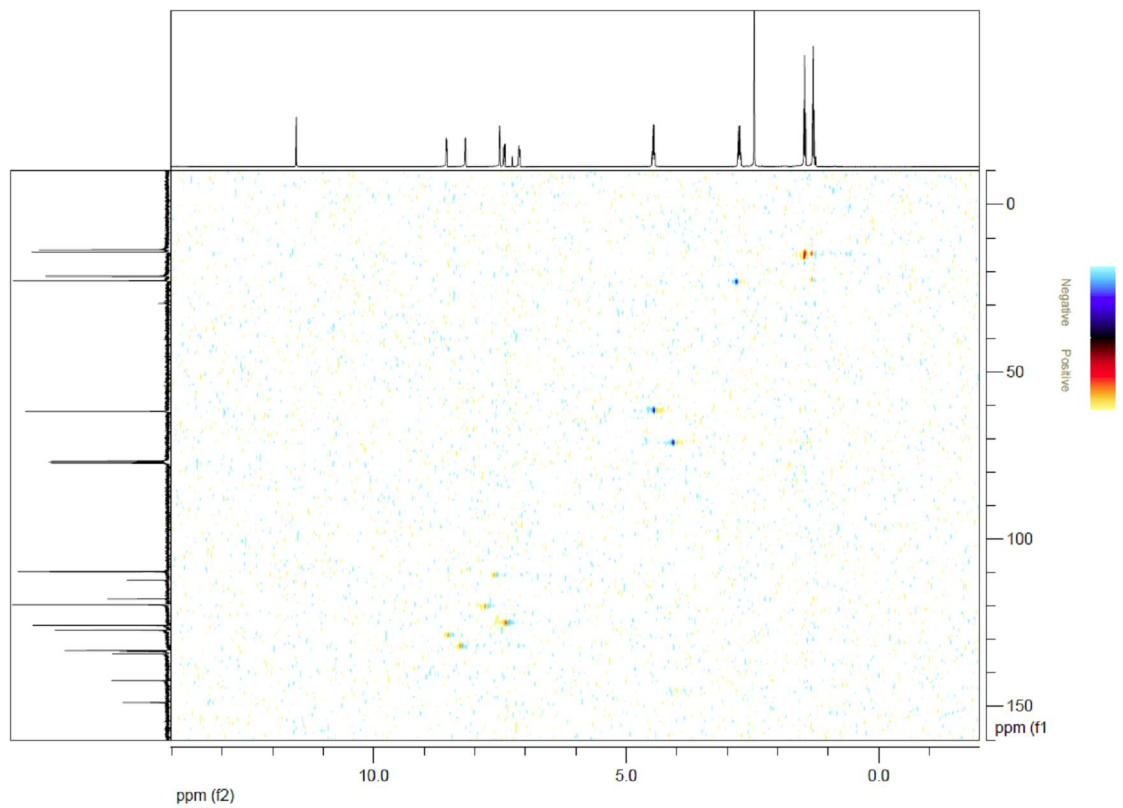


a99 ghsqc spectrum;

Experimental section



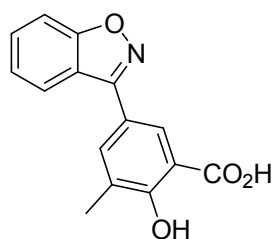
a99 ghmbc spectrum;



5.4.5 Preparation of free acid

General Procedure: The compound of isoxazole (1.0mmol, 1.0eq) was added to the solution of sodium hydroxygen (2mol/l) 10ml. The reaction was stired for overnight in the room temperature. The reaction was monitored by TLC using ethyl acetate/MeOH (5:1) as eluent. The reaction was very clear showing nearly quantitative conversion. The solution was added 10ml water and extracted with EtOAc (25mlX5), the organic layer were combined and washed with brine (10ml); dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by flash chromatography with short column (eluent: ethyl acetate/MeOH (10:1)) to give white solid product.

5-(benzo[d]isoxazol-3-yl)-2-hydroxy-3-methylbenzoic acid



C₁₅H₁₁NO₄
Exact Mass: 269.07
Mol. Wt.: 269.25

a110;

White solid;

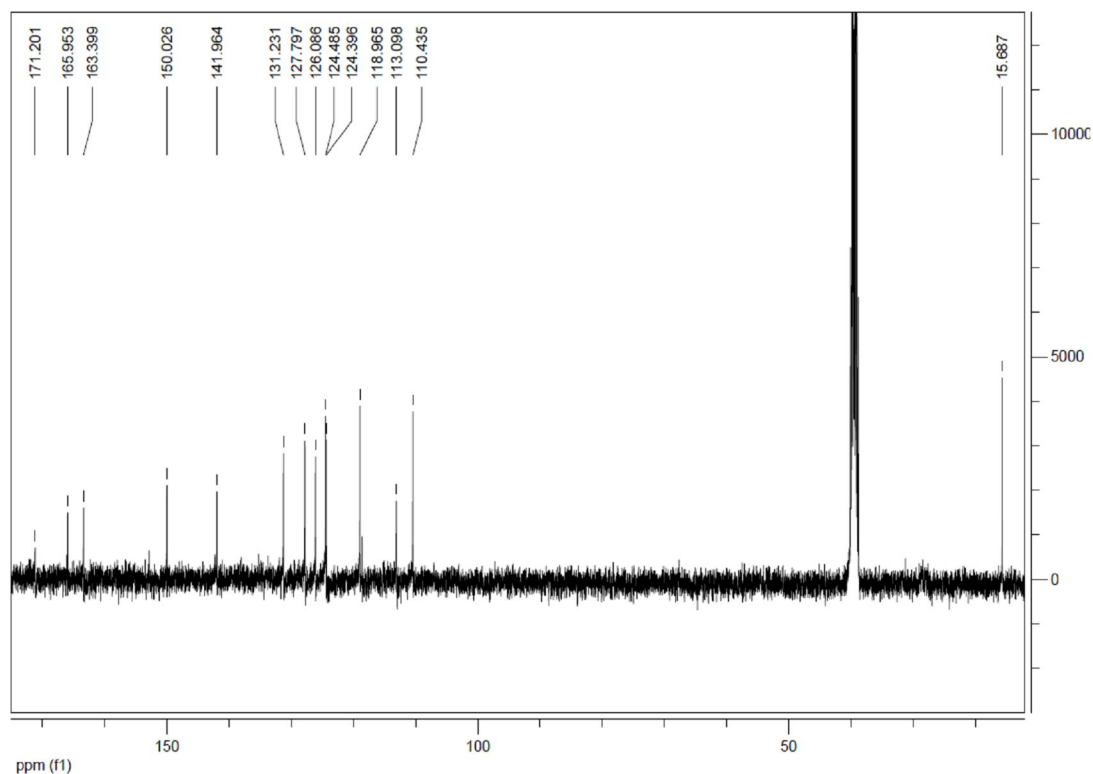
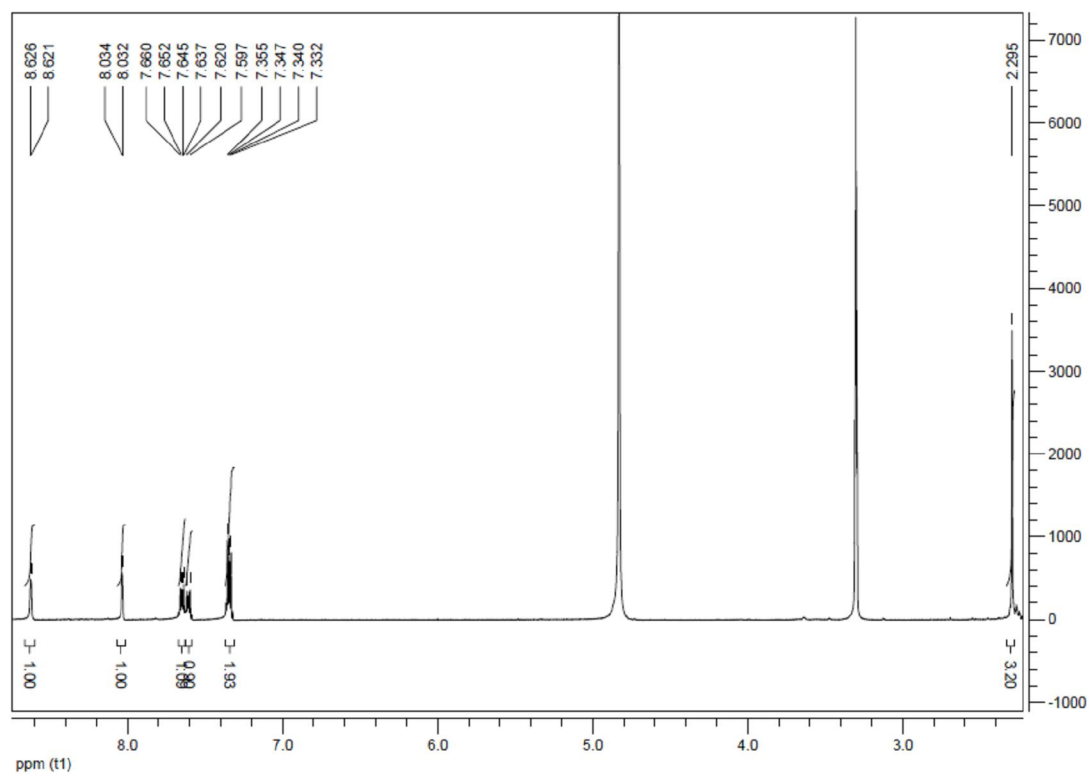
M.P.: 167-168°C;

TLC: R_f = 0.16 ethyl acetate/MeOH (5:1);

¹H NMR (400 MHz, CD₃OD): δ 8.62 (s, 1H), 8.03 (s, 1H), 7.65 (q, *J* = 3.2 Hz, 1H), 7.61 (q, *J* = 3.2 Hz, 1H), 7.35 (q, *J* = 3.2 Hz, 2H), 2.30 (s, 3H);

¹³C NMR (100 MHz, CD₃OD): δ 172.1, 166.0, 163.4, 150.0, 142.0, 131.2, 127.8, 126.1, 124.5, 124.4, 119.0, 113.1, 110.4, 15.7;

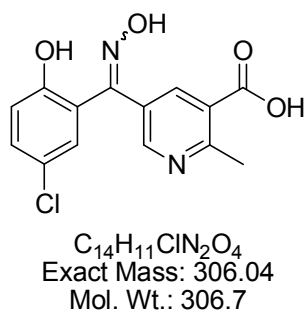
HRMS (ESI): Calculated for C₁₅H₁₃O₄N [M+H⁺]: 270.0761, Found: 270.0761;



5.4.6 Preparation of Nicotinic acid

Free acid (1mmol) and hydroxylamine hydrochloride (10mmol, 10eq) was mixed in solution of pyridine/ethanol= 1/6 (10ml), and the solution was heated to reflux for overnight. The solution was cooled down to room temperature and diluted with 10ml water. Pyridine and ethanol were removed under vacuum. To the solution concentrated 10ml water was added and extracted with EtOAc (25mlX4). Combined the organic layers were washed with brine (10ml) and dried with anhydrous Na₂SO₄ and evaporated to dryness. The residue was purified by flash chromatography (eluent: ethyl acetate/MeOH (10:1)) to give two white solid product E-oxime and Z-oxime, in approx 1:1 ratio. E and Z were very difficult to isolate and in some case all of the isomer could be purified.

(E)-5-((5-chloro-2-hydroxyphenyl)(hydroxyimino)methyl)-2-methylnicotinic acid



One isomer E or Z

a110;

White solid;

M.P.: 172-173°C;

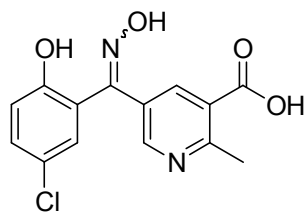
TLC: R_f = 0.26 ethyl acetate/MeOH (5:1);

¹H NMR (400 MHz, DMSO): δ 12.0 (bs, 1H), 10.48 (bs, 1H), 8.56 (s, 1H), 8.16 (s, 1H), 7.30-7.27 (m, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 2.72 (s, 3H);

¹³C NMR (100 MHz, DMSO): δ; 172.6, 167.9, 158.4, 155.2, 150.5, 137.9, 130.1, 129.3, 125.9, 123.2, 122.5, 118.1, 117.5, 24.3;

HRMS (ESI): Calculated for C₁₄H₁₂ClO₄N₂ [M+H⁺]: 307.0480, 309.0451; Found: 307.0480, 309.0449;

(Z)-2-ethyl-5-((hydroxyimino)(2-hydroxyphenyl)methyl)nicotinic acid



$C_{14}H_{11}ClN_2O_4$
 Exact Mass: 306.04
 Mol. Wt.: 306.7

One isomer E or Z

a111;

White solid;

M.P. : 162-163°C;

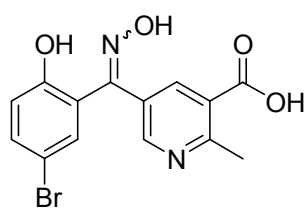
TLC : R_f = 0.30 ethyl acetate/MeOH (5:1);

1H NMR (400 MHz, DMSO): δ 7.70 (d, J = 2.4 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 7.29-7.7 (m, 1H), 6.95-6.92 (m, 2H), 3.32(q, J = 7.2 Hz, 2H), 2.22 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, DMSO): δ ; 172.2, 161.8, 156.0, 155.9, 135.9, 131.3, 131.2, 128.9, 127.8, 127.6, 122.4, 120.6, 117.5, 112.4, 30.8, 15.8;

HRMS (ESI): Calculated for $C_{15}H_{15}O_4N_2$ [$M+H^+$]: 287.1026, Found: 287.1026;

(E)-5-((5-bromo-2-hydroxyphenyl)(hydroxyimino)methyl)-2-methylnicotinic acid



$C_{14}H_{11}BrN_2O_4$
 Exact Mass: 349.99
 Mol. Wt.: 351.15

a112;

White solid;

M.P.: 171-173°C;

TLC: R_f = 0.17 ethyl acetate/MeOH (5:1);

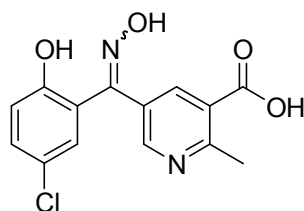
1H NMR (400 MHz, DMSO): δ 11.96 (bs, 1H), 10.49 (bs, 1H), 8.57 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 2.0 Hz, 1H), 7.40 (dd, J = 8.8, 2.4 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H),

6.84 (d, $J = 8.8$ Hz, 1H), 2.72 (s, 3H);

^{13}C NMR (100 MHz, DMSO): δ 167.9, 158.4, 155.6, 151.7, 150.6, 141.1, 138.0, 133.0, 132.1, 125.9, 123.8, 118.6, 109.9, 24.3;

HRMS (ESI): Calculated for $\text{C}_{14}\text{H}_{12}\text{BrO}_4\text{N}_2$ [$\text{M}+\text{H}^+$]: 350.9975, 352.9955; Found: 350.9977, 352.9954;

(Z)-5-((5-chloro-2-hydroxyphenyl)(hydroxyimino)methyl)-2-methylnicotinic acid



$\text{C}_{14}\text{H}_{11}\text{ClN}_2\text{O}_4$
Exact Mass: 306.04
Mol. Wt.: 306.7

a113;

White solid;

M.P.: 159-160°C;

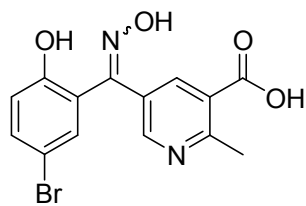
TLC: $R_f = 0.27$ ethyl acetate/MeOH (5:1);

^1H NMR (400 MHz, CD_3OD): δ 8.70 (d, $J = 1.6$ Hz, 1H), 8.63 (d, $J = 1.6$ Hz, 1H), 7.29 (dd, $J = 8.8, 2.8$ Hz, 1H), 7.21 (d, $J = 2.4$ Hz, 1H), 6.99 (d, $J = 8.8$ Hz, 1H), 2.95(s, 3H);

^{13}C NMR (100 MHz, CD_3OD): δ 172.6, 167.9, 158.4, 154.5, 149.7, 144.0, 142.4, 134.0, 131.8, 131.1, 125.2, 120.6, 118.7, 21.5;

HRMS (ESI): Calculated for $\text{C}_{14}\text{H}_{12}\text{ClO}_4\text{N}_2$ [$\text{M}+\text{H}^+$]: 307.0480, 309.0451; Found: 307.0481, 309.0450;

(Z)-5-((5-bromo-2-hydroxyphenyl)(hydroxyimino)methyl)-2-methylnicotinic acid



$C_{14}H_{11}BrN_2O_4$
Exact Mass: 349.99
Mol. Wt.: 351.15

a115;

White solid;

M.P.: 171-173°C;

TLC: R_f = 0.16 ethyl acetate/MeOH (5:1);

1H NMR (400 MHz, CD_3OD): δ 8.54 (s, 1H), 8.30 (s, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.27 (s, 1H), 6.86 (d, J = 8.8 Hz, 1H), 2.78 (s, 3H);

^{13}C NMR (100 MHz, CD_3OD): δ 168.5, 165.9, 159.8, 151.2, 149.1, 143.8, 141.3, 137.8, 134.3, 133.9, 119.1, 112.1, 23.9;

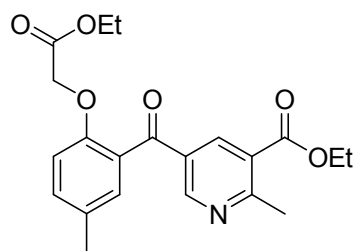
HRMS (ESI): Calculated for $C_{14}H_{12}BrO_4N_2$ [$M+H^+$]: 350.9975, 352.9955; Found: 350.9977, 352.9954;

5.4.7 Other modifications of the phenol moiety in pyridines

5.4.7.1 General procedure for the conversion of ethyl bromoacetic ester with pyridine derivatives

Pyridine derivative (1.0eq.), K_2CO_3 (1.0 eq.) and ethyl 2-bromoacetate (1.0 eq.) were dissolved in acetone (5 ml) and heated under an argon atmosphere for 10h at 50 °C. The acetone was removed in *vacuo*, water was added, and the mixture was extracted with EtOAc (3 × 20ml). The combined organic phases were dried over anhydrous $NaSO_4$, filtered and evaporated to give crude pyridine. The residue was purified by column chromatography.

Ethyl 5-(2-(2-ethoxy-2-oxoethoxy)-5-methylbenzoyl)-2-methylnicotinate



$C_{21}H_{23}NO_6$
Exact Mass: 385.15
Mol. Wt.: 385.41

a117;

White solid;

M.P.: 155-157°C;

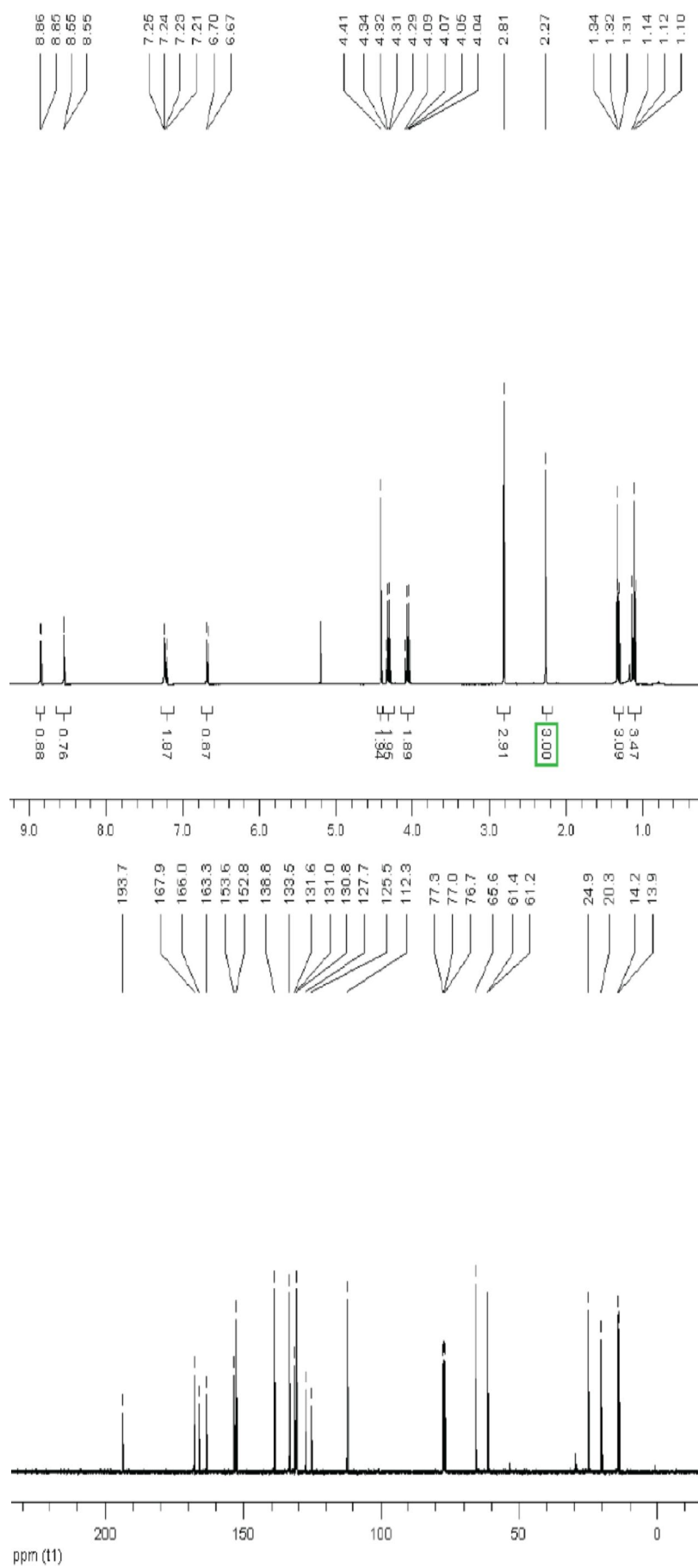
TLC: $R_f = 0.37$ PE/TtOAc (2:1);

1H NMR (400 MHz, MeOD): δ (ppm) = 8.85 (d, $J = 2.2$ Hz, 1H), 8.55 (d, $J = 2.2$ Hz, 1H), 7.29-7.11 (m, 2H), 6.68 (d, $J = 8.4$ Hz, 1H), 4.41 (s, 2H), 4.31 (q, $J = 7.1$ Hz, 2H), 4.06 (q, $J = 7.1$ Hz, 2H), 2.81 (s, 3H), 2.27 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 3H), 1.17 (t, $J = 7.1$ Hz, 3H);

^{13}C NMR (100 MHz, MeOD): δ (ppm) = 193.6, 167.9, 166.0, 163.3, 153.6, 152.7, 138.8, 133.4, 131.6, 131.0, 130.8, 127.6, 125.4, 112.3, 65.6, 61.4, 61.2, 24.9, 20.2, 14.1, 13.9;

GC-MS(EI): $t_R = 10.08$ min; m/z (rel. Int. [%]): 385 (20) $[M^+]$, 340 (29), 312 (79), 284 (76), 251 (70), 179 (100), 135 (96).

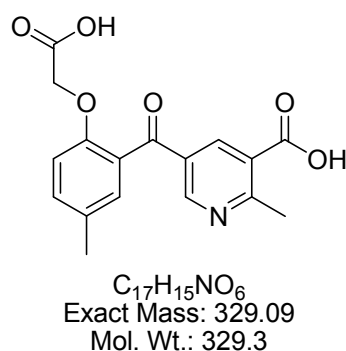
Experimental section



5.4.7.2 General procedure for hydrolysis to diacids

To a solution of ester **20** in THF/MeOH 2:1 (v/v) was added 1N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (3 × 20ml). The combined organic phases were dried over anhydrous MgSO₄, filtered and evaporated to give crude acid. The residue was purified by column chromatography.

5-(2-(carboxymethoxy)-5-methylbenzoyl)-2-methylnicotinic acid

**a118;**

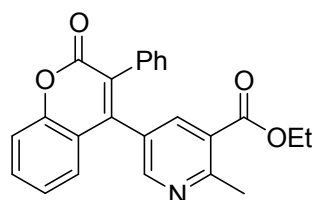
White solid;

M.P.: 175-176°C;**TLC:** R_f = 0.43 ethyl acetate/MeOH (5:2);**¹H NMR (400 MHz, DMSO-*d*₆):** δ 8.85 (d, J = 2.2 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H), 7.35 (ddd, J = 8.6 Hz, J = 2.3 Hz, J = 0.6 Hz, 1H), 7.26-7.23 (m, 1H), 6.97 (d, J = 8.6 Hz, 1H), 4.58 (s, 2H), 2.78 (s, 3H), 2.29 (s, 3H);**¹³C NMR (100 MHz, DMSO-*d*₆):** δ (ppm) = 193.6, 169.5, 167.0, 162.7, 153.3, 151.7, 138.3, 133.3, 130.4, 130.4, 129.7, 127.0, 125.8, 112.8, 64.8, 24.7, 19.8;**HRMS (ESI):** Calculated for C₁₇H₁₇NO₆ [M+H]⁺ 330.0972, found 330.0972.

5.4.7.3 General procedure for the synthesis of coumarin-derivates

Pyridine derivate (1.0 eq.), carbonyl diimidazole (2.0 eq.), K_2CO_3 (1.0 eq.), DMAP (0.1 eq.), and 2-substituted-acetic acid (2.0 eq.) were dissolved in DMF (5 ml) and heated under an argon atmosphere for 6h at 80 °C. After addition of EtOAc and brine, the biphasic mixture was several times extracted with brine. The combined organic phases were dried over anhydrous $NaSO_4$, filtered and evaporated to give crude phenol. The residue was purified by column chromatography.

Ethyl 2-methyl-5-(2-oxo-3-phenyl-2H-chromen-4-yl)nicotinate



$C_{24}H_{19}NO_4$
Exact Mass: 385.13
Mol. Wt.: 385.41

a119;

White solid;

M.P.: 175-176°C;

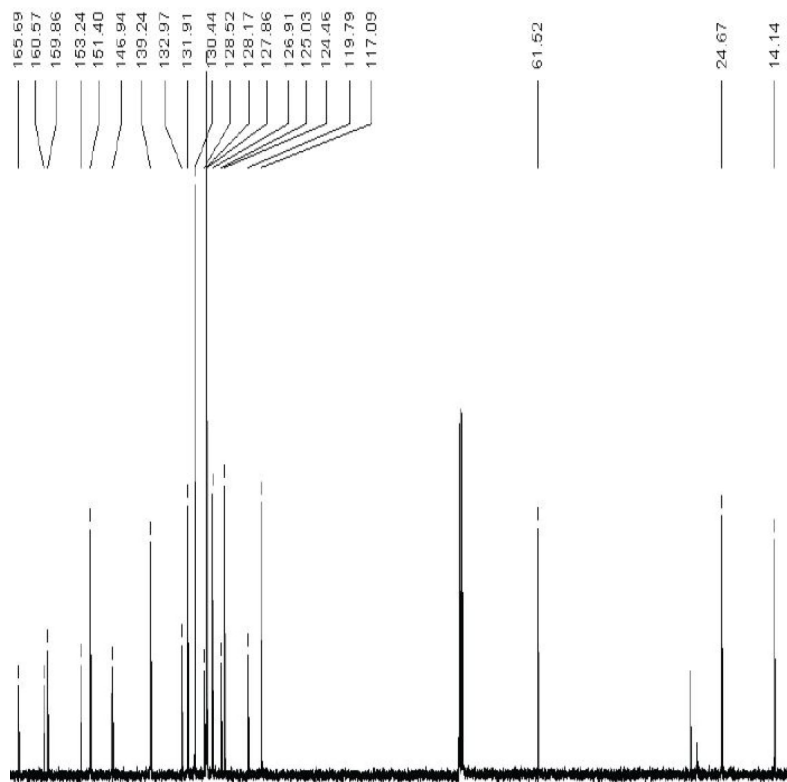
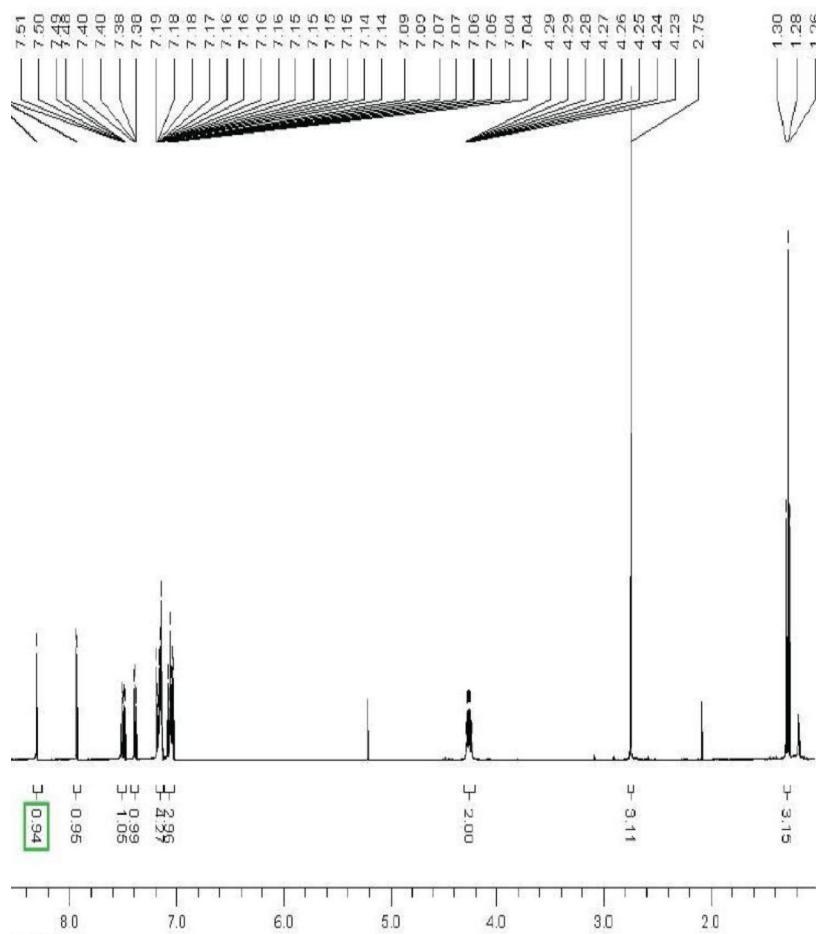
TLC: R_f = 0.42 PE/EtOAc (2:1);

1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.37 (d, J = 2.3 Hz, 1H), 8.05-7.95 (d, J = 2.3 Hz, 1H), 7.59-7.55 (m, 1H), 7.46-7.44 (m, 1H), 7.26-7.21 (m, 4H), 7.15-7.10 (m, 3H), 4.41-4.22 (q, J = 7.2 Hz, 2H), 2.38 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 165.7, 160.6, 159.9, 153.2, 151.4, 146.9, 139.2, 133.0, 131.9, 130.4, 128.5, 128.2, 127.9, 126.9, 125.0, 124.5, 119.8, 117.1, 61.5, 24.7, 14.2;

HRMS (ESI): Calculated for $C_{24}H_{20}NO_4$ $[M+H]^+$: 386.1387, found 386.1390.

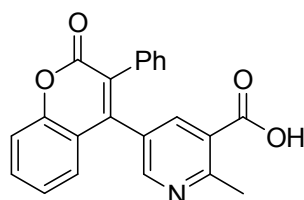
Experimental section



5.4.7.4 General procedure for hydrolysis of coumarins

To a solution of ester in THF/MeOH 2:1 (v/v) was added 1N NaOH solution (5.0 eq.) at 0°C and the reaction mixture was stirred for 16h (TLC control). The reaction mixture was acidified with 25% HCl to pH 3-4. After water was added, the mixture was extracted with EtOAc (3 × 20ml). The combined organic phases were dried over anhydrous NaSO₄, filtered and evaporated to give crude acid. The residue was purified by column chromatography.

2-methyl-5-(2-oxo-3-phenyl-2H-chromen-4-yl)nicotinic acid



C₂₂H₁₅NO₄
Exact Mass: 357.1
Mol. Wt.: 357.36

a120;

White solid;

M.P.: 175-176°C;

TLC: R_f = 0.37 ethyl acetate/MeOH (7:2);

¹H NMR (400 MHz, MeOD-*d*₄): δ 8.22 (d, *J* = 2.2 Hz, 1H), 8.10 (d, *J* = 2.2 Hz, 1H), 7.56 (ddd, *J* = 8.4 Hz, *J* = 7.3 Hz, *J* = 1.6 Hz, 1H), 7.40 (dd, *J* = 8.3 Hz, 0.8 Hz, 1H), 7.25-7.19 (m, 1H), 7.18-7.11 (m, 3H), 7.08 (ddd, *J* = 7.3 Hz, *J* = 4.7 Hz, *J* = 1.6 Hz, 3H), 2.67 (s, 3H);

¹³C NMR (400 MHz, MeOD-*d*₄): δ (ppm) = 167.2, 159.8, 158.1, 152.4, 150.7, 146.8, 138.6, 133.6, 131.8, 130.3, 127.7, 127.7, 127.5, 126.9, 124.6, 119.8, 116.4, 24.1;

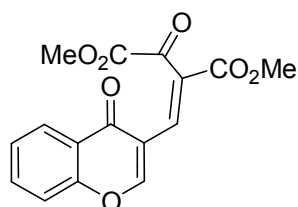
HRMS (ESI): Calculated for C₂₂H₁₆NO₄ [M+H]⁺: 358.10738, found 358.10736.

5.5 Experimental section: Chapter 3 (Substrate Controlled Branching Cascades)

5.5.1 Synthesis of common substrates

General procedure: The chromene (1.0mmol, 1.0eq), acetylene carboxylates, and PPh_3 (0.4mmol, 0.4eq) were mixed in 10ml toluene on the room temperature. The reaction mixture was stirred at room temperature for 8 hour under argon. The reaction was monitored by TLC using cyclohexane/ethyl acetate (5:1) as eluent. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate as the eluent

General procedure for the rearrangement of the adducts: TFA (1mL in 5 mL dichloromethane) was added slowly dropwise to the dichloromethane (5 mL) solution of the tricyclic benzopyrones (1 mmol). The reaction mixture was stirred at room temperature for 30 min under argon. The reaction was monitored by TLC using cyclohexane/ethyl acetate (7:3) as eluent. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate as the eluent



$\text{C}_{16}\text{H}_{12}\text{O}_7$
Exact Mass: 316.06
Mol. Wt.: 316.26

Yellow solid;

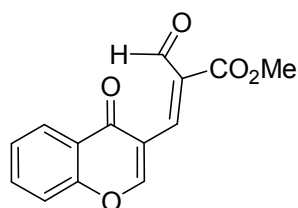
M.P.: 177°-178°C;

TLC: $R_f = 0.33$ (cyclohexane/ethyl acetate 6:4);

^1H NMR (400 MHz, CDCl_3): δ 8.32 (d, $J = 0.7$ Hz, 1H), 8.21-8.19 (dd, $J = 1.6$ Hz, $J = 8.0$ Hz, 1H), 7.63 (td, $J = 1.6, 7.8$ Hz, 1H), 7.50 (d, $J = 0.7$ Hz, 1H), 7.49-7.47 (dd, $J = 1.0, 7.4$ Hz, 1H), 7.43 (td, $J = 1.0, 7.4$ Hz, 1H), 3.98 (s, 3H), 3.82 (s, 3H).;

^{13}C NMR (100 MHz, CDCl_3): δ 180.8, 174.0, 164.8, 161.1, 159.6, 155.7, 134.6, 132.9, 131.6, 126.7, 126.2, 123.3, 118.3, 118.0, 53.1, 52.6.;

HRMS (ESI): Calculated for $\text{C}_{16}\text{H}_{13}\text{O}_7$ [$\text{M}+\text{H}^+$]: 317.0656, Found: 317.0657.



$\text{C}_{14}\text{H}_{10}\text{O}_5$
Exact Mass: 258.05
Mol. Wt.: 258.23

Yellow solid;

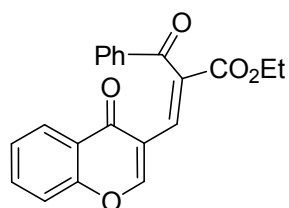
M.P. 120°-122°C;

TLC: $R_f = 0.39$ (cyclohexane/ethyl acetate 6:4);

^1H NMR (400 MHz, CDCl_3): δ 9.71 (s, 1H, CHO), 8.66 (d, $J = 0.8$ Hz, 1H), 8.28-8.24 (m, 2H), 7.73 (d, $J = 0.8$ Hz, 1H), 7.52-7.44 (m, 2H), 3.89 (s, 3H).;

^{13}C NMR (100 MHz, CDCl_3): δ 189.3, 174.8, 165.6, 158.4, 155.8, 140.8, 134.5, 133.8, 126.4, 126.3, 123.6, 118.4, 118.3, 52.6.;

HRMS (ESI): Calculated for $\text{C}_{14}\text{H}_{11}\text{O}_5$ [$\text{M}+\text{H}^+$]: 259.0601, Found: 259.0602.



$\text{C}_{21}\text{H}_{16}\text{O}_5$
Exact Mass: 348.1
Mol. Wt.: 348.35

Yellow solid;

M.P. 171°-173°C;

TLC: $R_f = 0.45$ (cyclohexane/ethyl acetate 6:4);

^1H NMR (400 MHz, CDCl_3): δ 8.18-8.16 (dd, $J = 1.3$ Hz, $J = 8.4$ Hz, 1H), 8.15 (d, $J = 1.0$ Hz, 1H), 8.05 (d, $J = 1.0$, 1H), 7.93-7.91 (dd, $J = 1.3$, 8.4 Hz, 1H), 7.63 (td, Hz, $J = 7.8$ Hz, 1H), 7.48-7.55-7.35 (m, 5H), 7.28-7.25 (m, 1H), 4.25-4.19 (q, $J = 7.1$ Hz, 2H), 1.17 (t, $J = 7.1$ Hz, 3H).;

^{13}C NMR (100 MHz, CDCl_3): δ 194.5, 175.2, 164.3, 156.2, 155.8, 140.6, 136.1, 134.1, 133.8, 132.9, 129.8, 129.0, 128.7, 128.5, 126.1, 125.7, 123.5, 119.0, 118.1, 61.5, 13.9.;

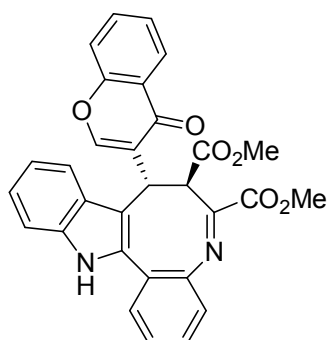
HRMS (ESI): Calculated for $\text{C}_{21}\text{H}_{17}\text{O}_5$ [$\text{M}+\text{H}^+$]: 349.1071, Found: 349.1072.

5.5.2. Bisnucleophilies

5.5.2.1 N, N-Bisnucleophilies

General procedure for synthesis of 8,13-dihydro-7*H*-benzo[2,3]azocino[4,5-*b*] indole-6-carboxylates and 10,14c-dihydroindolo[3,2-*c*]-pyrido[1,2-*a*] quinoline (b75-b81) from common precursor and bis-nucleophile b51.

