Università degli studi di Urbino "Carlo Bo"

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SYNTHESIS OF MONO AND POLY-HETEROCYCLES STARTING FROM 1,2-DIAZA-1,3-DIENES (OR PRECURSORS) AS BUILDING BLOCKS

Settore Scientifico Disciplinare: CHIM/06

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CHAPTER 1

General Introduction

1.1 HETEROCYCLES AN OVERVIEW

Heterocycles are common structural units in marketed drugs and in medicinal chemistry due to the central role they play in modern drug design. Why have organic chemists focused so much effort on understanding and synthesizing? One reason is that heterocyclic rings are present in the majority of known bioactive natural products, contributing to enormous structural diversity, but also in electronics, biology, optics, pharmacology, material sciences and so on. Caffeine is a prime example of an everyday chemical that is composed of heterocycles, as is nicotine, and there are plenty of others in pharmaceuticals and natural products we use on a natural basis. Parts of our DNA are even made up of compounds which contain heterocycles. Indeed, a 2014 study found that nearly 60% of all FDA-approved drugs in this category incorporate a nitrogen heterocycle. The most prevalent nitrogen ring system, found in a total of 72 unique small-molecule drugs, is piperidine, pyridine and piperazine are the second and third most common nitrogen heterocycles, appearing in 62 and 59 drugs, respectively. Significantly behind the top three is cephem, a β-lactam fused to a six-member sulfur-containing dihydrothiazine ring core found in 41 approved drugs followed by pyrrolidine accounting for 37 drugs (**Figure 1**).[1]

In the **Figure 2** are showed some examples of drugs containing nitrogenous heterocycles. Oxygen and sulphur are also well represented. Synthetic heterocycles a very large therapeutic uses such as antibacterial, antifungal, antimycobacterial, trypanocidal, anti-HIV activity, antileishmanial agents, genotoxic, antitubercular, antimalarial, herbicidal, analgesic, anti-inflammatory, muscle relaxants, anticonvulsant, anticancer and lipid peroxidation inhibitor, hypnotics, antidepressant, antitumoral, anthelmintic and insecticidal agents.[2]

The chemistry of these substances is quite different from that encountered carbocyclic systems, and an appreciation of these differences is important for the comprehension of biochemistry and molecular biology at fundamental level. It is not unusual for heterocyclic species to undergo rearrangements and transformations having no parallel in carbocyclic chemistry, which provides a good training ground for sharpening mechanistic skills. Heterocycles are able to get involved in an extraordinarily wide range of reaction types.

Depending on the pH of the medium, they may behave as acids or bases, forming anions or cations. Some interact readily with electrophilic reagents, others with nucleophiles, yet others with both. Some are easily oxidized, but resist reduction, while others can be quickly hydrogenated but are stable toward the action of oxidizing agents.

Certain amphoteric heterocyclic systems simultaneously demonstrate all of the above-mentioned properties. The ability of many heterocycles to produce stable complexes with metal ions has great biochemical significance. The presence of different heteroatoms makes tautomerism ubiquitous in the heterocyclic series. Such versatile reactivity is linked to the electronic distributions in heterocyclic molecules.[3]

In other words the introduction of a heteroatom into a cyclic compound imparts new properties. Heterocycles are chemically more flexible and better able to respond to the many demands of biochemical systems. For all these reasons, in the last decade, the development of new synthetic strategies to obtain heterocyclic systems is increased.

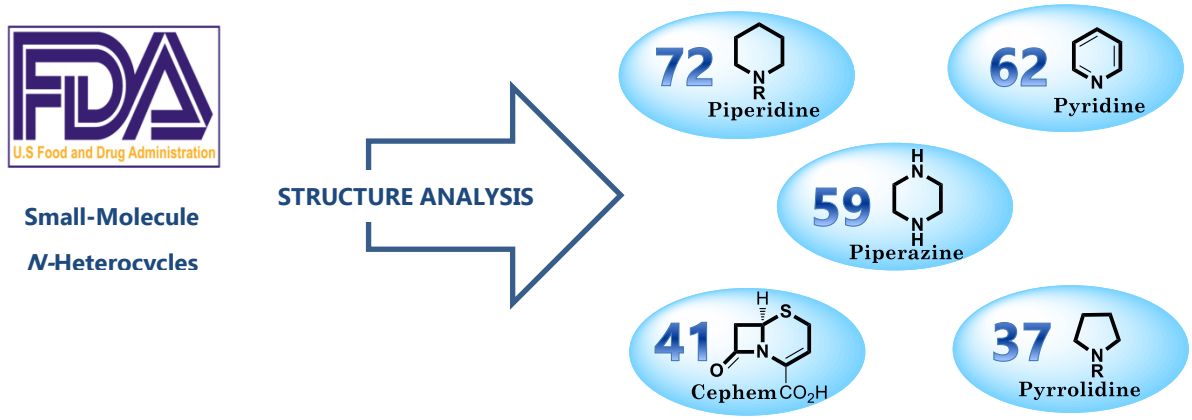


Figure 1. *The most frequent nitrogen heterocycles in U.S. FDA approved drugs.*

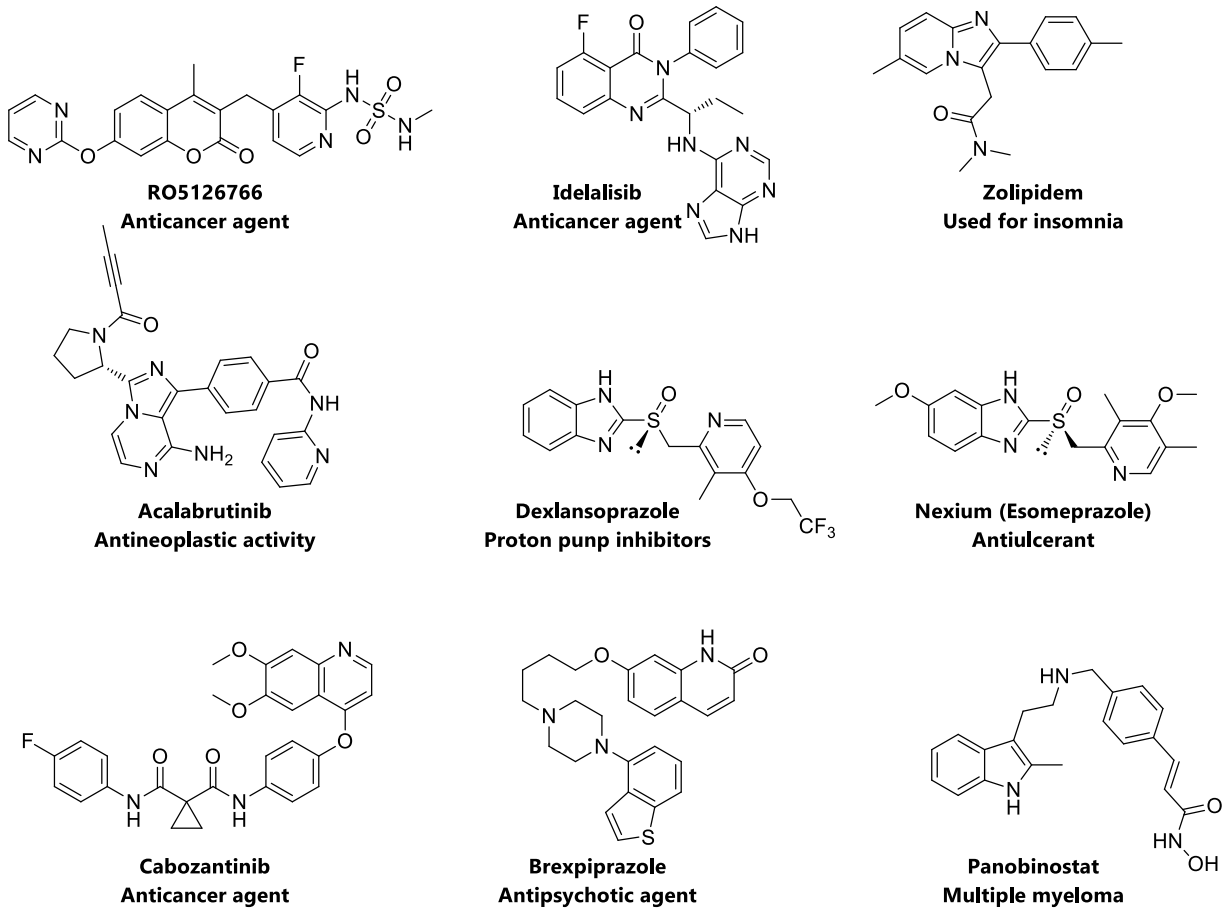


Figure 2. *Drugs containing heterocyclic.*

1.2 HETEROCYCLES AND DRUG DISCOVERY

Starting from the fact that man alone does not discover a molecule that is not already present in nature and given that heterocycles are very frequently expressed in bioactive natural products, medicinal chemistry efforts often revolve around simulating such structural motifs. Pharmaceutical drugs generally work by interacting with a binding site in a protein and common types of interactions include electrostatic, hydrophobic and hydrogen bonding. Heterocycles containing nitrogen, oxygen or sulphur atoms, whether heteroaromatic or not, offer excellent opportunities for hydrogen binding interactions with the functional groups in proteins.[4] However, as well as providing protein binding groups, heterocycles also affect the solubility, the lipophilicity and the polarity of drugs and their metabolism profile. At the beginning of drug discovery phase, pharmaceutical chemistry design hypotheses for accessing to new chemical species, for example novel heterocycles or substitution patterns that satisfy strict physicochemical requirements, provide new vectors in structure-based drug design and can afford new advanced properties. Heterocycles are able to undergo several manipulation to enhance their potency, selectivity, metabolic stability and other physicochemical capacity. Among the heterocycles, nitrogen containing heterocycles have received special attention in pharmaceuticals and medicinal chemistry due to their diverse medicinal potentials.[5]

Consequently, the synthesis of these heterocycles and their derivatives occupy an important place in the field of natural and synthetic organic chemistry. Despite the availability of numerous modern synthetic methodologies of heterocycles, the most frequent pathways used in medicinal chemistry employ reactions were discovered over 20 years ago.[6] The three common and recurrent reactions in this area are amide bond formation, Suzuki–Miyaura coupling, and SNAr substitution.

The goal is to highlight applications of new synthetic methodologies in the context of recent drug discovery and development projects, using recent state-of-the-art methods for heterocyclic synthesis such as functionalization that employs C–H sp^2 activation, multicomponent reactions, regio- and stereoselective procedures, reducing waste formation and production costs.

1.3. 1,2-DIAZA-1,3-DIENES AS USEFUL BUILDING BLOCKS

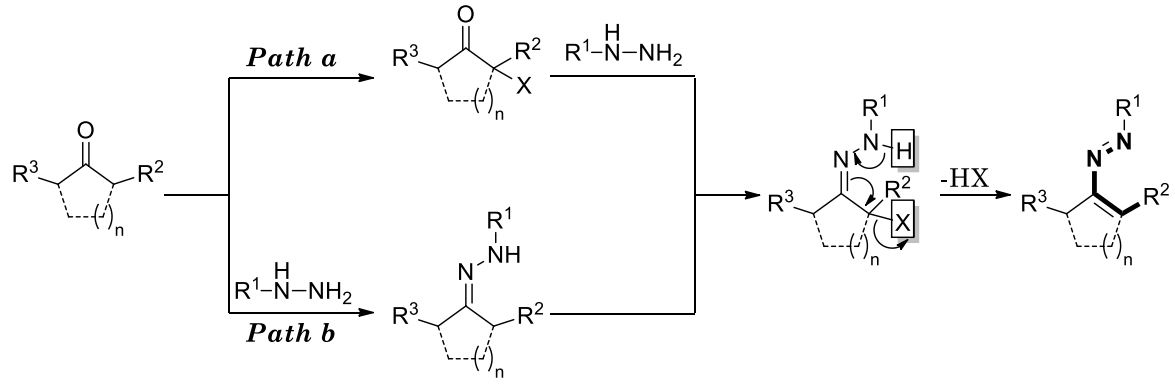
Among the approximately 20 million chemical compound identified by the end of the second millennium, more than two-thirds are fully or partially aromatic and roughly half are heterocyclic. They have contributed to the development of society from a biological and industrial point of view as well as to the understanding of life processes and the efforts to improve the quality of life. The remarkable activity in this field is demonstrated not only from the large number of contributions addressed to their fundamental properties, but also from the numerous academic articles dealing with the applications of molecules containing heterocycles in medicinal chemistry and materials science. To meet the demand for new methodologies for the synthesis of heterocyclic systems in target-oriented formation of naturally occurring and biologically active molecules, the chemistry of **azoalkenes** has been successfully explored.

The usefulness of azoalkenes (also named 1,2-diaza-1,3-dienes (DDs)) in the construction of several and multiple five- and six-membered heteroring systems is given from presence of a double bond carbon-carbon conjugated with a double bond nitrogen-nitrogen.[7] For that reason they are considered wonderful "*building blocks*" on the synthesis of different heterocyclic structures.

Those compounds have been mainly used as electron-deficient heterodienes in formal inverse hetero-Diels–Alder reactions (IEDDA) with electron-rich heterocycles or as Michael-type acceptors in conjugate 1,4-addition reactions.

1.4 SYNTHESIS AND PROPERTIES OF AZOALKENES

Azoalkenes are synthesized by base-treatment of hydrazone derivatives bearing a leaving group in the α-position to the C=N moiety. Two different paths are possible: (*path a*) the hydrazone derivatives are prepared from carbonyl compounds bearing the leaving group or (*path b*) the leaving group is introduced in the α-position of the hydrazone function. Both cyclic and acyclic ketones can be used in the preparation of DDs (**Scheme 1**). Sometimes, DDs are generated in situ.



Scheme 1. *General procedure for the synthesis of DDs.*

The chemical properties of those compounds are correlated to the electron-withdrawing effect of the azo group in the heterodiene system, that makes those systems excellent Michael acceptors. A particular DDs feature is an "*umpolung*" respect the classical reactivity of carbonyl compound, since these neutral compounds enable nucleophilic additions at the terminal carbon atom of the azoene system. This atom is originally located in the α-position to the ketone function from which DDs are prepared. It is well known that such a carbon atom is a nucleophilic rather than an electrophilic site. Therefore, the reactivity of DDs proceeds contrary to the natural polarity of the parent carbonyl derivatives and their employment represents a valid approach to reverse the normal polarity of carbon atom in α-position to the carbonyl group. Moreover the substituents on the carbon and nitrogen atoms influence the stability and the reactivity of azoalkenes. In general, electron-poor substituents (ester or amide groups) on terminal carbon and/or nitrogen encourage both the stability and the regioselective nucleophilic attacks at the terminal carbon, and permit further interesting reactions of the hydrazone 1,4-adduct intermediate. Aryl groups promote the stability but not the reactivity, while alkyl groups or terminal C=C bonds do not favour stability, and give rise to by-products.[8]

1.5 1,2-DIAZA-1,3-DIENES IN 1,4-MICHAEL ADDITION

The Michael addition is considered one of the most versatile methods in organic synthesis to build a new carbon-carbon bond. The typical reaction of DDs is the regioselective nucleophilic addition at the terminal carbon atom in 4-position of the heterodiene system by a variety of carbon and hetero nucleophiles such as nitrogen, sulphur, selenium and phosphorus. These 1,4-additions produce highly functionalized hydrazones and in this key step we can introduce various other nucleophile or electrophile sites into the system. In that way the hydrazone represents a potential starting materials for further interesting structural modifications through controlled regioselective reactions which lead to several and complex heterocycles. As a consequence different intramolecular closures are possible (Figure 2):

– sp^2 hydrazonic nitrogen could act like nucleophile (path A, B) after the loss of the hydrogen in α-position to the hydrazone moiety;

– sp^3 hydrazonic nitrogen could act like nucleophile (path C, D, E) thanks to its doublet;

– hydrazone C=N bond could be involved as electrophile (path F) for a further addition by new nucleophilic centres.

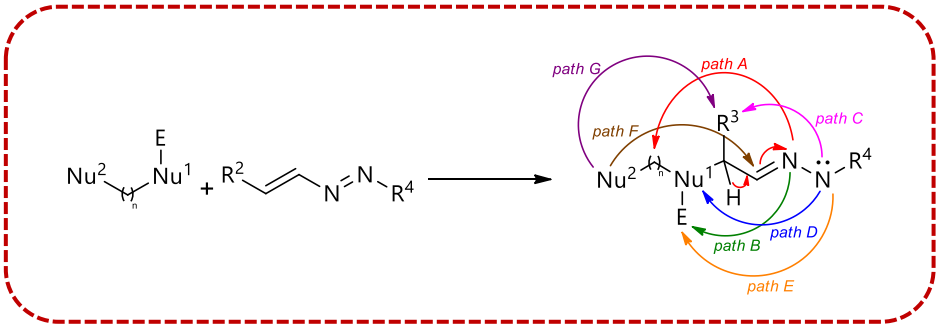


***Figure 2**. DDs as Michael acceptors.*

As a rule these reactions do not require anhydrous solvents or inert atmosphere but they occur under mild conditions and need simple work-up procedures.

The feature red colour of azoalkenes represents an useful "internal litmus" to check the progress of reaction, in fact the transformation of those compounds are accompanied with the change of the initial colour of the mixture to the final colourless or pale yellow state.

Figure 3 summarizes the heterocyclic systems obtained as a result of 1,4 addition on diazadiene system depending on the nature of the employed nucleophile.

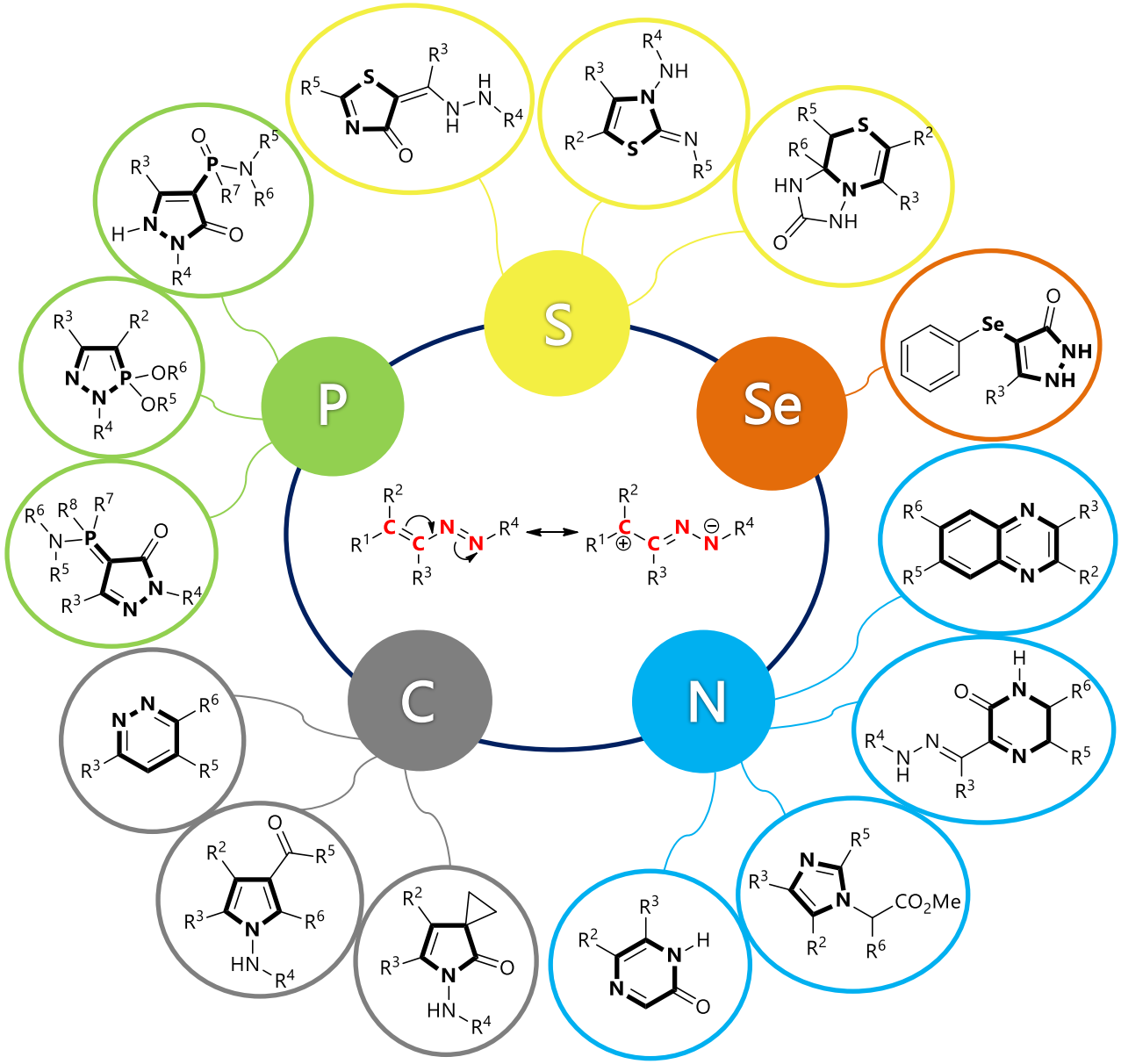


Figure 3. *Several examples of the synthesis of new heterocycles.*

The versatility of DDs as powerful building blocks for the construction of various nitrogen or multi-nitrogen-containing heterocycles including pyrroles, pyrazoles, imidazoles, thiazoles, selenazoles, 1,2,3-thiadiazoles, 1,2,3-selenadiazoles, 1,2,3-diazaphospholes, pyridazines, pyrazines, 1,4-thiazines, 1,2,4-triazines and mixed heterocyclic systems. Thus, by functionalization of the carbon atom adjacent to the masked carbonyl moiety of DDs, the construction of many types of five-, six- and also seven-membered heterocycles was realized. The reactions formally proceed through a number of chemical steps, in practice they can frequently be executed in one pot, requiring very simple work-up procedures and frequently affording the desired product in good yields.

1.6 1,2-DIAZA-1,3-DIENES IN INVERSE ELECTRON DEMAND DIELS-ALDER REACTION

The inverse electron demand Diels-Alder (IEDDA) type reaction is a cycloaddition between an electron-rich dienophile and an electron-poor diene. During the reaction three pi-bonds are broken and two sigma bonds and one new pi-bond are formed. When heteroatoms are involved we talk about hetero-Diels-Alder reaction and it can be used to form heterocyclic compounds.

In the IEDDA reaction, the LUMO-diene and HOMO-dienophile are closer in energy than the HOMO-diene and LUMO-dienophile of the classic Diels-Alder reaction. Thus, the LUMO-diene and HOMO-dienophile are the frontier orbitals that interact the most strongly and result in the most energetically favourable bond formation (**Figure 4**).

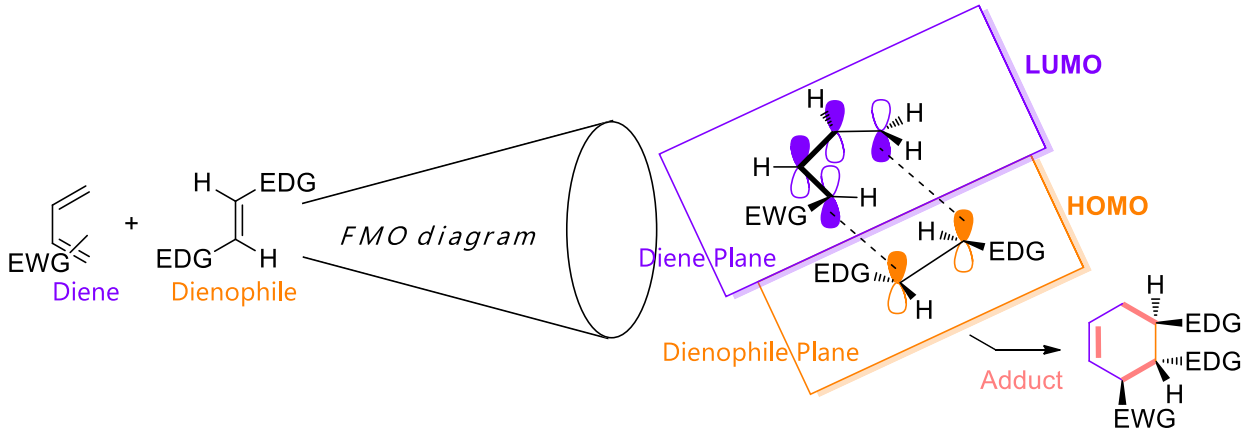


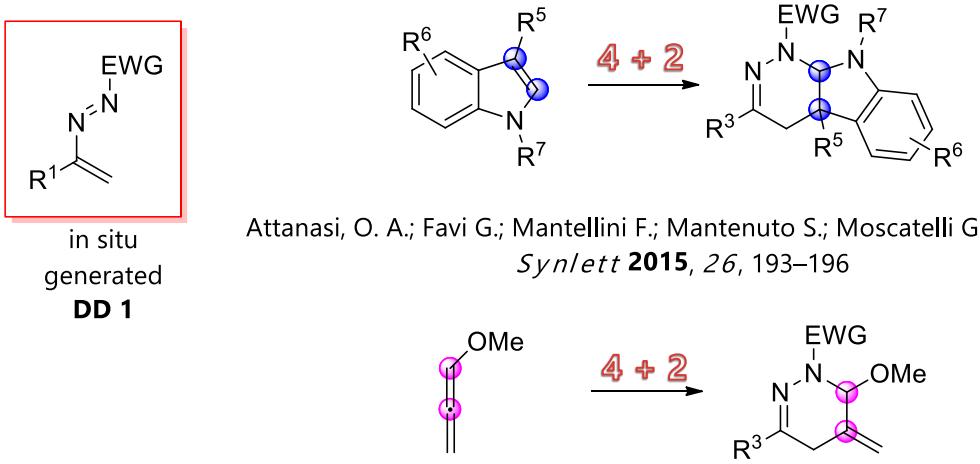
Figure 4. *Frontier Molecular Orbitals (FMO) of IEDDA*

Since the first studies of the inverse-electron-demand Diels–Alder reaction of 3,6-disubstituted 1,2,4,5-tetrazines was reported in 1959,[9] hetero Diels–Alder reactions with inverse electron demand have grown in interest because of their mighty applications in convergent synthesis of heterocyclic compounds from simpler starting materials.

1,2-Diaza-1,3-Dienes can be frequently applied in cycloaddition reactions with a wide variety of partners. In particular 4-unsubstituted electron-deficient azoalkenes that are very unstable and are typically generated in *situ*, serve as electron-deficient diene C2N2 components in [4+1], [4+2] and [4+3] cycloadditions to generate highly complex five-, six-, and seven-membered rings (**Scheme 2**).[10] In our groups was also carried out a IEDDA reaction between 4-substituted azoalkenes (not generated in *situ)* (**Scheme 4**).

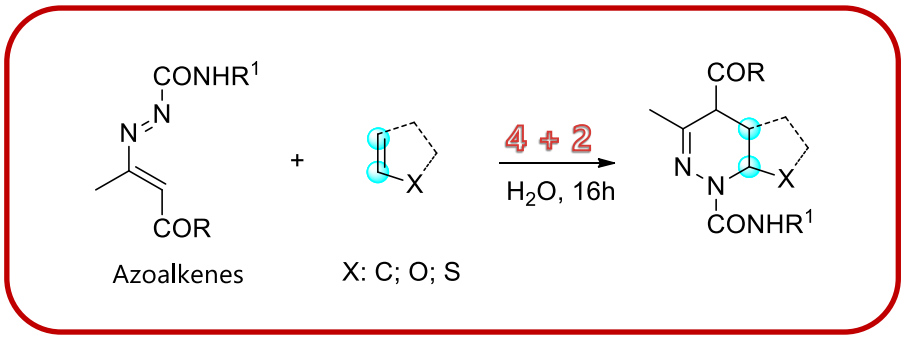
The procedure was conducted in water to lead to the formation of tetrahydropyridazines in good yields and with high degrees of stereochemical and regiochemical control.[11] This was the first example of an asymmetric "inverse electron-demand" [4+2] cycloaddition reaction made in an aqueous medium. Cycloadducts formed in this way are of extreme importance, not only for their pharmacological properties[12] but also as key intermediates in organic synthesis.

Tong, M.-C.; Chen, X.; Li, J.; Huang, R.; Tao, H.; Wang, C.-J.
Angew. Chem. Int. Ed. **2014**, *53*, 1.



Attanasi, O. A.; Favi G.; Mantellini F.; Mantenuto S.; Moscatelli G.; Nicolini S.;
Synlett **2015**, *26*, 193–196

Scheme 2. *Use of in situ generated 1,2-diaza-1,3-dienes (DDs) as C2N2 components in some recently reported annulation reactions.*



Schema 3. *IEDDA reaction of DD not generated in situ by our group.*

CHAPTER 2

Palladium(II)-Catalyzed Intramolecular Oxidative C−H/C−H Cross-Coupling Reaction of C3,N-Linked Biheterocycles: Rapid Access to Polycyclic Nitrogen Heterocycles.

2.1 INTRODUCTION

Nitrogen heterocycles are among the most significant components of natural and pharmaceutical products. Indeed an analysis of database of U.S. FDA approved drugs reveals that 59% of unique small-molecules drugs contain a nitrogen heterocycles.

In particular **indole** is a very important compound because of its presence in countless natural products and also because it is part of an essential amino acid (**tryptophan**).[13]

This project focuses on the development of catalytic systems for the selective functionalization of this interesting molecular scaffold that was named by Evans in the late 1980s: "*The Lords of the rings*" thanks to its wide range of biological activities.[14]

Despite the meaningful advancements made to develop atom- and step-economic strategies toward complex frameworks, especially those involving privileged moieties, rapid, alternative, and versatile approaches to assemble fused aza-heterocycles are still needed.

Recent research has demonstrated the efficiency of the functionalization of heterocyclic compounds, through the formation of C-C bonds (*Cross Dehydrogenative Coupling* ***CDC***), through metal-catalyzed reactions.[15] In the last decades, metal-catalyzed synthetic transformations are considered one of the most powerful and reliable tools for the development of more complex molecular structures, in an efficient and economical way and furthermore because pre-functionalization of substrates is not required. Although impressive intermolecular dehydrogenative cross-coupling[16] has been developed to date, the intramolecular variant[17] remains underdeveloped. Most C-H functionalization processes, both intermolecular and intramolecular, are limited to the use of expensive noble metals such as Ru, Rh or Ir as catalysts[18], so the use of cheaper metals is extremely desirable, among these, palladium (Pd) is an excellent alternative. In 2011, Greaney and co-workers reported an elegant Pd(II)-catalyzed intramolecular oxidative C−H coupling reaction of indole *N*-linked arene/heteroarene compounds for the fabrication of medium sized rings (**Figure 1**).[19]

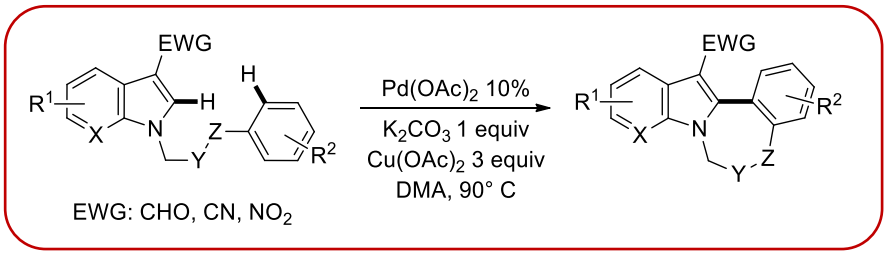


Figure 1. *Intramolecular oxidative coupling between indole and arenes by Greaney group.*

Though synthetically very attractive, this protocol suffers from the disadvantages of a limited substrate/heterocycle scope and generality. The presence of an electron-withdrawing group (EWG) in the C3-position of the indole ring was essential to ensure the success of the reaction probably because they increase the acidity of C2-H (sp^2). Moreover the work is mainly focused on the formation of seven- and eight-membered rings. Given our interest in heterocyclic chemistry, especially in tryptamine derivatives, we propose a distinct approach to the synthesis of polycyclic fused indoles via palladium catalyzed oxidative C−H/C−H cross-coupling from indole-based alkyl-linked biheterocycles (indole-imidazoles, indole-pyrroles, and indole-triazoles). While in the work of Greaney et al,[20] the aromatic compounds, which constitute the starting bi-heterocyclic structure, are bound starting from the N atom of the indole ring, through a suitable spacer, we intend to apply the intramolecular CDC reaction between indole and azole units that are connected through C3,N linkage, respectively (**Figure 2**).

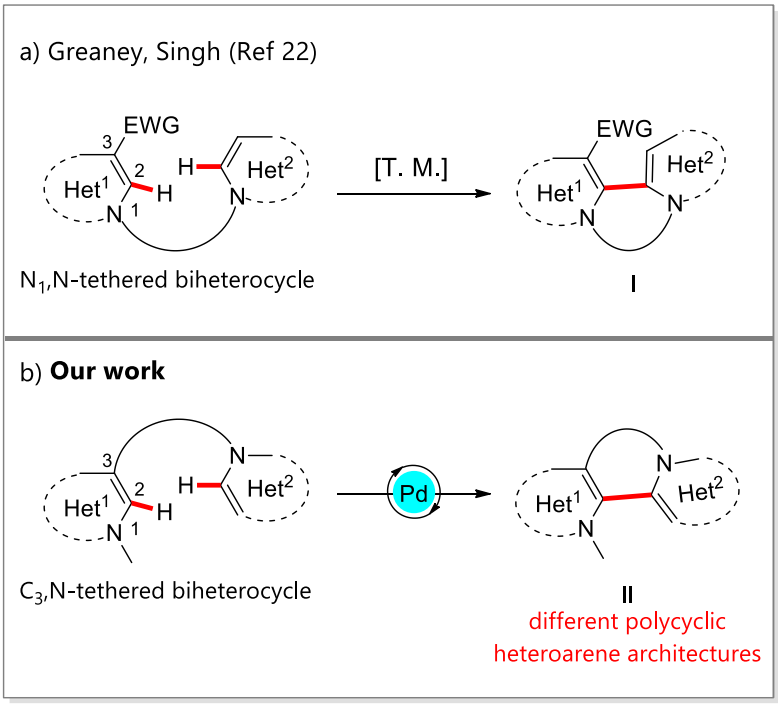


Figure 2*. Approaches of heterocyclic CDC reactions: synthesis of different fused polycyclic heteroarene architectures.*

According to this approach also the use of electron-attractor groups (EWG) is avoided. Consequently, by varying the heterocycle linked to the indole and the type of junction between two heteroarene rings, diversified polycyclic heteroarenes are obtained via a dual C(sp^2)−H functionalization process. For this study, the tryptamine (and homologue)-derived biheterocyles has been considered in light of its occurrence in a wide range of biologically active molecules, pharmaceuticals, and naturally occurring[20] compounds such as norketoyobyrine, rutaecarpine, cladoniamide G, isogranulatimide A and B, homofascaplisin B and C, vincamine, and yohimbine (**Figure 3**).

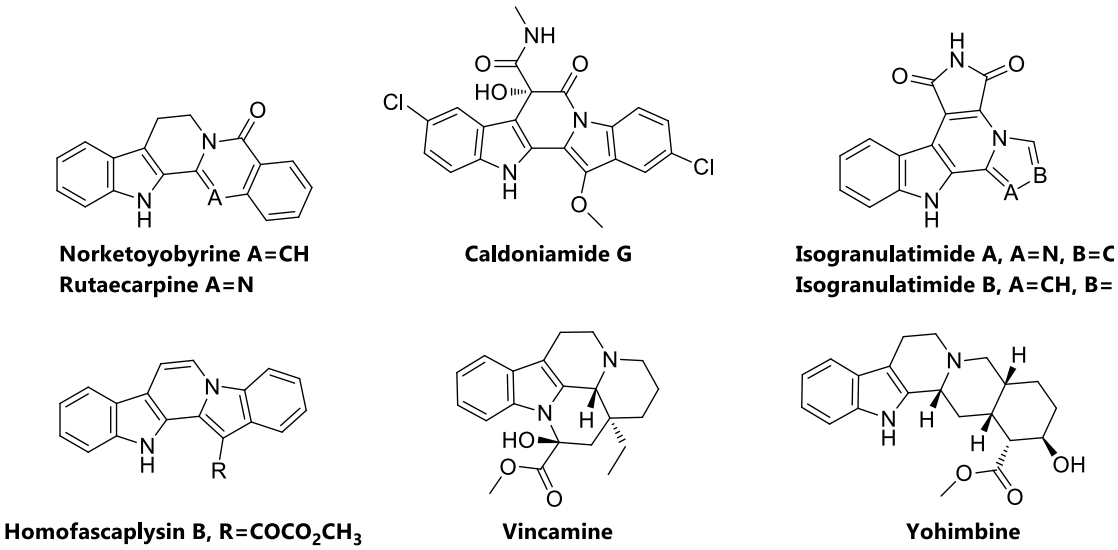


***Figure 3**. Selected naturally occurring compounds containing polycyclic fused indoles.*

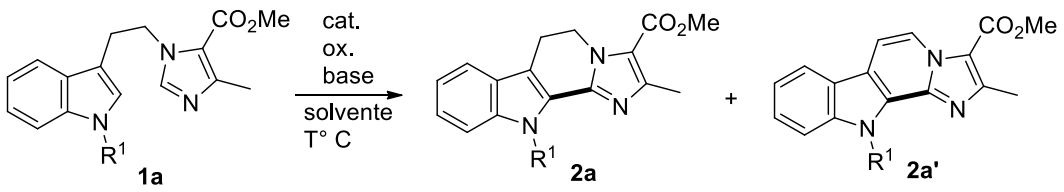
2.2 RESULTS AND DISCUSSION

We started our investigation to optimize the oxidative reaction of intramolecular cross coupling, to achieve satisfactory conditions for obtaining the tetra-heterocyclic product of interest.

The indole-imidazole nucleus **1a** is been the compound used for the optimization processes (**Table 1**), in which different reaction parameters were examined, such as catalyst, oxidant, base, additive, solvent, temperature and time. We began with $Pd(OAc)_2$ as the catalyst and Ag_2CO_3 as the oxidant in DMF at 140 °C for 9 h, affording the relative product **2a** in 47% yield along with overoxidized cross-coupling byproduct **2a'** in 23% yield. Screen of different oxidants: $Cu(OAc)_2{\cdot}H_2O$, $Cu(OAc)_2$, Ag_2CO_3, AgOAc, $AgNO_3$, $K_2S_2O_8$, BQ, I_2, PhI-$(OAc)_2$, Ag_2O, revealed AgOAc to be better in terms of yield and selectivity. Therefore, reaction conditions including $Pd(OAc)_2$ (10 mol %), AgOAc (3.0 equiv), and K_2CO_3 (1.0 equiv) in DMA at 130 °C under an air atmosphere became the best medium to supply exclusively desired product **2a** in 96% isolated yield. By changing the source of palladium have not been observed further improvements and the "*Pd free*" reaction did not work, highlighting the crucial role of this metal in the CDC process. Subsequent investigations have confirmed the importance of K_2CO_3, in fact its elimination has reduced efficiency and selectivity. Also, lowering the temperature from 130 to 110 and 90 °C the yield of the desired compound decreased to 88% and 60%, respectively. The presence of a catalytic amount of PivOH[21] has exhibited the formation of not negligible overoxidized cross-coupling product **2a'** due to the susceptibility of the benzylic type position of indole to oxidation with consequent aromatization. Again, a control experiment performed in the absence of oxidant revealed that, while Pd(II) was fundamental for this transformation, coupling product was also furnished in the presence of a stoichiometric amount of PivOH, albeit with lower efficiency and selectivity. Notably, no oxidative dimerizations at acidic CH bonds of both heterocycles were observed; the reactions occurred smoothly to lead to only intramolecular coupling products. Another test which consisted in irradiation with a halogen lamp in the presence of cyclohexene, as a sacrificial hydrogen acceptor, in acetonitrile according to the method described by Terpin and collaborators for the synthesis of isogranulatimide analogues was ineffective.[22] With the optimized reaction conditions in hand, the generality of the present Pd(II)-catalyzed intramolecular cross-dehydrogenative coupling reaction was investigated. A wide range of indole-based tethered biheterocycles incorporating manifold points of diversity (R^1 to R^7) performed consistently well in the reaction, giving structurally different polyheterocycle systems (**Scheme 1**).

In particular, branched and unbranched tryptamine tryptamine-derived indole-imidazoles with both electron-donating and -withdrawing substituents such as methyl, phenyl, methoxy, chloro, nitro on the benzo ring furnished the corresponding embedded six-membered ring systems (**2a−f**) in good to excellent yields.

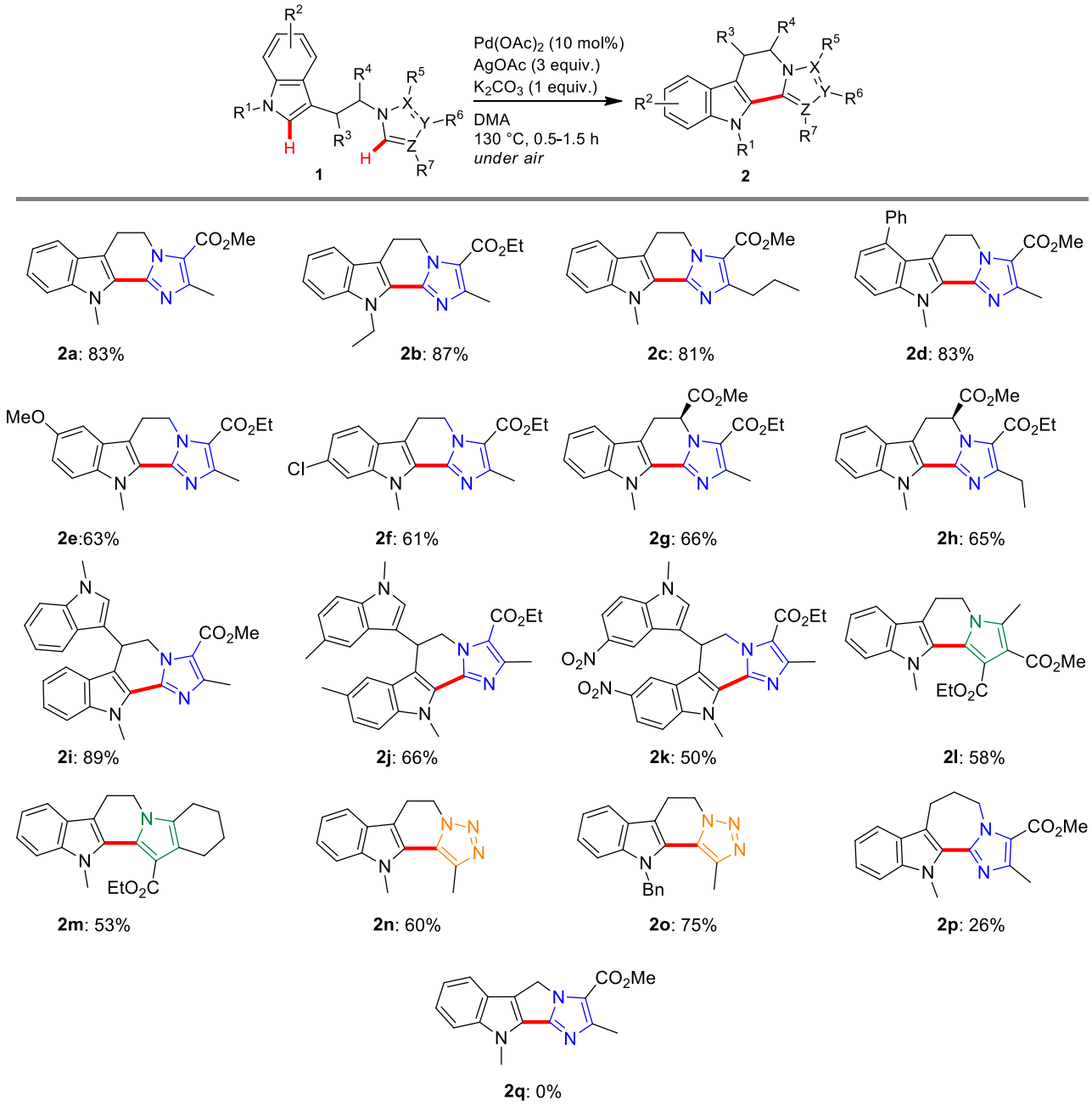
Most importantly, the reaction worked well to deliver fused tetracyclic products (**2g,h**) when tryptophan derived indole-imidazoles were employed. To our delight, no five-membered ring formation from C−H coupling reaction between both indole-2 moieties of bisindoles **1i−k** was observed. Thus, the 2,2′-cross-coupled products were obtained as single regioisomers with C−H activation occurring exclusively at the C-2 position of both the indole and azole units. It is worth noting that a desymmetrization of bisindole moieties takes place to give intriguing heteroarene architectures (**2i−k**). Also, alkyl and ester substituents can be accommodated on the imidazole portion. Notably, the reaction of indole derivatives with methyl, ethyl, and benzyl N-protecting groups were well tolerated under the standard conditions. Unfortunately, dehydrogenative coupling with a free N-H indole biheterocycle provided unsatisfactory yields, generating only a scarce amount of the overoxidized coupling compound (27% yield) while no reaction occurred with deactivated N-Ac indole.



entry	catalyst (mol %)	oxidant (equiv)	base (1 equiv)	additive (mol %)	solvent	T °C	t (h)	yield(%)[b] 2a	2a′
1	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2)	K_2CO_3	–	DMF	140	9	47	23
2	$Pd(OAc)_2$ (10)	$Cu(OAc)_2{\cdot}H_2O$ (2)	K_2CO_3	–	DMA	130	18	27	7
3	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (3)	K_2CO_3	–	DMA	130	5	60	–
4	**$Pd(OAc)_2$ (10)**	**AgOAc (3)**	**K_2CO_3**	**–**	**DMA**	**130**	**0.8**	**96**	**–**
5	$Pd(OAc)_2$ (10)	AgOAc (3)	–	–	DMA	130	4	55	20
6	$Pd(OAc)_2$ (10)	Ag_2O (2)	–	–	AcOH	130	7	–	14
7	$Pd(OAc)_2$ (10)	AgOAc (3)	K_2CO_3	–	DMA	110	2	88	–
8	$Pd(OAc)_2$ (10)	AgOAc (3)	K_2CO_3	–	DMA	90	13	60	–
9	$Pd(OAc)_2$ (10)	$AgNO_3$ (3)	K_2CO_3	–	DMA	130	1	34	14
10	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (3)	K_2CO_3	–	DMA	130	8	–	–
11	$Pd(OAc)_2$ (10)	BQ (3)	K_2CO_3	–	DMA	130	14	<5 [c]	–
12	$Pd(OAc)_2$ (10)	I_2 (3)	K_2CO_3	–	DMA	130	6	–	–
13	$Pd(OAc)_2$ (10)	$PhI(Oac)_2$ (3)	K_2CO_3	–	DMA	130	11	9	–
14	$PdCl_2$ (10)	AgOAc (3)	K_2CO_3	–	DMA	130	1.5	78	–
15	$Pd(PPh_3)Cl_2$ (10)	AgOAc (3)	K_2CO_3	–	DMA	130	1.5	83	–
16	$Pd(TFA)_2$ (10)	AgOAc (3)	K_2CO_3	–	DMA	130	0.8	79	–
17	$Pd(OAc)_2$ (10)	AgOAc (3)	–	PivOH (10)	DMA	130	0.9	60	8
18	$Pd(OAc)_2$ (10)	–	–	PivOH (100)	DMA	130	18	46	7

*[a]Reaction conditions: **1a** (0.2 mmol, 1 equiv), catalyst (10 mol%), oxidant (2.0–3.0 equiv), base (1.0 equiv), additive (10–100 mol%), solvent (2.0 mL) at 90–140 °C for the indicate time. [b]Yields determined after isolation by chromatography. [c]Starting **1a** was recovered.*

***Table 1.** Optimization process.[a]*

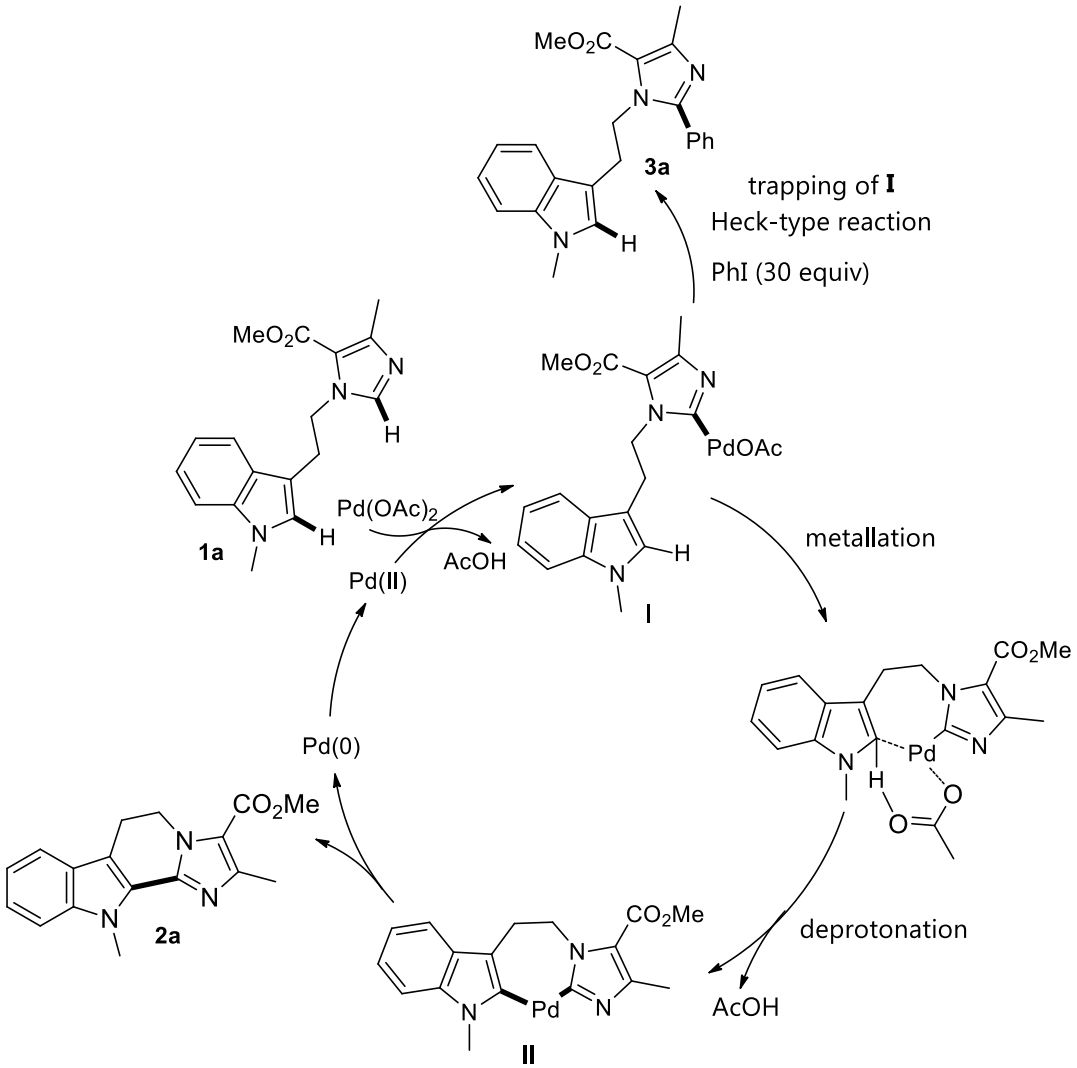


Scheme 1. *Substrate Scope for the Intramolecular Oxidative Coupling of Indole-Based Tethered Biheterocycles.*

The range of coupling partner amenable to indoles was not limited to imidazole derivatives. Sensitive indole-pyrrole **1l,m** and indole-triazole **1n,o** substrates were efficiently subjected to CDC in good yields. In particular, we achieved the synthesis of pentacyclic indole-fused indolizine derivative **2m**, which is structurally related to that of the marine alkaloids such as fascaplysin and homofascaplysin C.[23] Although these latter polycyclic heterocycles occupy an important place in medicinal chemistry and life science, their construction often requires multistep approaches and harsh reaction conditions and suffers from disadvantages of a limited substrate scope.[24,25]

To the best of our knowledge, our findings represent also the first examples of intramolecular C−H/C−H cross-coupling of indoles with pyrrole and 1,2,3-triazole partners. Again, when homotryptamine-derived indole-imidazole **1p** was subjected to palladium catalyzed oxidative C−H/C−H cross-coupling, an annulated seven-memered ring product (**2p**) with an unprecedented molecular architecture was obtained in 26% yield.

On the other hand, gramine-derived indole-imidazole **1q** did not furnish the desired tetracyclic product (**2q**). To understand the mechanistic details of the intramolecular oxidative cross-coupling process, basing on our data and literature precedent, the palladium-catalyzed CDC reaction under oxidative conditions could proceed through a Pd0/PdII cycle (**Scheme 2**).



Scheme 2 *Proposed Mechanism of the CDC Reaction.*

First, regioselective palladation at the C2 position of the imidazole forms complex **I**, an intermediate that could be successfully trapped with iodobenzene in a Heck-type process to give intermolecular cross-coupling product **3a**. Afterward, an intramolecular C−H cleavage via a Concerted Metalation−Deprotonation (CMD) pathway may be followed to generate intermediate **II**. Thus, the abstraction of more acidic hydrogen from the imidazole nucleus should be the favored process,[26] thereby rendering a base-assisted palladation likely to be operative. Finally, reductive elimination would produce the product **2a** and regenerate the catalyst. In line with the mechanism proposed, the prior palladation of the imidazole nucleus well justifies the exclusive formation of a six-membered ring (cf. **Scheme 1**, products **2i−k**) such that 2,2′-cross-coupled indole−indole five-membered products were not detected when bisindoles **1i−k** were employed.

2.3 CONCLUSION

This project is focused on the synthesis of new tetra-heterocyclic derivatives through the palladium-catalyzed intramolecular oxidative cross-coupling reaction (CDC), starting from indol-ethyl azoles (bi-eteroaromatic cycles), such as indole-imidazole, indole-pyrrole, indole-triazole. From this it emerged that the use of palladium, in particular $Pd(OAc)_2$, as a metal catalyst, is indispensable for the formation of the intramolecular C–C bond, thanks to its ability to complex the heterocycle/s and to stabilize the reaction intermediate . The reaction is tolerant of a rich array of functional groups, forming annulated heterocycles for application as versatile scaffolds in medicinal chemistry. Previous studies on these hetero-rings-containing indoles were featured lengthy and multistep routes; our approach is rapid, using a simple catalyst system, and should be amenable to a broad range of further applications in medium-ring heterocycle synthesis. It is important to stress that this procedure shows high efficiency, practicality (all reactions are performed in the air atmosphere), generality and selectivity. We believe this an operationally simple protocol could provide new access to polycyclic fused molecules relevant at industrial and medical level.

CHAPTER 3

Polycyclic Indolines by an Acid-Mediated Intramolecular Dearomative Strategy: Reversing Indole Reactivity in the Pictet–Spengler-Type Reaction.

3.1 INTRODUCTION

The Pictet–Spengler reaction has long been known as an efficient method for the preparation of tetrahydro-*β*-carboline frameworks.[27,28] In recent years, many developments have been made to incorporate this reaction into cascade sequence or multicomponent reactions based on the use of tryptamine-derived substrates. In this project indoline-fused polycycles were synthesized through a TFA-promoted intramolecular dearomative cyclization of indole-tethered pyrroles. Mechanistically, the strategic carbon-carbon bond formation is hypothesized to proceed via a Pictet–Spengler-type reaction wherein a reversal of conventional indole reactivity of tryptamine derivatives occurs. Polycyclic indolines constitute important structural motifs found in many indole alkaloids such as kopsanone, malagashanine, aspidophylline A, dasyrachine, vindolinine/vindoline, minfiensine, vincorine, picratidine, and strychnine. Due to their diverse architectures, properties, and pharmaceutical activities, polycyclic indoline structures have inspired synthetic chemists to develop novel synthetic methodologies.[29]

For the synthesis of indolinic systems, the dearomatization of indoles[30] represents an attractive, robust and economic-atomic strategy towards these fascinating polycyclic skeletons. In the last 15 years, the techniques used to obtain these compounds have required the use of a metal catalysis, therefore expensive, toxic, sensitive to oxygen and humidity, which requires non-commercial ligands or adding of additives/co-catalysts. In 2010, Chen et al. discovered a highly efficient, direct, and diastereoselective intramolecular reaction of indoles via a Lewis acid-catalyzed enamine–imine isomerization.[31] Recently, Jia and co-workers reported an elegant enantioselective arylative dearomatization of indoles via a Pd-catalyzed intramolecular reductive Heck reactions.[32] Almost at the same time, the Lautens research group developed diastereoselective indole dearomative bisfunctionalizations with cyanide and organoboron reagents via a domino arylation/Suzuki[33a] or arylation/cyanation[34b] sequence. More recently, Vincent's group reported the synthesis of 3,3-spiroindolines via $FeCl_3$-mediated cyclization of arylor alkene-containing 3-substituted *N*-Ac indoles.[34] Remove the metal impurities due to prolonged use of precious metal remains one of the main objectives, with the installation of complementary protocols for selective formation of new carbon-carbon bonds without metal catalyst. Therefore dearomative cyclization is of primary importance. Herein, we disclose the successful development of an efficient Brønsted acid-promoted dearomative cyclization for the synthesis of polycyclic C2,C3-fused indoline compounds.[35]

The synthetic versatility of this operationally simple, atom-economic approach is demonstrated in the preparation of the pyrido[1,2-a:3,4-*b*']diindole core of natural product homofascaplysin C.