2-(2-aminophenyl) indole (**b27**, 1,1 equiv.) was added to a anhydrous dichloromethane (25 mL) solution of ketoester (**b5**, 50 mg scale, 1 equiv.) under argon atmosphere. The color of solution turned straw yellow to red slowly. After completion of the reaction (monitored by TLC), then water (20 mL) was added to the reaction mixture to quench the reaction and the mixture extracted with ethyl acetate(2 *10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and then evaporated in vacuo. The crude residue was purified by column chromatography over silica gel using cyclohexane/ethyl acetate (4:1) as eluent to afford pure yellow solid-8,13-dihydro-7*H*-benzo[2,3]azocino[4,5-*b*] indole-6-carboxylates **b52** 62% and red solid-10,14c-dihydroindolo[3,2-*c*]-pyrido[1,2-*a*] quinoline **b53** 31%



$C_{30}H_{22}N_2O_6$
 Exact Mass: 506.15
 Mol. Wt.: 506.51

b54 (mixture of two diastereoisomers ~ 5:1),

Yield 62%;

Yellow solid;

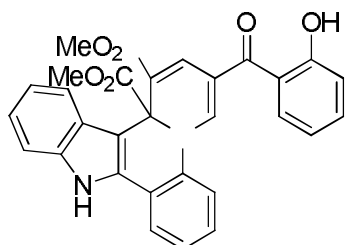
M.P.: 192°C;

TLC: R_f = 0.64 cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.95 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.52-7.48 (m, 2H), 7.34 (s, 1H), 7.32 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.25 (s, 1H), 7.23 (s, 1H), 7.16-7.10 (m, 2H), 5.41 (d, J = 12.0 Hz, 1H), 4.85 (d, J = 12.0 Hz, 1H), 3.84 (s, 3H), 3.57 (s, 3H);

^{13}C NMR (100MHz, $CDCl_3$): δ 176.2, 169.5, 163.4, 158.7, 155.8, 153.9, 146.2, 135.8, 133.1, 131.2, 130.3, 129.2, 127.3, 126.1, 125.9, 125.5, 124.7, 124.1, 123.6, 122.7, 122.1, 119.9, 119.1, 117.7, 114.2, 110.8, 53.1, 52.1, 48.6, 34.3;

HRMS (ESI): Calculated for $C_{30}H_{23}O_6N_2$ [$M+H^+$]: 507.1551, Found: 507.1546.



Chemical Formula: $C_{30}H_{23}N_2O_6$
 Exact Mass: 506.15
 Molecular Weight: 506.51

b55;

Yield 31%;

red solid;

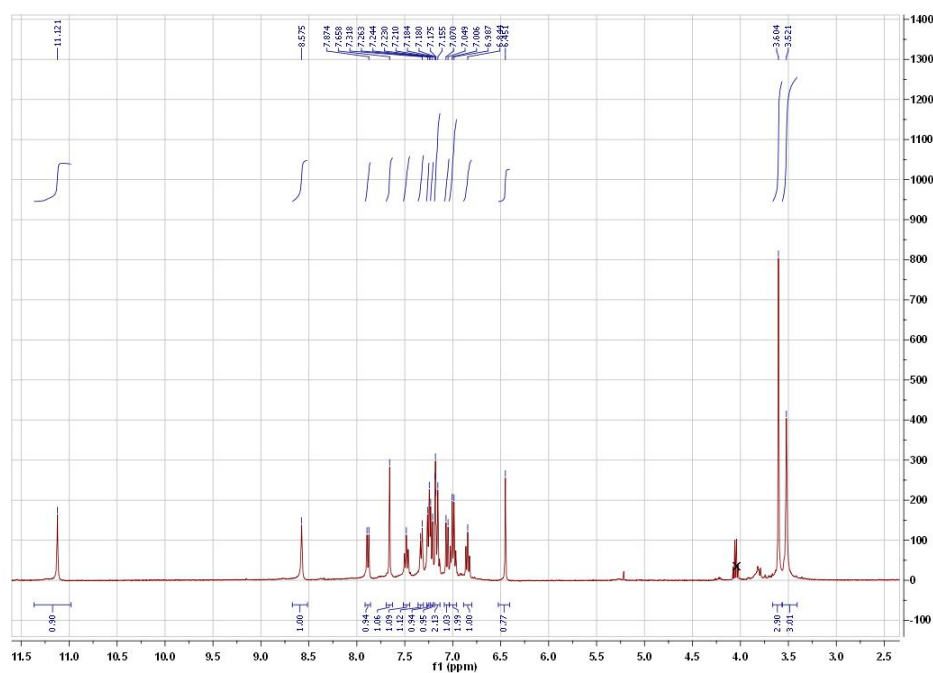
M.P.: 150°C;

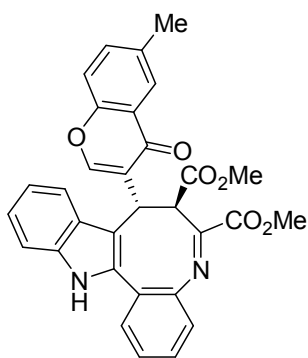
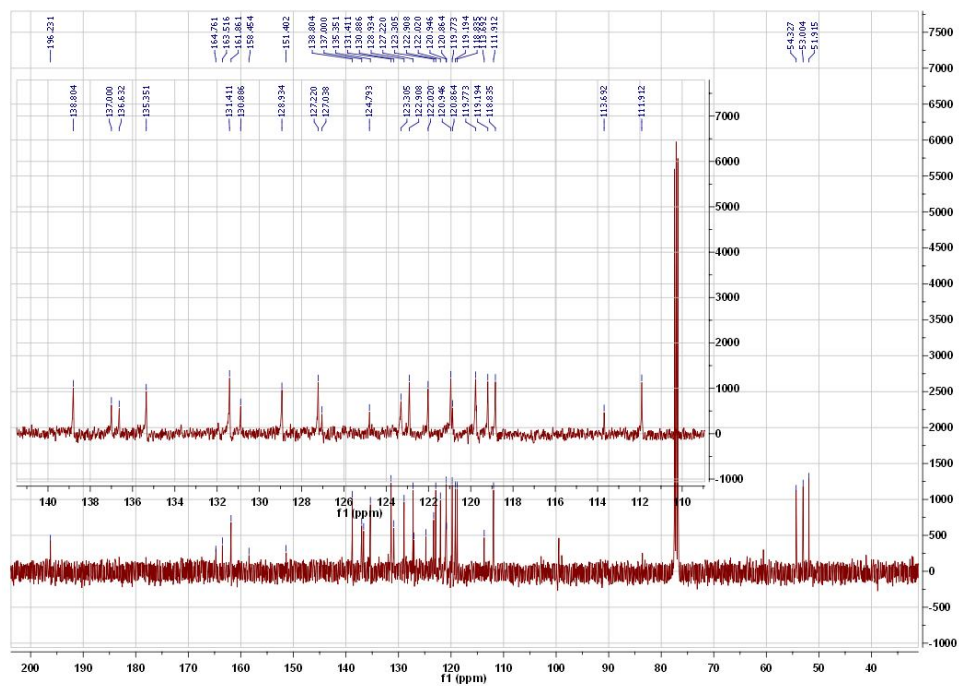
TLC: $R_f = 0.40$ cyclohexane/ethyl acetate (2:1);

^1H NMR (400 MHz, CDCl_3): δ 11.12 (s, 1H), 8.58 (s, 1H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.66 (s, 1H), 7.48 (d, $J = 7.6$ Hz, 1H), 7.33 (d, $J = 7.6$ Hz, 1H), 7.25 (d, $J = 7.2$ Hz, 1H), 7.22 (d, $J = 8.0$ Hz, 1H), 7.18-7.15 (m, 2H), 7.06 (t, $J = 8.4$ Hz, 1H), 7.00 (q, $J = 7.6$ Hz, 2H), 6.84 (d, $J = 7.6$ Hz, 1H), 6.45 (s, 1H), 3.60 (s, 3H), 3.52 (s, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 196.1, 164.6, 163.4, 161.7, 138.6, 136.8, 136.5, 135.2, 131.30, 131.25, 130.7, 128.8, 127.1, 126.9, 124.6, 123.1, 122.7, 121.9, 120.8, 120.7, 119.61, 119.57, 119.0, 118.7, 113.5, 111.8, 99.3, 52.8, 51.8;

HRMS (ESI): Calculated for $\text{C}_{30}\text{H}_{23}\text{O}_6\text{N}_2$ $[\text{M}+\text{H}^+]$: 507.1551, Found: 507.1542.;





$C_{31}H_{24}N_2O_6$
Exact Mass: 520.16
Mol. Wt.: 520.53

b56;

Yield 65%;

Yellow solid;

M.P.: 278°C;

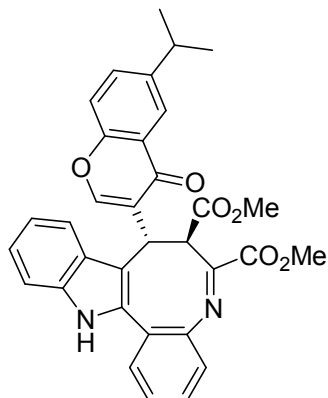
TLC: $R_f = 0.58$ cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.84 (s, 1H), 7.78 (s, 1H), 7.63 (d, $J = 8.0$ Hz, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.42 (t, $J = 7.6$ Hz, 1H), 7.30-7.22 (m, 3H), 7.18-7.16 (m, 1H), 7.11-7.01 (m, 3H), 5.32 (d, $J = 12.0$ Hz, 1H), 4.77 (d, $J = 12.0$ Hz, 1H), 3.76 (s, 3H), 3.49 (s, 3H), 2.24 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 169.5, 163.4, 158.8, 154.1, 153.8, 146.3, 135.8, 134.6, 134.3, 131.19, 131.16, 130.3, 129.2, 127.3, 126.2, 125.3, 123.8, 123.7, 122.8,

122.1, 120.0, 119.1, 117.5, 114.4, 110.7, 60.4, 53.1, 52.1, 48.7, 34.2;

HRMS (ESI): Calculated for $C_{31}H_{25}O_6N_2$ $[M+H]^+$: 521.1707, Found: 521.1701.



$C_{33}H_{28}N_2O_6$
Exact Mass: 548.19
Mol. Wt.: 548.59

b58

Yield 64%;

Yellow solid;

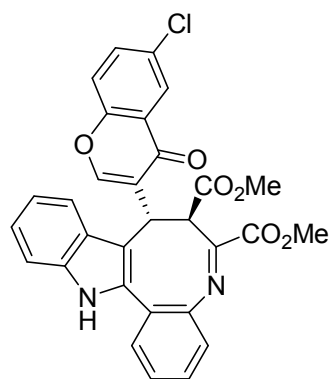
M.P.: 157°C;

TLC: R_f = 0.45 cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.93 (s, 1H), 7.92 (d, J = 2.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.43-7.35 (m, 3H), 7.25-7.21 (m, 1H), 7.16 (t, J = 7.2 Hz, 1H), 7.11 (t, J = 7.2 Hz, 1H), 5.40 (d, J = 12.0 Hz, 1H), 4.85 (d, J = 12.0 Hz, 1H), 3.86 (s, 3H), 3.57 (s, 3H), 2.92 (m, 1H), 1.20 (d, J = 6.8 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 169.5, 163.4, 158.8, 154.3, 153.8, 146.3, 145.6, 135.8, 132.1, 131.2, 130.4, 129.3, 127.4, 126.2, 125.2, 123.9, 123.7, 122.9, 122.7, 122.2, 120.0, 119.2, 117.4, 114.5, 110.7, 53.2, 52.2, 48.7, 34.3, 33.7, 23.9, 23.8;

HRMS (ESI): Calculated for $C_{33}H_{28}O_6N_2$ $[M+H]^+$: 549.2020, Found: 549.2014.



$C_{30}H_{21}ClN_2O_6$
 Exact Mass: 540.11
 Mol. Wt.: 540.95

b59;

Yield 59%;

Yellow solid;

M.P.: 185°C;

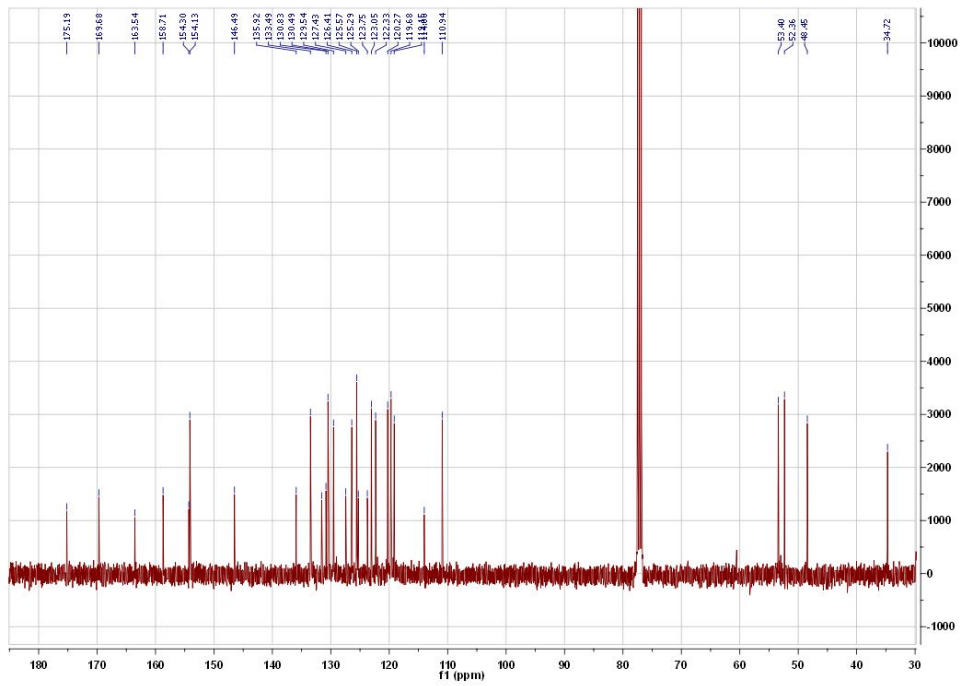
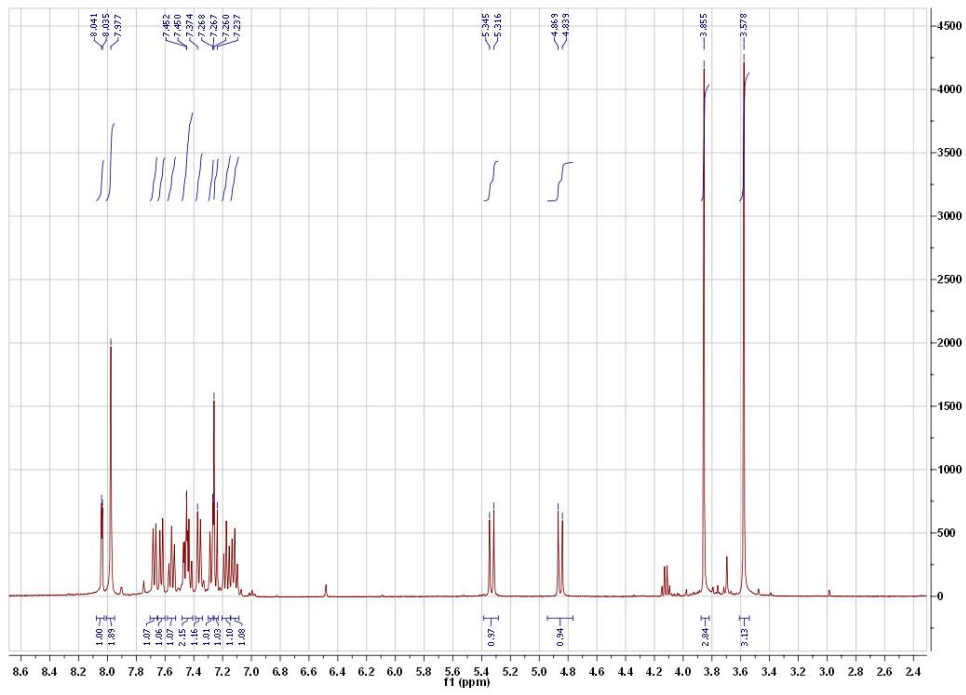
TLC: $R_f = 0.43$ cyclohexane/ethyl acetate (2:1);

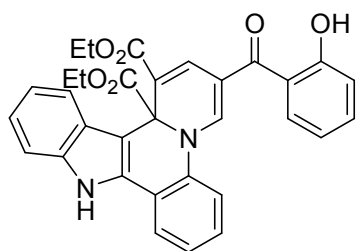
1H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, $J = 2.8$ Hz, 1H), 7.98 (s, 1H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.63 (d, $J = 7.6$ Hz, 1H), 7.56 (t, $J = 7.6$ Hz, 1H), 7.47-7.41 (m, 2H), 7.36 (d, $J = 7.6$ Hz, 1H), 7.29-7.24 (m, 2H), 7.19-7.10 (m, 2H), 5.33 (d, $J = 12.0$ Hz, 1H), 4.85 (d, $J = 12.0$ Hz, 1H), 3.86 (s, 3H), 3.58 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0, 169.5, 163.4, 158.6, 154.1, 154.0, 146.3, 135.8, 133.3, 131.4, 130.7, 130.3, 129.4, 127.3, 126.3, 125.4, 125.1, 123.6, 122.9, 122.2, 120.1, 119.5, 119.0, 113.8, 110.8, 53.2, 52.2, 48.3, 34.6;

HRMS (ESI): Calculated for $C_{30}H_{22}ClO_6N_2 [M+H^+]$: 541.1161, Found: 541.1154.

Experimental section





$C_{32}H_{26}N_2O_6$
Exact Mass: 534.18
Mol. Wt.: 534.56

b61:

Yield 29%;

Red solid;

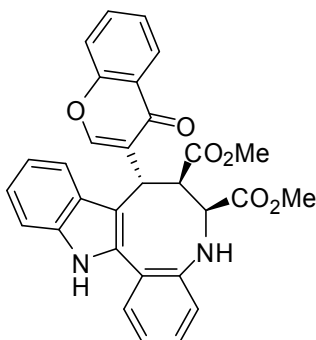
M.P.: 141°C;**TLC:** $R_f = 0.37$ cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 11.22 (s, 1H), 8.52 (s, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.77 (s, 1H), 7.55 (t, $J = 8.4$ Hz, 1H), 7.44 (d, $J = 6.8$ Hz, 1H), 7.40-7.35 (m, 3H), 7.27 (t, $J = 8.4$ Hz, 1H), 7.14 (s, 1H), 7.12 (s, 1H), 7.04 (t, $J = 7.2$ Hz, 1H), 6.95 (t, $J = 7.2$ Hz, 1H), 6.51 (s, 1H), 4.13 (q, $J = 6.8$ Hz, 2H), 4.01 (q, $J = 6.8$ Hz, 2H), 1.21 (t, $J = 6.8$ Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 164.0, 162.7, 161.7, 139.2, 136.8, 136.7, 135.2, 131.3, 130.8, 128.7, 127.1, 127.0, 124.8, 123.8, 122.9, 121.5, 120.9, 120.5, 119.8, 119.6, 118.9, 118.7, 113.9, 111.7, 99.6, 62.2, 54.1, 14.1, 13.6;

HRMS (ESI): Calculated for $C_{32}H_{26}O_6N_2$ [$M+H^+$]: 535.1864, Found: 535.1857;

A mixture of **b54** and 20%Pd(OH)₂/C(0.1eq) degassed methol under hydrogen balloon at the room temperature for overnight. The reaction was monitored by TLC. Filtered Pd(OH)₂/C with diatomite carefully, and concentrated to remove most of methol(not very dry), added water, the solution was extracted with EtOAc, the organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The product was purified by chromatography on silica gel eluted with a gradient of ethyl cyclohexane/ethyl acetate 10/1 to 4/1 to two products each 46% yield as yellow solids.



Chemical Formula: $C_{30}H_{24}N_2O_6$

Exact Mass: 508,1634

Molecular Weight: 508,5214

b62:

Yield 46%;

Yellow solid;

M.P.: 153-155°C;

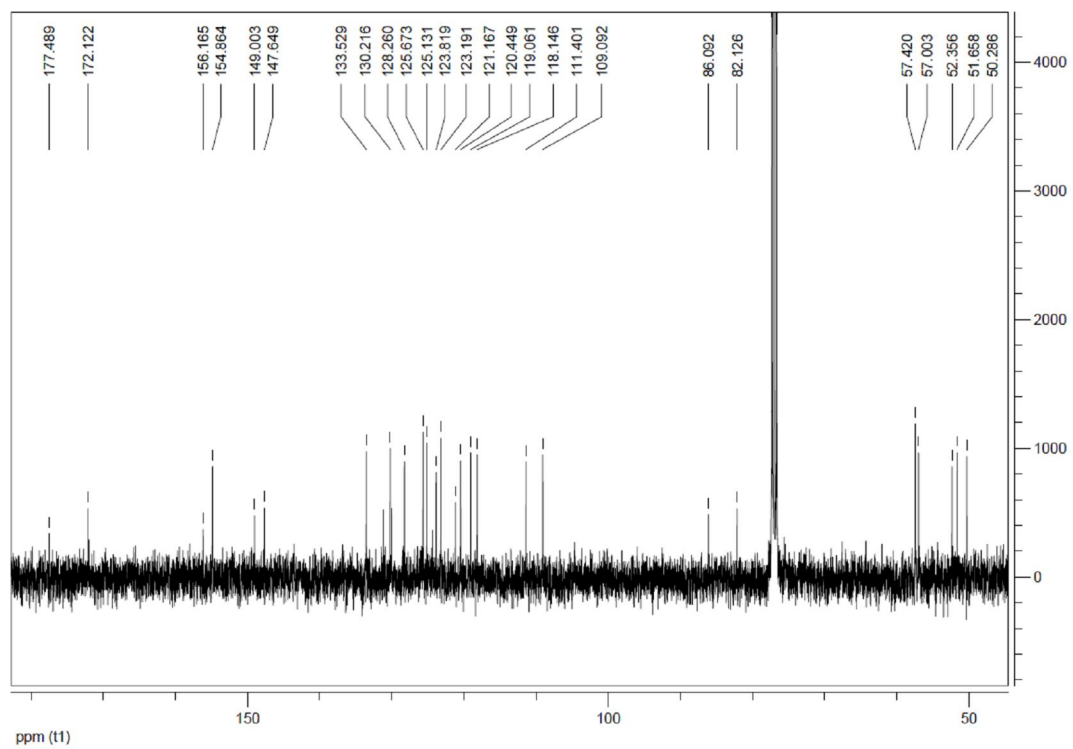
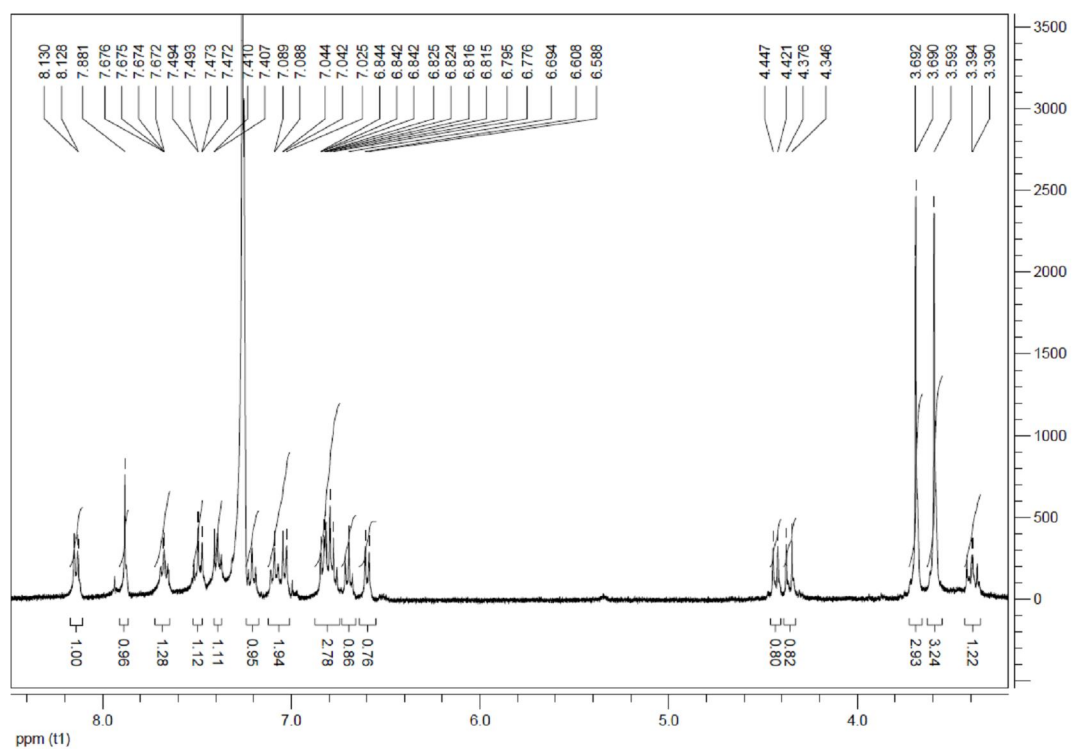
TLC: $R_f = 0.39$; cyclohexane/ethyl acetate (2:1);

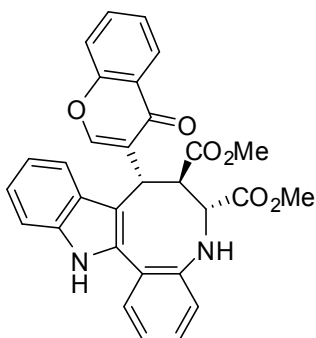
1H NMR (400 MHz, $CDCl_3$): 8.06 (d, $J = 8.0$ Hz, 1H), 7.81 (s, 1H), 7.60 (d, $J = 7.6$ Hz, 1H), 7.41 (d, $J = 8.0$ Hz, 1H), 7.32 (t, $J = 7.2$ Hz, 1H), 7.19 (s, 1H), 7.14 (t, $J = 7.6$ Hz, 1H), 7.02 (t, $J = 7.2$ Hz, 1H), 6.96 (d, $J = 7.6$ Hz, 1H), 6.71-6.68 (m, 3H), 6.62 (t, $J = 7.2$ Hz, 1H), 6.52 (d, $J = 7.2$ Hz, 1H), 4.36 (d, $J = 10.4$ Hz, 1H), 4.29 (d, $J = 12.0$ Hz, 1H), 3.62 (s, 3H), 3.52 (s, 3H), 3.32 (dt, $J = 12.0, 1.6$ Hz, 1H);

^{13}C NMR (100MHz, $CDCl_3$): 177.5, 172.1, 156.2, 154.9, 149.0, 147.6, 133.5, 131.2, 130.2, 130.0, 128.3, 125.7, 125.1, 124.4, 123.8, 123.2, 121.2, 120.4, 119.1, 118.1, 111.4, 109.1, 86.1, 82.1, 57.4, 57.0, 52.4, 51.7, 50.3;

HRMS (ESI): Calculated for $C_{30}H_{25}O_6N_2 [M+H^+]$: 509.1707, Found: 509.1698;

Experimental section





Chemical Formula: $C_{30}H_{24}N_2O_6$
 Exact Mass: 508,1634
 Molecular Weight: 508,5214

b63;

Yield 46%;

Yellow solid;

M.P. : 148.1°C;

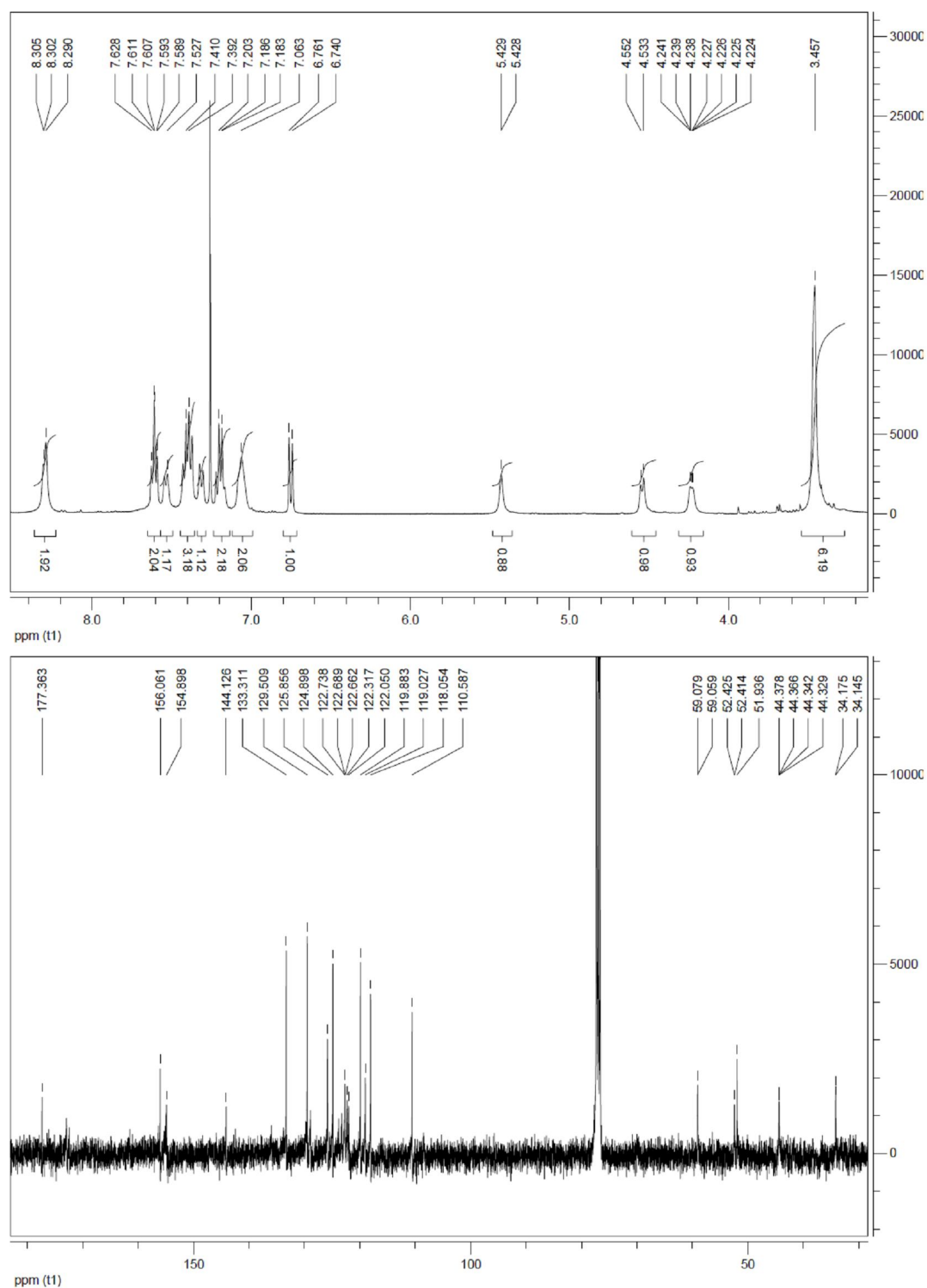
TLC : R_f = 0.36 cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): 8.29 (s, 2H), 7.61 (t, J = 7.6 Hz, 2H), 7.53 (t, J = 7.6 Hz, 1H), 7.40 (q, J = 7.6 Hz, 3H), 7.31 (d, J = 8.0 Hz, 1H), 7.22-7.17 (m, 2H), 7.06 (s, 2H), 6.75 (d, J = 8.0 Hz, 1H), 5.43 (s, 1H), 4.54 (d, J = 7.6 Hz, 1H), 4.23 (d, J = 7.6 Hz, 1H), 3.46 (s, 6H);

^{13}C NMR (100MHz, $CDCl_3$): 177.4, 173.0, 156.1, 154.9, 144.1, 133.3, 129.5, 129.0, 128.9, 125.9, 124.9, 123.8, 123.3, 122.74, 122.69, 122.66, 122.35, 122.32, 122.1, 122.0, 119.97, 119.88, 119.0, 118.1, 110.6, 59.1, 52.4, 51.9, 44.4, 34.1;

HRMS (ESI): Calculated for $C_{30}H_{24}O_6N_2$ [$M+H^+$]:509.1707, Found: 509.1700;

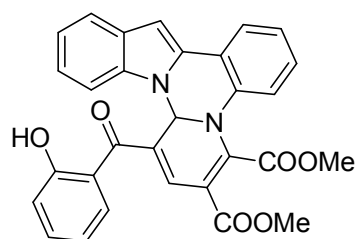
Experimental section



General procedure for synthesis of 9a*H*-indolo[1,2-*c*]pyrido[1,2-*a*]quinazolines (**5b**) from common precursor and bis-nucleophile **b27**.

Triethylamine (3,0 equiv.) was added to a degassed dichloromethane (20 mL) solution

of ketoester (1 mmol.) and 2-(2-aminophenyl)indole (1.2 mmol.). The reaction mixture was stirred at room temperature for 3-5 h under argon. The color of solution turned straw yellow into red slowly. The reaction was monitored by TLC using cyclohexane/ethyl acetate (2:1) as eluent. Water (20 mL) was then added to the reaction mixture and the mixture extracted with ethyl acetate (2*10 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and then evaporated in vacuo. The crude residue was purified by column chromatography over silica gel using cyclohexane/ethyl acetate (4:1) as eluent to afford red solid. Following is the spectroscopic data for the representative compounds.



C₃₀H₂₂N₂O₆
Exact Mass: 506.15
Mol. Wt.: 506.51

b68;

Yield 91%;

Red solid;

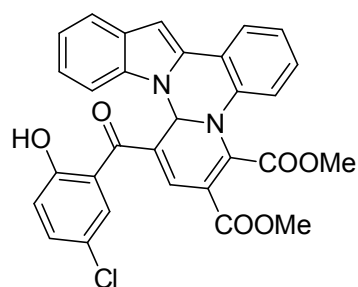
M.P.: 191°C;

TLC: R_f = 0.39 cyclohexane/ethyl acetate (2:1);

¹H NMR (400 MHz, CDCl₃): δ 11.04 (s, 1H), 8.15(s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.63-7.56 (m, 2H), 7.49-7.45 (m, 1H), 7.33-7.31 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H) 7.07 (s, 1H), 7.05-7.03 (m, 2H), 7.01 (s, 1H), 3.94 (s, 1H), 3.74 (s, 3H) , 3.63 (s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 195.1, 163.9, 162.6, 161.9, 149.3, 140.1, 136.9, 135.6, 134.4, 134.3, 131.1, 129.1, 128.8, 127.5, 127.3, 125.3, 123.1, 122.5, 121.4, 120.1, 119.3, 119.2, 118.9, 115.7, 111.3, 101.7, 100.3, 66.7, 53.1, 52.1;

HRMS (ESI): Calculated for C₃₀H₂₃O₆N₂ [M+H⁺]:507.1551, Found: 507.1544;



$C_{30}H_{21}ClN_2O_6$
 Exact Mass: 540.11
 Mol. Wt.: 540.95

b69;

Yield 86%;

Red solid;

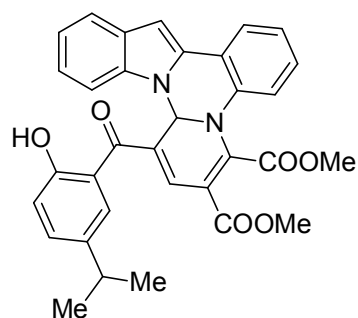
M.P.: 169°C;

TLC: $R_f = 0.41$ cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 10.71 (s, 1H), 8.40(s, 1H), 8.07 (s, 1H), 7.81-7.78 (m, 1H), 7.54 (dd, $J = 6.0, 3.2$ Hz, 1H), 7.44 (dd, $J = 9.2, 2.4$ Hz, 1H), 7.41-7.38 (m, 1H), 7.25-7.24 (m, 1H), 7.13 (dd, $J = 6.0, 3.2$ Hz, 1H), 7.04 (s, 1H) 7.00-6.97 (m, 2H), 6.94 (s, 1H), 6.92 (s, 1H), 3.97 (s, 1H), 3.69 (s, 3H), 3.56(s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 163.8, 162.5, 160.2, 140.6, 149.7, 137.2, 135.6, 135.4, 134.1, 131.7, 130.2, 129.3, 128.8, 127.6, 125.4, 124.0, 123.2, 122.5, 121.5, 120.5, 120.4, 120.2, 115.1, 111.2, 102.0, 100.5, 66.9, 53.2, 52.2;

HRMS (ESI): Calculated for $C_{30}H_{21}ClO_6N_2$ [$M+H^+$]: 541.1088, Found: 541.1153;



$C_{33}H_{28}N_2O_6$
 Exact Mass: 548.19
 Mol. Wt.: 548.59

B70;

Yield 87%;

Red solid;

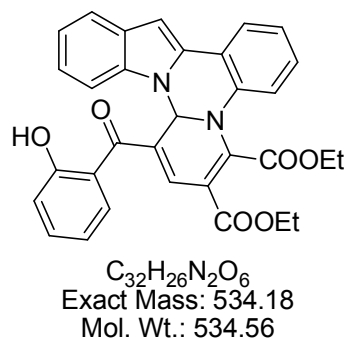
M.P.: 177°C;

TLC: R_f = 0.37 cyclohexane/ethyl acetate (2:1);

^1H NMR (400 MHz, CDCl_3): δ 10.86 (s, 1H), 8.19(s, 1H), 7.87-7.85 (m, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.2 Hz, 2H), 7.37-7.30 (m, 3H), 7.16 (s, 1H), 7.09-7.01 (m, 3H), 3.95 (s, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.00 (m, 1H), 1.35 (d, J = 7.2 Hz, 6H);

^{13}C NMR (100 MHz, CDCl_3): δ 195.1, 163.9, 162.6, 159.9, 149.0, 140.2, 139.4, 136.7, 135.6, 134.7, 134.4, 134.3, 129.1, 128.4, 127.5, 127.4, 125.3, 123.0, 122.5, 121.4, 120.1, 118.8, 118.5, 115.9, 111.2, 101.5, 100.3, 66.5, 53.1, 51.9, 33.3, 24.1, 24.0;

HRMS (ESI): Calculated for $\text{C}_{33}\text{H}_{29}\text{O}_6\text{N}_2$ [$\text{M}+\text{H}^+$]: 549.2020, Found: 549.2012;



B71;

Yield 88%;

Red solid;

M.P.: 179°C;

TLC: R_f = 0.48 cyclohexane/ethyl acetate (2:1);

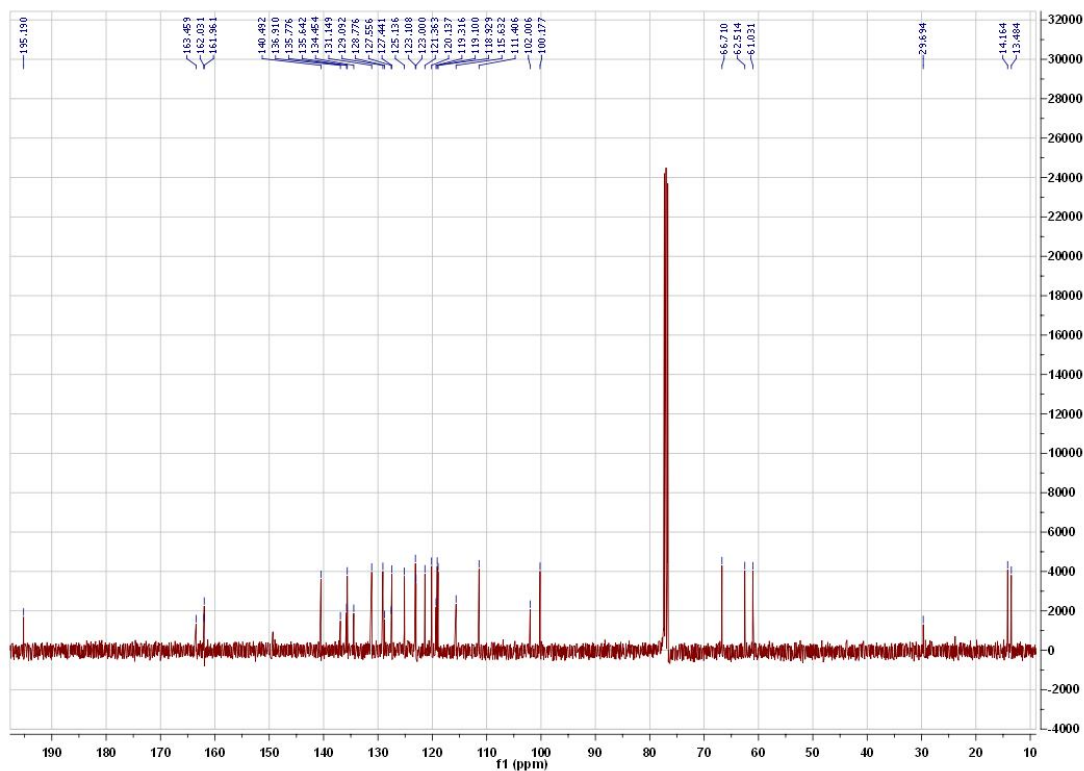
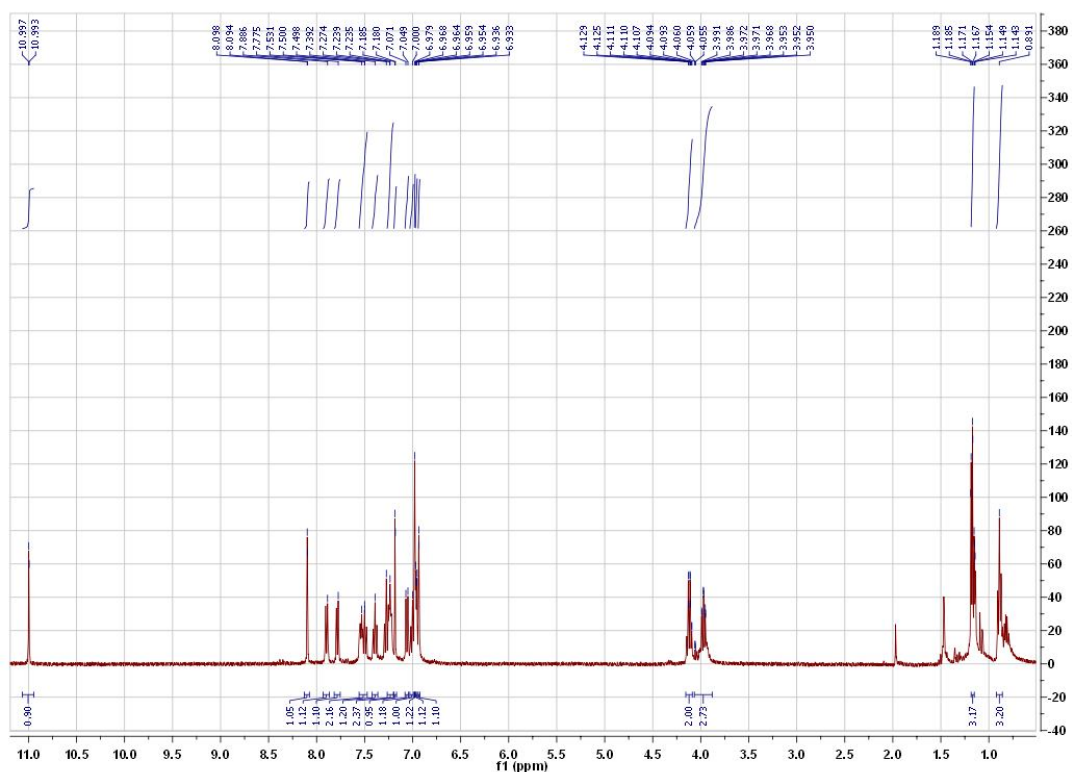
^1H NMR (400 MHz, CDCl_3): δ 10.99 (s, 1H), 8.09(s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.55-7.48 (m, 2H), 7.39 (t, J = 7.6 Hz, 1H), 7.25-7.22 (m, 2H), 7.18 (d, J = 2.0 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H) 7.02-6.95 (m, 3H), 6.93 (s, 1H), 4.11 (q, J = 7.2 Hz, 2H), 4.06-3.95 (m, 3H), 1.17 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H);

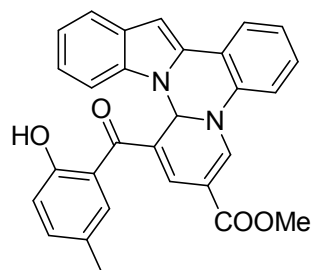
^{13}C NMR (100 MHz, CDCl_3): δ 195.2, 163.5, 162.03, 161.96, 149.3, 140.5, 140.0, 135.8, 135.6, 134.5, 131.1, 129.1, 128.8, 127.6, 127.4, 125.1, 123.1, 123.0, 121.4,

Experimental section

120.1, 119.3, 119.1, 118.9, 115.6, 111.4, 102.0, 100.2, 66.7, 62.5, 61.0, 14.2, 13.5;

HRMS (ESI): Calculated for $C_{32}H_{27}O_6N_2 [M+H]^+$: 535.1864, Found: 535.1857;





$C_{29}H_{22}N_2O_4$
Exact Mass: 462.16
Mol. Wt.: 462.5

b72;

Yield 71%;

Yellow solid;

M.P.: 151°C;

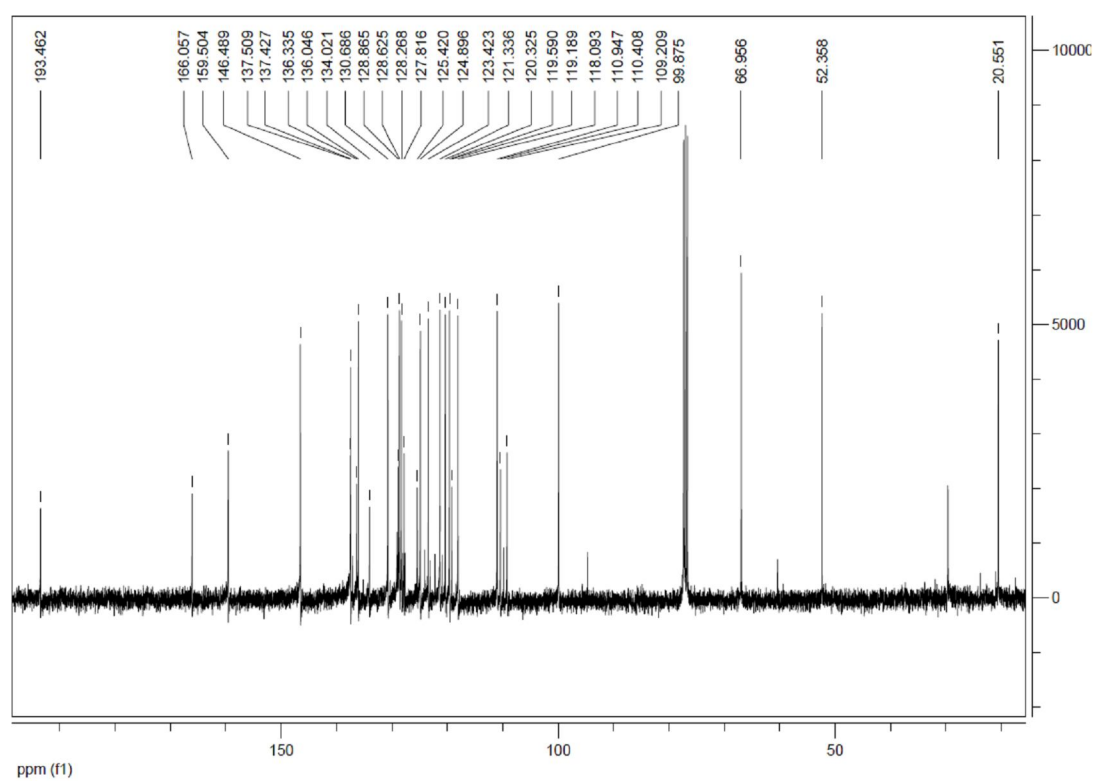
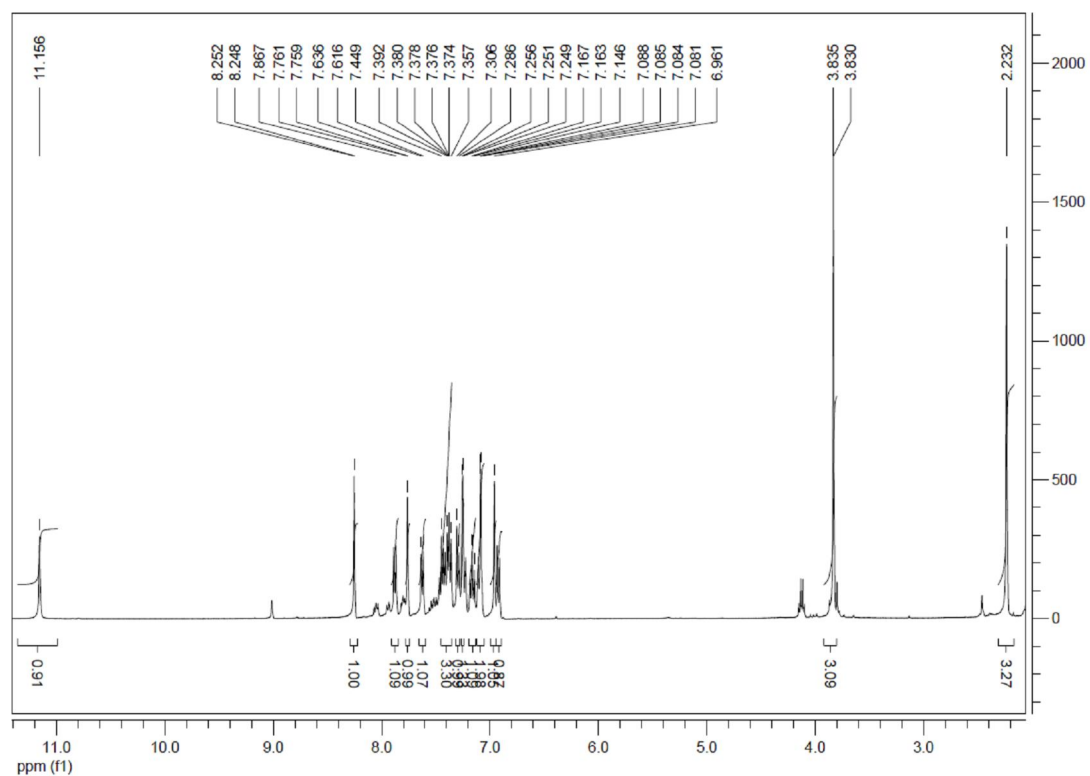
TLC: $R_f = 0.43$ hexane/EA (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 11.16 (s, 1H), 8.25 (d, $J = 2.4$ Hz, 1H), 7.87 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.60 (s, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.45-7.36 (m, 3H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.26-7.25 (m, 1H), 7.16 (dt, $J = 8.0, 1.6$ Hz, 1H), 7.18-7.08 (m, 2H), 6.96 (s, 1H), 6.92 (d, $J = 8.0$ Hz, 1H), 3.83 (s, 3H), 2.23 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 166.1, 159.5, 146.5, 137.5, 137.4, 136.3, 136.0, 134.0, 130.7, 128.9, 128.6, 128.3, 127.8, 125.4, 124.9, 123.4, 121.3, 120.3, 119.6, 119.2, 118.1, 110.9, 110.4, 109.2, 99.9, 67.0, 52.4, 20.6;

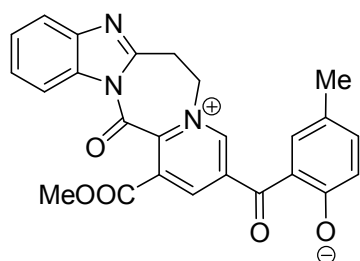
HRMS (ESI): Calculated for $C_{29}H_{23}O_4N_2$ [$M+H^+$]: 463.1652, Found: 463.1638;

Experimental section



General procedure for synthesis of benzimidazo[1,2-*d*]pyrido[1,2-*a*]-[1,4]diazepinium-3-carbonyl)phenolate internal salts (b78-b81) from common precursor 1 and bis-nucleophile b28.

Triethylamine (3.0 mmol.) was added to a anhydrous dichloromethane (10 mL) solution of ketoester (1 mmol, 1 equiv.) and 2-(1H-benzo[d]imidazol-2-yl) ethanamine 2xHCl salt (1 mmol.). The reaction mixture was stirred at room temperature for 2-4 h under argon. The color of solution turned colorless into yellow slowly. The reaction was monitored by TLC using dichloromethane/methanol (5:1) as eluent. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate as the eluent.



$C_{25}H_{19}N_3O_5$
Exact Mass: 441.13
Mol. Wt.: 441.44

b77;

Yield 91%;

Yellow solid;

M.P.: 154°C;

TLC: R_f = 0.61 DCM/methol (5:1);

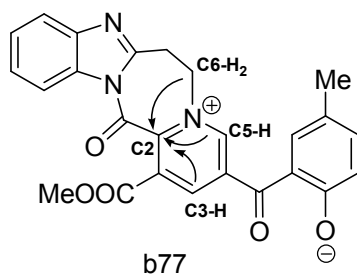
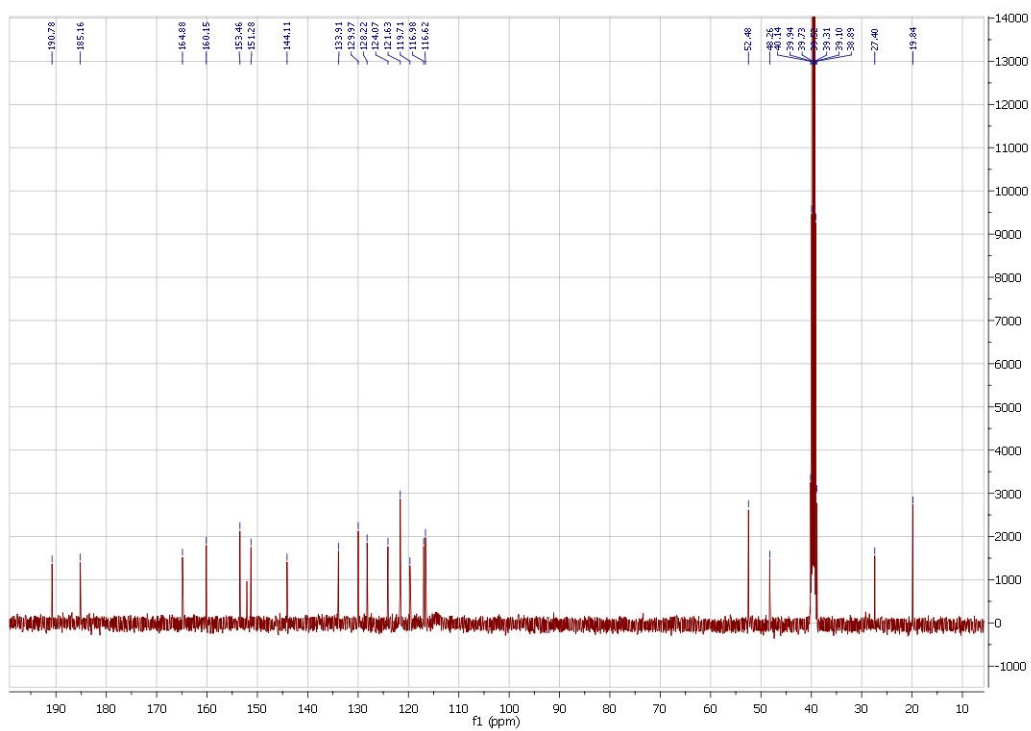
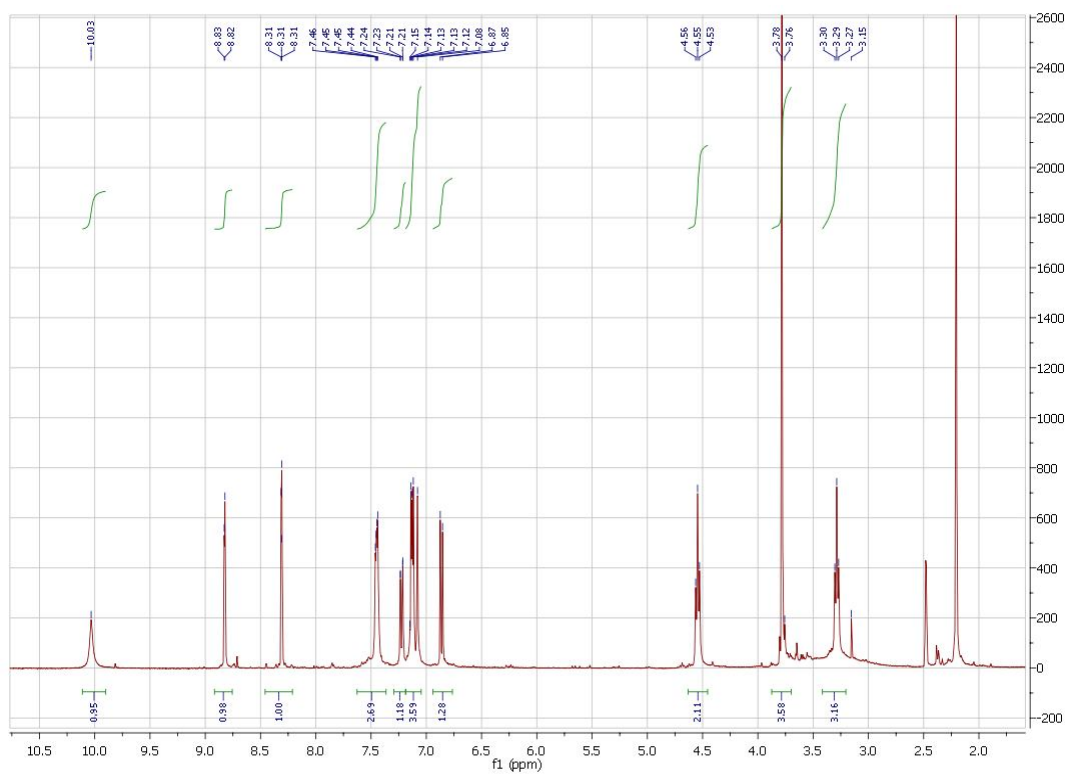
1H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.39 (d, J = 2.0 Hz, 1H), 7.48 (t, J = 4.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 1H), 7.17-7.15 (m, 2H), 7.12 (s, 1H), 6.92 (d, J = 8.4 Hz, 1H), 4.64 (t, J = 6.4 Hz, 2H), 3.89 (s, 3H), 3.54-3.52 (m, 2H), 2.18 (s, 3H) ;

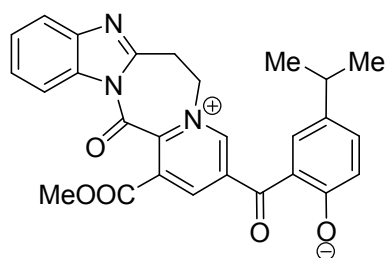
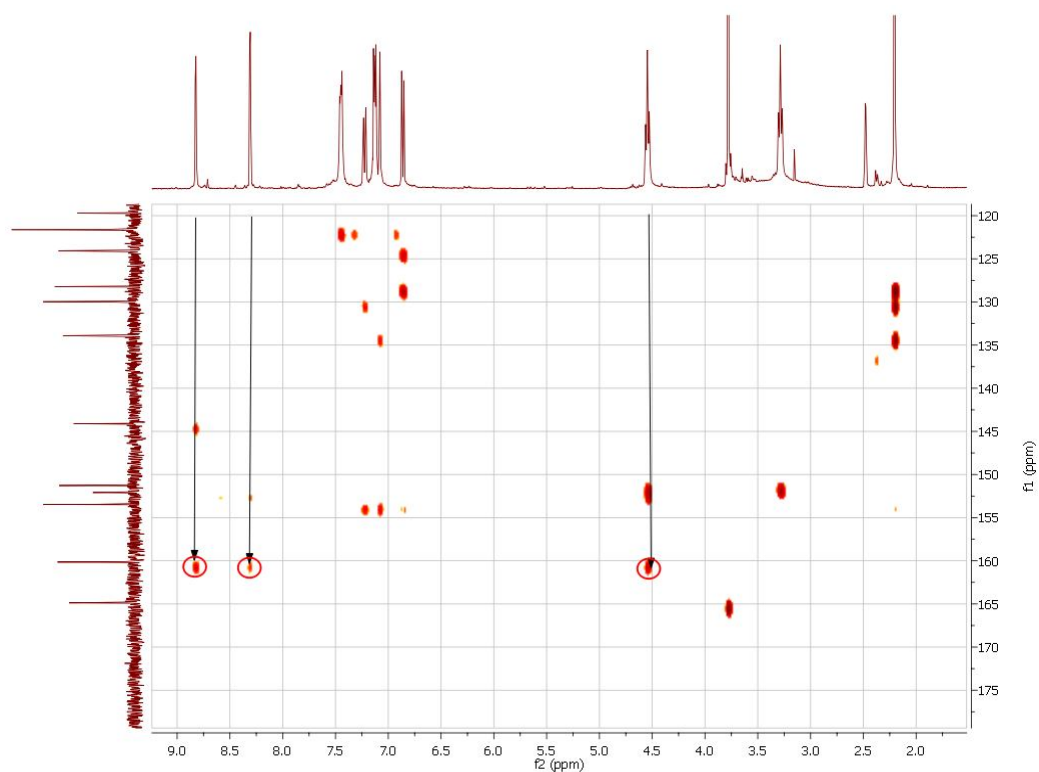
^{13}C NMR (100 MHz, DMSO): δ 193.5, 184.2, 164.9, 160.6, 160.1, 149.7, 149.6, 144.6, 137.7, 131.0, 128.7, 123.21, 123.13, 123.12, 123.10, 121.6, 121.58, 118.5, 118.2, 117.7, 109.8, 52.9, 49.4, 27.9, 20.4;

HRMS (ESI): Calculated for $C_{25}H_{21}O_6N_3$ [$M+H^+$]: 460.1503, Found: 460.1495;

1H , ^{13}C and HMBC Spectra measured in DMSO- d_6 solvent

Experimental section





$C_{27}H_{23}N_3O_5$
 Exact Mass: 469.16
 Mol. Wt.: 469.49

b78;

Yield 82%;

Yellow solid;

M.P.: 149°C;

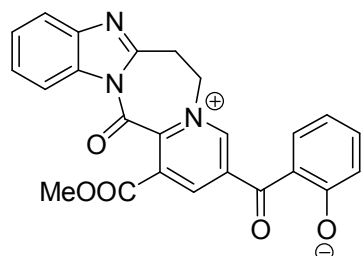
TLC: R_f = 0.32 DCM/methol (5:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.40 (s, 1H), 7.48 (d, J = 4.0 Hz, 2H), 7.36 (dd, J = 8.0, 2.0 Hz, 1H), 7.20 (d, J = 2.4 Hz, 1H), 7.16-7.13 (m, 2H), 6.95 (d, J = 8.8 Hz, 1H), 4.64 (t, J = 6.4 Hz, 2H), 3.85 (s, 3H), 3.54 (m, 2H), 2.87-2.68 (m, 1H), 1.16 (d, J = 6.8 Hz, 6H) ;

^{13}C NMR (100 MHz, DMSO): δ 193.4, 184.1, 164.9, 160.5, 160.0, 149.9, 144.7,

139.7, 135.1, 128.7, 123.16, 123.13, 123.12, 123.08, 123.07, 123.04, 123.01, 121.2, 118.5, 118.2, 52.9, 49.4, 33.0, 28.0, 23.9;

HRMS (ESI): Calculated for $C_{27}H_{25}O_6N_3$ $[M+H]^+$: 488.1816, Found: 488.1807;



$C_{24}H_{17}N_3O_5$
Exact Mass: 427.12
Mol. Wt.: 427.41

B79;

Yield 93%;

Yellow solid;

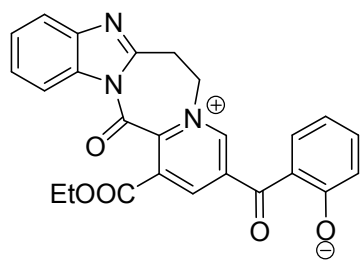
M.P.: 147°C;

TLC: R_f = 0.40 DCM/methol (5:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.34 (dd, J = 12.8, 2.4 Hz, 2H), 7.49 (dd, J = 5.6, 0.8 Hz, 2H), 7.40 (t, J = 6.2 Hz, 1H), 7.17 (dd, J = 6.0, 3.2 Hz, 2H), 7.09 (dd, J = 8.0, 1.6 Hz, 1H), 6.98 (dd, J = 8.4, 0.8 Hz, 1H), 6.48 (dt, J = 7.6, 1.2 Hz, 1H), 4.55 (t, J = 6.0 Hz, 2H), 3.86 (s, 3H), 3.47 (t, J = 6.2 Hz, 2H);

^{13}C NMR (100 MHz, DMSO): δ 190.7, 185.1, 166.7, 164.8, 160.1, 155.9, 152.1, 151.2, 151.1, 143.9, 138.3, 138.2, 133.3, 130.0, 124.0, 121.5, 119.8, 119.3, 116.76, 116.72, 114.55, 114.50, 52.4, 48.5, 27.3;

HRMS (ESI): Calculated for $C_{24}H_{19}O_6N_3$ $[M+H]^+$: 446.1347, Found: 446.1338;



$C_{25}H_{19}N_3O_5$
Exact Mass: 441.13
Mol. Wt.: 441.44

b80;

Yield 88%;

Yellow solid;

M.P.: 152°C;

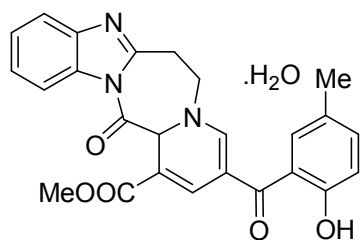
TLC: R_f = 0.34 DCM/methol (5:1);

1H NMR (400 MHz, DMSO): δ 10.33(s, 1H), 8.78 (d, J = 2.8 Hz, 1H), 8.35 (d, J = 2.8 Hz, 1H), 7.45 (dd, J = 6.0, 3.2 Hz, 2H), 7.40 (dt, J = 7.6, 1.6 Hz, 1H), 7.24 (dd, J = 7.6, 1.6 Hz, 1H), 7.13 (dd, J = 6.0, 3.2 Hz, 2H), 6.97 (d, J = 8.4 Hz, 1H), 6.81 (t, J = 7.2 Hz, 1H), 4.56 (t, J = 6.8 Hz, 2H), 4.30 (q, J = 7.2 Hz, 2H), 3.29 (t, J = 6.8 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, DMSO): δ 190.7, 185.3, 164.3, 160.0, 155.9, 152.0, 151.2, 143.9, 133.2, 130.0, 124.0, 121.4, 120.0, 119.3, 116.71, 116.68, 61.6, 48.4, 27.3, 13.7;

HRMS (ESI): Calculated for $C_{25}H_{21}O_6N_3$ [$M+H^+$]: 460.1503, Found: 460.1491;

A mixture of **b78** and 20%Pd(OH)₂/C(0.1eq) degassed methol under hydrogen balloon at the room temperature for overnight. The reaction was monitored by TLC, Filtered Pd(OH)₂/C with diatomite carefully and concentrated to remove most of methol(not very dry), added water, the solution was extracted with EtOAc, the organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The product was purified by chromatography on silica gel eluted with a gradient of ethyl acetate /methanol 40/1 to 20/1 to 72% yield as yellow solids.



$C_{25}H_{23}N_3O_6$
 Exact Mass: 461.16
 Mol. Wt.: 461.47

b81;

Yield 41%;

White solid;

M.P.: 159°C;

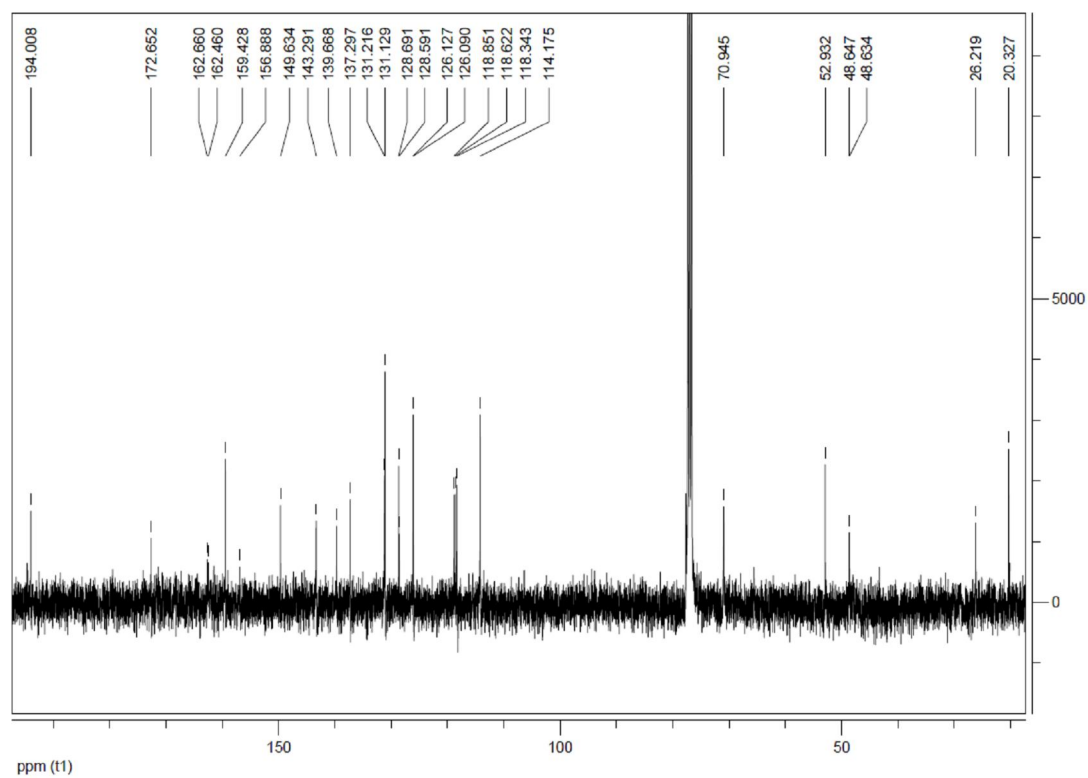
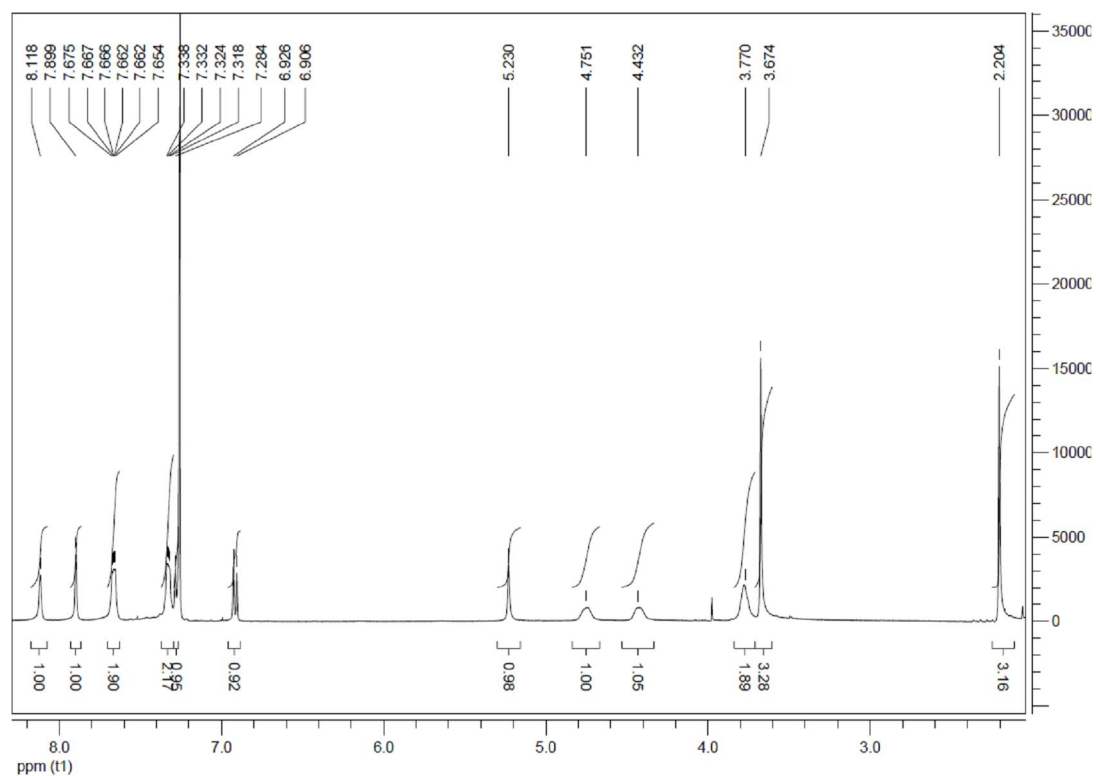
TLC: $R_f = 0.43$ DCM/methol (10:1);

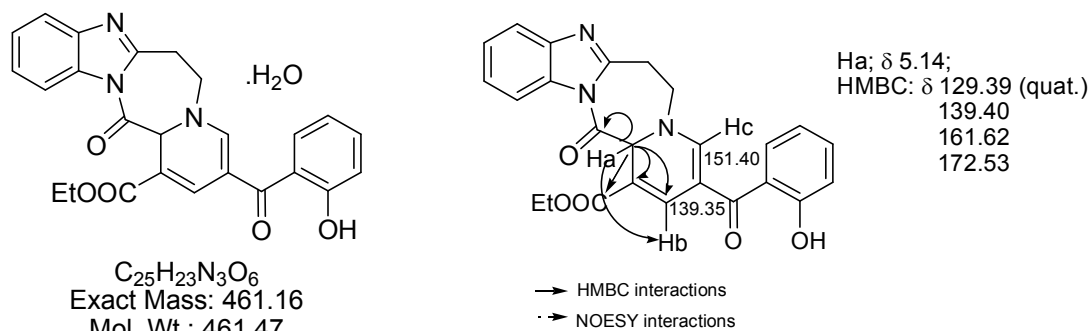
1H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.90 (s, 1H), 7.68-7.65 (m, 2H), 7.34-7.32 (m, 2H), 7.28-7.26 (m, 2H), 6.91 (d, $J = 8.0$ Hz, 1H), 5.23 (s, 1H), 4.75 (s, 1H), 4.43 (s, 1H), 3.77 (s, 2H), 3.67 (s, 3H), 2.20 (s, 3H) ;

^{13}C NMR (100 MHz, DMSO): δ 194.0, 172.7, 162.7, 162.5, 159.4, 156.9, 149.6, 143.3, 137.3, 131.2, 131.1, 128.7, 128.6, 126.12, 126.09, 118.9, 118.6, 118.3, 114.2, 70.9, 52.9, 48.6, 26.2, 20.3;

HRMS (ESI): Calculated for $C_{25}H_{24}O_6N_3$ [$M+H^+$]: 462.1660, Found: 462.1648;

Experimental section




b82;

Yield 72%;

Yellow solid;

M.P.: 134.1°C;

TLC: R_f = 0.38 ethyl acetate /methanol (10:1);

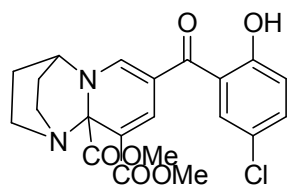
1H NMR (400 MHz, $CDCl_3$): δ 11.22 (bs, 1H), 7.95 (s, 1H), 7.86 (s, 1H), 7.53 (s, 2H), 7.42 (t, J = 8.0 Hz, 1H), 7.21-7.19 (m, 2H), 7.07 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 7.6 Hz, 1H), 5.15 (s, 1H), 4.56-4.42 (m, 2H), 4.27-4.17 (m, 2H), 3.44 (t, J = 6.0 Hz, 2H), 2.91 (dd, J = 30.4, 1.6 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): 194.4, 172.2, 162.1, 161.4, 150.6, 143.8, 138.7, 136.2, 131.3, 129.1, 122.7, 119.2, 118.6, 117.2, 70.8, 62.3, 50.1, 27.9, 14.1;

HRMS (ESI): Calculated for $C_{25}H_{23}O_6N_3$ [$M+H^+$]: 462.1660, Found: 462.1651;

General procedure for synthesis of tetrahydro-1,4-ethanopyrido[1,2-a]-pyrimidens (**b86**) from common precursor 1 and bis-nucleophile **b26**.

4-aminopiperidine (1.2 equiv.) was added to a degassed dichloromethane (15 mL) solution of **b5** (1.0 equiv., 30-40 mg scale). The reaction mixture was stirred at room temperature for 3-6 h under argon. The reaction was monitored by TLC using ethyl acetate /methol (5:1) as eluent. After evaporation of the solvent, the product was purified by column chromatography over silica gel with cyclohexane/ethyl acetate as the eluent to yield **b86**.

**b86,**

Yield 87%;

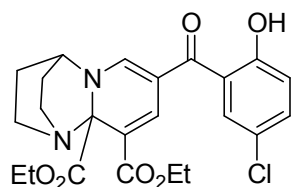
Yellow solid;

M.P.: 173°C;**TLC:** R_f = 0.20 ethyl acetate /methanol (5:1);

^1H NMR (400 MHz, CD_3OD): δ 7.87-7.81 (m, 1H), 7.38-7.30 (m, 2H), 7.19 (s, 1H), 6.93-6.81 (m, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.53-3.44 (m, 3H), 3.18 (t, J = 12.0 Hz, 2H), 2.26-2.18 (m, 2H), 1.93-1.86 (m, 2H);

^{13}C NMR (100 MHz, CDCl_3): δ 193.8, 171.0, 164.0, 159.8, 146.3, 134.4, 132.9, 130.0, 120.2, 120.0, 119.8, 114.7, 106.1, 85.2, 56.7, 54.2, 53.5, 52.0, 45.7, 35.4, 32.9;

HRMS (ESI): Calculated for $\text{C}_{21}\text{H}_{21}\text{ClO}_6\text{N}_2$ [$\text{M}+\text{H}^+$]: 433.1161, Found: 433.1158.