3.2 RESULTS AND DISCUSSION

The nucleophilic Friedel–Crafts type reactivity of indoles has been widely exploited in organic synthesis (enamine-type reactivity), while recent advances in asymmetric catalysis resulted in a surge in utilizing the less discussed electrophilic properties of iminium-type intermediates (**Figure 1**) in complex annulations of indoles.[36]

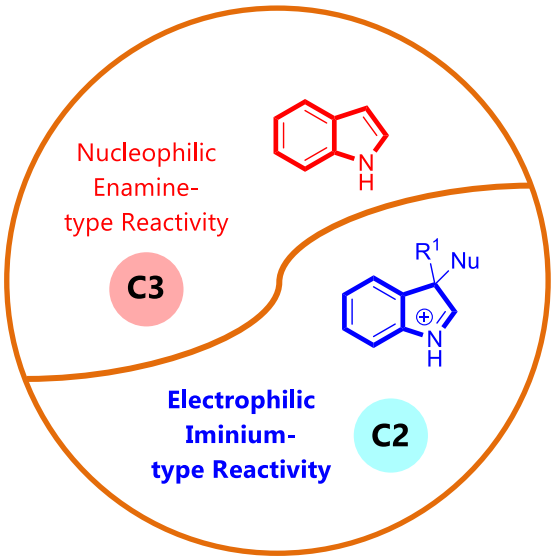


Figure 1. *Different reactivity of the indole.*

For the intramolecular in-*situ* trapping of the incipient C2 electrophile in the resulting indolium, a built-in (hetero)nucleophile such as an amino or hydroxy group is involved. However, the use of aryl/heteroaryl nucleophiles[37] to access polycyclic indoline frameworks using this iminium-trapping approach still remains a challenging task and is therefore highly desirable. This less exploited reactivity profile of indoles combined with our continuing interest in synthesizing new tryptamine-derived architectures[38] offered a starting point to identify suitable reaction conditions to allow for protonative dearomatizations of indole-tethered pyrroles (**Figure 2**).

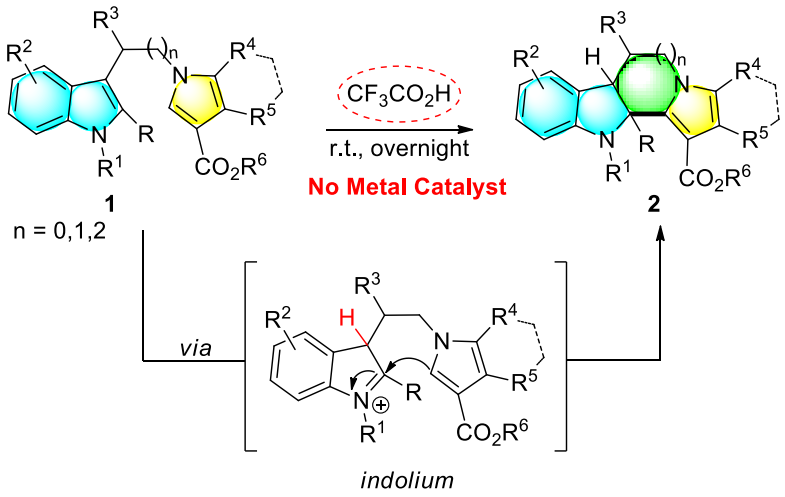
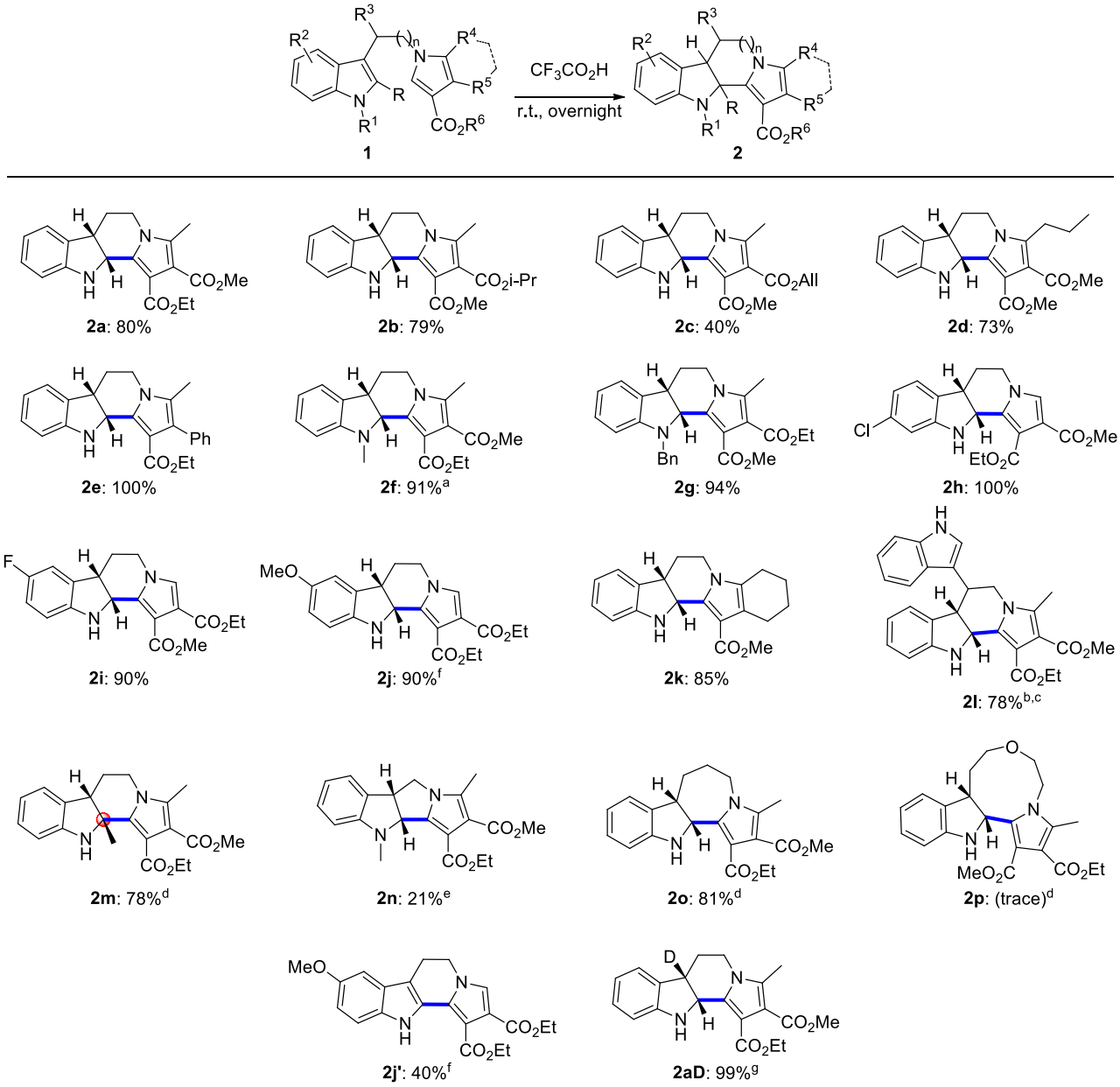


Figure 2. *Intramolecular iminium-type reactivity of indoles.*

Only one example is reported in the literature that uses the species of electrophilic iminium formed in *situ* after C3 protonation of the indole tryptamine nucleus and this it takes place between two indolic subunits.[39] As a result, two different 2,2'-diindole derivatives were obtained irrespective of which indole portion was protonated, with a preference for indolium ion formation arising from the protonation of the more basic C3-unsubstituted indole double bond. Thus, the utility of this reaction would be greatly enhanced if it could be applied to other indole-based tethered biheterocycles such as the indole-pyrrole[39] system. Using this literature example as a guide, indolepyrrole **1a** was subjected to neat TFA at room temperature. To our delight, the reaction proceeded in 84% yield with exclusive formation of tetrahydro-5*H*-indolizino[8,7-*b*]indole (**2a**). The propensity to form indoline can be attributed to the preferential protonation of the indole core to produce indolium, which undergoes an intramolecular cross-Mannich reaction by the CH bond of the pyrrole. A variety of indole-based C3,*N*-linked biheterocycles of general structure **1**[40] were prepared and screened as potential substrates for the present acid-promoted intramolecular dearomative cross-coupling reaction. As shown in **Scheme 1**, differently substituted indolepyrroles bearing an electron-neutral (4-H) or electron-deficient (5-F, 6-Cl) indole framework reacted smoothly to afford fused tetracyclic compounds in excellent yields. Under identical acidic conditions, the presence of an electron rich (5-OMe) group delivered the oxidative coupling product **2j'**[41] in 40% yield without any appreciable formation of dearomatization cross-coupling product **2j**. Also, alkyl, aryl, and ester substituents on the pyrrole portion were also tolerated in this transformation to afford the desired fused tetraheterocycles. Notably, protection of the indole nitrogen was unnecessary.

Despite the propensity of indolium species to form 2,2′-dimers,[42] no intermolecular acid-catalyzed homodimerizations of C3-substituted indoles **1** were formed in our cases. Most importantly, the reaction worked well to furnish product **2l** when branched tryptamine-derived indolepyrrole **1l** was employed. It is worth noting that the desymmetrization of bisindole moieties[43] occurs to give an intriguing hexacyclic architecture. The substrate bearing a methyl group at the C2-position of the indole ring afforded polycyclic indoline **2m** with a newly formed azaquaternary center in 78% yield. Dehomologation of the chain of substrate **1a** resulted in a decreased yield of the five-membered ring product **2n**. Also, the intramolecular dearomative cross-coupling reaction proceeded successfully to deliver the seven-membered ring product **2o** when the C3-carbon chain was extended. Unfortunately, when the indole-pyrrole **1p** was subjected to cyclization only trace amounts of the embedded nine-membered fused ring system **2p** was observed. In addition, compound **2aD** was recovered in almost quantitative yield (99%) when CF_3COOD was used. It is important to note that the current reaction proceeded in a highly diastereoselective manner, and only one diastereoisomer was obtained for the examples.[44]

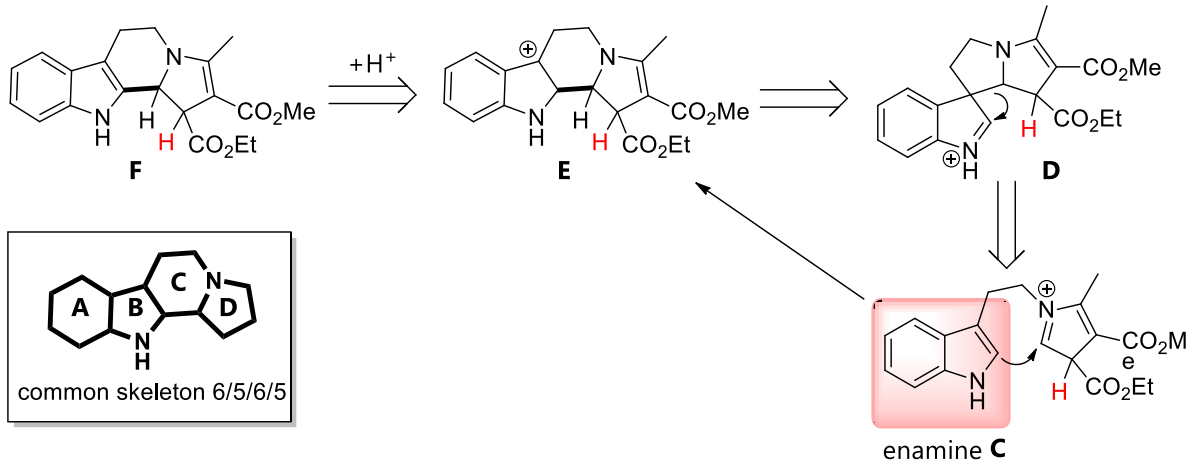


Scheme 1. *Scope of the Reaction.*[a] [a]*Standard reaction conditions:* ***1*** *(0.2 mmol), TFA (1 mL), rt, overnight, unless otherwise noted.* [b]*(0.2 mmol), TFA (4 equiv), DCM (1 mL), 55 °C.* [c]*dr: 9:1 (see the Supporting Information for details).* [d]*90 °C.* [e]*60 °C, 10 h.* [f]*Only the oxidized cross-coupling product* ***2j'*** *was isolated (40%).* [g]*CF3COOD was used.*

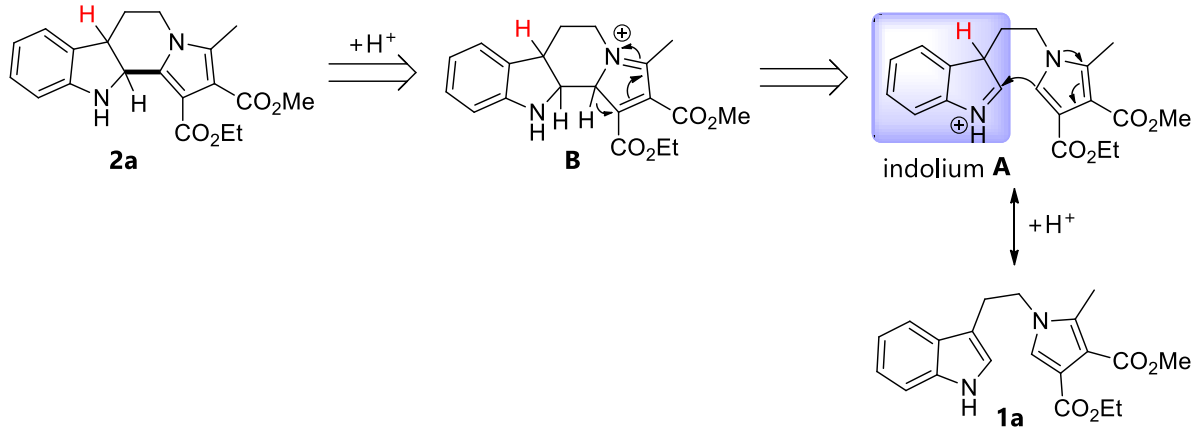
Importantly, the use of free (NH) indoles as substrates in this protocol could provide the opportunity for various further chemical manipulations such as *N*-glycosylation[45] and *N*-arylation,[46] which are important in pharmaceutical (i.e., antitumor antibiotics) and material systems (i.e., sensitizers for dye-sensitized solar cells). Based on these findings, a plausible mechanism was proposed using indole-pyrrole **1a** as an example (**Scheme 2**).

In the presence of TFA, substrate **1a** proceeds via the initial formation of indolium ion **A**, which upon attack of the pyrrole nucleophile generates intermediate **B**. Finally, a proton elimination on **B** driven by aromatization furnishes the product **2a**. Evidence for indolium formation was given by the formation of **2aD**, which is deuterated exclusively at the C3 position of the indole ring. Thus, an alternative pathway involving C-3 protonation of the pyrrole moiety of **1a** (intermediate C) and subsequent intramolecular attack by the indole C-2 to give dearomatized intermediate **F** via intermediate **E** is excluded.[47]

Classical Pictet-Spengler reaction:



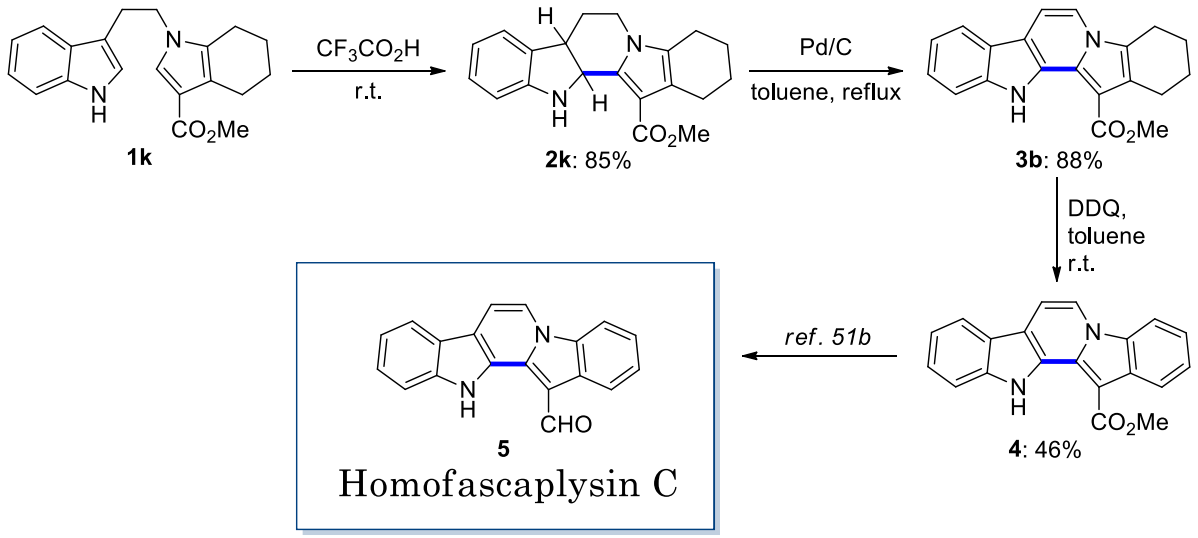
This work: Reversed Pictet-Spengler reaction:



Scheme 2 *Proposed mechanism: enamine versus iminium type reactivity of indole in Pictet-Spengler reactions.*

It should be pointed out that this acid-promoted intramolecular Friedel–Crafts cyclization can be recognized as a Pictet–Spengler-type reaction in which dearomatization of the indole ring occurs. Distinct from classical Pictet–Spengler[48] reaction derived from tryptamine derivatives, the rare and

straightforward addition of heteroarenes (pyrroles) to an indolium ion such as **A** was developed. This means that between two different heteroaryl units such as pyrrole and indole, the iminium intermediate is selectively formed by protonation of the indole instead of the pyrrole nucleus (**A** *vs* **C**), in contrast to what has been hypothesized by Yan and coworkers.[49] Thus, the construction of the six-membered ring (C-ring) of **2a** from indole-pyrrole biheterocyclic system (A,B,D-ring) was realized by a reversed (non classical) Pictet-Spengler reaction. Since the vast majority of natural products featuring the indolizino[8,7-b]indole (A/B/C/D) moiety presents an aromatized cycle B (**F**), the possibility of chemoselectively synthetize their rarely represented D aromatized congeners (**2**) is very attractive. Besides, the scope of the reaction was not limited to tryptamine-based biheterocycles, so that the construction of hitherto unknown structures (five and seven-membered C ring) was feasible. Also, substitution at C2 of the indole ring was tolerated in the process. Given our success with the cyclization of substrates **2**, we decided to apply the present approach to the synthesis of natural product homofascaplysin C.[39,50] Accordingly, the intramolecular dearomative coupling of **1k** in TFA gave the corresponding product **2k** in 85% yield. Our next endeavor was to obtain pyrido[1,2-*a*:3,4-*b*]-diindole core **4** from substrate **2k**, thereby providing a concise synthesis of this characteristic fused pentacyclic framework. Upon treatment with Pd/C in refluxing toluene, a partial oxidation of **2k** was achieved,[51] affording compound **3b** in 88% yield. A further oxidation with DDQ in toluene at room temperature resulted in the formation of the fully aromatized diindole **4** (46% yield), which is the direct precursor of the target molecule **5** (**Scheme 3**).[51b]



Scheme 3. *New approach to the synthesis of homofascaplysin C.*

3.3 CONCLUSION

In conclusion, we have developed an efficient TFA-promoted dearomative cyclization of indole tethered pyrroles that gives rapid access to a variety of challenging indoline-fused polycycles including pyrido[1,2-*a*:3,4-*b*]-diindole core of homofascaplysin C alkaloid. The reaction described here, which is realized via indolium chemistry, represents a significant advance in the field of C-C dearomative cross-coupling reactions. This protocol has advantages of mild reaction conditions, easily accessible starting materials, simple purification of the products and wide range of substrates and it offers the possibility to incorporate five, six and seven member rings between the bi-heterocyclic components trough a complete regioselectivity. The approach here described permits to maximize the amount of raw material that ends up in the product (atom economy) avoiding the production of waste. These conveniences with the absence of a metal catalysis refer to a more sustainable chemistry and therefore to a lower environmental impact.

CHAPTER 4

Zn(II)-Catalyzed Addition of Aromatic/Heteroaromatic C(sp2)–H to Azoalkenes: A Polarity-Reversed Arylation of Carbonyl Compounds.

4.1 INTRODUCTION

Arenes and heteroarenes are essential substructures of numerous compounds with activities that are relevant to a variety of important areas of research, ranging particularly from medicinal chemistry and biology to materials sciences. As a result, the selective preparation of these omnipresent moieties is of the highest relevance to synthetic chemists, both in industry and academia. In addition to electrophilic aromatic substitution reactions, a kind of valuable approaches to the synthesis of substituted (hetero)arenes was developed.[52] As result, there is an ever-growing number of methods reported in the literature,[53] most of them involving the addition of organometallic species[54] or preformed enolates/azaenolate to halide/pseudohalide.[55] The direct installation of an aryl/heteroaryl substituent into the α-position of ketone has proven to be a transformation of great utility in pharmaceutical, agrochemical, and organic synthesis.[56] Despite significant advances in transition-metal-promoted carbon−carbon bond-forming reactions that have been made over the years, a general catalytic arylation/heteroarylation exploiting the C−H bonds of (hetero)aromatics,[57] the most abundant moiety in organic molecules, remains elusive. From the viewpoints of efficiency, sustainability, and atom- and step-economy, the replacement of C−X with C−H bonds that are unreactive under traditional approaches is therefore highly appealing. A polarity-reversed strategy[58] to introduce aryl substituents into the α-position of carbonyl compounds would employ unconventional reactivity patterns, such as azoalkenes[8,59] ("umpoled" carbonyl compounds) in the context of a Michael addition.[60,61] With this objective, the transformation of a carbonyl group into a hydrazone functionality (d^2-to-a^2) represents an intriguing alternative to conventional strategies (**Figure 1**). Realizing the need for a practical and more sustainable catalytic arylation/heteroarylation method, we report herein the first Lewis acid catalyzed addition of activated (hetero)aromatic C−H substrates[62] (π nucleophiles) to azoalkenes.[63] This protocol is remarkable in its efficiency and selectivity upon employing available nonpreactivated starting materials such as arenes or heterocycles themselves. In addition, it avoids the use of strong bases, oxidants, and precious/toxic transition metals such as palladium and nickel, making this reaction an attractive complementary approach to produce α-aryl ketone surrogates under mild reaction conditions.

Umpolung Arylation

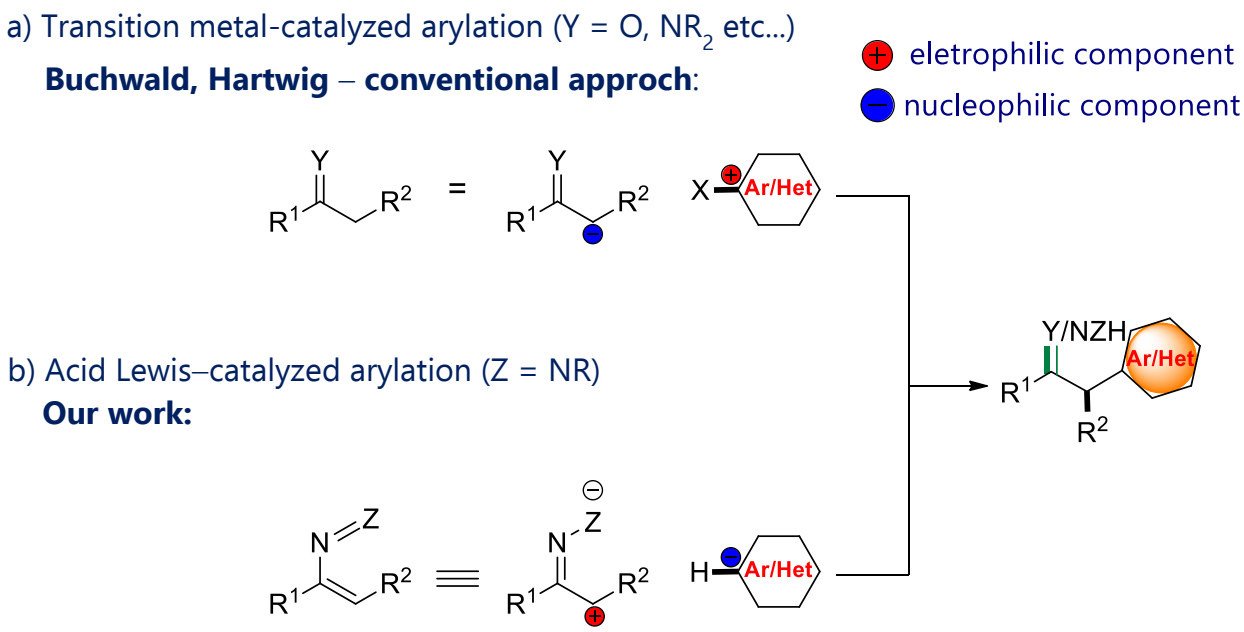


Figure 1. *Comparison of component polarization in conventional and umpolung α-arylation reaction.*

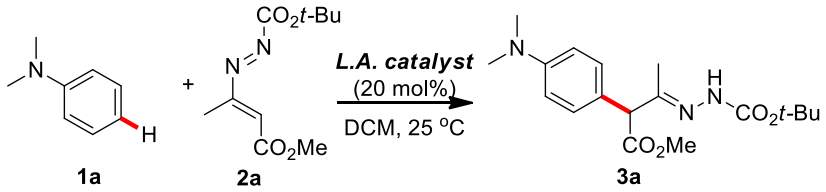
4.2 RESULTS AND DISCUSSION

To put our idea into practice, we started with the model reaction between *N, N*-dimethylaniline (**1a**) and azo alkene **2a**, which was screened with common Lewis acid catalysts in CH_2Cl_2 (**Table 1**). Notably, no product was detected in the absence of catalyst over 48 h at room temperature (**Table 1, entry 1**). Satisfyingly, the reaction was productive with different Zn(II) salts. Among them, low-cost $ZnCl_2$[64] catalyst was found to be superior, affording a yield of 64% for **3a** (**entry 4**). We observed that the efficiency of the reaction was improved to 78% yield when 1.3 equiv of azoalkene **2a** was used (**entry 12**). On the other hand, lowering the catalyst loading from 20 to 10 mol % resulted in a decrease in yield, giving **3a** in a 67% yield (**entry 13**). Interestingly, in the presence of other Lewis acids such as $InBr_3$, $FeCl_3$, CuI, $Cu(OTf)_2$, $Bi(OTf)_3$, and $Sc(OTf)_3$, no product or significantly lower yields were obtained. With the optimized reaction conditions in hand, we next focused our attention on the substrate scope (**Scheme 1**). In all cases, the reaction reached completion within 4 h at room temperature, and exclusive *para*-substitution was observed.

As highlighted in **Scheme 1A**, aromatic and heteroaromatic substrates were employed as nucleophiles in the Michael reaction to give the corresponding compounds **3a**–**o**.

For example, good yields were obtained when simple arenes such as *N,N*-diethylaniline (**1b**) and N-methyl-N-(prop-2-yn-1-yl)-aniline (**1c**) were coupled with azoalkene **1b** to give **3b** and **3c**,

respectively. The use of *N,N*-dimethyl-1-naphthylamine (**1d**) generated the product **3d** in excellent yield (95%). Furthermore, *N,N*-dimethylanilines 1e and 1f bearing electron-donating substituents such as methyl and methoxy on the phenyl ring performed very well to give the desired products (**3e** and **3f** 73% and 86%, respectively).



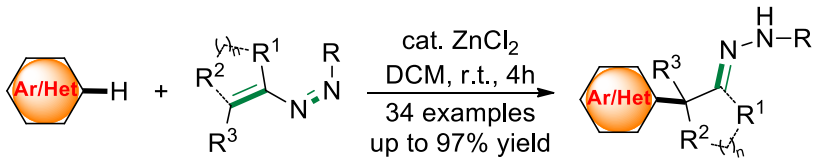
1a **2a** **3a**

Entry	Catalyst	Time (h)	Yield (%)
1	–	48	0
2	$InBr_3$	48	0
3	$Zn(OAc)_2$	48	<5
4	$ZnCl_2$	1	64
5	$ZnBr_2$	4	46
6	$FeCl_3$	18	<5
7	CuI	48	0
8	$Cu(OTf)_2$	0.4	0
9	$Zn(OTf)_2$	5	61
10	$Bi(OTf)_2$	48	5
11	$Sc(OTf)_3$	24	23
12	**$ZnCl_2$**	**1**	**78**
13	$ZnCl_2$	1	67

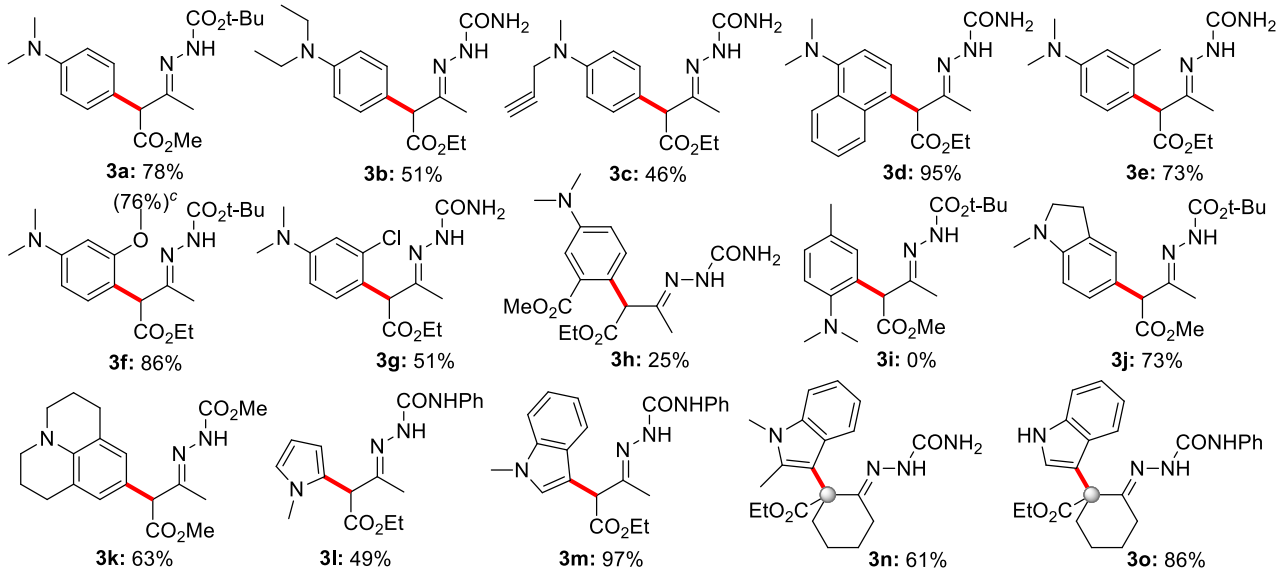
[a]*Reaction conditions:* ***1a*** *(0.5 mmol),* ***2a*** *(0.5 mmol), cat. (0.1 mmol, 20 mol %), DCM (2.0 mL), 25 °C for the indicated time.* [b]*Isolated yields.* [c]*1.3 equiv of 2a was used. d10 mol % of catalyst*

Table 1. *Michael Addition of N,N-Dimethylaniline (1a) with Azoalkene 2a*[a].

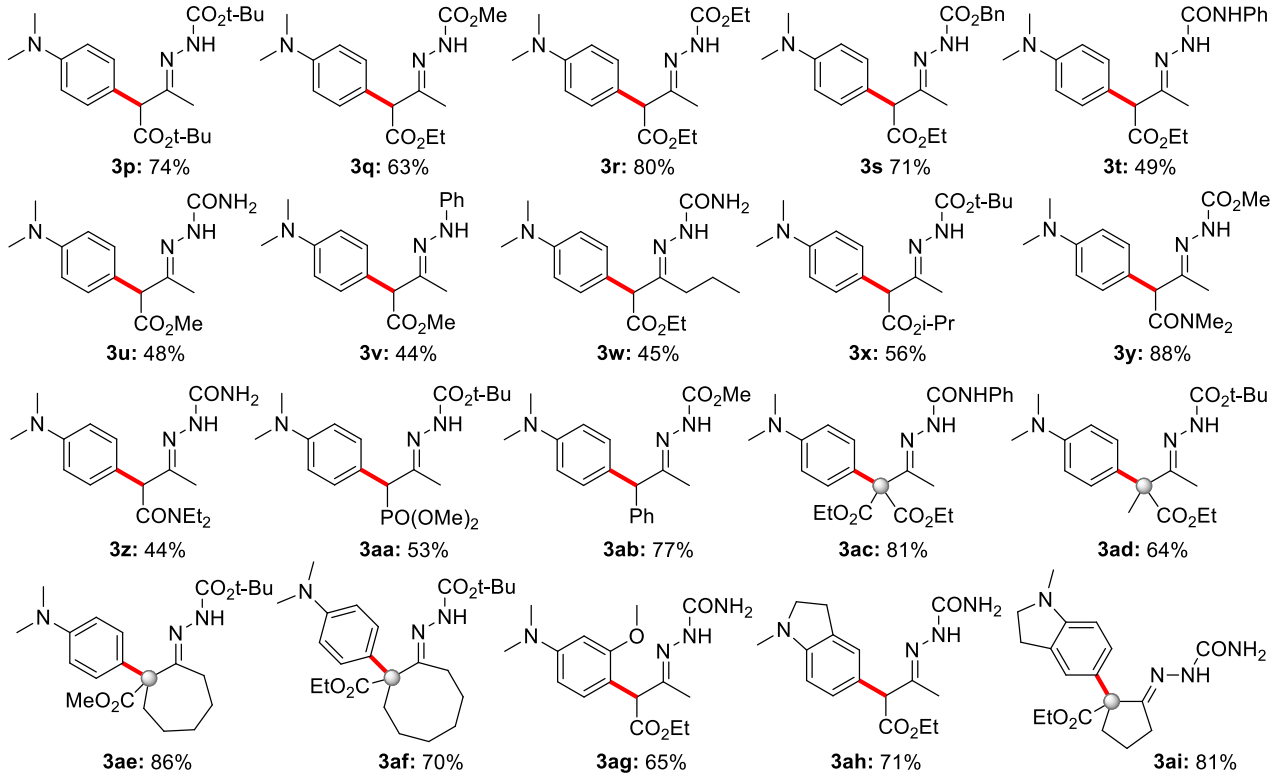
In comparison, the reaction of electron-withdrawing chlorine and ester *N,N*-dimethylanilines exhibited lower reactivity, affording products **3g** (51%) and **3h** (25%) in lower yields, presumably due to their reduced nucleophilicity. Notably, when *N,N*-dimethyl-p-toluidine (**3i**) was used as a substrate, no *ortho*-substitution was observed. In addition, (hetero)cyclic reactants, e.g., *N*-methylindoline (**1j**), julolidine (**1k**), *N*-methylpyrrole (**1l**), *N*-methylindole (**1m**), *N*-methyl-2-methylindole (**1n**), and *N*H-indole (**1o**),were readily converted into the desired Michael adducts **3j**−**o** in satisfactory isolated yields (49−97%). Thus, a remarkably broad range of substituents can be accommodated to the hydrazone products, and importantly, it also provides access to synthetically challenging α-quaternary centers (e.g., **3n**, **3o**, **3ab**, **3ac**, **3ad**, **3ae**, and **3a**i). In addition, incorporation of a five-, six-, seven-, or eight-membered ring in the hydrazone structure was also well tolerated. Regarding the *N*-protecting groups for the *N1* atom of azoalkenes, it was found that better results were obtained in the cases of alkoxycarbonyl groups than aminocarbonyl groups (**Scheme 1**, **3a** *vs.* **3u**, **3e** *vs.* **3af** and **3f** *vs.* **3ag**). Finally, our reaction was performed on a gram scale, yielding 1.33 g of the desired product **3a** without loss of yield (76%). It should be noted that no detectable formation of the bis-adducts was observed in any case.[63b]



A: Arenes/Heteroarenes



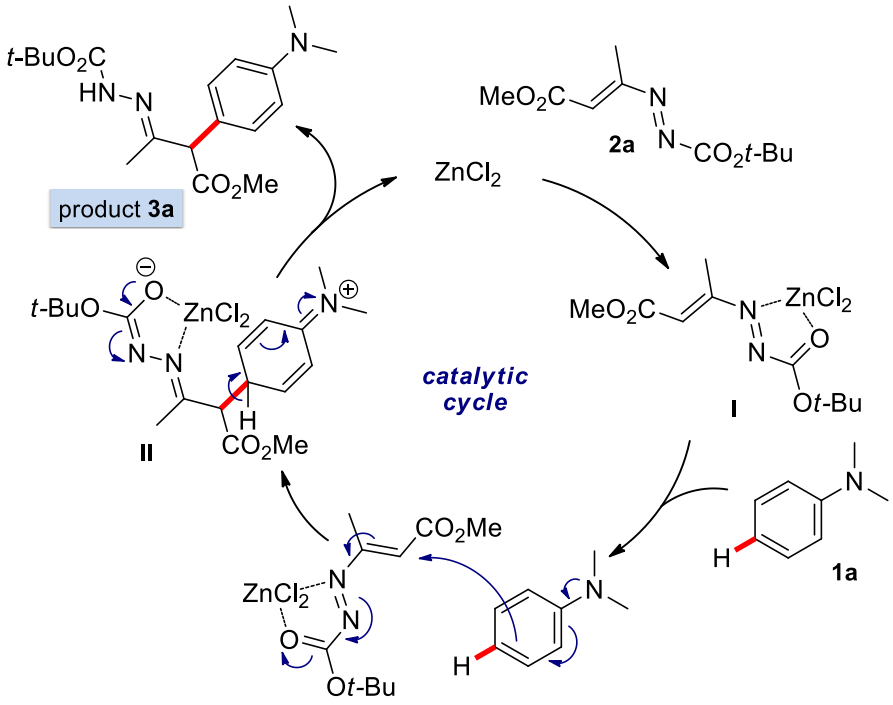
B: 1,2-Diaza-1,3-dienes



[a]*Reaction conditions:* ***1*** *(0.5 mmol),* ***2*** *(0.65 mmol), ZnCl2 (0.1 mmol, 20 mol %), DCM (2.0 mL), 25 °C, 4 h.* [b]*Isolated yields.* [c]***3a*** *(1.33 g) was obtained on 5.0 mmol scale.*

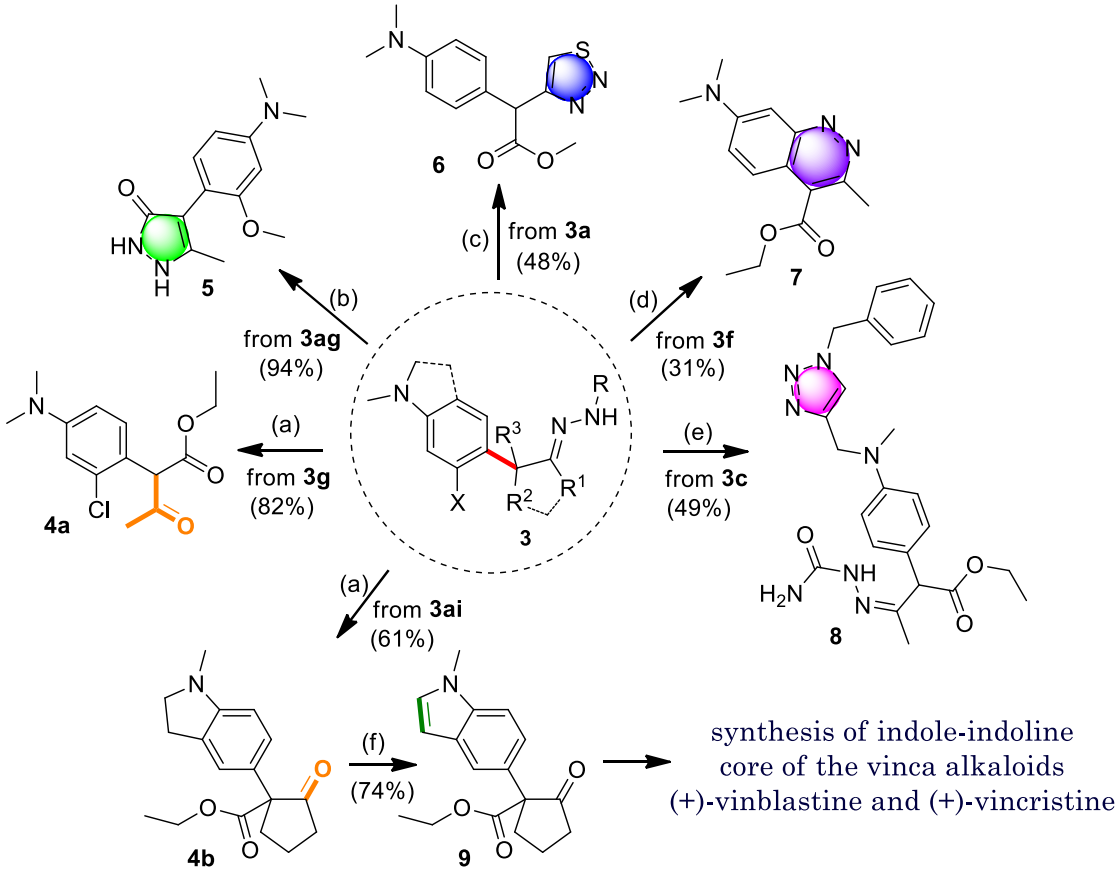
Scheme 1. *Substrate Scope*[a,b]

A plausible reaction mechanism was proposed for Michael addition catalyzed by $ZnCl_2$ between *N, N*-dimethylaniline (**1a**) and azoalkane **2a** (**Scheme 2**). The compound **2a** was activated after chelation to Zn (II) to generate intermediate **I**,[65] which undergoes a nucleophilic addition of *N, N*-dimethylaniline (**1a**) from the *para* position to form the intermediate **II**. Following hydrazone re-aromatization and protonation by [1,5-H] shift led to adduct **3a** with regeneration of the catalyst Zn (II).



Scheme 2. *Proposed Mechanism for ZnCl2-Catalyzed Michael Reaction.*

To demonstrate the usefulness of these ketone hydrazones such as synthesis blocks, have been various transformations investigated (**Scheme 3**). As a preliminary test of these, regeneration of the carbonyl function[66] (*path a*) from representative hydrazones **3g** and **3ai** to give ketones **4a** and **4b**,[67] respectively, was conducted. Cyclization of hydrazone **3ag** under basic conditions furnished 1*H*-pyrazol-3(2*H*)-one **5** in 94% yield (*path b*). In addition, transformation of **3a** into 1,2,3-thiadiazole **6** via a Hurd−Mori-type reaction was realized using thionyl chloride (*path c*).[68] Subsequent six-membered heterocyclization of **3f** afforded cinnoline **7** in the presence of $Cu(OAc)_2$ H_2O as a promoter (*path d*).[69] Then a further functionalization with participation of an alkyne group by CuAAC (azide−alkyne cycloaddition)[70] of **3c** with benzyl azide yielded the 1,2,3-triazole derivative **8** in 49% yield (*path e*). Finally, the synthetic potential of this arylation method was tested by carrying out the preparation of compound **9** (from **4b**[68]) as precursor of bis-indoles related to the core of (+)-vinblastine and (+)-vincristine (*path f*).[71]



[a]*Reaction conditions:* [a]*Amberlyst-15H, $(CH_3)_2CO/H_2O$ 9:1, reflux, 2 h;* [b]*K_2CO_3, EtOH, reflux, 3 h;* [c]*$SOCl_2$, DCM, rt, 2 h.* [d]*$Cu(OAc)_2{\cdot}H_2O$, toluene, reflux, 1.5 h;* [e]*benzyl azide, $Cu(OAc)_2{\cdot}H_2O$, sodium ascorbate, DCM/H_2O 1:1, rt, 3.5 h,* [f]*Pd/C, toluene, reflux, 6 h.*

Scheme 3. *Synthetic Applications.*[a]

4.3 CONCLUSION

In conclusion, we have developed an efficient, practical, and scalable approach to the synthesis of α-(hetero)aryl hydrazones including those with an α-quaternary center. This umpolung arylation/heteroarylation reaction requires the simple combination of an electron-rich (hetero)aromatic substrate and an azoalkene and proceeds in a highly *para*-selective manner. The method enables unprecedented, atom-economical access to a variety of simple α-aryl carbonyl surrogates directly from readily available starting materials (no preactivation of (hetero)aryl reagents is needed), avoiding the use of expensive/toxic catalysts and high temperatures and minimizing the production of salts waste. We are sure that this transformation, which overcomes the limits/complications associated with traditional α-(hetero)- arylation, represents a robust alternative to existing methods. Furthermore, the synthetic usefulness of these challenging synthons was demonstrated.

CHAPTER 5

Synthesis of Polycylic Fused Indoline Scaffolds through a Substrates-Guided Reactivity Switch.

5.1 INTRODUCTION

To further investigate the reactivity of the indole, Zn(II)-catalyzed divergent synthesis of functionalized polycyclic indolines through formal [3+2] and [4+2] cycloadditions of indoles with 1,2-diaza-1,3-dienes (DDs) is reported. Indoline is an important structural motif present in several biologically active compounds from both natural and synthetic origins. The occurrence of this heterocyclic unity in these structures is closely related to the biological activities they exhibit.[72] The indoline substructure,[73] particularly that C2,C3-fused, is ubiquitously present in many naturally alkaloids, as vincorine, minfiensine, gliocladin C, kopsnone, pleiomaltinine, and communesin F are shown in **Figure 1**.

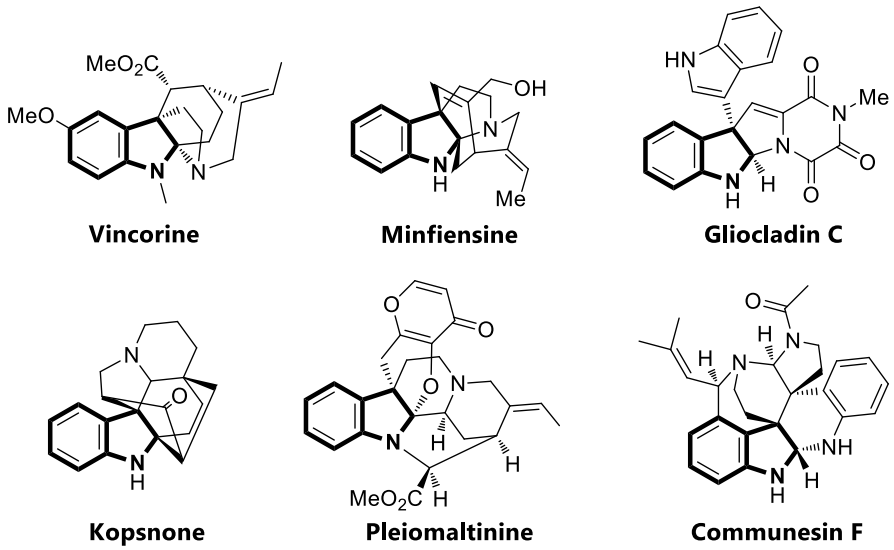


Figure 1. *Examples of naturally occurring compounds containing 2,3-fused indolines.*

The desire to build such appealing polycyclic frameworks, particularly those with a bridgehead amino acetal C2 carbons, has inspired the development of elegant methodologies over the past several years. Following the initial discovery of the inverse electron-demand [4+2] cycloaddition reaction of electron-rich alkenes (furans, pyrroles and indoles) with 1,2-diaza-1,3-dienes (DDs) by Gilchrist *et al.*,[74] other elegant studies by the groups of Wang[10a] and Tan[59b] have been recently reported exploiting indoles as nucleophiles. By taking advantage of unique reactivity of DDs[75] and intrigued by these and our recent findings in the manipulation of indolyl cores,[76] we reasoned that the proper combination of indole and 1,2-diaza-1,3-diene elements might allow us to design a substrate-controlled divergent approach.

In this design, DDs would be used as C2N1 or C2N2 units (1,3 or 1,4 dipole synthons) to realize [3+2] and [4+2] annulation reactions of indoles, respectively (**Figure 2**). Thus, by tuning the substituents of both substrates upon the influence of the same catalyst, two series of fused indoline-based scaffolds such as tetrahydro-1*H*-pyridazino[3,4-*b*]indoles and tetrahydropyrrolo[2,3-*b*]indoles would be generated with chemodivergence.

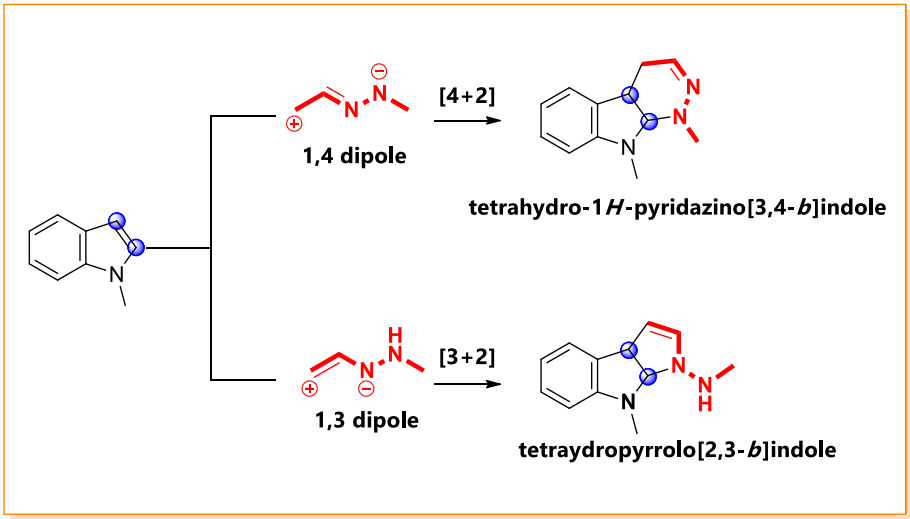
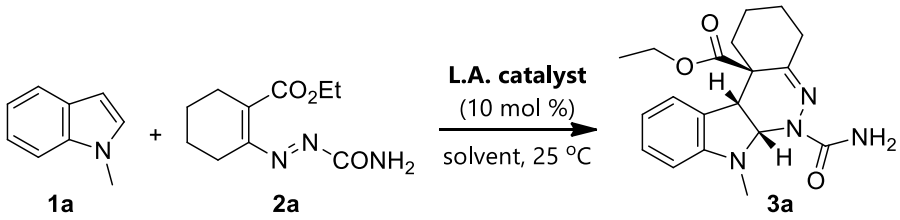


Figure 2. *Working hypothesis: chemodivergent synthesis of polycylic fused indoline scaffolds.*

Taking advantage of the reciprocal reactivity/nature of substituents of the reagents, the same couple of these furnished different types of functionalyzed poly-azaheterocycles embedding the indolinic skeleton as common privileged substructure. The reaction proceeded with a higly diastereselective manner from designed indole and 1,2-diaza-1,3-diene substrates with C3 and/or C4 position(s) substituted, respectively.

5.2 RESULTS AND DISCUSSION

We began our work by studying the reaction between indole **1a** and cyclic 1,2-diaza-1,3-diene **2a** (**Table 1**). No reaction took place, and both compounds remained inactive in the absence of Lewis acid catalyst (**entry 1**). Various Lewis acid catalysts such as $Sc(OTf)_3$, $Zn(OAc)_2$, $ZnSO_4$, $Zn(OTf)_2$, $SmCl_3{\cdot}6H_2O$, $LiClO_4$, LiCl, $CuCl_2$, $Cu(OTf)_2$, $CuBr_2$, $InBr_3$, $ZnBr_2$, $ZnCl_2$ and different solvents (dichloromethane, acetone, tetrahydrofuran, acetonitrile and cyclohexane) were examined but many of them produced unsatisfactory yields. The best result was achieved using a combination of $ZnCl_2$ (10 mol%) and CH_2Cl_2 (0.25 M) at room temperature. Noteworthy, compound **3a** was obtained as a single regio- and diastereoisomer (50% yield, **entry 15**). The substrate scope has been extended to several 2,3-unsubstituted indoles **1a**–**n** and cyclic DDs **2a**–**h** under the optimized reaction conditions, and a variety of tetrahydro-1*H*-pyridazino[3,4-b]indoles (tetracyclic fused ring (6-5-6-6/7/8) systems) **3a**–**y** were synthesized (**Scheme 1**).

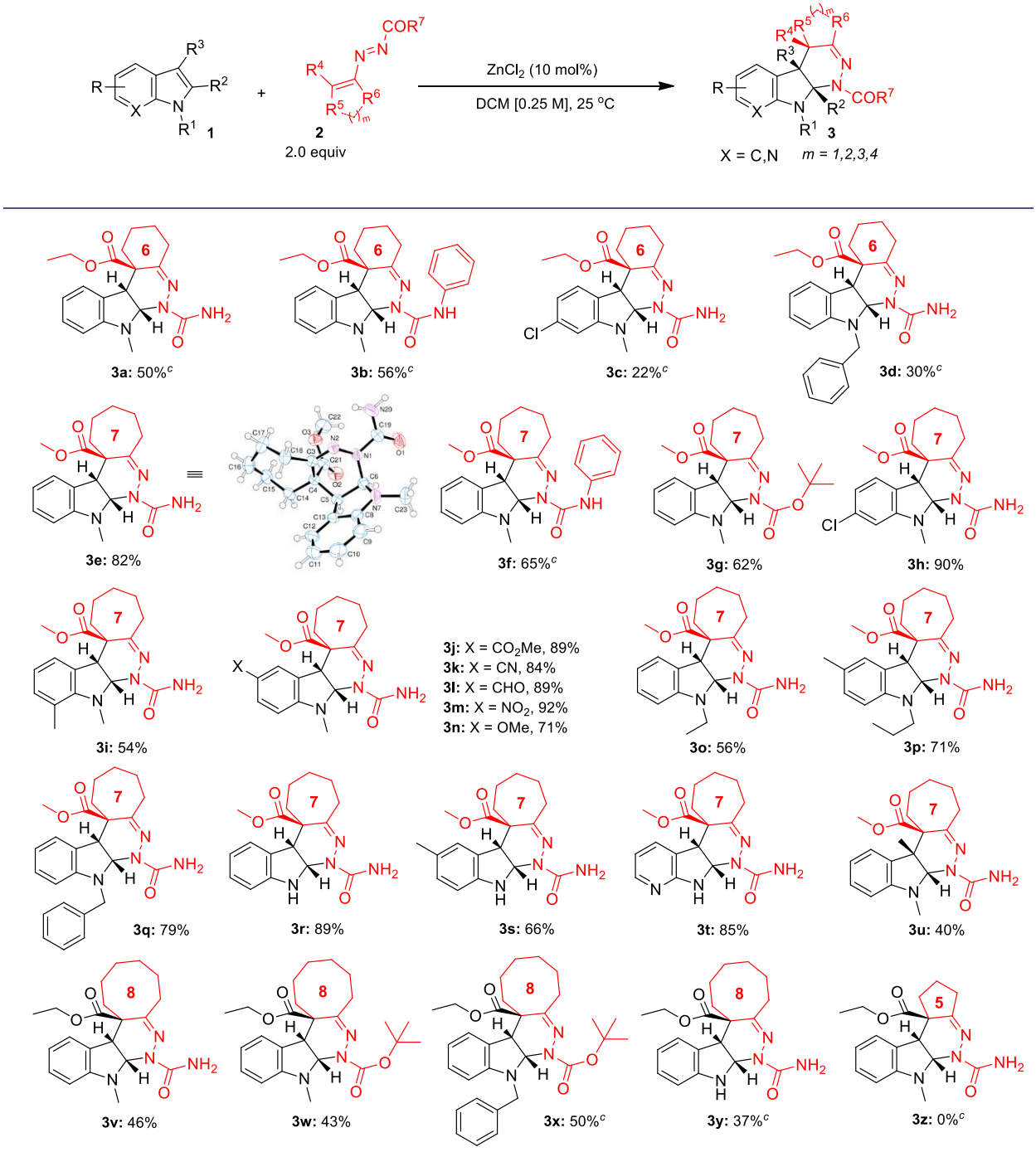


1a 2a 3a

Entry	Catalyst	Solvent	Yield (%)[b]
1	–	CH_2Cl_2	0
2	$Sc(OTf)_3$	CH_2Cl_2	0
3	$Zn(OAc)_2$	CH_2Cl_2	0
4	$ZnSO_4$	CH_2Cl_2	0
5	$Zn(OTf)_2$	CH_2Cl_2	0
6	$SmCl_3$ $6H_2O$	CH_2Cl_2	<5
7	$LiClO_4$	CH_2Cl_2	0
8	LiCl	CH_2Cl_2	0
9	$CuCl_2$	CH_2Cl_2	0
10	$Cu(OTf)_2$	CH_2Cl_2	<5
11	$CuBr_2$	CH_2Cl_2	0
12	$InBr_3$	CH_2Cl_2	0
13	$ZnBr_2$	CH_2Cl_2	37
14	$ZnCl_2$	CH_2Cl_2	39
15[c]	$ZnCl_2$	CH_2Cl_2	50
16[c]	$ZnCl_2$	Acetone	43
17[c]	$ZnCl_2$	THF	40
18[c]	$ZnCl_2$	CH_3CN	23

*[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), cat. (0.03 mmol, 10 mol %), DCM (2.0 mL), 25 °C for 12 h. [b]Yields determined by ^1H NMR analysis of the crude mixture using 1,1,2,2 tetrachloroethane as the internal standard. [c]2.0 equiv of **1a** was used.*

Table 1. *Optimization Conditions for Reaction of N-Methylindole (**1a**) with Cyclic Azoalkene **2a**.[a]*



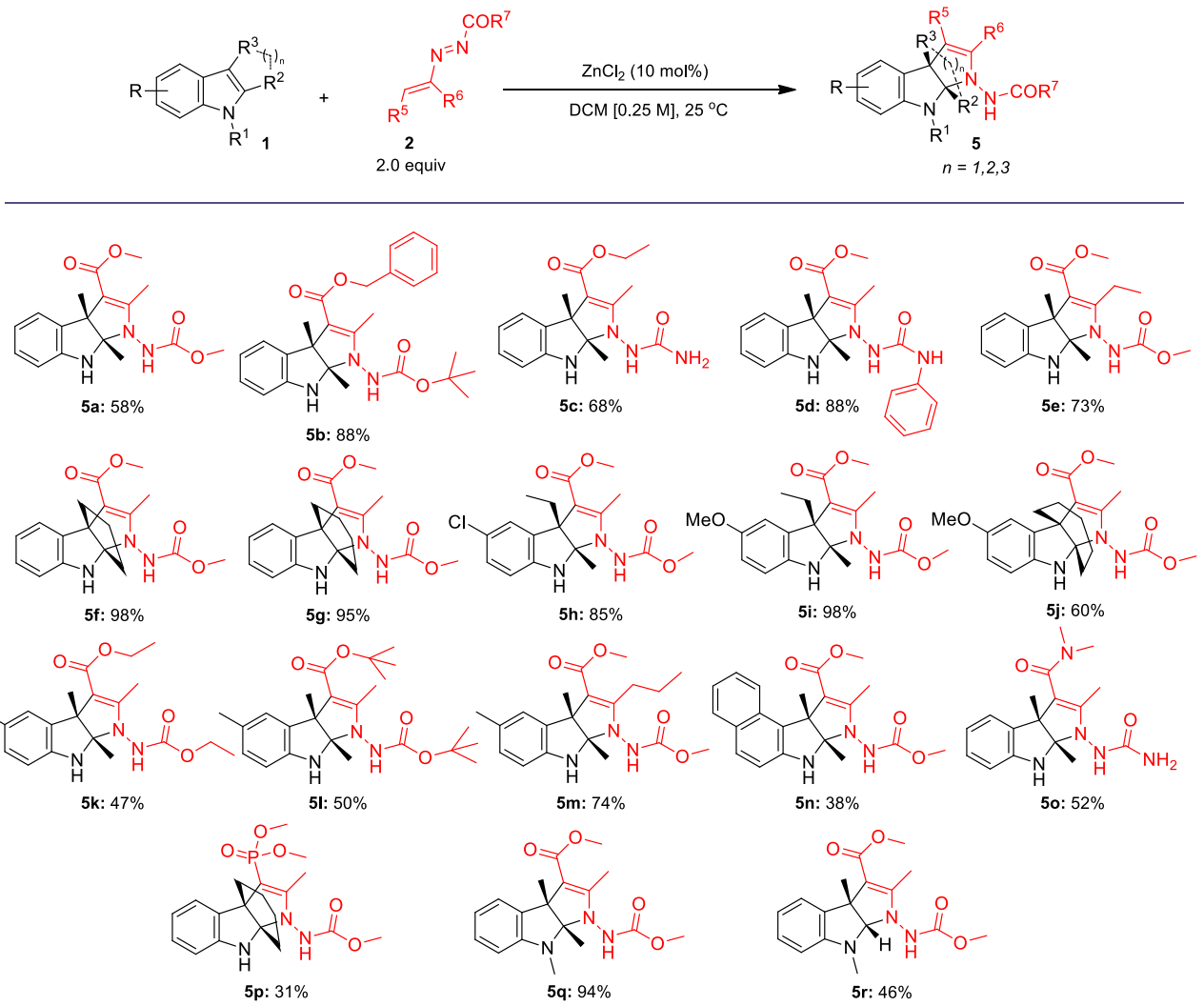
[a]*Reaction conditions:* ***1*** *(2.0 mmol),* ***2*** *(1.0 mmol), $ZnCl_2$ (0.1 mmol, 10 mol %), DCM (2.0 mL), 25 °C.* [b]*Isolated yields.* [c]*Ring-opened product* ***4*** *was also isolated.*

Scheme 1. *Scope of Zn(II)-Catalyzed formal [4+2] Cycloaddition Reactions to Tetrahydro-1H-pyridazino[3,4-b]indoles.*[a,b]

As shown in **Scheme 1**, indoles **1a–n** with different electronic characters were suitable for the reaction with 6-membered cyclic DDs giving the relative fused indoline heterocycles **3a–d** in moderate to good yields. The Zn-catalyzed [4+2] cycloaddition reactions were further extended to 7- and 8-membered cyclic DDs.