**b87;**

Yield 85%;

Yellow solid;

M.P.: 159°C;**TLC:** R_f = 0.18 ethyl acetate /methanol (5:1);

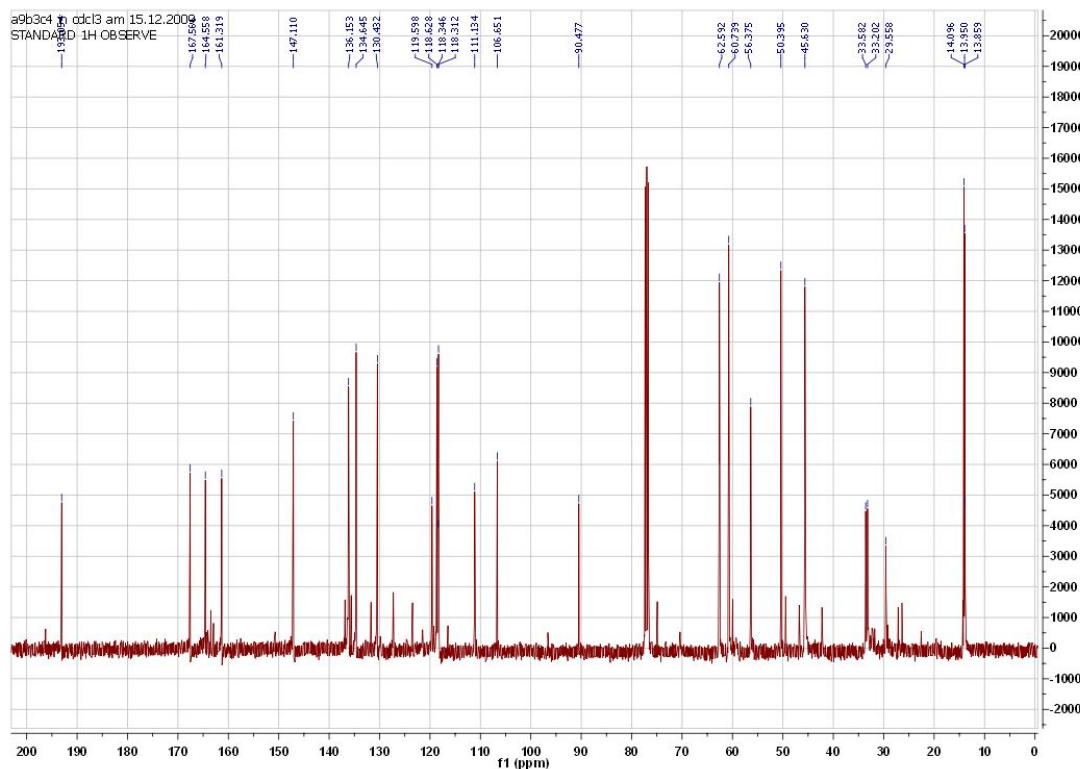
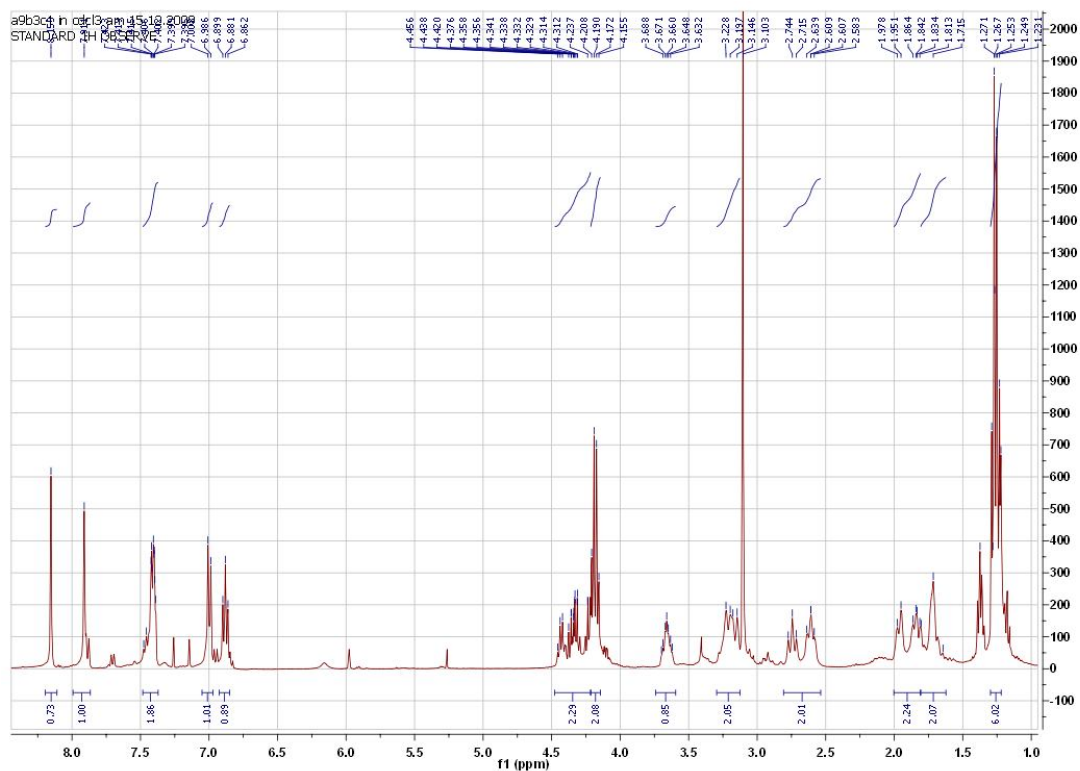
^1H NMR (400 MHz, CDCl_3): δ 7.89-7.82 (m, 1H), 7.39-7.30 (m, 2H), 7.19 (s, 1H), 6.93-6.79 (m, 1H), 4.42-4.14 (m, 4H), 3.15 (t, J = 12.0 Hz, 2H), 2.67 (dt, J = 12.0, 1.2 Hz, 1H), 2.55-2.53 (m, 2H), 1.73-1.65 (m, 2H), 1.34 (t, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 6H);

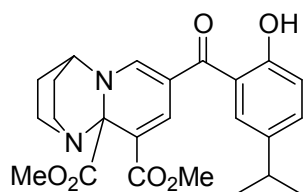
^{13}C NMR (100 MHz, CDCl_3): δ 193.1, 167.5, 164.6, 161.3, 147.1, 136.2, 134.6,

Experimental section

130.4, 119.6, 118.6, 118.3, 111.1, 106.7, 90.5, 62.6, 60.7, 56.4, 50.4, 45.6, 33.2, 29.6, 14.1, 13.9;

HRMS (ESI): Calculated for $C_{23}H_{25}ClO_6N_2 [M+H]^+$: 461.1474, Found: 461.1465.



**b88;**

Yield 86%;

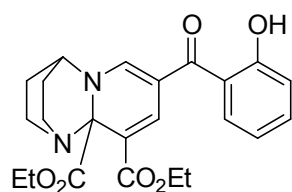
Yellow solid;

M.P.: 178°C;**TLC:** $R_f = 0.25$ ethyl acetate /methol (5:1);

$^1\text{H NMR}$ (400 MHz, CD_3OD): δ 8.09 (d, $J = 1.6$ Hz, 1H), 7.88 (d, $J = 1.6$ Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 1H), 7.22 (d, $J = 1.6$ Hz, 1H), 6.87 (d, $J = 8.4$ Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.53-3.44 (m, 2H), 3.22-3.15 (m, 2H), 3.09-3.04 (m, 1H), 2.88 (m, $J = 7.2$ Hz, 1H), 2.26-2.19 (m, 2H), 1.94-1.88 (m, 2H), 1.24 (d, $J = 6.8$ Hz, 6H);

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 193.3, 170.9, 166.1, 159.2, 145.3, 138.8, 133.9, 133.3, 128.2, 119.4, 117.9, 113.7, 106.9, 85.5, 54.9, 54.2, 51.8, 45.8, 44.5, 33.2, 30.8, 23.9, 14.8;

HRMS (ESI): Calculated for $\text{C}_{24}\text{H}_{28}\text{O}_6\text{N}_2$ [$\text{M}+\text{H}^+$]: 441.2020, Found: 441.2015;

**b89;**

Yield 91%;

Yellow solid;

M.P.: 160°C;**TLC:** $R_f = 0.21$ ethyl acetate /methol (5:1);

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.15 (s, 1H), 7.91 (s, 1H), 7.48-7.39 (m, 2H), 7.00 (d, $J = 8.8$ Hz, 1H), 6.88 (t, $J = 7.2$ Hz, 1H), 4.46-4.24 (m, 2H), 4.18 (q, $J = 7.2$ Hz, 2H),

3.70-3.62 (m, 1H), 3.21-3.15 (m, 2H), 2.78-2.58 (m, 2H), 1.98-1.81 (m, 2H), 1.80-1.64 (m, 2H), 1.27 (t, $J = 7.2$ Hz, 6H);

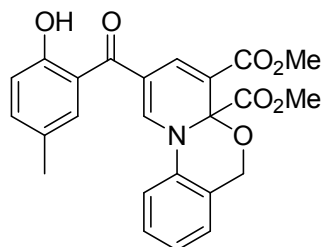
^{13}C NMR (100 MHz, CDCl_3): δ 193.1, 167.6, 164.6, 161.3, 147.1, 136.2, 134.6, 130.4, 119.6, 118.6, 118.4, 111.1, 106.7, 90.5, 62.6, 60.7, 56.4, 50.4, 45.6, 33.6, 29.6, 14.1, 14.0;

HRMS (ESI): Calculated for $\text{C}_{23}\text{H}_{26}\text{O}_6\text{N}_2$ [$\text{M}+\text{H}^+$]: 427.1864, Found: 427.1863;

5.5.2.2 N, O-bisnucleophilies

General procedure for synthesis of benzopyrido-oxazine **b91** from common precursor and bis-nucleophile **b31**.

To a solution of keton ester (2 mmol) in anhydrous dichloromethane (15 mL/mmol) was added 2-aminobenzyl alcohol (2.4 mmol), and the solution was stirred at room temperature for 3-6 h at argon atmosphere. The color of reaction turned straw yellow into deep yellow after about 30 minutes. The reaction was monitored by TLC using cyclohexane/ethyl acetate (2:1) as eluent. Water was added to quench the reaction. The solution was extracted with DCM, and then washed with brine. The organic layer was separated, dried over Na_2SO_4 , evaporated, and purified by column chromatography on silica gel using cyclohexane/ethyl acetate (4:1) as eluant to afford yellow solid. Following is the spectroscopic data for the representative compounds.



$\text{C}_{24}\text{H}_{21}\text{NO}_7$
Exact Mass: 435.13
Mol. Wt.: 435.43

b92;

Yield 91%;

Yellow solid;

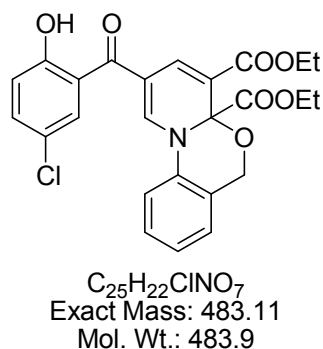
M.P.: 132°C;

TLC: $R_f = 0.37$ cyclohexane/ethyl acetate (2:1);

^1H NMR (400 MHz, CDCl_3): δ 8.04 (d, $J = 1.6$ Hz, 1H), 7.97 (d, $J = 1.6$ Hz, 1H), 7.39 (d, $J = 2.0$ Hz, 1H), 7.35-7.26 (m, 3H), 7.23 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.13 (d, $J = 7.2$ Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 5.72 (d, $J = 14.8$ Hz, 1H), 5.09 (d, $J = 14.8$ Hz, 1H), 3.80 (s, 3H), 3.60 (s, 3H), 2.32 (s, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 193.6, 167.8, 165.2, 159.4, 144.3, 136.3, 135.9, 133.9, 130.6, 129.6, 128.2, 127.8, 127.4, 125.5, 119.25, 119.15, 118.2, 114.4, 108.2, 66.0, 53.3, 52.0, 20.6;

HRMS (ESI): Calculated for $\text{C}_{24}\text{H}_{22}\text{O}_7\text{N}$ [$\text{M}+\text{H}^+$]: 436.1391, Found: 436.1387;



b93;

Yield 90%;

Yellow solid;

M.P. : 165°C;

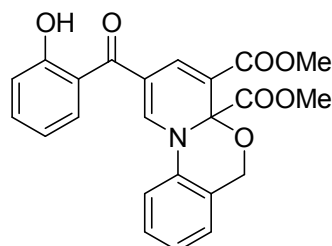
TLC : $R_f = 0.34$ cyclohexane/ethyl acetate (2:1);

^1H NMR (400 MHz, CDCl_3): δ 11.10 (s, 1H), 7.95(d, $J = 1.6$ Hz, 1H), 7.89 (d, $J = 1.6$ Hz, 1H), 7.52 (d, $J = 2.4$ Hz, 1H), 7.34 (dd, $J = 8.8, 2.8$ Hz, 1H), 7.27 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.24 (td, $J = 7.2, 1.6$ Hz, 1H), 7.19-7.16 (m, 1H), 7.06 (d, $J = 7.6$ Hz, 1H), 6.93 (d, $J = 8.8$ Hz, 1H), 5.63 (d, $J = 14.8$ Hz, 1H), 5.03 (d, $J = 14.8$ Hz, 1H), 4.22 (t, $J = 7.2$ Hz, 2H), 4.01 (q, $J = 7.2$ Hz, 2H), 1.25 (t, $J = 7.2$ Hz, 3H), 0.92 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 192.2, 167.0, 164.5, 156.0, 144.5, 136.2, 134.6, 133.0,

129.8, 129.8, 128.2, 127.6, 125.4, 123.4, 120.4, 112.0, 119.3, 115.3, 107.7, 66.1, 62.4, 61.0, 14.2, 13.7;

HRMS (ESI): Calculated for $C_{25}H_{23}O_7N$ $[M+H^+]$: 484.1158, Found: 484.1150.



$C_{23}H_{19}NO_7$
Exact Mass: 421.12
Mol. Wt.: 421.4

b94;

Yield 94%;

Yellow solid;

M.P.: 139°C;

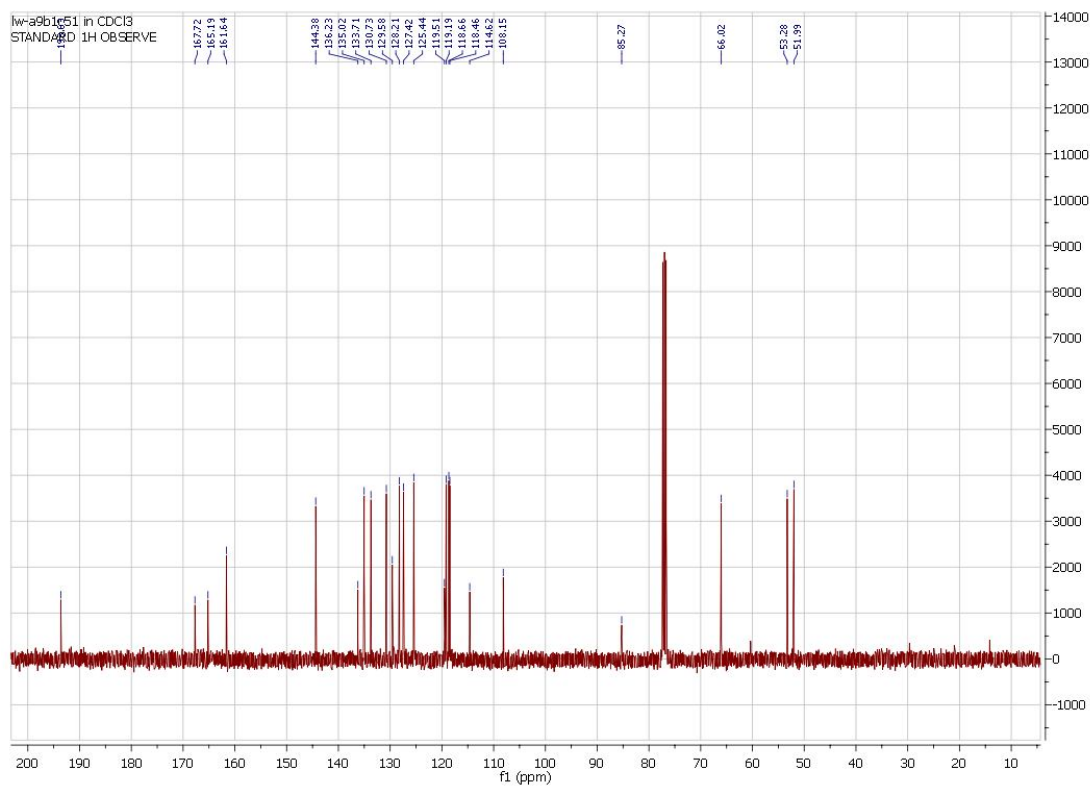
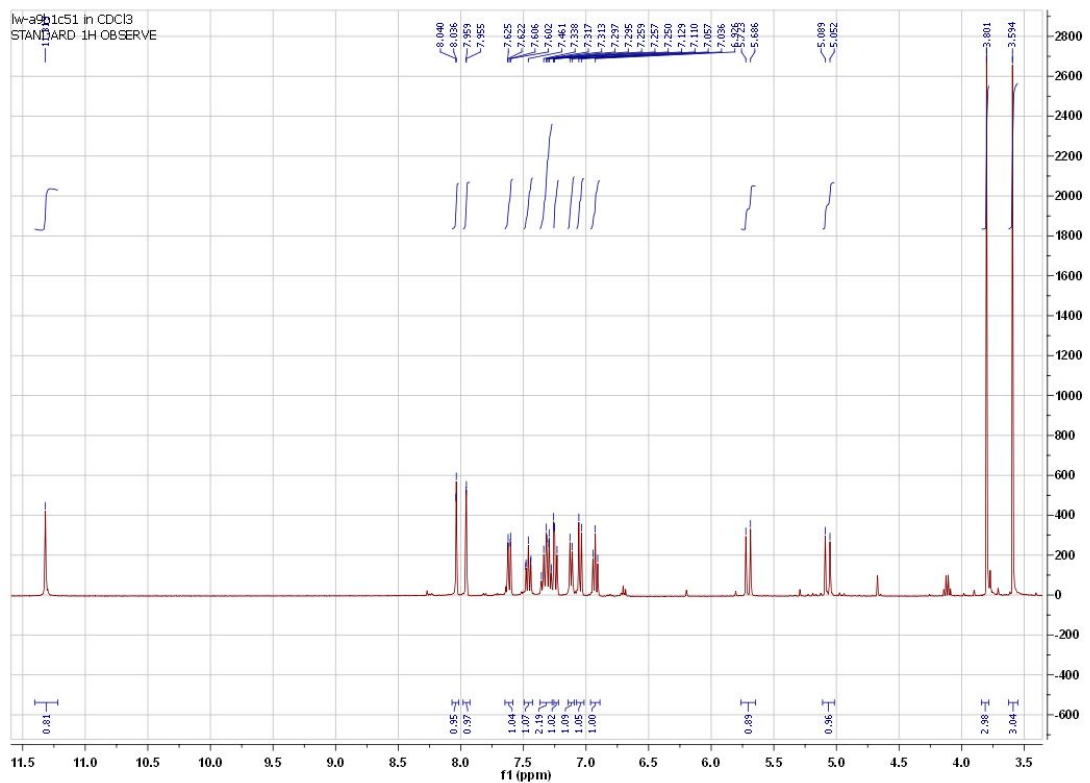
TLC: $R_f = 0.37$ cyclohexane/ethyl acetate (2:1);

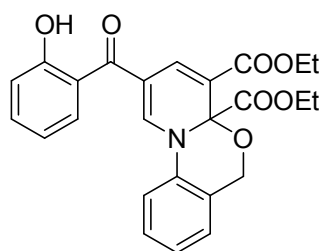
1H NMR (400 MHz, $CDCl_3$): δ 11.33 (s, 1H), 8.04(d, $J = 1.6$ Hz, 1H), 7.96 (d, $J = 1.2$ Hz, 1H), 7.62 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.47 (td, $J = 7.2, 1.6$ Hz, 1H), 7.36-7.28 (m, 2H), 7.24 (d, $J = 8.0$ Hz, 1H), 7.12 (d, $J = 7.2$ Hz, 1H), 7.05 (d, $J = 8.0$ Hz, 1H), 6.93 (t, $J = 7.6$ Hz, 1H), 5.70 (d, $J = 14.8$ Hz, 1H), 5.07 (d, $J = 14.8$ Hz, 1H), 3.80 (s, 3H), 3.59 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 167.7, 165.2, 161.6, 144.4, 136.2, 135.0, 133.7, 130.7, 129.6, 128.2, 127.4, 125.4, 119.5, 119.2, 118.7, 118.5, 114.6, 108.2, 66.0, 53.3, 52.0;

HRMS (ESI): Calculated for $C_{23}H_{20}O_7N$ $[M+H^+]$: 422.1234, Found: 422.1232.

Experimental section





$C_{25}H_{23}NO_7$
Exact Mass: 449.15
Mol. Wt.: 449.45

b95;

Yield 89%;

Yellow solid;

M.P.: 119°C;**TLC:** $R_f = 0.49$ cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 11.30 (s, 1H), 8.00 (d, $J = 12.0$ Hz, 1H), 7.89 (d, $J = 12.0$ Hz, 1H), 7.56 (t, $J = 9.2$ Hz, 1H), 7.42-7.39 (m, 1H), 7.27-7.18 (m, 3H), 7.06-6.99 (m, 2H), 6.88-6.85 (m, 1H), 5.64 (d, $J = 8.0$ Hz, 1H), 5.01 (t, $J = 8.0$ Hz, 1H), 4.20 (q, $J = 6.4$ Hz, 2H), 4.00 (q, $J = 6.4$ Hz, 2H), 1.25 (t, $J = 6.4$ Hz, 3H), 0.93 (t, $J = 6.4$ Hz, 3H);

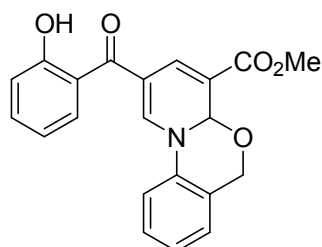
^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 173.6, 163.8, 158.0, 144.4, 135.01, 134.99, 133.5, 130.8, 128.1, 127.42, 127.39, 125.42, 125.40, 119.4, 118.7, 118.6, 118.48, 118.45, 66.1, 62.3, 61.0, 14.2, 13.7;

HRMS (ESI): Calculated for $C_{25}H_{23}O_7N$ [$M+H^+$]: 450.1547, Found: 450.1542.

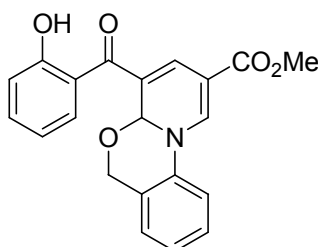
General procedure for synthesis of benzopyrido-oxazine **b91** from common precursor and bis-nucleophile **b31**.

To a solution of keton aldehyde (2 mmol) in anhydrous dichloromethane (15 mL/mmol) was added (2-aminophenyl) methanol **b31** (2.4 mmol), and the solution was stirred at room temperature for 3-6 h at argon atmosphere. The color of reaction turned straw yellow into deep yellow slowly. The reaction was monitored by TLC using cyclohexane/ethyl acetate (2:1) as eluent. Water was added to quench the reaction. The solution was extracted with DCM, and then washed with brine. The

organic layer was separated, dried over Na_2SO_4 , evaporated, and purified by column chromatography on silica gel using cyclohexane/ethyl acetate (4:1) as eluant to afford yellow solid. Following is the spectroscopic data for the representative compounds.



$\text{C}_{21}\text{H}_{17}\text{NO}_5$
Exact Mass: 363.11
Mol. Wt.: 363.36



$\text{C}_{21}\text{H}_{17}\text{NO}_5$
Exact Mass: 363.11
Mol. Wt.: 363.36

b98; a; + b99; b;

Yield 93%; (a+b)

White solid;

M.P.: 131-133°C;

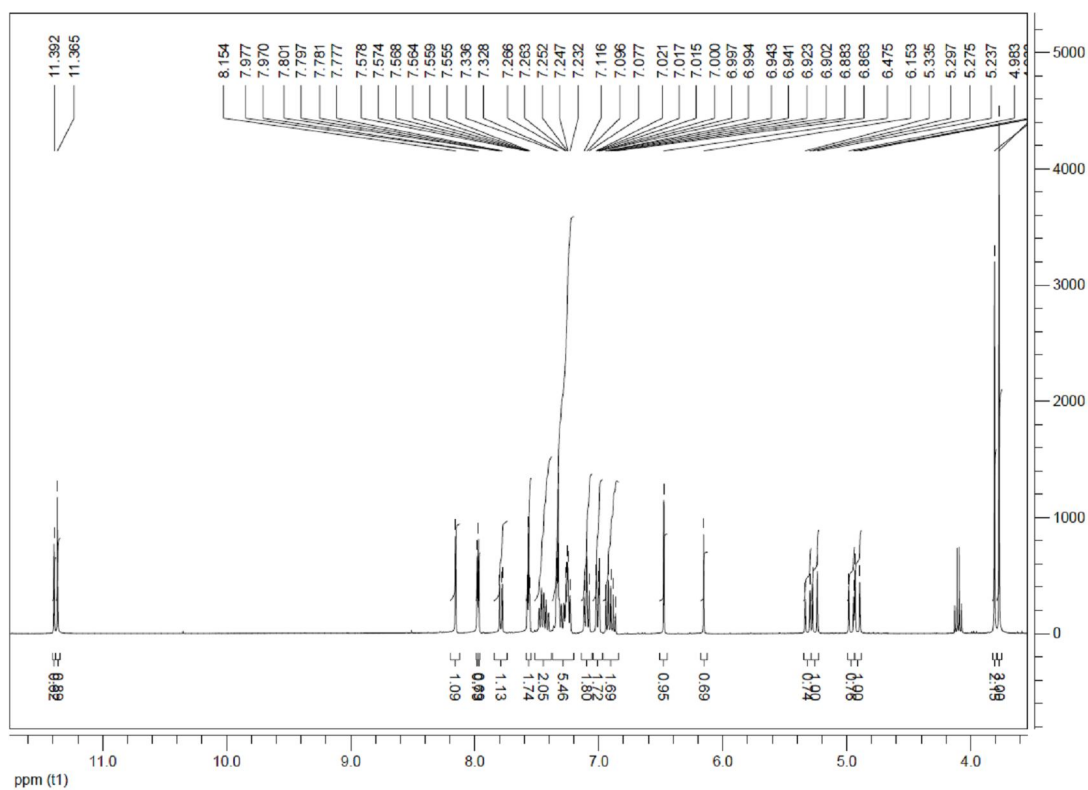
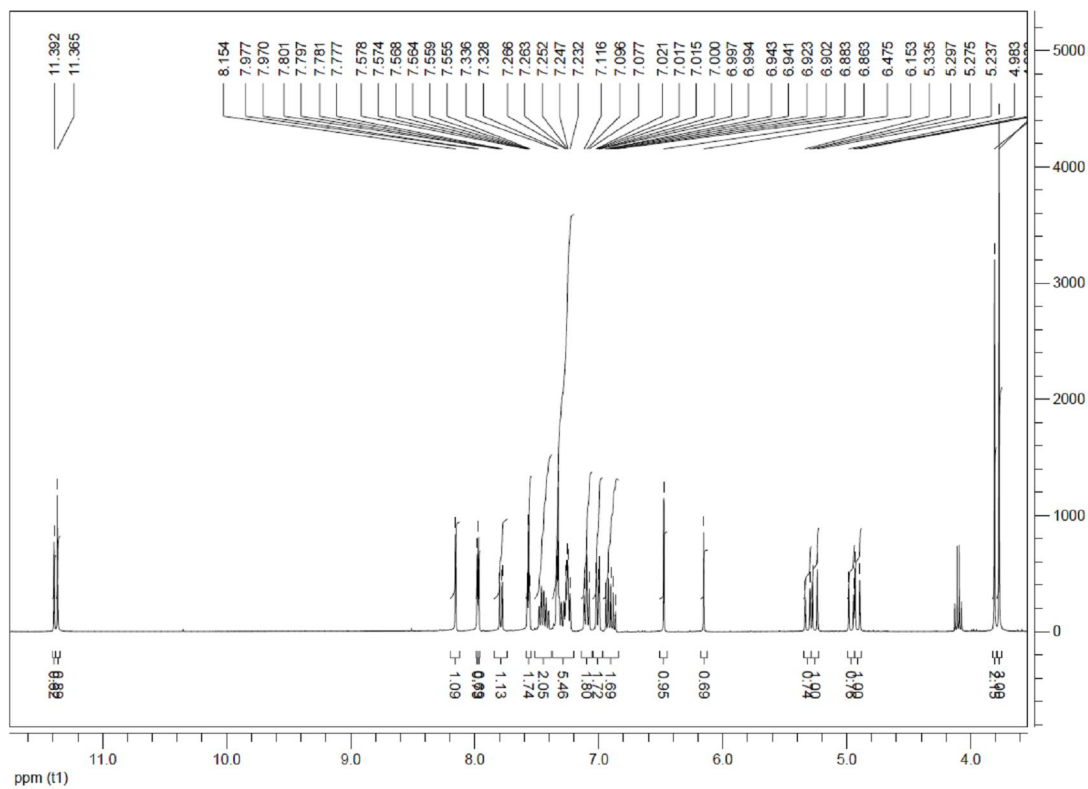
TLC: $R_f = 0.41$ cyclohexane/ethyl acetate (2:1);

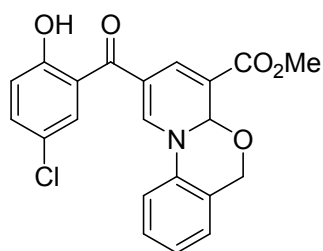
^1H NMR (400 MHz, CDCl_3): δ 11.39 (s, 1H), 7.98 (s, 1H), 7.97 (s, 1H), 7.58-7.55 (m, 1H), 7.34-7.23 (m, 3H), 7.10 (t, $J = 8.0$ Hz, 1H), 7.02-6.99 (m, 1H), 6.94-6.86 (m, 1H), 6.15 (s, 1H), 5.32 (d, $J = 15.2$ Hz, 1H), 4.96 (t, $J = 15.2$ Hz, 1H), 3.81 (s, 3H);

^{13}C NMR (100 MHz, CDCl_3 , a+b): δ 197.5, 193.8, 171.0, 165.7, 165.6, 161.9, 161.6, 144.3, 141.7, 138.7, 138.6, 135.4, 135.3, 134.8, 134.3, 131.8, 130.8, 129.0, 128.7, 127.8, 127.7, 126.7, 126.4, 125.73, 125.7, 118.8, 118.5, 118.3, 118.1, 118.0, 117.7, 111.9, 109.0, 100.3, 81.3, 81.1, 68.3, 68.2, 50.3, 51.8, 51.5;

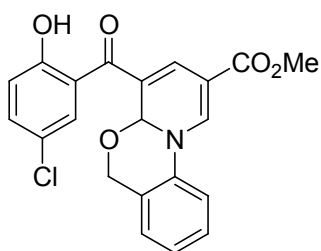
HRMS (ESI): Calculated for $\text{C}_{21}\text{H}_{18}\text{O}_5\text{N}$ [$\text{M}+\text{H}^+$]: 364.1242, Found: 364.1240.

Experimental section





$C_{21}H_{16}ClNO_5$
Exact Mass: 397.07
Mol. Wt.: 397.81



$C_{21}H_{17}NO_5$
Exact Mass: 363.11
Mol. Wt.: 363.36

b100; a; + b101; b;

Yield 89%; (a+b)

White solid;

M.P.: 142-144°C;

TLC: $R_f = 0.43$ cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 11.11 (bs, 1H), 7.93 (s, 1H), 7.89 (d, $J = 1.6$ Hz, 1H), 7.61 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.58 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.37-7.34 (m, 1H), 7.31-7.22 (m, 1H), 7.06 (t, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 2.4$ Hz, 1H), 6.41 (d, $J = 0.8$ Hz, 1H), 3.77 (s, 3H);

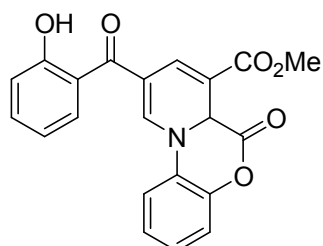
^{13}C NMR (100 MHz, $CDCl_3$, a+b): δ 197.5, 193.8, 171.0, 155.7, 165.6, 161.9, 161.6, 144.3, 141.7, 138.7, 138.6, 135.4, 135.3, 134.8, 134.3, 131.8, 130.8, 129.0, 128.7, 127.8, 127.7, 126.7, 126.4, 125.73, 125.69, 119.6, 119.5, 118.8, 118.5, 118.3, 118.0, 117.7, 111.9, 109.0, 100.3, 81.3, 81.1, 68.3, 68.2, 51.8, 51.5;

HRMS (ESI): Calculated for $C_{21}H_{16}O_5NCl[M+H^+]$: 397.1166, Found: 397.1165

General procedure for synthesis of benzopyrido-oxazine **b106** from common precursor and bis-nucleophile **b32**.

To a solution of keton ester **b5** (2 mmol) in anhydrous dichloromethane (15 mL/mmol) was added 2-aminophenol **b32** (2.4 mmol) and TEA (3.0 mmol), and the solution was stirred at room temperature for 3-6 h at argon atmosphere. The color of reaction turned straw yellow into deep yellow after about 1 hour. The reaction was monitored

by TLC using cyclohexane/ethyl acetate (2:1) as eluent. Water was added to quench the reaction. The solution was extracted with DCM, and then washed with brine. The organic layer was separated, dried over Na₂SO₄, evaporated, and purified by column chromatography on silica gel using cyclohexane/ethyl acetate (4:1) as eluant to afford yellow solid. Following is the spectroscopic data for the representative compounds.



C₂₁H₁₅NO₆
Exact Mass: 377.09
Mol. Wt.: 377.35

b106;

Yield 89%;

White solid;

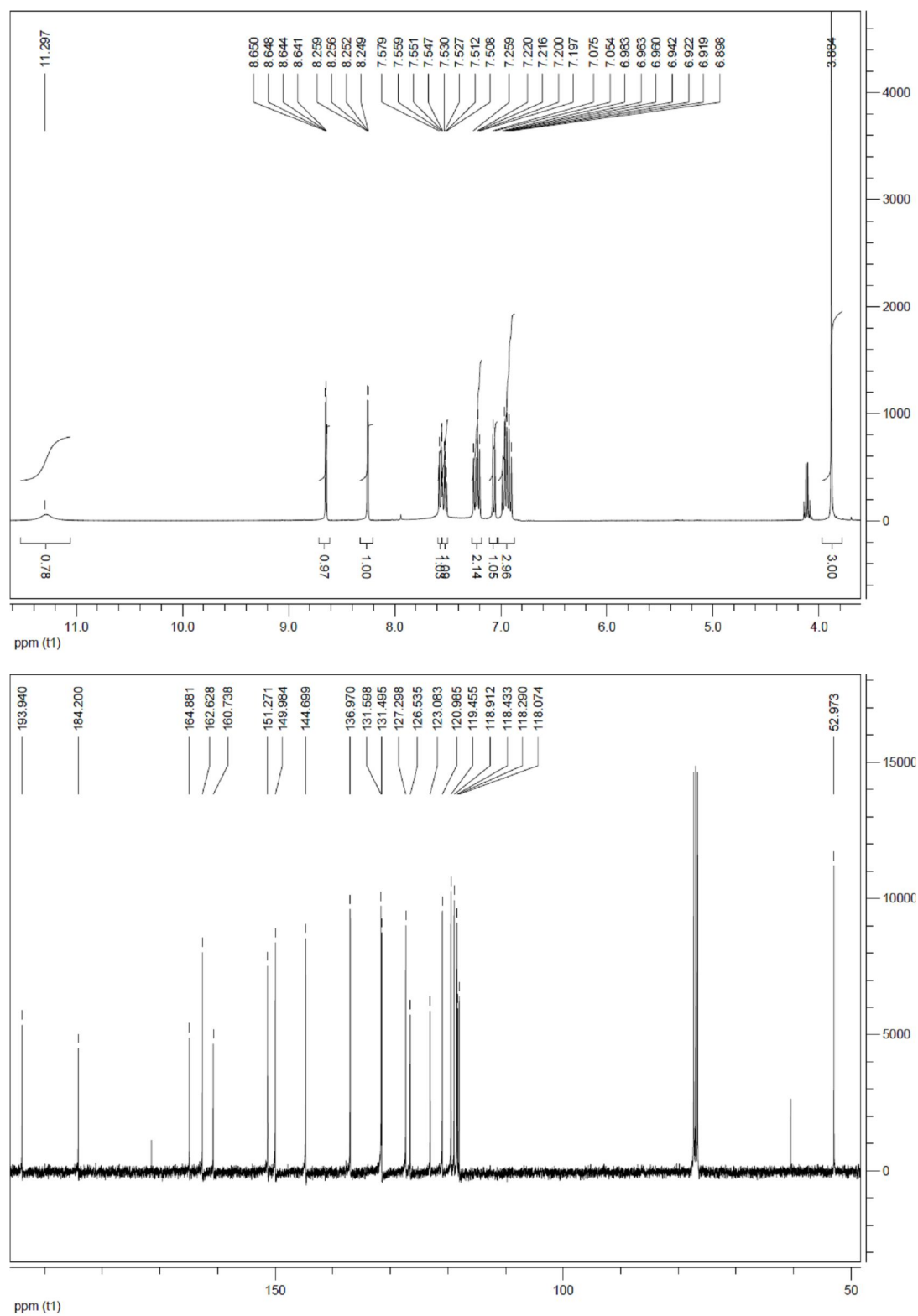
M.P.: 151-153°C;

TLC: R_f = 0.41 cyclohexane/ethyl acetate (2:1);

¹H NMR (400 MHz, CDCl₃): δ 11.30 (bs, 1H), 8.65 (d, *J* = 2.8 Hz, 1H), 8.25 (d, *J* = 2.8 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.53 (td, *J* = 8.0, 1.6 Hz, 1H), 7.26-7.20 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.98-6.90 (m, 3H), 3.88 (s, 3H);

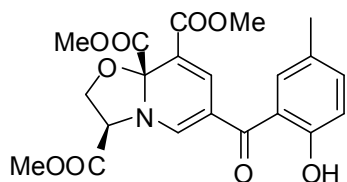
¹³C NMR (100 MHz, CDCl₃): δ 193.9, 184.2, 164.9, 162.6, 160.7, 151.3, 150.0, 144.7, 137.0, 131.6, 131.5, 127.3, 126.5, 123.1, 121.0, 119.5, 118.9, 118.4, 118.3, 118.1, 53.0;

Experimental section



General procedure for synthesis of benzopyrido-oxazine **b107** from common precursor and bis-nucleophile **b33**.

To a solution of keton ester **b5** (1 mmol) in anhydrous dichloromethane (15 mL/mmol) was added L-serine methyl ester **b33** (1.2 mmol) and collidine (1.5 mmol), and the solution was stirred at room temperature for 3-6 h at argon atmosphere. The color of reaction turned straw yellow into deep yellow after about 1 hour. The reaction was monitored by TLC using cyclohexane/ethyl acetate (2:1) as eluent. Water was added to quench the reaction. The solution was extracted with DCM, and then washed with brine. The organic layer was separated, dried over Na₂SO₄, evaporated, and purified by column chromatography on silica gel using cyclohexane/ethyl acetate (4:1) as eluant to afford yellow solid. Following is the spectroscopic data for the representative compounds.



Chemical Formula: C₂₁H₂₁NO₉

Exact Mass: 431,1216

Molecular Weight: 431,3927

b111a;

Yellow solid;

M.P.: 112°C-114;

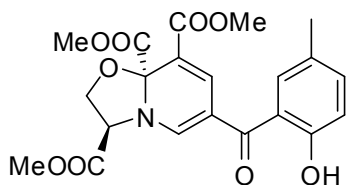
TLC: R_f = 0.48 cyclohexane/ethyl acetate (2:1);

¹H NMR (400 MHz, CDCl₃): δ 11.15 (s, 1H), 7.97 (d, *J* = 1.2 Hz, 1H), 7.54 (d, *J* = 1.6 Hz, 1H), 7.33 (s, 1H), 7.25 (m, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.62 (m, 2H), 4.26 (m, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 2.30 (s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 193.1, 168.7, 167.9, 164.6, 159.4, 146.3, 136.03, 135.98, 133.3, 130.9, 127.7, 119.3, 118.0, 113.8, 109.8, 91.5, 63.7, 62.2, 53.2, 52.0, 20.6;

HRMS (ESI): Calculated for C₂₁H₂₂O₉N [M+H⁺]: 432.1189, Found: 432.1190;

Optical rotation: [α]_D²⁵ = +53.3 (C = 0.05, MeOH).



Chemical Formula: C₂₁H₂₁NO₉

Exact Mass: 431,1216

Molecular Weight: 431,3927

b111b;

Yellow solid;

M.P.: 112°C;

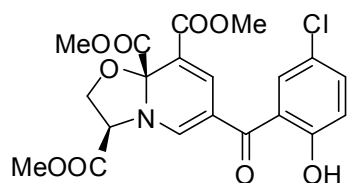
TLC: R_f = 0.37 cyclohexane/ethyl acetate (2:1);

¹H NMR (400 MHz, CDCl₃): δ 11.14 (s, 1H), 7.98 (d, *J* = 1.2 Hz, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.33 (s, 1H), 7.25 (m, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 4.72 (m, 2H), 3.30 (m, 1H), 3.80 (m, 9H), 2.30 (s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 193.2, 168.7, 167.9, 164.6, 161.7, 146.3, 136.1, 133.3, 130.9, 119.6, 118.7, 118.3, 114.0, 109.8, 91.5, 63.7, 62.3, 53.3, 52.0, 29.6;

HRMS (ESI): Calculated for C₂₁H₂₂O₉N [M+H⁺]: 432.1189, Found: 432.1192;

Optical rotation: [α]_D²⁵ = +33.0 (C = 0.14, MeOH).