We were glad to find that the use of 7-membered DDs gave rise to the best results in terms of isolated yields. Also, the wide functional group tolerance was nicely demonstrated by the fact that both electron-donating (5-OMe, 5-, 7-Me) and electron-withdrawing (6-Cl, 5-CO_2Me, 5-CN, 5-CHO, 5-NO_2) groups were all well tolerated providing efficient access to the fused indoline heterocycles **3e–s**. Interestingly, the use of 7-azaindole substrate also worked well to give the product **3t** in 85% isolated yield. Furthermore, 1,3-dimethyl indole (**1o**) was also proven to be a good candidate for this transformation (**3u**, 40%). The formal [4+2] annulation was then widened to DDs bearing cyclooctane, and the reactions furnished the relative products **3v–y** with lower yields than those of 7-membered cyclic DDs. Additionally, the generality of N-terminal protective group on DDs as well as for the N atom of indoles was explored. Remarkably, free N-H indoles were also compatible with this protocol, albeit slightly lower yields were observed, probably owing to reduced nucleophilicity at C3 and reduced electrophilicity at C2 of starting indole (**Scheme 1**, **3s** *vs.* **3p**, and **3y** *vs.* **3v**). No annulation occurred when 5-membered cyclic DD was employed under the optimized reaction conditions (**3z**, 0%), in this case only formation of ring-opened [4+2] product **4** was recovered. The relative configuration of the cycloadducts **3** were determined by X-ray diffraction analysis of **3e**[77] and those of other compounds were assigned by analogy. During the investigation on the ring size effect of the 1,2-diaza-1,3-diene substrate, it was also noted the formation of ring-opened [4+2] byproduct **4** highlighting the easiness of re-aromatization of **3** to give more stable indole derivative. The sensitivity of **3** to re-aromatization process was confirmed by complete transformation of **3b** into **4a** in the presence of Amberlyst 15(H), thus suggesting that formation of products **3** and **4** might go through the same intermediate (*vide infra*, **Scheme 4b**). This undesired event appears to be the cause for lowering [4+2] cycloaddition product yields found in some cases. Notably, this pathway remains exclusive when the reaction was conducted with 1,2-dimethyl indole (**1p**), in line with what was previously observed in the reaction of (*NH/NMe*)indoles with non-cyclic DDs.[75a,76e] Therefore, given the failure of the cycloaddition reaction with the use of 3- and 2,3-unsubstituted indoles and to further showcase the flexibility of this catalytic annulation strategy, we next moved our attention to exploring the reactivity of differently substituted indoles (*e.g.*, 2,3-disubstituted indoles) with linear DDs.

Curiously, when DD **2j** bearing a proton at the terminal C-4 position was applied to the same conditions, the expected [4+2] cycloaddition product was not observed. Instead, the [3+2] cycloaddition product **5a** was obtained in 58% yield. A series of differently 2,3-disubstituted indole entities **1q–y** containing electron-donating groups (5-OMe, and 5-Me) or electron-withdrawing groups (5-Cl) smoothly underwent annulation with 4-ester, 4-amide or 4-phosphonate N-protected linear DDs **2j–s** to give the relative products in good yields (**Scheme 2**). Intriguingly, 1,3-dimethyl indole (**1o**) reacted with **2j** to afford the [3+2] cycloaddition product **5r** in 46% yield.



[a] *Reaction conditions:* ***1*** *(0.6 mmol),* ***2*** *(0.4 mmol), ZnCl2 (0.04 mmol, 10 mol %), DCM (2.0 mL), 25 °C.* [b] *Isolated yields.*

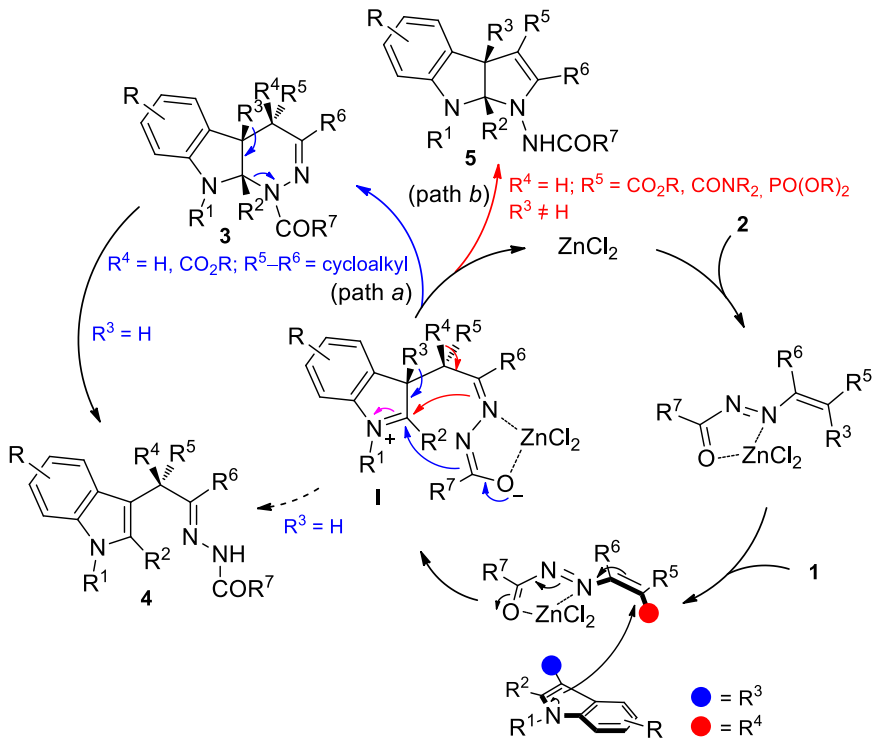
Scheme 2. *Scope of Zn(II)-Catalyzed formal [3+2] Cycloaddition Reactions to Tetrahydropyrrolo[2,3-b]indoles.*[a,b]

The structure of compounds **5a–r** was confirmed by subjecting **5q** to N-N bond cleavage using the Magnus' method.[78] Treatment of compound **5q** with ethyl bromoacetate/Cs_2CO_3/MeCN at 50 °C followed by heating to 80 °C resulted in N-N′ bond cleavage to the corresponding *NH*-free tetrahydropyrrolo[2,3-b]indole **6a** in 64% isolated yield (**Scheme 4a**).

As a synthetic strategy, this [3+2] annulation affords, in a single operation, the structurally rigid 6-5-5 tricyclic subunit with a substituent at the 3-position of the indole nucleus, which is the basic structure of pharmaceutically valuable natural products.[79] Besides, this non-classical approach provides access to functionalized pyrroloindoline system with substitution patterns that are otherwise inaccessible using tryptamines[80] as precursors.

Based on the above-mentioned findings and reported literature[75,76e] a plausible reaction mechanism as outlined in **Scheme 3** was proposed. $ZnCl_2$ acts as a Lewis acid to promotes the regioselective addition of indole **1** to DD **2**. The reactivity of transient zwitterionic intermediate **I** towards azacyclization (5-*exo*- *vs.* 6-*exo*-trig) depends upon the mechanism involved, which is strongly influenced by the structure of the substrates (both the R^3 and R^4).

Whereas cyclic DDs undergo a formal [4+2] cycloaddition[81] (path *a*), acyclic ones more simply engage in [3+2] cycloaddition subsequent to a fast 1,3-H shift (in practice, a CH/NH tautomerism) which actives the "internal" hydrazonic (sp^2) nitrogen atom of zwitterionic intermediate **I** to the five ring closure (path *b*). We speculate that the preferential reaction pathway to tetrahydropyrrolo[2,3-*b*]indoles over the [4+2] cycloaddition products is ascribable to the presence of the strongly acidic proton (R^4 = H) located in α-position to the hydrazonic function of **I**, which being prone to CH/NH tautomerism, triggers the formation of **5**. The fact that the indole **1o** gave both [4+2] and [3+2] cycloadducts using cyclic and linear DDs (**3u** *vs.* **5r**) supported this. Moreover, it was quite interesting to note that, when 6-membered cyclic 1,2-diaza-1,3-diene **2i** was reacted with **1r**, the exclusive formation of [4+2] cycloaddition product **3aa** was observed (**Scheme 4c**). Similarly, the use of linear 1,2-diaza-1,3-diene **2t** yielding the product **3ab** (**Scheme 4d**). Our control experiments suggest that the divergent protocol also depends on the delicate balance of acidity of this proton (if present), which selectively drives the direction of the heterocyclization process. More precisely, the [3+2] cycloaddition is favored by the presence of EWG groups like esters, amides or phosphonates in C4 position of the starting DD system (R^4 = H; R^5 = CO_2R, $CONR_2$ and $PO(OR)_2$) that causes the acidity of that proton to be greatly increased.



Scheme 3. *A Plausible Reaction Mechanism for Zn(II)-Catalyzed Annulation Reactions.*

With this work, we have demonstrated that the substituents of 1,2-diaza-1,3-diene substrate is the critical factor dictating chemoselectivity in annulation process. Importantly, the presence of a H atom in C3 position of the indole ring results responsible for the observed ring-opened [4+2] product **4**. As already evidenced this event become exclusive when (*N*H/*N*Me)indole or 1,2-dimethyl indole **1o** is used as the nucleophile.

To our surprise when R3 = H, neither the formation of the [3+2] annulation product nor the ring-opened [3+2] product of type **7** described by Tan and coworkers was observed (**Figure 3**). This shows that when R3 = H, the indole re-aromatization process from the key intermediate I towards **4** compared to the five-ring closure to generate product **5** is the preferred one.

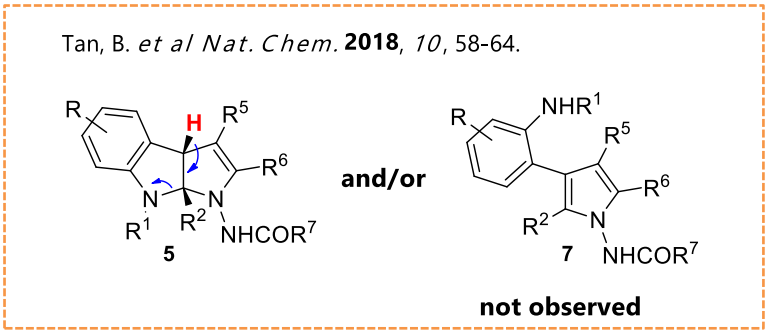
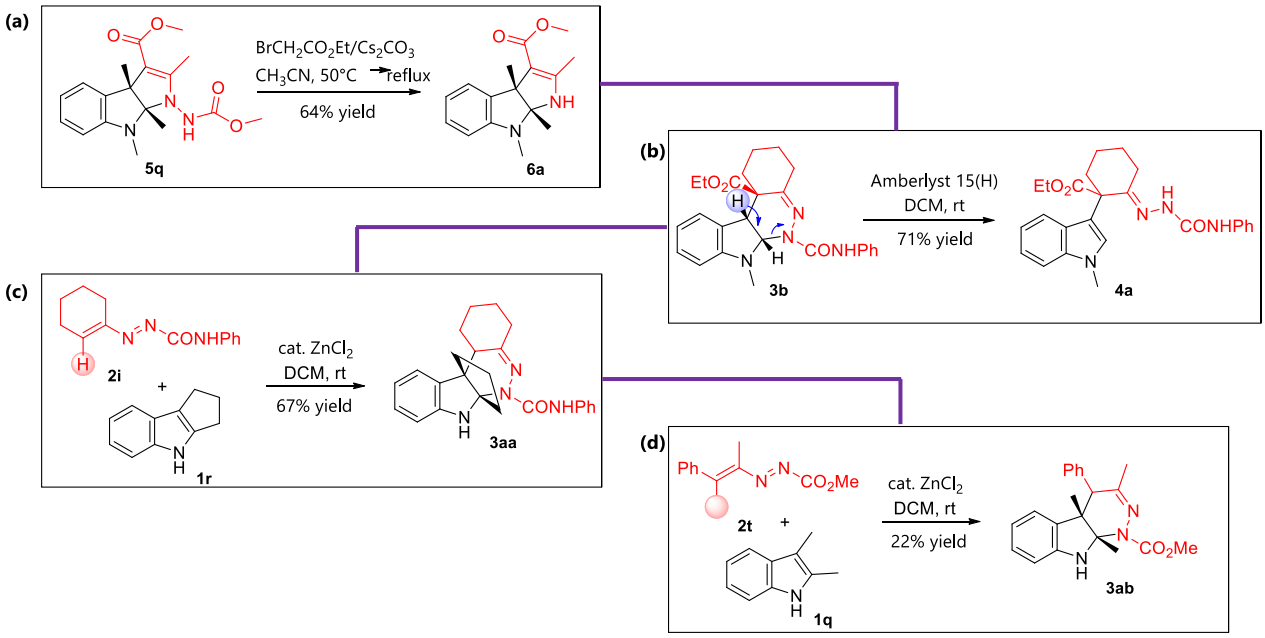


Figure 3*. [3+2] annulation product* ***5*** *(R3 = H) and/or its indole ring-opened product (aniline-indole)* ***7****, whose structures are shown below, were not generated under our reaction conditions. (see ref. 59b).*



Scheme 4. *Control experiments.*

5.3 CONCLUSION

In summary, we have successfully described a substituent controlled synthesis of two kinds of functionalized indoline fused heterocycles under mild conditions. By virtue to the versatility of these latter in switching reactivities, efficient procedure to obtain tetrahydro-1*H*-pyridazino[3,4-*b*]indoles and tetrahydropyrrolo[2,3-*b*]indoles has been developed. Remarkably, the reactions feature a high step- and atom-economy, high chemo- and diatereoselectivity, broad substrate scope, good functional group tolerance, and readily accessible starting materials. The successful construction of unique rigid polycyclic skeletons, particularly those with a challenging bridgehead *N*,*N*-aminal quaternary centers enrich the chemistry of both indoles and 1,2-diaza-1,3-dienes.

CHAPTER 6

Divergent construction of fused and non-fused N-polyheterocycles via formal [4+2] Annulation of Indoles with Cyclic Azoalkenes.

6.1 INTRODUCTION

With attention to indole nucleus as a privileged scaffold[82] and in continuation of our interest in the construction of novel azaheterocycles[83], atom and step-economy procedures to access valuable structures that represent analogues of biologically and pharmacologically active molecules are further investigated. Specifically, two interesting classes of fused and non-fused *N*-polyheterocyclic compounds **3** and **4** are synthesized starting from the same precursor C2,C3-fused indoline-tetrahydropiridazine **1** (**Figure 1**).

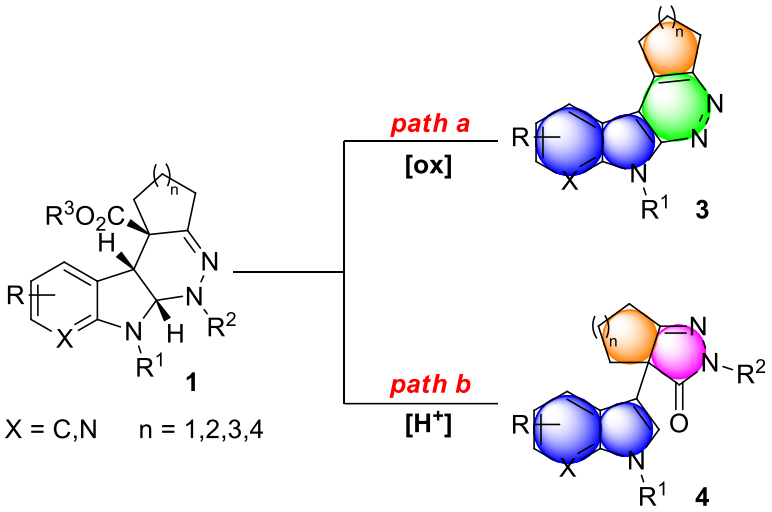


Figure 1. *Divergent synthesis to obtain fused and non-fused N-polyheterocycles.*

The tetracyclic fused indole-pyridazine system **3** can be considered as aza-analogous of *β*-carboline, the unique tricyclic pyrido-[3,4-*b*] indole core amenable to an important family of bioactive natural products widely distributed in nature.[84] Therefore, fusion of the indole moiety with the pyridazine scaffold that potentially generates an interesting collection of isomeric compounds (**a–d**) has attracted our attention. A large number of reports dedicated to synthesis of these derivatives and studies on their pharmacologic activities appeared in the literature during the last 2-3 decades. These systems have been discovered exhibiting useful properties including activity against Alzheimer's disease, Parkinson's disease, and Down's syndrome as well as antitumor, antihypertensive, antiinflammatory, antibacterial, tuberculostatic, inotropic, hypnotic, anticonvulsive, monoamine oxidase inhibitory, phosphodiesterase inhibitory, and thromboxane inhibitory activity. Many examples of literature deal with 5*H*-pyridazino[4,3-*b*]indoles (**a**)[85] or 5*H*-pyridazino[4,5-*b*]indoles (**b**) [86] or 3*H*-pyridazino[4,5-*b*]indol-4(5*H*)-ones (**c**) [87], while 9*H*-pyridazine[3,4-*b*]indoles (**d**) are much less investigated (**Figure 2**).

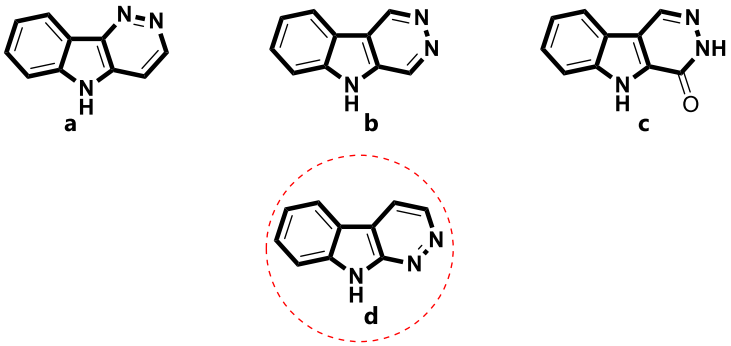


Figure 2. *Different isomeric systems of pyridazino-indoles.*

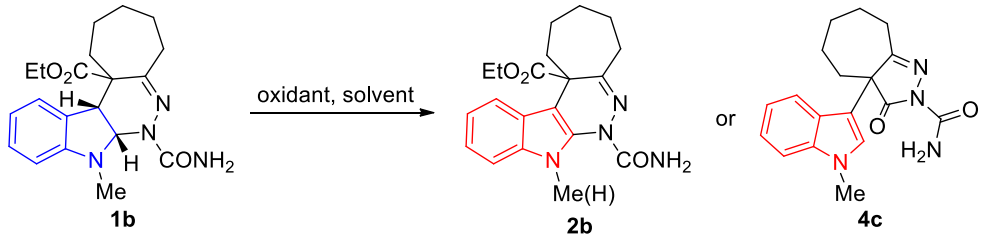
Among the latter, Kobayashi *et al.* in 1964 proposed the synthesis of various 3-phenyl-9*H*-pyridazine[3,4-*b*]indoles by heating 3-phenacyl-oxindoles and hydrazine hydrate in acetic acid solution.[88] In 1992 Shimojy and co-workers a series of methyl 9*H*-pyridazino[3,4-*b*]indole-3-carboxylates and related compounds were synthesized using a Diels-Alder reaction of 3-(1*H*-indol-3-yl)-2-propenoates with dibenzyl dicarboxylate. Several compounds were found to have high affinity for the benzodiazepine receptor.[89]

Herein, we described a successful procedure providing the fused indole-pyridazine scaffold of type **3** through oxidation and hydrolysis reactions of compound **1** (**Figure 1**, *path a)*. A different pathway for unusual non-fused derivative indole-pyrazol-5-one **4** (**Figure 1**, *path b*), was also possible starting from the same cycloadduct (**1**). A survey of the literature shows that only one example of such structures is reported.[90]

6.2 RESULTS AND DISCUSSION

The construction of product **1**, formally deriving by [4+2] cycloadduction of indoles and azoalkenes, allowed to us to investigated the oxidation process with the objective to restore the aromaticity of the indolic portion of the bi-heterocyles. For this purpose, a screening of different oxidants was carried out (**Table 1**). The compound **1b** has been subjected to common oxidants such as BQ, Pd/C, $Na_2Cr_2O_7$, I_2, and PCC[91] but they did not provide the desired product and the same result occurred using NBS/TBPB[92]. When DDQ was employed in combination with different solvents such as toluene, CH_2Cl_2 and dioxane, fused indole-tetrahydropyridazine derivative **2b** were isolated in low yields (**Table 1**, **entries 1**,**2**,**3**). Among all the oxidants tested, the best result was achieved with MnO_2 in large stoichiometric excess using benzene as a solvent at 70°C.[93] Under these reaction conditions compound **2b** was achieved in 55% yield (**Table 1**, **entry 6**).

To our surprise, the use of Lewis acids also known as oxidizing agents such as $Cu(NO_3)_2 \cdot 3H_2O$, $CuCl_2 \cdot 2H_2O$ and CAN $[(NH_4)_2Ce(NO_3)_6]$, furnished the non fused indole-pyrazole derivative **4c** arousing our interest (Table **1**, entries **11**, **12**, **13**). With these results in hand, representative 6, 7, 8 membered ring cycloadducts were subjected to oxidation conditions leading to the desired compound **2**. Additionally, demethylation of the *N*-indole residue was also observed in the oxidation step, probably resulting from further oxidation of the alkyl group and consequent decarboxylation of the same.[94] However, the process was not further investigated.



Entry	Oxidant	Equiv.	Solvent	Time (h)	Yield 2b (%)	Yield 4c (%)
1	DDQ	1	toluene	24	21	–
2	DDQ	1.5	CH_2Cl_2	15	27	–
3	DDQ	1	dioxane	2	trace	–
4	NBS/TBPB[a]	0.4	CCl_4	5	–	–[d]
5	BQ[a]	4	toluene	12	–	–
6	**MnO_2[b]**	**25**	**benzene**	**24**	**55**	**–[d]**
7	Pd/C	1	AcOEt	24	–	–[d]
8	$Na_2Cr_2O_7$[a]	1	$CHCl_3$	12	–	–[d]
9	I_2[a]	2	MeOH	24	–	–[d]
10	PCC[a]	3	CH_2Cl_2	2	–	–
11	$Cu(NO_3)_2 \cdot 3H_2O$	2	CH_2Cl_2	18	–	43
12	$CuCl_2 \cdot 2H_2O$[c] [99]	0.1	DMSO	8	–	80
13	CAN	1	CH_2Cl_2	24	–	38

[a] *Reflux*, [b] *70°C*; [c] *100°C*; [d] Starting **1b** was recovered.

Table 1. *Screening of different oxidants.*

Encouraged by the initial findings, the next step was to realize the overall oxidation to pyridazine aromatic system. Thus, the so obtained partially oxidized pyridazines **2** were subjected to basic alcoholysis to realize decarboxylation of the ester residue and hydrolysis of urea moiety, which provided the indole-pyridazine derivatives **3** of interest (**Figure 3**) in satisfactory yields. This allowed us to propose an easy and innovative synthesis of 9*H*-pyridazine[3,4-*b*]indoles which are important scaffolds in pharmaceutical and medicinal chemistry.

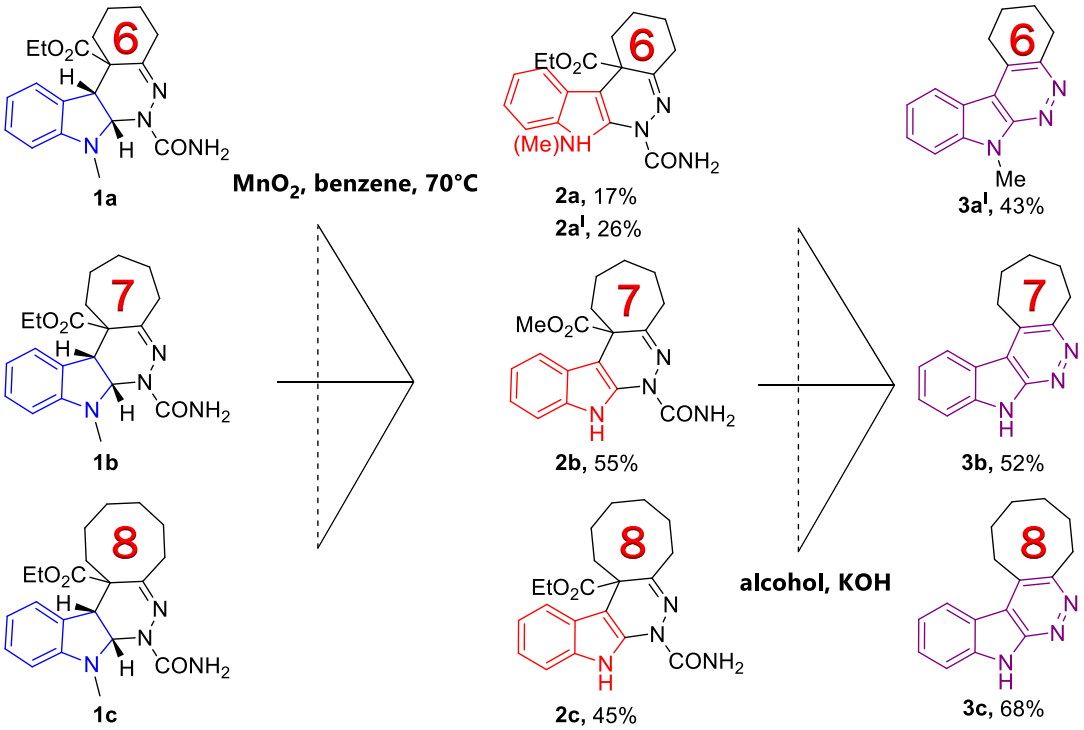
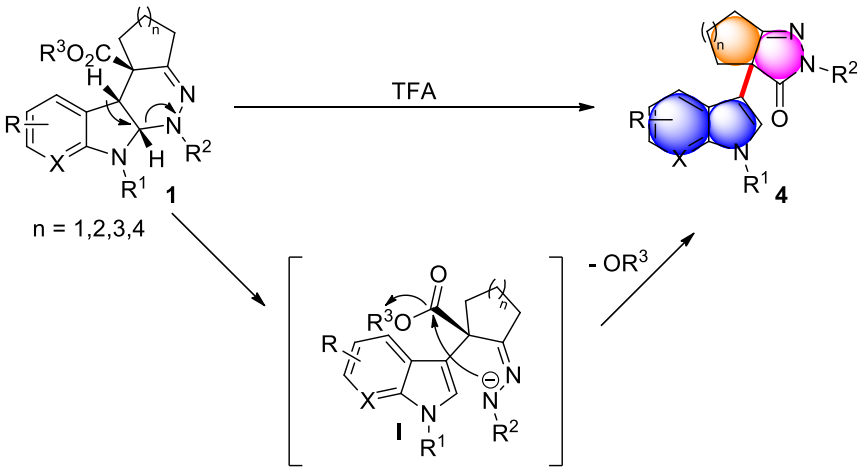


Figure 3. *Oxidation reactions of representative compounds.*

The unexpected formation of compound **4** from cycloadduct **1** in the first oxidation step, prompted us to consider the use of Lewis/Brønsted acids for this transformation (**Table 1**, **entries 11, 12, 13**). Thus, following the starkly different reaction profiles between the formation of **3** and **4**, a divergent synthesis of fused and non-fused polyheterocycles was developed. The use of trifluoroacetic acid (TFA) induced the ring opening of the cycloadduct **1** to give non-fused *N*-polyheterocyclic compound **4** in nearly quantitative yield. A plausible mechanism for this transformation was proposed as shown in **Scheme 1**. Intermediate **I** is generated from cycloadduct **1** via ring opening process, which then undergoes intramolecular nucleophilic acyl substitution to form pyrazole-based bi-heterocycle **4**.



Scheme 1. *Probable reaction mechanism to obtain non-fused indole-pyrazol-5-one systems.*

All the tetracyclic compounds embedding 6, 7 and 8 membered-ring well tolerated the acidic environment (**Figure 4**). Changing the substituents (alkyl, benzyl) on the *N*-indole ring, the reaction proceeded satisfactorily (**4f**, **4g**, **4i**). Also the free *N*H-indole was proven to be a good candidate for this transformation furnishing the relative products **4h**, **4j**, **4p** in very excellent yields. The wide functional groups tolerance of this procedure was validated from the introduction of electron-donator (**4i**, **4j**) or electron-attractor (**4k**, **4l**, **4m**, **4n**) substituents on the aromatic component which led to the corresponding pyrazole systems in almost quantitative yields. Interesting to note that no purification of the obtained products by flash chromatography column was necessary because of their crystallization from the reaction medium. To date, only one example of the synthesis of compound **4** was reported in the literature. In this work, Shi and co-workers realized an umpolung of C3 indole reactivity, using 2-indolylmethanols as an electrophile and pyrazole system as a nucleophile to obtain the strategic C-C bond formation.[95]

Differently from Shi's work, in our case the same C-C bond formation is realized exploiting the reversal of polarity of the DD system taking advantage the intrinsic reactivity of the pertinent functional groups. This proves an attractive synthetic approach toward these unusual heterocyclic structures.

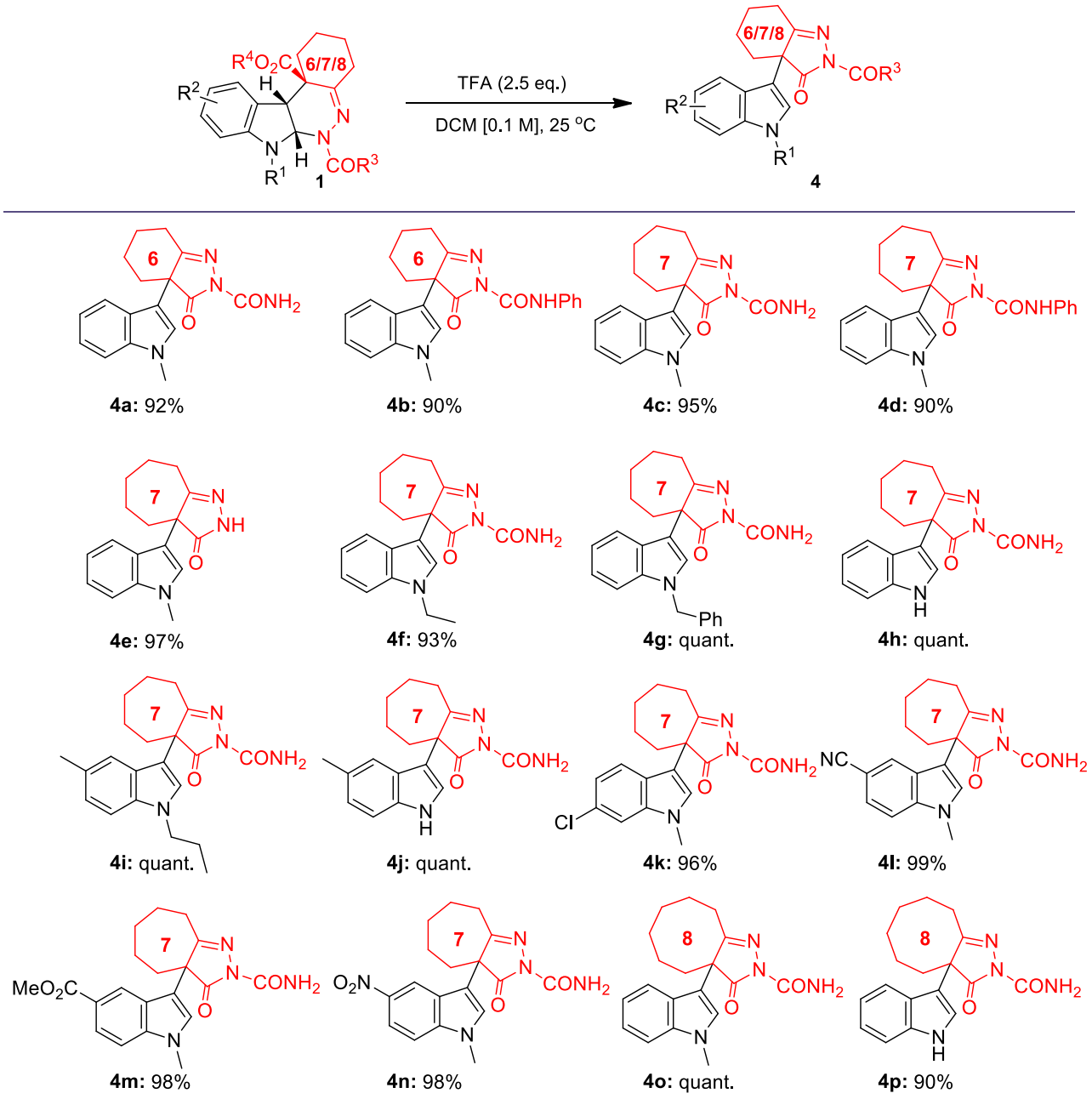


Figure 4. *Substrate scope of the synthesis of non-fused indole-pyrazol-5-one systems.*

6.3 CONCLUSION

In summary, a divergent synthesis of fused and non-fused *N*-polyheterocycles starting from common C2,C3-fused indoline-tetrahydropiridazines has been realized. Strategically, the combination of indole and azoalkene partners as C2 and C2N2 synthons respectively, opens the way to two different classes of *N*-polyheterocyclic compounds such as 9*H*-pyridazino[3,4-*b*]indoles **3** and 4-indol-pyrazol-5-ones **4**. The selective oxidation of indoline nucleus to indole, hydrolysis of ester and urea residues followed by decarboxylation and concomitant aromatization lead to the tetracyclic fused indole-pyridazines **3**. On the other hand, non-fused indole-pyrazol-5-ones of type **3** are easily prepared by subjecting the same C2,C3-fused indoline-tetrahydropiridazines to treatment with TFA. This synthetic method represents a robust strategy for producing libraries of chemical compounds that have a structural connection with biologically active natural-like molecules. Starting material availability, functional group tolerance, mild conditions, efficiency and selectivity are relevant aspects of these simple procedures.

CHAPTER 7

Metal and Oxidant-Free Brønsted Acid-Mediated Cascade Reaction to Substituted Benzofurans.

7.1 INTRODUCTION

Benzofuran is considered as an important class of heterocyclic compounds. It is present in numerous bioactive natural products as well as pharmaceuticals and polymers[96]. Several derivatives of benzofuran have been recognized as biologically and pharmacologically relevant molecules (**Figure 1**)[97].

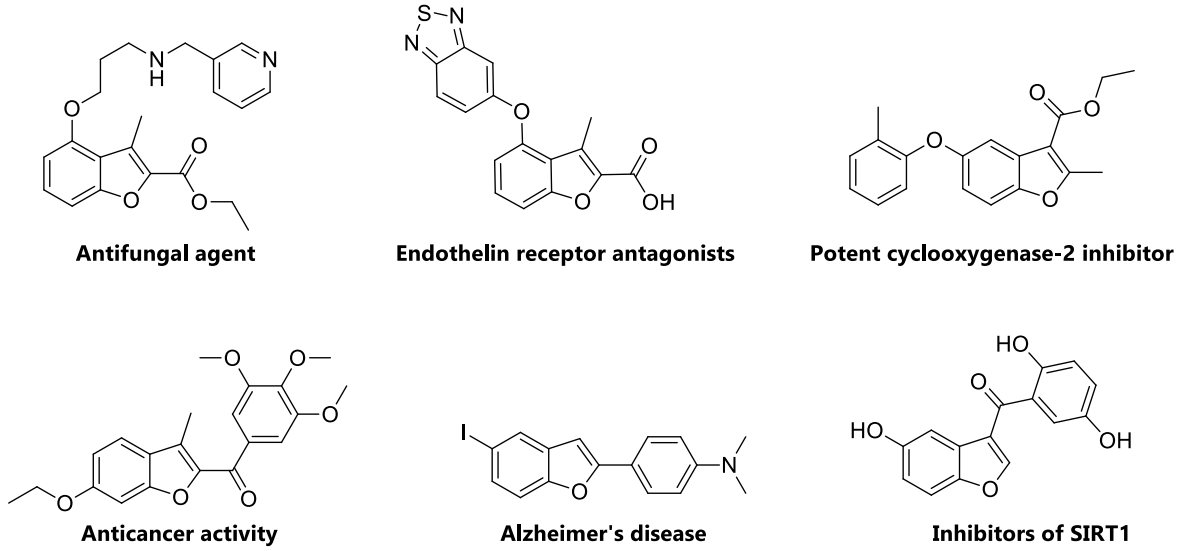


Figure 1. *Biological significance of benzofurans.*

Medicinal and organic chemists are actively involved in the synthesis of benzofuran ring containing molecules due to its clinical importance. For this reason we have developed a **metal** and **oxidant free** Brønsted acid-mediated cascade reaction to substituted benzofurans employing resorcinols or 2-naphthol and 1,2-diaza-1,3-dienes (DDs) (**Figure 2**).

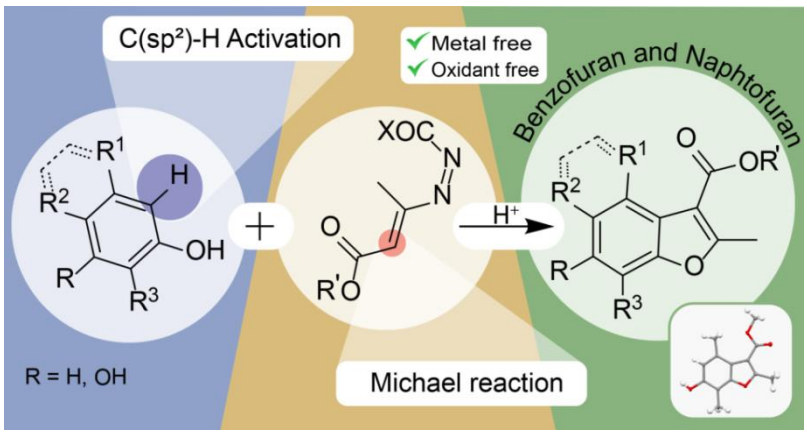


Figure 2. *Resorcinol or naphthol-derivatives as precursors of benzofuran-3-carboxylate.*

The reaction happens through an uncommon Michael reaction between aromatic derivatives as aromatic C(sp^2)−H nucleophiles and DDs as acceptors. Michael's reaction is a formidable tool available for the synthetic chemist to form new bonds.[98] The mild conditions, the high yields obtained, the perfect atom economy, the high tolerance to other functions, and the possibility to easily create carbon−carbon, carbon−nitrogen, carbon−oxygen, carbon− sulfur, carbon−selenium, and carbon−phosphorus bonds are the main reasons for the success of this reaction. In the formation of the carbon−carbon bond, the nucleophile is usually an sp^3 carbon activated by one or two electron-withdrawing groups in α position. The use of sp carbons,[99] or aromatic sp^2 carbons as nucleophiles is much less frequent, usually requiring harsh reaction conditions or complicated work-up procedure and are limited in the substrate scope. In particular, few examples of nucleophilic aromatic carbons are present in the literature; recently, an interesting tris-(pentafluorophenyl)-borane-catalyzed addition of aniline derivatives to *α,β*-unsaturated ketones has been reported by Werner.[100] Franzén and Bah described the addition of *N,N*-dimethylaniline to 4-oxobutanoates with carbocationic catalysts,[101] while Bertrand proposed a cationic anti-Bredt di(amino)carbene gold(I) complex-catalyzed hydroarylation of enones with *N,N*-dialkyl aniline.[102] Regarding the use of phenols and resorcinols, recently Katiyar suggested the trifluoro acetic catalyzed construction of 4H-chromenes via Michael addition of phenols to benzylidene oxobutanoates;[103] Ajavakom synthesized dihydroquinolines through initial Michael addition of aminophenol to methyl propiolate using CuI as the catalyst,[104] while Bodalski reported the self-catalyzed Michael reactions of selected hydroxy arenes with dicyclohexyl-ammonium acrylate bearing electron withdrawing groups at the C-2 carbon atom.[105] Two other examples have been previously reported by our group: the synthesis of cynnolines and pyrazolones by the initial addition of the strongly activated 1,3,5-tris(dialkylamino)benzene derivatives to 1,2-diaza-1,3-dienes (DDs),[64] and the last work on arylation of hydrazonic functions through an umpolung approach that involves the Michael-type reaction between anilino substrates and DDs.[76e]

As regards the synthesis of benzofuran system, in the last approaches the use of phenols and *β*-ketoesters by Guo *et al.*[106] in the iron-catalyzed oxidative reaction represents an elegant variation of the Pechmann condensation (**Figure 3**, **path B**), in which benzofurans are created instead of coumarins (1-benzopyrans or 2*H*-chromen-2-one, **Figure 3**, **path A**).

Considering that the DDs are easily generated from *β*-ketoesters,[8,9] the method that we proposed can be also considered a Pechmann variation in which the first step of the reaction sequence is a Michael type addition of an sp^2 carbon to the azo-ene of DDs.

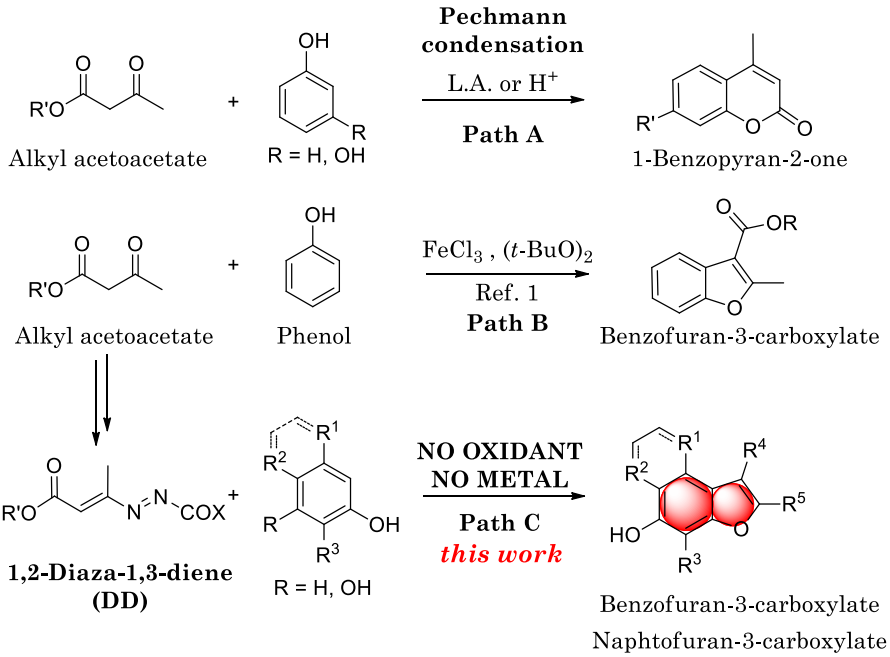
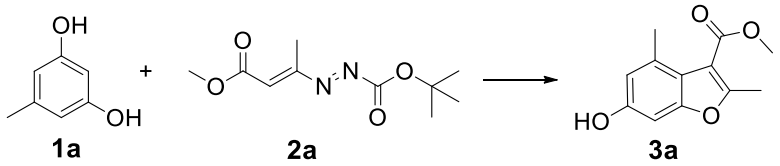


Figure 3. *Phenol- or resorcinol-derivatives as precursors of 1-benzopyran-2-ones or benzofuran-3-carboxylate.*

7.2 RESULTS AND DISCUSSION

Our studies began with the reaction between 5-methylbenzene-1,3-diol (orcinol)[107] **1a** and DD **2a** chosen as the representative model (**Table 1**). **1a** and **2a** do not react in toluene under reflux. Then, our attention was focused on identifying an effective catalyst or promoter. To tentatively raise the nucleophilicity of resorcinol **1a**, some bases such as K_2CO_3, MeONa, DIPEA, and DBU were tested in tetrahydrofuran (THF) (**Table 1**, **entries 1−4**). Unfortunately, in these latter cases, only complicated mixtures were obtained. We have therefore undertaken a different approach testing different Lewis acids such as $ZnCl_2$, $CuCl_2$, CuI, $FeCl_3$, SmI_3, $Y(OTf)_3$, $Sc(OTf)_3$, $InBr_3$, $Bi(OTf)_3$, $ZnBr_2$, $SnCl_2$, and $CuSO_4$, in toluene at room temperature (**Table 1**, **entries 5−16**). It is known that the coordination between the Lewis acid and the azo-ene enhances the electrophilicity of DD **2**.[11a,b] Monitoring these reactions by TLC analysis, we observed a similar pattern in all cases that is the initial formation of a first spot, that partially turns into a less polar product that was identified as the desired benzofuran **3a**. All attempts to isolate the first intermediate failed. On the basis of our previous experience,[108] we hypothesized that initially an hydrazonic adduct is formed (**Scheme 3**), which subsequently intramolecularly cyclizes producing the furanic ring. The best result was obtained using $CuCl_2$, but the yield was poor (23%, **entry 6**). An increase of the temperature was investigated to tentatively convert completely the initial intermediate.

Performing the reaction at 70 °C, or refluxing it, the yields were increased even if they remained unsatisfactory (26, 33%, **entries 17**, **18**, respectively). Better results were obtained by initially conducting the reaction at room temperature (until the disappearance of the reagents), thus refluxing it (41%, **entry 19**). We then tested different molar ratios of the starting materials: when two equivalents of DD **2a** were employed, the reaction yield did not improve (31%, **entry 20**). Unfortunately, in this case, DD **2a** reacts with itself by means of [4 + 2] cycloaddition,[109] and the yield of **3a** does not increase significantly. By reacting two equivalents of resorcinol **1a**, benzofuran **3a** was formed with 50% yield (**entry 21**). Analyzing the reaction, we can deduce that to produce the desired benzofuran **3a**, an elimination of the hydrazinic counterpart of DDs occurs. To facilitate the release in the reaction medium of the corresponding tert-butyl carbazate, a more polar solvent such as a mixture of acetonitrile/acetone (95/5) together with the addition of an equivalent of Amberlyst 15H were tested. The role of acetone is to trap carbazate forming the corresponding hydrazonic derivative.[110] With satisfaction, we have noted that under these conditions **3a** was obtained in 82% yield (**entry 22**).



1a **2a** **3a**

Entry[a]	Solvent	T (C°)	Catalyst/Promoter	RATIO 1a/2a	Yields (%)[b]
1	THF	r.t.	K_2CO_3[c]	1/1	–[d]
2	THF	r.t.	MeONa[e]	1/1	–[d]
3	THF	r.t.	DIPEA[e]	1/1	–[d]
4	THF	r.t.	DBU[f]	1/1	–[d]
5	Toluene	r.t.	$ZnCl_2$[g]	1/1	17
6	Toluene	r.t.	$CuCl_2$[g]	1/1	23
7	Toluene	r.t.	CuI[g]	1/1	–[d]
8	Toluene	r.t.	$FeCl_3$[g]	1/1	19
9	Toluene	r.t.	SmI_3[g]	1/1	12
10	Toluene	r.t.	$Y(OTf)_3$[g]	1/1	16
11	Toluene	r.t.	$Sc(OTf)_3$[g]	1/1	8
12	Toluene	r.t.	$InBr_3$[g]	1/1	–[d]
13	Toluene	r.t.	$Bi(OTf)_3$[g]	1/1	9
14	Toluene	r.t.	$ZnBr_2$[g]	1/1	–[d]
15	Toluene	r.t.	$SnCl_2$[g]	1/1	12
16	Toluene	r.t.	$CuSO_4$[g]	1/1	–[d]
17	Toluene	70	$CuCl_2$[g]	1/1	26
18	Toluene	reflux	$CuCl_2$[g]	1/1	33
19[h]	Toluene	rt→reflux	$CuCl_2$[g]	1/1	41
20[h]	Toluene	rt→reflux	$CuCl_2$[g]	1/2	31
21[h]	Toluene	rt→reflux	$CuCl_2$[g]	2/1	50
22[h]	Acetonitrile/acetone[i]	rt→reflux	$CuCl_2$[g]/Amberlyst 15H[j]	2/1	82
23[h]	Acetonitrile/acetone[i]	rt→reflux	Amberlyst 15H[j]	2/1	83

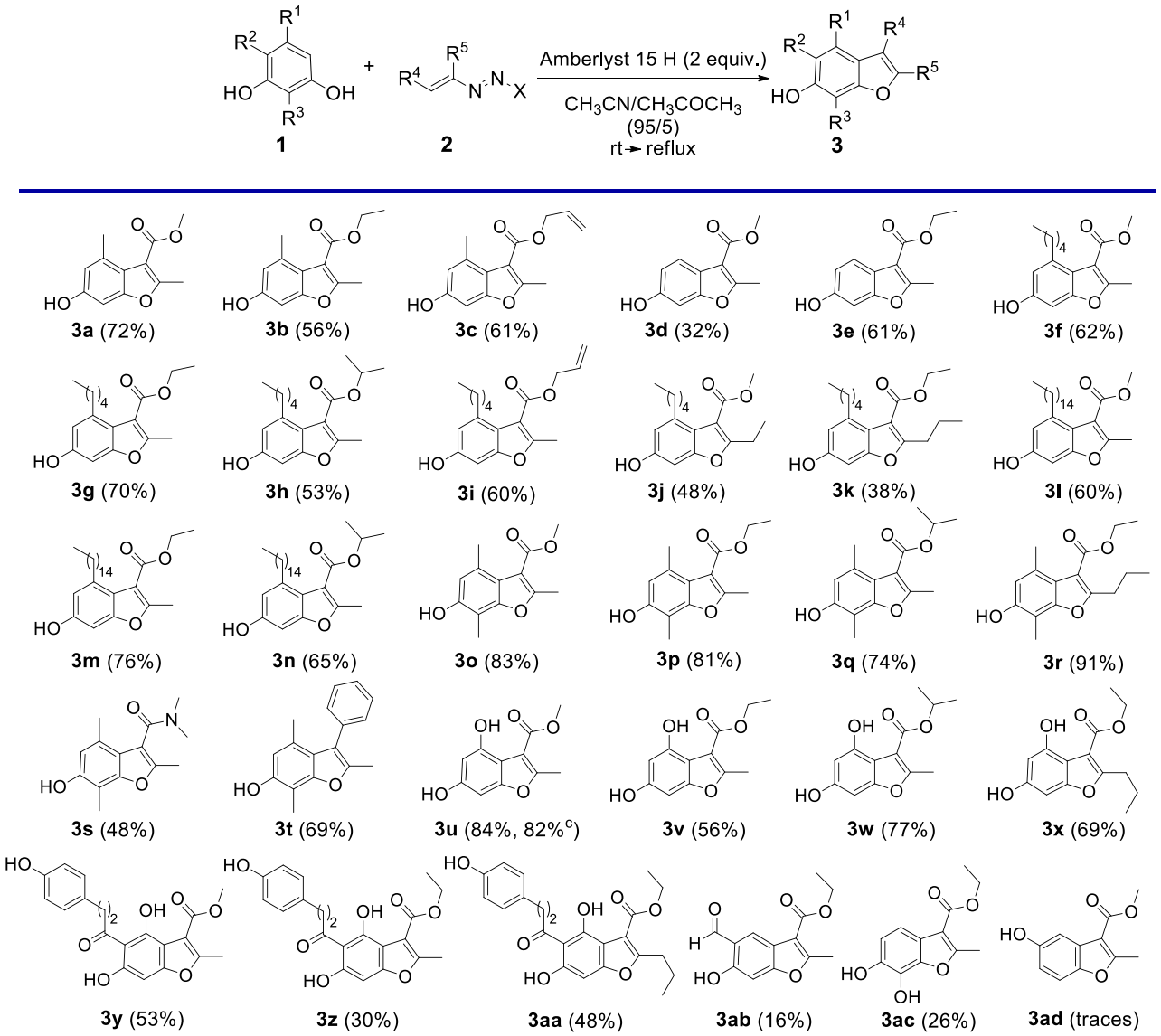
[a]The reactions were conducted on 0.2 mmol scale in 2.0 mL of solvent. [b]Isolated Yields. [c]2.0 equiv. [d]Complicated mixture. [e]1.0 equiv. [f]0.5 equiv. [g]0.2 equiv. [h]The reaction was conducted at room temperature until the disappearance of the limiting reagent, thus refluxing the reaction until the

Table 1. *Reaction Conditions Optimization.*

Finally, we also tested the reaction under the same conditions, but without the addition of $CuCl_2$: with surprise and considerable pleasure, we have isolated the desired **3a** in 83% (**entry 23**). Then, Amberlyst 15H is able to effectively promote the formation of

benzofuran, avoiding the use of metal catalysts with all connected drawbacks such as toxicity, higher cost, and the eventual necessity of complex ligands and threshold values in pharmaceutical products. It is noteworthy that the reaction between the 2-chloro acetoacetate (DDs' precursors) and **1a** does not provide **3a** either using Lewis acids or Amberlyst 15H.