Chemical Formula: C₂₀H₁₈ClNO₉

Exact Mass: 451,0670

Molecular Weight: 451,8112

b112a;

Yellow solid;

M.P.: 100-101°C;

TLC: R_f = 0.32 cyclohexane/ethyl acetate (2:1);

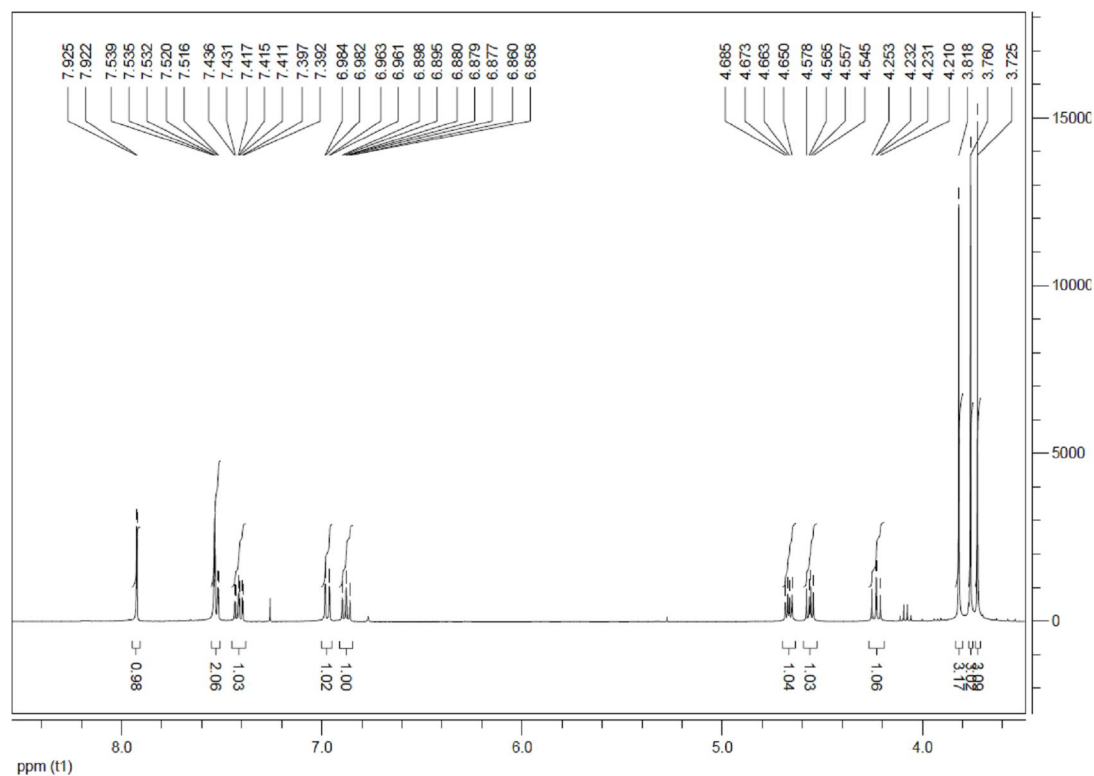
¹H NMR (400 MHz, CDCl₃): δ 7.92 (d, *J* = 1.4 Hz, 1H), 7.53 (m, 2H), 7.42 (m, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.88 (m, 1H), 4.67 (dd, *J* = 5.1, 8.9 Hz, 1H), 4.56 (dd, *J* = 5.1, 8.3 Hz, 1H), 4.23 (dd, *J* = 8.4, 8.9 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.72 (s,

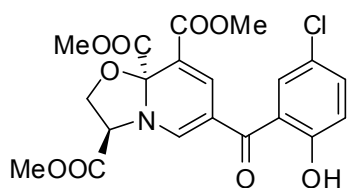
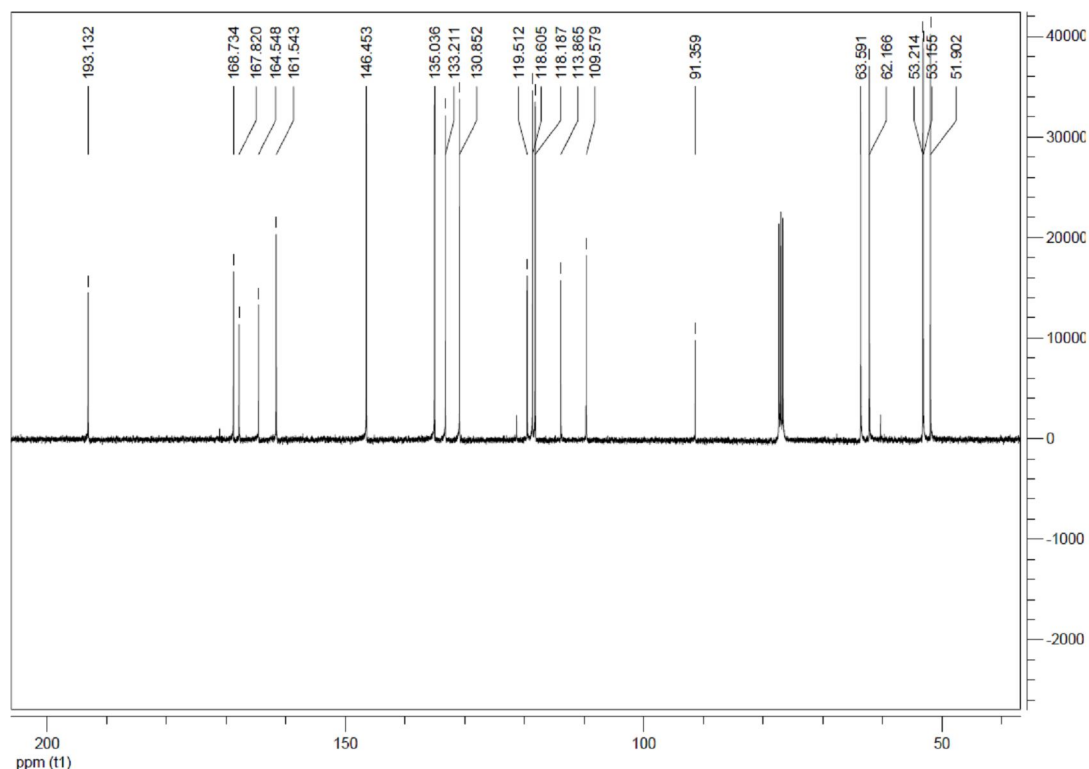
3H);

^{13}C NMR (100 MHz, CDCl_3): δ 193.1, 168.7, 167.8, 164.5, 161.5, 146.5, 135.0, 133.2, 130.9, 119.5, 118.6, 118.2, 113.9, 109.6, 91.4, 63.6, 62.2, 53.2, 51.9 ;

HRMS (ESI): Calculated for $\text{C}_{20}\text{H}_{19}\text{ClO}_9\text{N}$ $[\text{M}+\text{H}^+]$: 452.0736, Found: 452.0736.

Optical rotation: $[\alpha]_D^{25} = -20.7$ (C = 0.04, MeOH).





Chemical Formula: $C_{20}H_{18}ClNO_9$

Exact Mass: 451,0670

Molecular Weight: 451,8112

b112b;

Yellow solid;

M.P.: 158°C;

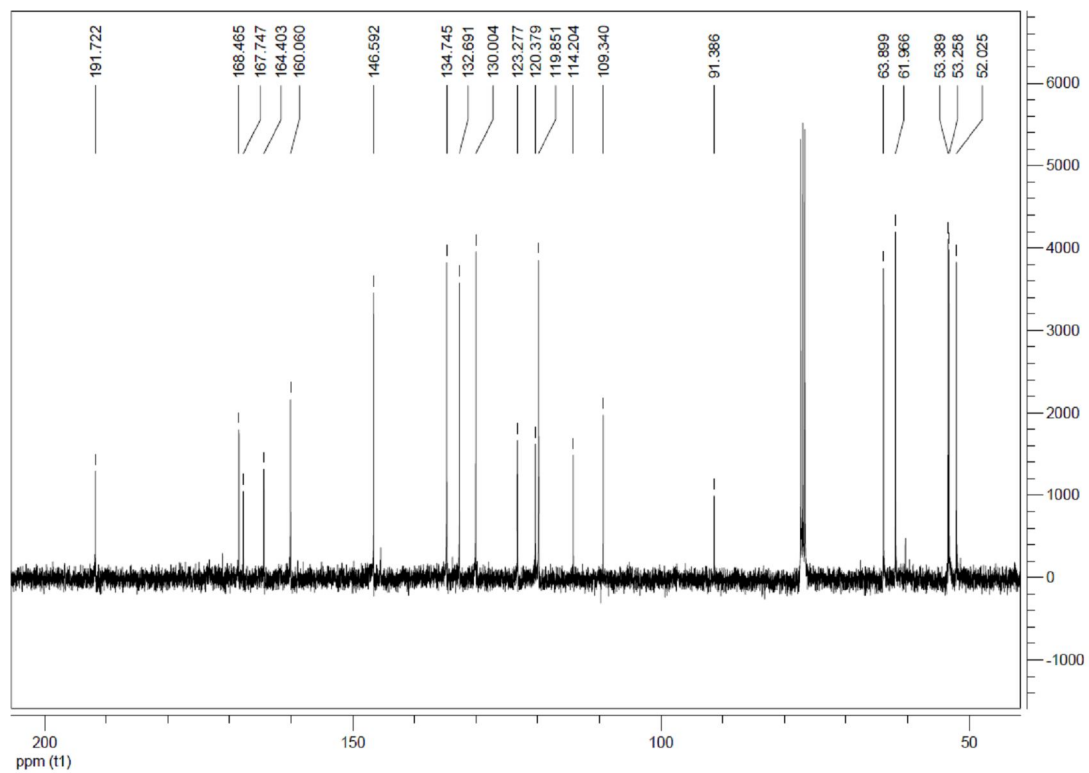
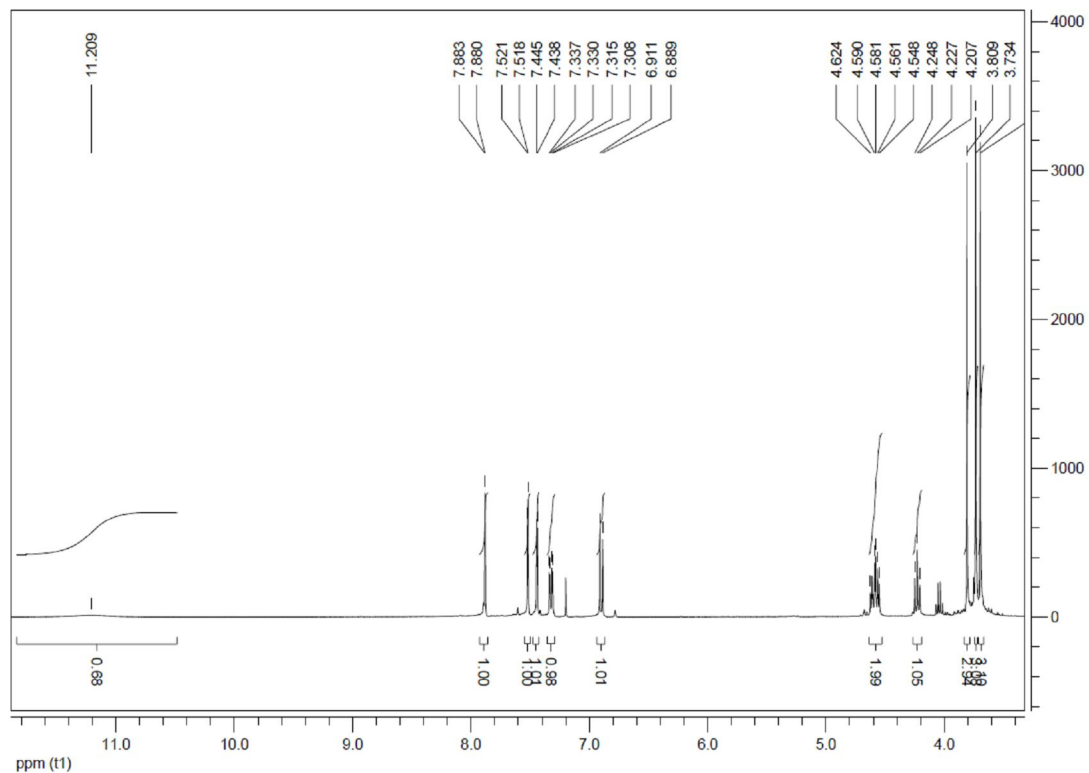
TLC: $R_f = 0.24$ cyclohexane/ethyl acetate (2:1);

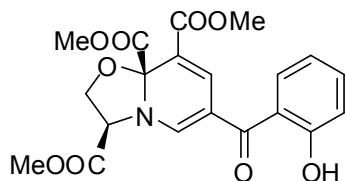
1H NMR (400 MHz, $CDCl_3$): δ 11.21 (bs, 1H), 7.88 (m, 1H), 7.52 (m, 1H), 7.44 (d, $J = 2.6$ Hz, 1H), 7.32 (dd, $J = 2.6, 8.9$ Hz, 1H), 6.90 (d, $J = 8.9$ Hz, 1H), 4.58 (m, 2H), 4.22 (t, $J = 8.2$ Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.69 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 168.5, 167.7, 164.4, 160.1, 146.6, 134.7, 132.7, 130.0, 123.3, 120.4, 119.9, 114.2, 109.3, 91.4, 63.9, 62.0, 53.4, 52.0;

HRMS (ESI): Calculated for $C_{20}H_{19}ClO_9N$ [$M+H^+$]: 452.0736, Found: 452.0738.

Optical rotation: $[\alpha]_D^{25} = +42.2$ (C = 0.25, MeOH).





Chemical Formula: $C_{20}H_{19}NO_9$
 Exact Mass: 417,1060
 Molecular Weight: 417,3662

b113a;

Yellow solid;

M.P.: 105°C;

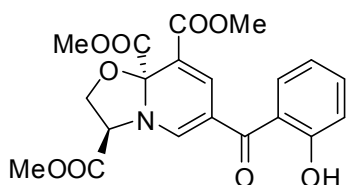
TLC: $R_f = 0.35$ cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.56 (m, 2H), 7.44 (m, 1H), 7.16 (m, 2H), 7.02 (d, $J = 8.2$ Hz, 1H), 6.90 (t, $J = 7.6$ Hz, 1H), 4.61 (m, 2H), 4.26 (t, $J = 8.2$ Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.1, 168.7, 167.8, 164.5, 161.5, 146.5, 135.0, 133.2, 130.9, 119.5, 118.6, 118.2, 113.9, 109.6, 91.4, 63.6, 62.2, 53.2, 51.9;

HRMS (ESI): Calculated for $C_{20}H_{20}O_9N$ $[M+H^+]$: 417.3662, Found: 418.1129.

Optical rotation: $[\alpha]_D^{25} = +32.4$ ($C = 0.09$, MeOH).



Chemical Formula: $C_{20}H_{19}NO_9$
 Exact Mass: 417,1060
 Molecular Weight: 417,3662

b113b;

Yellow solid;

M.P.: 106°C;

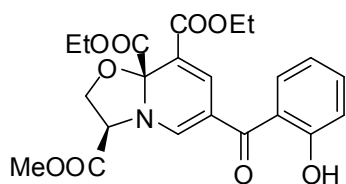
TLC: $R_f = 0.28$ cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.56 (m, 2H), 7.44 (t, $J = 7.7$ Hz, 1H), 6.99 (d, $J = 8.4$ Hz, 1H), 6.90 (t, $J = 7.6$ Hz, 1H), 4.61 (m, 2H), 4.25 (t, $J = 8.4$ Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 168.7, 167.8, 164.6, 161.3, 135.1, 133.3, 130.9, 119.6, 118.6, 118.3, 114.0, 109.8, 91.5, 63.6, 62.3, 53.3, 52.0;

HRMS (ESI): Calculated for $C_{20}H_{20}O_9N$ $[M+H^+]$: 417.3662, Found: 418.1133.

Optical rotation: $[\alpha]_D^{25} = +60.0$ ($C = 0.03$, MeOH).



Chemical Formula: $C_{22}H_{23}NO_9$
 Exact Mass: 445,1373
 Molecular Weight: 445,4193

b114a;

Yellow solid;

M.P.: 109-110°C;

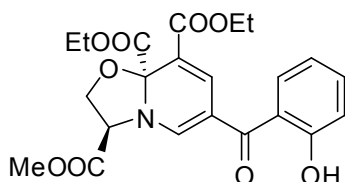
TLC: $R_f = 0.22$ cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 11.31 (bs, 1H), 7.93 (d, $J = 1.4$ Hz, 1H), 7.54 (m, 2H), 7.42 (m, 1H), 6.97 (d, $J = 8.4$ Hz, 1H), 6.88 (t, $J = 7.6$ Hz, 1H), 4.60 (m, 2H), 4.24-4.16 (m, 5H), 3.81 (s, 3H), 1.28 (t, $J = 6.1$ Hz, 3H), 1.25 ((t, $J = 6.0$ Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 168.8, 167.4, 164.1, 161.6, 146.5, 135.0, 132.7, 130.9, 121.4, 119.6, 118.6, 118.2, 114.6, 109.7, 91.5, 63.6, 62.1, 60.9, 53.2, 14.2, 13.9;

HRMS (ESI): Calculated for $C_{22}H_{24}O_9N$ $[M+H]^+$: 446.1437, Found: 446.1437.

Optical rotation: $[\alpha]_D^{25} = +18.3$ ($C = 0.29$, MeOH).



Chemical Formula: $C_{22}H_{23}NO_9$
 Exact Mass: 445,1373
 Molecular Weight: 445,4193

b114b;

Yellow solid;

M.P.: 122°C;

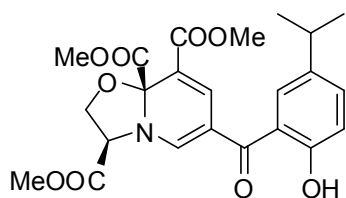
TLC: $R_f = 0.14$ cyclohexane/ethyl acetate (2:1);

^1H NMR (400 MHz, CDCl_3): δ 11.36 (bs, 1H), 7.93 (d, $J = 1.6$ Hz, 1H), 7.54 (m, 2H), 7.42 (m, 1H), 6.99 (d, $J = 8.4$ Hz, 1H), 6.88 (t, $J = 8.0$ Hz, 1H), 4.61 (m, 2H), 4.24-4.16 (m, 5H), 3.81 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 193.3, 168.8, 167.4, 164.2, 161.7, 146.3, 135.1, 132.9, 131.0, 118.7, 118.6, 118.3, 114.7, 111.8, 109.9, 91.6, 63.7, 62.2, 60.9, 53.2, 14.2, 13.9;

HRMS (ESI): Calculated for $\text{C}_{22}\text{H}_{24}\text{O}_9\text{N}$ [$\text{M}+\text{H}^+$]: 446.1440, Found: 446.1442.

Optical rotation: $[\alpha]_D^{25} = +15.0$ ($C = 0.06$, MeOH).



Chemical Formula: $\text{C}_{23}\text{H}_{25}\text{NO}_9$

Exact Mass: 459,1529

Molecular Weight: 459,4459

b115a;

Yellow solid;

M.P.: 128°C;

TLC: $R_f = 0.41$ cyclohexane/ethyl acetate (2:1);

^1H NMR (400 MHz, CDCl_3): δ 11.08 (bs, 1H), 7.48 (d, $J = 1.4$ Hz, 1H), 7.32 (d, $J = 2.1$ Hz, 1H), 7.26 (dd, $J = 2.3, 8.5$ Hz, 1H), 6.89 (d, $J = 8.5$ Hz, 1H), 4.56 (m, 2H), 4.21 (t, $J = 10.5$ Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 2.81 (m, 1H), 1.17 (d, $J = 7.2$ Hz, 6H);

^{13}C NMR (100 MHz, CDCl_3): δ 193.4, 168.7, 167.9, 164.6, 159.6, 146.2, 138.9, 133.7, 133.6, 128.4, 119.3, 118.0, 113.7, 110.0, 91.5, 63.7, 62.2, 53.3, 52.0, 33.1, 24.0, 23.8;

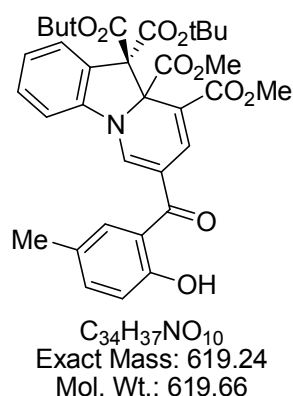
HRMS (ESI): Calculated for $\text{C}_{23}\text{H}_{26}\text{O}_9\text{N}$ [$\text{M}+\text{H}^+$]: 460.1600, Found: 460.1596.

Optical rotation: $[\alpha]_D^{25} = -64.2$ ($C = 0.012$, MeOH).

5.5.2.3 N, C; O, C; and C, C-bisnucleophilies

General procedure for synthesis of benzoindolizine derivatives b118 from common precursor and bis-nucleophile b57.

To a solution of keton ester (2 mmol) in anhydrous ethanol (20 mL/mmol) was added di-tert-butyl 2-(2-aminophenyl)malonate (**b57**, 1.2 equiv.) and 2.6-lutidine (1.5 equiv.) followed by adding Silver triflate (10 mol%, 0.2mmol). The reaction mixture was stirred at preheated oil-bath at 60°C for 4-8 h under argon atmosphere because there was no reaction, and almost starts compounds left in the room temperature. The aim of the preheated oil-bath inspired the start compounds and avoided the side-reactions. The color of the solution turned colorless into red in this temperature quickly. The reaction was monitored by TLC using cyclohexane/ethyl acetate (4:1). The mixture was cooled to room temperature, and water was added to quench the reaction. The solution was evaporated under vacuum to remove the excess of ethanol. The solution was extracted with EtOAc, then washed with brine. The organic layer was separated, dried over Na₂SO₄, evaporated, and purified by column chromatography on silica gel using cyclohexane/ethyl acetate (10:1) as eluant to afford red solid. Following is the spectroscopic data for the representative compounds.



b119;

Yield 83%;

Red solid;

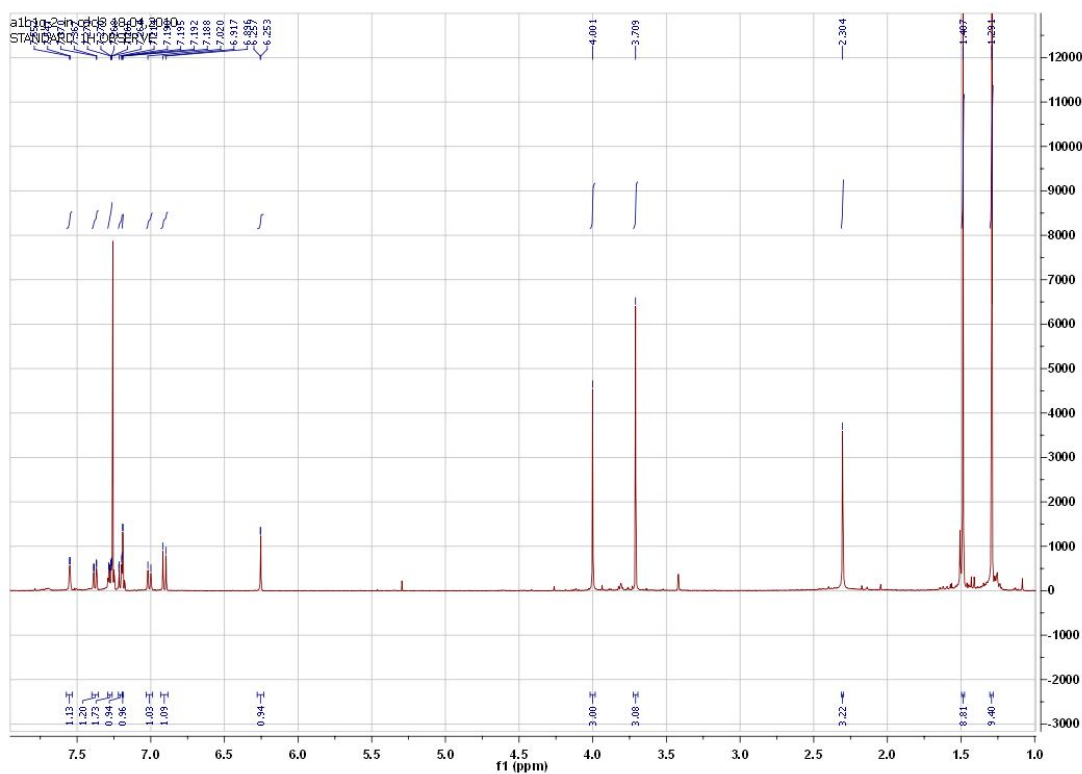
M.P.: 151°C;

TLC: $R_f = 0.45$ cyclohexane/ethyl acetate (4:1);

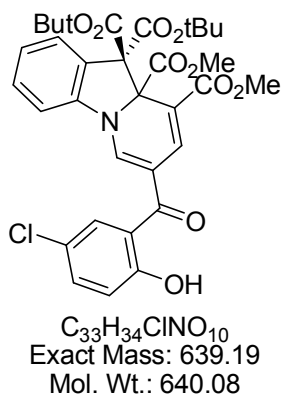
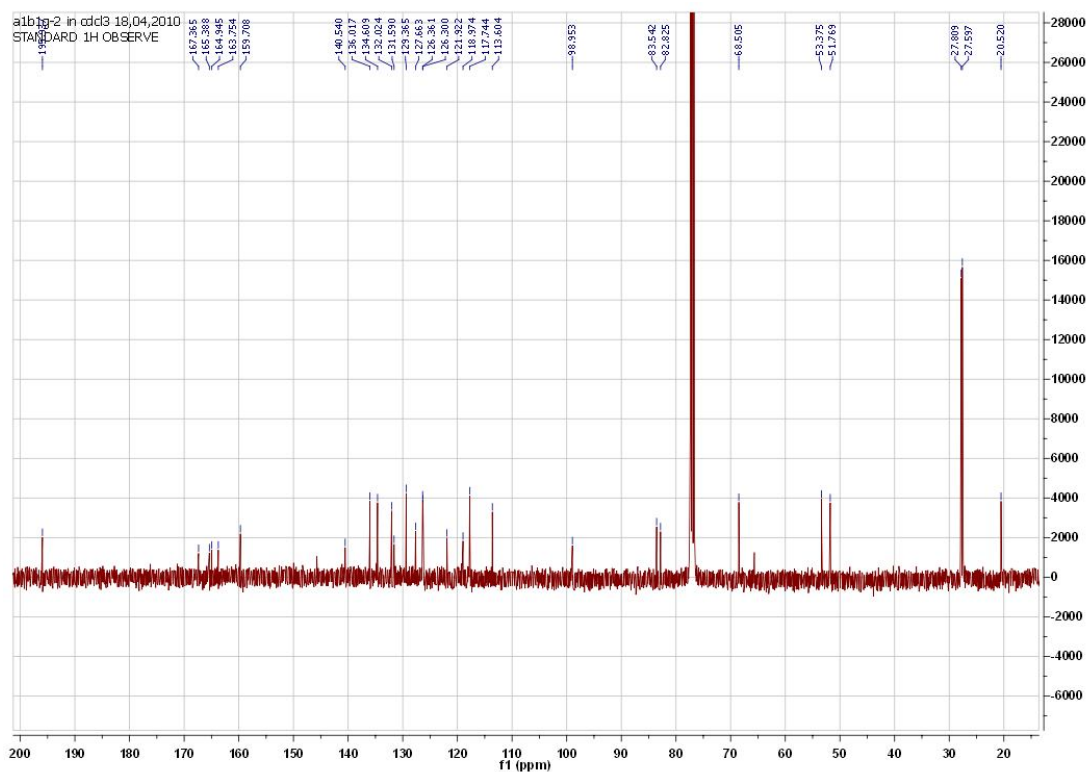
^1H NMR (400 MHz, CDCl_3): δ 7.55 (d, $J = 2.0$ Hz, 1H), 7.38 (d, $J = 1.2$ Hz, 1H), 7.29-7.26 (m, 2H), 7.20 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.19 (d, $J = 1.6$ Hz, 1H), 7.02 (d, $J = 8.4$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 6.26 (d, $J = 5.6$ Hz, 1H), 4.00 (s, 3H), 3.71 (s, 3H), 2.31 (s, 3H), 1.49 (s, 9H), 1.29 (s, 9H);

^{13}C NMR (100 MHz, CDCl_3): δ 196.0, 167.4, 165.4, 164.9, 163.8, 159.7, 140.5, 136.0, 134.6, 132.0, 131.6, 129.4, 127.7, 126.4, 126.3, 121.9, 119.0, 117.7, 113.6, 98.9, 83.5, 82.8, 68.5, 53.4, 51.9, 27.8, 27.6, 20.5;

HRMS (ESI): Calculated for $\text{C}_{34}\text{H}_{38}\text{O}_{10}\text{N}$ [$\text{M}+\text{H}^+$]: 620.2417, Found: 620.2487



Experimental section



b120;

Yield 79%;

Red solid;

M.P.: 143°C;

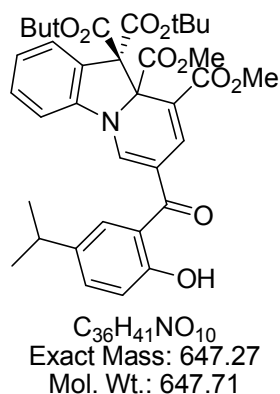
TLC: $R_f = 0.43$ cyclohexane/ethyl acetate (4:1);

¹H NMR (400 MHz, CDCl₃): δ 10.85 (s, 1H), 7.69 (s, 1H), 7.40-7.33 (m, 3H), 7.19-7.16 (m, 2H), 7.00 (d, $J = 8.0$ Hz, 1H), 6.94 (d, $J = 8.8$ Hz, 1H), 6.25 (s, 1H), 3.99 (s, 3H), 3.71 (s, 3H), 1.48 (s, 9H), 1.29 (s, 9H);

¹³C NMR (100 MHz, CDCl₃): δ 194.7, 168.4, 167.4, 164.7, 163.6, 160.1, 140.3, 135.1,

134.79, 134.76, 131.5, 131.2, 129.4, 126.5, 126.3, 124.5, 123.5, 121.6, 120.2, 119.5, 113.6, 83.7, 83.1, 68.5, 53.4, 51.9, 27.8, 27.6;

HRMS (ESI): Calculated for $C_{33}H_{35}ClO_{10}N$ $[M+H^+]$: 641.1944, Found: 640.1935;



b121;

Yield 87%;

Red solid;

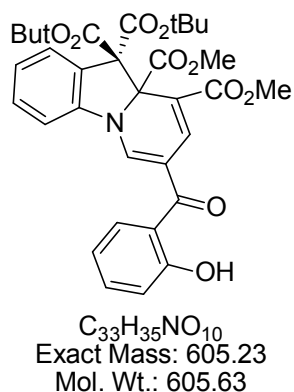
M.P.: 156°C;

TLC: R_f = 0.41 cyclohexane/ethyl acetate (4:1);

1H NMR (400 MHz, $CDCl_3$): δ 10.96 (s, 1H), 7.61 (s, 1H), 7.37 (s, 1H), 7.35 (s, 1H), 7.32 (s, 1H), 7.30 (d, J = 1.6 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.27 (s, 1H), 3.99 (s, 3H), 3.67 (s, 3H), 2.82-2.90 (m, 1H), 1.48 (s, 9H), 1.28 (s, 9H), 1.21 (d, J = 5.2 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 168.3, 165.2, 164.8, 159.8, 138.7, 135.4, 133.7, 129.5, 129.3, 128.8, 127.7, 126.5, 126.1, 121.2, 118.8, 117.6, 113.8, 109.8, 83.5, 82.8, 68.7, 53.8, 53.4, 51.6, 33.4, 27.9, 27.6, 23.9;

HRMS (ESI): Calculated for $C_{36}H_{42}O_{10}N$ $[M+H^+]$: 648.2803, Found: 648.2797;

**b122;**

Yield 89%;

Red solid;

M.P.: 135°C;**TLC:** $R_f = 0.68$ cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 7.78 (dd, $J = 7.6, 2.0$ Hz, 1H), 7.48-7.44 (m, 1H), 7.37 (dd, $J = 7.6, 0.8$ Hz, 1H), 7.29-7.25 (m, 1H), 7.22-7.18 (m, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 6.95 (dt, $J = 7.6, 1.2$ Hz, 1H), 6.27 (d, $J = 1.6$ Hz, 1H), 4.00 (s, 3H), 3.70 (s, 3H), 1.49 (s, 9H), 1.28 (s, 9H);

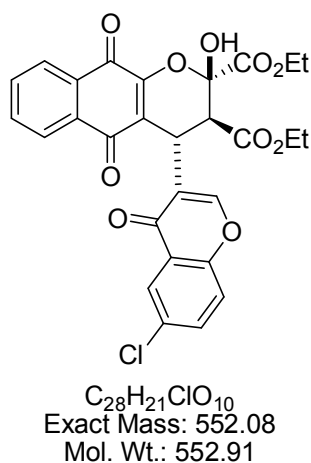
^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 167.4, 165.2, 164.7, 163.7, 161.9, 140.5, 135.1, 134.8, 132.1, 129.3, 126.4, 126.3, 121.9, 119.2, 118.6, 118.0, 113.6, 109.8, 98.9, 95.9, 83.6, 82.8, 68.5, 53.4, 51.8, 27.8, 27.6;

HRMS (ESI): Calculated for $C_{33}H_{36}O_{10}N$ [$M+H^+$]: 606.2334, Found: 606.2329;

General procedure for synthesis of 8,13-dihydro-7*H*-benzo[2,3]azocino[4,5-*b*]indole-6-carboxylates and 10,14c-dihydroindolo[3,2-*c*]-pyrido[1,2-*a*]quinoline (**b130**) from common precursor and bis-nucleophile **b35**.

2-hydroxy-1,4-naphthoquinone (1,1 equiv.) was added to a degassed acetic anhydride/acetic acid(1:3) (4 mL) solution of ketone ester (30 mg, 1 equiv.). The reaction mixture was stirred at preheating oil-bath 150°C refluxing for 4min under argon. The color of solution turned straw yellow into red immediately. The reaction was monitored by TLC using cyclohexane/ethyl acetate (1:1) as eluent. The solution was

added 50mL water to quench the reaction and cooled down to room temperature under the argon protected for 2-3 hours. The excess of acetic anhydride combined with the water very slow, otherwise excess of acetic anhydride will interfere the following steps include difficult it in column. The saturation solution of Na_2CO_3 was added to remove acetic acid to PH near 7. After evaporation of the solvent, the solution was extracted with EtOAc, and then washed with brine. The organic layer was separated, dried over Na_2SO_4 , evaporated, and purified by column chromatography on silica gel using cyclohexane/ethyl acetate (2:1) to offer the yellow solid. Following is the spectroscopic data for the representative compounds.