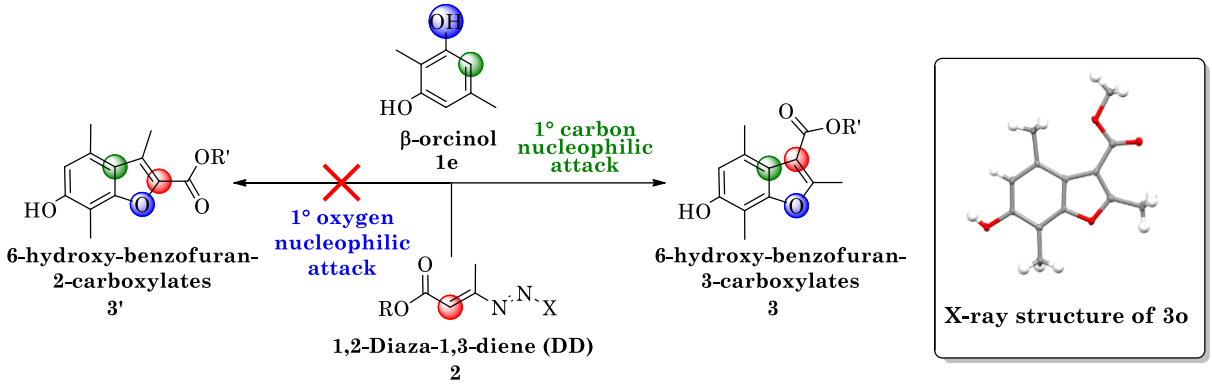
By identifying the optimal conditions, the reaction scope was extended to benzene-1,3-diol (resorcinol) **1b**[111,112] and to other different alkyl-resorcinols[113] such as 5-pentylbenzene-1,3-diol (5-pentyl resorcinol or olivetol) **1c**,[114] 5-pentadecilbenzene-1,3- diol (5-pentadecilresorcinol, or adipostatin A) **1d**,[115] 2,5- dimethylbenzene-1,3-diol (2,5-dimethyl resorcinol or *β*-orcinol) **1e**, benzene-1,3,5-triol (phloroglucinol) **1f**, [116] phloretin **1g**, [117] 2,4-dihydroxybenzaldehyde (*β*-resorcinolaldehyde) **1h** and 3,4,5-trihydroxybenzoic acid (gallic acid) **1i**.[118,119] Different benzofurans **3a**−**3ac** were easily obtained in moderate to good yields (**Scheme 1**) by means of a cyclization that involves the formation of new carbon−oxygen and carbon−carbon bonds. The reaction was performed on a gram scale, yielding the desired product **3u** without loss of yield (82%).



*[a]Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), Amberlyst 15H (2.0 equiv), acetonitrile/acetone (95/5), 5 mL, 25 °C, 0.5 h, then reflux, 4.0 h. [b]Isolated yields. [c]**3u** (1.452 g) was obtained in a 8.0 mmol scale (referred to **1a**).*

***Scheme 1**. Substrate Scope.[a,b]*

Depending on the number and the positions of the substituents on the aromatic ring of **1**, different regioisomers can be obtained (**Schemes 2-3**).

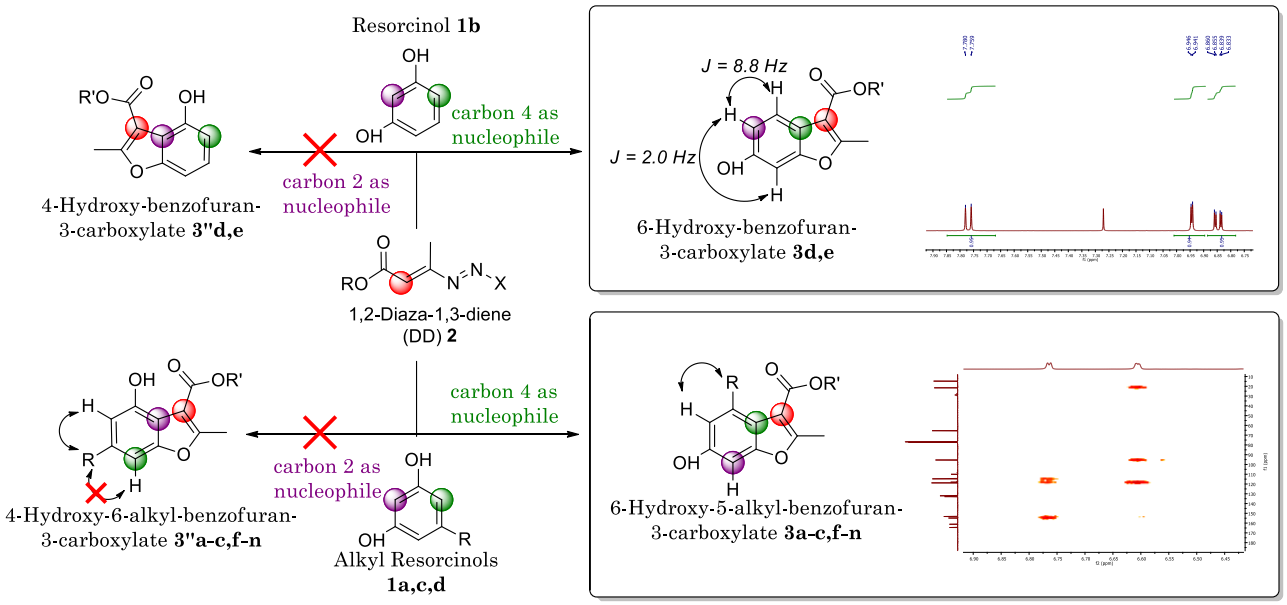


***Scheme 2**. Possible regioisomers generated by a first nucleophilic attack of the oxygen or carbon.*

To determine the exact concatenation leading to the formation of the furanic ring, we assume that the first reactive center of DDs is the carbon in position 4 of the azo-enic system that behaves as a Michael acceptor (highlighted in red in **Scheme 2**).[11,12] Depending on whether the first nucleophilic attack is due to carbon or oxygen, the two regioisomers, 6-hydroxy-benzofuran-3-carboxylate **3** or 6-hydroxy-benzofuran-2-carboxylate **3'**, can be obtained, respectively. The X-ray analysis of compound **3o** unequivocally confirms that the carbon−carbon bond is first formed, validating that the Michael reaction between DDs **2** and resorcinols **1** occurs via aromatic C(sp^2) nucleophiles (**Scheme 3**). On the other hand, in the cases of resorcinol **1b** and alkyl resorcinols **1a**,**c**,**d**, also the carbon that acts as a nucleophile must be individuated. The more activated pronucleophile sp^2 carbons of the resorcinol derivatives are in position 2 and 4. Then, the isomers 4-hydroxy- or 6-hydroxy-benzofuran-3-carboxylates **3''** or **3**, can be produced, respectively. In the case of benzofurans **3d**,**e** derived from resorcinol **1b**, the splitting pattern together with the ^{1}H NMR coupling constants of 8.8 Hz and 2.0 Hz clearly indicate that 6-hydroxy-benzofuran-3-carboxylate **3** is the regioisomer generated. In the benzofurans **3a**−**c**,**f**−**n**, obtained from the alkyl resorcinols **1a**,**c**,**d**, the splitting pattern and the H−H coupling constants do not provide information to determine the exact regioselectivity which, however, can be established by heteronuclear H−C correlations. The HMBC experiments conducted on compounds **3a**−**c**,**f**−**n** clearly indicate that only one of the two residual aromatic protons correlates with the aliphatic carbon, effectively excluding the formation of 4-hydroxy-6-alkyl-benzofuran regioisomer **3''a**−**c**,**f**−**n**.

Then in these cases, the sp^2 carbon in position 4 (highlighted in green) of the alkyl resorcinols acts as a nucleophile despite the steric hindrance of the alkyl residue (**1a**: R = CH_3, **1c**: R = C_5H_{11}, **1d**: R =

$C_{15}H_{31}$, **Scheme 3**). The structures of benzofurans **3y**–**3aa** deriving from the phloretin **1g** were determined by 2D-NMR experiments. The absence of coupling constants between the aromatic protons indicates that ethyl 5-formyl-6-hydroxy-2-methylbenzofuran-3-carboxylate **3ab** is the

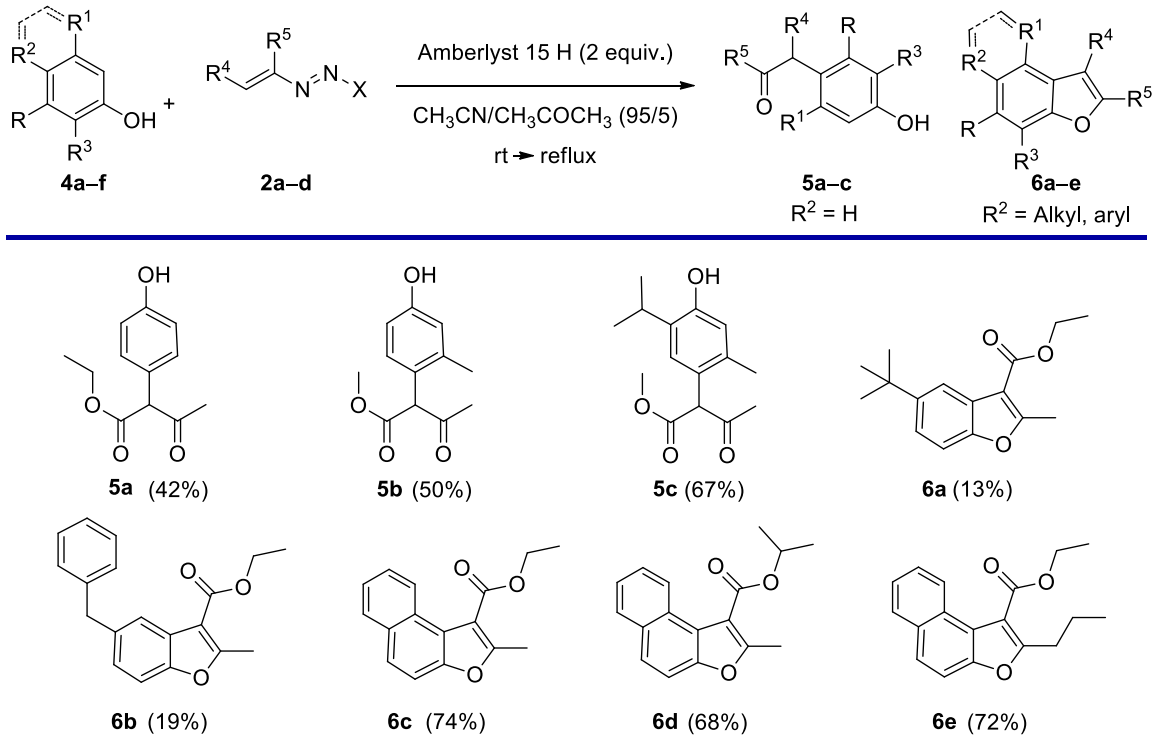


regioisomer obtained by employing *β*-resorcinolaldehyde **1h** as the reagent.

***Scheme 3**. Possible regioisomers generated by nucleophilic attack of the aromatic carbon in position 2 or 4.*

The substituents on the aromatic ring play a decisive role; from **Table 1**, it can be noted that electron donor groups favor the reaction. The position of the substituents on the aromatic ring is also crucial; the reaction occurs when the two hydroxyl groups are in meta. In this case, the activating effect of the two electron donor groups converges on the same sp^2 carbon. On the contrary, the reaction between the 1,4-benzenediol **1j** and DD **2a** furnished a complicated reaction mixture where only minimal traces of the corresponding benzofuran **3ad** are present (**Scheme 1**). Here, the synergic activating effect of the two hydroxyl groups is missing. Yields decrease by inserting electron withdrawing groups on the aromatic ring as in the case of phloretin **1g**, and resorcinolaldehyde **1h** (compounds **3y**–**3ab**, **Table 1**). A particular behavior was observed in the reaction of gallic acid **1i**: together with the formation of the furan ring, a decarboxylation reaction occurs leading to the formation of ethyl 6,7-dihydroxy-2-methylbenzofuran-3-carboxylate **3ac** (**Scheme 1**).[120] Under the same conditions, the reactivity of the phenol derivatives **4a**–**e** and 2 naphthol **4f** was also investigated. The reactions of phenol **4a** or ortho-, and meta-substituted phenols **4b**,**c** with DDs **2a**,**b** furnished alkyl 2-(4-hydroxyphenyl)-3-oxobutanoates **5a**–**c** confirming that the carbon–carbon bond is initially formed (**Scheme 4**). The general trend observed in the

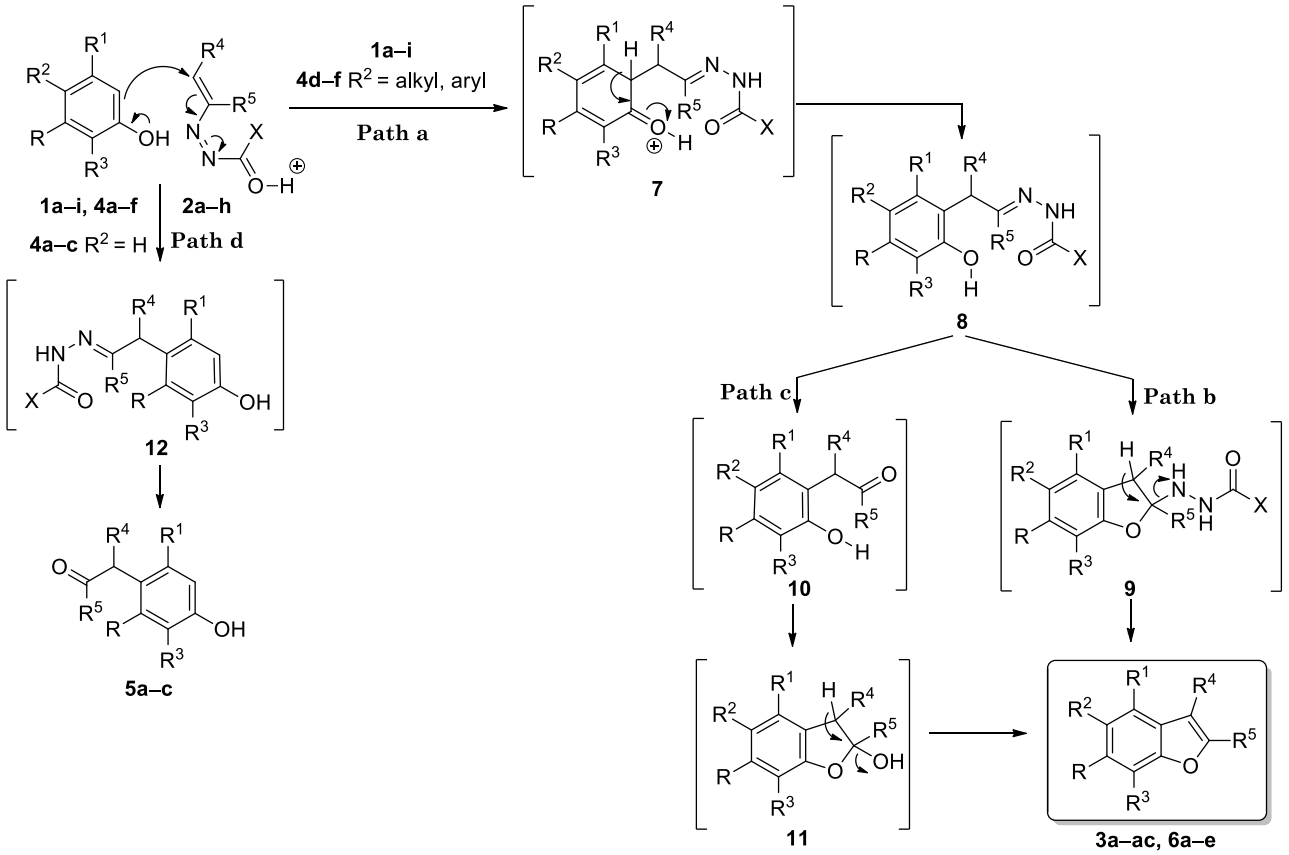
previous reactions is confirmed: a greater number of electron donor substituents improves the yields. Probably for steric reasons, the sp^2 carbon in the para position to the hydroxyl function is privileged as a nucleophile site, and furthermore, it could be noted that the acid reaction conditions promote the hydrolysis of the hydrazonic function. To favor cyclization, 4-tert-butyl- and 4-benzyl-phenols **4d**,**e**, blocked in the para position, were tested obtaining the corresponding benzofurans **6a**,**b** but only in 13 and 19% yields (**Scheme 4**). A different behavior was observed when the 2-naphthol **4f**[121] was employed as the starting material: the electronic features of the polycyclic system enhanced the nucleophilicity of the sp^2 carbon in position one and the corresponding naphtho[2,1-b]furan-1-carboxylates **6c**−**e** were obtained in good yields (68−74%, **Scheme 4**).



[a] *Reaction conditions:* ***4*** *(1.0 mmol),* ***2*** *(0.5 mmol), Amberlyst 15H (2.0 equiv.), acetonitrile/acetone (95/5), 5 mL, 25 °C, 0.5 h, then reflux, 4.0 h.* [b] *Isolated yields.*

Scheme 4: *Reaction between phenols* ***4a*** *e or -naphthol* ***4f*** *and DDs* ***2a–d****.*[a,b]

The plausible mechanism for the formation of benzofurans **3a**−**ac**, **6a**−**e** (**Scheme 5**, *path a*) involves the preliminary nucleophilic attack of the activated aromatic carbon of **1a**−**i** onto the terminal carbon atom of the azo-ene system of DDs **2a**−**h** with consequent formation of the α-functionalized hydrazone intermediates **7**. The restoration of benzene aromaticity via [1,3] proton shift triggers the formation of dihydrobenzofuran **8** due to the nucleophilic attack of oxygen on the hydrazonic function (**Scheme 5**, *path b*). The final elimination of the hydrazine residue provides the desired benzofurans **3a**−**ac**, **6a**,**b** or naphthofurans **6c**−**e**. Considering the reaction between DDs **2a**,**b** and phenols **4a**−**c** (**Scheme 5**, *path d*), in which the para position is free, the aromatic C(sp^2) in position 4 acts as a nucleophile leading to the corresponding α-aryl hydrazone intermediates **12**. As in this case the ring closure is impossible, the hydrazonic function is hydrolyzed to the corresponding ketone furnishing alkyl 2-(4-hydroxyphenyl)-3-oxobutanoates **5a**−**c** that are in equilibrium with their enolic tautomeric form. Even in the formation of the benzofurans **3** it is not excluded that the hydrazonic function can be preliminarily hydrolyzed, and the second nucleophilic attack can involve the ketonic moiety (**Scheme 5**, *path c*). However, in both cases, the acid reaction environment initially activates the DDs making them better electrophiles, and also promotes the ring closure activating the hydrazone/ketone moiety and facilitating the final elimination of the hydrazine/water portion.



***Scheme 5**. Plausible Mechanism of the Reaction*

7.3 CONCLUSION

In conclusion, we have developed a metal- and oxidant-free annulation between resorcinols or naphthol and DDs for the preparation of hydroxy-benzofuran-3-carboxylates or napthofuran-3-carboxylates with complete regioselectivity. A wide range of resorcinols was employed and the reaction exhibited a good functional group tolerance and scalability. The selection of the starting materials enables the choice of up to five different variations in the architecture of the final products. The absence of metal catalysts and the easy work-up procedure together with the robustness, represent the key strength of this new approach to benzofurans. New carbon−carbon and carbon−oxygen couplings determine the construction of the benzofuran ring. The resorcinol frameworks act as a double nucleophile: the studies have confirmed that the aromatic carbon first operates. Then this reaction also represents a rare example of a Michael reaction between aromatic derivatives as aromatic C(sp^2)−H nucleophiles and DDs as acceptors under mild conditions.

CHAPTER 8

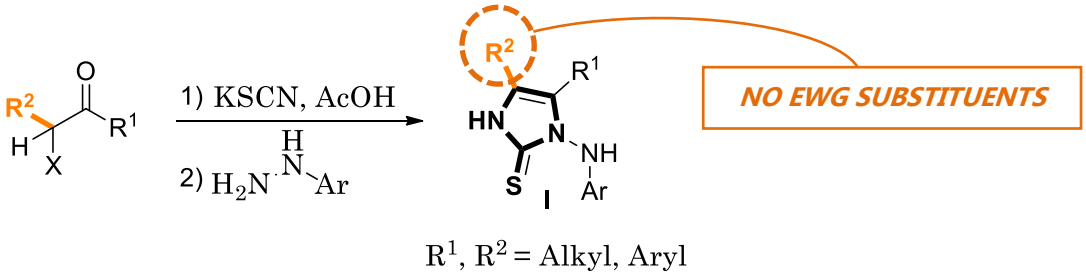
Sequential MCR via Staudinger/aza-Wittig versus cycloaddition reaction to access diversely functionalized 1-amino-1H-imidazole-2(3H)-thiones.

8.1 INTRODUCTION

Imidazole is a very important heterocycle because it is present in many natural products, especially alkaloids, moreover it is the nucleus of significant biological building blocks, like histidine and the related hormone histamine. The imidazole ring is also contained in several drugs, such as certain antifungal drugs, the nitroimidazole series of antibiotics, and the sedative midazolam.[122]

Among imidazole derivatives, imidazole-2-thiones have been associated to a special class of biologically relevant thiourea derivatives[123] endowed with antithyroid[124], antiproliferative[125], MPP (Matrix MetalloProteinases) inhibitory[126] property and can be used as building blocks for the synthesis of *N*-aminoimidazole with antiretroviral activity.[127]

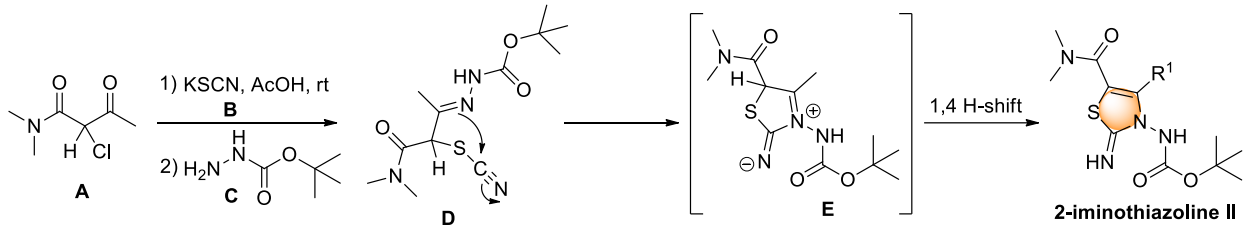
To date, the most widespread method used for the synthesis of *N*-substituted 1-amino-1*H*-imidazol-2(3*H*)-thiones can be referred to the Schantl's protocol which consists in reacting α-haloketones with potassium thiocyanate and monosubstituted arylhydrazines in weak acidic medium (**Scheme 1**).[128] However if this method appears robust, it seems to suffer of some limitations in terms of insertion of electron-withdrawing groups placed on the α-halohydrazone precursors of conjugated azoalkene intermediates. Our goal was to develop a synthesis of 1-imidazole-2-thionic systems by expanding the substrate scope with introduction of several substitutents in α position of halohydrazone.



Scheme 1 *Schantl's protocol for the synthesis of N-substituted 1-amino-1H-imidazole-2(3H)-thione derivatives* ***I****.*

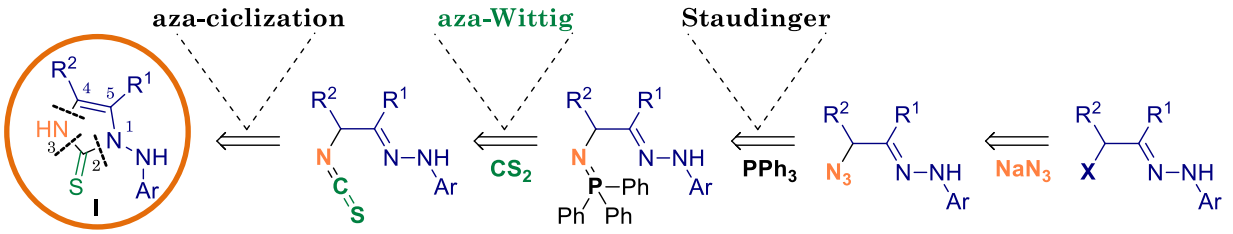
Schantl's method is a multistep reaction that it proceeds via the formation of conjugated azoalkenes, derived from α-thiocyanatohydrazones **D** (**Scheme 2**), and dipolarophile isothiocyanic acid intermediate that in turn undergo a [3+2] cycloaddition reaction providing substituted 1-arylamino-1*H*-imidazole-2(3*H*)-thione **I** scaffolds[129]. In this regard, for our research purposes, we tried to apply this method reacting 2-chloro-*N*,*N*-dimethyl-3-oxobutanamide (**A**), potassium thiocyanate (**B**) and *tert*-butyl hydrazinecarboxylate (**C**) in acetic acid to obtain the corresponding *N*-substituted 1-amino-1*H*-imidazole-2(3*H*)-thione derivative **I** but without success.

As shown in **Scheme 2**, instead of the cycloaddition of intrest, a 5-exo-dig cyclization reaction leading to 2-iminothiazole **II** took place. This evidence is in agreement with the result obtained by Lagoja and coworkers where a pathway involving the key α-thiocyanatohydrazone intermediate **D** is invoked[128]. The structure of the iminothiazoline **II** was confirmed by comparison of the spectral data of the same compound obtained by means of a different procedure previously described by some of us that foresees the conjugated hydrothiocyanation of the pertinent conjugated azoalkene in acidic medium followed by intramolecular cyclization.[130]



***Scheme 2**. Pathway for the formation of 2-iminothiazoline heterocycle **II**.*

Inspired by our previous experience,[8,9] and in order to perform a complete regioselective-oriented method for the desired 1-amino-1*H*-imidazole-2(3*H*)-thiones **I**, we have planned a different strategy that avoids the use of bidentate-nucleophilic reagents such as the potassium thiocyanate. In the construction of **I**, three strategic disconnections between the N1-C2, C2-N3 and N3-C4 were hypothesized (**Scheme 3**).

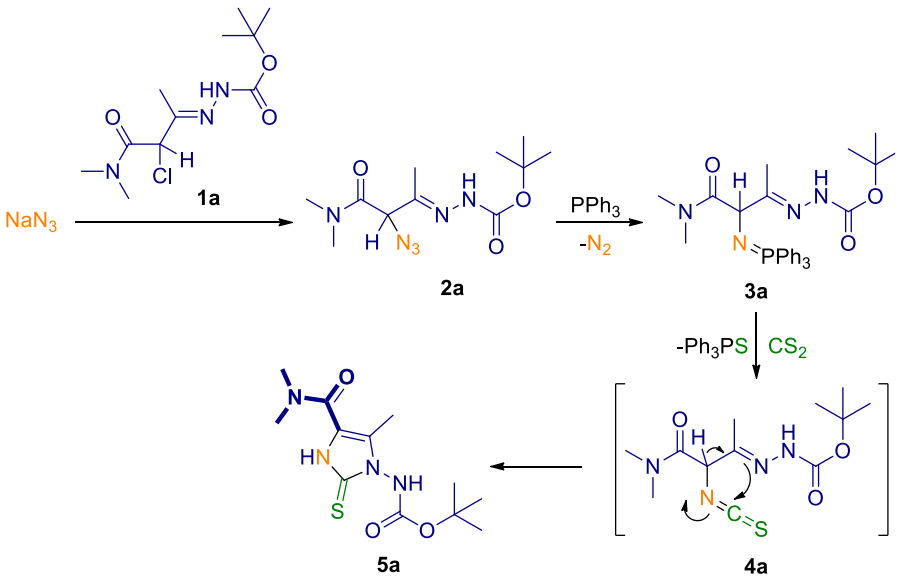


***Scheme 3**. Our hypothesized disconnection of 1-amino-1H-imidazole-2(3H)-thione **I** derivatives.*

We reasoned that the azidation process of the pertinent α-halohydrazone derivative followed by tandem Staudinger/aza-Wittig reaction with CS_2 could have been a successful route.[131]

8.2 RESULTS AND DISCUSSION

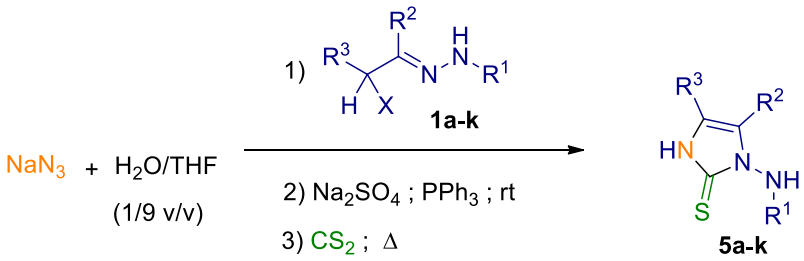
To validate our hypothesis we began to explore the process step by step. Thus, α-chlorohydrazone derivative **1a** (2.0 mmol) dissolved in THF (9.0 mL) subjected to α-azidation using an ice-cooled aqueous solution of NaN_3 (2.0 mmol / 1.0 mL) under magnetic stirring at room temperature. After the evaporation of the solvent and an appropriate extraction, the α-azidohydrazone derivative **2a** was obtained in 70% yield. In the next step, the addition of a stoichiometric amount of PPh_3 to **2a** (1.0 mmol) dissolved in CH_2Cl_2 (5.0 mL) furnished the iminophosphorane derivative **3a** by precipitation from the reaction medium (66%). Then, **3a** (0.65 mmol) was dissolved in 5.0 mL of THF/MeOH mixture (4:1) and treated with an excess of CS_2 at reflux to afford, after column chromatography purification, the corresponding *N*-substituted 1-amino-2,3-dihydro-1*H*-imidazole-2-thione derivative **5a** (53%) arising from intramolecular cyclization of the α-isothiocyanate hydrazone intermediate **4a** (**Scheme 4**).



Scheme 4. *Step by step synthetic pathway for N-substituted 1-amino-2,3-dihydro-1H-imidazole-2-thione derivative* ***5a****.*

Motivated by this result, we aimed to develop a one-pot sequential multicomponent reaction (MCR)[132] as alternative method for regioselective synthesis of a new series of imidazole-2-thiones-containing structure as suitable precursor for drug-like compounds.[133] In a typical experiment, to an ice-cooled aqueous solution of NaN_3 (1.0 mmol/0.5 mL of H_2O), α-halohydrazone derivative **1a** (1.0 mmol) solved in THF (4.5 mL) was added at room temperature under magnetic stirring. After a TLC check confirming the disappearance of **1a** and the formation of the α-azido derivative **2a** (0.5-2.0 h), Na_2SO_4 (0.5 g) was added in order to dehydrate the reaction environment.

Then, a solution of PPh_3 (1.1 mmol) in THF (1.0 mL) and CS_2 (1.0 mL) were added in sequence and the reaction was heated to reflux. The formation of the N-substituted 1-amino-2,3-dihydro-1H-imidazole-2-thione derivative **5a** was revealed by the complete disappearance of **2a** and by the observation of $Ph_3P=S$ as byproduct (TLC check). Our sequential one-pot MCR approach to N-substituted 1-amino-1H-imidazole-2(3H)-thiones **5a**-**k** (53-85%) is depicted in **Scheme 5**. It is to be noted that for **5a**, the efficiency of the reaction benefits by this latter protocol increasing the overall yield from 25% (obtained employing the step by step procedure) to 79% (**Table 1**). Moreover, the implemented strategy broadens the substitution patterns at the amino-N1 and at C4 of the heterocycle skeleton with electron-withdrawing groups (**5a**-**e**), and tolerates the aromatic (amino-N1) and aliphatic (C4) groups, as for **5j**[129c,e,f] (**Table 1**).



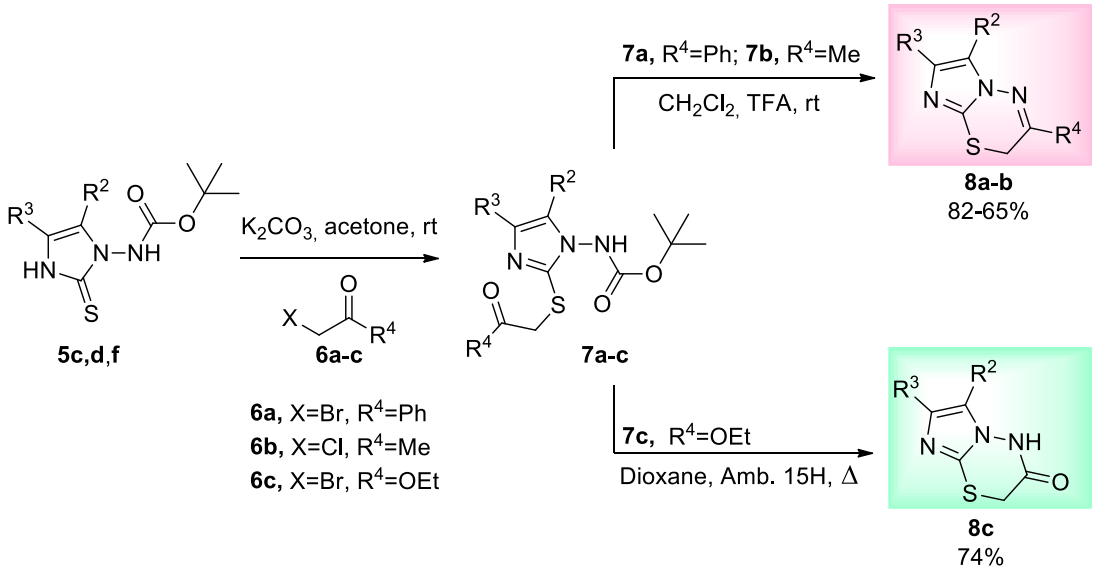
Scheme 5. *New MCR method for N-substituted 1-amino-2,3-dihydro-1H-imidazole-2-thione derivatives* ***5a-k****.*

Entry		α-Hydrazone 1				5	*One-pot* MCR Yield (%)[a, b]
		R^1	R^2	R^3	X		
1	**1a**	CO_2*But*	Me	$CON(Me)_2$	Cl	**5a**	25[a]; 79[b]
2	**1b**	CONHPh	Me	$CON(Me)_2$	Cl	**5b**	53[b]
3	**1c**	CO_2*But*	Me	$CON(Et)_2$	Br	**5c**	72[b]
4	**1d**	CO_2*But*	Me	H	Cl	**5d**	69[b]
5	**1e**	CO_2*But*	Me	$CONH_2$	Br	**5e**	58[b]
6	**1f**	CO_2*But*	Me	CONHPh	Br	**5f**	67[b]
7	**1g**	CONHPh	Me	H	Cl	**5g**	82[b]
8	**1h**	COPh	Me	H	Cl	**5h**	59[b]
9	**1i**	CONHPh	Me	Me	Cl	**5i**	85[b]
10	**1j**	4-NO_2-Ph	Me	Me	Cl	**5j**	84[b]
11	**1k**	CO_2*But*	Ph	H	Br	**5k**	66[b]

[a]Overall yield of isolated product ***5a*** *from the step by step reaction based on* ***1a****; [b] Overall yield of isolated products* ***5a-k*** *from one-pot MCR based on* ***1a-k****.*

Table 1*. Substrate scope of the MCRs synthetic pathway for N-substituted 1-amino-2,3-dihydro-1H-imidazole-2-thione derivatives* ***5a-k.***

These results not only lie in the wide scenario of the heterocyclic scaffolds obtainable through tandem Staudinger/aza-Wittig sequence[132, 134 , 135] but the concurrent presence of reactive functionalities in the target compounds **5a**-**k** ensures postmodifications in view of heterobicyclic structures. In fact, the tautomerism thionoamide/thioloimide permits the introduction of a further element of diversity at the sulphur atom producing imidazole derivatives suitable to be combined with the useful 1-amino-Boc protected group[136] directly installed by this approach, as for **5a**, **5c**-**f, 5k**. Thus, as an example, **5c**,**d,f** (1.0 mmol) solved in acetone (10.0 mL), were reacted with 2-bromo-1-phenylethanone (**6a**) (1.0 mmol), 1-chloropropan-2-one) (**6b**) (1.0 mmol) and ethyl 2-bromoacetate (**6c**) (1.0 mmol), respectively, in the presence of K_2CO_3 (1.0 mmol). After the removal of solvent followed by extraction, the corresponding α-(imidazol-2-ylthio) carbonyl compounds **7a**-**c** were obtained as solid after column chromatography purification (84-93%) (**Scheme 6**). The subsequent cleavage of the Boc-protecting group under omogeneous[137] or heterogeneous acidic conditions[138] generated intermediates with a free amino function active for the intramolecular condensation with the carbonyl appendage in 2-position of the ring, affording new 2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine derivatives **8a**,**b** or 2*H*-imidazo[2,1-*b*][1,3,4]thiadiazinone derivative **8c** (**Scheme 6, Table 2**).



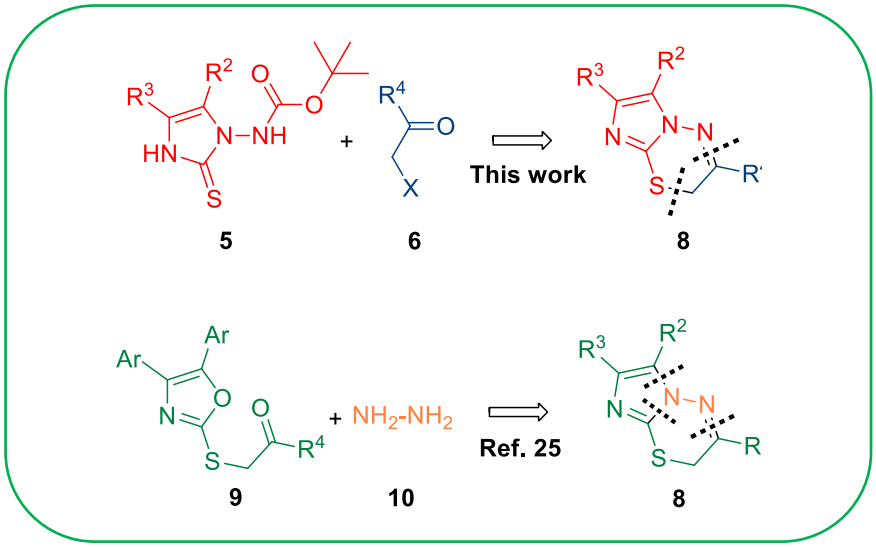
Scheme 6*. Synthetic approach to 2H-imidazo[2,1-b][1,3,4]thiadiazine derivatives.*

5			6			7	Yield (%)[a]	8	Yield (%)[b]
	R^2	R^3		X	R^4				
5c	Me	$CON(Et)_2$	**6a**	Br	Ph	**7a**	84	**8a**	**82**
5d	Me	H	**6b**	Cl	Me	**7b**	93	**8b**	**65**
5f	Me	CONHPh	**6c**	Br	OEt	**7c**	92	**8c**	**74**

[a] *Yield of isolated product **7a-c** based on **6a-c**;* [b] *Yield of isolated product **8a-c** based on **7a-c**.*

***Table 2**. Substrate scope of the reaction between 1-amino-2,3-dihydro-1H-imidazole-2-thione derivatives **5** with a-haloketones **6a,b** or a-haloester **6c**.*

It is worthwhile to note that the proposed synthetic pathway can offer an alternative method for obtaining 2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine derivatives **8** with respect to the ring transformation of α-(oxazol-2-ylthio) ketones **9** on treatment with hydrazine hydrate **10**,[139] together with the possibility of wide diversification of the substituents at the different positions of the *N* bridgeheaded heterobicyclic structures (**Scheme 7**).



***Scheme 7**. Different synthetic approaches to 2H-imidazo[2,1-b][1,3,4]thiadiazine derivatives.*

8.3 CONCLUSCION

A Multicomponent Reaction (MCR) strategy, alternative to the known cycloaddition reaction, towards variously substituted 1-amino-1*H*-imidazole-2(3*H*)-thione derivatives has been successfully developed. The novel approach involves α-halohydrazones whose azidation process followed by tandem Staudinger/aza-Wittig reaction with CS_2 in a sequential MCR regioselectively leads to the target compounds avoiding the formation of the regioisomer iminothiazoline heterocycle. The approach can be applied to a range of differently substituted α-halohydrazones bearing also electron-withdrawing groups confirming the wide scope and the substituent tolerance of the process for the synthesis of the target compounds. Interestingly, the concurrent presence of reactive functionalities in the scaffolds so obtained, ensures postmodifications in view of *N*-bridgedheaded heterobicyclic structures.

CHAPTER 9

Synthesis of azepinone derivatives by reaction of cycloalkanones with 1,2-diaza-1,3-dienes. Preliminary results.

9.1 INTRODUCTION

Compounds containing medium-sized (from 7 to 12 membered) rings are not commonly used in the development of pharmaceutical drug compounds despite their significance in many bioactive natural products. This is associated with the lack of efficient methods to create these compounds using synthetic chemical means. In fact their synthesis is notoriously difficult because of inherent unfavorable enthalpic and entropic factors, as well as undesired transannular interactions.[140]

In particular formation of 7 and 8 term lactams remain a largely unsolved issue.

In the laboratory of J. Rodriguez's research group has been developed an enantioselective Michael addition/four-atom ring expansion cascade reaction involving cyclobutanones activated by a *N*-aryl secondary amide group and ortho-amino nitrostyrenes for the preparation of functionalized eight-membered benzolactams using bifunctional aminocatalysts (**Figure 1**).[141]

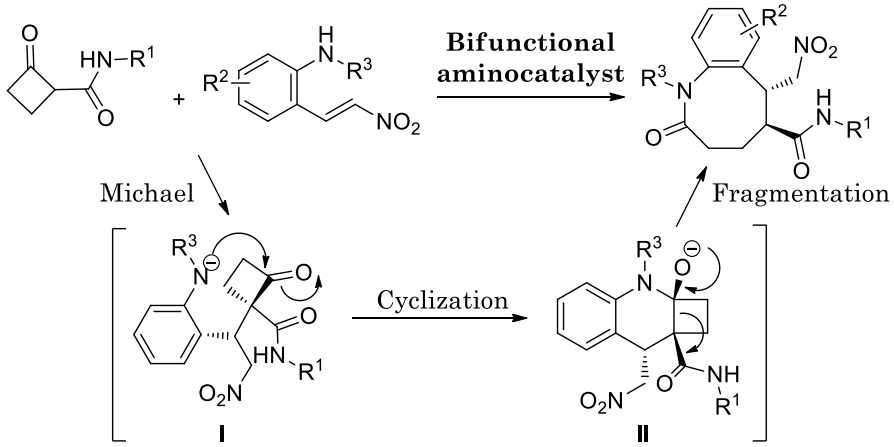
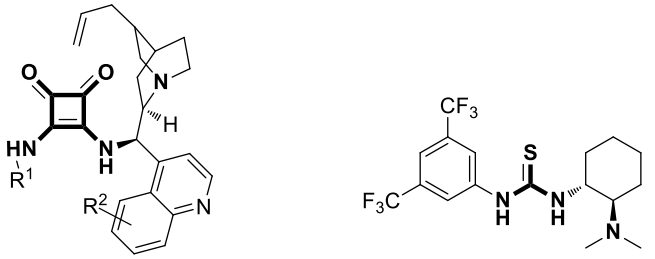


Figure 1. *Enantioselective approaches to benzolactams derivatives by Rodriguez's group.*

The concept of ''bifunctionality'' is realized when a Lewis basic functional group is introduced into the catalyst along with hydrogen-bond donors, which work synergistically to achieve the activation of both the nucleophile and the electrophile in a catalytic asymmetric reaction.[142a]

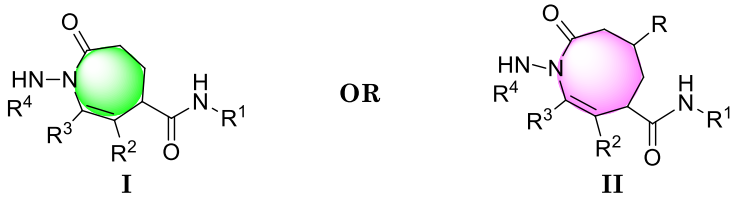
Bifunctional squaramides and thioureas (**Figure 2**) have emerged as powerful hydrogen-bonding catalysts for promoting a wide array of useful asymmetric reactions, which provides convenient methods for the construction of complex molecular structures and chiral biologically active compounds.[142b]



Squaramides based catalysts **Takemoto catalyst**

Figure 2. *Bifunctional aminocatalysts.*

During the period of my permanence at Ism2 of Marseille, the reactivity of 1,2-diaza-1,3-dienes systems as good Michael acceptors with different activated cycloalkanones to obtain attractive substituted heterocyclic scaffolds such as *4,5-dihydro-azepin-2(3H)-one* (**Figure 3**, **I**) or *3,4,5,6-tetrahydroazocin-2(1H)-one* (**Figure 3**, **II**) was investigated.



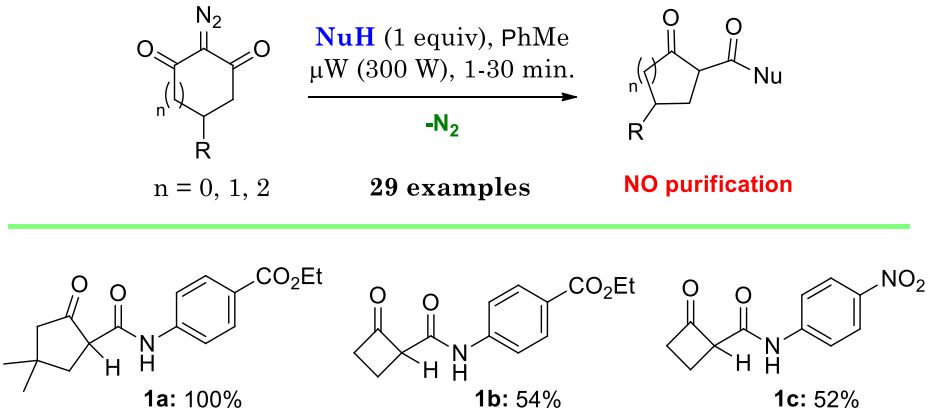
I **OR** **II**

4,5-Dihydro-1*H*-azepin-2(3*H*)-one **3,4,5,6-Tetrahydroazocin-2(1*H*)-one**

Figure 3. *Different azepinone derivatives obtained by reaction of DDs with activated cyclobutanones.*

9.2 RESULTS AND DISCUSSION

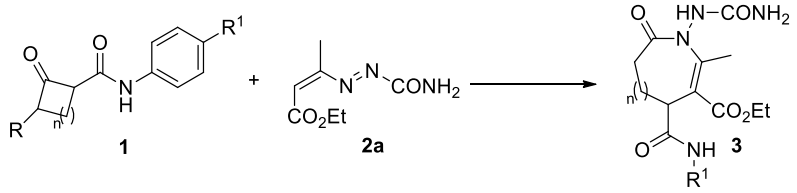
Activated cycloalkanones are easily achieved by a microwave-assisted Wolff rearrangement of cyclic 2-diazo-1,3-diketones in the presence of a stoichiometric amount of alcohol, amine or thiol as nucleophiles (**Scheme 1**) according to the literature procedure.[142]



Scheme 1. *Protocol for the synthesis of α-carbonylated cycloalkanones.*

Three different cycloalkanones **1a**, **1b** and **1c** (**Scheme 1**) have been synthesized starting from 5,5-dimethyl-2-diazo-1,3-cyclohexandione and 2-diazocyclopentane-1,3-dione respectively as electrophiles and a *N*-aryl secondary amide para-activated as nucleophiles in toluene to microwave irradiation (300 W). Thus, with these cycloalkanones **1** in hand, preliminary tests were carried out on azoene **2a** under various reaction conditions to investigate the reactivity and selectivity of the method. Based on the work of J. Rodriguez's goup[142a] a simple K_2CO_3 inorganic base was initially used as a catalyst (**Table 1**, **entry 1**) starting from the five membered ring *β*-ketoamide **1a**. After 2h the formation of the eight terms azepinone derivative **3a** (**Figure 3**, **II**) was isolated in 50% yield. The best result was obtained using *t*-BuOK as a base (**Table 1**, **entry 3**). Subsequently the 5-membered cycloalkanone **1a** was replaced by cyclobutanone **1b** to obtain the corresponding more stable 7-terms azepinone (**Figure 3**, **I**). Under these basic conditions the 4,5-dihydro-azepin-2(3*H*)-one derivative **3b** was isolated in 70% yield (**Table 1**, **entry 4**). In order to perform an asymmetric synthesis of intriguing medium size rings, a chiral catalyst was also tested instead of the inorganic base. To this end, the use of chiral Takemoto's catalyst (**Figure 2**) provided the desired product **3a** in 62% yield starting from compounds **1a** and **2a** (**Table 1**, **entry 5**).

On the other hand, cyclobutanone substrates **1b** and **1c** did not provide satisfactory results (**Table 1**, **entries 6**–**7**). Further X-ray crystallographic analysis will be conducted in order to have useful information about the structure and exact stereochemistry of the final obtained product **3**.



Entry	1	Catalysis (10-20%)	Solvent	T° C	Time (h)	3	Yield (%)
1	1a	K_2CO_3	toluene	r.t.	2	3a	50
2	1a	NaH	THF	r.t	5	–	–
3	1a	*t*-BuOK	THF (dry)	r.t	2	3a	64
4	**1b**	***t*-BuOK**	**THF (dry)**	**r.t**	**1**	**3b**	**70**
5	1a	Takemoto	toluene	70	24	3a	62
6	1b	Takemoto	THF (dry)	r.t	4	–	–*
7	1c	Takemoto	toluene	r.t	o.n.	3c	33

** Two unidentified spots after chromatography column.*

Table 1. *Screening process of different reaction conditions.*

9.3 FUTURE OBJECTIVES

The future perspective will be focused on the realization of the synthesis of new medium-sized lactams based on a Michael addition/ring expansion cascade reaction from activated cycloalkanones and 1,2-diaza-1,3-dienes. Preliminary findings led to the formation of putative azepinone derivatives of interest, which will be further investigated to confirm their structures. In order to demonstrated the functional group tolerance of this reaction, the next step will be therefore to investigate the substrate scope by introducing various substitutes in both substrates. The final goal of the work will be instead projected Toward the elaboration of an enantioselective version of the present transformation with the aim of developing a synthesis of otherwise inaccessible optically active molecules from readily available starting materials under mild conditions.

CHAPTER 10

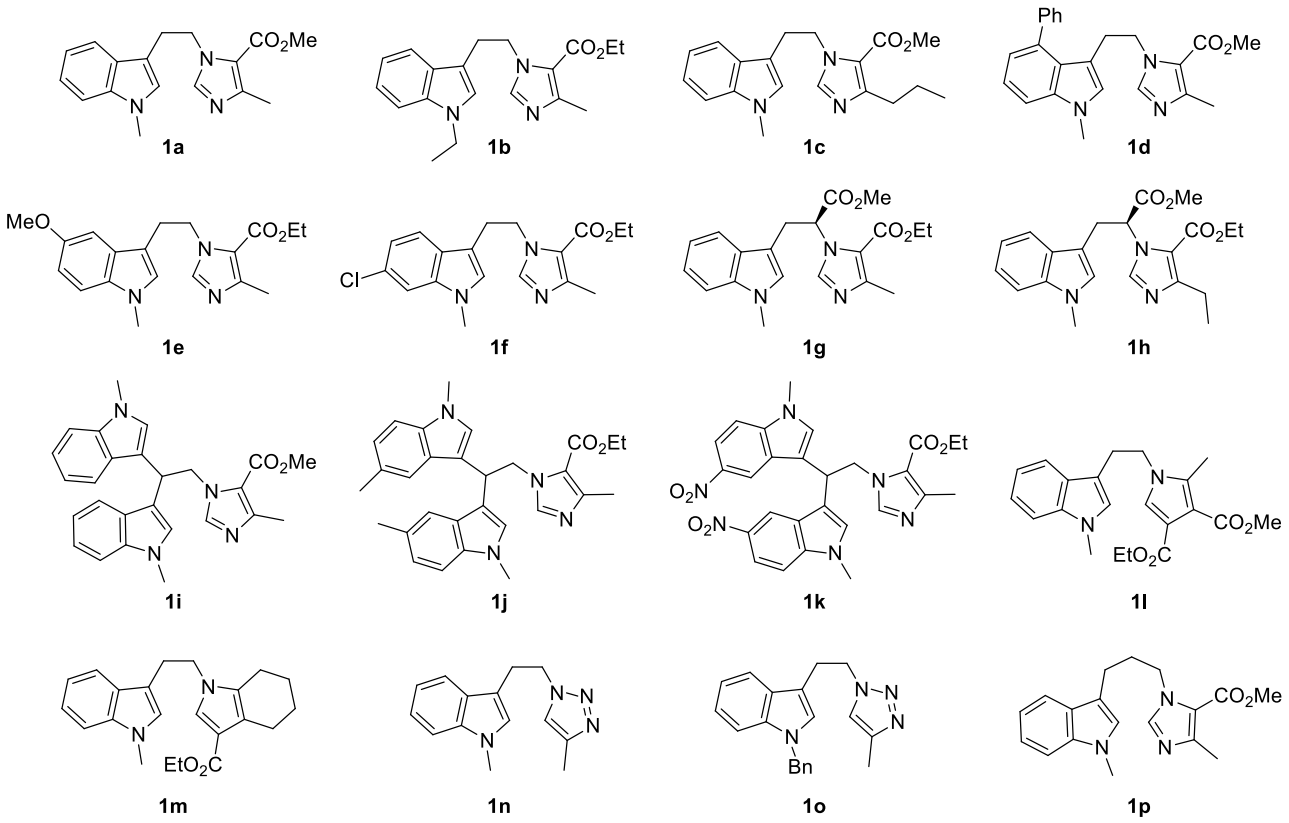
Experimental Session

General Remarks.

Chromatographic purification of compounds was carried out on silica gel (60–200 μm). TLC analysis was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulphuric acid followed by heating on a hot plate. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using $[D_6]$DMSO or $CDCl_3$ on K_2CO_3 as solvent. Chemical shift (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent and are sorted in ascending order within each group. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, td = triplet of doublet, q = quartet, quint = quintet, sex = sextet, sept = septet, m = multiplet and br = broad signal. All coupling constants (J value) are given in Hertz [Hz]. FT-IR spectra were obtained as Nujol mulls or neat. High-and low-resolution mass spectroscopy was performed on a Micromass Q-ToF Micro mass spectrometer (Micromass, Manchester, UK) using an ESI source. Melting points were determined in open capillary tubes and are uncorrected. Elemental analyses were within ± 0.4 of the theoretical values (C, H, N).

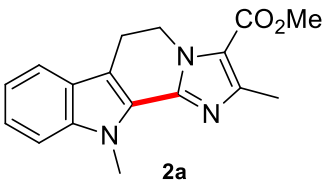
CHAPTER 2: Palladium(II)-Catalyzed Intramolecular Oxidative C−H/C−H Cross-Coupling Reaction of C3,N-linked Biheterocycles: Rapid Access to Polycyclic Nitrogen Heterocycles.

Starting materials:



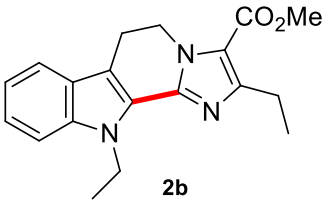
The following starting materials bi-azaheterocycles indolyl- azoles were obtained using literature procedure of ours group.[41]

General procedure for the intramolecular Pd(II)-catalyzed dehydrogenative coupling reaction (2a−p): bi-heterocycle compound (**1a**−**p**) (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), AgOAc (0.6 mmol), K_2CO_3 (0.2 mmol), are weighed to air and transferred into a test tube equipped with a magnetic stirrer bar. The DMA (2 mL) was added and the uncapped test tube was placed in an oil bath at 130 °C, afterwards the mixture was stirred under air for the indicate time (TLC check). The crude mixture was then purified by column chromatography on silica gel to afford product (**2a**−**p**).



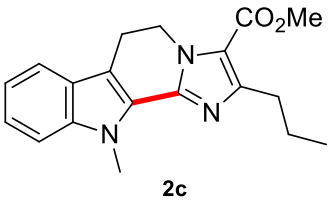
2a

Methyl 2,11-dimethyl-6,11-dihydro-5*H*-imidazo[1',2':1,2]pyrido[3,4-*b*]indole-3-carboxylate (2a): Indole-Imidazole **2a** was isolated by column chromatography (ethyl acetate/cyclohexane 5:95) in 96% yield (56.8 mg); White solid; mp: 187–189 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.45 (s, 3 H), 3.17 (t, *J* = 7.6 Hz, 2 H), 3.82 (s, 3 H), 4.13 (s, 3 H), 4.56 (t, *J* = 7.6 Hz, 2 H), 7.10 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1 H), 7.24 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 16.1, 20.4, 31.7, 44.3, 51.8, 110.7, 111.3, 118.4, 119.7, 120.3, 123.5, 125.3, 125.6, 138.8, 142.6, 147.5, 161.4; IR (nujol): ν_{max} = 1694 cm^{-1}; MS (EI) *m/z* (%) = 295 (100) (M$^+$); anal. calcd. for $C_{17}H_{17}N_3O_2$ (295.34): C 69.14, H 5.80, N 14.23; found: C 68.99, H 5.89, N 14.66.



2b

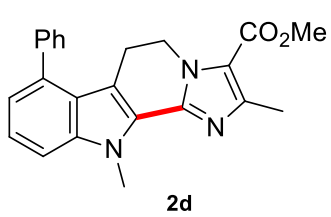
Methyl 2,11-diethyl-6,11-dihydro-5*H*-imidazo[1',2':1,2]pyrido[3,4-*b*]indole-3-carboxylate (2b): Indole-Imidazole **2b** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 87% yield (56.3 mg); White solid; mp: 110–112 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.24 (t, *J* = 7.2 Hz, 3 H), 1.32 (t, *J* = 7.2 Hz, 3 H), 2.88 (q, *J* = 7.2 Hz, 2 H), 3.19 (t, *J* = 7.6 Hz, 2 H), 3.85 (s, 3 H), 4.59 (t, *J* = 7.6 Hz, 2 H), 4.74 (q, *J* = 7.2 Hz, 2 H), 7.11 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.24 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 7.60 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.1, 15.8, 20.4, 22.7, 39.4, 44.3, 51.8, 110.7, 111.5, 117.7, 119.8, 120.2, 123.5, 124.9, 125.5, 137.6, 142.5, 153.1, 161.3; IR (nujol): ν_{max} = 1707 cm^{-1}; MS (ESI) *m/z* = 324 [M + H]$^+$; anal. calcd. for $C_{19}H_{21}N_3O_2$ (323.39): C 70.57, H 6.55, N 12.99; found: C 70.43, H 6.46, N 13.11.



2c

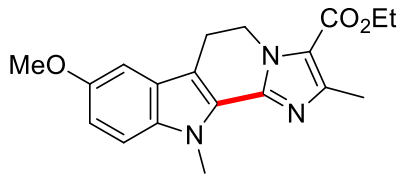
Methyl 11-methyl-2-propyl-6,11-dihydro-5*H*-imidazo[1',2':1,2]pyrido[3,4-*b*]indole-3-carboxylate (2c): Indole-Imidazole **2c** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 81% yield (52.4 mg); White solid; mp: 125–127 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.97 (t, *J* = 7.2 Hz, 3 H), 1.70 (sex, *J* = 7.2 Hz, 2 H), 2.84 (t, *J* = 7.2 Hz, 2 H), 3.19 (t, *J* = 7.6 Hz, 2 H), 3.84 (s, 3 H), 4.16 (s, 3 H), 4.58 (t, *J* = 7.6 Hz, 2 H), 7.12 (t, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 8.0 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.60 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.3, 20.4, 22.7, 31.1, 31.7, 44.3, 51.8, 110.7, 111.3, 118.1, 119.6, 120.3, 123.5, 125.3, 125.8, 138.8, 142.7, 151.7, 161.4; IR (nujol): ν_{max} = 1706 cm^{-1}; MS (ESI) *m/z*

= 324 $[M + H]^+$; anal. calcd. for $C_{19}H_{21}N_3O_2$ (323.39): C 70.57, H 6.55, N 12.99; found: C 70.41, H 6.61, N 13.14.



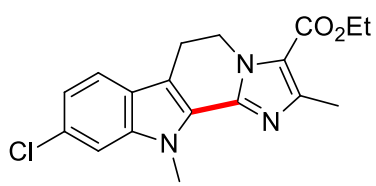
2d

Methyl 2,11-dimethyl-7-phenyl-6,11-dihydro-5*H*-imidazo[1',2':1,2]pyrido[3,4-*b*]indole-3-carboxylate (2d): Indole-Imidazole **2d** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 83% yield (61.7 mg); Yellowish solid; mp: 210–212 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.46 (s, 3 H), 2.67 (t, *J* = 7.6 Hz, 2 H), 3.80 (s, 3 H), 4.20 (s, 3 H), 4.35 (t, *J* = 7.6 Hz, 2 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 7.32 (t, *J* = 8.0 Hz, 1 H), 7.40−7.51 (m, 5 H), 7.53 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 16.1, 23.0, 31.9, 44.0, 51.8, 109.9, 111.0, 118.3, 121.7, 123.0, 123.4, 126.4, 127.7, 128.5, 129.8, 135.6, 139.2, 140.8, 142.5, 147.6, 161.3; IR (nujol): ν_{max} = 1686 cm^{-1}; MS (EI) *m/z* (%) = 371 (100) (M^+); anal. calcd. for $C_{23}H_{21}N_3O_2$ (371.43): C 74.37, H 5.70, N 11.31; found: C 74.24, H 5.62, N 11.47.



2e

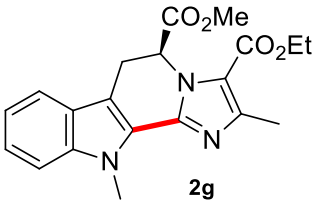
Ethyl 8-methoxy-2,11-dimethyl-6,11-dihydro-5*H*-imidazo[1',2':1,2]pyrido[3,4-*b*]indole-3-carboxylate (2e): Indole-Imidazole **2e** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 63% yield (42.8 mg); White solid; mp: 148–150 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.34 (t, *J* = 7.2 Hz, 3 H), 2.46 (s, 3 H), 3.15 (t, *J* = 7.6 Hz, 2 H), 3.79 (s, 3 H), 4.11 (s, 3 H), 4.30 (t, *J* = 7.2 Hz, 2 H), 4.57 (t, *J* = 7.6 Hz, 2 H), 6.89 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1 H), 7.08 (d, *J* = 2.4 Hz, 1 H), 7.40 (d, *J* = 8.8 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.7, 16.2, 20.5, 31.8, 44.2, 55.6, 60.5, 100.8, 110.8, 111.5, 114.1, 118.3, 125.6, 126.0, 134.1, 142.6, 147.4, 154.5, 161.0; IR (nujol): ν_{max} = 1699 cm^{-1}; MS (ESI) *m/z* = 340 $[M + H]^+$; anal. calcd. for $C_{19}H_{21}N_3O_3$ (339.39): C 67.24, H 6.24, N 12.38; found: C 67.33, H 6.32, N 12.23.



2f

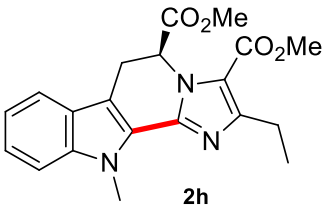
Ethyl 9-chloro 2,11-dimethyl-6,11-dihydro-5*H*-imidazo[1',2':1,2]pyrido[3,4-*b*]indole-3-carboxylate (2f): Indole-Imidazole **2f** was isolated by column chromatography (ethyl acetate/cyclohexane 5:95) in 61% yield (50.0 mg); White solid; mp: 157–159 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.34 (t, *J* = 7.2 Hz, 3 H), 2.45 (s, 3 H), 3.16 (t, *J* = 7.6 Hz, 2 H), 4.12 (s, 3 H), 4.30 (t, *J* = 7.2 Hz, 2 H), 4.56 (t, *J* = 7.6 Hz, 2 H), 7.11 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1 H), 7.57−7.62 (m, 2 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.6, 16.2, 20.3, 32.0,

44.1, 60.5, 110.7, 111.4, 118.6, 120.7, 121.0, 124.1, 126.7, 128.2, 139.1, 142.1, 147.4, 160.9; IR (nujol): ν_{max} = 1686 cm^{-1}; MS (EI) *m/z* (%) = 345 (62), 343 (100) (M^+); anal. calcd. for $C_{18}H_{18}ClN_3O_2$ (343.81): C 62.88, H 5.28, N 12.22; found: C 63.01, H 5.35, N 12.31.



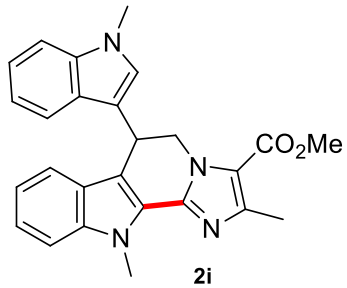
2g

3-Ethyl 5-methyl 2,11-dimethyl-6,11-dihydro-5*H*-imidazo[1',2':1,2]pyrido[3,4-*b*]indole-3,5-dicarboxylate (2g): Indole-Imidazole **2g** was isolated by column chromatography (ethyl acetate/cyclohexane 5:95) in 71% yield (52.2 mg); Whitish oil; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.31 (t, *J* = 7.2 Hz, 3 H), 2.51 (s, 3 H), 3.49 · 3.70 (m, 2 H), 3.58 (s, 3 H), 4.15 (s, 3 H), 4.21 · 4.35 (m, 2 H), 6.04 · 6.08 (m, 1 H), 7.11 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.26 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 14.5, 16.1, 23.9, 31.8, 53.3, 56.2, 60.7, 108.5, 110.8, 118.6, 119.8, 120.5, 123.8, 125.1, 125.2, 138.8, 142.3, 147.5, 160.9, 171.2; IR (nujol): ν_{max} = 1755, 1689 cm^{-1}; MS (EI) *m/z* (%) = 367 (100) (M^+); anal. calcd. for $C_{20}H_{21}N_3O_4$ (367.40): C 65.38, H 5.76, N 11.44; found: C 65.50, H 5.87, N 11.29.



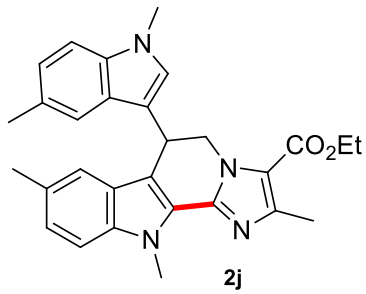
2h

Dimethyl 2-ethyl-11-methyl-6,11-dihydro-5*H*-imidazo[1',2':1,2]pyrido[3,4-*b*]indole-3,5-dicarboxylate (2h): Indole-Imidazole **2h** was isolated by column chromatography (ethyl acetate/cyclohexane 5:95) in 70% yield (51.4 mg); White solid; mp: 139–141 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.27 (t, *J* = 7.6 Hz, 3 H), 2.83 · 3.00 (m, 2 H), 3.49 · 3.71 (m, 2 H), 3.59 (s, 3 H), 3.83 (s, 3 H), 4.18 (s, 3 H), 6.05 · 6.09 (m, 1 H), 7.12 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.27 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 14.1, 22.6, 24.0, 31.8, 52.0, 53.3, 56.1, 108.6, 110.8, 117.8, 119.8, 120.5, 123.8, 125.1, 125.2, 138.8, 142.6, 152.9, 161.3, 171.2; IR (nujol): ν_{max} = 1748, 1691 cm^{-1}; MS (EI) *m/z* (%) = 367 (100) (M^+), 308 (81), 226 (63); anal. calcd. for $C_{20}H_{21}N_3O_4$ (367.40): C 65.38, H 5.76, N 11.44; found: C 65.26, H 5.85, N 11.32.



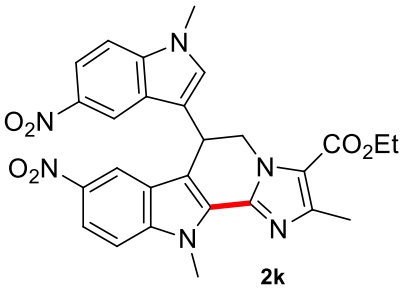
2i

Methyl 2,11-dimethyl-6-(1-methyl-1*H*-indol-3-yl)-6,11-dihydro-5*H*-imidazo[1',2':1,2]pyrido[3,4-*b*]indole-3-carboxylate (2i): Indole-Imidazole **2i** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 92% yield (78.1 mg); White solid; mp: 209–211 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.46 (s, 3 H), 3.62 (s, 3 H), 3.73 (s, 3 H), 4.23 (s, 3 H), 4.64 (dd, J_1 = 12.8 Hz, J_2 = 5.6 Hz, 1 H), 4.97−5.09 (m, 2 H), 6.70 (s, 1 H), 6.92 (t, J = 8.0 Hz, 1 H), 7.01 (t, J = 8.0 Hz, 1 H), 7.11 (d, J = 8.0 Hz, 1 H), 7.15 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.19 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.38 (d, J = 8.0 Hz, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.59 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 16.2, 29.8, 31.8, 32.7, 50.4, 51.7, 110.4, 110.7, 114.1, 114.4, 118.4, 119.2, 119.3, 119.9, 120.2, 121.7, 123.4, 125.0, 125.7, 126.7, 128.1, 137.4, 138.9, 142.5, 147.7, 161.3; IR (nujol): ν_{max} = 1691 cm^{-1}; MS (EI) *m/z* (%) = 424 (100) (M$^+$); anal. calcd. for $C_{26}H_{24}N_4O_2$ (424.49): C 73.56, H 5.70, N 13.20; found: C 73.42, H 5.78, N 13.08.



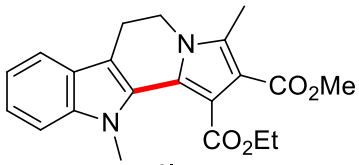
2j

Ethyl 6-(1,5-dimethyl-1*H*-indol-3-yl)-2,8,11-trimethyl-6,11-dihydro-5*H*-imidazo[1',2':1,2]pyrido[3,4-*b*]indole-3-carboxylate (2j): Indole-Imidazole **2j** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 72% yield (67.2 mg); White solid; mp: 207–209 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.22 (t, J = 7.2 Hz, 3 H), 2.26 (s, 3 H), 2.40 (s, 3 H), 2.45 (s, 3 H), 3.53 (s, 3 H), 4.10−4.20 (m, 2 H), 4.20 (s, 3 H), 4.49 (dd, J_1 = 12.8 Hz, J_2 = 5.6 Hz, 1 H), 4.99 (dd, J_1 = 5.6 Hz, J_2 = 4.0 Hz, 1 H), 5.15 (dd, J_1 = 12.8 Hz, J_2 = 4.0 Hz, 1 H), 6.40 (s, 1 H), 6.99 (d, dt, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1 H), 7.02−7.07 (m, 2 H), 7.24 (d, J = 8.4 Hz, 1 H), 7.41 (d, J = 8.4 Hz, 1 H), 7.45 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.5, 16.2, 21.5, 21.7, 29.4, 31.8, 32.6, 50.4, 60.4, 110.1, 110.5, 113.6, 114.0, 118.4, 118.7, 119.2, 123.3, 125.2, 125.8, 126.8, 127.6, 128.0, 128.9, 136.0, 137.6, 142.4, 147.7, 160.8; IR (nujol): ν_{max} = 1688 cm^{-1}; MS (EI) *m/z* (%) = 466 (100) (M$^+$); anal. calcd. for $C_{29}H_{30}N_4O_2$ (466.57): C 74.65, H 6.48, N 12.01; found: C 74.79, H 6.37, N 12.08.



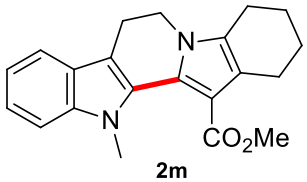
2k

Ethyl 2,11-dimethyl-6-(1-methyl-5-nitro-1*H*-indol-3-yl)-8-nitro-6,11-dihydro-5*H*-imidazo[1',2':1,2]pyrido[3,4-*b*]indole-3-carboxylate (2k): Indole-Imidazole **2k** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 64% yield (67.7 mg); Yellow solid; mp: 273–277 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.19 (t, *J* = 7.2 Hz, 3 H), 2.47 (s, 3 H), 3.68 (s, 3 H), 4.10−4.20 (m, 2 H), 4.33 (s, 3 H), 4.62 (dd, J_1 = 12.8 Hz, J_2 = 5.6 Hz, 1 H), 5.21 (dd, J_1 = 5.6 Hz, J_2 = 4.0 Hz, 1 H), 5.46 (dd, J_1 = 12.8 Hz, J_2 = 4.0 Hz, 1 H), 6.88 (s, 1 H), 7.60 (d, *J* = 8.4 Hz, 1 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 8.05−8.11 (m, 2 H), 8.28 (d, *J* = 2.0 Hz, 1 H), 8.74 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.4, 16.2, 28.6, 32.6, 33.3, 50.5, 60.7, 111.2, 111.6, 115.5, 116.5, 116.6, 117.2, 117.3, 118.3, 119.2, 124.1, 125.6, 129.5, 132.1, 140.4, 141.0, 141.1, 141.6, 141.8, 147.9, 160.6; IR (nujol): ν_{max} = 1685 cm^{-1}; MS (EI) *m/z* (%) = 528 (100) (M$^+$); anal. calcd. for $C_{27}H_{24}N_6O_6$ (528.52): C 61.36, H 4.58, N 15.90; found: C 61.22, H 4.60, N 16.01.



2l

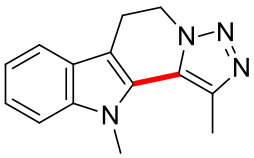
1-Ethyl 2-methyl 3,11-dimethyl-6,11-dihydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2l): Indole-Pyrrole **2l** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 58% yield (45.6 mg); Whitish oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.28 (t, *J* = 7.2 Hz, 3 H), 2.52 (s, 3 H), 3.04 (t, *J* = 6.8 Hz, 2 H), 3.61 (s, 3 H), 3.73 (s, 3 H), 4.04 (t, *J* = 6.8 Hz, 2 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 7.10 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1 H), 7.20 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 11.5, 14.6, 20.8, 32.3, 42.2, 52.6, 60.0, 110.7, 110.6, 118.9, 120.2, 122.2, 122.6, 125.7, 129.4, 136.5, 139.0, 164.1, 167.4; IR (nujol): ν_{max} = 1728, 1697 cm^{-1}; MS (EI) *m/z* (%) = 366 (100) (M$^+$); anal. calcd. for $C_{21}H_{22}N_2O_4$ (366.41): C 68.84, H 6.05, N 7.65; found: C 68.70, H 6.16, N 7.54.



2m

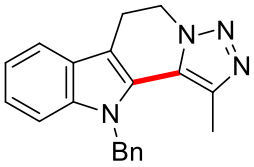
Methyl 12-methyl-2,3,4,6,7,12-hexahydro-1*H*-pyrido[1,2-a:3,4-*b*']diindole-13-carboxylate (2m): Indole-Pyrrole **2m** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 39% (53% based on starting material recovered) yield (26.1 mg); White solid; mp: 157–159 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.28−1.84 (m, 4 H), 2.57−2.67 (m, 4 H), 2.99 (t, *J* = 6.8 Hz, 2 H), 3.57 (s, 3 H), 3.74 (s, 3 H), 3.87 (t, *J* = 6.8 Hz, 2 H), 7.09 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.17 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 21.2, 21.9, 22.8, 23.4, 23.5, 33.4, 41.5, 51.2, 108.3, 109.1,

110.7, 118.7, 118.9, 120.1, 122.0, 124.7, 125.9, 130.0, 131.5, 139.2, 165.8; IR (nujol): ν_{max} = 1704 cm^{-1}; MS (ESI) *m/z* = 335 $[M + H]^+$; anal. calcd. for $C_{21}H_{22}N_2O_2$ (334.41): C 75.42, H 6.63, N 8.38; found: C 75.57, H 6.70, N 8.52.



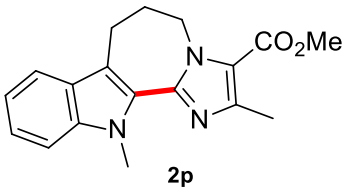
2n

1,11-Dimethyl-6,11-dihydro-5*H*-[1,2,3]triazolo[1',5':1,2]pyrido[3,4-*b*]indole (2n): Indole-Triazole **2n** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 65% yield (31.0 mg); White solid; mp: 150–152 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.62 (s, 3 H), 3.16 (t, *J* = 7.2 Hz, 2 H), 3.96 (s, 3 H), 4.58 (t, *J* = 7.2 Hz, 2 H), 7.12 (td, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.24 (td, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 13.7, 20.8, 33.2, 46.4, 110.0, 110.8, 119.3, 120.3, 123.0, 125.7, 127.2, 135.6, 138.7; IR (nujol): no significative signals were detected; MS (EI) *m/z* (%) = 238 (100) (M^+); anal. calcd. for $C_{14}H_{14}N_4$ (238.29): C 70.57, H 5.92, N 23.51; found: C 70.72, H 5.89, N 23.59.



2o

11-benzyl-1-methyl-6,11-dihydro-5*H*-[1,2,3]triazolo[1',5':1,2]pyrido[3,4-*b*]indole (2o): Indole-Triazole **2o** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 61% yield (38.4 mg); White solid; mp: 209–211 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.35 (s, 3 H), 3.23 (t, *J* = 7.2 Hz, 2 H), 4.61 (t, *J* = 7.2 Hz, 2 H), 5.67 (s, 2 H), 6.98–7.02 (m, 2 H), 7.10–7.38 (m, 6 H), 7.66 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 13.2, 20.8, 46.4, 48.7, 111.0, 111.4, 119.6, 120.8, 123.3, 125.7, 126.1, 126.2, 127.1, 127.7, 129.2, 135.4, 128.4, 138.5; IR (nujol): no significative signals were detected; MS (EI) *m/z* (%) = 314 (100) (M^+); anal. calcd. for $C_{20}H_{18}N_4$ (314.38): C 76.41, H 5.77, N 17.82; found: C 76.35, H 5.88, N 17.95.

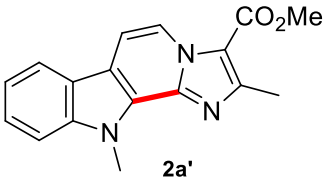


2p

Methyl 2,12-dimethyl-5,6,7,12-tetrahydroimidazo[1',2':1,2]azepino[3,4-*b*]indole-3-carboxylate (2p): Indole-Triazole **2p** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 26% yield (16.1 mg); White solid; mp: 118–120 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.13–2.22 (m, 2 H), 2.47 (s, 3 H), 3.07 (t, *J* = 7.2 Hz, 2 H), 3.84 (s, 3 H), 4.08 (s, 3 H), 4.51–4.55 (m, 2 H), 7.11 (t, *J* = 7.6 Hz, 1 H), 7.29 (t, *J* = 8.4 Hz, 1 H), 7.50 (d, *J* = 8.4 Hz, 1 H), 7.60 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 16.4, 23.7, 27.7, 32.6, 45.0, 51.8, 110.5, 115.9, 118.6, 119.4, 119.9, 124.0, 125.3, 127.3, 138.6, 144.7,

146.9, 161.6; IR (nujol): ν_{max} = 1705 cm^{-1}; MS (EI) *m/z* (%) = 309 (100) (M^+); anal. calcd. for $C_{18}H_{19}N_3O_2$ (309.36): C 69.88, H 6.19, N 13.58; found: C 70.02, H 6.08, N 13.69.

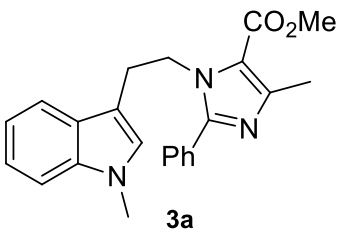
Procedure for DDQ Oxidation of 2a to 2a': To a solution of compound **2a** (0.5 mmol) in toluene (5 mL) DDQ (1 mmol) was added and the mixture refluxed for 4 hours. After removal of the solvent, the crude mixture was purified by column chromatography on silica gel to afford product **2a'**.



2a'

Methyl 2,11-dimethyl-11*H*-imidazo[1',2':1,2]pyrido[3,4-*b*]indole-3-carboxylate (2a'): Indole-Imidazole **2a'** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 55% yield (80.7 mg); White solid; mp: 171–173 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 2.70 (s, 3 H), 3.94 (s, 3 H), 4.44 (s, 3 H), 7.34 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.55 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 8.20 (d, *J* = 8.0 Hz, 1 H), 9.03 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 17.0, 32.2, 51.9, 108.3, 110.8, 113.0, 117.3, 119.6, 120.8, 121.0, 122.0, 126.5, 126.6, 138.3, 140.7, 150.9, 161.7; IR (nujol): ν_{max} = 1684 cm^{-1}; MS (EI) *m/z* (%) = 293 (100) (M^+); anal. calcd. for $C_{17}H_{15}N_3O_2$ (293.32): C 69.61, H 5.15, N 14.33; found: C 69.48, H 5.17, N 14.21.

Trapping of palladated imidazole intermediate by Heck-type reaction (Scheme 2): An uncapped test tube was charged with indole-imidazole (**1a**) (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), AgOAc (0.6 mmol), PhI (6 mmol), K_2CO_3 (0.2 mmol) and DMA (1 mL). The tube was then placed in an oil bath at 90 °C, afterwards the mixture was stirred under air for 3.5 hours (TLC check). The crude mixture was then purified by column chromatography on silica gel to afford intermolecular C-H/C-X coupling product (**3a**) in 6% yield together with the oxidative intramolecular product (**2a**).



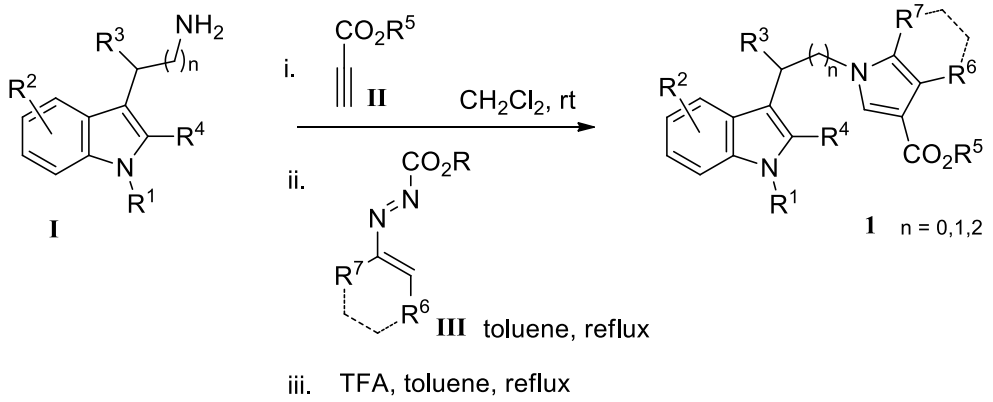
3a

Methyl 4-methyl-1-[2-(1-methyl-1*H*-indol-3-yl)ethyl]2-phenyl-1*H*-imidazole-5-carboxylate (3a): Indole-Imidazole **3a** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 6% yield (4.6 mg); ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 2.44 (s, 3 H), 2.95 (t, *J* = 7.6 Hz, 2 H), 3.67 (s, 3 H), 3.87 (s, 3 H), 4.45 (t, *J* = 7.6 Hz, 2 H), 6.86−6.92 (m, 2 H), 7.07 · 7.13 (m, 2 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.38 · 7.49 (m, 5 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 16.2, 27.1, 32.6, 47.3, 51.8, 109.8, 109.9, 118.4, 118.8, 118.9, 121.5,

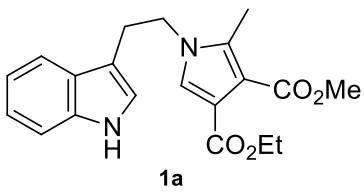
127.6, 127.7, 128.8, 129.5, 129.7, 130.4, 137.0, 147.4, 151.0, 161.5; MS (EI) *m/z* (%) = 373 (100) (M^+); anal. calcd. for $C_{23}H_{23}N_3O_2$ (373.45): C 73.97, H 6.21, N 11.25; found: C 73.84, H 6.16, N 11.38.

CHAPTER 3: *Polycyclic Indolines by an Acid-Mediated Intramolecular Dearomative Strategy: Reversing Indole Reactivity in the Pictet–Spengler-Type Reaction.*

General procedure for the Synthesis of Indole-Containing Pyrroles (1)[41]**:**

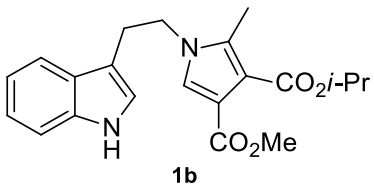


A mixture of indole derivative **I** (1 mmol), and alkynoate **II** (1.1 mmol) was stirred in dichloromethane (2 mL) overnight at room temperature. After the disappearance of the reagents, DD III (1.5 mmol) in toluene (4 mL) was added and the reaction was refluxed for 2 h. Catalytic amount of TFA (2 drops) was added once the DD was consumed completely (TLC check) and the reaction was refluxed for additional 2-4 h. After removal of the solvent, the crude mixture was purified by column chromatography on silica gel to afford product **1**.



1a

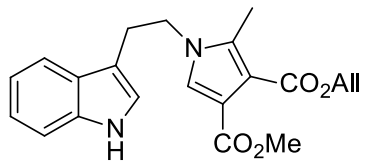
4-Ethyl 3-methyl 1-[2-(1*H*-indol-3-yl)ethyl]-2-methyl-1*H*-pyrrole-3,4-dicarboxylate (1a): The chemical-physical data of compound **1a** are in agreement with those reported.[41]



1b

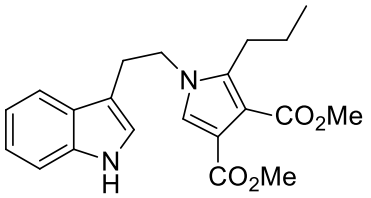
3-Isopropyl 4-methyl 1-[2-(1*H*-indol-3-yl)ethyl]-2-methyl-1*H*-pyrrole-3,4-dicarboxylate (1b): Indole-Pyrrole **1b** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 50% yield (184.2 mg); White solid; mp: 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.33 (d, *J* = 6.4 Hz, 6 H), 2.27 (s, 3 H), 3.14 (t, *J* = 7.2 Hz, 2 H), 3.78 (s, 3 H), 4.08 (t, *J* = 7.2 Hz, 2 H), 5.20 (sept, *J* = 6.4 Hz, 1 H), 6.81 (s, 1 H), 7.06 (s, 1 H), 7.16 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz,

1 H), 7.23 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.38 (d, J = 8.0 Hz, 1 H), 7.54 (d, J = 8.0 Hz, 1 H), 8.16 (br, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.6, 21.9, 27.0, 47.5, 51.2, 67.5, 111.1, 111.4, 113.5, 114.6, 118.0, 119.6, 122.2, 122.4, 125.7, 126.8, 134.5, 136.2, 164.7, 164.9; IR (nujol): ν_{max} = 3302, 1703, 1683 cm^{-1}; MS (ESI) *m/z* = 369 $[M + H]^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.58, H 6.65, N 7.51.



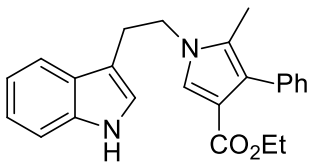
1c

3-Allyl 4-methyl 1-[2-(1*H*-indol-3-yl)ethyl]-2-methyl-1*H*-pyrrole-3,4-dicarboxylate (1c): Indole-Pyrrole **1c** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 28% yield (102.6 mg); Yellow oil; ^{1}H NMR (400 MHz, $[D_6]$DMSO, 25 °C): δ = 2.22 (s, 3 H), 3.08 (t, J = 7.4 Hz, 2 H), 3.65 (s, 3 H), 4.15 (t, J = 7.4 Hz, 2 H), 4.61−4.65 (m, 2 H), 5.20−5.24 (m, 1 H), 5.31−5.37 (m, 1 H), 5.91−6.00 (m, 1 H), 6.98 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.05−7.11 (m, 2 H), 7.34 (d, J = 8.0 Hz, 1 H), 7.39 (s, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 10.87 (s, 1 H); ^{13}C NMR (100 MHz, $[D_6]$DMSO, 25 °C): δ = 10.6, 26.8, 47.5, 51.4, 64.7, 110.6, 111.8, 112.1, 114.0, 117.9, 118.6, 118.8, 121.5, 123.7, 127.0, 127.3, 133.4, 135.4, 136.5, 164.2, 164.6; IR (nujol): ν_{max} = 3359, 1716, 1690 cm^{-1}; MS (ESI) *m/z* (%) = 367 $[M + H]^+$; anal. calcd. for $C_{21}H_{22}N_2O_4$ (366.41): C 68.84, H 6.05, N 7.65; found: C 68.71, H 6.11, N 7.56.



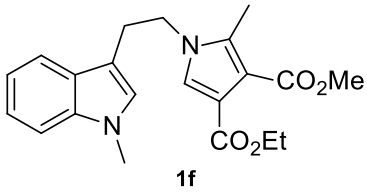
1d

Dimethyl 1-[2-(1*H*-indol-3-yl)ethyl]-2-propyl-1*H*-pyrrole-3,4-dicarboxylate (1d): Indole-Pyrrole **1d** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 31% yield (114.2 mg); Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.89 (t, J = 7.6 Hz, 3 H), 1.45−1.55 (m, 2 H), 2.65 (t, J = 7.6 Hz, 2 H), 3.18 (t, J = 7.6 Hz, 2 H), 3.79 (s, 3 H), 3.83 (s, 3 H), 4.11 (t, J = 7.6 Hz, 2 H), 6.84 (d, J = 2.0 Hz, 1 H), 7.08 (s, 1 H), 7.17 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.24 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 8.09 (br, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.8, 23.2, 26.6, 27.4, 47.3, 51.3, 51.4, 111.2, 111.4, 112.6, 114.7, 118.0, 119.7, 122.3, 122.3, 125.8, 126.8, 136.2, 139.5, 164.5, 165.7; IR (nujol): ν_{max} = 3382, 1729, 1703 cm^{-1}; MS (ESI) *m/z* (%) = 369 $[M + H]^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.53, H 6.49, N 7.52.



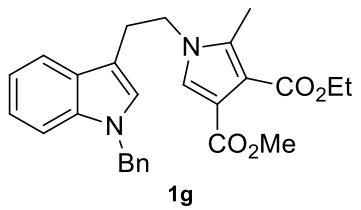
1e

Ethyl 1-[2-(1*H*-indol-3-yl)ethyl)]-5-methyl-4-phenyl-1*H*-pyrrole-3-carboxylate (1e): Indole-Pyrrole **1e** was isolated by column chromatography (ethyl acetate/cyclohexane 2:8) in 54% yield (201.1 mg); White solid; mp: 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.16 (t, *J* = 7.2 Hz, 3 H), 2.02 (s, 3 H), 3.22 (t, *J* = 7.6 Hz, 2 H), 4.10–4.17 (m, 4 H), 6.89 (d, *J* = 1.6 Hz, 1 H), 7.16 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.23 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.26–7.30 (m, 3 H), 7.34 (s, 1 H), 7.35–7.40 (m, 3 H), 7.55 (d, *J* = 7.6 Hz, 1 H), 8.08 (br, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.0, 14.2, 27.3, 48.0, 59.2, 111.3, 111.8, 113.0, 118.2, 119.3, 119.6, 122.2, 123.1, 125.8, 126.0, 127.1, 127.3, 127.5, 130.6, 135.6, 136.1, 164.8; IR (nujol): ν_{max} = 3382, 1703 cm^{-1}; MS (ESI) *m/z* (%) = 396 $[M + Na]^+$, 373 $[M + H]^+$; anal. calcd. for $C_{24}H_{24}N_2O_2$ (372.46): C 77.39, H 6.49, N 7.52; found: C 77.25, H 6.57, N 7.59.



1f

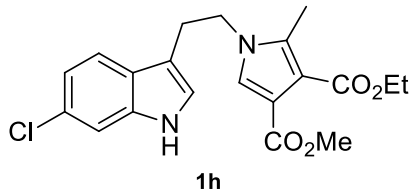
4-Ethyl 3-methyl 2-methyl-1-[2-(1-methyl-1*H*-indol-3-yl)ethyl]-1*H*-pyrrole-3,4-dicarboxylate (1f): Indole-Pyrrole **1f** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 100% yield (368.4 mg); White solid; mp: 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.32 (t, *J* = 7.2 Hz, 3 H), 2.29 (s, 3 H), 3.13 (t, *J* = 7.4 Hz, 2 H), 3.73 (s, 3 H), 3.84 (s, 3 H), 4.06 (t, *J* = 7.4 Hz, 2 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 6.70 (s, 1 H), 7.08 (s, 1 H), 7.15 (dt, J_1 = 8.0 Hz, J_2 = 1 Hz, 1 H), 7.26 (dt, J_1 = 8.0 Hz, J_2 = 1 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.7, 14.3, 27.0, 32.6, 47.8, 51.3, 59.9, 109.5, 109.6, 112.8, 114.9, 118.2, 119.1, 121.8, 126.0, 127.1, 127.2, 135.1, 137.0, 164.1, 165.9; IR (nujol): ν_{max} = 1729, 1703 cm^{-1}; MS (ESI) *m/z* (%) = 369 $[M + H]^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.53, H 6.68, N 7.52.



1g

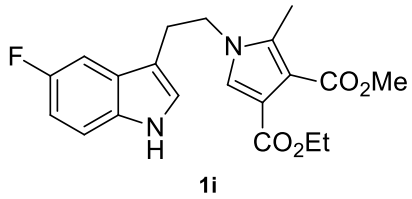
3-Ethyl 4-methyl 1-[2-(1-benzyl-1*H*-indol-3-yl)ethyl]-2-methyl-1*H*-pyrrole-3,4-dicarboxylate (1g): Indole-Pyrrole **1g** was isolated by column chromatography (ethyl acetate/cyclohexane 2:8) in 82% yield (364.5 mg); Whitish oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.36 (t, *J* = 7.2 Hz, 3 H), 2.28 (s, 3 H), 3.15 (t, *J* = 7.2 Hz, 2 H), 3.79 (s, 3 H), 4.09 (t, *J* = 7.2 Hz, 2 H), 4.33 (q, *J* = 7.2 Hz, 2 H), 5.24 (s, 2 H), 6.76 (s, 1 H), 7.07–7.11 (m, 3 H), 7.14–7.34 (m, 6 H), 7.56 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.7, 14.3, 27.0, 47.6, 49.9, 51.2, 60.1, 110.0, 110.3, 113.1, 114.7, 118.3, 119.4, 122.1, 125.9, 126.5, 126.8, 127.5, 127.6,

128.7, 134.9, 136.6, 137.2, 164.5, 165.3; IR (nujol): ν_{max} = 1729, 1693 cm^{-1}; MS (ESI) *m/z* (%) = 445 [M + H]$^+$; anal. calcd. for $C_{27}H_{28}N_2O_4$ (444.52): C 72.95, H 6.35, N 6.30; found: C 72.81, H 6.27, N 6.39.



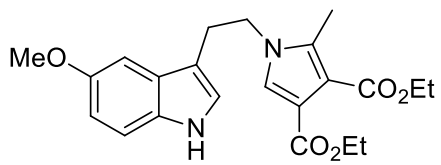
1h

3-Ethyl 4-methyl 1-[2-(6-chloro-1*H*-indol-3-yl)ethyl]-2-methyl-1*H*-pyrrole-3,4-dicarboxylate (1h): Indole-Pyrrole **1h** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 32% yield (124.5 mg); White solid, mp 105−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.34 (t, *J* = 7.2 Hz, 3 H), 2.22 (s, 3 H), 3.11 (t, *J* = 7.2 Hz, 2 H), 3.78 (s, 3 H), 4.07 (t, *J* = 7.2 Hz, 2 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 6.77 (d, *J* = 2.4 Hz ,1 H), 7.02 (s, 1 H), 7.11 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1 H), 7.36 (dd, J_1 = 2.0 Hz, J_2 = 0.4 Hz, 1 H), 7.39 (dd, J_1 = 8.4 Hz, J_2 = 0.4 Hz, 1 H), 8.17 (br, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.6, 14.2, 26.8, 47.4, 51.2, 60.2, 111.3, 111.3, 113.1, 114.7, 118.9, 120.4, 123.1, 125.4, 125.8, 128.2, 134.9, 136.5, 164.5, 165.3; IR (nujol): ν_{max} = 3382, 1729, 1693 cm^{-1}; MS (ESI) *m/z* (%) = 411 [M + Na]$^+$, 389 [M + H]$^+$; anal. calcd. for $C_{20}H_{21}ClN_2O_4$ (388.84): C 61.78, H 5.44, N 7.20; found: C 68.91, H 5.52, N 7.15.



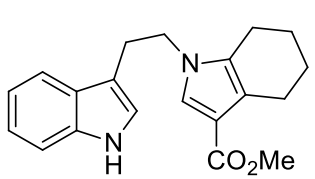
1i

4-Ethyl 3-methyl 1-[2-(5-fluoro-1*H*-indol-3-yl)ethyl]-2-methyl-1*H*-pyrrole-3,4-dicarboxylate (1i): Indole-Pyrrole **1i** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 44% yield (164.0 mg); White solid; mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.31 (t, *J* = 7.2 Hz, 3 H), 2.21 (s, 3 H), 3.10 (t, *J* = 7.0 Hz, 2 H), 3.82 (s, 3 H), 4.06 (t, *J* = 7.0 Hz, 2 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 6.80 (d, *J* = 2.4 Hz, 1 H), 6.96 (dt, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1 H), 7.03 (s, 1 H), 7.17 (dd, J_1 = 9.4 Hz, J_2 = 2.4 Hz, 1 H), 7.28 (dd, J_1 = 8.8 Hz, J_2 = 4.4 Hz, 1 H), 8.17 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.6, 14.3, 26.9, 47.3, 51.3, 60.0, 102.9 ($^2J_{CF}$ = 23.3 Hz), 110.7 ($^2J_{CF}$ = 26.1 Hz), 111.2 ($^4J_{CF}$ = 4.6 Hz), 112.1 ($^3J_{CF}$ = 9.5 Hz), 112.7, 115.1, 124.3, 125.8, 127.2 ($^3J_{CF}$ = 9.4 Hz), 132.7, 135.1, 157.9 ($^1J_{CF}$ = 234 Hz), 164.1, 165.9; IR (nujol): ν_{max} = 3378, 1721, 1685 cm^{-1}; MS (ESI) *m/z* (%) = 395 [M + Na]$^+$, 373 [M + H]$^+$; anal. calcd. for $C_{20}H_{21}FN_2O_4$ (372.39): C 64.51, H 5.68, N 7.52; found: C 64.63, H 5.60, N 7.61.



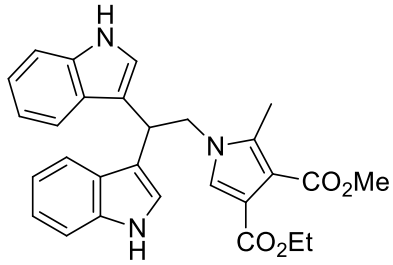
1j

Diethyl 1-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]-2-methyl-1*H*-pyrrole-3,4-dicarboxylate (1j): Indole-Pyrrole **1j** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 61% yield (243.1 mg); Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.30−1.35 (m, 6 H), 2.21 (s, 3 H), 3.10 (t, *J* = 7.2 Hz, 2 H), 3.85 (s, 3 H), 4.06 (t, *J* = 7.2 Hz, 2 H), 4.21−4.32 (m, 4 H), 6.78 (d, *J* = 2.2 Hz, 1 H), 6.84 (d, *J* = 2.2 Hz, 1 H), 6.87 (s, 1 H), 7.05 (s, 1 H), 7.25 (d, *J*= 9.0 Hz,1 H), 8.23 (br, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.6, 14.2, 14.3, 27.0, 47.6, 55.8, 60.0, 60.2, 99.9, 110.9, 112.1, 112.3, 113.0, 115.0, 123.2, 125.7, 127.2, 131.3, 134.8, 154.1, 164.2, 165.4; IR (nujol): ν_{max} = 3348, 1708, 1678 cm^{-1}; MS (ESI) *m/z* (%) = 399 [M + H]$^{+}$; anal. calcd. for $C_{22}H_{26}N_2O_5$ (398.45): C 66.32, H 6.58, N 7.03; found: C 66.45, H 6.50, N 7.11.



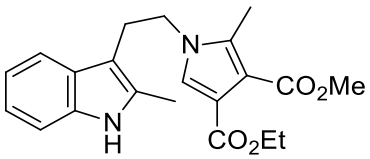
1k

Methyl 1-[2-(1*H*-indol-3-yl)ethyl]-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylate (1k): The chemical-physical data of compound 1k are in agreement with those reported.[41]



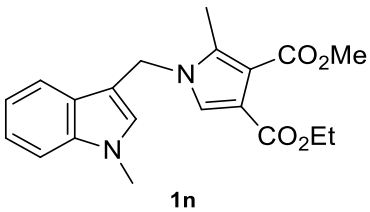
1l

4-Ethyl 3-methyl 1-[2,2-di(1*H*-indol-3-yl)ethyl]-2-methyl-1*H*-pyrrole-3,4-dicarboxylate (1l): Bis-indole-Pyrrole **1l** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 65% yield (305.2 mg); White solid; mp 110−112 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.17 (t, *J* = 7.0 Hz, 3 H), 2.18 (s, 3 H), 3.65 (s, 3 H), 4.08 (q, *J* = 7.0 Hz, 2 H), 4.69 (d, *J* = 7.6 Hz, 2 H), 4.91 (t, *J* = 7.6 Hz, 1 H), 6.90 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 2 H), 7.03 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 2 H), 7.19 (s, 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.37 (d, *J* = 2.4 Hz, 2 H), 7.56 (d, *J* = 8.0 Hz, 2 H), 10.91 (d, *J* = 2.4 Hz, 2 H);^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 10.8, 14.6, 35.6, 51.0, 51.3, 59.6, 111.8, 112.1, 113.9, 115.2, 118.6, 119.3, 121.3, 123.2, 126.8, 127.5, 135.3, 136.8, 163.7, 165.6; IR (nujol): ν_{max} = 3390, 3368, 1704, 1675 cm^{-1}; MS (ESI) *m/z* (%) = 470 [M + H]$^{+}$; anal. calcd. for $C_{28}H_{27}N_3O_4$ (469.53): C 71.62, H 5.80, N 8.95; found: C 71.74, H 5.89, N 8.88.



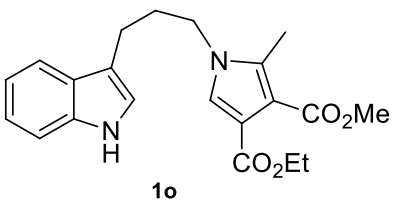
1m

4-Ethyl 3-methyl 2-methyl-1-[2-(2-methyl-1*H*-indol-3-yl)ethyl]-1*H*-pyrrole-3,4-dicarboxylate (1m): Indole-Pyrrole **1m** was isolated by column chromatography (ethyl acetate/cyclohexane 3:7) in 27% yield (99.4 mg); Whitish oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.22 (t, *J* = 7.2 Hz, 3 H), 2.06 (s, 3 H), 2.07 (s, 3 H), 2.99 (t, *J* = 7.0 Hz, 2 H), 3.68 (s, 3 H), 4.03 (t, *J* = 7.0 Hz, 2 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 6.95 (dt, J_1 = 7.6 Hz, J_2 = 1.0 Hz, 1 H), 7.00 (dt, J_1 = 7.6 Hz, J_2 = 1.0 Hz, 1 H), 7.24 (d, *J* = 7.6 Hz, 1 H), 7.28 (s, 1 H), 7.47 (d, *J*= 7.6 Hz, 1 H), 10.73 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 10.3, 11.0, 14.6, 25.9, 47.3, 51.4, 59.7, 106.3, 110.8, 112.4, 114.3, 117.6, 118.7, 120.5, 127.0, 128.4, 133.3, 135.0, 135.5, 163.7, 165.6; IR (nujol): ν_{max} = 3343, 1705, 1677 cm^{-1}; MS (ESI) *m/z* (%) = 369 [M + H]$^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.60, H 6.62, N 7.51.



1n

4-Ethyl 3-methyl 2-methyl-1-[(1-methyl-1*H*-indol-3-yl)methyl]-1*H*-pyrrole-3,4-dicarboxylate (1n): Indole-Pyrrole **1n** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 68% yield (241.0 mg); Yellow oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.19 (t, *J* = 7.2 Hz, 3 H), 2.37 (s, 3 H), 3.67 (s, 3 H), 3.77 (s, 3 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 5.26 (s, 2 H), 7.05 (dt, J_1 = 8.2 Hz, J_2 = 0.8 Hz, 1 H), 7.18 (dt, J_1 = 8.2 Hz, J_2 = 0.8 Hz, 1 H), 7.35 (s, 1 H), 7.36 (s, 1 H), 7.44 (d, *J* = 8.2 Hz, 1 H), 7.53 (d, *J* = 8.2 Hz, 1 H);^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.9, 14.3, 32.7, 42.9, 51.3, 59.9, 108.9, 109.6, 113.0, 114.7, 118.3, 119.8, 122.2, 126.1, 126.3, 127.8, 135.1, 137.2, 164.2, 165.9; IR (nujol): ν_{max} = 1716, 1628 cm^{-1}; MS (ESI) *m/z* (%) = 377 [M + Na]$^+$, 355 [M + H]$^+$; anal. calcd. for $C_{20}H_{22}N_2O_4$ (354.40): C 67.78, H 6.26, N 7.90; found: C 67.67, H 6.35, N 7.82.

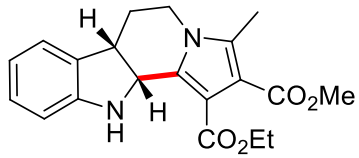


1o

4-Ethyl 3-methyl 1-[3-(1*H*-indol-3-yl)propyl]-2-methyl-1*H*-pyrrole-3,4-dicarboxylate (1o): Indole-Pyrrole **1o** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 53% yield (195.3 mg); White solid; mp 140−142 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.23 (t, *J* = 7.2 Hz, 3 H), 2.05 (quint, *J* = 7.4 Hz, 2 H), 2.27 (s, 3 H), 2.68 (t, *J* = 7.4 Hz, 2 H), 3.69 (s, 3 H), 3.96 (t, *J* = 7.4 Hz, 2 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 6.97 (dt, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 1 H), 7.07 (dt, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 1 H), 7.16 (d, *J* = 2.4 Hz, 1 H), 7.34 (d, *J* = 7.4 Hz, 1 H), 7.37 (s, 1 H), 7.48 (d, *J* = 7.4 Hz, 1 H), 10.80 (s, 1 H);^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ =

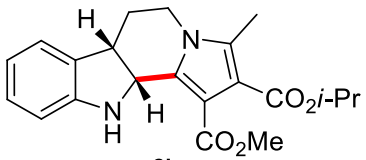
10.6, 14.6, 22.1, 31.0, 46.7, 51.4, 59.8, 111.8, 112.6, 113.6, 114.4, 118.6, 118.6, 121.3, 122.7, 126.8, 127.4, 134.8, 136.7, 163.7, 165.6; IR (nujol): ν_{max} = 3343, 1705, 1677 cm^{-1}; MS (ESI) *m/z* (%) = 391 [M + Na]$^+$, 369 [M + H]$^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.59, H 6.51, N 7.68.

***General procedure for the TFA-promoted Intramolecular Cross Coupling Reaction (2)*:** bi-heterocycle compound (**1**) (0.2 mmol) was dissolved in TFA (1 mL), afterwards the solution was stirred at room temperature for the indicate time (TLC check). The crude mixture was then purified by column chromatography on silica gel to afford product (**2**).



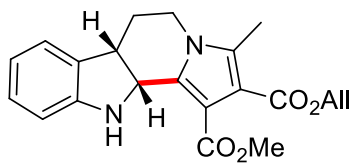
2a

1-Ethyl 2-methyl 3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2a): Indoline-Pyrrole **2a** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 84% yield (59.5 mg); White solid; mp: 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.34 (t, *J* = 7.0 Hz, 3 H), 2.08−2.26 (m, 2 H), 2.32 (s, 3 H), 3.49−3.55 (m, 1 H), 3.66−3.72 (m, 1 H), 3.82 (s, 3 H), 3.83−3.89 (m, 1 H), 4.24−4.35 (m, 2 H), 5.03 (d, *J* = 8.4 Hz, 1 H), 6.65 (d, *J* = 7.6 Hz, 1 H), 6.75 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 7.07 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 7.14 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.4, 14.3, 25.5, 38.4, 40.7, 51.4, 55.0, 60.2, 109.9, 112.2, 113.2, 118.7, 123.6, 128.2, 130.0, 132.2, 135.1, 150.1 165.1, 166.2; IR (nujol): ν_{max} = 3390, 1719, 1676 cm^{-1}; MS (EI) *m/z* (%) = 355 [M + H]$^+$; anal. calcd. for $C_{20}H_{22}N_2O_4$ (354.40): C 67.78, H 6.26, N 7.90; found: C 67.84, H 6.19, N 8.01.



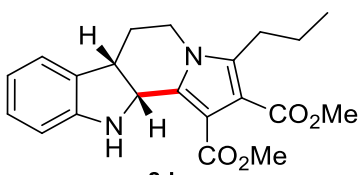
2b

2-Isopropyl 1-methyl 3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2b): Indoline-Pyrrole **2b** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 79% yield (58.2 mg); White solid; mp: 98–100 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.23 (t, *J* = 6.4 Hz, 6 H), 2.05 (q, *J* = 6.4 Hz, 2 H), 2.25 (s, 3 H), 3.52 (q, *J* = 6.4 Hz, 1 H), 3.73 (s, 3 H), 3.73−3.77 (m, 2 H), 4.94 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1 H), 5.03 (sept, *J* = 6.4 Hz, 1 H), 5.62 (d, *J* = 1.6 Hz, 1 H), 6.60−6.64 (m, 2 H), 6.96 (t, *J* = 7.6 Hz, 1 H), 7.15 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 10.3, 22.0, 22.1, 25.7, 38.0, 40.6, 51.5, 54.6, 67.2, 109.5, 111.2, 113.4, 118.0, 124.1, 128.1, 130.4, 132.1, 135.3, 151.0, 164.9, 165.1; IR (nujol): ν_{max} = 3373, 1701, 1683 cm^{-1}; MS (ESI) *m/z* = 391 [M + Na]$^+$, 369 [M + H]$^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.33, H 6.49, N 7.52.



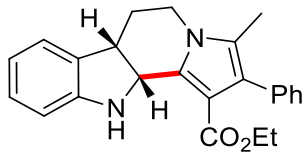
2c

2-Allyl 1-methyl 3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2c): Fused Indoline **2c** was isolated by column chromatography (ethyl acetate/cyclohexane 2:98) in 41% yield (30.1 mg); White solid; mp: 117–119 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.05 (q, *J* = 6.0 Hz, 2 H), 2.27 (s, 3 H), 3.52 (q, *J* = 7.0 Hz, 1 H), 3.71 (s, 3 H), 3.75–3.81 (m, 2 H), 4.64–4.67 (m, 2 H), 4.95 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1 H), 5.22–5.25 (m, 1 H), 5.31–5.37 (m, 1 H), 4.64 (d, *J* = 1.6 Hz, 1 H), 5.92–6.02 (m, 1 H), 6.60–6.64 (m, 2 H), 6.96 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 7.15 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 10.4, 25.7, 38.0, 40.2, 40.6, 51.6, 54.5, 64.9, 109.5, 111.5, 112.6, 118.1, 118.2, 124.1, 128.1, 130.5, 132.8, 133.3, 135.4, 151.0, 165.0; IR (nujol): ν_{max} = 3359, 1716, 1690 cm^{-1} MS (ESI) *m/z* = 389 [M + Na]$^+$, 367 [M + H]$^+$; anal. calcd. for $C_{21}H_{22}N_2O_4$ (366.41): C 68.84, H 6.05, N 7.65; found: C 68.96, H 6.13, N 7.68.



2d

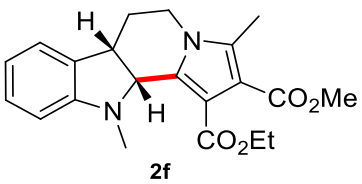
Dimethyl 3-propyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2d): Fused Indoline **2d** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 73% yield (53.8 mg); White solid; mp: 114–116 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.85 (t, *J* = 7.4 Hz, 3 H), 1.44 (sex, *J* = 7.4 Hz, 2 H), 1.97–2.09 (m, 2 H), 2.62–2.70 (m, 2 H), 3.57–3.62 (m, 1 H), 3.71 (s, 3 H), 3.74 (s, 3 H), 3.78–3.86 (m, 2 H), 5.08 (d, *J* = 8.8 Hz, 1 H), 6.53 (br, 1 H), 6.73–6.76 (m, 2 H), 7.03 (t, *J* = 7.6 Hz, 1 H), 7.22 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 13.9, 22.7, 26.0, 26.4, 38.1, 40.7, 51.7, 51.8, 54.5, 110.8, 111.8, 113.3, 124.3, 128.3, 131.6, 134.2, 136.3, 158.5, 158.8, 164.8, 165.9; IR (nujol): ν_{max} =3383, 1729, 1703 cm^{-1}; MS (ESI) *m/z* = 391 [M + Na]$^+$, 369 [M + H]$^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.33, H 6.52, N 7.69.



2e

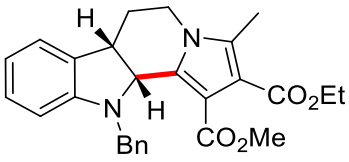
Ethyl 3-methyl-2-phenyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1-carboxylate (2e): Fused Indoline **2e** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 100% yield (74.4 mg); White solid; mp: 115–117 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.98 (t, *J* = 7.2 Hz, 3 H), 2.03 (s, 3 H), 2.08–2.15 (m, 2 H), 3.59 (q, *J* = 7.0 Hz, 1 H), 3.82 (t, *J* = 5.6 Hz, 2 H), 3.97–4.06 (m, 2 H), 5.18 (d, *J* = 8.0 Hz, 1 H), 6.32 (br, 1 H), 6.74–6.79 (m, 2 H), 7.04 (t, *J* = 7.4 Hz, 1 H), 7.16–7.18 (m, 2 H), 7.24–7.27 (m, 2 H), 7.31–7.35 (m, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$,

25 °C): δ = 9.9, 13.7, 25.9, 38.5, 40.9, 55.8, 59.6, 111.7, 111.8, 118.0, 119.5, 122.1, 122.2, 123.3, 124.0, 126.1, 127.3, 128.5, 130.5, 130.6, 135.8, 166.0; IR (nujol): ν_{max} = 3395, 1671 cm^{-1}; MS (ESI) *m/z* = 395 $[M + Na]^+$, 373 $[M + H]^+$; anal. calcd. for $C_{24}H_{24}N_2O_2$ (372.46): C 77.39, H 6.49, N 7.52; found: C 77.51, H 6.41, N 7.39.



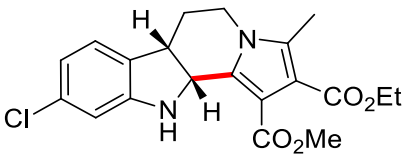
2f

1-Ethyl 2-methyl 3,11-dimethyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2f): Fused Indoline **2f** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 91% yield (67.1 mg); White solid; mp: 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.34 (t, *J* = 7.2 Hz, 3 H), 1.95–2.10 (m, 2 H), 2.39 (s, 3 H), 2.67 (s, 3 H), 3.60–3.70 (m, 2 H), 3.83 (s, 3 H), 3.85–3.92 (m, 1 H), 4.26–4.36 (m, 2 H), 5.04 (d, *J* = 9.3 Hz, 1 H), 6.44 (d, *J* = 7.4 Hz, 1 H), 6.74 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 7.10–7.16 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.4, 14.3, 31.5, 33.0, 38.2, 39.9, 51.3, 59.7, 60.3, 107.1, 111.9, 114.4, 118.2, 124.2, 128.4, 130.7, 131.5, 133.9, 152.8, 165.0, 166.0; IR (nujol): ν_{max} = 1705, 1697 cm^{-1}; MS (ESI) *m/z* = 391 $[M + Na]^+$, 369 $[M + H]^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.59, H 6.48, N 7.53.