**b125;**

(Mixture of two diastereoisomers ~ 5:1);

Yield 84%;

Yellow solid;

M.P.: 168.4°C;

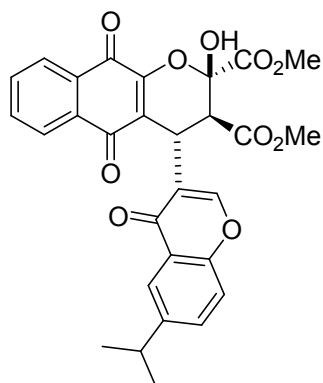
TLC: R_f = 0.44 cyclohexane/ethyl acetate (1:1);

^1H NMR (400 MHz, CDCl_3): δ 8.30 (s, 1H), 8.04 (t, J = 2.8 Hz, 1H), 7.99 (s, 1H), 7.84-7.83 (m, 1H), 7.62-7.60 (m, 2H), 7.55 (dt, J = 8.8, 2.8 Hz, 1H), 7.41 (dd, J = 8.8, 1.6 Hz, 1H), 5.24 (s, 1H), 4.42-4.36 (m, 2H), 4.31 (t, J = 7.2 Hz, 1H), 4.17-4.01 (m, 2H), 3.97 (d, J = 10.8 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100MHz, CDCl_3): δ 183.4, 178.5, 175.3, 168.1, 168.0, 157.1, 154.4, 151.3,

133.9, 133.7, 133.2, 131.8, 131.0, 130.9, 126.2, 126.1, 125.0, 124.9, 122.3, 122.1, 119.9, 94.6, 63.8, 61.7, 45.6, 31.2, 13.9, 13.7;

HRMS (ESI): Calculated for $C_{28}H_{22}O_{10}$ $[M+H^+]$:553.0896, Found: 553.0892;



$C_{29}H_{24}O_{10}$
Exact Mass: 532.14
Mol. Wt.: 532.49

b126;

Yield 85%;

Yellow solid;

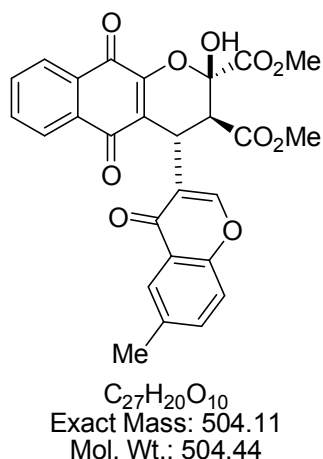
M.P.: 155.7°C;

TLC: R_f = 0.38 cyclohexane/ethyl acetate (1:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.91 (s, 1H), 7.88-7.86 (m, 1H), 7.64-7.62 (m, 2H), 7.52 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 4.38 (d, J = 10.8 Hz, 1H), 4.12 (d, J = 10.8 Hz, 1H), 3.96 (s, 3H), 3.64 (s, 3H), 2.96 (m, 1H), 1.22 (d, J = 7.2 Hz, 6H);

^{13}C NMR (100MHz, $CDCl_3$): δ 183.4, 178.6, 176.8, 168.69, 168.67, 157.1, 154.6, 146.2, 135.4, 134.0, 133.3, 132.8, 132.0, 131.0, 126.4, 126.3, 126.2, 123.8, 122.8, 122.1, 118.1, 94.7, 54.3, 52.6, 45.9, 33.8, 31.4, 23.9, 23.8;

HRMS (ESI): Calculated for $C_{29}H_{24}O_{10}$ $[M+H^+]$:533.1442, Found: 533.1437;



b127;

Yield 88%;

Yellow solid;

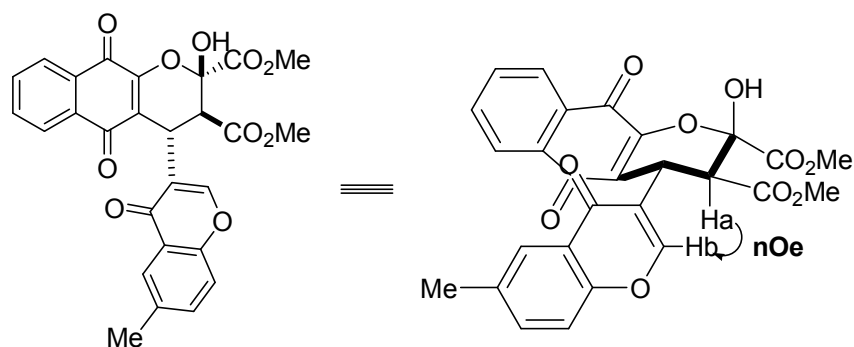
M.P.: 163.4°C;

TLC: R_f = 0.41 cyclohexane/ethyl acetate (1:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.07 (d, J = 6.8 Hz, 1H), 7.97-7.84 (m, 2H), 7.64-7.61 (m, 2H), 7.45 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 4.38 (d, J = 10.8 Hz, 1H), 4.11 (d, J = 10.8 Hz, 1H), 3.95 (s, 3H), 3.64 (s, 3H), 2.38 (s, 3H);

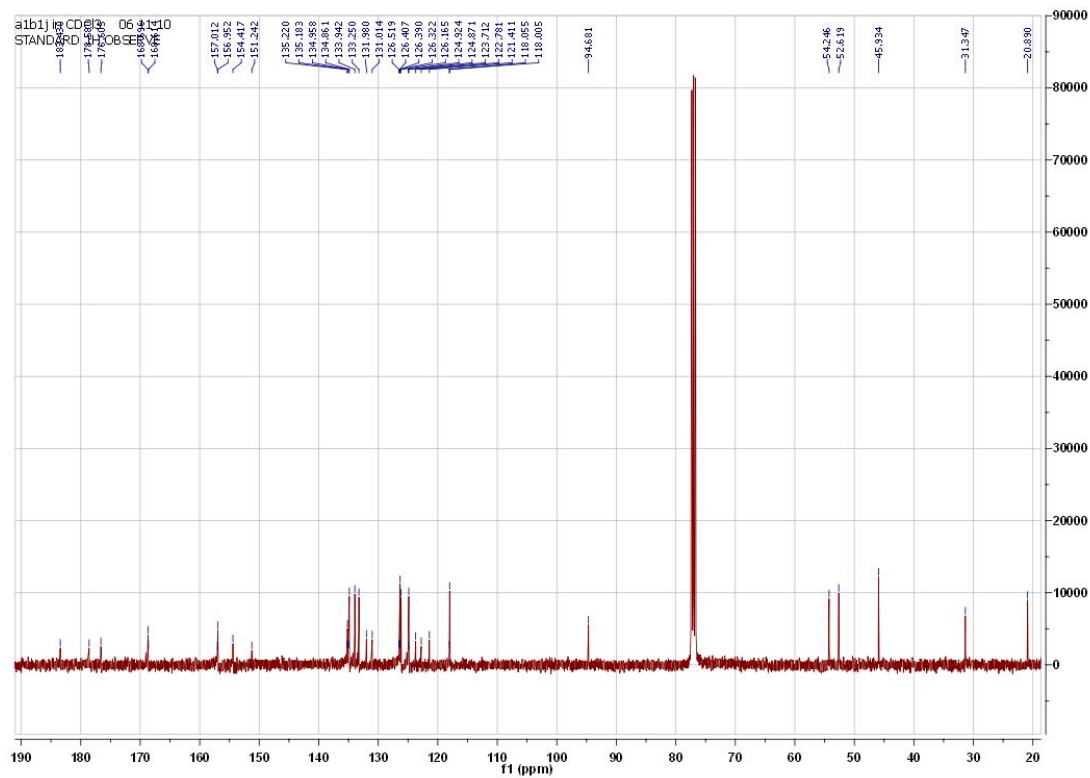
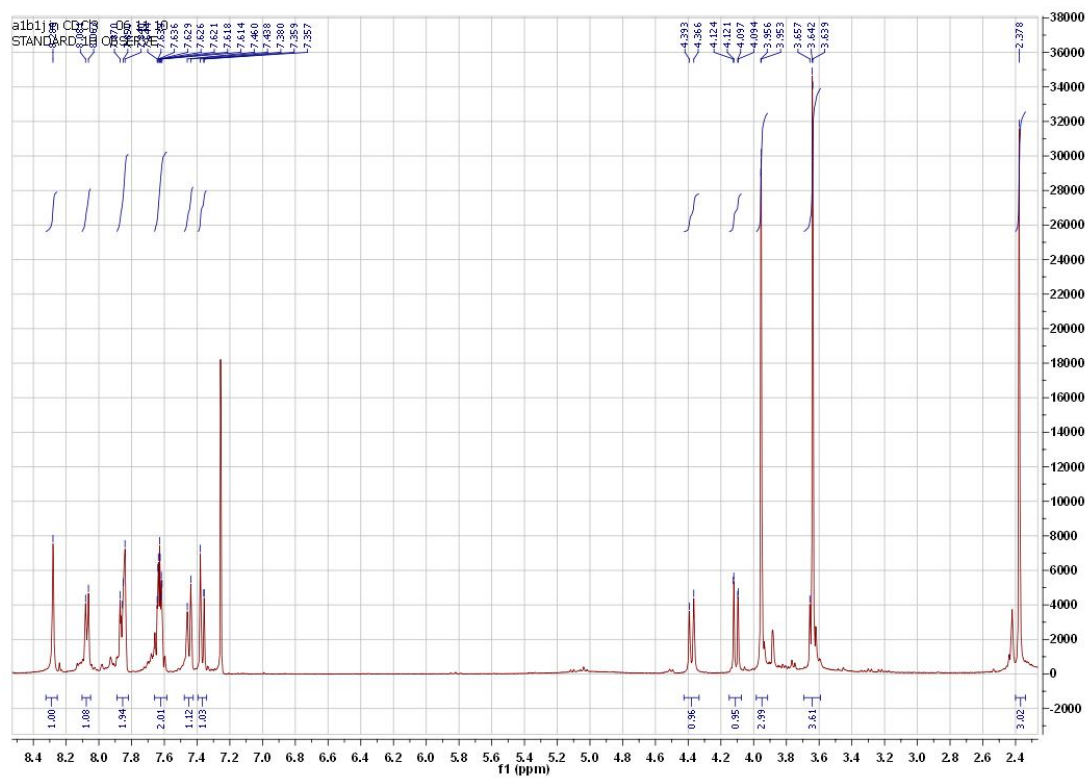
^{13}C NMR (100 MHz, $CDCl_3$): δ 183.4, 178.6, 176.6, 168.7, 168.6, 157.0, 154.4, 151.2, 135.2, 134.9, 133.9, 133.3, 132.0, 131.0, 126.3, 126.2, 124.9, 123.7, 122.8, 121.4, 118.0, 94.7, 54.2, 52.6, 45.9, 31.3, 20.9;

HRMS (ESI): Calculated for $C_{27}H_{21}O_{10}$ [$M+H^+$]: 505.1129, Found: 505.1123;

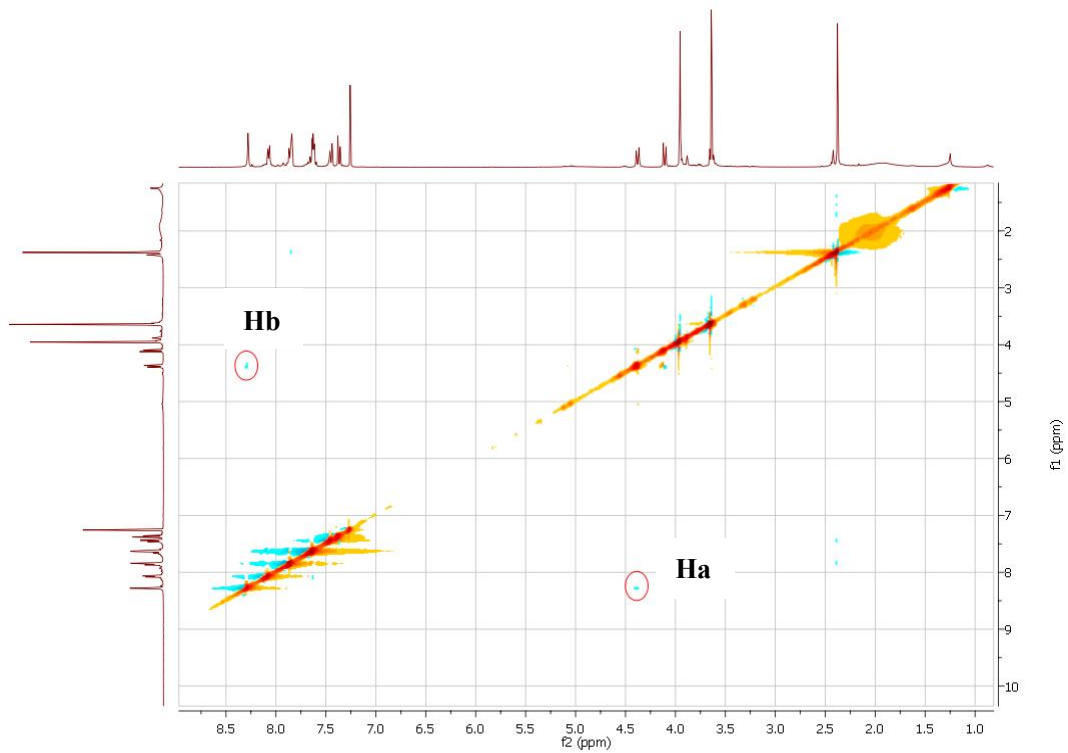
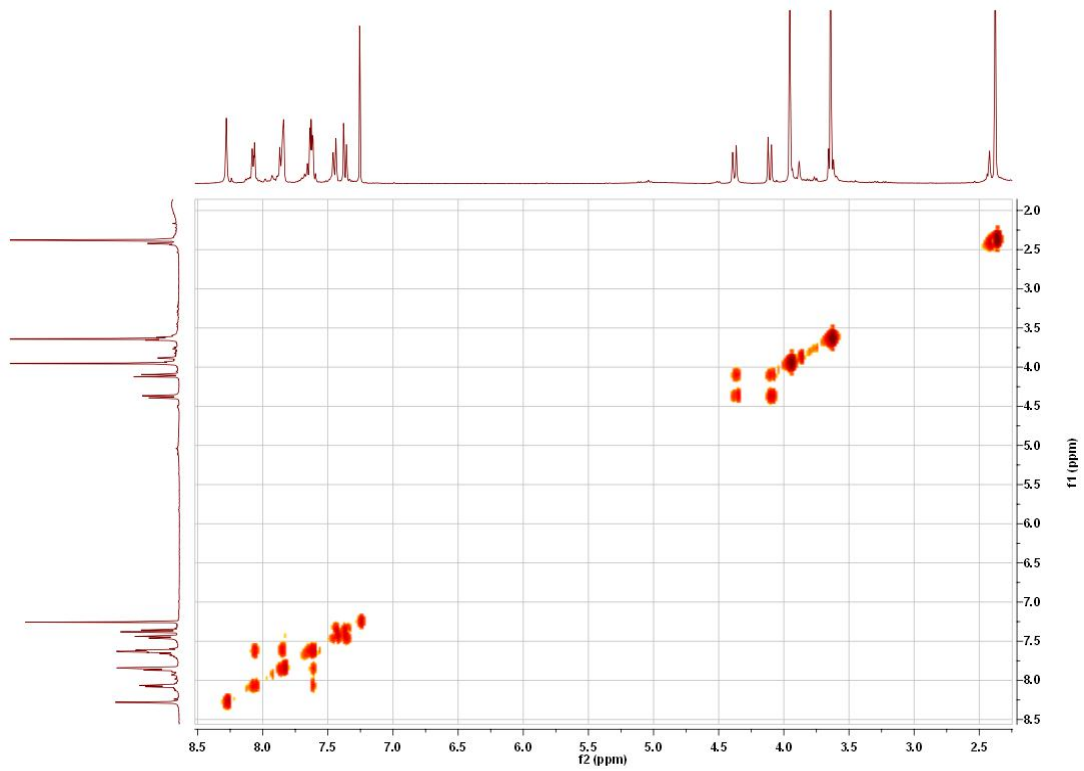


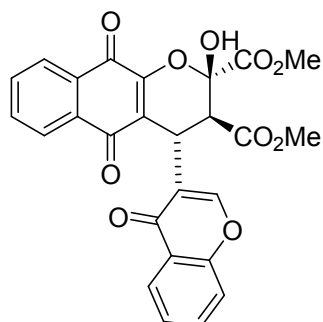
b127

Experimental section



Experimental section





$C_{26}H_{18}O_{10}$
Exact Mass: 490.09
Mol. Wt.: 490.42

b128;

Yield 90%;

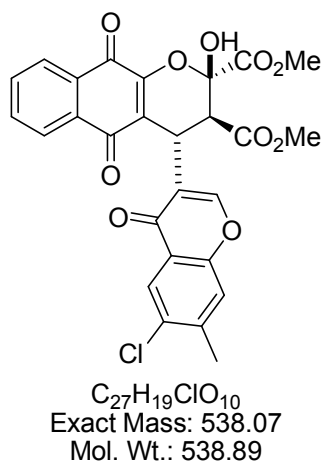
Yellow solid;

M.P.: 149.8°C;**TLC:** R_f = 0.22 cyclohexane/ethyl acetate (1:1);

¹H NMR (400 MHz, CDCl₃): δ 7.92 (d, J = 7.6 Hz, 1H), 7.84-7.77 (m, 2H), 7.73 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 6.8 Hz, 1H), 7.44 (dt, J = 6.8, 1.6 Hz, 1H), 7.01 (dt, J = 6.8, 1.6 Hz, 1H), 6.89 (d, J = 3.6 Hz, 1H), 6.55-6.53 (m, 1H), 5.85 (dd, J = 9.6, 2.0 Hz, 1H), 3.98 (d, J = 11.6 Hz, 1H), 3.84 (d, J = 11.6 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.54 (d, J = 9.6 Hz, 1H);

¹³CNMR (100MHz, CDCl₃): δ 183.9, 179.3, 170.8, 169.0, 165.6, 160.5, 157.7, 148.8, 137.8, 137.1, 136.7, 134.3, 131.6, 128.8, 127.9, 125.5, 124.9, 122.8, 121.6, 118.3, 109.8, 83.6, 62.3, 54.0, 53.2, 36.6;

HRMS (ESI): Calculated for $C_{26}H_{19}O_{10}$ [$M+H^+$]: 491.0973, Found: 491.0968;

**b129;**

Yield 86%;

Yellow solid;

M.P.: 163.7°C;**TLC:** R_f = 0.31 cyclohexane/ethyl acetate (1:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 8.09-8.06 (m, 1H), 8.00 (s, 1H), 7.87-7.85 (m, 1H), 7.65-7.62 (m, 2H), 7.36 (s, 1H), 4.37 (d, J = 10.8 Hz, 1H), 4.06 (d, J = 10.8 Hz, 1H), 3.96 (s, 3H), 3.88-3.86 (m, 1H), 3.65 (s, 3H);

^{13}C NMR (100MHz, $CDCl_3$): δ 183.6, 179.2, 177.9, 170.1, 169.2, 157.0, 155.4, 151.5, 134.0, 133.3, 132.0, 131.0, 126.41, 126.37, 126.2, 125.3, 123.1, 121.6, 120.00, 119.98, 114.5, 94.6, 54.3, 52.7, 45.9, 31.3, 20.7;

HRMS (ESI): Calculated for $C_{27}H_{20}O_{10}Cl$ [$M+H^+$]: 539.0740, Found: 539.0735;

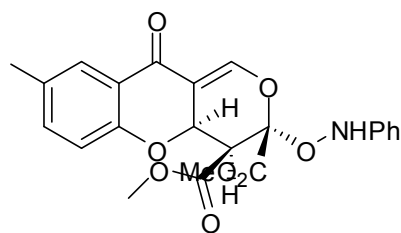
5.5.3 Mononucleophilic

General procedure for stereoselective synthesis of substituted tricyclic benzopyrones (**b138**) from common precursor 1 and bisnucleophiles **b40** and **b41**.

N-phenylhydroxylamine (1.2 equiv.) was added to a degassed dichloromethane (15 mL) solution of keton ester/ keton aldehyde (30 mg, 1 equiv.). The reaction mixture was stirred at room temperature for 2-4 h under argon. The color of solution kept colorless in this process. The reaction was monitored by TLC using cyclohexane/ethyl acetate

(2:1) as eluent. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate as the eluent. Following is the spectroscopic data for the representative compounds.

Triethylamine (1.5 equiv.) was added to a degassed dichloromethane (15 mL) solution of keton ester/ keton aldehyde (30 mg, 1 equiv.) and N-benzylhydroxylamine (1.2 equiv.). The reaction mixture was stirred at room temperature for 2-4 h under argon. The color of the solution turned colorless to straw yellow. The reaction was monitored by TLC using cyclohexane/ethyl acetate (2:1) as eluent. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate (5:1) as the eluent. Following is the spectroscopic data for the representative compounds.



Chemical Formula: $C_{23}H_{21}NO_8$

Exact Mass: 439,1267

Molecular Weight: 439,4147

b134;

Yield 93%;

White solid;

M.P.: 169°C;

TLC: $R_f = 0.41$ cyclohexane/ethyl acetate (2:1);

(Diastereomer ratio 84:16);

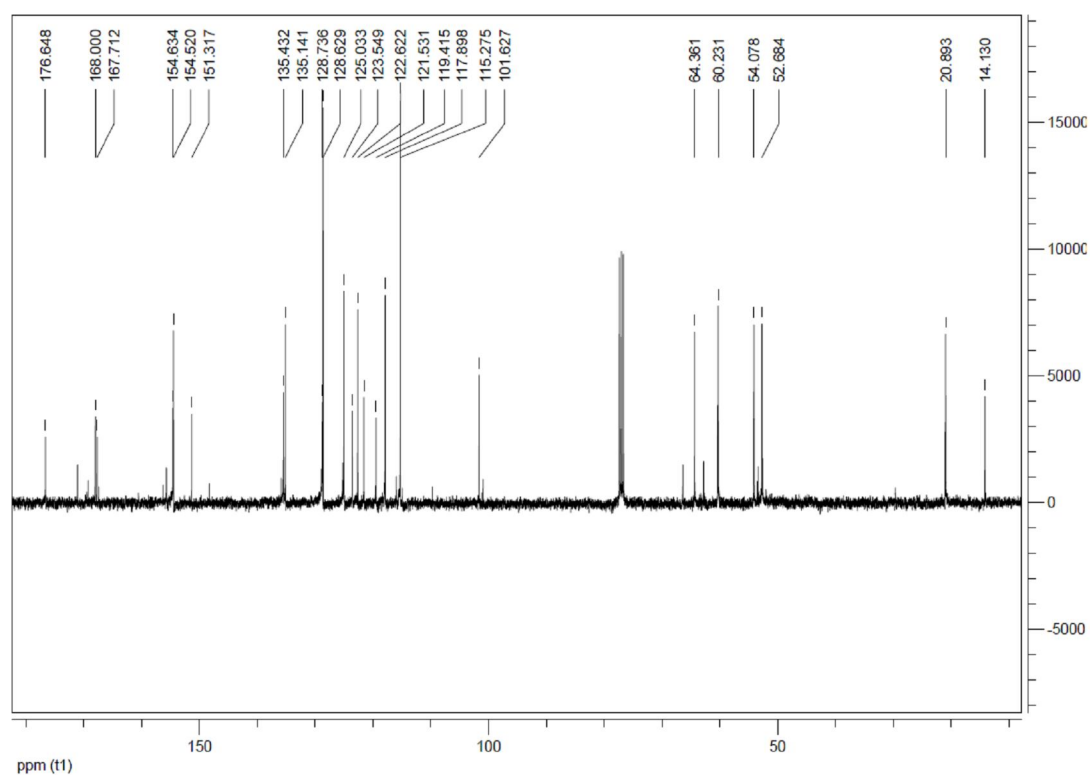
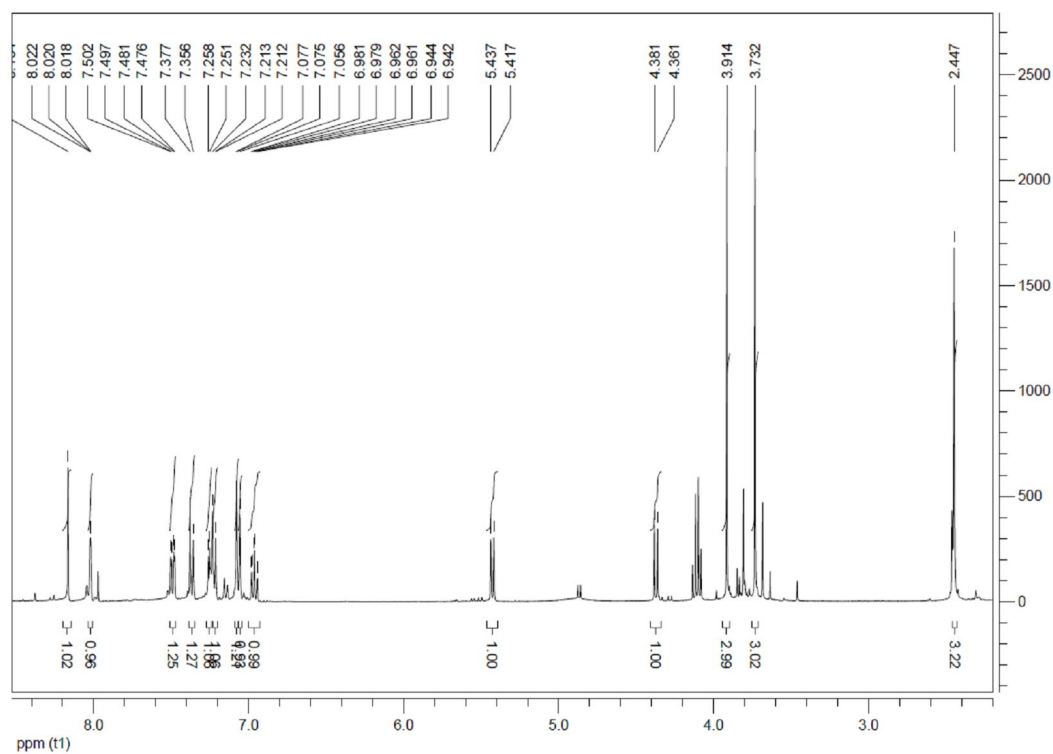
1H NMR (400 MHz, $CDCl_3$): 8.16 (s, 1H), 8.02 (s, 1H), 7.49 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.37 (d, $J = 8.4$ Hz, 1H), 7.26-7.25 (m, 1H), 7.23-7.21 (m, 1H), 7.08 (s, 1H), 7.06 (s, 1H), 6.96 (td, $J = 7.6, 0.8$ Hz, 1H), 5.42 (d, $J = 8.0$ Hz, 1H), 4.37 (d, $J = 8.0$ Hz, 1H), 3.91 (s, 3H), 3.73 (s, 3H), 2.45 (s, 3H);

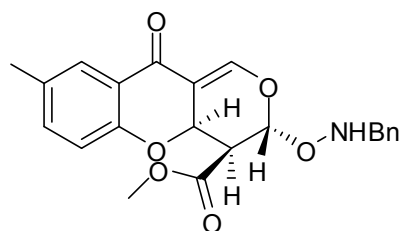
^{13}C NMR (100 MHz, $CDCl_3$): 176.6, 168.0, 167.7, 154.6, 154.5, 151.3, 135.4, 135.1,

Experimental section

128.7, 128.6, 125.0, 123.5, 122.6, 121.5, 119.4, 117.9, 115.3, 101.6, 64.4, 60.2, 54.1, 52.7, 20.9;

HRMS (ESI): Calculated for $C_{23}H_{22}O_8N$ $[M+H]^+$: 440.1332, Found: 440.1335;





Chemical Formula: $C_{22}H_{21}NO_6$

Exact Mass: 395,1369

Molecular Weight: 395,4052

b135;

Yield 87%;

White solid;

M.P.: 101-102°C;

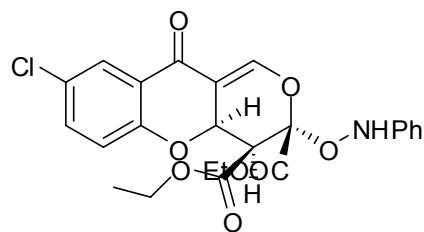
TLC: $R_f = 0.33$, cyclohexane/ethyl acetate (2:1);

(Diastereomer ratio 91:9);

1H NMR (400 MHz, $CDCl_3$): 7.94 (s, 1H), 7.63 (s, 1H), 7.42 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.25-7.23 (m, 3H), 7.12-7.05 (m, 3H), 5.55 (d, $J = 8.8$ Hz, 1H), 4.13 (d, $J = 14.0$ Hz, 1H), 3.94 (d, $J = 14.0$ Hz, 1H), 4.04 (q, $J = 8.8$ Hz, 1H), 3.84 (d, $J = 5.6$ Hz, 1H), 3.67 (s, 3H), 2.39 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): 177.0, 171.5, 155.1, 154.4, 136.5, 135.8, 135.5, 128.6, 128.2, 127.3, 125.2, 123.6, 119.4, 117.7, 97.8, 66.1, 60.8, 52.6, 20.9;

HRMS (ESI): Calculated for $C_{22}H_{22}O_6N$ [$M+H^+$]: 396.1442, Found: 396.1439;



Chemical Formula: $C_{24}H_{22}ClNO_8$

Exact Mass: 487,1034

Molecular Weight: 487,8864

b136;

Yield 90%;

White solid;

M.P.: 135°C;

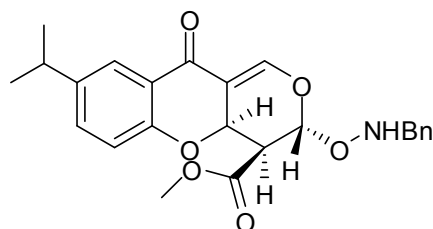
TLC: $R_f = 0.40$ cyclohexane/ethyl acetate (2:1);

(Diastereomer ratio 84:16);

^1H NMR (400 MHz, CDCl_3): δ 8.12 (s, 2H), 7.54 (d, $J = 9.2$ Hz, 1H), 7.36 (d, $J = 9.2$ Hz, 1H), 7.16 (t, $J = 7.6$ Hz, 2H), 7.00 (s, 1H), 6.98 (s, 1H), 6.89 (t, $J = 7.2$ Hz, 1H), 5.34 (d, $J = 7.6$ Hz, 1H) 4.86 (s, 1H), 4.26 (q, $J = 7.2$ Hz, 2H), 4.12 (q, $J = 7.2$ Hz, 2H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.27 (q, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 175.3, 167.2, 154.9, 154.6, 151.3, 134.1, 131.4, 128.7, 128.6, 125.2, 124.8, 122.6, 122.1, 119.9, 118.4, 115.3, 101.6, 63.9, 63.6, 61.7, 60.3, 13.9, 13.8;

HRMS (ESI): Calculated for $\text{C}_{24}\text{H}_{22}\text{ClO}_8\text{N}$ [$\text{M}+\text{H}^+$]:488.1100, Found: 488.1103;



Chemical Formula: $\text{C}_{24}\text{H}_{25}\text{NO}_6$

Exact Mass: 423,1682

Molecular Weight: 423,4584

b137;

Yield 86%;

White solid;

M.P. 109°C;

TLC: $R_f = 0.37$ cyclohexane/ethyl acetate (2:1);

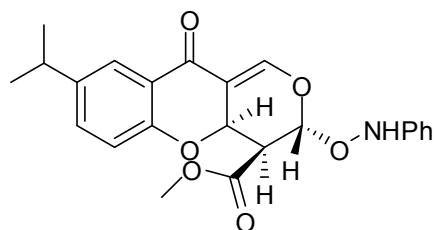
(Diastereomer ratio 88:12);

^1H NMR (400 MHz, CDCl_3): δ 8.08 (d, $J = 2.0$ Hz, 1H), 7.72 (s, 1H), 7.58 (dd, $J = 8.4$, 2.4 Hz, 1H), 7.36 (t, $J = 8.4$ Hz, 1H), 7.33 (s, 1H), 7.31 (s, 1H), 7.21-7.14 (m, 3H), 5.63 (d, $J = 5.6$ Hz, 1H), 4.19 (d, $J = 14.0$ Hz, 1H), 4.03 (d, $J = 14.0$ Hz, 1H), 3.92 (d, $J = 5.6$ Hz, 1H), 3.76 (d, $J = 5.6$ Hz, 1H), 3.75 (s, 3H), 3.08-3.01 (m, 1H), 1.30 (d, $J = 6.8$ Hz,

6H);

¹³C NMR (100 MHz, CDCl₃): δ 177.6, 171.5, 155.1, 154.6, 146.8, 136.6, 133.3, 128.6, 128.2, 127.3, 123.7, 122.6, 119.3, 117.9, 97.8, 66.2, 60.70, 60.68, 52.6, 33.8, 23.88, 23.86;

HRMS (ESI): Calculated for C₂₄H₂₅O₆N [M+H⁺]:424.1755, Found: 424.1752;



Chemical Formula: C₂₃H₂₃NO₆
 Exact Mass: 409,1525
 Molecular Weight: 409,4318

b138;

Yield 88%;

White solid;

M.P.: 114°C;

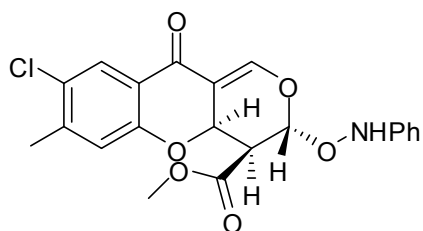
TLC: R_f = 0.43 cyclohexane/ethyl acetate (2:1);

(Diastereomer ratio 85/15);

¹H NMR (400 MHz, CDCl₃): δ 8.07 (s, 1H), 7.87 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.19 (s, 1H), 7.17 (s, 1H), 7.05-7.02 (m, 2H), 6.98 (t, *J* = 8.0 Hz, 1H), 5.77 (br s, 1H), 4.35 (dd, *J* = 5.0; 1.4 Hz, 1H), 3.73 (d, *J* = 5.0 Hz, 1H), 3.68 (s, 3H), 3.03-2.96 (m, 1H), 1.24 (d, *J* = 6.8 Hz, 6H);

¹³C NMR (100 MHz, CDCl₃): δ 177.1, 171.0, 155.7, 154.9, 149.4, 147.0, 133.5, 129.6, 128.8, 126.3, 124.3, 122.7, 120.3, 118.6, 118.1, 97.8, 66.9, 61.2, 52.7, 33.8, 23.94, 23.89;

HRMS (ESI): Calculated for C₂₃H₂₄O₆N [M+H⁺]:410.1598, Found: 410.1597.



Chemical Formula: $C_{21}H_{18}ClNO_6$

Exact Mass: 415,0823

Molecular Weight: 415,8237

b139;

Yield 89%;

White solid;

M.P.: 114°C;

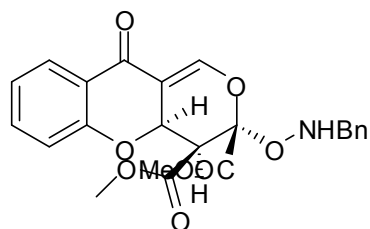
TLC: $R_f = 0.38$ cyclohexane/ethyl acetate (2:1);

(Diastereomer ratio 81:19);

1H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.86 (s, 1H), 7.33 (s, 1H), 7.20-7.16 (m, 3H), 7.03 (s, 1H), 7.01 (s, 1H), 6.98 (t, $J = 7.2$ Hz, 1H), 5.77 (br s, 1H), 4.39 (d, $J = 4.8$ Hz, 1H), 3.75 (d, $J = 1.0$ Hz, 1H), 3.69 (d, $J = 5.0$ Hz, 1H), 3.68 (s, 3H), 2.46 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 170.8, 155.7, 154.7, 144.0, 128.8, 125.6, 125.4, 124.5, 120.6, 120.0, 119.9, 118.6, 113.9, 109.8, 97.8, 66.7, 61.1, 52.8, 20.9;

HRMS (ESI): Calculated for $C_{21}H_{19}ClO_6N [M+H^+]$: 416.0895, Found: 416.0893.



Chemical Formula: $C_{23}H_{21}NO_8$

Exact Mass: 439,1267

Molecular Weight: 439,4147

b140;

Yield 94%;

White solid;

M.P.: 110-111°C;

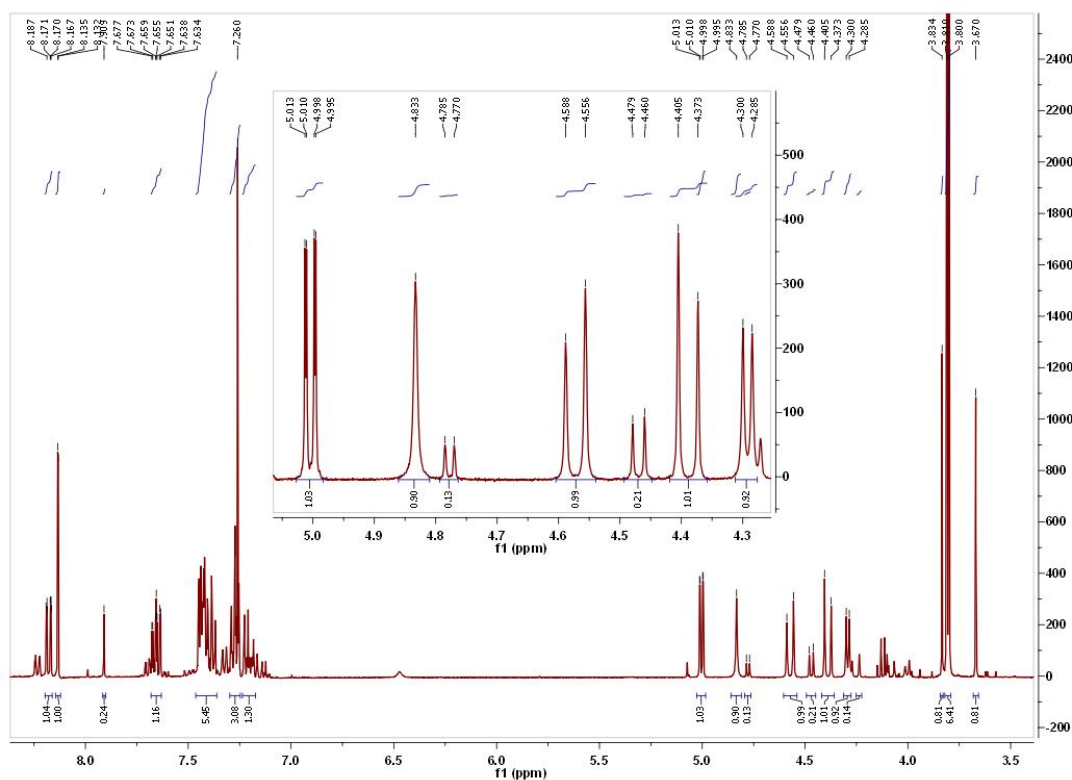
TLC: $R_f = 0.46$ cyclohexane/ethyl acetate (2:1);

(Diastereomer ratio 90:10) ;

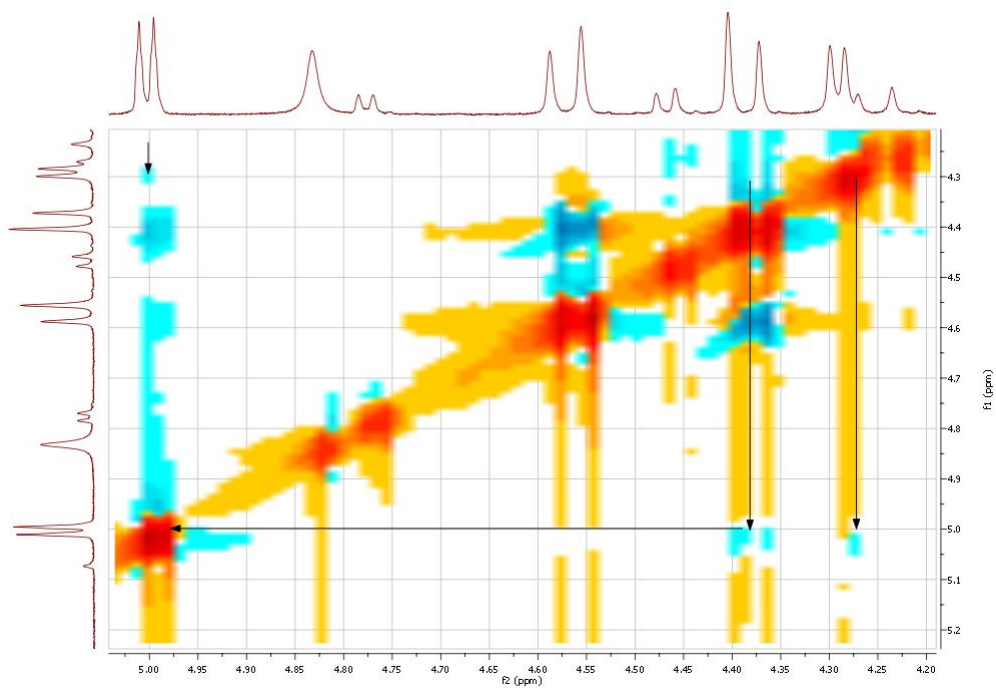
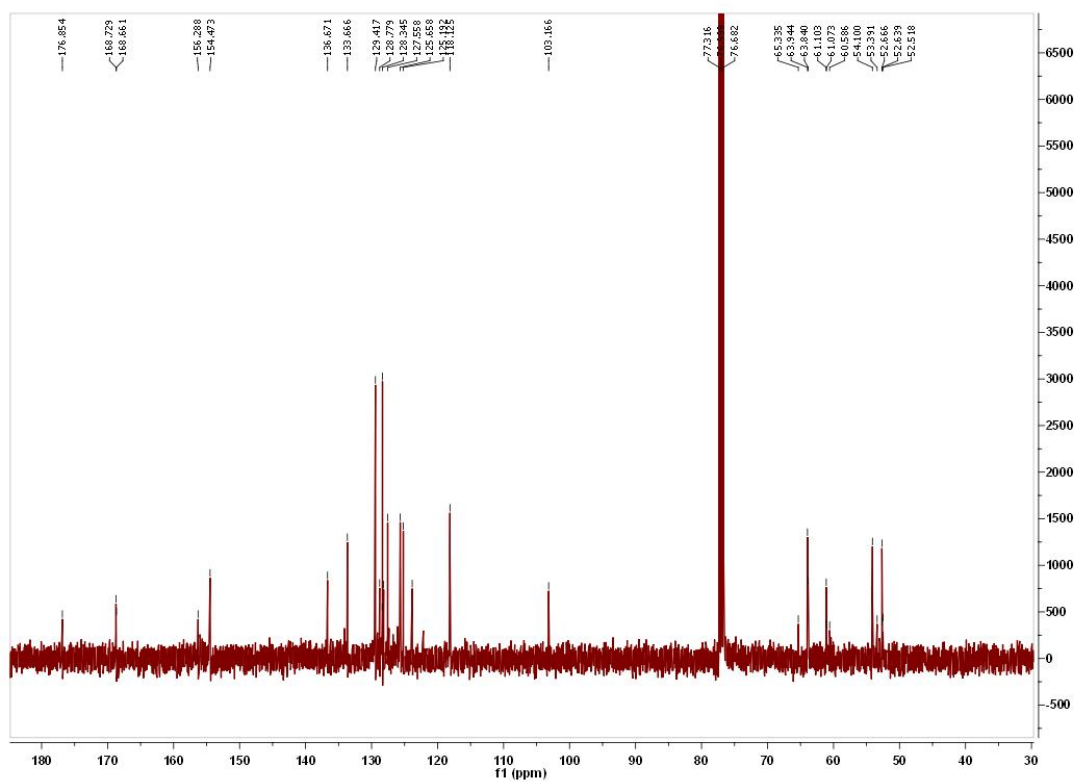
^1H NMR (400 MHz, CDCl_3): 8.17 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.14 (s, 1H), 7.65 (td, $J = 8.0, 1.2$ Hz, 1H), 7.44-7.42 (m, 3H), 7.38 (td, $J = 7.6, 1.2$ Hz, 1H), 7.28-7.25 (m, 2H), 7.22-7.18 (m, 1H), 5.00 (dd, $J = 6.0, 1.2$ Hz, 1H), 4.87 (s, 1H), 4.57 (d, $J = 12.8$ Hz, 1H), 4.38 (d, $J = 12.8$ Hz, 1H), 4.29 (d, $J = 5.6$ Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H);

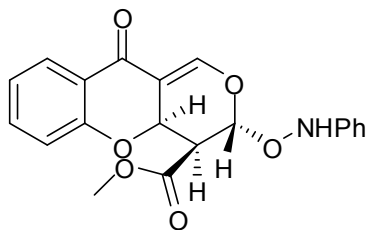
^{13}C NMR (100 MHz, CDCl_3): 176.8, 168.7, 168.6, 156.2, 154.4, 136.6, 133.6, 129.4, 128.7, 128.3, 127.5, 125.6, 125.1, 123.8, 118.1, 103.1, 63.9, 63.8, 61.1, 54.0, 52.6;

HRMS (ESI): Calculated for $\text{C}_{23}\text{H}_{22}\text{O}_8\text{N}[\text{M}+\text{H}^+]$:440.1340, Found: 440.1335;



Experimental section





Chemical Formula: $C_{20}H_{17}NO_6$
 Exact Mass: 367,1056
 Molecular Weight: 367,3521

b141;

Yield 88%;

White solid;

M.P.: 115°C;