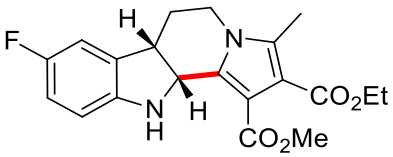
2g

2-Ethyl 1-methyl 11-benzyl-3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2g): Fused Indoline **2g** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 94% yield (83.6 mg); Whitish oil; ^{1}H NMR (400 MHz, $[D_6]$DMSO, 25 °C): δ = 1.21 (t, *J* = 7.0 Hz, 3 H), 1.93–2.05 (m, 2 H), 2.34 (s, 3 H), 3.41–3.48 (m, 1 H), 3.50 (s, 3 H), 3.82–3.85 (m, 1 H), 4.03 (d, *J* = 16.8 Hz, 1 H), 4.06–4.11 (m, 1 H), 4.14 (q, *J* = 7.0 Hz, 2 H), 4.45 (d, *J* = 16.8 Hz, 1 H), 5.33 (d *J* = 9.6 Hz, 1 H), 6.18 (d, *J* = 8.0 Hz, 1 H), 6.62 (dt, J_1 = 7.4 Hz, J_2 = 0.8 Hz, 1 H), 6.93 (dt, J_1 = 7.4 Hz, J_2 = 0.8 Hz, 1 H), 7.02 (d, *J* = 6.8 Hz, 2 H), 7.16 (t, *J* = 6.8 Hz, 2 H), 7.23 (t, *J* = 6.8 Hz, 2 H); ^{13}C NMR (100 MHz, $[D_6]$DMSO, 25 °C): δ = 10.4, 14.5, 31.9, 38.0, 40.6, 48.4, 51.5, 57.7, 59.9, 106.5, 111.6, 114.4, 118.0, 124.9, 126.9, 127.0, 128.4, 128.7, 130.4, 131.4, 134.6, 139.1, 151.7, 164.8, 165.2; IR (nujol): ν_{max} = 1729, 1693 cm^{-1}; MS (ESI) *m/z* = 467 $[M + Na]^+$, 445 $[M + H]^+$; anal. calcd. for $C_{27}H_{28}N_2O_4$ (444.52): C 72.95, H 6.35, N 6.30; found: C 73.04, H 6.24, N 6.21.



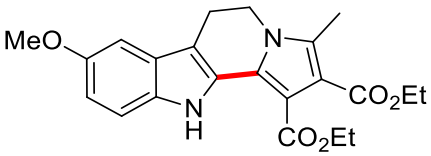
2h

2-Ethyl 1-methyl 9-chloro-3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2h): Fused Indoline **2h** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 100% yield (77.7 mg); White solid; mp: 105–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.33 (t, *J* = 7.2 Hz, 3 H), 2.06 · 2.22 (m, 2 H), 2.32 (s, 3 H), 3.46–3.51 (m, 1 H), 3.65–3.72 (m, 1 H), 3.81–3.88 (m, 1 H), 3.82 (s, 3 H), 4.24–4.35 (m, 2 H), 5.03 (d, *J* = 8.4 Hz, 1 H), 6.59 (d, *J* = 1.6 Hz, 1 H), 6.68 (dd, J_1 = 7.8 Hz, J_2 = 1.6 Hz, 1 H), 7.01 (dd, J_1 = 7.8 Hz, J_2 = 0.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.4, 14.3, 25.5, 37.8, 40.5, 51.4, 55.3, 60.3, 109.7, 111.8, 113.5, 118.2, 124.2, 128.3, 132.2, 133.8, 134.8, 151.5, 165.6, 165.7; IR (nujol): ν_{max} = 3359, 1716, 1690 cm^{-1}; MS (ESI) *m/z* = 411 [M + Na]$^+$, 389 [M + H]$^+$; anal. calcd. for $C_{20}H_{21}ClN_2O_4$ (388.84): C 61.78, H 5.44, N 7.20; found: C 61.89, H 5.36, N 7.25.



2i

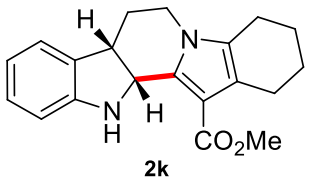
2-Ethyl 1-methyl 8-fluoro-3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2i): Fused Indoline **2i** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 90% yield (67.0 mg); White solid; mp: 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.33 (t, *J* = 7.2 Hz, 3 H), 2.06–2.24 (m, 2 H), 2.32 (s, 3 H), 3.47–3.52 (m, 1 H), 3.65–3.72 (m, 1 H), 3.81 (s, 3 H), 3.84–3.89 (m, 1 H), 4.21–4.36 (m, 2 H), 4.64 (br, 1 H), 5.04 (d, *J* = 8.4 Hz, 1 H), 6.57 (dd, J_1 = 8.8 Hz, J_2 = 4.4 Hz, 1 H), 6.76 (dt, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1 H), 6.86 (dd, J_1 = 8.2 Hz, J_2 = 2.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.3, 14.2, 25.3, 38.6, 40.6, 51.4, 55.5, 60.2, 110.2 ($^3J_{CF}$ = 7.8 Hz), 110.1 ($^2J_{CF}$ = 23.7 Hz), 112.2, 113.3, 114.3 ($^2J_{CF}$ = 23.1 Hz), 131.6 ($^3J_{CF}$ = 7.4 Hz), 132.2, 134.7, 146.0, 156.9 ($^1J_{CF}$ = 234 Hz), 165.1, 166.2; IR (nujol): ν_{max} = 3378, 1721, 1685 cm^{-1}; MS (ESI) *m/z* = 373 [M + H]$^+$; anal. calcd. for $C_{20}H_{21}FN_2O_4$ (372.39): C 64.51, H 5.68, N 7.52; found: C 64.38, H 5.61, N 7.45.



2j'

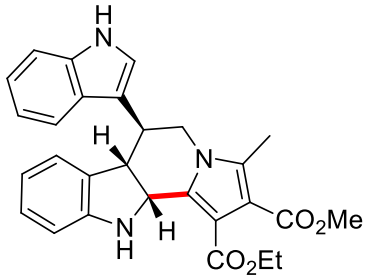
Diethyl 8-methoxy-3-methyl-6,11-dihydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2j'): Fused Indole **2j'** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 40% yield (31.7 mg); White solid, mp: 135–137 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 2.38 (s, 3 H), 3.10 (t, *J* = 7.2 Hz, 2 H), 3.78 (s, 3 H), 4.11 (t, *J* = 7.2 Hz, 2 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 6.77 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1 H), 7.04 (d, J_1 = 2.4 Hz, 1 H), 7.52 (d,

J = 8.8 Hz, 1 H), 10.5 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 10.9, 14.4, 14.6, 20.1, 42.2, 55.7, 60.3, 60.7, 100.1, 107.9, 108.7, 113.3, 113.4, 113.7, 126.1, 126.4, 128.3, 131.8, 134.8, 154.2, 165.3, 165.7; IR (nujol): ν_{max} = 3348, 1708, 1678 cm^{-1}; MS (ESI) *m/z* = 419 [M + Na]$^+$, 397 [M + H]$^+$;anal. calcd. for $C_{22}H_{24}N_2O_4$ (396.44): C 66.65, H 6.10, N 7.07; found: C 66.77, H 6.17, N 6.99.



2k

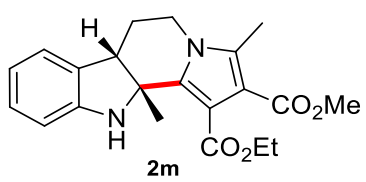
Methyl 2,3,4,6,7,7a,12,12a-octahydro-1*H*-pyrido[1,2-a:3,4-*b*]diindole-13-carboxylate (2k): Fused Indoline **2k** was isolated by column chromatography on neutral alumina (ethyl acetate/cyclohexane 30:70) in 85% yield (54.9 mg); White solid; mp: 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.70−1.82 (m, 4 H), 2.06−2.20 (m, 2 H), 2.40−2.51 (m, 2 H), 2.63−2.76 (m, 2 H), 3.45−3.51 (m, 1 H), 3.61−3.68 (m, 1 H), 3.82−3.87 (m, 1 H), 3.83 (s, 3 H), 5.16 (d, *J* = 8.0 Hz, 1 H), 5.34 (br, 1 H), 6.65 (d, *J* = 7.4 Hz, 1 H), 6.74 (dt, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 1 H), 7.07 (dt, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 1 H), 7.15 (d, *J* = 7.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 21.3, 22.7, 23.2, 23.4, 25.8, 38.8, 40.2, 50.6, 55.2, 109.7, 109.8, 118.4, 119.1, 123.6, 127.4, 128.0, 130.8, 134.6, 150.5, 166.7; IR (nujol): ν_{max} = 3378, 1688 cm^{-1}; MS (EI) *m/z* (%) = 323 [M + H]$^+$; anal. calcd. for $C_{20}H_{22}N_2O_2$ (322.40): C 74.51, H 6.88, N 8.69; found: C 74.60, H 6.99, N 8.57.



2l
major

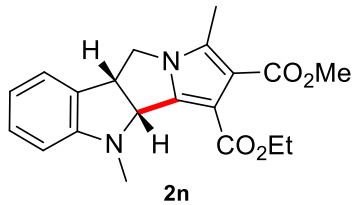
1-Ethyl 2-methyl 6-(1*H*-indol-3-yl)-3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2l): Fused Indoline **2l** was isolated as an inseparable mixture of diastereomers in a 9:1 ratio by column chromatography (ethyl acetate/cyclohexane 25:75) in 78% yield (73.4 mg); White solid; The stereochemistry of the major diastereoisomer was tentatively assigned by comparison of its ^{1}H NMR spectral data with that of similar structures;[34] major diastereomer; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 2.23 (s, 3 H), 3.49−3.55 (m, 1 H), 3.72 (s, 3 H), 3.90 (t, *J* = 8.4 Hz, 1 H), 4.04−4.06 (m, 2 H), 4.17−4.28 (m, 2 H), 5.10 (d, *J* = 8.0 Hz, 1 H), 5.67 (br, 1 H), 6.31−6.37 (m, 2 H), 6.68 (d, *J* = 8.0 Hz, 1 H), 6.88−6.97 (m, 2 H), 7.06−7.12 (m, 2 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 1 H), 10.99 (d, *J* = 2.0 Hz, 1 H);^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 10.4, 14.5, 33.9, 43.3, 46.8, 51.6, 55.3, 60.1, 109.5, 111.6, 112.1, 113.1, 113.3, 117.7, 118.9, 119.3, 121.5, 123.9, 125.3, 126.8, 128.0, 130.3, 132.3, 134.9, 136.7, 150.9, 164.6, 166.0; IR (nujol): ν_{max} = 3410, 3371, 1717, 1688 cm^{-1}; MS (EI) *m/z*

(%) = 492 $[M + Na]^+$, 470 $[M + H]^+$; anal. calcd. for $C_{28}H_{27}N_3O_4$ (469.53): C 71.62, H 5.80, N 8.95; found: C 71.71, H 5.87, N 9.06.



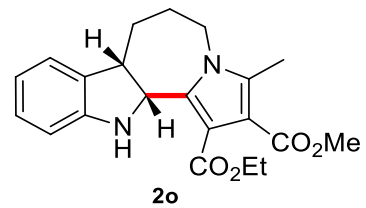
2m

1-Ethyl 2-methyl 3,11a-dimethyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2m): Fused Indoline **2m** was isolated by column chromatography (ethyl acetate/cyclohexane 2:8) in 78% yield (57.5 mg); Whitish oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ =1.24 (t, *J* = 7.2 Hz, 3 H), 1.53 (s, 3 H), 2.13–2.18 (m, 1 H), 2.20 (s, 3 H), 2.32–2.39 (m, 1 H), 3.25 (t, *J* = 4.8 Hz, 1 H), 3.57–3.63 (m, 1 H), 3.67 (s, 3 H), 3.84–3.90 (m, 1 H), 4.19–4.25 (m, 2 H), 6.05 (s, 1 H), 6.57 (d, *J* = 7.6 Hz, 1 H), 6.62 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 6.93 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 7.14 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 10.4, 14.4, 22.5, 26.8, 26.9, 46.6, 51.6, 60.7, 62.9, 109.3, 110.7, 113.2, 118.2, 123.7, 128.2, 128.6, 131.6, 139.1, 150.3, 165.7, 166.6; IR (nujol): ν_{max} = 3343, 1733, 1686 cm^{-1}; MS (EI) *m/z* (%) = 369 $[M + H]^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.32, H 6.65, N 7.54.



2n

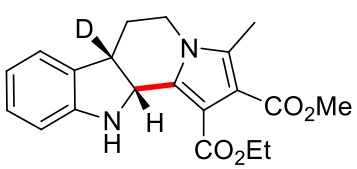
3-Ethyl 2-methyl 1,4-dimethyl-3b,4,8b,9-tetrahydropyrrolizino[1,2-*b*]indole-2,3-dicarboxylate (2n): Fused Indoline **2n** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 21% yield (15.1 mg); White solid, mp: 199–201 °C (with decomposition); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.89 (t, *J* = 7.6 Hz, 3 H), 2.43 (s, 3 H), 3.00 (s, 3 H), 3.78–3.83 (m, 1 H), 3.95 (s, 3 H), 3.98–4.00 (m, 1 H), 4.29–4.34 (m, 1 H), 4.50 (q, *J* = 7.6 Hz, 2 H), 5.34 (d, *J* = 8.4 Hz, 1 H), 6.50 (d, *J* = 7.6 Hz, 1 H), 6.71 (t, *J* = 7.6 Hz, 1 H), 7.12 (d, *J* = 7.6 Hz, 1 H), 7.17 (t, *J* = 7.6 Hz, 1 H);^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.3, 29.6, 35.2, 48.7, 51.7, 52.6, 69.0, 77.1, 107.8, 110.9, 111.3, 117.8, 123.7, 128.0, 129.1, 134.6, 144.9, 152.9, 164.1, 169.6; IR (nujol): ν_{max} = 1719, 1626 cm^{-1}; MS (EI) *m/z* (%) = 377 $[M + Na]^+$, 355 $[M + H]^+$; anal. calcd. for $C_{20}H_{22}N_2O_4$ (354.40): C 67.78, H 6.26, N 7.90; found: C 67.89, H 6.18, N 7.94.



2o

1-Ethyl 2-methyl 3-methyl-5,6,7,7a,12,12a-hexahydropyrrolo[1',2':1,2]azepino[3,4-*b*]indole-1,2-dicarboxylate (2o): Fused Indoline **2o** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 81% yield (59.7 mg); White solid; mp 142–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.99 (t, *J* = 7.2 Hz, 3 H), 1.80 (t, *J* = 12.8 Hz, 1 H), 2.05–2.31 (m, 3 H), 2.46 (s, 3 H), 3.57–3.67 (m, 2 H), 3.68–3.75 (m, 1 H), 3.73 (s,

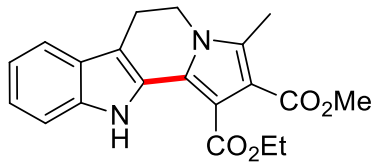
3 H), 3.86 (d, *J* = 10.0 Hz, 1 H), 4.06 (dd, J_1 = 12.4 Hz, J_2 = 4.4 Hz, 1 H), 4.19 (d, *J* = 10.0 Hz, 1 H), 5.38 (br, 1 H), 6.98–7.03 (m, 2 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 7.20 (t, *J* = 7.2 Hz, 1 H);^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.7, 13.8, 20.0, 34.2, 43.2, 47.1, 51.0, 58.8, 60.5, 111.3, 114.3, 114.5, 123.9, 124.3, 128.6, 132.5, 133.8, 137.7, 143.7, 165.0, 166.3; IR (nujol): ν_{max} = 3343, 1705, 1677 cm^{-1}; MS (EI) *m/z* (%) = 391 [M + Na]$^+$, 369 [M + H]$^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.59, H 6.59, N 7.49.



2aD

1-Ethyl 2-methyl 6a-deutero-3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2aD): Indoline-Pyrrole **2aD** was isolated by column chromatography on neutral alumina (ethyl acetate/cyclohexane 20:80) in 99% yield (70.4 mg); Whitish oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.25 (t, *J* = 7.2 Hz, 3 H), 1.98–2.04 (m, 1 H), 2.07–2.14 (m, 1 H), 2.23 (s, 3 H), 3.55–3.63 (m, 1 H), 3.73 (s, 3 H), 3.74–3.80 (m, 1 H), 4.13–4.28 (m, 2 H), 4.91 (s, 1 H), 5.19 (br, 1 H), 6.55 (d, *J* = 7.6 Hz, 1 H), 6.65 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 6.98 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 7.05 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.4, 14.3, 25.4, 38.0 (1 C, t, $^1J_{CD}$ = 20.4 Hz), 40.7, 51.4, 54.9, 60.2, 109.7, 112.1, 113.2, 118.5, 123.6, 128.2, 129.9, 132.2, 135.2, 150.3, 165.1, 166.3; IR (nujol): ν_{max} = 3390, 1714, 1706 cm^{-1}; MS (EI) *m/z* (%) = 356 [M + H]$^+$; anal. calcd. for $C_{20}H_{21}DN_2O_4$ (355.41): C 67.59, H 6.52, N 7.88; found: C 67.45, H 6.59, N 7.96.

Procedure for Oxidation of 2a to 2a'[41]: A mixture of compound **2a** (0.3 mmol), Pd/C (10%, 4 mg) and ethyl acetate (2 mL) was refluxed for 2 hours (TLC check). After removal of the solvent, the crude mixture was purified by column chromatography on silica gel to afford product **2a'**.

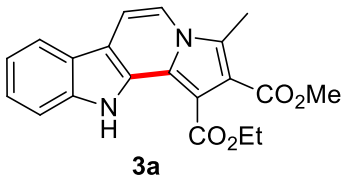


2a'

1-Ethyl 2-methyl 3-methyl-6,11-dihydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2a'): Indole-Pyrrole **2a'** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 62% yield (65.5 mg); White solid; mp: 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.37 (t, *J* = 7.2 Hz, 3 H), 2.42 (s, 3 H), 3.19 (t, *J* = 7.2 Hz, 2 H), 3.87 (s, 3 H), 4.07 (t, *J* = 7.2 Hz, 2 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 7.13 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.22 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.54 (d, *J* = 7.6 Hz, 1 H), 10.66 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.8, 14.2, 20.4, 42.2, 51.6, 60.7, 107.9, 111.9, 113.7, 118.3, 119.8, 122.8, 122.9, 125.6, 126.4, 129.5, 134.0, 136.1, 166.2, 166.4; IR (nujol): ν_{max} = 3382,

1729, 1703, cm^{-1}; MS (EI) *m/z* (%) = 375 $[M + Na]^+$, 353 $[M + H]^+$; anal. calcd. for $C_{20}H_{20}N_2O_4$ (352.38): C 68.17, H 5.72, N 7.95; found: C 68.04, H 5.80, N 8.06.

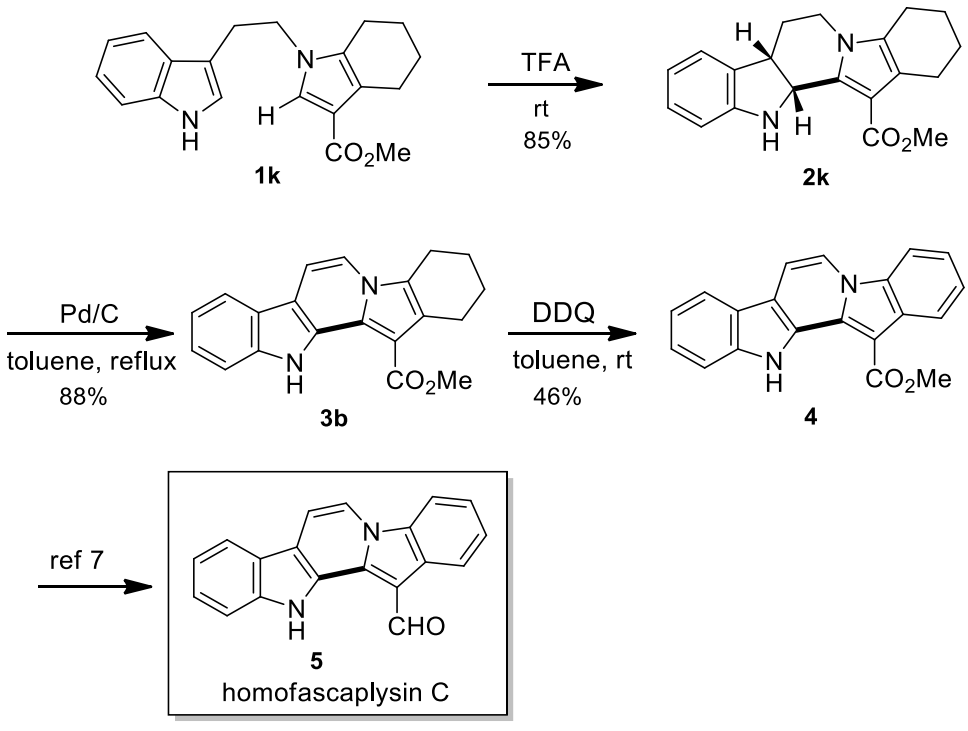
Procedure for Oxidation of 2a' to 3a: DDQ (0.3 mmol) was added portionwise to a solution of compound **2a'** (0.15 mmol) in toluene (2 mL) and the mixture was stirred for 1 hour (TLC check). After removal of the solvent, the crude mixture was purified by column chromatography on silica gel to afford product **3a.**



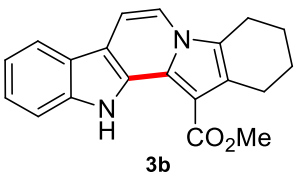
3a

1-Ethyl 2-methyl 3-methyl-11*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate: Indole-Pyrrole **3a** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 74% yield (38.9 mg); Yellowish solid; mp: 181–183 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.36 (t, *J* = 7.2 Hz, 3 H), 2.57 (s, 3 H), 3.90 (s, 3 H), 4.38 (q, *J* = 7.2 Hz, 2 H), 7.29 (t, *J* = 7.6 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.81 (d, *J* = 7.2 Hz, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 8.04 (d, *J* = 7.2 Hz, 1 H), 8.15 (d, *J* = 7.6 Hz, 1 H), 11.5 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 10.3, 14.1, 52.0, 60.1, 99.6, 107.8, 112.8, 113.8, 116.9, 118.1, 119.6, 120.0, 121.9, 124.4, 125.0, 125.9, 127.7, 137.6, 164.6, 166.2; IR (nujol): ν_{max} = 3282, 1728, 1720, cm^{-1}; MS (EI) *m/z* (%) = 373 $[M + Na]^+$, 351 $[M + H]^+$, 349 $[M - H]^+$; anal. calcd. for $C_{20}H_{18}N_2O_4$ (350,37): C, 68.56, H, 5.18, N, 8.00; found: C 68.42, H 5.07, N 8.11.

Approach to the Synthesis of Homofascaplysin C.



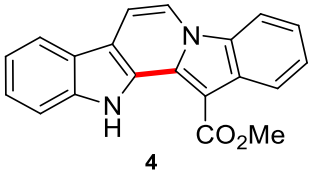
***Procedure for Oxidation of 2k to 3b*:** A mixture of compound **2k** (0.15 mmol), Pd/C (10%, 2 mg) and toluene (2 mL) was refluxed for 1.5 hours (TLC check). After removal of the solvent, the crude mixture was purified by column chromatography on neutral alumina to afford product **3b**.



3b

Methyl 2,3,4,12-tetrahydro-1*H*-pyrido[1,2-*a*:3,4-*b*']diindole-13-carboxylate (3b): Fused Indole **3b** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 88% yield (42.1 mg); White solid; mp: 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.86–2.02 (m, 4 H), 2.75 (t, *J* = 6.0 Hz, 2 H), 2.98 (t, *J* = 6.0 Hz, 2 H), 3.96 (s, 3 H), 7.25–7.29 (m, 1 H), 7.39–7.43 (m, 2 H), 7.55 (d, *J* = 7.2 Hz, 1 H), 7.60 (d, *J* = 8.0 Hz, 1 H), 7.98 (d, *J* = 8.0 Hz, 1 H), 11.62 (s, 1 H); ^{13}C NMR (100 MHz, , $CDCl_3$, 25 °C): δ = 21.7, 22.5, 23.4, 24.1, 51.0, 100.5, 106.3, 111.7, 113.4, 114.8, 119.3, 119.6, 122.7, 123.4, 123.9, 124.6, 127.1, 129.4, 137.4, 167.9; IR (nujol): ν_{max} = 3302, 1670 cm^{-1}; MS (EI) *m/z* (%) = 224 $[M + H]^+$; anal. calcd. for $C_{20}H_{18}N_2O_2$ (318.31): C 75.45, H 5.70, N 8.80; found: C 75.37, H 5.61, N 8.94.

Procedure for Oxidation of 3b to 4: DDQ (0.33 mmol) was added portionwise to a solution of compound **3b** (0.15 mmol) in toluene (2 mL) and the mixture was stirred for 2 hours (TLC check). The crude mixture was purified by column chromatography on neutral alumina to afford product **4**.



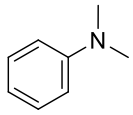
4

Methyl 12*H*-pyrido[1,2-*a*:3,4-*b*']diindole-13-carboxylate (4): Fused Indole **4** was isolated by column chromatography (ethyl acetate/cyclohexane 5:95) in 46% yield (21.7 mg), Yellow solid, mp: 163–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.10 (s, 3 H), 7.31 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.38 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.46–7.52 (m, 3 H), 7.65 (td, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 8.02 (td, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 8.21 (d, *J* = 7.2 Hz, 1 H), 8.31 (d, *J* = 8.0 Hz, 1 H), 12.08 (br, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 51.3, 94.7, 106.1, 110.3, 112.2, 116.6, 116.9, 119.9, 120.2, 121.5, 122.0, 122.3, 124.8, 125.8, 127.6, 128.4, 131.7, 133.3, 138.0, 167.9; IR (nujol): ν_{max} = 3382, 1729 cm^{-1}; MS (EI) *m/z* (%) = 315 $[M + H]^+$; anal. calcd. for $C_{20}H_{14}N_2O_2$ (314.34): C 76.42, H 4.49, N 8.91; found: C 76.29, H 4.54, N 8.789.

CHAPTER 4: Zn(II)-Catalyzed Addition of Aromatic/Heteroaromatic C(sp2)–H to Azoalkenes: A Polarity-Reversed Arylation of Carbonyl Compounds.

Experimental procedure

Arenes/Heteroarenes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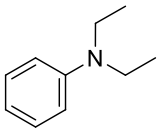
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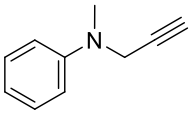
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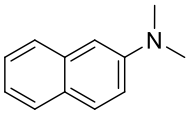
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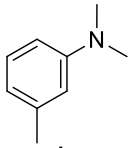
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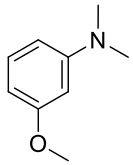
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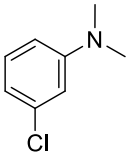
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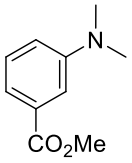
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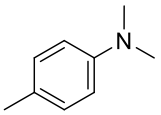
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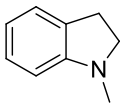
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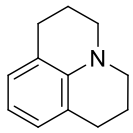
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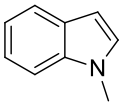
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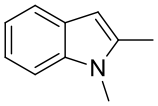
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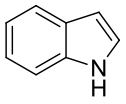
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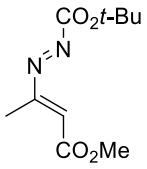
Azoalkenes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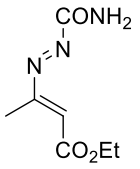
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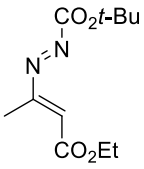
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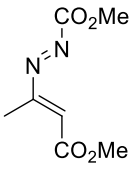
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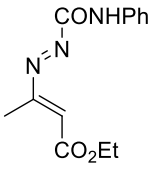
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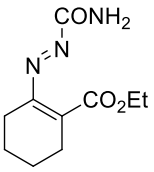
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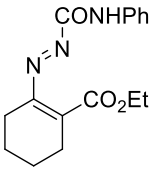
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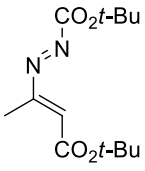
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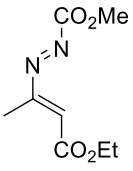
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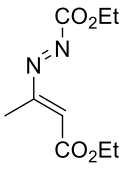
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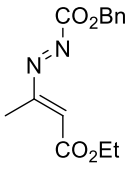
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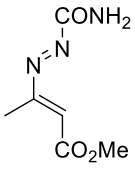
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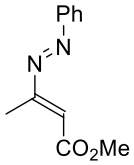
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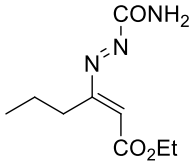
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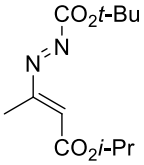
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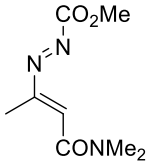
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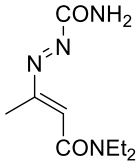
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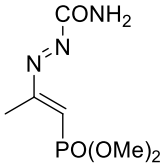
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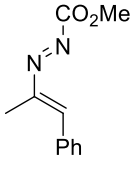
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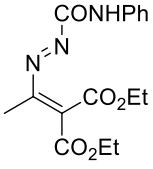
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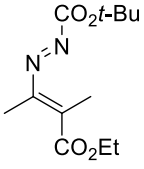
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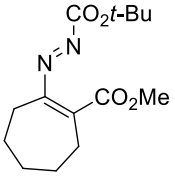
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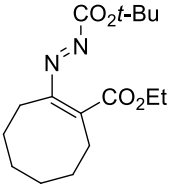
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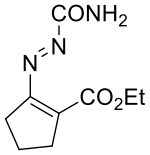
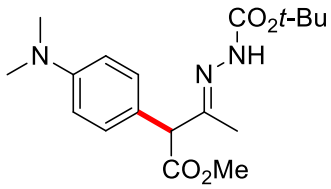

2x

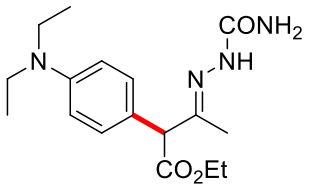
The following starting materials **1a**-**o** were commercially available reagents, and used without further purification. *N*-Methylindoline (**1j**) was prepared from corresponding *N*H-indoline following literature procedure.[143] 1,2-Diaza-1,3-dienes (DDs) **2a**–**x** were synthesized from the corresponding hydrazones following literature procedure.[144]

General procedure for the Michael-type addition of arenes/heteroarenes 1a–o with azoalkenes 2a–x: A mixture of arenes/heterarenes **1a**–**o** (0.5 mmol), azoalkene **2** (0.65 mmol) and zinc dichloride (0.1 mmol, 13.6 mg) was stirred in dichloromethane (2 mL). After the disappearance of azoalkenes **2a**–**x** (TLC check), the crude mixture was purified by column chromatography on silica gel to afford product **3a**–**ai**.



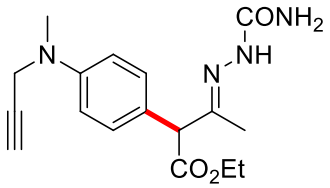
3a

***tert*-Butyl 2-(3-(4-(dimethylamino)phenyl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate:** compound **3a** was isolated by column chromatography (ethyl acetate/cyclohexane 20: 80) in 78% yield (136.3 mg); white solid; mp: 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.50 (s, 9 H), 1.76 (s, 3 H), 2.92 (s, 6 H), 3.71 (s, 3 H), 4.74 (s, 1 H), 6.67 (d, *J* = 8.8 Hz, 2 H), 7.11 (d, *J* = 8.8 Hz, 2 H), 7.53 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.1, 28.2, 40.4, 51.9, 58.5, 81.1, 112.5, 122.5, 129.1, 130.7, 149.9, 152.6, 171.9; IR (nujol): ν_{max} = 3358, 1725, 1717 cm^{-1}; MS (ESI) *m/z* = 350 $[M + H]^+$; anal. calcd. for $C_{18}H_{27}N_3O_4$ (349,42): C 61.87, H 7.79, N 12.03; found: C 62.03, H 7.69, N 11.92.



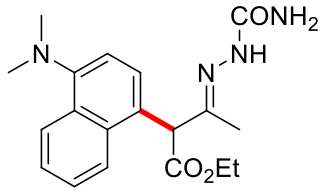
3b

Ethyl 3-(2-carbamoylhydrazono)-2-(4-(diethylamino)phenyl)butanoate: compound **3b** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 80:20) in 51% yield (85.3 mg); yellow oil; ^{1}H NMR (400 MHz, $[D_6]$DMSO, 25 °C): δ = 1.06 (t, *J* = 7.2 Hz, 6 H), 1.17 (t, *J* = 7.2 Hz, 3 H), 1.73 (s, 3 H) , 3.29 (q, *J* = 7.2 Hz, 4 H), 4.06–4.15 (m, 2 H), 4.49 (s, 1 H), 6.26 (br, 2 H), 6.60 (d, *J* = 8.8 Hz, 2 H), 7.02 (d, *J* = 8.8 Hz, 2 H), 9.24 (s, 1 H); ^{13}C NMR (100 MHz, $[D_6]$DMSO, 25 °C): 12.4, 14.1, 14.8, 43.6, 58.2, 60.4, 111.3, 121.5, 129.6, 146.5, 146.7, 157.3, 171.1; IR (nujol): ν_{max} = 3496, 3369, 3256, 1731, 1689 cm^{-1}; MS (ESI) m/z = 335 [M + H]+; anal. calcd. for $C_{17}H_{26}N_4O_3$ (334,41): C 61.06, H 7.84, N 16.75; found: C 61.22, H 7.76, N 16.64.



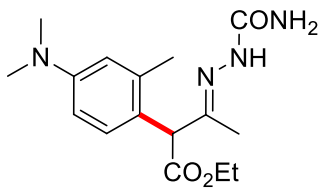
3c

Ethyl 3-(2-carbamoylhydrazono)-2-(4-(methyl(prop-2-yn-1-yl)amino)phenyl)butanoate: compound **3c** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 80:20) in 46% yield (76.1 mg); yellow oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.18 (t, *J* = 7.2 Hz, 3 H), 1.73 (s, 3 H), 2.86 (s, 3 H), 3.07 (t, *J* = 7.2 Hz, 1 H), 4.08-4.15 (m, 4 H), 4.55 (s, 1 H), 6.21 (br, 2 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 7.09 (d, *J* = 8.8 Hz, 2 H), 9.21 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): 14.1, 14.8, 38.1, 41.3, 58.1, 60.5, 74.4, 79.9, 113.7, 124.3, 129.3, 146.2, 148.1, 157.1, 170.8; IR (nujol): ν_{max} = 3467, 3384, 3195, 2110, 1732, 1689 cm^{-1}; MS (ESI) *m/z* = 353 [M + Na]$^+$, 331 [M + H]$^+$; anal. calcd. for $C_{17}H_{22}N_4O_3$ (330,38): C 61.80, H 6.71, N 16.96; found: C 61.97, H 6.61, N 16.85.



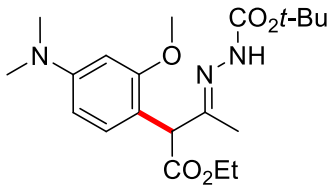
3d

Ethyl 3-(2-carbamoylhydrazono)-2-(4-(dimethylamino)naphthalen-1-yl)butanoate: compound **3d** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 80:20) in 95% yield (169.3 mg); white solid; mp: 143–145 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.18 (t, *J* = 7.2 Hz, 3 H), 1.75 (s, 3 H) , 2.81 (s, 6 H), 4.13–4.20 (m, 2 H), 5.38 (s, 1 H), 6.28 (br, 2 H), 7.10 (d, *J* = 8.0 Hz, 1 H), 7.21 (d, *J* = 8.0 Hz, 1 H), 7.51–7.55 (m, 2 H), 8.06-8.10 (m, 1 H), 8.19–8.22 (m, 1 H), 9.26 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): 14.0, 14.8, 44.8, 55.5, 60.7, 113.5, 123.9, 124.5, 125.0, 125.9, 126.2, 126.3, 128.4, 132.7, 145.4, 150.4, 157.1, 171.2; IR (nujol): ν_{max} = 3497, 3380, 3186, 1735, 1702 cm^{-1}; MS (ESI) *m/z* = 357 [M + H]$^+$; anal. calcd. for $C_{19}H_{24}N_4O_3$ (356,42): C 64.03, H 6.79, N 15.72; found: C 64.16, H 6.70, N 15.61.



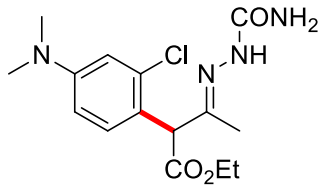
3e

Ethyl 3-(2-carbamoylhydrazono)-2-(4-(dimethylamino)-2-methylphenyl)butanoate: compound **3e** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 70:30) in 73% yield (117.0 mg); white solid; mp: 154–156 °C; ^{1}H NMR (400 MHz[D$_6$]DMSO, 25 °C): δ = 1.17 (t, *J* = 7.2 Hz, 3 H), 1.72 (s, 3 H), 2.19 (s, 3 H), 2.86 (s, 6 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 4.67 (s, 1 H), 6.17 (br, 2 H), 6.52–6.58 (m, 2 H), 6.88 (d, *J* = 9.2 Hz, 1 H), 9.19 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.1, 14.8, 19.7, 39.9, 55.3, 60.3, 110.1, 114.2, 121.5, 128.7, 137.1, 145.8, 149.5, 157.1, 171.2; IR (nujol): ν_{max} = 3416, 3398, 3327, 1735, 1691 cm^{-1}; MS (ESI) *m/z* = 321 [M + H]$^+$; anal. calcd. for $C_{16}H_{24}N_4O_3$ (320.39): C 59.98, H 7.55, N 17.49; found: C 59.82, H 7.46, N 17.37.



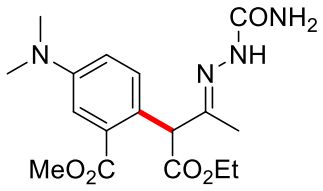
3f

***tert*-Butyl 2-(3-(4-(dimethylamino)-2-methoxyphenyl)-4-ethoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate:** compound **3f** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 35:65) in 86% yield (169.2 mg); white solid; mp: 102–104 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.16 (t, *J* = 7.2 Hz, 3 H), 1.44 (s, 9 H), 1.75 (s, 3 H) , 2.90 (s, 6 H), 3.75 (s, 3 H), 4.03–4.11 (m, 2 H), 4.61 (s, 1 H), 6.24–6.30 (m, 2 H), 6.84 (d, *J* = 8.4 Hz, 1 H), 9.48 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): 14.1, 15.2, 28.1, 40.1, 52.8, 55.3, 60.1, 79.0, 96.1, 104.4, 111.5, 129.6, 150.7, 151.2, 152.9, 157.5, 170.9; IR (nujol): ν_{max} = 3218, 1743, 1732 cm^{-1}; MS (ESI) *m/z* = 416 [M + Na]$^+$, 394 [M + H]$^+$; anal. calcd. for $C_{20}H_{31}N_3O_5$ (393,48): C 61.05, H 7.94, N 10.68; found: C 60.89, H 8.06, N 10.81.



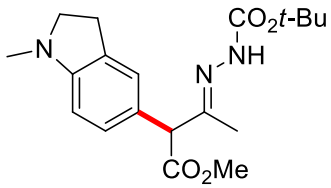
3g

Ethyl 3-(2-carbamoylhydrazono)-2-(2-chloro-4-(dimethylamino)phenyl)butanoate: compound **3g** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 80:20) in 51% yield (86.9 mg); white solid; mp: 150–152 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.17 (t, *J* = 7.2 Hz, 3 H), 1.78 (s, 3 H), 2.90 (s, 6 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.82 (s, 1 H), 6.08 (br, 2 H), 6.69 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1 H), 6.71 (d, *J* = 2.4 Hz, 1 H),7.01 (d, *J* = 8.4 Hz, 1 H), 9.31 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): 13.9, 15.5, 39.7, 55.3, 60.6, 111.1, 111.9, 119.7, 130.3, 134.1, 144.9, 150.5, 156.9, 170.1; IR (nujol): ν_{max} = 3445, 3420, 3190, 1738, 1704 cm^{-1}; MS (ESI) *m/z* = 341 [M + H]$^+$; anal. calcd. for $C_{15}H_{21}ClN_4O_3$ (340.81): C 52.86, H 6.21, N 16.44; found: C 52.99, H 6.27, N 16.32.



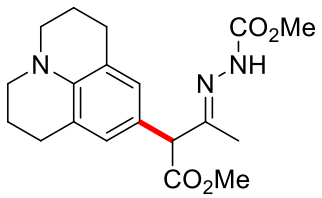
3h

Methyl 2-(3-(2-carbamoylhydrazono)-1-ethoxy-1-oxobutan-2-yl)-5-(dimethylamino)benzoate: compound **3h** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 25% yield (45.6 mg); white oil; ^{1}H NMR (400 MHz[D$_6$]DMSO, 25 °C): δ = 1.17 (t, *J* = 7.2 Hz, 3 H), 1.74 (s, 3 H), 2.76 (s, 6 H), 3.80 (s, 3 H), 4.07–4.16 (m, 2 H), 4.62 (s 1 H), 6.19 (br, 2 H), 6.95 (d, *J* = 8.4 Hz, 1 H), 7.26 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz,1 H), 7.41 (d, *J* = 2.4 Hz, 1 H), 9.24 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 13.9, 14.9, 42.8, 51.9, 57.7, 60.6, 116.4, 119.8, 124.8, 131.2, 132.5, 145.7, 150.6, 157.1, 168.3, 170.5; IR (nujol): ν_{max} = 3467, 3362, 3327, 1743, 1738, 1708 cm^{-1}; MS (ESI) *m/z* = 365 [M + H]$^+$; anal. calcd. for $C_{17}H_{24}N_4O_5$ (364.39): C 56.03, H 6.64, N 15.38; found: C 56.18, H 6.48, N 15.26.



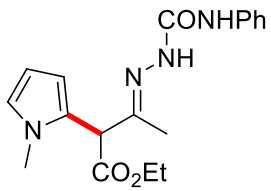
3j

***tert*-Butyl 2-(4-methoxy-3-(1-methylindolin-5-yl)-4-oxobutan-2-ylidene)hydrazinecarboxylate:** compound **3j** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 70:30) in 73% yield (131.9 mg); white solid; mp: 141–143 °C; ^{1}H NMR (400 MHz[D$_6$]DMSO, 25 °C): δ = 1.44 (s, 9 H), 1.72 (s, 3 H), 2.67 (s, 3 H), 2.84 (t, *J* = 8.0 Hz, 2 H), 3.23 (t, *J* = 8.0 Hz, 2 H), 3.61 (s, 3 H), 4.48 (s 1 H), 6.44 (d, *J* = 8.0 Hz, 1 H), 6.86 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1 H), 6.90 (d, *J* = 1.6 Hz, 1 H), 9.53 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 15.1, 28.0, 28.1, 35.7, 51.7, 55.6, 58.6, 79.1, 106.6, 124.1, 124.5, 127.8, 130.2, 150.9, 152.8, 152.9, 171.3; IR (nujol): ν_{max} = 3425, 1734, 1708 cm^{-1}; MS (ESI) *m/z* = 362 [M + H]$^+$; anal. calcd. for $C_{19}H_{27}N_3O_4$ (361.44): C 63.14, H 7.53, N 11.63; found: C 62.96, H 7.64, N 11.71.



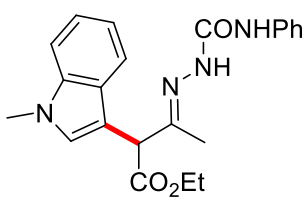
3k

Methyl 2-(3-(1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinolin-9-yl)-4-methoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate: compound **3k** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 50:50) in 63% yield (113.3 mg); pale yellow oil; ^{1}H NMR (400 MHz[D$_6$]DMSO, 25 °C): δ = 1.75 (s, 3 H), 1.84 (qui, *J* = 6.4 Hz, 4 H), 2.63 (t, *J* = 6.4 Hz, 4 H), 3.07 (t, *J* = 6.4 Hz, 4 H), 3.61 (s, 3 H), 3.65 (s, 3 H), 4.38 (s 1 H), 6.55 (s, 2 H), 9.83 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.8, 21.4, 27.1, 49.2, 51.7, 58.3, 59.7, 120.8, 121.6, 126.8, 142.0, 151.6, 154.5, 171.3; IR (nujol): ν_{max} = 3378, 1741, 1697 cm^{-1}; MS (ESI) *m/z* = 360 [M + H]$^+$; anal. calcd. for $C_{19}H_{25}N_3O_4$ (359.42): C 63.49, H 7.01, N 11.69; found: C 63.66, H 6.95, N 11.57.



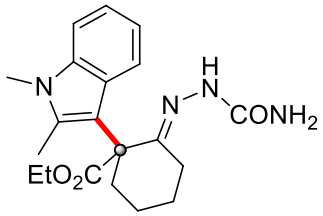
3l

Ethyl 2-(1-methyl-1*H*-pyrrol-2-yl)-3-(2-(phenylcarbamoyl)hydrazono)butanoate: compound **3l** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 90:10) in 49% yield (83.9 mg); white solid; mp: 134–136 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.21 (t, *J* = 7.2 Hz, 3 H), 1.86 (s, 3 H), 3.50 (s, 3 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 4.93 (s, 1 H), 5.89–5.93 (m, 1 H), 5.96–5.99 (m, 1 H), 6.71–6.74 (m, 1 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 7.29 (t, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 8.60 (s, 1 H), 9.76 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): 13.9, 14.5, 33.5, 51.7, 60.9, 106.5, 107.7, 118.9, 122.3, 122.9, 125.9, 128.6, 138.8, 145.9, 153.2, 169.9; IR (nujol): ν_{max} = 3460, 3386, 1738, 1689 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{23}N_4O_3$ [M + H]$^+$: 343.1770; found: 343.1791.



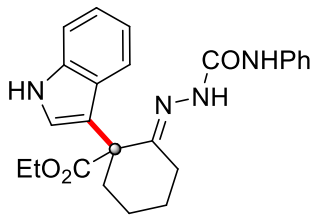
3m

Ethyl 2-(1-methyl-1*H*-indol-3-yl)-3-(2-(phenylcarbamoyl)hydrazono)butanoate: compound **3m** was isolated by column chromatography on silica gel (ethyl acetate/ cyclohexane 30:70) in 49% yield (96.2 mg); white solid; mp: 151–153°C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.21 (t, *J* = 7.2 Hz, 3 H), 1.87 (s, 3 H), 3.78 (s, 3 H), 4.15–4.22 (m, 2 H), 5.07 (s, 1 H), 6.99 (t, *J* = 8.0 Hz, 1 H), 7.03 (t, *J* = 8.0 Hz, 1 H), 7.17 (t, *J* = 8.0 Hz, 1 H), 7.27 (t, *J* = 8.0 Hz, 2 H), 7.35 (s, 1 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 1 H), 8.59 (s, 1 H), 9.75 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): 14.1, 14.6, 32.4, 51.3, 60.8, 107.9, 109.9, 118.8, 119.1, 119.2, 121.4, 122.3, 126.9, 128.4, 128.6, 136.6, 138.9, 147.1, 153.4, 170.9; IR (nujol): ν_{max} = 3353, 3201, 1743, 1692 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{25}N_4O_3$ [M + H]$^+$: 393.1927; found: 393.1969.



3n

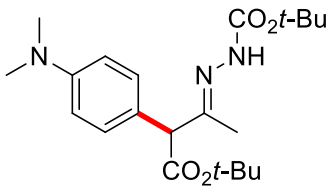
Ethyl 2-(2-carbamoylhydrazono)-1-(1,2-dimethyl-1*H*-indol-3-yl)cyclohexanecarboxylate: compound **3n** was isolated by column chromatography on silica gel (ethyl acetate/ cyclohexane 60:40) in 61% yield (113.0 mg); white solid; mp: 207–210 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.09 (t, *J* = 7.2 Hz, 3 H), 1.38–1.59 (m, 4 H), 2.14-2.23 (m, 2 H), 2.25 (s, 3 H), 2.67–2.91 (m, 2 H), 3.64 (s, 3 H), 3.94–4.13 (m, 2 H), 5.84 (br, 2 H), 6.91 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.04 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.37 (t, *J* = 9.2 Hz, 2 H), 9.57 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): 11.6, 13.9, 21.5, 24.8, 25.5, 29.3, 35.7, 56.9, 60.3, 108.1, 109.3, 118.6, 119.4, 119.8, 126.3, 135.0, 136.2, 152.6, 157.4, 173.2; IR (nujol): ν_{max} = 3510, 3393, 3182, 1734, 1687 cm^{-1}; MS (ESI) *m/z* = 371 [M + H]$^+$; anal. calcd. for $C_{20}H_{26}N_4O_3$ (370,45): C 64.84, H 7.07, N 15.12; found: C 64.69, H 6.99, N 14.99.



3o

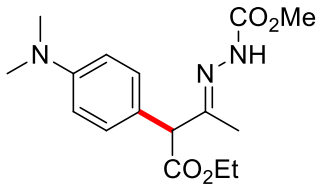
Ethyl 1-(1*H*-indol-3-yl)-2-(2-(phenylcarbamoyl)hydrazono)cyclohexanecarboxylate: compound **3o** was isolated by column chromatography on silica gel (ethyl acetate/ cyclohexane 50:50) in 86% yield (179.9 mg); white solid; mp: 193–195 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.12 (t, *J* = 7.2 Hz, 3 H), 1.40–1.59 (m, 2 H), 1.77–1.92 (m, 2 H), 2.10–2.22 (m, 2 H), 2.67–2.73 (m, 1 H), 3.03–3.08 (m, 1 H), 4.06–4.18 (m, 2 H), 6.46 (d, *J* = 8.0 Hz, 2 H), 6.84 (t, *J* = 7.2 Hz, 1 H), 6.92 (t, *J* = 7.2 Hz, 1 H), 7.06 (t, *J* = 7.6 Hz, 2 H), 7.12 (t, *J* = 7.6 Hz, 1 H), 7.24 (d, *J* = 2.4 Hz, 1 H), 7.34 (s, 1 H), 7.47 (d, *J* = 8.0 Hz, 1 H),

7.49 (d, *J* = 8.0 Hz, 1 H), 10.02 (s, 1 H), 11.12 (d, *J* = 2.4 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): 14.1, 22.7, 25.4, 25.6, 35.6, 55.6, 60.7, 111.7, 114.4, 117.5, 118.7, 120.7, 120.9, 121.9, 123.1, 126.3, 128.3, 136.7, 138.1, 151.0, 153.4, 172.6; IR (nujol): ν_{max} = 3301, 3207, 3070, 1737, 1660 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{27}N_4O_3$ [M + H]$^+$: 419.2083; found: 419.2082.



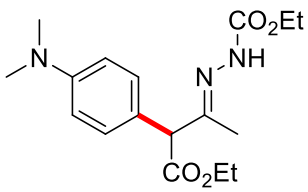
3p

***tert*-Butyl 2-(4-(tert-butoxy)-3-(4-(dimethylamino)phenyl)-4-oxobutan-2-ylidene)hydrazinecarboxylate:** compound **3p** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 74% yield (144.9 mg); white solid; mp: 112–114°C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.41 (s, 9 H), 1.44 (s, 9 H), 1.69 (s, 3 H), 2.87 (s, 6 H), 4.34 (s, 1 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 7.02 (d, *J* = 8.8 Hz, 2 H), 9.45 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.8, 27.7, 28.1, 40.1, 59.2, 79.1, 80.5, 112.2, 123.1, 129.1, 149.5, 151.1, 152.9, 169.9; IR (nujol): ν_{max} = 3359, 1728, 1721 cm^{-1}; MS (ESI) *m/z* = 392 [M + H]$^+$; anal. calcd. for $C_{21}H_{33}N_3O_4$ (391,50): C 64.42, H 8.50, N 10.73; found: C 64.29, H 8.61, N 10.84.



3q

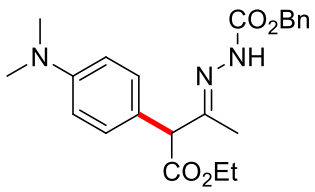
Methyl 2-(3-(4-(dimethylamino)phenyl)-4-ethoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate: compound **3q** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 63% yield (101.2 mg); white solid; mp: 162–164 °C; ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 1.24 (t, *J* = 7.2 Hz, 3 H), 1.78 (s, 3 H), 2.92 (s, 6 H), 3.80 (s, 3 H), 4.16–4.21 (m, 2 H), 4.71 (s, 1 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 7.11 (d, *J* = 8.8 Hz, 2 H), 7.81 (br, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 13.1, 14.1, 40.6, 52.9, 58.6, 61.0, 112.9, 129.1, 129.9, 149.5, 150.9, 154.4, 171.1; IR (nujol): ν_{max} = 3213, 1738, 1732 cm^{-1}; MS (ESI) *m/z* = 322 [M + H]$^+$; anal. calcd. for $C_{16}H_{23}N_3O_4$ (321.37): C 59.80, H 7.21, N 13.08; found: C 59.66, H 7.30, N 13.20.



3r

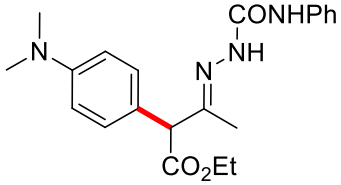
Ethyl 2-(3-(4-(dimethylamino)phenyl)-4-ethoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate: compound **3r** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 80% yield (134.1 mg); white solid; mp: 122–124 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.19 (t, *J* = 7.2 Hz, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 1.74 (s, 3 H), 2.88 (s, 6 H), 4.07–4.16 (m, 4 H), 4.49 (s, 1 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 7.05 (d, *J* = 8.8 Hz, 2 H), 9.74 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 13.9, 14.4, 14.7, 39.9, 58.2, 60.2, 60.3, 112.2, 122.6, 129.2, 149.6, 151.4, 153.9, 170.5; IR (nujol): ν_{max} = 3225, 1732, 1727 cm^{-1}; MS (ESI) *m/z* = 358 [M + Na]$^+$,

336 $[M + H]^+$; anal. calcd. for $C_{17}H_{25}N_3O_4$ (335,40): C 60.88, H 7.51, N 12.53; found: C 61.03, H 7.43, N 12.44.



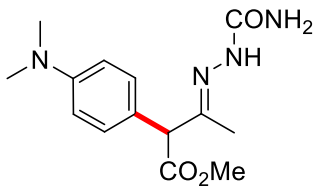
3s

Benzyl 2-(3-(4-(dimethylamino)phenyl)-4-ethoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate: compound **3s** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 71% yield (141.1 mg); white solid; mp: 127–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.24 (t, *J* = 7.2 Hz, 3 H), 1.77 (s, 3 H), 2.93 (s, 6 H), 4.14–4.23 (m, 2 H), 4.75 (s, 1 H), 5.23 (s, 2 H), 6.68 (d, *J* = 8.4 Hz, 2 H), 7.12 (d, *J* = 8.4 Hz, 2 H), 7.32–7.40 (m, 5 H), 7.74 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.1, 14.1, 40.5, 58.6, 61.0, 67.4, 112.6, 128.2, 128.3, 128.4, 128.5, 129.1, 135.7, 149.8, 151.3, 153.6, 171.3; IR (nujol): ν_{max} = 3221, 1721, 1718 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{28}N_3O_4$ $[M + H]^+$: 398.2080; found: 398.2063.



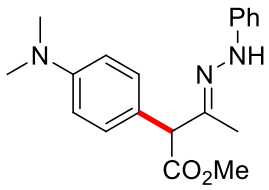
3t

Ethyl 2-(4-(dimethylamino)phenyl)-3-(2-(phenylcarbamoyl)hydrazono)butanoate: compound **3t** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 20:80) in 49% yield (93.7 mg); white solid; mp: 122–124 °C; ^{1}H NMR (400 MHz, $[D_6]$DMSO, 25 °C): δ = 1.20 (t, *J* = 7.2 Hz, 3 H), 1.83 (s, 3 H), 2.89 (s, 6 H), 4.10–4.22 (m, 2 H), 4.69 (s, 1 H), 6.72 (d, *J* = 8.4 Hz, 2 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 7.11 (d, *J* = 8.4 Hz, 2 H), 7.28 (t, *J* = 7.6 Hz, 2 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 8.48 (s, 1 H), 9.73 (s, 1 H); ^{13}C NMR (100 MHz, $[D_6]$DMSO, 25 °C): δ = 14.0, 14.9, 40.0, 58.1, 60.5, 112.2, 118.6, 122.3, 122.7, 128.6, 129.3, 138.8, 147.7, 149.6, 153.3, 170.9; IR (nujol): ν_{max} = 3311, 3190, 1732, 1698 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{27}N_4O_3$ $[M + H]^+$: 383.2083; found: 383.2047.



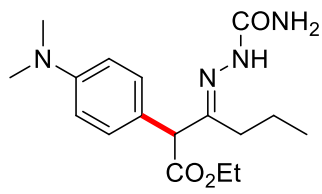
3u

Methyl 3-(2-carbamoylhydrazono)-2-(4-(dimethylamino)phenyl)butanoate: compound **3u** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 10:0) in 48% yield (70.2 mg); white solid; mp: 164–166 °C; ^{1}H NMR (400 MHz, $[D_6]$DMSO, 25 °C): δ = 1.72 (s, 3 H), 2.87 (s, 6 H), 3.64 (s, 3 H), 4.56 (s, 1 H), 6.19 (br, 2 H) 6.68 (d, *J* = 8.8 Hz, 2 H), 7.05 (d, *J* = 8.8 Hz, 2 H), 9.21 (s, 1 H); ^{13}C NMR (100 MHz, $[D_6]$DMSO, 25 °C): 14.7, 40.1, 51.8, 58.1, 112.2, 122.7, 129.3, 146.2, 149.7, 157.2, 171.4; IR (nujol): ν_{max} = 3493, 3372, 3182, 1731, 1693 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{21}N_4O_3$ $[M + H]^+$: 293.1614; found: 293.1622.



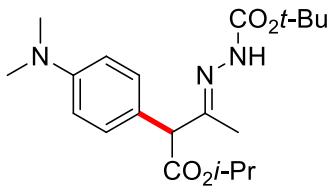
3v

Methyl 2-(4-(dimethylamino)phenyl)-3-(2-phenylhydrazono)butanoate: compound **3v** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 10:90) in 44% yield (71.6 mg); white solid; mp: 104–106 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.78 (s, 3 H), 2.87 (s, 6 H), 3.65 (s, 3 H), 4.55 (s, 1 H), 6.69 (d, *J* = 8.4 Hz, 3 H), 7.03 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 7.16 (t, *J* = 8.4 Hz, 2 H), 8.88 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.6, 40.1, 51.6, 58.3, 112.2, 112.4, 118.4, 123.4, 128.7, 129.5, 143.2, 146.2, 149.6, 171.6; IR (nujol): ν_{max} = 3332, 1738 cm^{-1}; MS (ESI) *m/z* = 326 [M + H]$^+$; anal. calcd. for $C_{19}H_{23}N_3O_2$ (325,40): C 70.13, H 7.12, N 12.91; found: C 70.39, H 7.05, N 12.79.



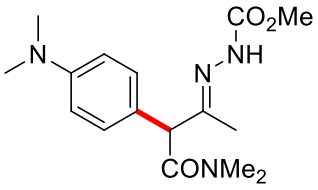
3w

Ethyl 3-(2-carbamoylhydrazono)-2-(4-(dimethylamino)phenyl)hexanoate: compound **3w** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 80:20) in 45% yield (75.2 mg); white solid; mp: 129–131 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.79 (t, *J* = 7.2 Hz, 3 H), 1.16 (t, *J* = 7.2 Hz, 3 H), 1.23–1.30 (m, 2 H), 1.94–2.01 (m, 1 H), 2.26–2.35 (m, 1 H), 2.87 (s, 6 H), 4.02–4.13 (m, 2 H), 4.51 (s, 1 H), 6.12 (br, 2 H) 6.67 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 9.39 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): 13.7, 14.1, 18.1, 30.1, 40.1, 56.6, 60.3, 112.1, 122.8, 129.7, 146.2, 149.7, 157.2, 170.9; IR (nujol): ν_{max} = 3463, 3356, 3190, 1736, 1692 cm^{-1}; MS (ESI) *m/z* = 357 [M + Na]$^+$, 335 [M + H]$^+$; anal. calcd. for $C_{17}H_{26}N_4O_3$ (334,41): C 61.06, H 7.84, N 16.75; found: C 61.24, H 7.74, N 16.66.



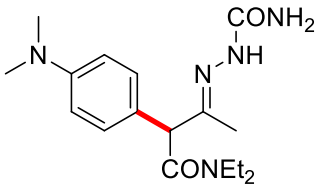
3x

***tert*-Butyl 2-(3-(4-(dimethylamino)phenyl)-4-isopropoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate:** compound **3q** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 56% yield (105.7 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.21 (d, *J* = 6.4 Hz, 3 H), 1.23 (d, *J* = 6.4 Hz, 3 H), 1.49 (s, 9 H), 1.75 (s, 3 H), 2.92 (s, 6 H), 4.69 (s, 1 H), 5.06 (sept, *J* = 6.4 Hz, 1 H), 6.67 (d, *J* = 8.8 Hz, 2 H), 7.11 (d, *J* = 8.8 Hz, 2 H), 7.49 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 15.1, 21.6, 28.2, 40.3, 58.5, 67.9, 79.3, 112.3, 122.9, 129.4, 149.7, 151.0, 153.2, 170.4; IR (nujol): ν_{max} = 3361, 1735, 1728 cm^{-1}; MS (ESI) *m/z* = 378 [M + H]$^+$; anal. calcd. for $C_{20}H_{31}N_3O_4$ (377,48): C 63.64, H 8.28, N 11.13; found: C 63.51, H 8.35, N 11.25.



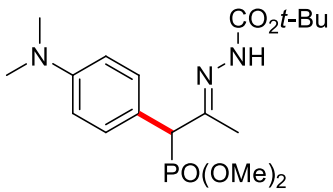
3y

Methyl 2-(4-(dimethylamino)-3-(4-(dimethylamino)phenyl)-4-oxobutan-2-ylidene)hydrazinecarboxylate: compound **3y** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 10:90) in 88% yield (140.9 mg); white solid; mp: 145–147 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.68 (s, 3 H), 2.79 (s, 3 H), 2.84 (s, 3 H), 2.88 (s, 6 H), 3.65 (s, 3 H), 4.73 (s, 1H), 6.69 (d, *J* = 8.8 Hz, 2 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 9.74 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 15.2, 34.9, 36.8, 51.6, 56.1, 112.4, 123.1, 128.9, 149.4, 154.0, 154.6, 170.4; IR (nujol): ν_{max} = 3211, 1723, 1720 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{25}N_4O_3$ [M + H]$^+$: 321.1927; found: 321.1936.



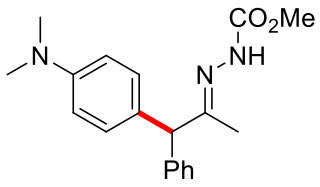
3z

2-(4-(Diethylamino)-3-(4-(dimethylamino)phenyl)-4-oxobutan-2-ylidene)hydrazinecarboxamide: compound **3z** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 98:2) in 44% yield (73.4 mg); yellow oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.94–1.03 (m, 6 H), 1.69 (s, 3 H), 2.86 (s, 6 H), 3.10–3.22 (m, 4 H), 4.67 (s, 1 H), 6.18 (br, 2 H) 6.68 (d, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 9.06 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): 12.8, 15.3, 40.1, 41.5, 55.7, 112.3, 123.9, 129.2, 148.6, 149.5, 157.4, 169.7; IR (nujol): ν_{max} = 3463, 3223, 3191, 1721, 1695 cm^{-1}; MS (ESI) *m/z* = 334 [M + H]$^+$; anal. calcd. for $C_{17}H_{27}N_5O_2$ (333,43): C 61.24, H 8.16, N 21.00; found: C 61.36, H 8.26, N 20.87.



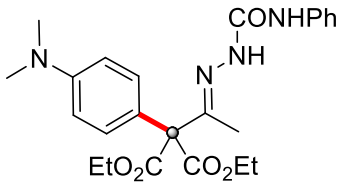
3aa

***tert*-Butyl 2-(1-(dimethoxyphosphoryl)-1-(4-(dimethylamino)phenyl)propan-2-ylidene)hydrazinecarboxylate:** compound **3aa** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 90:10) in 53% yield (105.8 mg); white solid; mp: 154–157 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.46 (s, 9 H), 1.78 (s, 3 H), 2.87 (s, 6 H), 3.60 (d, $^{3}J_{HP}$ = 10.4 Hz, 3 H), 3.61 (d, $^{3}J_{HP}$ = 10.4 Hz, 3 H), 4.14 (d, $^{2}J_{HP}$ = 23.6 Hz, 1 H), 6.67 (d, *J* = 8.8 Hz, 2 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 9.53 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 16.3, 28.6, 40.5, 52.1 ($^{1}J_{CP}$ = 137.0 Hz), 53.1 ($^{2}J_{CP}$ = 6.7 Hz), 53.4 ($^{2}J_{CP}$ = 6.7 Hz), 79.7, 112.3, 121.3 ($^{2}J_{CP}$ = 6.7 Hz), 130.5, 130.6, 150.1, 153.5; IR (nujol): ν_{max} = 3164, 1738, cm^{-1}; MS (ESI) *m/z* = 422 [M + Na]$^+$, 400 [M + H]$^+$; anal. calcd. for $C_{18}H_{30}N_3O_5P$ (399,42): C 54.13, H 7.57, N 10.52; found: C 54.28, H 7.47, N 10.43.



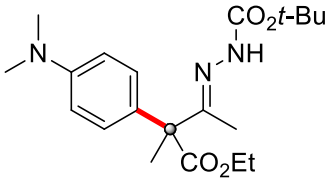
3ab

Methyl 2-(1-(4-(dimethylamino)phenyl)-1-phenylpropan-2-ylidene)hydrazinecarboxylate: Compound **3ab** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 40:60) in 77% yield (125.3 mg); white solid; mp: 133–135 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.79 (s, 3 H), 2.86 (s, 6 H), 3.64 (s, 3 H), 4.91 (s, 1 H), 6.67 (d, *J* = 8.8 Hz, 2 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 7.15 (d, *J* = 7.2 Hz, 2 H), 7.21 (t, *J* = 7.2 Hz 1 H), 7.29 (t, *J* = 7.2 Hz, 2 H), 9.76 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 15.9, 40.2, 51.6, 57.8, 112.4, 126.2, 128.0, 128.1, 128.6, 129.2, 129.3, 141.6, 149.1, 154.5; IR (nujol): ν_{max} = 3212, 1688 cm^{-1}; MS (ESI) *m/z* = 326 [M + H]$^+$; anal. calcd. for $C_{19}H_{23}N_3O_2$ (325,40): C 70.13, H 7.12, N 12.91; found: C 69.96, H 7.22, N 13.03.



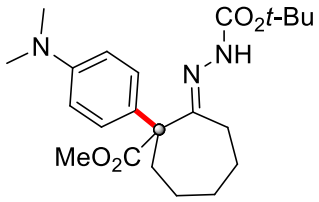
3ac

Diethyl 2-(4-(dimethylamino)phenyl)-2-(1-(2-(phenylcarbamoyl)hydrazono)ethyl)malonate: compound **3ac** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 20:80) in 81% yield (184.1 mg); white solid; mp: 123–125 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.23 (t, *J* = 7.2 Hz, 6 H), 1.77 (s, 3 H), 2.91 (s, 6 H), 4.28 (q, *J* = 7.2 Hz, 4 H), 6.72 (d, *J* = 9.2 Hz, 2 H), 7.02 (t, *J* = 7.6 Hz, 1 H), 7.12 (d, *J* = 9.2 Hz, 2 H), 7.31 (t, *J* = 7.2 Hz, 2 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 8.09 (s, 1 H), 9.90 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 13.8, 16.3, 39.8, 61.5, 70.7, 111.6, 118.3, 121.5, 122.5, 128.9, 129.4, 138.4, 147.9, 149.6, 152.8, 168.3; IR (nujol): ν_{max} = 3345, 3332, 1738, 1732, 1697 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{31}N_4O_5$ [M + H]$^+$: 455.2294; found: 455.2265.



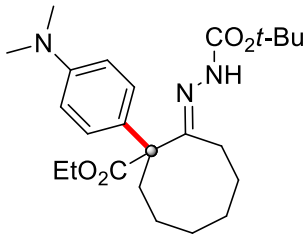
3ad

***tert*-Butyl 2-(3-(4-(dimethylamino)phenyl)-4-ethoxy-3-methyl-4-oxobutan-2-ylidene)hydrazinecarboxylate:** compound **3ad** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 20:80) in 64% yield (120.8 mg); pale yellow oil; ^{1}H NMR (400 MHz, DMSO, 25 °C): δ = 1.18 (t, *J* = 7.2 Hz, 3 H), 1.45 (s, 9 H), 1.59 (s, 3 H), 1.65 (s, 3 H), 2.87 (s, 6 H), 4.07–4.16 (m, 2 H), 6.66 (d, *J* = 8.8 Hz, 2 H), 6.99 (d, *J* = 8.8 Hz, 2 H), 9.43 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 13.9, 15.1, 23.2, 28.1, 40.1, 58.0, 60.5, 79.0, 111.9, 127.8, 128.4, 149.1, 152.9, 153.4, 173.2; IR (nujol): ν_{max} = 3223, 1738, 1711 cm^{-1}; MS (ESI) *m/z* = 400 [M + Na]$^+$, 378 [M + H]$^+$; anal. calcd. for $C_{20}H_{31}N_3O_4$ (377.48): C 63.64, H 8.28, N 11.13; found: C 63.79, H 8.19, N 11.02.



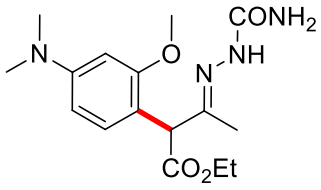
3ae

***tert*-Butyl 2-(2-(4-(dimethylamino)phenyl)-2-(methoxycarbonyl)cycloheptylidene)hydrazinecarboxylate:** compound **3ae** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 25:75) in 86% yield (173.5 mg); white solid; mp: 168–171 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.15–1.38 (m, 2 H), 1.46 (s, 9 H), 1.51–1.78 (m, 6 H), 2.68–2.73 (m, 1 H), 2.86 (s, 6 H), 2.87–2.91 (m, 1 H), 3.48 (s, 3 H), 6.64 (d, *J* = 8.8 Hz, 2 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 9.74 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 24.1, 24.9, 27.5, 28.1, 30.3, 36.6, 40.1, 51.5, 61.1, 79.1, 112.0, 127.9, 129.9, 148.9, 152.8, 155.6, 174.4; IR (nujol): ν_{max} = 3241, 1732, 1696 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{34}N_3O_4$ [M + H]$^+$: 404.2549; found: 404.2509.



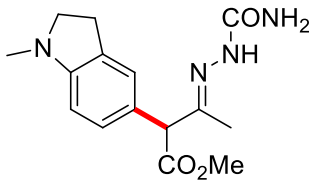
3af

***tert*-Butyl 2-(2-(4-(dimethylamino)phenyl)-2-(ethoxycarbonyl)cyclooctylidene)hydrazinecarboxylate:** compound **3af** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 20:80) in 70% yield (151.1 mg); white solid; mp: 181–183 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.10 (d, *J* = 7.2 Hz, 3 H), 1.33–1.94 (m, 9 H), 1.45 (s, 9 H), , 2.11–2.19 (m, 1 H), 2.31–2.38 (m, 1 H), 2.58–2.65 (m, 1 H), 2.86 (s, 6 H), 3.86–4.06 (m, 2 H), 6.64 (d, *J* = 8.8 Hz, 2 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 9.45 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 13.9, 23.1, 23.3, 24.5, 26.2, 26.9, 28.1, 30.6, 40.1, 59.9, 61.0, 79.1, 111.6, 127.6, 128.9, 148.9, 152.8, 155.7, 172.8; IR (nujol): ν_{max} = 3257, 1732, 1697 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{38}N_3O_4$ [M + H]$^+$: 432.2862; found: 432.2849.



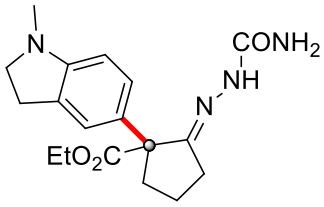
3ag

Ethyl 3-(2-carbamoylhydrazono)-2-(4-(dimethylamino)-2-methoxyphenyl)butanoate: compound **3ag** was isolated by column chromatography on silica gel (ethyl acetate) in 65% yield (109.3 mg); white solid; mp: 157–160 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.15 (t, *J* = 7.2 Hz, 3 H), 1.75 (s, 3 H) , 2.89 (s, 6 H), 3.74 (s, 3 H), 4.07 (q, *J* = 7.2 Hz, 2 H), 4.65 (s, 1 H), 6.15 (br, 2 H), 6.26 (d, *J* = 2.4 Hz, 1 H), 6.28 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz,1 H), 6.83 (d, *J* = 8.4 Hz, 1 H), 9.20 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): 14.1, 15.1, 40.2, 52.7, 55.3, 60.2, 96.0, 104.4, 111.6, 129.6, 146.2, 151.2, 157.1, 157.5, 171.1; IR (nujol): ν_{max} = 3445, 3421, 3190, 1738, 1704 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{25}N_4O_4$ [M + H]$^+$: 337.1876; found: 337.1867.



3ah

Ethyl 3-(2-carbamoylhydrazono)-2-(1-methylindolin-5-yl)butanoate: compound **3ah** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 80:20) in 71% yield (113.1 mg); pale yellow oil; ^{1}H NMR (400 MHz[D_6]DMSO, 25 °C): δ = 1.17 (t, *J* = 7.2 Hz, 3 H), 1.72 (s, 3 H), 2.67 (s, 3 H), 2.84 (t, *J* = 8.0 Hz, 2 H), 3.23 (t, *J* = 8.0 Hz, 2 H), 4.05–4.14 (m, 2 H), 4.50 (s 1 H), 6.19 (br, 2 H), 6.44 (d, *J* = 8.0 Hz, 1 H), 6.88 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz,1 H), 6.92 (d, *J* = 1.6 Hz, 1 H), 9.19 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 14.1, 14.7, 28.0, 35.7, 55.6, 58.5, 60.4, 106.6, 124.2, 124.5, 127.7, 130.2, 146.5, 152.7, 157.2, 170.9; IR (nujol): ν_{max} = 3386, 3329, 3254, 1738, 1696 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{23}N_4O_3$ [M + H]$^+$: 319.1770; found: 319.1728.



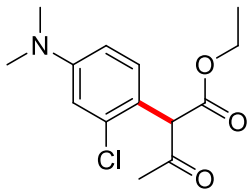
3ai

Ethyl 2-(2-carbamoylhydrazono)-1-(1-methylindolin-5-yl)cyclopentanecarboxylate: compound **3ai** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 100:0) in 81% yield (139.5 mg); white solid; mp: 123–125 °C; ^{1}H NMR (400 MHz[D_6]DMSO, 25 °C): δ = 1.11 (t, *J* = 7.2 Hz, 3 H), 1.49–1.58 (m, 1 H), 1.68–1.78 (m, 1 H), 2.19–2.25 (m, 1 H), 2.37 (t, *J* = 7.6 Hz, 2 H), 2.42–2.47 (m, 1 H), 2.67 (s, 3 H), 2.84 (t, *J* = 8.0 Hz, 2 H), 3.22 (t, *J* = 8.0 Hz, 2 H), 4.07 (q, *J* = 7.2 Hz, 2 H), 6.03 (br, 2 H), 6.42 (d, *J* = 8.0 Hz, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 6.95 (s, 1 H), 9.16 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 14.0, 20.8, 27.8, 28.1, 35.8, 36.9, 55.6, 60.5, 61.4, 106.2, 123.2, 126.3, 128.4, 129.6, 152.1, 156.6, 156.9, 172.7; IR (nujol): ν_{max} = 3362, 3348, 3298, 1739, 1698 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{25}N_4O_3$ [M + H]$^+$: 345.1927; found: 345.1933.

Gram scale synthesis of product 3a

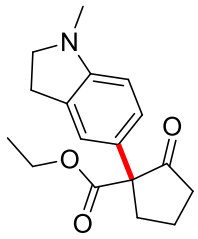
To show the utility of this catalytic Michael-type reaction, preparative-scale synthesis of product **5a** was carried out under the optimal reaction conditions. As displayed in **Scheme 7** of the thesis, there were no changes in the reactivity, yield and regioselectivity, suggesting that this process should have the potential for large-scale chemical production.

Procedure of hydrolysis of hydrazones 3g and 3ai **(see Scheme 3):** hydrazone **3** (0.2 mmol) was refluxed in 5 mL of acetone/water (9:1 mixture) in the presence of Amberlyst-15H (100 mg) for 2 h (TLC check). The reaction mixture was filtered off and the solution was concentrated under reduced pressure and then extracted with ethyl acetate. The organic phase was dried on anhydrous sodium sulphate and evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography eluting with cyclohexane/ethyl acetate mixtures to obtain ketone derivative. The products are purified by column chromatography on silica gel.



4a

Ethyl 2-(2-chloro-4-(dimethylamino)phenyl)-3-oxobutanoate: compound **4a** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 82% yield (46.6 mg); as a mixture of inseparable isomers (determined by ^{1}H NMR). White oil. The spectra shows the presence of both enol and ketone forms in a ratio of 52:48 (ketone:enol). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C) (*denotes enol form signals): δ = 1.09* (t, *J* = 6.8 Hz, 3 H), 1.18 (t, *J* = 6.8 Hz, 3 H), 1.74* (s, 3 H), 2.15 (s, 3 H), 2.91* (s, 6 H), 2.92 (s, 6 H), 4.06–4.21 (m, 4 H), 5.15 (s, 1 H), 6.64* (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz,1 H), 6.69 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz,1 H), 6.73* (d, *J* = 2.8 Hz, 1 H), 6.74 (d, *J* = 2.8 Hz, 1 H), 7.03* (d, *J* = 8.8 Hz, 1 H), 7.05 (d, *J* = 8.8 Hz, 1 H), 13.01* (s, 1 H).

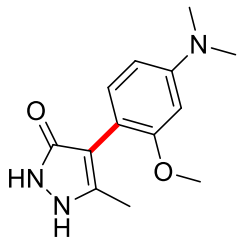


4b

Ethyl 1-(1-methylindolin-5-yl)-2-oxocyclopentanecarboxylate: compound **4b** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 20:80) in 61% yield (35.1 mg); white oil; ^{1}H NMR (400 MHz, DMSO, 25 °C): δ = 1.13 (t, *J* = 7.2 Hz, 3 H), 1.75–1.91 (m, 2 H), 2.27–2.41 (m, 2 H), 2.44–2.51 (m, 1 H), 2.57–2.64 (m, 1 H), 2.68 (s, 3 H), 2.84 (t, *J* = 8.0 Hz, 2 H), 3.23 (t, *J* = 8.0 Hz, 2 H), 4.07 (q, *J* = 7.2 Hz, 2 H), 6.44 (d, *J* = 8.0 Hz, 1 H), 6.95 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 7.01 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO, 25 °C): 14.4, 19.4, 28.6, 34.6, 36.2, 37.4, 56.1, 61.5, 64.5, 106.8, 123.7, 124.9, 126.8, 130.4, 153.1, 171.4, 212.5; IR (nujol): ν_{max} = 1732, 1717 cm^{-1}; MS

(ESI) *m/z* = 288 $[M + H]^+$; anal. calcd. for $C_{17}H_{21}NO_3$ (287.35): C 71.06, H 7.37, N 4.87; found: C 70.94, H 7.43, N 4.98.

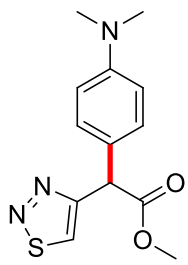
***Cyclization of 3ag to 1H-pyrazol-3(2H)-one 5*:** To a solution of **3ag** (0.07 mmol) in MeOH (2 mL), K_2CO_3 (0.07 mmol, 10.7 mg) was added. The solution was refluxed until the disappearance of the reagent **3ag** (4 h, monitored by TLC). The reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel to provide the product **5**.



5

4-(4-(Dimethylamino)-2-methoxyphenyl)-3-methyl-1*H*-pyrazol-5-ol: compound **5** was isolated by column chromatography on silica gel (methanol/ethyl acetate 05:95) in 94% yield (16.3 mg); white solid; mp: 195–197 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.98 (s, 3 H), 2.90 (s, 6 H), 3.72 (s, 3 H), 6.30 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, 1 H), 6.33 (d, J = 2.4 Hz, 1 H), 6.95 (d, J = 8.0 Hz, 1 H), 10.34 (br, 2 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): 11.1, 40.4, 54.9, 96.5, 100.1, 104.6, 109.6, 131.8, 137.4, 150.6, 157.4, 158.9; IR (nujol): ν_{max} = 3277, 3206, 1688 cm^{-1}; MS (ESI) *m/z* = 248 $[M + H]^+$; anal. calcd. for $C_{13}H_{17}N_3O_2$ (247.29): C 63.14, H 6.93, N 16.99; found: C 62.97, H 7.01, N 17.10.

Synthesis of 1,2,3-triazole 6 via Hurd-Mori type reaction: Thionyl chloride (0.22 mmol, 15.0 µL) was added dropwise to a stirred solution of **3a** (0.2 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was allowed to stand at room temperature until the disappearance of **3a** (2 h, monitored by TLC). At the end of the reaction, the crude was neutralized with a saturated solution of $NaHCO_3$ and then extracted with ethyl acetate. The organic phase was washed with H_2O, dried on anhydrous sodium sulphate and then evaporated under reduced pressure. Product **6** was purified by chromatography on silica gel column.

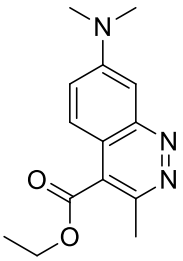


6

Methyl 2-(4-(dimethylamino)phenyl)-2-(1,2,3-thiadiazol-4-yl)acetate: compound **6** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 48% yield (26.7 mg); white solid; mp: 183–185 °C; ^{1}H NMR (400 MHz, DMSO, 25 °C): δ = 2.88 (s, 6 H), 3.67 (s, 3 H), 5.68 (s, 1 H), 6.70 (d, J = 8.8 Hz, 2 H), 7.22 (d, J = 8.8 Hz, 2 H), 8.92 (s, 1 H); ^{13}C NMR (100 MHz, DMSO, 25 °C): 40.1, 49.2, 52.2, 112.4, 124.1, 129.0, 135.7, 149.8, 161.1, 171.3; IR

(nujol): ν_{max} = 1736 cm^{-1}; MS (ESI) *m/z* = 278 $[M + H]^+$; anal. calcd. for $C_{13}H_{15}N_3O_2S$ (277.34): C 56.30, H 5.45, N 15.15; found: C 56.46, H 5.36, N 15.06.

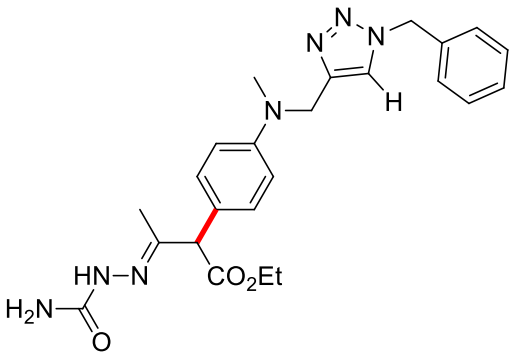
***Cyclization of 3f to cinnoline 7*:** To a solution of **3f** (0.1 mmol) in toluene (2 mL), $Cu(OAc)_2{\cdot}H_2O$ (30 mol%, 6.0 mg) was added. The solution was refluxed until the disappearance of the reagent **3f** (1.5 h, monitored by TLC). The reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel to give the product **7**.



7

Ethyl 7-(dimethylamino)-3-methylcinnoline-4-carboxylate: compound **7** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 40:60) in 31% yield (8.1 mg); orange oil; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.38 (t, *J* = 7.2 Hz, 3 H), 2.77 (s, 3 H), 3.18 (s, 6 H), 4.51 (q, *J* = 7.2 Hz, 2 H), 7.34 (d, *J* = 2.4 Hz, 1 H), 7.64 (dd, J_1 = 9.6 Hz, J_2 = 2.4 Hz, 1 H), 7.75 (d, *J* = 9.6 Hz, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 13.9, 19.8, 39.8, 62.1, 103.3, 113.9, 123.3, 123.8, 123.9, 145.2, 150.7, 150.8, 166.1; IR (nujol): ν_{max} = 1734 cm^{-1}; MS (ESI) *m/z* = 260 $[M + H]^+$; anal. calcd. for $C_{14}H_{17}N_3O_2$ (259,30): C 64.85, H 6.61, N 16.20; found: C 65.01, H 6.54, N 16.11.

***Synthesis of 1,2,3-triazole 8 via 'click' reaction*:** To a solution of **3c** (0.3 mmol, 116.8 mg) and benzyl azide (0.33 mmol, 51.6 mg) in CH_2Cl_2(1 mL)–H_2O (1 mL), $Cu(OAc)_2{\cdot}H_2O$ (0.165 mmol, 38.7 mg) and sodium ascorbate (0.045 mmol, 10.5 mg) were added. The reaction was allowed under magnetic stirring at room temperature until the disappearance of the hydrazone **3c** (3 h, monitored by TLC). After the adding of further amount of CH_2Cl_2 (2 mL), the crude was washed with aqueous saturated solution of NH_4Cl and then with H_2O and dried over anhydrous sodium sulphate. The organic phase was then filtered and concentrated under reduced pressure. The product **8** was purified by column chromatography on silica gel.

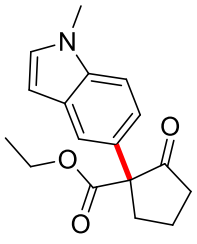


8

Ethyl 2-(4-(((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)(methyl)amino)phenyl)-3-(2-carbamoylhydrazono)butanoate : the compund **8** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 90:10) in 49% yield (68.2 mg); white solid; mp: 199–201 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.17 (t, *J* = 6.8 Hz, 3 H), 1.70 (s, 3 H), 3.35 (s, 3

H), 4.09 (q, *J* = 6.8 Hz, 2 H), 4.50 (s, 1 H), 4.54 (s, 2 H), 5.53 (s, 2 H), 6.21 (br, 2 H), 6.76 (d, *J* = 8.8 Hz, 2 H), 7.03 (d, *J* = 8.8 Hz, 2 H), 7.20–7.25 (m, 2 H), 7.28–7.36 (m, 3 H), 7.99 (s, 1 H), 9.18 (s, 1 H) ; ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): 14.5, 14.7, 38.2, 46.9, 52.6, 58.1, 60.4, 112.4, 122.9, 123.0, 127.7, 128.0, 128.7, 129.3, 136.1, 144.3, 146.3, 148.0, 157.2, 170.8; IR (nujol): ν_{max} = 3357, 3279, 3204, 1736, 1688 cm^{-1}; MS (ESI) *m/z* = 486 [M + Na]$^+$, 464 [M + H]$^+$; anal. calcd. for $C_{24}H_{29}N_7O_3$ (463.53): C 62.19, H 6.31, N 21.15; found: C 62.36, H 6.20, N 21.03.

***Procedure for Oxidation of 4b to 9**:* A mixture of compound **4b** (0.15 mmol), Pd/C (10%, 3 mg) and toluene (2 mL) was refluxed for 6 h (TLC check). After filtration of the solution, the solvent was removed under reduced pressure and the crude mixture was purified by column chromatography on silica gel to afford product **9**.[39]



9

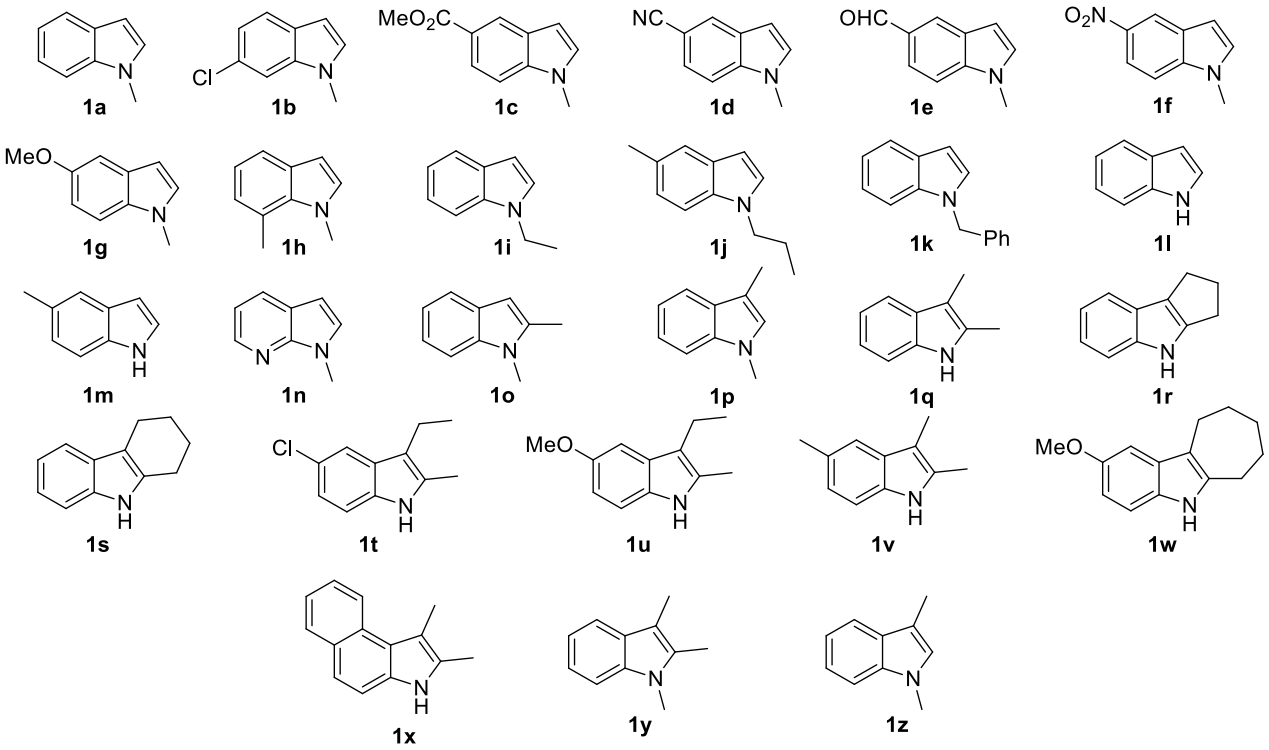
Ethyl 1-(1-methyl-1*H*-indol-5-yl)-2-oxocyclopentanecarboxylate: compound **9** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 10:90) in 74% yield (31.7 mg); white oil; ^{1}H NMR (400 MHz, DMSO, 25 °C): δ = 1.12 (t, *J* = 7.2 Hz, 3 H), 1.77–1.95 (m, 2 H), 2.31–2.46 (m, 2 H), 2.58–2.76 (m, 2 H), 3.77 (s, 3 H), 4.09 (q, *J* = 7.2 Hz, 2 H), 6.41 (d, *J*= 3.2 Hz, 1 H), 7.12 (dd, J_1 = 8.8 Hz, J_2 = 1.6 Hz, 1 H), 7.31 (d, *J* = 3.2 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 1 H), 7.49 (d, *J* = 1.6 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO, 25 °C): 13.9, 18.9, 32.4, 34.6, 37.1, 61.0, 64.6, 100.5, 109.5, 118.9, 120.7, 126.5, 127.7, 130.0, 135.5, 171.0, 212.1; IR (nujol): ν_{max} = 1734, 1716 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}NO_3$ [M + H]$^+$: 286.1443; found: 286.1421.

CHAPTER 5: Synthesis of Polycylic Fused Indoline Scaffolds through a Substrates-Guided Reactivity Switch.

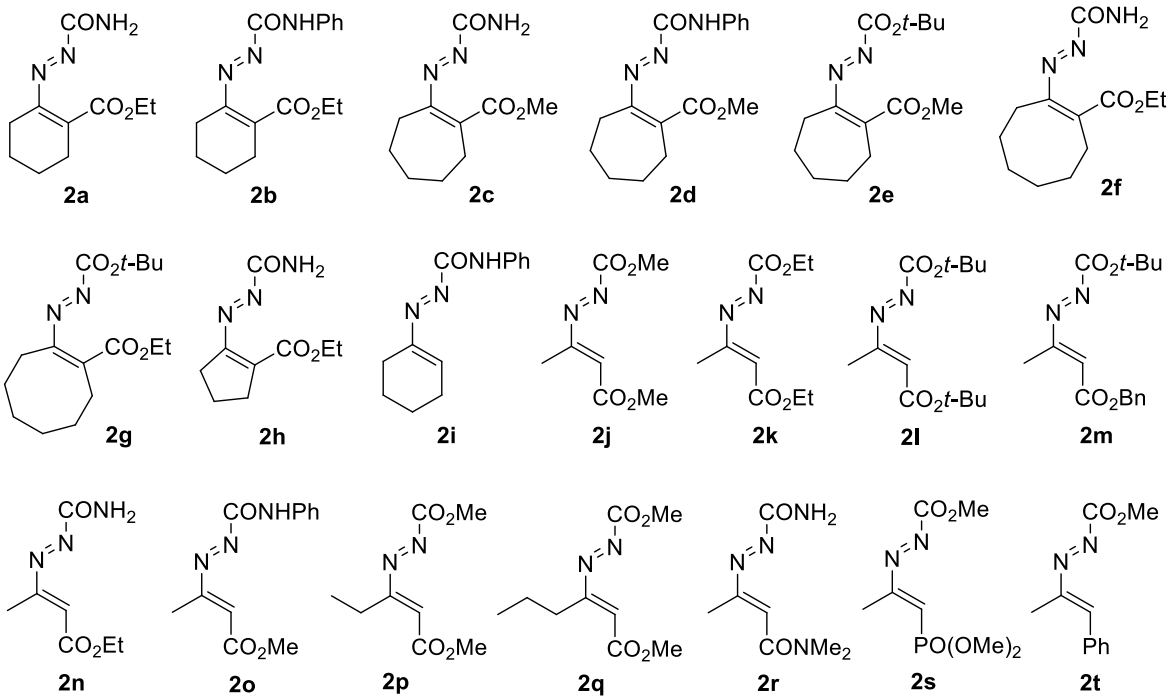
Experimental procedures.

Starting materials:

Indoles

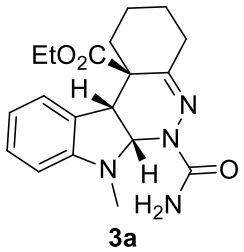


Azoalkenes



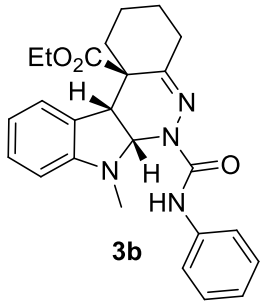
The following starting materials were either purchased and used as it is or they were synthesized using known literature procedures. Indoles **1a**,**l**,**m**,**o**,**q**,**r** are commercially available reagents, and used without further purification. *N*-Alkylindole derivatives **1b**–**k**,**n**,**p** were prepared from corresponding commercially available *N*H-indoles following literature procedures. 1,2-Diaza-1,3-dienes (DDs) **2a**–**t** were synthesized from the corresponding hydrazones following literature procedures.[143,144]

General procedure for the formal [4+2] cycloaddition reactions of indoles 1 with cyclic azoalkenes 2: A mixture of indole **1** (2.0 mmol), azoalkene **2** (1.0 mmol) and zinc dichloride (0.1 mmol, 13.6 mg) was stirred in dry dichloromethane (2 mL). After the disappearance of azoalkene 2 (TLC check), the crude mixture was purified by column chromatography on silica gel to afford product **3**.



3a

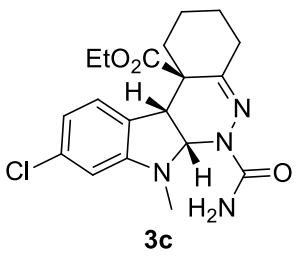
Ethyl 6-carbamoyl-7-methyl-2,3,4,6,6a,7,11b,11c-octahydro-1*H*-indolo[2,3-*c*]cinnoline-11c-carboxylate: the product **3a** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 50% yield (178.2 mg); white solid; mp: 183–185 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.95 (dt, J_1 = 12.0 Hz, J_2 = 4.4 Hz, 1 H), 1.26 (t, J = 7.2 Hz, 3 H), 1.24–1.35 (m, 2 H), 1.50–1.63 (m, 2 H), 1.78–1.84 (m, 1 H), 2.26 (dt, J_1 = 12.0 Hz, J_2 = 4.4 Hz, 1 H), 2.44–2.51 (m, 1 H), 2.58 (s, 3 H), 3.44 (d, J = 7.2 Hz, 1 H), 4.20–4.35 (m, 2 H), 5.50 (d, J = 7.2 Hz, 1 H), 6.62 (d, J = 7.6 Hz, 1 H), 6.79 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 6.80 (br, 2 H), 7.07 (d, J = 7.6 Hz, 1 H), 7.19 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.3, 23.7, 27.4, 33.1, 33.8, 35.5, 42.4, 45.6, 61.8, 69.4, 108.7, 118.9, 125.7, 126.5, 129.3, 151.7, 155.3, 157.3, 173.3; IR (nujol): ν_{max} = 3485, 3471, 1724, 1692 cm^{-1}; MS (ESI) *m/z* = 357 [M + H]$^+$; anal. calcd. for $C_{19}H_{24}N_4O_3$ (356.42): C 64.03, H 6.79, N 15.72; found: C 63.91, H 6.84, N 15.82.



3b

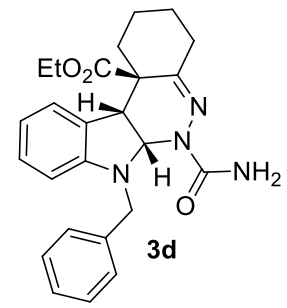
Ethyl 7-methyl-6-(phenylcarbamoyl)-2,3,4,6,6a,7,11b,11c-octahydro-1*H*-indolo[2,3-*c*]cinnoline-11c-carboxylate: the product **3b** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 56% yield (242.3 mg); white solid; mp: 183–185 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.02 (dt, J_1 = 12.8 Hz, J_2 = 4.4 Hz, 1 H), 1.27 (t, J = 7.2 Hz, 3 H), 1.30–1.41 (m, 2 H), 1.50–1.52 (m, 1 H), 1.62 (d, J = 13.2 Hz, 1 H), 1.82–1.84 (m, 1 H), 2.30 (dt, J_1 = 12.8 Hz, J_2 = 4.4 Hz, 1 H), 2.60 (s, 3 H), 2.68 (d, J = 13.2 Hz, 1 H), 3.52 (d, J = 7.2

Hz, 1 H), 4.19–4.34 (m, 2 H), 5.58 (d, J = 7.2 Hz, 1 H), 6.62 (d, J = 8.0 Hz, 1 H), 6.78 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 7.02–7.08 (m, 2 H), 7.18 (dt, J_1 = 7. 6 Hz, J_2 = 0.8 Hz, 1 H), 7.31 (t, J = 8.0 Hz, 2 H), 7.68 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2 H), 9.31 (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.4, 23.4, 27.3, 33.1, 34.3, 34.9, 41.8, 45.3, 61.9, 69.5, 109.2, 119.2, 120.3, 123.2, 125.8, 126.8, 128.9, 129.5, 139.2, 151.6, 153.4, 154.8, 172.8; IR (nujol): ν_{max} = 3388, 1728, 1690 cm^{-1}; MS (ESI) *m/z* = 433 [M + H]$^+$; anal. calcd. for $C_{25}H_{28}N_4O_3$ (432.51): C 69.42, H 6.53, N 12.95; found: C 69.30, H 6.59, N 13.06.



3c

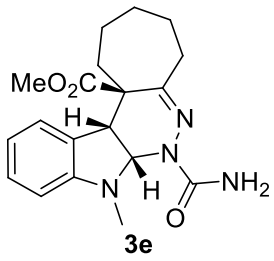
Ethyl 6-carbamoyl-9-chloro-7-methyl-2,3,4,6,6a,7,11b,11c-octahydro-1*H*-indolo[2,3-*c*]cinnoline-11c-carboxylate: the product **3c** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 22% yield (86.1 mg); white solid; mp: 188–190 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.96 (dt, J_1 = 12.8 Hz, J_2 = 4.4 Hz, 1 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.27–1.32 (m, 2 H), 1.51–1.53 (m, 1 H), 1.58 (d, J = 13.2 Hz, 1 H), 1.78–1.80 (m, 1 H), 2.23 (dt, J_1 = 12.8 Hz, J_2 = 4.4 Hz, 1 H), 2.45 (d, J = 13.2 Hz, 1 H), 2.56 (s, 3 H), 3.46 (d, J = 7.2 Hz, 1 H), 4.18–4.29 (m, 2 H), 5.55 (d, J = 7.2 Hz, 1 H), 6.63 (d, J = 2.0 Hz, 1 H), 6.76 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 6.77 (br, 2 H), 7.01 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.3, 23.3, 27.1, 32.9, 33.6, 34.8, 41.4, 44.8, 61.8, 69.2, 109.0, 118.4, 125.9, 126.9, 134.0, 153.1, 153.5, 156.8, 172.8; IR (nujol): ν_{max} = 3280, 3206, 1732, 1692 cm^{-1}; MS (ESI) *m/z* = 413 [M + Na]$^+$, 391 [M + H]$^+$; anal. calcd. for $C_{19}H_{23}ClN_4O_3$ (390.86): C 58.38, H 5.93, N 14.33; found: C 58.51, H 5.98, N 14.23.



3d

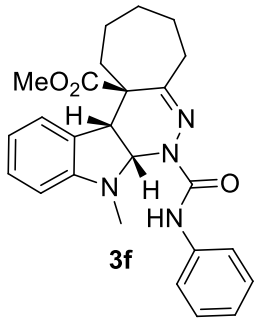
Ethyl 7-benzyl-6-carbamoyl-2,3,4,6,6a,7,11b,11c-octahydro-1*H*-indolo[2,3-*c*]cinnoline-11c-carboxylate: the product **3d** was isolated by column chromatography (ethyl acetate/cyclohexane 35:65) in 30% yield (129.7 mg); white solid; mp: 162–164 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.03–1.11 (m, 1 H), 1.27 (t, J = 7.2 Hz, 3 H), 1.30–1.37 (m, 2 H), 1.50–1.59 (m, 2 H), 1.85–1.89 (m, 1 H), 2.26 (dt, J_1 = 12.8 Hz, J_2 = 4.8 Hz, 1 H), 2.50–2.55 (m, 1 H), 3.49 (d, J = 6.8 Hz, 1 H), 3.96 (d, J = 16.0 Hz, 1 H), 4.20–4.32. (m, 2 H), 4.49 (d, J = 16.0 Hz, 1 H), 5.88 (d, J = 6.8 Hz, 1 H), 6.27 (d, J = 7.6 Hz, 1 H), 6.71 (t, J = 7.6 Hz, 1 H), 6.74 (br, 2 H), 7.01–7.07 (m, 2 H), 7.19–7.32 (m, 5 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.4, 23.6, 27.6, 33.1, 35.2, 42.2, 45.1, 50.4, 61.8, 68.6, 108.5, 118.7, 125.8, 126.7, 127.1, 127.2, 128.7, 129.3, 140.1, 150.9, 154.1, 157.1, 173.1; IR (nujol): ν_{max} = 3271, 3194, 1738, 1688 cm^{-1}; MS (ESI) *m/z* = 433

[M + H]$^+$; anal. calcd. for $C_{25}H_{28}N_4O_3$ (432.51): C 69.42, H 6.53, N 12.95; found: C 69.31, H 6.49, N 13.06.



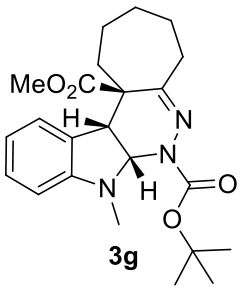
3e

Methyl 7-carbamoyl-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-12c-carboxylate: the product **3e** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 82% yield (280.8 mg); white solid; mp: 165–167 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.20–135 (m, 2 H), 1.41–1.55 (m, 1 H), 1.71–1.82 (m, 3 H), 1.98 (t, *J* = 12.8 Hz, 2 H), 2.32 (t, *J* = 12.8 Hz, 1 H), 2.55 (dd, J_1 = 14.4 Hz, J_2 = 5.6 Hz, 1 H), 3.65 (s, 3 H), 4.29 (d, *J* = 9.6 Hz, 1 H), 5.75 (dd, J_1 = 9.6 Hz, J_2 = 2.0 Hz, 1 H), 6.40 (d, *J* = 2.0 Hz, 1 H), 6.47 (br, 2 H), 6.44 (d, *J* = 7.6 Hz, 1 H), 6.49 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 692 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.14 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 24.8, 25.2, 29.6, 32.2, 36.7, 51.1, 52.3, 53.1, 69.0, 108.0, 116.8, 124.5, 125.6, 128.2, 151.6, 157.6, 161.9, 172.8; IR (nujol): ν_{max} = 3426, 3251, 3228, 1737, 1692 cm^{-1}; MS (ESI) *m/z* = 343 [M + H]$^+$; anal. calcd. for $C_{18}H_{22}N_4O_3$ (342.39): C 63.14, H 6.48, N 16.36; found: C 62.99, H 6.56, N 16.48.



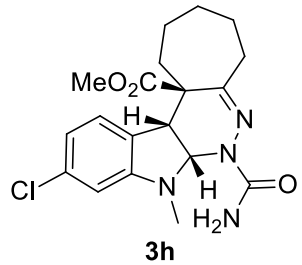
3f

Methyl 8-methyl-7-(phenylcarbamoyl)-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-12c-carboxylate: the product **3f** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 65% yield (281.2 mg); white solid; mp: 140–142 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.22–1.38 (m, 2 H), 1.54–1.64 (m, 1 H), 1.80–1.93 (m, 4 H), 2.05–2.10 (m, 1 H), 2.28–2.35 (m, 1 H), 2.70 (d, *J* = 6.8 Hz, 1 H), 2.73 (s, 3 H), 3.60 (s, 3 H), 4.65 (d, *J* = 9.6 Hz, 1 H), 6.16 (d, *J* = 9.6 Hz, 1 H), 6.32 (d, *J* = 7.6 Hz, 1 H), 6.55 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 7.01–7.06 (m, 2 H), 7.21 (d, *J* = 7.6 Hz, 1 H), 7.29 (t, *J* = 8.0 Hz, 2 H), 7.61 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 2 H), 8.67 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 25.1, 25.4, 30.6, 32.3, 33.1, 37.1, 52.7, 53.4, 55.7, 74.5, 105.5, 116.9, 120.4, 123.2, 124.7, 126.6, 128.9, 129.1, 139.3, 152.8, 154.0, 172.3, 173.4; IR (nujol): ν_{max} = 3345, 1725, 1691 cm^{-1}; MS (ESI) *m/z* = 433 [M + H]$^+$; anal. calcd. for $C_{25}H_{28}N_4O_3$ (432.51): C 69.42, H 6.53, N 12.95; found: C 69.29, H 6.58, N 13.06.



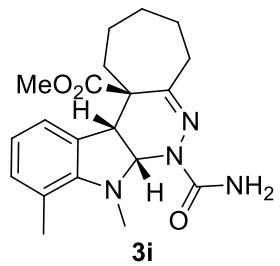
3g

***tert*-Butyl 12c-methyl 8-methyl-1,2,3,4,5,7a,8,12c-octahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-7,12c(12b*H*)-dicarboxylate:** the product **3g** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 62% yield (256.4 mg); white solid; mp: 124–126 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.18–1.34 (m, 2 H), 1.46 (s, 9 H), 1.69–1.82 (m, 4 H), 2.03 (dd, J_1 = 14.0 Hz, J_2 = 7.2 Hz, 1 H), 2.30 (t, J = 14.0 Hz, 1 H), 2.47 (d, J = 7.6 Hz, 2 H), 2.71 (s, 3 H), 3.59 (s, 3 H), 4.60 (d, J = 9.2 Hz, 1 H), 5.92 (d, J = 9.2 Hz, 1 H), 6.31 (d, J = 7.6 Hz, 1 H), 6.51 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 7.01 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 7.18 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 24.9, 25.3 28.3, 30.8, 31.4, 33.0, 36.9, 52.5, 54.1, 54.9, 76.1, 80.8, 105.2, 116.7, 124.4, 126.6, 129.1, 129.2, 152.6, 173.6, 174.0; IR (nujol): ν_{max} = 1732, 1730 cm^{-1}; MS (ESI) *m/z* = 414 [M + H]$^+$; anal. calcd. for $C_{23}H_{31}N_3O_3$ (413.51): C 66.81, H 7.56, N 10.16; found: C 66.96, H 7.60, N 10.05.



3h

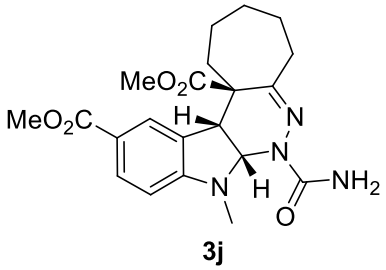
Methyl 7-carbamoyl-10-chloro-8-methyl-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-12c-carboxylate: the product **3h** was isolated by column chromatography (ethyl acetate/cyclohexane 45:55) in 90% yield (351.8 mg); white solid; mp: 161–163 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.81–0.87 (m, 1 H), 1.16–1.35 (m, 3 H), 1.51–1.56 (m, 1 H), 1.74–1.89 (m, 4 H), 2.01–2.04 (m, 1 H), 2.15–2.21 (m, 1 H), 2.52–2.60 (m, 1 H), 2.69 (s, 3 H), 3.60 (s, 3 H), 4.57 (d, J = 9.6 Hz, 1 H), 6.10 (d, J = 9.6 Hz, 1 H), 6.32 (d, J = 2.0 Hz, 1 H), 6.50 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 7.14 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 25.0, 25.3, 30.6, 31.6, 32.9, 37.1, 52.6, 53.2, 54.7, 74.0, 104.7, 115.7, 123.8, 127.7, 134.1, 154.2, 157.3, 171.6, 173.4; IR (nujol): ν_{max} = 3287, 3215, 1730, 1701 cm^{-1}; MS (ESI) *m/z* = 391 [M + H]$^+$; anal. calcd. for $C_{19}H_{23}ClN_4O_3$ (390.86): C 58.38, H 5.93, N 14.33; found: C 58.51, H 5.97, N 14.25.



3i

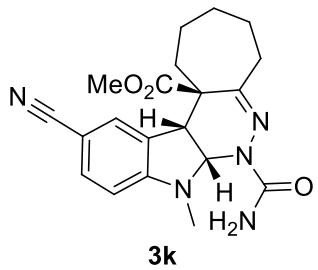
Methyl 7-carbamoyl-8,9-dimethyl-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-12c-carboxylate: the product **3i** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 54% yield (200.1 mg); yellow oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.18–1.33 (m, 2 H), 1.45–1.56 (m, 1 H), 1.71–1.83 (m, 4 H), 2.03 (dd, J_1 = 14.0 Hz, J_2 = 7.2 Hz, 1 H), 2.17 (s, 3 H), 2.21–2.32 (m, 1 H), 2.53 (dd, J_1 = 14.0 Hz, J_2 = 7.2 Hz, 1 H), 2.91 (s, 3 H), 3.59 (s, 3 H), 4.66 (d, J = 10.0 Hz, 1 H), 5.81 (d, J = 10.0

Hz, 1 H), 6.40 (br, 2 H), 6.58 (t, *J* = 7.6 Hz, 1 H), 6.82 (d, *J* = 7.6 Hz, 1 H), 7.07 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.1, 18.9, 24.7, 24.9, 30.3, 33.1, 36.7, 52.1, 52.9, 54.3, 76.8, 118.6, 118.8, 123.8, 126.6, 131.4, 152.1, 157.4, 169.0, 173.2; IR (nujol): ν_{max} = 3227, 3217, 1735, 1693 cm^{-1}; MS (ESI) *m/z* = 371 [M + H]$^+$; anal. calcd. for $C_{20}H_{26}N_4O_3$ (370.44): C 69.84, H 7.07, N 15.12; found: C 69.69, H 6.99, N 15.24.



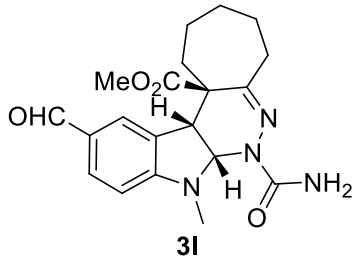
3j

Dimethyl 7-carbamoyl-8-methyl-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-11,12c-dicarboxylate: the product **3j** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 89% yield (368.9 mg); white solid; mp: 218–220 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.16–1.33 (m, 2 H), 1.53 (q, *J* = 12.4 Hz, 1 H), 1.77–1.83 (m, 4 H), 2.07–2.19 (m, 2 H), 2.57 (dd, J_1 = 14.0 Hz, J_2 = 6.8 Hz, 1 H), 2.76 (s, 3 H), 3.62 (s, 3 H), 3.76 (s, 3 H), 4.65 (d, *J* = 9.6 Hz, 1 H), 6.20 (d, *J* = 9.6 Hz, 1 H), 6.31 (d, *J* = 8.0 Hz, 1 H), 6.50 (br, 2 H), 7.67 (s, 1 H), 7.70 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 24.9, 25.3, 30.7, 30.9, 32.8, 37.0, 51.8, 52.7, 53.1, 54.8, 73.7, 103.7, 116.8, 124.6, 127.6, 132.2, 156.4, 157.3, 166.6, 172.3, 173.3; IR (nujol): ν_{max} = 3267, 3211, 1729, 1727, 1684 cm^{-1}; MS (ESI) *m/z* = 415 [M + H]$^+$; anal. calcd. for $C_{21}H_{26}N_4O_5$ (414.45): C 60.86, H 6.32, N 13.52; found: C 70.01, H 6.26, N 13.41.