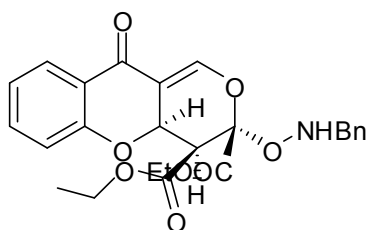
TLC: $R_f = 0.49$ cyclohexane/ethyl acetate (2:1);

(Diastereomer ratio 82:18);

1H NMR (400 MHz, $CDCl_3$): δ 8.28 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.99 (s, 1H), 7.74 (dt, $J = 7.2, 1.6$ Hz, 1H), 7.52-7.47 (m, 2H), 7.26-7.22 (m, 1H), 7.11 (s, 1H), 7.09 (d, $J = 0.8$ Hz, 1H), 7.07-7.03 (m, 2H), 5.85 (d, $J = 6.8$ Hz, 1H), 4.50 (d, $J = 4.8$ Hz, 1H), 3.78 (d, $J = 4.8$ Hz, 1H), 3.74 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 170.9, 155.8, 149.4, 134.4, 128.7, 126.0, 125.8, 124.3, 120.7, 118.4, 118.21, 118.19, 113.9, 97.8, 66.6, 61.1, 52.7;

HRMS (ESI): Calculated for $C_{20}H_{18}O_6N$ [$M+H^+$]:368.1129, Found: 368.1130



Chemical Formula: $C_{25}H_{25}NO_8$
 Exact Mass: 467,1580
 Molecular Weight: 467,4679

b142;

Yield 91%;

White solid;

M.P.: 105°C;

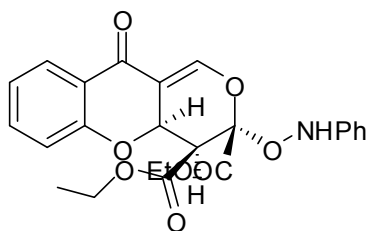
TLC: $R_f = 0.40$ cyclohexane/ethyl acetate (2:1);

(Diastereomer ratio 87:13);

^1H NMR (400 MHz, CDCl_3): δ 8.09 (d, $J = 8.0$ Hz, 1H), 8.05 (s, 1H), 7.58-7.54 (m, 1H), 7.36-7.33 (m, 3H), 7.31-7.27 (m, 2H), 7.18 (t, $J = 7.2$ Hz, 1H), 7.11 (t, $J = 7.2$ Hz, 1H), 4.93 (d, $J = 5.9$ Hz, 1H), 4.48 (d, $J = 13.2$ Hz, 1H), 4.31 (d, $J = 12.8$ Hz, 1H), 4.48 (d, $J = 13.0$ Hz, 1H); 4.31 (d, $J = 12.8$ Hz, 1H); 4.20 (d, $J = 7.2$ Hz, 1H), 4.21-4.16 (m, 4H), 1.19 (t, $J = 7.2$ Hz, 3H), 1.09 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 176.7, 168.3, 168.2, 156.2, 154.6, 136.7, 133.6, 129.4, 128.5, 128.2, 128.1, 127.4, 125.6, 125.1, 118.0, 103.1, 63.7, 63.6, 63.4, 61.5, 61.1, 14.0, 13.7;

HRMS (ESI): Calculated for $\text{C}_{25}\text{H}_{26}\text{O}_8\text{N}$ [$\text{M}+\text{H}^+$] : 468.1653, Found: 468.1646;



Chemical Formula: $\text{C}_{24}\text{H}_{23}\text{NO}_8$

Exact Mass: 453,1424

Molecular Weight: 453,4413

b143;

Yield 93%;

White solid;

M.P.: 147°C;

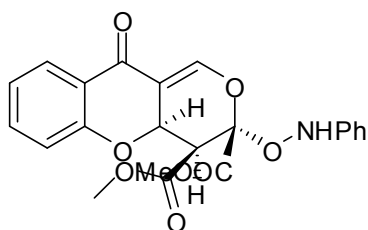
TLC: $R_f = 0.39$ cyclohexane/ethyl acetate (2:1);

(Diastereomer ratio 87:13);

^1H NMR (400 MHz, CDCl_3): δ 8.15 (d, $J = 8.0$ Hz, 1H), 8.11 (s, 1H), 7.58 (d, $J = 7.2$ Hz, 1H), 7.38-7.30 (m, 2H), 7.14 (t, $J = 7.2$ Hz, 2H), 7.05-6.95 (m, 2H), 6.86 (t, $J = 7.2$ Hz, 1H), 5.35 (t, $J = 8.0$ Hz, 1H), 4.98 (d, $J = 7.2$ Hz, 1H), 4.28 (q, $J = 7.6$ Hz, 2H), 4.10 (q, $J = 7.6$ Hz, 2H), 1.24 (t, $J = 7.6$ Hz, 3H), 1.09 (t, $J = 7.6$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 176.4, 167.3, 167.2, 156.2, 154.7, 151.3, 133.8, 128.6, 128.5, 125.7, 125.3, 123.8, 122.4, 121.8, 118.5, 118.0, 115.3, 101.6, 64.1, 63.5, 61.5, 60.2, 13.8, 13.7;

HRMS (ESI): Calculated for $\text{C}_{24}\text{H}_{24}\text{O}_8\text{N}$ [$\text{M}+\text{H}^+$]:454.1489, Found: 454.1491;



Chemical Formula: $\text{C}_{22}\text{H}_{19}\text{NO}_8$
 Exact Mass: 425,1111
 Molecular Weight: 425,3882

b144;

Yield 95%;

White solid;

M.P.: 138°C;

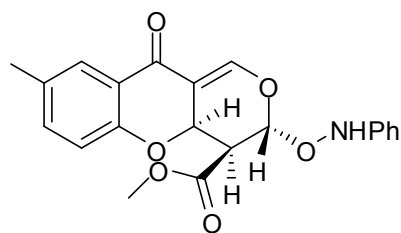
TLC: R_f = 0.61 cyclohexane/ethyl acetate (2:1);

(Diastereomer ratio 82:18);

^1H NMR (400 MHz, CDCl_3): δ 8.54 (d, J = 8.4 Hz, 1H), 8.48 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.56-7.52 (m, 2H), 7.38 (s, 1H), 7.36 (s, 1H), 7.27 (t, J = 7.6 Hz, 1H), 5.72 (q, J = 8.0 Hz, 1H), 5.13(s, 1H), 4.69(d, J = 8.0 Hz, 1H), 4.22(s, 3H), 4.03(s, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 176.6, 168.0, 167.7, 156.4, 154.7, 151.3, 133.9, 128.8, 128.7, 125.8, 125.7, 125.4, 123.9, 122.7, 121.8, 119.4, 118.2, 115.3, 101.6, 64.4, 60.2, 54.2, 52.7;

HRMS (ESI): Calculated for $\text{C}_{22}\text{H}_{20}\text{O}_8\text{N}$ [$\text{M}+\text{H}^+$]:426.1186, Found: 426.1183;



Chemical Formula: C₂₁H₁₉NO₆
 Exact Mass: 381,1212
 Molecular Weight: 381,3787

b145;

Yield 88%;

White solid;

M.P.: 105°C;

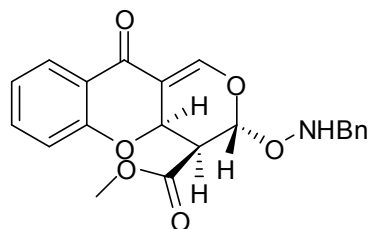
TLC: R_f = 0.40 cyclohexane/ethyl acetate (2:1);

(Diastereomer ratio 81:19);

¹H NMR (400 MHz, CDCl₃): δ 8.07 (s, 1H), 7.95 (s, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.24 (t, *J* = 8.8 Hz, 2H), 7.11 (s, 1H), 7.09 (s, 1H), 7.05 (t, *J* = 7.2 Hz, 1H), 5.84 (s, 1H), 5.29 (s, 1H), 4.44 (d, *J* = 5.2 Hz, 1H), 3.79 (d, *J* = 5.2 Hz, 1H), 3.75 (s, 3H), 2.48 (s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 177.0, 171.0, 155.7, 154.7, 149.4, 136.0, 135.7, 128.7, 125.2, 124.3, 123.7, 120.4, 118.5, 118.0, 117.9, 113.9, 97.8, 66.8, 61.1, 52.7, 21.0;

HRMS (ESI): Calculated for C₂₁H₂₀O₈N [M+H⁺]: 382.1290, Found: 382.1285;



Chemical Formula: C₂₁H₁₉NO₆
 Exact Mass: 381,1212
 Molecular Weight: 381,3787

b146;

Yield 89%;

White solid;

M.P.: 132°C;

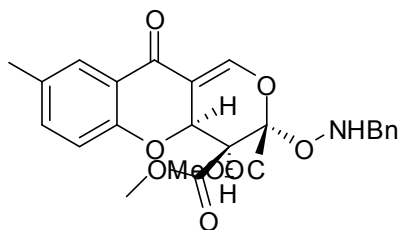
TLC: $R_f = 0.34$ (cyclohexane/ethyl acetate 6:4);

(Diastereomer ratio 88:12);

^1H NMR (400 MHz, CDCl_3): 8.24 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.72 (s, 1H), 7.69 (td, $J = 8.0, 1.6$ Hz, 1H), 7.46-7.41 (m, 2H), 7.33-7.30 (m, 2H), 7.19-7.13 (m, 3H), 7.04 (d, $J = 10.8$ Hz, 1H), 5.63 (d, $J = 10.8$ Hz, 1H), 4.22 (d, $J = 13.6$ Hz, 1H), 4.02 (d, $J = 13.6$ Hz, 1H), 3.93 (d, $J = 5.6$ Hz, 1H), 3.75 (s, 3H), 3.94 (d, $J = 5.6$ Hz, 1H);

^{13}C NMR (100 MHz, CDCl_3): 176.9, 171.4, 156.0, 155.1, 136.4, 134.2, 128.6, 128.1, 127.3, 125.9, 125.6, 123.9, 119.6, 117.9, 97.8, 66.0, 60.8, 60.7, 52.6;

HRMS (ESI): Calculated for $\text{C}_{21}\text{H}_{20}\text{O}_6\text{N}$ [$\text{M}+\text{H}^+$]: 382.1285, Found: 382.1287;



Chemical Formula: $\text{C}_{24}\text{H}_{23}\text{NO}_8$
 Exact Mass: 453,1424
 Molecular Weight: 453,4413

b147;

Yield 94%;

White solid;

M.P.: 126°C;

TLC: $R_f = 0.35$ cyclohexane/ethyl acetate (2:1);

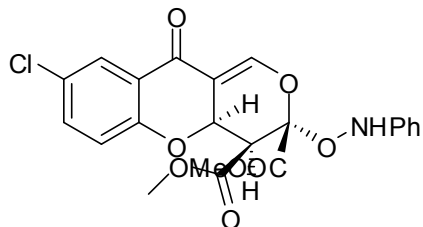
(Diastereomer ratio 86:14);

^1H NMR (400 MHz, CDCl_3): 8.11 (s, 1H), 8.00 (s, 1H), 7.95 (s, 1H), 7.47 (d, $J = 1.6$ Hz, 1H), 7.44-7.39(m, 3H), 7.34-7.31 (m, 1H), 7.22-7.18(m, 1H), 5.06 (d, $J = 2.4$ Hz, 1H), 5.01-4.99 (m, 1H), 4.58-4.36 (dd, $J = 56.8, 12.8$ Hz, 2H), 4.27 (dd, $J = 6.0, 2.4$ Hz, 1H), 3.80 (s, 3H) , 3.79 (s, 3H) , 2.43 (s, 3H);

^{13}C NMR (100 MHz, CDCl_3): 176.9, 168.8, 154.5, 154.3, 136.7, 134.9, 129.4, 128.3,

127.5, 124.9, 117.8, 103.1, 70.7, 64.0, 61.1, 54.0, 52.6, 20.9;

HRMS (ESI): Calculated for C₂₄H₂₄O₈N [M+H⁺]: 454.1495, Found: 454.1493;



Chemical Formula: C₂₂H₁₈ClNO₈
 Exact Mass: 459,0721
 Molecular Weight: 459,8332

b148;

Yield 92%;

White solid;

M.P.: 138°C;

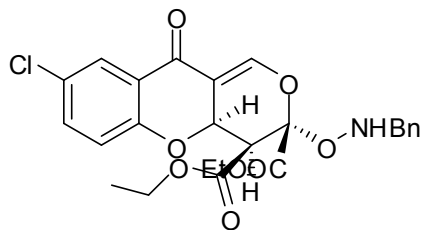
TLC: R_f = 0.35 cyclohexane/ethyl acetate (2:1);

(Diastereomer ratio 85:15);

¹H NMR (400 MHz, CDCl₃): δ 8.13 (s, 2H), 7.56 (td, *J* = 9.2, 2.8 Hz, 1H), 7.37 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.20-7.16 (m, 2H), 7.01-6.99 (m, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 5.37 (d, *J* = 8.0 Hz, 1H), 4.77(s, 1H), 4.28 (d, *J* = 8.0 Hz, 1H), 3.87(s, 3H), 3.68(s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 175.5, 167.8, 167.6, 154.8, 154.7, 151.2, 134.2, 131.5, 128.8, 128.7, 125.2, 124.8, 122.8, 122.0, 119.9, 119.2, 115.3, 101.7, 64.2, 60.2, 54.2, 52.8;

HRMS (ESI): Calculated for C₂₂H₁₉ClO₈N [M+H⁺]:460.0795, Found: 460.0791;



Chemical Formula: C₂₅H₂₄ClNO₈

Exact Mass: 501,1190

Molecular Weight: 501,9130

b149;

Yield 88%;

White solid;

M.P.: 119°C;

TLC: R_f = 0.49 cyclohexane/ethyl acetate (2:1);

(Diastereomer ratio 86/14);

¹H NMR (400 MHz, CDCl₃): δ 8.04 (d, *J* = 6.8 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.36-7.30 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.12 (d, *J* = 7.2 Hz, 1H), 4.91 (d, *J* = 5.9 Hz, 1H), 4.49 (d, *J* = 12.8 Hz, 1H), 4.30 (d, *J* = 12.8 Hz, 1H); 4.21-4.12 (m, 5H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H);

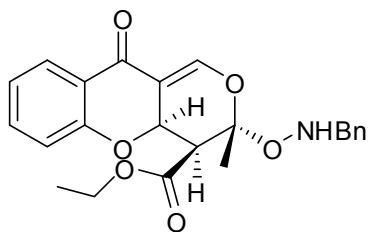
¹³CNMR (100MHz, CDCl₃): δ 175.5, 168.14, 168.10, 154.8, 154.5, 136.6, 133.8, 131.1, 129.4, 128.9, 128.3, 127.5, 125.0, 124.7, 119.8, 103.1, 63.7, 63.6, 63.4, 61.6, 61.1, 14.0, 13.7;

HRMS (ESI): Calculated for C₂₅H₂₅ClO₈N [M+H⁺]: 502.1263, Found: 502.1256.

Synthesis **b154** with (Z)-methyl 3-oxo-2-((4-oxo-4H-chromen-3-yl)-methylene)-butanoate **b150** and N-benzylhydroxylamine **b40**

Triethylamine (1.5 equiv.) was added to a degassed dichloromethane (15 mL) solution of keton ester/ keton aldehyde (30 mg, 1 equiv.) and N-benzylhydroxylamine (1.2 equiv.). The reaction mixture was stirred at room temperature for 2-4 h under argon. The color of the solution turned colorless to straw yellow. The reaction was monitored by TLC using cyclohexane/ethyl acetate (2:1) as eluent. After evaporation of the

solvent, the crude product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate (5:1) as the eluent. Following is the spectroscopic data for the representative compounds.



Chemical Formula: $C_{23}H_{23}NO_6$
Exact Mass: 409,1525
Molecular Weight: 409,4318

b154;

Yield 89%;

White solid;

M.P.: 129°C;

TLC: $R_f = 0.35$ cyclohexane/ethyl acetate (2:1);

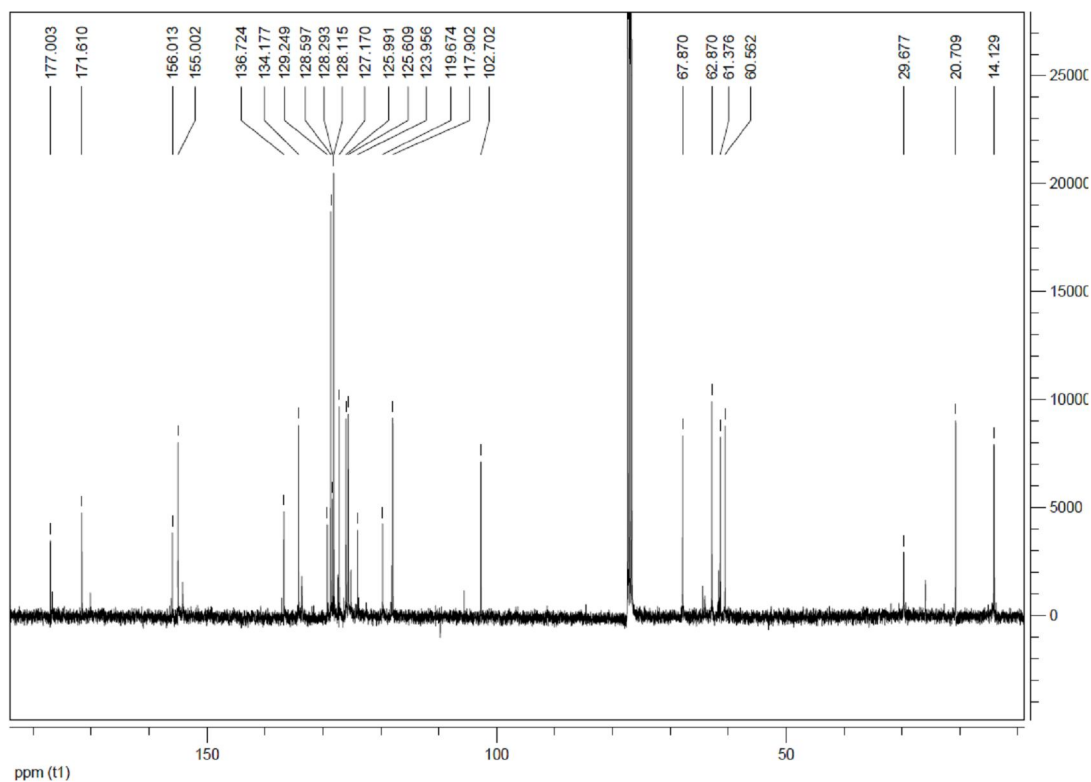
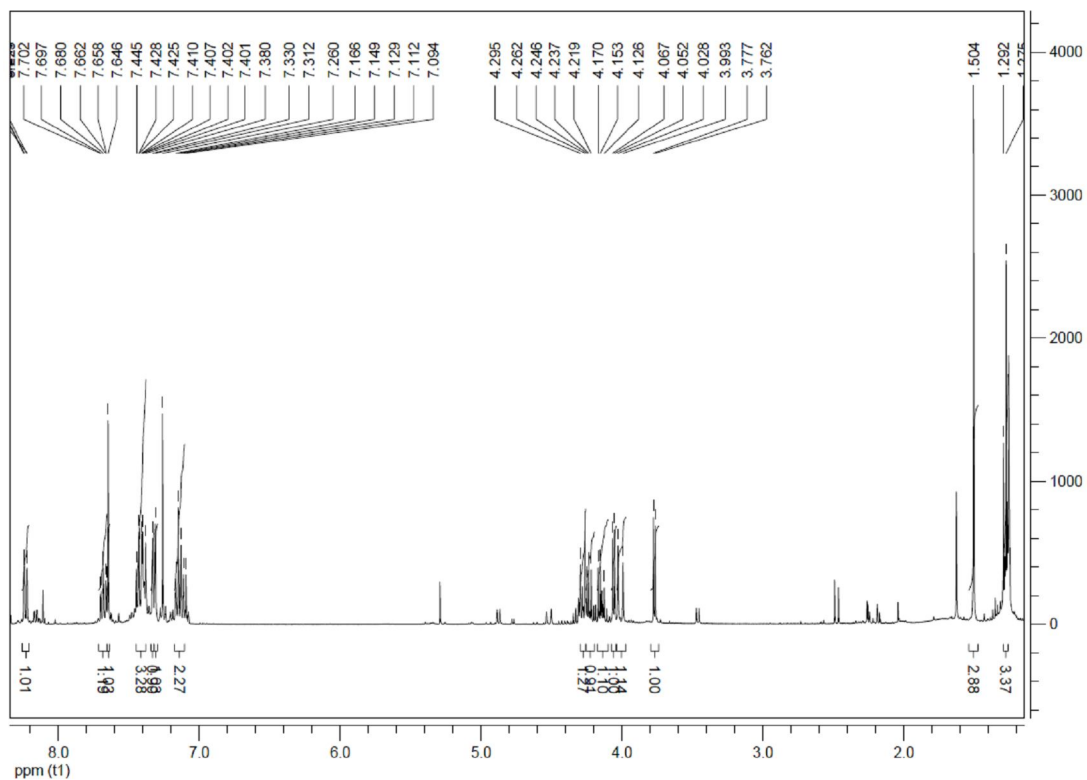
(Diastereomer ratio 82:18);

1H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.70 (td, $J = 8.8, 2.0$ Hz, 1H), 7.65 (s, 1H), 7.45-7.38 (m, 3H), 7.33 (s, 1H), 7.31 (s, 1H), 7.17-7.09 (m, 2H), 4.30-3.99 (dd, $J = 107.6, 14.0$ Hz, 2H), 4.25-4.13 (m, 2H), 4.06 (d, $J = 6.0$ Hz, 1H), 3.77 (d, $J = 6.0$ Hz, 1H), 1.50 (s, 3H), 1.28 (t, $J = 6.8$ Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 171.6, 156.0, 122.0, 136.7, 134.2, 129.2, 128.6, 128.3, 128.1, 127.2, 126.0, 125.6, 124.0, 119.7, 117.9, 102.7, 67.9, 62.9, 61.4, 60.6, 20.7, 14.1;

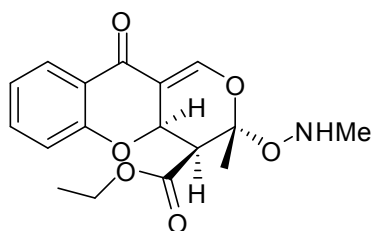
HRMS (ESI): Calculated for $C_{23}H_{24}O_6N [M+H^+]$: 410.1600, Found: 410.1596;

Experimental section



Synthesis **b158** with (Z)-methyl 3-oxo-2-((4-oxo-4H-chromen-3-yl)-methylene)-butanoate **b150** and N-hydroxymethylamine **b42**

Triethylamine (1,5 equiv.) was added to a degassed dichloromethane (15 mL) solution of keton ester/ keton aldehyde (30 mg, 1 equiv.) and N-hydroxymethylamine (1.2 equiv.). The reaction mixture was stirred at room temperature for 2-4 h under argon. The color of the solution turned colorless to straw yellow. The reaction was monitored by TLC using cyclohexane/ethyl acetate (2:1) as eluent. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate (5:1) as the eluent. Following is the spectroscopic data for the representative compounds.



Chemical Formula: $C_{17}H_{19}NO_6$

Exact Mass: 333,1212

Molecular Weight: 333,3359

b158;

Yield 83%;

White solid;

M.P.: 142°C;

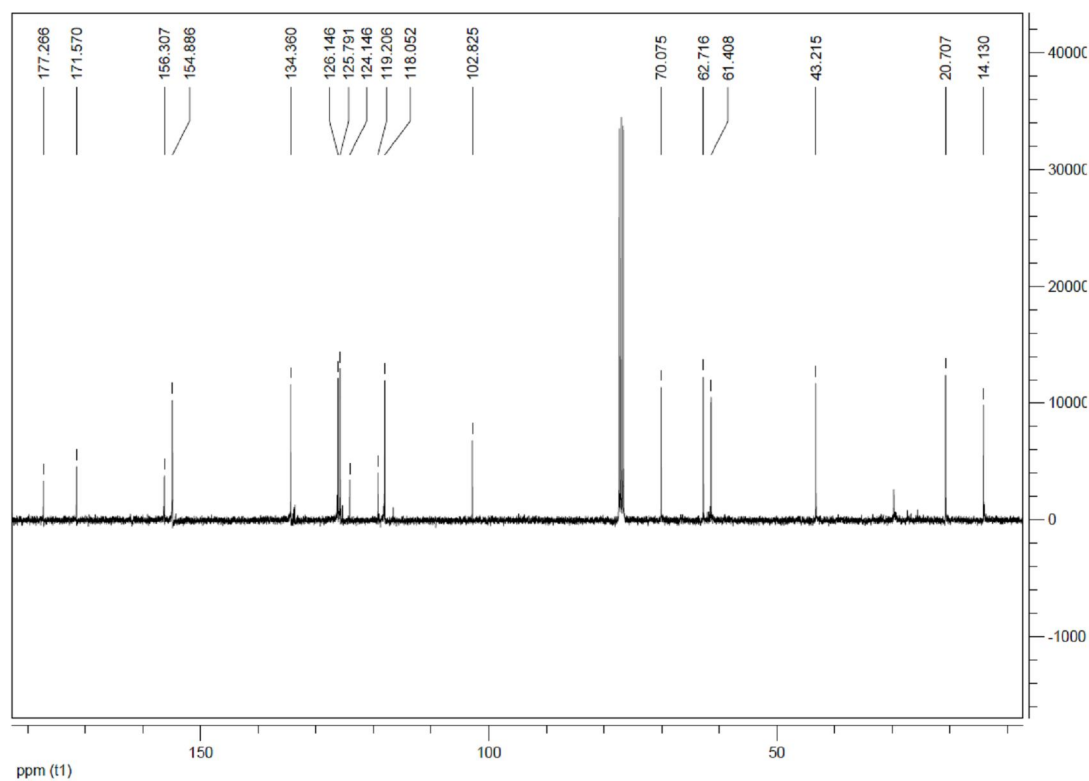
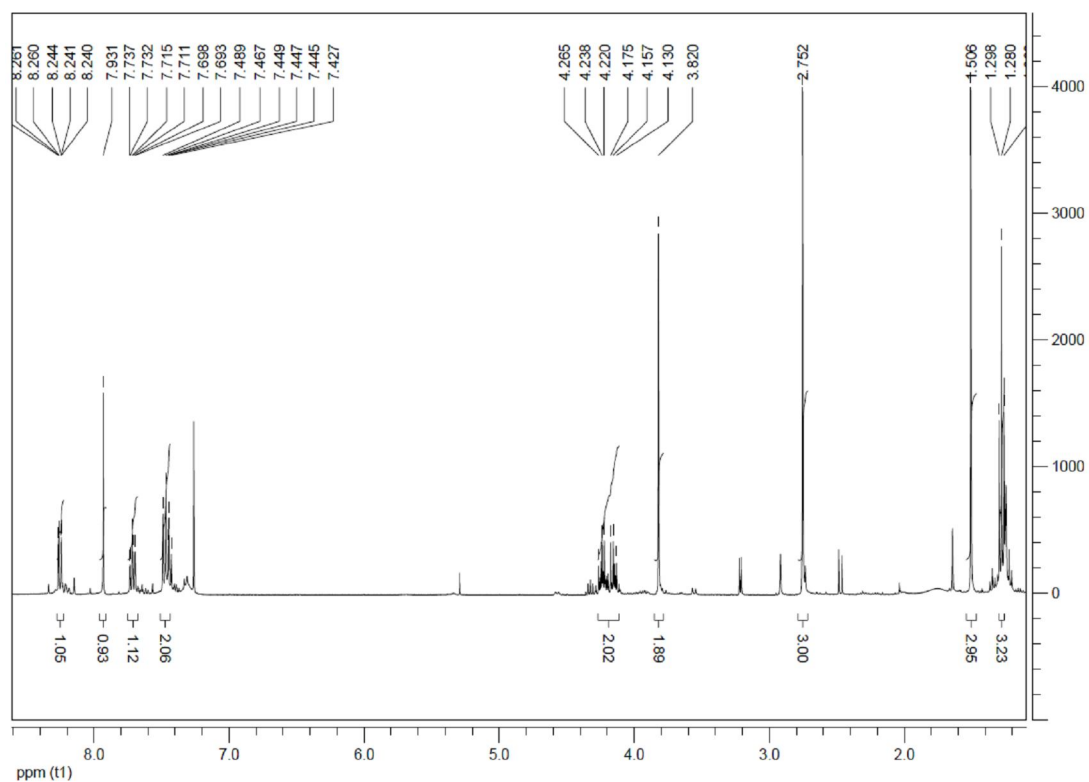
TLC: $R_f = 0.44$ cyclohexane/ethyl acetate (2:1);

(Diastereomer ratio 86:14);

1H NMR (400 MHz, $CDCl_3$): δ 8.25 (dd, $J = 8.0, 2.8$ Hz, 1H), 7.93 (s, 1H), 7.72 (td, $J = 8.8, 2.0$ Hz, 1H), 7.46 (t, $J = 8.4$ Hz, 2H), 4.27-4.13 (m, 2H), 3.82 (s, 2H), 2.75 (s, 3H), 1.51 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 3H);

^{13}C NMR (100MHz, $CDCl_3$): δ 177.3, 171.6, 158.3, 154.9, 134.4, 126.1, 125.8, 124.1, 119.2, 118.1, 102.8, 70.1, 62.7, 61.4, 43.2, 20.7, 14.1;

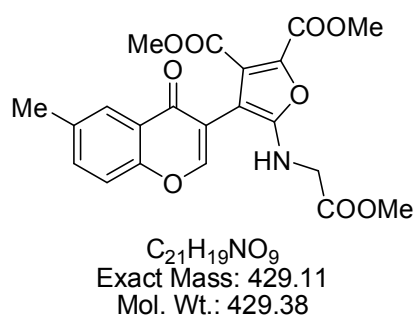
HRMS (ESI): Calculated for $C_{17}H_{20}O_6N$ [$M+H^+$]:334.1300, Found: 334.1287;



5.5.4 Zwitterions

General procedure for synthesis of substituted 3-(furan-3-yl)-4H-chromen-4-ones (**b165**) from common precursor and bisnucleophile **b44**.

Methyl isocyanoacetate (1.1 mmol.) was added to a anhydrous dichloromethane (15 mL) solution of ketoester (1mmol). The color of solution kept color in this process. The reaction mixture was stirred at room temperature for 3-6 h under argon. The reaction was monitored by TLC using cyclohexane/ethyl acetate (2:1) as eluent. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate (4:1) as the eluent. Following is the spectroscopic data for the representative compounds.

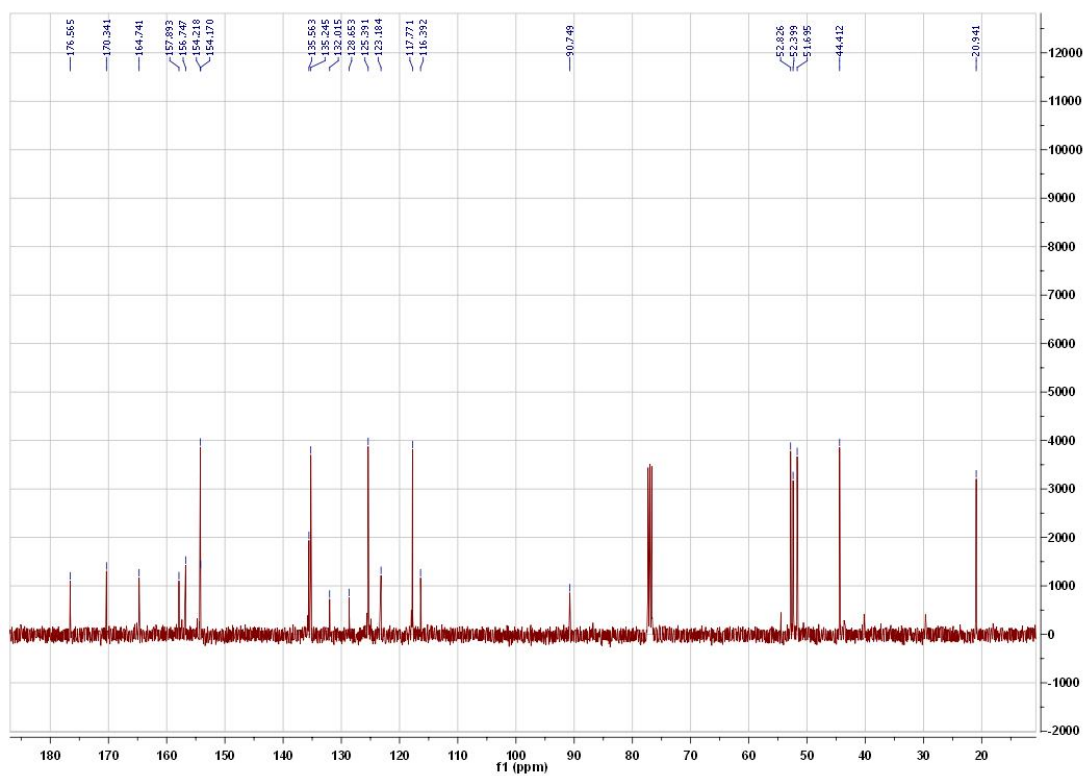
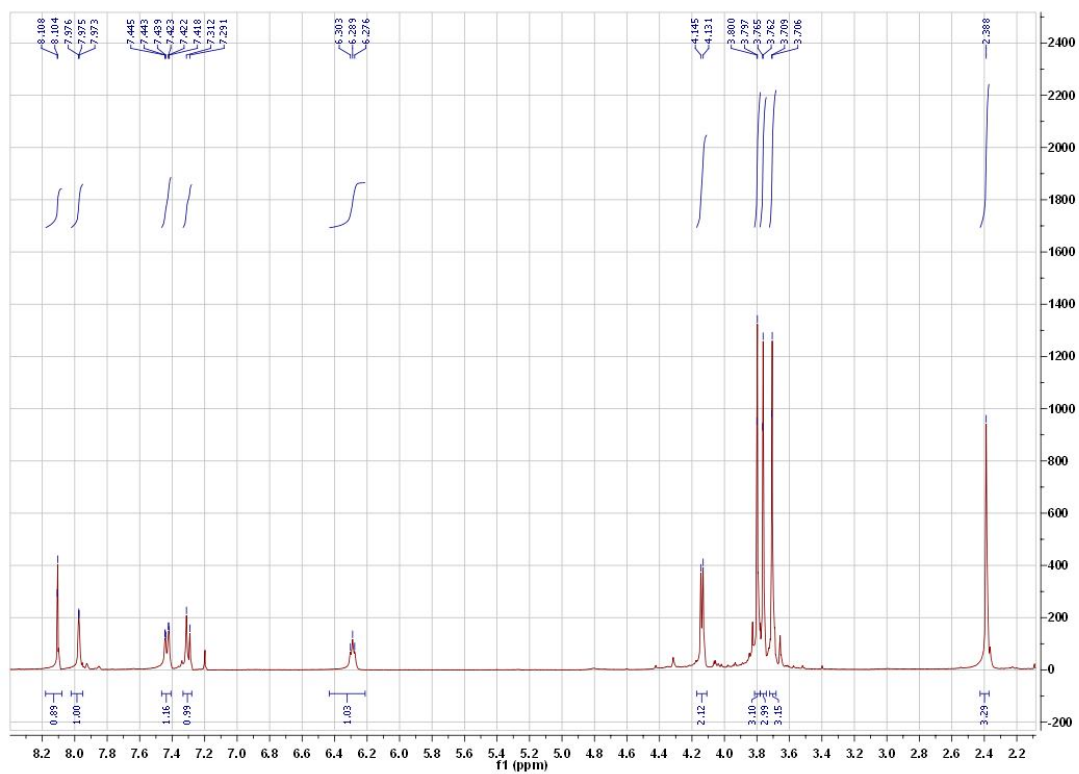
**b162;**

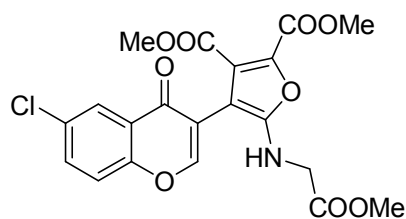
Yield 94%;

White solid;

M.P.: 163°C;**TLC:** R_f = 0.35 cyclohexane/ethyl acetate (2:1); **1H NMR (400 MHz, $CDCl_3$):** δ 8.11 (s, 1H), 7.97 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 6.29 (t, J = 5.2 Hz, 1H), 4.15 (d, J = 5.2 Hz, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 2.39 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 176.6, 170.3, 164.7, 157.9, 156.8, 154.22, 154.17, 135.6, 135.3, 132.0, 128.7, 125.4, 123.2, 117.8, 116.4, 90.8, 52.8, 52.4, 51.7, 44.4, 20.9;**HRMS (ESI):** Calculated for $C_{21}H_{20}O_9N$ [$M+H^+$]:430.1133, Found: 430.1130;

Experimental section





$C_{20}H_{16}ClNO_9$
Exact Mass: 449.05
Mol. Wt.: 449.8

b163;

Yield 91%;

White solid;

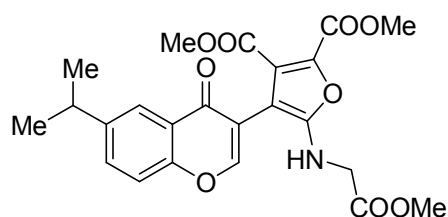
M.P.: 142°C;

TLC: R_f = 0.28 cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 2.4 Hz, 1H), 8.21 (s, 1H), 7.64 (dd, J = 9.2, 2.8 Hz, 1H), 7.45 (d, J = 8.8 Hz, 1H), 6.23 (t, J = 5.6 Hz, 1H), 4.21 (d, J = 5.6 Hz, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 170.3, 157.9, 156.8, 154.6, 154.52, 154.48, 134.3, 134.2, 131.6, 125.7, 125.6, 124.4, 119.9, 119.8, 116.9, 52.9, 52.5, 51.8, 44.4;

HRMS (ESI): Calculated for $C_{20}H_{17}ClO_9N$ [$M+H^+$]:450.0586, Found: 450.0585;



$C_{23}H_{23}NO_9$
Exact Mass: 457.14
Mol. Wt.: 457.43

b164;

Yield 93%;

White solid;

M.P.: 157°C;

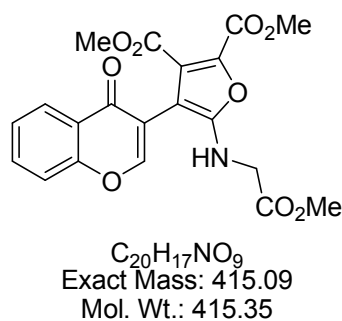
TLC: R_f = 0.41 cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.11(s, 1H), 8.05 (s, 1H), 7.52 (dd, J = 8.4, 1.2 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 6.29 (t, J = 6.0 Hz, 1H), 4.15 (d, J = 6.4 Hz, 2H), 3.80 (s,

3H), 3.77 (s, 3H), 3.72 (s, 3H), 2.99 (m, $J = 7.2$ Hz, 1H), 1.24 (d, $J = 7.2$ Hz, 6H);

^{13}C NMR (100 MHz, CDCl_3): δ 176.9, 170.4, 164.8, 157.9, 156.8, 154.4, 154.2, 146.6, 133.1, 128.7, 126.2, 122.9, 118.0, 116.4, 109.8, 52.9, 52.5, 51.7, 44.5, 33.9, 23.9;

HRMS (ESI): Calculated for $\text{C}_{23}\text{H}_{24}\text{O}_9\text{N}$ [$\text{M}+\text{H}^+$]:458.1446, Found: 458.1441;



b165;

Yield 95%;

White solid;

M.P.: 153°C;

TLC: $R_f = 0.16$ cyclohexane/ethyl acetate (2:1);

^1H NMR (400 MHz, CDCl_3): δ 8.27 (dd, $J = 8.0, 1.2$ Hz, 1H), 8.19 (s, 1H), 7.69 (dt, $J = 7.2, 1.6$ Hz, 1H), 7.47 (d, $J = 8.8$ Hz, 1H), 7.42 (t, $J = 8.0$ Hz, 1H), 6.33 (t, $J = 5.6$ Hz, 1H), 4.21 (d, $J = 6.0$ Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H);

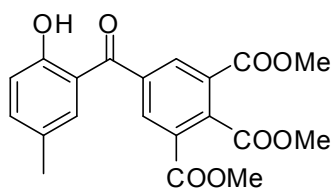
^{13}C NMR (100 MHz, CDCl_3): δ 175.7, 170.5, 163.8, 157.5, 154.4, 134.1, 134.0, 126.39, 126.37, 126.3, 125.9, 118.3, 118.1, 114.4, 109.8, 54.6, 52.9, 51.8, 44.6;

HRMS (ESI): Calculated for $\text{C}_{20}\text{H}_{18}\text{O}_9\text{N}$ [$\text{M}+\text{H}^+$]:416.0976, Found: 416.0973;

General procedure for synthesis of substituted (**b193**) from common precursor and **b67**.

Methyl isocyanoacetate (1.1 mmol.) was added to an anhydrous dichloromethane (15 mL) solution of ketoester (1mmol) with TEA (1.5mmol). The color of solution kept color in this process. The reaction mixture was stirred at room temperature for 3-6 h under argon. The reaction was monitored by TLC using cyclohexane/ethyl acetate (2:1) as eluent. After evaporation of the solvent, the crude product was purified by column

chromatography on silica gel with cyclohexane/ethyl acetate (4:1) as the eluent. Following is the spectroscopic data for the representative compounds.



Chemical Formula: C₂₀H₁₈O₈
 Exact Mass: 386,1002
 Molecular Weight: 386,3521

b170;

Yield 93%;

White solid;

M.P.: 143°C;

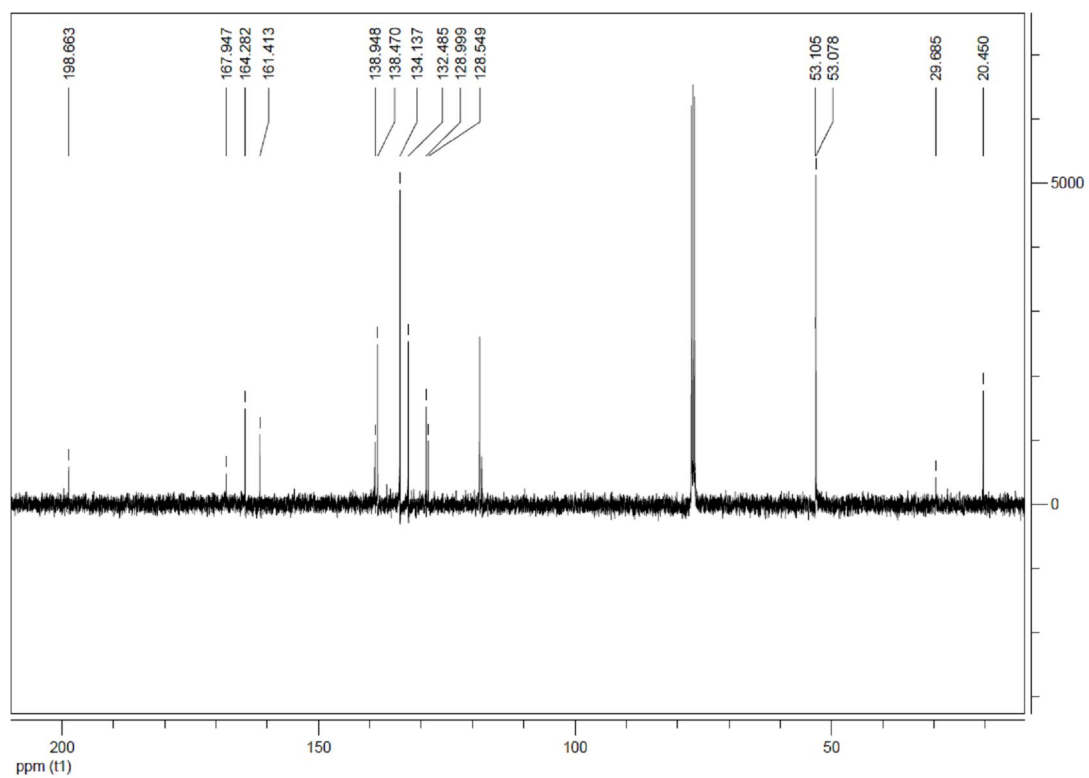
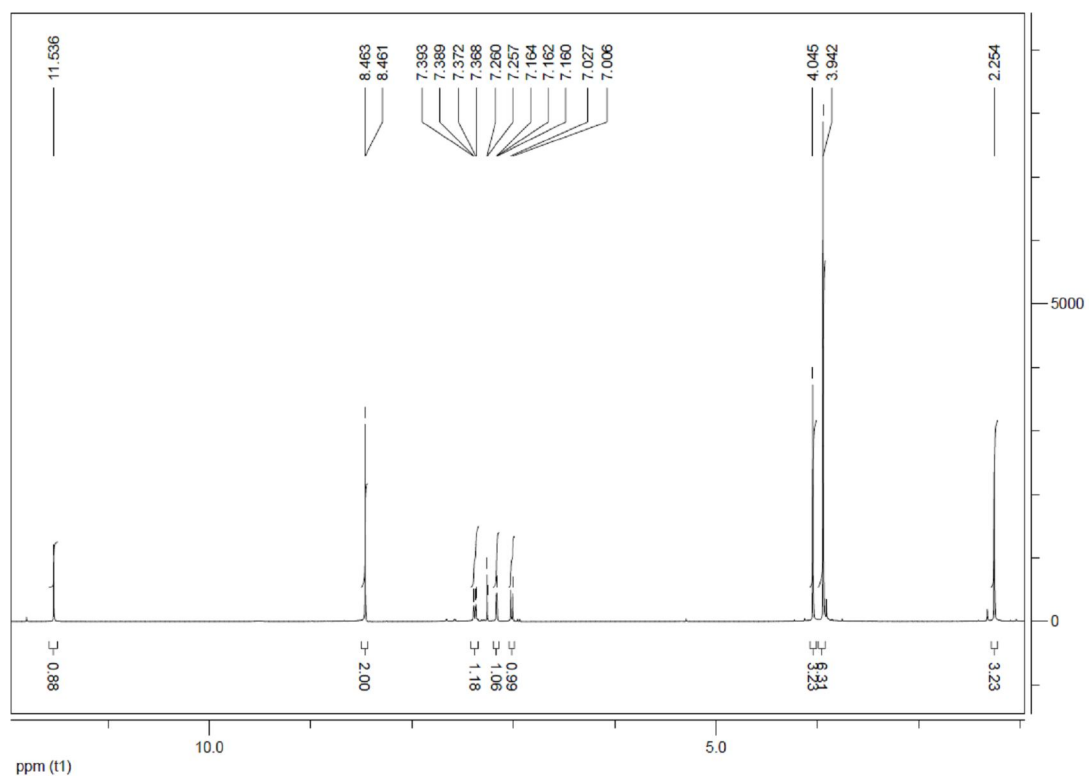
TLC: R_f = 0.22 cyclohexane/ethyl acetate (5:1);

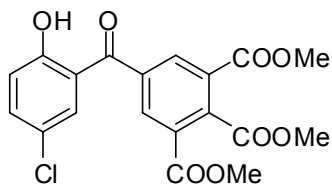
¹H NMR (400 MHz, CDCl₃): δ 11,54 (s, 1H), 8,46(s, 2H), 7,39 (dd, *J* = 1,8 & 8,5 Hz, 1H), 7,16 (s, 1H), 7,02 (d, *J* = 8,5 Hz, 1H), 4,05 (s, 3H), 3,94 (s, 6H), 2,25 (s, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 198.7, 167.9, 164.3, 161.4, 138.9, 138.5, 134.1, 132.5, 129.0, 128.5, 53.11, 53.08, 20.5;

HRMS (ESI): Calculated for C₂₀H₁₇O₈ [M-H⁺]: 385.0927, Found: 385.0924

Experimental section





Chemical Formula: $C_{19}H_{15}ClO_8$

Exact Mass: 406,0455

Molecular Weight: 406,7706

b171;

Yield 89%;

White solid;

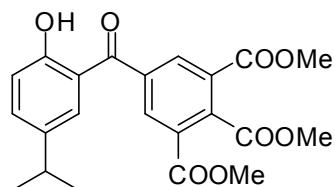
M.P.: 148°C;

TLC: $R_f = 0.21$ cyclohexane/ethyl acetate (5:1);

1H NMR (400 MHz, $CDCl_3$): δ 11,60 (s, 1H), 8,47(s, 2H), 7,52 (d, $J = 9,0$ Hz, 1H), 7,38 (m, 1H), 7,08 (dd, $J = 1,1$ & 8,9 Hz, 1H), 4,05 (s, 3H), 3,95 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 167.7, 164.1, 161.9, 139.5, 138.0, 137.2, 134.1, 131.7, 129.3, 124.1, 120.5, 119.1, 109.8, 53.17, 53.14;

HRMS (ESI): Calculated for $C_{19}H_{14}ClO_8$ [$M-H^+$]:405.0383, Found: 405.0380.



Chemical Formula: $C_{22}H_{22}O_8$

Exact Mass: 414,1315

Molecular Weight: 414,4053

b172;

Yield 91%;

White solid;

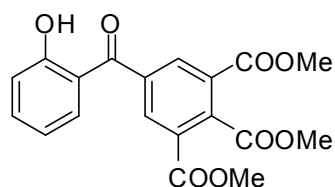
M.P.: 154°C;

TLC: $R_f = 0.18$ cyclohexane/ethyl acetate (5:1);

1H NMR (400 MHz, $CDCl_3$): δ 11,52 (s, 1H), 8,54(s, 2H), 7,45 (dd, $J = 8.6, 1.2$ Hz, 1H), 7,28 (m, 1H), 7,05 (d, $J = 8,6$ Hz, 1H), 4,05 (s, 3H), 3,94 (s, 6H), 2,83 (m, 1H), 1,19 (d, $J = 6,9$ Hz, 6H);

^{13}C NMR (100 MHz, CDCl_3): δ 193.8, 168.0, 164.2, 161.6, 139.6, 138.7, 136.0, 134.7, 130.1, 129.0, 118.6, 118.1, 53.12, 53.04, 33.1, 23.9 ;

HRMS (ESI): Calculated for $\text{C}_{22}\text{H}_{22}\text{O}_8$ [$\text{M}-\text{H}^+$]:413.1240, Found: 413.1238



Chemical Formula: $\text{C}_{19}\text{H}_{16}\text{O}_8$
 Exact Mass: 372,0845
 Molecular Weight: 372,3255

b173;

Yield 94%;

White solid;

M.P.: 140°C;

TLC: R_f = 0.19 cyclohexane/ethyl acetate (5:1);

^1H NMR (400 MHz, CDCl_3): δ 11,72 (s, 1H), 8,48(s, 2H),7,57 (m, 1H), 7,43 (dd, J = 8.0, 1.7 Hz, 1H), 7,12 (dd, J = 0,7 & 8,4 Hz, 1H), 6,92 (m, 1H), 4,03 (s, 3H), 3,94 (s, 6H);

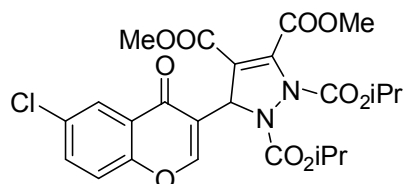
^{13}C NMR (100 MHz, CDCl_3): δ 198.6, 167.8, 164.2, 163.4, 138.7, 137.3, 134.3, 132.9, 129.0, 119.3, 118,8. 118.5, 50.1;

HRMS (ESI): Calculated for $\text{C}_{19}\text{H}_{15}\text{O}_8$ [$\text{M}-\text{H}^+$]:371.0769, Found: 371.0769;

General procedure for synthesis of diisopropyl 3-(4-oxo-4*H*-chromen-3-yl)-1*H*-pyrazole-1,2(3*H*)-dicarboxylates (**b177**) from common precursor and bisnucleophile **b47**.

Triphenylphosphine (1.3 mmol.) was added to an anhydrous THF (15 mL) solution of keton ester (1 mmol.) and Diisopropyl azodicarboxylate (1.2 mmol.) at the argon atmosphere. The reaction mixture was stirred at room temperature for 2-5 h under argon. The color of solution turned straw yellow to deep yellow immediately, then tuned to

straw yellow slowly. The reaction was monitored by TLC using cyclohexane/ethyl acetate (2:1) as eluent. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate (4:1) as the eluent to offer yellow solid.



$C_{24}H_{25}ClN_2O_{10}$
Exact Mass: 536.12
Mol. Wt.: 536.92

b177;

Yield 86%;

Yellow solid;

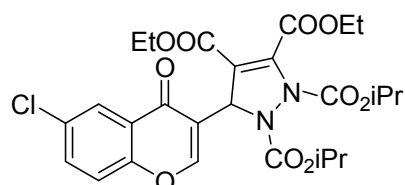
M.P.: 121°C;

TLC: $R_f = 0.39$ cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, $J = 2.4$ Hz, 1H), 7.93 (s, 1H), 7.50 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.33 (d, $J = 8.8$ Hz, 1H), 5.63 (s, 1H), 5.08 (d, $J = 2.4$ Hz, 1H), 4.94 (d, $J = 2.4$ Hz, 1H), 3.89 (s, 3H), 3.60 (s, 3H), 1.34-1.25 (m, 12H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 162.5, 162.0, 154.5, 154.4, 152.8, 146.5, 133.9, 131.2, 125.6, 125.5, 120.9, 120.4, 119.8, 119.7, 109.8, 72.2, 71.7, 63.0, 53.2, 52.1, 22.0, 21.9, 21.8;

HRMS (ESI): Calculated for $C_{24}H_{26}ClO_{10}N_2$ $[M+H]^+$: 537.1271, Found: 537.1263;



$C_{26}H_{29}ClN_2O_{10}$
Exact Mass: 564.15
Mol. Wt.: 564.97

b178;

Yield 84%;

Yellow solid;

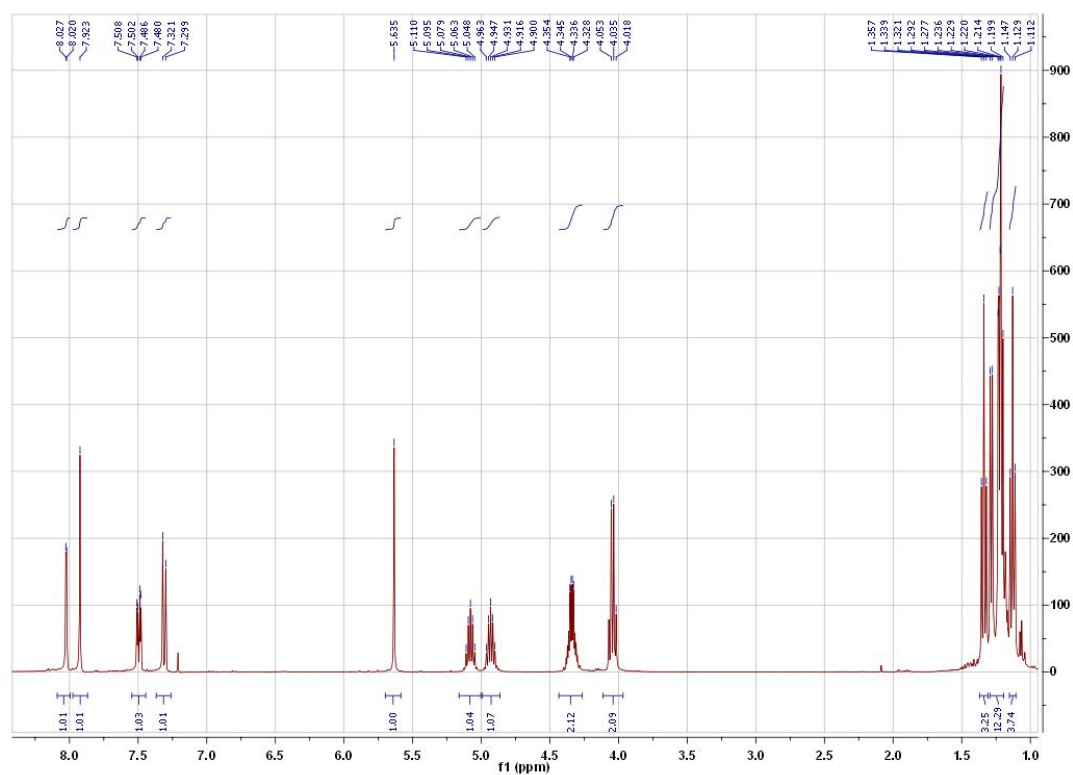
M.P.: 130°C;

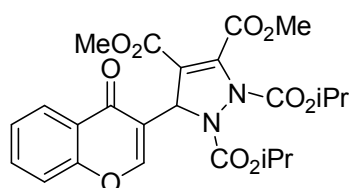
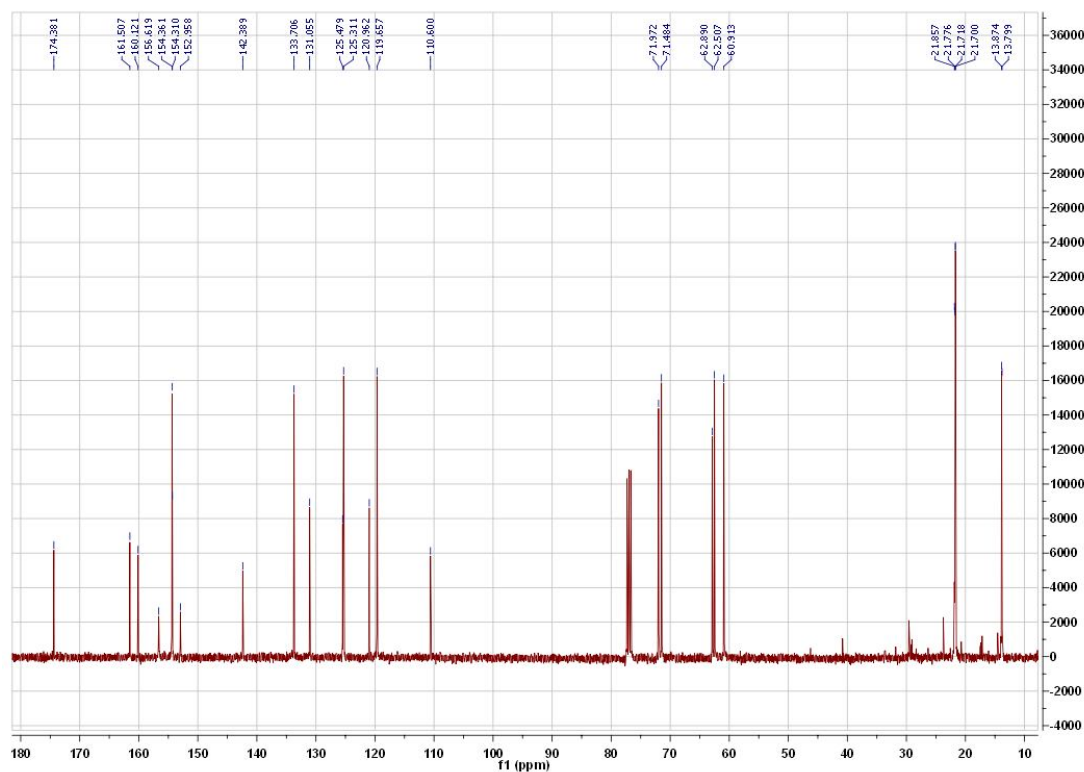
TLC: $R_f = 0.43$ cyclohexane/ethyl acetate (2:1);

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.02 (d, $J = 2.8$ Hz, 1H), 7.92 (s, 1H), 7.49 (dd, $J = 9.2$, 2.4 Hz, 1H), 7.31 (d, $J = 8.8$ Hz, 1H), 5.64 (s, 1H), 5.08 (d, $J = 2.4$ Hz, 1H), 4.93 (d, $J = 2.4$ Hz, 1H), 4.34 (q, $J = 7.2$ Hz, 2H), 4.05 (q, $J = 7.2$ Hz, 2H), 1.34 (t, $J = 7.2$ Hz, 3H), 1.29-1.20 (m, 12H), 1.13 (t, $J = 7.2$ Hz, 3H);

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 174.4, 161.5, 160.1, 156.6, 154.4, 154.3, 153.0, 142.4, 133.7, 131.1, 125.5, 125.3, 121.0, 119.7, 110.6, 72.0, 71.5, 62.9, 62.5, 60.9, 21.9, 21.8, 21.7, 21.7, 13.9, 13.8;

HRMS (ESI): Calculated for $\text{C}_{26}\text{H}_{30}\text{ClO}_{10}\text{N}_2$ $[\text{M}+\text{H}^+]$: 565.1584, Found: 565.1579;





$C_{24}H_{26}N_2O_{10}$
 Exact Mass: 502.16
 Mol. Wt.: 502.47

b179;

Yield 91%;

Yellow solid;

M.P.: 156°C;

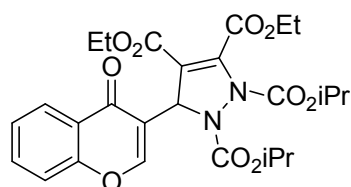
TLC: $R_f = 0.41$ cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, $J = 8.0$ Hz, 1H), 7.99 (d, $J = 2.0$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.40 (d, $J = 8.4$ Hz, 1H), 7.34 (t, $J = 8.0$ Hz, 1H), 5.70 (s, 1H), 5.14 (d, $J = 2.4$ Hz, 1H), 4.99 (d, $J = 2.4$ Hz, 1H), 3.95 (s, 3H), 3.65 (s, 3H), 1.34-1.25 (m, 12H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 162.0, 160.8, 156.6, 156.1, 154.3, 153.2,

142.6, 133.6, 126.0, 125.1, 124.6, 120.8, 117.9, 111.0, 72.0, 71.5, 63.1, 53.2, 52.0, 21.9, 21.8, 21.74, 21.71;

HRMS (ESI): Calculated for $C_{24}H_{27}O_{10}N_2$ [$M+H^+$]: 503.1587, Found: 503.1654;



$C_{26}H_{30}N_2O_{10}$
Exact Mass: 530.19
Mol. Wt.: 530.52

b180;

Yield 89%;

Yellow solid;

M.P.: 126°C;

TLC: R_f = 0.36 cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8.0 Hz, 1H), 7.94 (s, 1H), 7.58 (d, J = 7.2 Hz, 1H), 7.37 (dd, J = 8.0, 2.0 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 5.67 (s, 1H), 5.11 (d, J = 2.4 Hz, 1H), 4.97 (d, J = 2.4 Hz, 1H), 4.38 (t, J = 7.2 Hz, 2H), 4.08 (t, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H), 1.31-1.21 (m, 12H), 1.16 (t, J = 7.2 Hz, 3H);

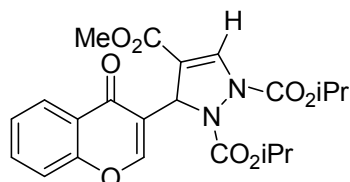
^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 161.6, 160.3, 156.7, 156.1, 154.3, 153.3, 142.4, 133.5, 126.1, 125.1, 124.7, 121.0, 117.9, 111.2, 71.9, 71.4, 63.1, 62.6, 60.9, 22.0, 21.9, 21.79, 21.76, 14.0, 13.9;

HRMS (ESI): Calculated for $C_{26}H_{31}O_{10}N_2$ [$M+H^+$]: 531.1973, Found: 531.1965;

General procedure for synthesis of (**b184**) from common precursor and bisnucleophile **b47**.

Triphenylphosphine (1.3 mmol.) was added to a anhydrous THF (15 mL) solution of aldehyde (1 mmol.) and Diisopropyl azodicarboxylate (1.2 mmol.) at the argon atmosphere. The reaction mixture was stirred at room temperature for 2-5 h under argon. The color of solution turned straw yellow to deep yellow immediately, then tuned to

straw yellow slowly. The reaction was monitored by TLC using cyclohexane/ethyl acetate (2:1) as eluent. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel with cyclohexane/ethyl acetate(4:1) as the eluent to offer yellow solid.



$C_{22}H_{24}N_2O_8$
Exact Mass: 444.15
Mol. Wt.: 444.43

b184;

Yield 86%;

Yellow solid;

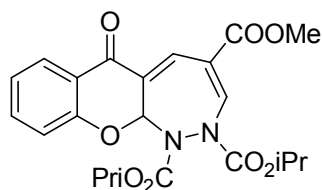
M.P.: 156°C;

TLC: $R_f = 0.45$ cyclohexane/ethyl acetate (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.00 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.95 (s, 1H), 7.67 (s, 1H), 7.52 (dt, $J = 7.2, 1.6$ Hz, 1H), 7.30 (d, $J = 8.4$ Hz, 1H), 7.24 (t, $J = 7.2$ Hz, 1H), 5.63 (m, $J = 1.2$ Hz, 1H), 5.08 (m, $J = 2.4$ Hz, 1H), 4.93 (d, $J = 2.4$ Hz, 1H), 3.56 (s, 3H), 1.26-1.14 (m, 12H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 162.7, 156.6, 156.1, 155.8, 154.1, 139.1, 133.3, 125.4, 124.9, 124.3, 120.6, 117.7, 110.1, 71.3, 71.0, 62.9, 51.2, 21.64, 21.61, 21.60, 21.5;

HRMS (ESI): Calculated for $C_{22}H_{25}O_8N_2$ [$M+H^+$]:445.1605, Found: 445.1600;

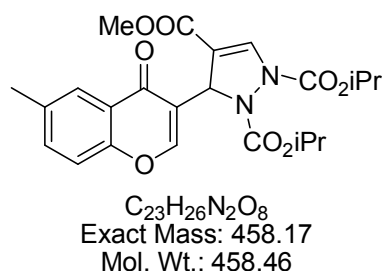


$C_{22}H_{24}N_2O_8$
Exact Mass: 444.15
Mol. Wt.: 444.43

b185;

Yield 13%;

White solid;

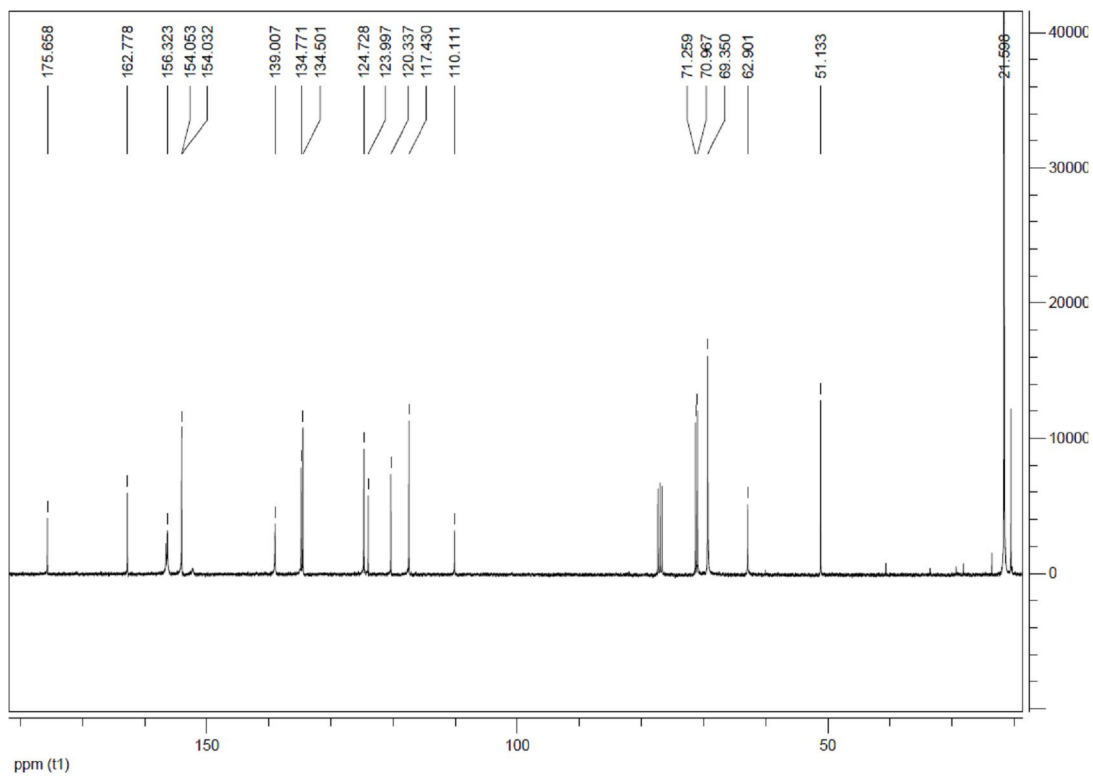
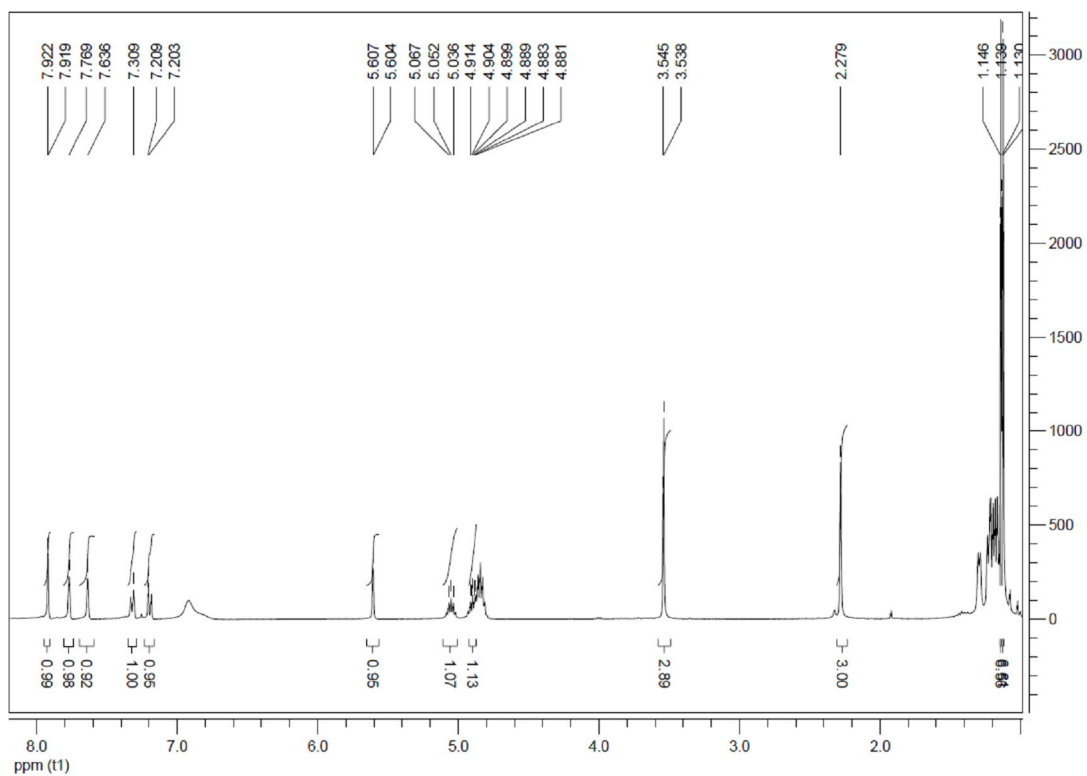
M.P.: 147°C;**TLC:** $R_f = 0.50$ hexane/EA (2:1); **^1H NMR (400 MHz, CDCl_3):** δ 8.86 (s, 1H), 8.06 (s, 1H), 8.03 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.54-7.51 (m, 1H), 7.11-7.03 (m, 2H), 5.74 (s, 1H), 5.03-4.97 (m, 1H), 4.77-4.71 (m, 1H), 3.85 (s, 3H), 1.44-1.39 (m, 6H), 1.30-1.23 (m, 6H); **^{13}C NMR (100 MHz, CDCl_3):** δ 177.4, 166.3, 158.9, 143.1, 137.3, 135.9, 130.9, 129.4, 127.1, 122.4, 121.9, 119.1, 117.3, 106.4, 89.7, 74.3, 72.3, 52.6, 21.72, 21.69, 20.9, 20.7;**HRMS (ESI):** Calculated for $\text{C}_{22}\text{H}_{25}\text{O}_8\text{N}_2$ [$\text{M}+\text{H}^+$]: 445.1605, Found: 445.1602;**b186;**

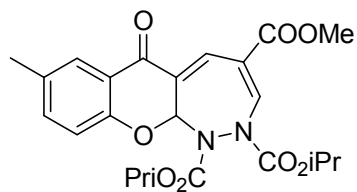
Yield 73%;

White solid;

M.P.: 156°C;**TLC:** $R_f = 0.45$ hexane/EA (2:1); **^1H NMR (400 MHz, CDCl_3):** δ 7.92 (s, 1H), 7.77 (s, 1H), 7.64 (s, 1H), 7.31 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.21 (dd, $J = 8.8, 2.0$ Hz, 1H), 5.61 (s, 1H), 5.07-5.04 (m, 1H), 4.91-4.88 (m, 1H), 3.54 (s, 3H), 2.28 (s, 3H), 1.14 (d, $J = 6.8$ Hz, 6H), 1.13 (d, $J = 6.8$ Hz, 6H); **^{13}C NMR (100 MHz, CDCl_3):** δ 175.7, 162.8, 156.6, 156.3, 154.1, 154.0, 139.0, 134.8, 134.5, 124.7, 124.0, 120.3, 117.4, 110.1, 71.0, 62.9, 51.1, 21.60, 21.57, 21.51;**HRMS (ESI):** Calculated for $\text{C}_{23}\text{H}_{27}\text{O}_8\text{N}_2$ [$\text{M}+\text{H}^+$]: 459.1762, Found: 459.1761;

Experimental section





$C_{23}H_{26}N_2O_8$
 Exact Mass: 458.17
 Mol. Wt.: 458.46

b187;

Yield 11%;

White solid;

M.P.: 142°C;

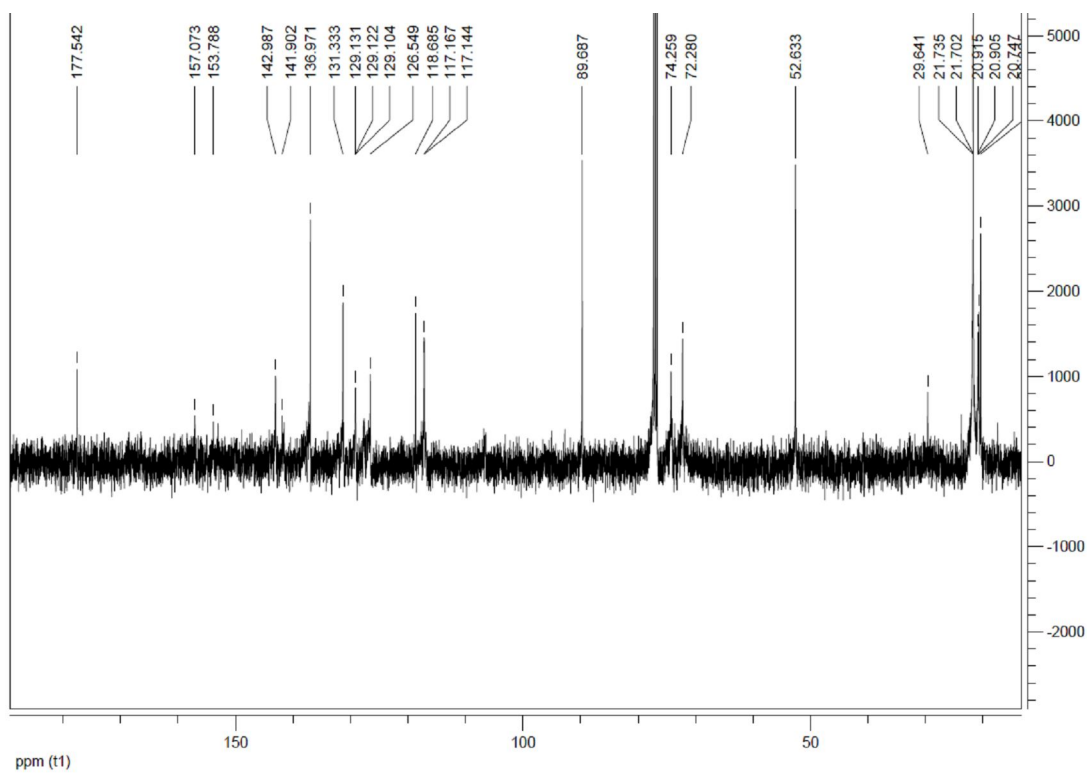
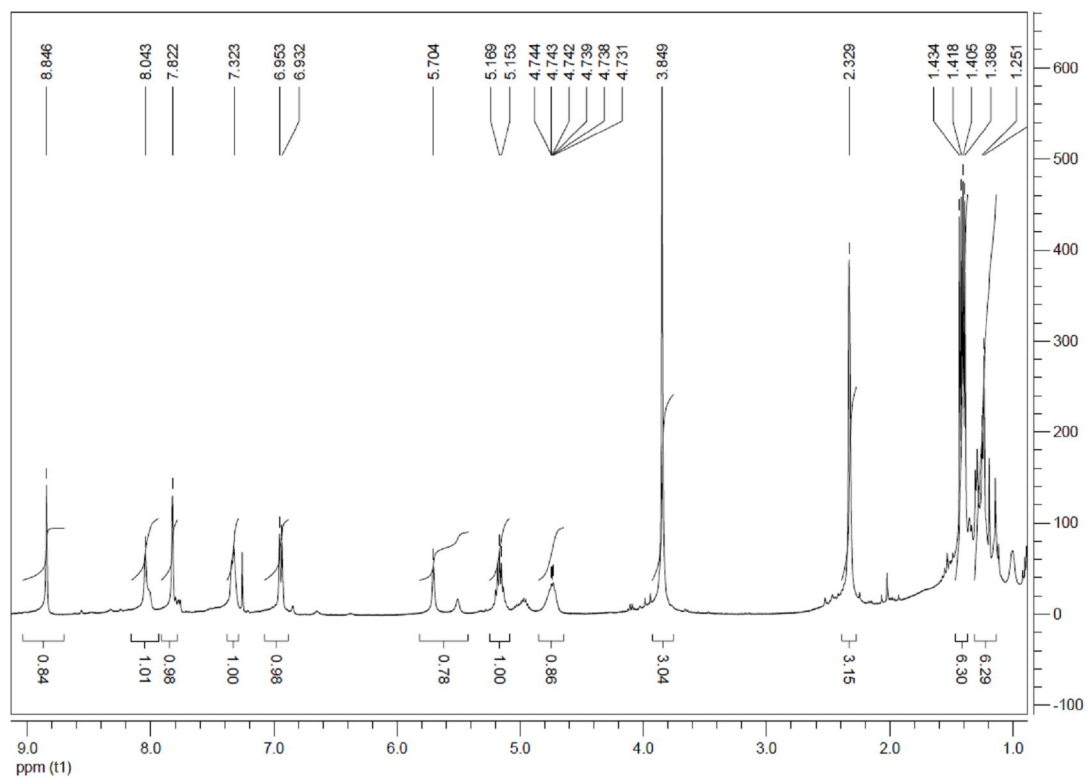
TLC: R_f = 0.47 hexane/EA (2:1);

1H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.04 (s, 1H), 7.82 (s, 1H), 7.33 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 5.70 (s, 1H), 5.17-5.15 (m, 1H), 4.74-4.73 (m, 1H), 3.65 (s, 3H), 2.33 (s, 3H), 1.43-1.39 (m, 6H), 1.31-1.14 (m, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 157.1, 153.8, 143.0, 141.9, 137.0, 131.3, 129.13, 129.12, 129.10, 126.5, 118.7, 117.2, 117.1, 89.7, 74.3, 72.3, 52.6, 21.73, 21.70, 20.9, 20.7, 20.4;

HRMS (ESI): Calculated for $C_{23}H_{27}O_8N_2$ [$M+H^+$]: 459.1762, Found: 459.1758;

Experimental section



6. Reference

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