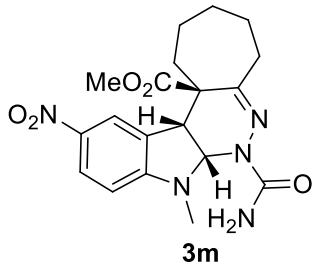
3k

Methyl 7-carbamoyl-11-cyano-8-methyl-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-12c-carboxylate: the product **3k** was isolated by column chromatography (ethyl acetate/cyclohexane 45:55) in 84% yield (320.4 mg); white solid; mp: 272–275 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.16–1.25 (m, 1 H), 1.32–1.41 (m, 1 H), 1.48–1.59 (m, 1 H), 1.78–1.91 (m, 4 H), 2.05 (dd, J_1 = 14.0 Hz, J_2 = 6.8 Hz, 1 H), 2.15–2.22 (m, 1 H), 2.57 (dd, J_1 = 14.0 Hz, J_2 = 6.8 Hz, 1 H), 2.75 (s, 3 H), 3.61 (s, 3 H), 4.65 (d, *J* = 9.6 Hz, 1 H), 6.21 (d, *J* = 9.6 Hz, 1 H), 6.37 (d, *J* = 8.4 Hz, 1 H), 6.55 (br, 2 H), 7.44 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1 H), 7.49 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 24.9, 25.3, 30.5, 30.8, 32.7, 37.0, 52.7, 53.1, 54.6, 73.5, 96.7, 104.6, 121.0, 125.6, 129.9, 134.9, 155.7, 157.2, 172.5, 173.2; IR (nujol): ν_{max} = 3293, 3219, 1724, 1686 cm^{-1}; MS (ESI) *m/z* = 382 [M + H]$^+$; anal. calcd. for $C_{20}H_{23}N_5O_3$ (381.43): C 62.98, H 6.08, N 18.36; found: C 62.83, H 6.15, N 18.47.



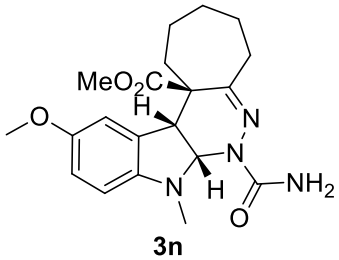
3l

Dimethyl 7-carbamoyl-8-methyl-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-11,12c-dicarboxylate: the product **3l** was isolated by column chromatography (ethyl acetate/cyclohexane 60:40) in 89% yield (342.2 mg); white solid; mp: 212–214 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.15–1.35 (m, 2 H), 1.48–1.57 (m, 1 H), 1.73–1.87 (m, 4 H), 2.08–2.24 (m, 2 H), 2.57 (dd, J_1 = 14.4 Hz, J_2 = 7.2 Hz, 1 H), 2.79 (s, 3 H), 3.61 (s, 3 H), 4.68 (d, J = 10.0 Hz, 1 H), 6.24 (d, J = 10.0 Hz, 1 H), 6.40 (d, J = 8.0 Hz, 1 H), 6.62 (br, 2 H), 7.60 (d, J = 8.0 Hz, 1 H), 7.61 (s, 1 H), 9.60 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 24.9, 25.3, 30.7, 30.8, 32.8, 37.1, 52.7, 52.8, 54.8, 73.8, 103.9, 125.4, 126.1, 127.3, 134.8, 157.2, 157.5, 172.7, 173.3, 190.1; IR (nujol): ν_{max} = 3261, 3213, 1736, 1725, 1690 cm^{-1}; MS (ESI) *m/z* = 385 [M + H]$^+$; anal. calcd. for $C_{20}H_{24}N_4O_4$ (384.43): C 62.49, H 6.29, N 14.57; found: C 6.35, H 6.33, N 14.44.



3m

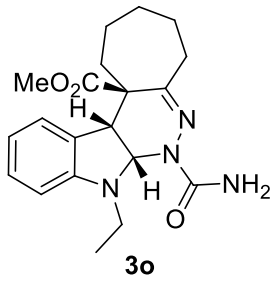
Methyl 7-carbamoyl-8-methyl-11-nitro-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-12c-carboxylate: the product **3m** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 92% yield (369.3 mg); yellow solid; mp: 183–182 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.19–1.39 (m, 2 H), 1.48–1.59 (m, 1 H), 1.73–1.94 (m, 4 H), 2.14–2.17 (m, 2 H), 2.54–2.61 (m, 1 H), 2.81 (s, 3 H), 3.62 (s, 3 H), 4.72 (d, J = 9.6 Hz, 1 H), 6.31 (d, J = 9.6 Hz, 1 H), 6.39 (d, J = 9.2 Hz, 1 H), 6.61 (br, 2 H), 7.94 (d, J = 2.0 Hz, 1 H), 8.01 (dd, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 24.4, 24.9, 30.1, 30.4, 32.1, 36.5, 52.2, 52.3, 54.2, 73.5, 102.8, 122.6, 124.8, 127.5, 136.4, 156.6, 157.2, 172.5, 172.6; IR (nujol): ν_{max} =3362, 3347, 1736, 1692 cm^{-1}; MS (ESI) *m/z* = 402 [M + H]$^+$; anal. calcd. for $C_{19}H_{23}N_5O_5$ (401.41): C 56.85, H 5.78, N 17.45; found: C 57.02, H 5.69, N 17.33.



3n

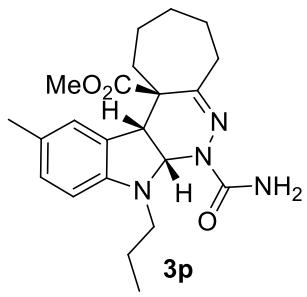
Methyl 7-carbamoyl-11-methoxy-8-methyl-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-12c-carboxylate: the product **3n** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 71% yield (274.4 mg); white solid; mp: 164–166 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.15–1.35 (m, 2 H), 1.47–1.55 (m, 1 H), 1.70–1.81 (m, 3 H), 1.89–2.03 (m, 2 H), 2.14–2.22 (m, 1 H), 2.56 (dd, J_1 = 14 Hz, J_2 = 6.8 Hz, 1 H), 2.64 (s, 3 H), 3.61 (s, 3 H), 3.65 (s, 3 H), 4.51 (d, J = 9.6 Hz,

1 H), 5.95 (d, *J* = 9.6 Hz, 1 H), 6.24 (d, *J* = 8.4 Hz, 1 H), 6.50 (br, 2 H), 6.64 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1 H), 6.79 (d, *J* = 2.4 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 25.1, 25.4, 30.5, 32.9, 33.6, 37.1, 52.7, 53.3, 54.3, 56.0, 74.7, 106.0, 113.3, 114.5, 126.5, 147.5, 151.8, 157.7, 169.6, 173.6; IR (nujol): ν_{max} = 3274, 3215, 1726, 1676 cm^{-1}; MS (ESI) *m/z* = 387 [M + H]$^+$; anal. calcd. for $C_{20}H_{26}N_4O_4$ (386.44): C 62.16, H 6.78, N 14.50; found: C 62.31, H 6.84, N 14.39.



3o

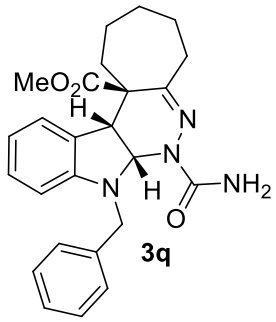
Methyl 7-carbamoyl-8-ethyl-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-12c-carboxylate: the product **3o** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 56% yield (207.5 mg); white solid; mp: 114–117 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.96 (t, *J* = 6.8 Hz, 3 H), 1.15–1.34 (m, 2 H), 1.47–1.57 (m, 1 H), 1.73–1.88 (m, 3 H), 1.97–2.06 (m, 1 H), 2.19–2.28 (m, 1 H), 2.57 (dd, J_1 = 14.0 Hz, J_2 = 7.2 Hz, 1 H), 3.07 (sex, , *J* = 7.2 Hz, 1 H), 3.30 (q, *J* = 6.8 Hz, 2 H), 3.59 (s, 3 H), 4.59 (d, *J* = 10.0 Hz, 1 H), 6.15 (d, *J* = 10.0 Hz, 1 H), 6.25 (d, *J* = 7.6 Hz, 1 H), 6.35 (br, 2 H), 6.47 (t, *J* = 7.6 Hz, 1 H), 6.98 (t, *J* = 7.6 Hz, 1 H), 7.14 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 11.3, 24.5, 24.9, 30.3, 32.7, 36.7, 38.5, 52.1, 53.4, 54.2, 71.6, 104.4, 115.7, 124.2, 126.4, 128.6, 151.2, 157.1, 171.1, 173.2; IR (nujol): ν_{max} = 3372, 3346, 1729, 1691 cm^{-1}; MS (ESI) *m/z* = 371 [M + H]$^+$; anal. calcd. for $C_{20}H_{26}N_4O_3$ (370.44): C 64.84, H 7.07, N 15.12; found: C 64.71, H 7.11, N 15.23.



3p

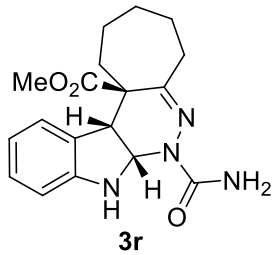
Methyl 7-carbamoyl-11-methyl-8-propyl-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-12c-carboxylate: the product **3p** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 71% yield (283.0 mg); white solid; mp: 119–121 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.78 (t, *J* = 7.2 Hz, 3 H), 1.16–1.59 (m, 4 H), 1.71–1.93 (m, 3 H), 2.02 (dd, J_1 = 13.2 Hz, J_2 = 7.2 Hz, 1 H), 2.16 (s, 3 H), 2.23 (q, *J* = 13.2 Hz, 3 H), 2.57 (dd, J_1 = 13.2 Hz, J_2 = 7.2 Hz, 1 H), 2.90–2.98 (m, 1 H), 3.11–3.20 (m, 1 H), 3.60 (s, 3 H), 4.56 (d, *J* = 10.0 Hz, 1 H), 6.12 (d, *J* = 10.0 Hz, 1 H), 6.15 (d, *J* = 8.0 Hz, 1 H),6.42 (br, 2 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.96 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 11.8, 20.1, 20.9, 25.0, 25.5, 30.7, 33.2, 37.2, 46.9, 52.6, 53.9, 54.6, 72.9, 104.8, 124.5, 124.7, 127.6, 129.2, 150.2, 157.5, 171.3, 173.8; IR (nujol): ν_{max} = 3291, 3219, 1732, 1688 cm^{-1}; MS (ESI) *m/z*

= 399 $[M + H]^+$; anal. calcd. for $C_{22}H_{30}N_4O_3$ (398.50): C 66.31, H 7.59, N 14.06; found: C 66.46, H 7.63, N 13.96.



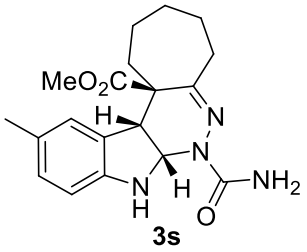
3q

Methyl 8-benzyl-7-carbamoyl-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-12c-carboxylate: the product **3q** was isolated by column chromatography (ethyl acetate/cyclohexane 35:65) in 79% yield (341.7 mg); white solid; mp: 158–160 °C; ^{1}H NMR (400 MHz[D_6]DMSO, 25 °C): δ = 1.19–1.37 (m, 2 H), 1.57 (q, *J* = 12.4 Hz, 1 H), 1.72–1.86 (m, 3 H), 1.92 (t, *J* = 12.4 Hz, 1 H), 2.07 (dd, J_1 = 14.0 Hz, J_2 = 6.8 Hz, 1 H), 2.30 (t, *J* = 12.4 Hz, 1 H)), 2.65 (dd, J_1 = 14.0 Hz, J_2 = 6.8 Hz, 1 H), 3.60 (s, 3 H), 4.22 (d, *J* = 16.8 Hz, 1 H), 4.61 (d, *J* = 16.8 Hz, 1 H), 4.71 (d, *J* = 10.0 Hz, 1 H), 6.09 (d, *J* = 8.0 Hz, 1 H), 6.20 (br, 2 H), 6.30 (d, *J* = 10.0 Hz, 1 H), 6.51 (t, *J* = 7.6 Hz, 1 H), 6.91 (t, *J* = 7.6 Hz, 1 H), 7.16–7.30 (m, 6 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 24.6, 25.0, 30.3, 32.8, 36.8, 49.1, 52.2, 53.7, 54.3, 72.9, 105.2, 116.4, 124.3, 126.5, 126.6, 126.8, 128.3, 128.5, 138.7, 151.8, 157.2, 171.5, 173.3; IR (nujol): ν_{max} = 3279, 3208, 1733, 1678 cm^{-1}; MS (ESI) *m/z* = 433 $[M + H]^+$; anal. calcd. for $C_{25}H_{28}N_4O_3$ (432.51): C 69.42, H 6.53, N 12.95; found: C 69.57, H 6.59, N 12.84.



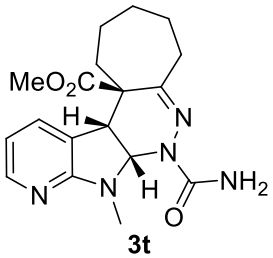
3r

Methyl 7-carbamoyl-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-12c-carboxylate: the product **3r** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 89% yield (304.7 mg); white solid; mp: 165–167 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.20–135 (m, 2 H), 1.41–1.55 (m, 1 H), 1.71–1.82 (m, 3 H), 1.98 (t, *J* = 12.8 Hz, 2 H), 2.32 (t, *J* = 12.8 Hz, 1 H), 2.55 (dd, J_1 = 14.4 Hz, J_2 = 5.6 Hz, 1 H), 3.65 (s, 3 H), 4.29 (d, *J* = 9.6 Hz, 1 H), 5.75 (dd, J_1 = 9.6 Hz, J_2 = 2.0 Hz, 1 H), 6.40 (d, *J* = 2.0 Hz, 1 H), 6.47 (br, 2 H), 6.44 (d, *J* = 7.6 Hz, 1 H), 6.49 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 692 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.14 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 24.8, 25.2, 29.6, 32.2, 36.7, 51.1, 52.3, 53.1, 69.0, 108.0, 116.8, 124.5, 125.6, 128.2, 151.6, 157.6, 161.9, 172.8; IR (nujol): ν_{max} = 3426, 3251, 3228, 1737, 1692 cm^{-1}; MS (ESI) *m/z* = 343 $[M + H]^+$; anal. calcd. for $C_{18}H_{22}N_4O_3$ (342.39): C 63.14, H 6.48, N 16.36; found: C 62.97, H 6.56, N 16.49.



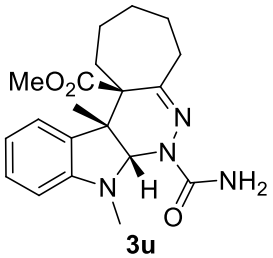
3s

Methyl 7-carbamoyl-11-methyl-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-12c-carboxylate: the product **3s** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 66% yield (235.2 mg); white solid; mp: 198–200 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.23–1.51 (m, 3 H), 1.71–1.86 (m, 3 H), 2.16 (s, 3 H), 1.95 (dd, J_1 = 14.4 Hz, J_2 = 5.6 Hz, 1 H), 2.05 (t, J = 12.8 Hz, 1 H), 2.31 (t, J = 12.8 Hz, 1 H), 2.56 (dd, J_1 = 14.4 Hz, J_2 = 5.6 Hz, 1 H), 3.67 (s, 3 H), 4.20 (d, J = 9.2 Hz, 1 H), 5.74 (dd, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 1 H), 6.09 (s, 1 H), 6.38 (d, J = 7.6 Hz, 1 H), 6.41 (br, 2 H), 6.75 (d, J = 7.6 Hz, 1 H), 6.95 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 20.5, 24.7, 25.2, 29.3, 31.9, 36.6, 50.7, 52.1, 52.8, 69.1, 108.1, 124.9, 125.4, 126.1, 128.5, 149.1, 157.4, 160.7, 172.7; IR (nujol): ν_{max} = 3327, 3271, 1734, 1693 cm^{-1}; MS (ESI) *m/z* = 357 [M + H]$^+$; anal. calcd. for $C_{19}H_{24}N_4O_3$ (356.41): C 64.03, H 6.79, N 15.72; found: C 63.90, H 6.83, N 15.84.



3t

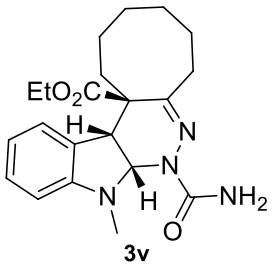
Methyl 7-carbamoyl-8-methyl-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[c]pyrido[3',2':4,5]pyrrolo[3,2-*e*]pyridazine-12c-carboxylate: the product **3t** was isolated by column chromatography (ethyl acetate/cyclohexane 80:20) in 85% yield (303.8 mg); white solid; mp: 222–224 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.16–1.32 (m, 2 H), 1.51 (q, J = 12.4 Hz, 1 H), 1.77–1.85 (m, 4 H), 1.98–2.05 (m, 1 H), 2.14–2.20 (m, 1 H), 2.58 (dd, J_1 = 14.4 Hz, J_2 = 6.8 Hz, 1 H), 2.76 (s, 3 H), 3.60 (s, 3 H), 4.58 (d, J = 10.0 Hz, 1 H), 6.12 (d, J = 10.0 Hz, 1 H), 6.27 (br, 1 H), 6.40 (t, J = 6.8 Hz, 1 H), 6.59 (br, 1 H), 7.42 (d, J = 7.2 Hz, 1 H), 7.74 (d, J = 4.8 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 24.9, 25.3, 29.2, 30.7, 32.9, 37.1, 51.7, 52.7, 54.8, 71.1, 112.0, 118.7, 133.6, 147.1, 157.4, 162.4, 172.2, 173.2; IR (nujol): ν_{max} = 3355, 3296, 1736, 1689 cm^{-1}; MS (ESI) *m/z* = 358 [M + H]$^+$; anal. calcd. for $C_{18}H_{23}N_5O_3$ (357.41): C 60.49, H 6.49, N 19.59; found: C 60.63, H 6.41, N 19.48.



3u

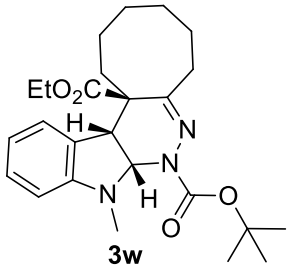
Methyl 7-carbamoyl-8,12b-dimethyl-1,2,3,4,5,7,7a,8,12b,12c-decahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-12c-carboxylate: the product **3u** was isolated by column chromatography (ethyl acetate/cyclohexane 60:40) in 40% yield (148.2 mg); white solid; mp: 127–129 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.12–1.43 (m, 3 H), 1.52 (s, 3 H), 1.65–1.80 (m, 3 H), 1.91–2.05 (m, 2 H), 2.13–2.24 (m, 1 H), 2.53–2.57 (m, 1 H), 2.71 (s, 3 H), 3.59 (s, 3 H), 5.39 (s, 1 H), 6.38 (d, J = 7.6 Hz, 1 H), 6.45 (br, 2 H), 6.58 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz,

1 H), 7.02 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 7.17 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 22.2, 24.9, 25.1, 29.0, 29.7, 31.8, 36.2, 51.5, 52.3, 55.7, 78.6, 106.0, 117.3, 123.6, 128.2, 132.0, 150.9, 156.5, 166.0, 172.2; IR (nujol): ν_{max} = 3347, 3298, 1729, 1698 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{27}N_4O_3$[M + H]+: 371.2083; found: 371.2069.



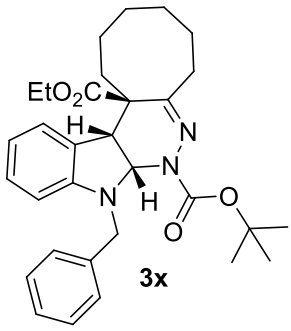
3v

Ethyl 8-carbamoyl-9-methyl-2,3,4,5,6,8,8a,9,13b,13c-decahydro-1*H*-cycloocta[5,6]pyridazino[3,4-*b*]indole-13c-carboxylate: the product **3v** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 49% yield (188.4 mg); white solid; mp: 182–184 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.22–1.33 (m, 2 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.50–1.74 (m, 7 H), 1.91–1.97 (m, 1 H), 2.35–2.38 (m, 2 H), 2.74 (s, 3 H), 3.73 (d, J = 8.4 Hz, 1 H), 4.24 (q, J = 7.2 Hz, 2 H), 5.61 (d, J = 8.4 Hz, 1 H), 6.52 (d, J = 8.0 Hz, 1 H), 6.67 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 6.72 (br, 2 H), 6.97 (d, J = 8.0 Hz, 1 H), 7.13 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 13.8, 23.4, 25.7, 25.7, 25.8, 29.0, 33.1, 34.0, 45.9, 50.2, 61.0, 71.4, 106.8, 117.6, 124.7, 125.5, 138.7, 151.7, 156.5, 157.6, 172.1; IR (nujol): ν_{max} = 3408, 3394, 1720, 1684 cm^{-1}; MS (ESI) *m/z* = 385 [M + H]$^+$; anal. calcd. for $C_{21}H_{28}N_4O_3$ (384.47): C 65.60, H 7.34, N 14.57; found: C 65.74, H 7.26, N 14.48.



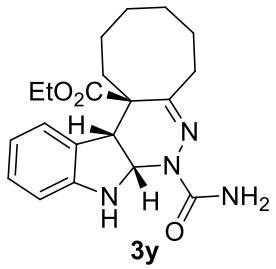
3w

***tert*-Butyl 13c-ethyl 9-methyl-3,4,5,6,8a,9,13b,13c-octahydro-1*H*-cycloocta[5,6]pyridazino[3,4-*b*]indole-8,13c(2H)-dicarboxylate:** the product **3w** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 43% yield (189.9 mg); white solid; mp: 157–159 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.19 (t, J = 7.2 Hz, 3 H), 1.31–1.42 (m, 1 H), 1.47 (s, 9 H), 1.52–1.70 (m, 6 H), 1.91–2.13 (m, 2 H), 2.14–2.18 (m, 1 H), 2.25–2.34 (m, 1 H), 2.72 (s, 3 H), 3.37 (s, 1 H), 3.98–4.18 (m, 2 H), 4.40 (d, J = 9.2 Hz, 1 H), 5.74 (d, J = 9.2 Hz, 1 H), 6.36 (d, J = 8.0 Hz, 1 H), 6.53 (t, J = 7.6 Hz, 1 H), 7.02 (t, J = 7.6 Hz, 1 H), 7.14 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 13.7, 24.7, 25.2, 25.6, 27.7, 27.8, 31.0, 31.3, 32.6, 53.2, 53.3, 60.9, 74.9, 80.4, 105.3, 116.7, 124.4, 125.2, 128.6, 151.9, 152.5, 170.2, 171.8; IR (nujol): ν_{max} = 1732, 1724 cm^{-1}; MS (ESI) *m/z* = 442 [M + H]$^+$; anal. calcd. for $C_{25}H_{35}N_3O_4$ (441.56): C 68.00, H 7.99, N 9.52; found: C 67.87, H 7.93, N 9.64.



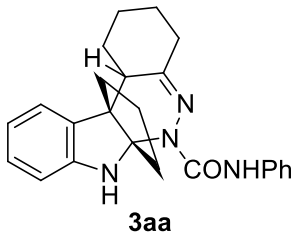
3x

***tert*-Butyl 13c-ethyl 9-benzyl-3,4,5,6,8a,9,13b,13c-octahydro-1*H*-cycloocta[5,6]pyridazino[3,4-*b*]indole-8,13c(2H)-dicarboxylate:** the product **3x** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 50% yield (258.8 mg); yellowish oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.17 (t, *J* = 7.2 Hz, 3 H), 1.23 (s, 9 H), 1.38–1.78 (m, 8 H), 1.93–2.01 (m, 1 H), 2.11–2.16 (m, 1 H), 2.26–2.30 (m, 1 H), 2.43–2.49 (m, 1 H), 3.93–4.14 (m, 2 H), 4.24 (d, *J* = 17.2 Hz, 1 H), 4.65 (d, *J* = 17.2 Hz, 1 H), 4.73 (d, *J* = 9.6 Hz, 1 H), 6.02 (d, *J* = 9.6 Hz, 1 H), 6.10 (d, *J* = 8.0 Hz, 1 H), 6.52 (t, *J* = 7.6 Hz, 1 H), 6.92 (t, *J* = 7.6 Hz, 1 H), 7.17–7.32 (m, 6 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 13.7, 24.5, 25.6, 25.8, 27.5, 28.3, 31.7, 32.3, 49.2, 53.8, 55.8, 60.8, 75.5, 80.2, 104.9, 116.6, 124.1, 125.6, 126.1, 126.6, 128.4, 128.5, 138.7, 151.1, 152.4, 171.9, 173.5; IR (nujol): ν_{max} = 1731, 1723 cm^{-1}; MS (ESI) *m/z* = 518 [M + H]$^+$; anal. calcd. for $C_{31}H_{39}N_3O_4$ (517.66): C 71.93, H 7.59, N 8.12; found: C 71.76, H 7.65, N 8.26.



3y

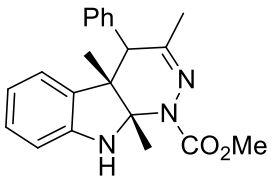
Ethyl 8-carbamoyl-2,3,4,5,6,8,8a,9,13b,13c-decahydro-1*H*-cycloocta[5,6]pyridazino[3,4-*b*]indole-13c-carboxylate: the product **3y** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 37% yield (136.9 mg); white solid; mp: 168–170 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.07–1.19 (m, 1 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.32–1.64 (m, 8 H), 1.90–1.99 (m, 1 H), 2.37–2.46 (m, 1 H), 2.66 (dd, J_1 = 14.4 Hz, J_2 = 6.8 Hz, 1 H), 3.44 (d, *J* = 8.8 Hz, 1 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 5.55 (dd, J_1 = 8.8 Hz, J_2 = 4.0 Hz, 1 H), 6.10 (d, *J* = 4.0 Hz, 1 H), 6.59 (t, *J* = 7.2 Hz, 1 H), 6.64 (d, *J* = 8.0 Hz, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 6.71 (s, 2 H), 7.01 (t, *J* = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 13.9, 21.3, 21.9, 24.2, 26.0, 27.9, 35.1, 45.6, 49.3, 61.1, 68.3, 109.4, 117.8, 124.3, 124.9.1, 128.6, 150.3, 151.9, 158.1, 172.0; IR (nujol): ν_{max} = 3332, 3315, 3298, 1731, 1688 cm^{-1}; MS (ESI) *m/z* = 371 [M + H]$^+$; anal. calcd. for $C_{20}H_{26}N_4O_3$ (370.44): C 64.84, H 7.07, N 15.12; found: C 64.98, H 6.99, N 15.02.



3aa

***N*-phenyl-3,4,7,11c-tetrahydro-1*H*-6a,11b-propanoindolo[2,3-*c*]cinnoline-6(2*H*)-carboxamide**: the product **3aa** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 67% yield (258.9 mg); white oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.40–2.18 (m, 15 H), 6.14–6.61 (m, 3 H), 6.93–7.01 (m, 3 H), 7.26 (t, *J* = 7.6 Hz, 2 H), 7.41–7.58 (m, 2 H), 8.54 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 20.7, 20.8, 21.2. 22.1,

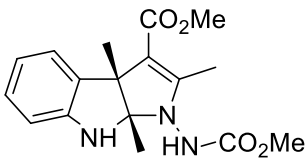
22.4, 25.1, 25.2, 26.4, 68.9, 100.6, 108.9, 113.2, 117.8, 118.5, 121.8, 122.9, 127.1, 128.6, 133.5, 139.5, 150.1, 156.2; IR (nujol): ν_{max} = 3375, 3246, 1696 cm^{-1}; MS (ESI) *m/z* = 387 $[M + H]^+$; anal. calcd. for $C_{24}H_{26}N_4O$ (386.49): C 74.58, H 6.78, N 14.50; found: C 74.42, H 6.86, N 14.62.



3ab

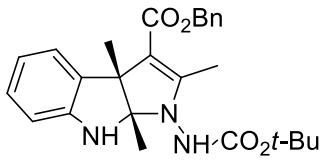
Methyl 3,4a,9a-trimethyl-4-phenyl-4,4a,9,9a-tetrahydro-1*H*-pyridazino[3,4-*b*]indole-1-carboxylate: the product **3ab** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 22% yield (76.9 mg); white solid; mp: 186–188 °C, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.49 (s, 3 H), 1.67 (s, 3 H), 2.10 (s, 3 H), 3.39 (s, 1 H), 3.90 (s, 3 H), 5.38 (s, 1 H), 6.25 (d, *J* = 8.0 Hz, 1 H), 6.62 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 6.67 (d, *J* = 8.0 Hz, 1 H), 6.81–6.85 (m, 2 H), 6.88 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.01–7.12 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 21.7, 23.4, 24.3, 52.3, 53.5, 54.9, 82.8, 108.9, 118.3, 123.9, 127.1, 127.4, 128.3, 130.0, 131.5, 134.2, 147.7, 155.3, 157.8; IR (nujol): ν_{max} = 3290, 1736 cm^{-1}; MS (ESI) m/z = 433 [M + H]+; anal. calcd. for $C_{21}H_{23}N_3O_2$ (349.43): C 72.18, H 6.63, N 12.03; found: C 72.03, H 6.72, N 12.17.

General procedure for the formal [3+2] cycloaddition reactions of indoles 1 with linear azoalkenes 2: A mixture of indole **1** (0.6 mmol), azoalkene **2** (0.4 mmol) and zinc dichloride (0.04 mmol, 5.45 mg) was stirred in dry dichloromethane (2 mL). After the disappearance of azoalkene **2** (TLC check), the crude mixture was purified by column chromatography on silica gel to afford product **5**.



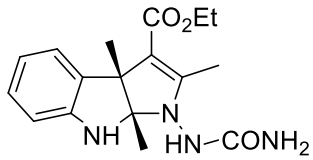
5a

Methyl 1-((methoxycarbonyl)amino)-2,3a,8a-trimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-3-carboxylate: the product **5a** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 20:80) in 58% yield (76.9 mg); White solid; mp: 128–130 °C; ^{1}H NMR (400 MHz, $[D_6]$DMSO, 25 °C): δ = 1.26 (s, 3 H), 1.46 (s, 3 H), 2.01 (s, 3 H), 3.59 (s, 3 H), 3.65 (s, 3 H), 6.13 (s, 1 H), 6.42 (d, *J* = 7.6 Hz, 1 H), 6.55 (t, *J* = 7.6 Hz, 1 H), 6.88 (t, *J* = 7.6 Hz, 1 H), 7.28 (d, *J* = 7.6 Hz, 1 H), 9.31 (s, 1 H); ^{13}C NMR (100 MHz, $[D_6]$DMSO, 25 °C): δ = 12.0, 18.6, 19.6, 26.3, 49.8, 52.1, 55.3, 92.8, 107.3, 117.3, 124.7, 126.9, 133.8, 148.7, 157.1, 159.1, 165.5; IR (nujol): ν_{max} = 3274, 1739, 1698 cm^{-1}; MS (ESI) m/z = 332 [M + H]+; anal. calcd. for $C_{17}H_{21}N_3O_4$ (331.36): C 61.62, H 6.39, N 12.68; found: C 61.74, H 6.31, N 12.57.



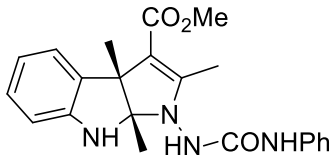
5b

Benzyl 1-((*tert*-butoxycarbonyl)amino)-2,3a,8a-trimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-3-carboxylate: the product **5b** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 20:80) in 88% yield (158.3 mg); White solid; mp: 149–151 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.27 (s, 3 H), 1.43 (s, 9 H), 1.46 (s, 3 H), 2.03 (s, 3 H), 5.10 (s, 2 H), 6.13 (s, 1 H), 6.41 (d, *J* = 7.6 Hz, 1 H), 6.45 (t, *J* = 7.6 Hz, 1 H), 6.86 (t, *J* = 7.6 Hz, 1 H), 7.20 (d, *J* = 7.6 Hz, 1 H), 7.29–7.54 (m, 5 H), 9.02 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 12.1, 18.4, 19.8, 27.9, 55.4, 64.1, 79.5, 92.8, 101.5, 107.8, 117.2, 124.9, 126.8, 127.7, 127.9, 128.3, 133.9, 137.1, 148.6, 155.6, 159.9, 164.9; IR (nujol): ν_{max} = 3363, 3324, 1741, 1696 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{32}N_3O_4$[M + H]$^+$: 450.2393; found: 450.2411.



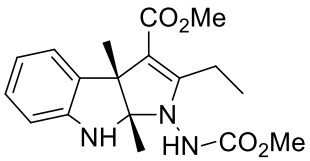
5c

Ethyl 2,3a,8a-trimethyl-1-ureido-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-3-carboxylate: the product **5c** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 70:30) in 68% yield (89.9 mg); White solid; mp: 170–173 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.23 (t, *J* = 7.2 Hz, 3 H), 1.28 (s, 3 H), 1.51 (s, 3 H), 2.07 (s, 3 H), 4.05 (q, *J* = 7.2 Hz, 2 H), 6.01 (br, 1 H), 6.17 (br, 2 H), 6.43 (d, *J* = 6.4 Hz, 1 H), 6.56 (t, *J* = 6.4 Hz, 1 H), 6.88 (t, *J* = 6.4 Hz, 1 H), 7.30 (d, *J* = 6.4 Hz, 1 H), 7.63 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 12.1, 14.3, 15.1, 18.6, 55.2, 58.2, 64.8, 92.9, 107.7, 117.0, 117.1, 124.9, 126.6, 126.7, 159.3, 159.7, 164.9; IR (nujol): ν_{max} = 3482, 3647, 3325, 3338, 1731, 1684 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}N_4O_3$[M + H]$^+$: 331.1770; found: 331.1791.



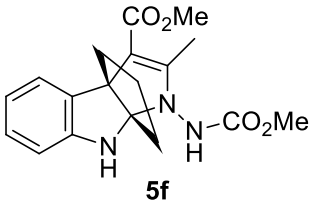
5d

Methyl 2,3a,8a-trimethyl-1-(3-phenylureido)-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-3-carboxylate: The product **5d** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 70:30) in 88% yield (138.1 mg); White solid; mp: 226–228 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.33 (s, 3 H), 1.54 (s, 3 H), 2.10 (s, 3 H), 3.62 (s, 3 H), 6.15 (br, 1 H), 6.41–6.72 (m, 2 H), 6.86–7.05 (m, 2 H), 7.19–7.77 (m, 5 H), 8.41 (br, 2 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 12.3, 13.9, 18.8, 26.3, 49.8, 55.4, 93.0, 108.1, 117.6, 118.3, 118.9, 122.1, 124.8, 126.9, 128.5, 139.1, 148.5, 155.6, 159.6, 165.5; IR (nujol): ν_{max} = 3389, 3282, 3270, 1726, 1694 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{25}N_4O_3$[M + H]$^+$: 393.1927; found: 393.1963.



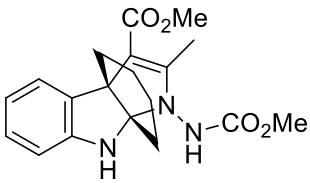
5e

Methyl 2-ethyl-1-((methoxycarbonyl)amino)-3a,8a-dimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-3-carboxylate: The product **5e** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 25:75) in 73% yield (100.9 mg); White solid; mp: 157–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.07 (t, *J* = 7.2 Hz, 3 H), 1.42 (s, 3 H), 1.62 (s, 3 H), 2.47–2.68 (m, 2 H), 3.68 (s, 3 H), 3.80 (s, 3 H), 3.86 (br, 1 H), 6.38 (br, 1 H), 6.57 (d, *J* = 7.6 Hz, 1 H), 6.80 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.01 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.48 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.5, 19.4, 19.7, 20.0, 50.4, 53.1, 56.4, 93.4, 105.9, 109,5, 120.1, 126.0, 127.5, 134.2, 147.6, 156.9, 163.8, 165.8; IR (nujol): ν_{max} = 3332, 3275, 1727, 1692 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{24}N_3O_4$[M + H]$^+$: 346.1767; found: 346.1761.



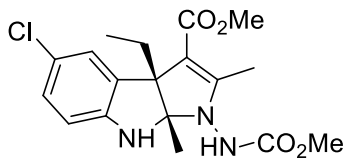
5f

Methyl 11-((methoxycarbonyl)amino)-10-methyl-1,2,3,4-tetrahydro-3a,8b-(epiminoetheno)cyclopenta[*b*]indole-9-carboxylate: The product **5f** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 20:80) in 98% yield (134.8 mg); White solid; mp: 150–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.60–1.88 (m, 3 H), 2.14 (s, 3 H), 2.16–2.45 (m, 3 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 4.16 (br, 1 H), 6.61 (d, *J* = 7.6 Hz, 1 H), 6.62 (br, 1 H), 6.79 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.02 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.54 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.4, 25.3, 40.2, 41.0, 50.5, 53.2, 67.3, 99.9, 104.3, 110.3, 120.7, 125.9, 127.8, 135.4, 148.7, 157.3, 159.5, 166.6; IR (nujol): ν_{max} = 3370, 3302, 1718, 1662 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}N_3O_4$[M + H]$^+$: 344.1610; found: 344.1606.



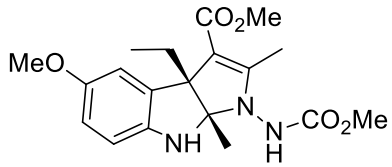
5g

Methyl 10-((methoxycarbonyl)amino)-11-methyl-6,7,8,9-tetrahydro-5*H*-8a,4b-(epiminoetheno)carbazole-12-carboxylate: The product **5g** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 95% yield (135.8 mg); Yellowish solid; mp: 121–123 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.40 (s, 8 H), 2.04 (s, 3 H), 3.58 (s, 3 H), 3.64 (s, 3 H), 6.04 (s, 1 H), 6.45 (d, *J* = 7.6 Hz, 1 H), 6.57 (t, *J* = 7.6 Hz, 1 H), 6.89 (t, *J* = 7.6 Hz, 1 H), 7.26 (d, *J* = 7.6 Hz, 1 H), 9.27 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 12.0, 18.5, 18.9, 26.3, 28.5, 30.3, 49.8, 52.0, 55.0, 91.3, 103.7, 108.3, 117.4, 124.4, 126.8, 132.6, 149.6, 157.1, 165.6; IR (nujol): ν_{max} = 3370, 3302, 1736, 1697 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{24}N_3O_4$[M + H]$^+$: 358.1767; found: 358.1782.



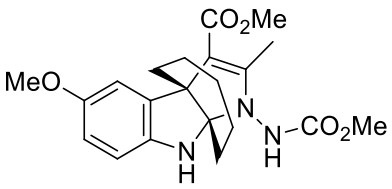
5h

Methyl 5-chloro-3a-ethyl-1-((methoxycarbonyl)amino)-2,8a-dimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-3-carboxylate: the product **5h** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 85% yield (129.2 mg); White solid; mp: 113–115 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.60–0.89 (m, 3 H), 1.31 (s, 3 H), 1.63–1.79 (m, 1 H), 2.05 (s, 3 H), 2.26–2.42 (m, 1 H), 3.58 (s, 3 H), 3.64 (s, 3 H), 6.27 (br, 1 H), 6.39 (d, J = 8.4 Hz, 1 H), 6.89 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1 H), 7.19 (d, J = 2.0 Hz, 1 H), 9.34 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 9.0, 11.9, 15.1, 17.9, 24.3, 49.9, 52.1, 59.2, 64.8, 93.3, 99.5, 108.6, 120.3, 124.9, 126.5, 148.1, 156.9, 165.3; IR (nujol): ν_{max} = 3360, 3266, 1739, 1694 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{23}N_3O_4Cl$ [M + H]$^+$: 380.1377; found: 380.1374.



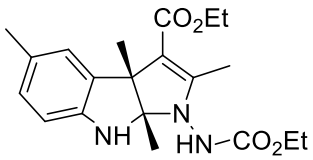
5i

Methyl 3a-ethyl-5-methoxy-1-((methoxycarbonyl)amino)-2,8a-dimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-3-carboxylate: the product **5i** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 98% yield (147.2 mg); white solid; mp: 153–155 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.69–0.91 (m, 3 H), 1.30 (s, 3 H), 1.60–1.79 (m, 1 H), 2.06 (s, 3 H), 2.27–2.45 (m, 1 H), 3.58 (s, 3 H), 3.63 (s, 3 H), 3.64 (s, 3 H), 5.64 (s, 1 H), 6.34 (d, J = 8.0 Hz, 1 H), 6.49 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, 1 H), 6.87 (d, J = 2.4 Hz, 1 H), 9.28 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 9.6, 12.4, 18.5, 25.0, 50.3, 52.5, 55.8, 59.9, 65.4, 93.9, 100.3, 108.5, 112.3, 112.5, 143.6, 152.5, 157.6, 160.5, 166.1; IR (nujol): ν_{max} = 3369, 3267, 1754, 1693 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{26}N_3O_5$[M + H]$^+$: 376.1872; found: 376.1837.



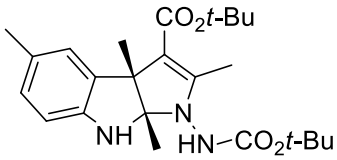
5j

Methyl 2-methoxy-13-((methoxycarbonyl)amino)-12-methyl-5,6,7,8,9,10-hexahydro-5a,10a-(epiminoetheno)cyclohepta[*b*]indole-11-carboxylate: The product **5j** was isolated by column chromatography on silica gel (ethyl acetate/cyclohexane 30:70) in 60% yield (96.4 mg); Brown solid; mp: 166–168 °C; ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 1.42 (s, 10 H), 2.16 (s, 3 H), 3.62 (br, 1 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 6.49 (d, J = 8.4 Hz, 1 H), 6.57 (dd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, 1 H), 6.72 (br, 1 H), 7.14 (d, J = 8.4 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 12.9, 24.3, 25.5, 27.0, 30.8, 33.9, 35.8, 50.3, 52.9, 55.9, 63.2, 95.9, 110.2, 112.0, 113.1, 137.3, 140.7, 154.3, 156.9, 160.1, 166.2; IR (nujol): ν_{max} = 3392, 3317, 1738, 1691 cm^{-1}; MS (ESI) m/z = 332 [M + H]+; anal. calcd. for $C_{21}H_{27}N_3O_5$ (401.45): C 62.83, H 6.78, N 10.47; found: C 62.98, H 6.70, N 12.36.



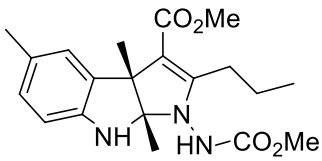
5k

Ethyl 1-((ethoxycarbonyl)amino)-2,3a,5,8a-tetramethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-3-carboxylate: the product **5k** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 47% yield (70.2 mg); white solid; mp: 151–153 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.15–1.31 (m, 9 H), 1.44 (s, 3 H), 2.02 (s, 3 H), 2.15 (s, 3 H), 3.98–4.20 (m, 4 H), 5.88 (s, 1 H), 6.33 (d, *J* = 8.0 Hz, 1 H), 6.69 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1 H), 7.13 (d, *J* = 1.2 Hz, 1 H), 9.19 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 11.9, 14.3, 14.4, 15.4, 18.4, 19.7, 20.6, 55.3, 58.1, 60.6, 93.0, 102.3, 107.7, 125.4, 127.1, 133.8, 146.3, 156.5, 159.2, 165.2; IR (nujol): ν_{max} = 3343, 3306, 1734, 1689 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{28}N_3O_4$[M + H]$^+$: 374.2080; found: 374.2091.



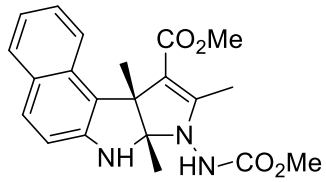
5l

***tert*-Butyl 1-((*tert*-butoxycarbonyl)amino)-2,3a,8a-trimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-3-carboxylate:** the product **5l** was isolated by column chromatography (ethyl acetate/cyclohexane 20:50) in 50% yield (85.9 mg); Whitish oil; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.23 (s, 3 H), 1.43 (s, 9 H), 1.46 (s, 9 H), 1.49 (s, 3 H), 1.97 (s, 3 H), 2.16 (s, 3 H), 5.86 (s, 1 H), 6.32 (d, *J* = 8.0 Hz, 1 H), 6.69 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.17 (d, *J* = 8.0 Hz, 1 H), 8.88 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 11.9, 18.3, 20.6, 27.8, 27.9, 28.4, 55.3, 77.9, 79.3, 92.9, 103.3, 107.8, 125.4, 127.0, 134.4, 146.4, 155.8, 155.8, 158.8, 165.1; IR (nujol): ν_{max} = 3439, 3304, 1738, 1696 cm-1; MS (ESI) m/z = 430 [M + H]+; anal. calcd. for $C_{24}H_{35}N_3O_4$ (429.52): C 67.11, H 8.21, N 9.78; found: C 67.26, H 8.12, N 9.69.



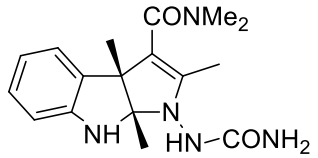
5m

Methyl 1-((methoxycarbonyl)amino)-3a,5,8a-trimethyl-2-propyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-3-carboxylate: the product **5m** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 74% yield (110.6 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.92 (t, *J* = 7.2 Hz, 3 H), 1.21 (t, *J* = 7.2 Hz, 1 H), 1.40 (s, 3 H), 1.61 (s, 3 H), 2.28 (s, 3 H), 2.42–2.64 (m, 2 H), 3.47 (q, *J* = 7.2 Hz, 1 H), 3.68 (s, 3 H), 3.79 (s, 3 H), 3.80 (br, 1 H), 6.31 (br, 1 H), 6.49 (d, *J* = 8.0 Hz, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 7.30 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): 14.3, 15.4, 19.5, 20.1, 21.1, 28.1, 50.3, 53.1, 56.4, 65.9, 93.7, 106.5, 109.4, 126.7, 128.0, 129.3, 134.4, 145.3, 162.4, 165.9; IR (nujol): ν_{max} = 3394, 3272, 1729, 1691 cm-1; HRMS (ESI) calcd for $C_{20}H_{28}N_3O_4$[M + H]$^+$: 374.2080; found: 374.2091.



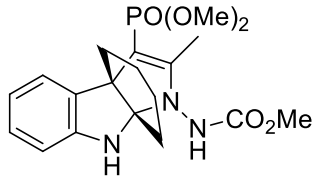
5n

Methyl 8-((methoxycarbonyl)amino)-7a,9,10a-trimethyl-7,7a,8,10a-tetrahydrobenzo[e]pyrrolo[2,3-*b*]indole-10-carboxylate: the product **5n** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 38% yield (58.1 mg); white solid; mp: 137.139 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.63 (s, 3 H), 1.79 (s, 3 H), 2.06 (s, 3 H), 3.72 (s, 3 H), 3.86 (s, 3 H), 5.26 (s, 1 H), 6.80 (s, 1 H), 6.93 (d, *J* = 8.4 Hz, 1 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.61 (d, *J* = 8.4 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.5, 17.4, 21.2, 50.6, 53.4, 74.0, 79.8, 104.4, 113.7, 120.5, 121.5, 121.6, 126.9, 129.5, 129.8, 1309, 131.3, 148.2, 157.1, 159.5, 166.8; IR (nujol): ν_{max} = 1732, 1730 cm^{-1}; MS (ESI) *m/z* = 414 $[M + H]^+$; anal. calcd. for $C_{21}H_{23}N_3O_4$ (381.42): C 66.13, H 6.08, N 11.02; found: C 65.98, H 6.16, N 11.16.



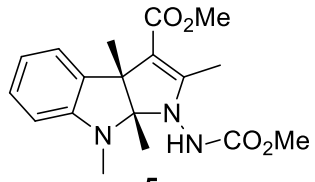
5o

Pentamethyl-1-ureido-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-3-carboxamide: the product **5o** was isolated by column chromatography (methanol/ethyl acetate 05:95) in 52% yield (68.5 mg); white solid; mp: 190–193 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.25 (s, 3 H), 1.46 (s, 3 H), 1.58 (s, 3 H), 2.32 (s, 3 H), 2.73 (s, 3 H), 6.04 (s, 1 H), 6.16 (br, 2 H), 6.44 (d, *J* = 8.0 Hz, 1 H), 6.53 (t, *J* = 7.2 Hz, 1 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 6.89 (t, *J* = 7.2 Hz, 1 H), 7.04 (br, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 11.0, 14.1, 18.0, 18.9, 20.7, 56.9, 59.7, 92.6, 107.9, 117.3, 121.8, 127.0, 132.3, 142.7, 148.9, 159.9, 167.2; IR (nujol): ν_{max} = 3489, 3337, 3326, 3297, 1698, 16898 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}N_5O_2[M + H]^+$: 330.1930; found: 330.1932.



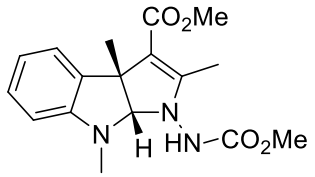
5p

Methyl (12-(dimethoxyphosphoryl)-11-methyl-6,7,8,9-tetrahydro-5*H*-8a,4b-(epiminoetheno)carbazol-10-yl)carbamate: the product **5p** was isolated by column chromatography (ethyl acetate/cyclohexane 90:10) in 31% yield (50.6 mg); white solid; mp: 198–200 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 0.91–1.54 (m, 7 H), 1.75–1.96 (m, 1 H), 1.91 (s, 3 H), 3.18 (s, 3 H), 3.35 (s, 3 H), 3.62 (s, 3 H), 6.01 (s, 1 H), 6.46 (d, *J* = 7.6 Hz, 1 H), 6.59 (t, *J* = 7.6, 1 H), 6.91 (t, *J* = 7.6, 1 H), 7.20 (d, *J* = 7.6 Hz, 1 H), 9.14 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 11.6, 14.1, 19.3 ($^{2}J_{CP}$ = 35.0 Hz), 20.7, 26.3, 31.5, 50.8 ($^{2}J_{CP}$ = 30.9 Hz), 51.9, 56.1 ($^{3}J_{CP}$ = 10.1 Hz), 59.7, 91.7, 108.4, 117.4, 124.1, 127.0, 149.7, 157.0, 160.0, 170.3; IR (nujol): ν_{max} = 3319, 3283, 1695 cm^{-1}; MS (ESI) *m/z* = 408 $[M + H]^+$; anal. calcd. for $C_{19}H_{26}N_3O_5P$ (407.40): C 56.01, H 6.43, N 10.31; found: C 56.16, H 6.35, N 10.18.



5q

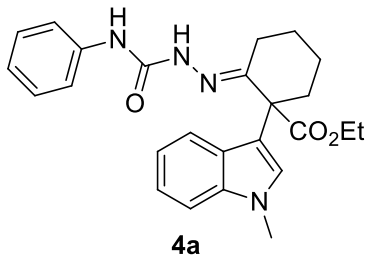
Methyl 1-((methoxycarbonyl)amino)-2,3a,8,8a-tetramethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-3-carboxylate: the product **5q** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 94% yield (129.9 mg); white solid; mp: 155–157 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.28 (s, 3 H), 1.42 (s, 3 H), 1.97 (s, 3 H), 2.72 (s, 3 H), 3.61 (s, 3 H), 3.68 (s, 3 H), 6.35 (d, *J* = 7.6 Hz, 1 H), 6.58 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 6.98 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.31 (d, *J* = 7.6 Hz, 1 H), 9.48 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 11.9, 13.9, 20.5, 26.3, 28.8, 49.9, 52.2, 55.3, 95.3, 102.6, 104.8, 117.2, 123.6, 127.3, 133.4, 148.6, 156.8, 165.7; IR (nujol): ν_{max} = 3369, 1741, 1693 cm^{-1}; MS (ESI) *m/z* = 346 [M + H]$^+$; anal. calcd. for $C_{18}H_{23}N_3O_4$ (345.39): C 62.59, H 6.71, N 12.17; found: C 62.43, H 6.80, N 12.31.



5r

Methyl 1-((methoxycarbonyl)amino)-2,3a,8-trimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-3-carboxylate: the product **5r** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 46% yield (60.9 mg); white solid; mp: 127–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.67 (s, 3 H), 2.09 (s, 3 H), 2.96 (s, 3 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 4.92 (s, 1 H), 6.45 (d, *J* = 7.6 Hz, 1 H), 6.72 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 6.84 (br, 1 H), 7.09 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 7.52 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.5, 25.4, 34.8, 50.5, 53.2, 54.5, 65.9, 96.1, 106.9, 118.8, 124.9, 127.9, 134.7, 149.7, 156.1, 160.0, 166.5; IR (nujol): ν_{max} = 3287, 1739, 1701 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{22}N_3O_4$[M + H]$^+$: 332.1610; found: 332.1639.

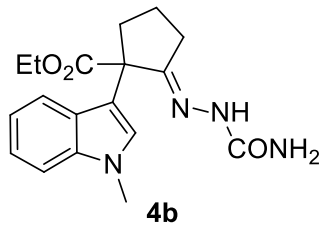
***Procedure for ring-opening reaction of tetrahydro-1H-pyridazino[3,4-b]indole 3b*:** To a solution of compound **3b** (0.4 mmol) in dichloromethane (2 mL) Amberlyst 15(H) (500 mg/mmol) or TFA (0.4 mmol) was added. After the disappearance of starting **3b** (TLC check, 20 h), the crude mixture was purified by column chromatography on silica gel to afford product **4a**.



4a

Ethyl 1-(1-methyl-1*H*-indol-3-yl)-2-(2-(phenylcarbamoyl)hydrazono)cyclohexanecarboxylate: the product **4a** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 71% yield (122.8 mg); white solid; mp: 210–212 °C, ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.13 (t, *J* = 7.2 Hz, 3 H), 1.44–1.55 (m, 2 H), 1.79–1.85 (m, 2 H), 2.11–2.23 (m, 2 H), 2.68 (d, *J* = 14.4 Hz, 1 H), 3.04 (d, *J* = 14.4 Hz, 1 H), 3.79 (s, 3 H), 4.05–4.19 (m, 2 H), 6.48 (d, *J* = 8.4 Hz, 2 H), 6.85 (dt, J_1 = 8.4 Hz, J_2 =

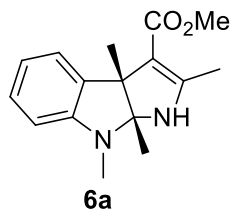
1.2 Hz, 1 H), 6.96 (dt, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1 H), 7.07 (t, J = 8.4 Hz, 2 H), 7.18 (dt, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1 H), 7.25 (s, 1 H), 7.33 (s, 1 H), 7.51 (t, J = 8.4 Hz, 2 H), 10.02 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 13.9, 22.6, 25.3, 25.5, 32.4, 35.6, 55.5, 60.7, 109.8, 113.5, 117.5, 118.8, 120.8, 120.9, 121.9, 126.6, 127.5, 128.3, 137.1, 138.1, 151.0, 153.3, 172.5; IR (nujol): ν_{max} = 3190, 3088, 1726, 1681 cm^{-1}; MS (ESI) *m/z* = 433 [M + H]$^+$; anal. calcd. for $C_{25}H_{28}N_4O_3$ (432.51): C 69.42, H 6.53, N 12.95; found: C 69.57, H 6.44, N 12.87.



4b

Ethyl 2-(2-carbamoylhydrazono)-1-(1-methyl-1*H*-indol-3-yl)cyclopentanecarboxylate: the product **4b** [see manuscript, Scheme 1] was isolated by column chromatography (ethyl acetate/cyclohexane 90:10) in 67% yield (229.4 mg); white solid; mp: 168–170 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.08 (t, J = 7.2 Hz, 3 H), 1.62–1.87 (m, 2 H), 2.29–2.36 (m, 1 H), 2.43–2.56 (m, 3 H), 3.73 (s, 3 H), 4.04–4.12 (m, 2 H), 5.92 (br, 2 H), 6.98 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.09 (s, 1 H), 7.12 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.38 (d, J = 8.0 Hz, 1 H), 7.44 (d, J = 8.0 Hz, 1 H), 9.14 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.1, 21.4, 27.9, 32.3, 36.2, 56.8, 60.6, 109.8, 113.4, 118.4, 120.2, 121.0, 126.1, 127.5, 137.2, 156.4, 156.9, 172.7; IR (nujol): · $_{max}$ = 3470, 3200, 3160, 1733, 1696 cm^{-1}; MS (ESI) *m/z* = 343 [M + H]$^+$; anal. calcd. for $C_{18}H_{22}N_4O_3$ (342.39): C 63.14, H 6.48, N 16.36; found: C 62.98, H 6.58, N 16.45.

***Ethyl bromoacetate-assisted cleavage of the N-N bond in 5q* (*Magnus' procedure*)**[79]: Ethyl 2-bromoacetate (1.5 eq) and Cs_2CO_3 (2.5 eq) were added to a solution of compound **5q** (0.3 mmol) in acetonitrile (2 mL). The mixture was heated at 50 °C until the starting material was consumed (TLC check, 1 h) and then refluxed for additional 1.5 h (TLC check). The crude mixture was filtered and then purified by column chromatography on silica gel to afford the product **6a**.



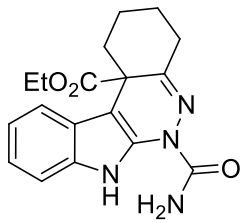
6a

Methyl 2,3a,8,8a-tetramethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-3-carboxylate: the product **6a** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 64% yield (52.3 mg); white oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.27 (s, 3 H), 1.39 (s, 3 H), 2.03 (s, 3 H), 2.67 (s, 3 H), 3.55 (s, 3 H), 6.30 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 6.52 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 6.92 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.26 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.45 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 14.5, 17.4, 19.8, 28.2, 49.3, 56.4, 90.9, 101.6, 104.9, 116.9, 123.8, 126.8, 134.7, 149.3, 159.3, 165.9; IR (nujol): ν_{max} = 3369, 1741 cm^{-1}; MS (ESI) *m/z* = 273

$[M + H]^+$; anal. calcd. for $C_{16}H_{20}N_2O_2$ (272.34): C 70.56, H 7.40, N 10.29; found: C 70.41, H 7.47, N 10.39.

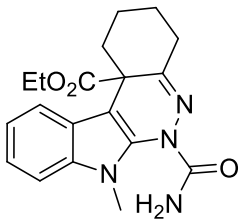
CHAPTER 6: *Divergent construction of fused and non-fused N-polyheterocycles via formal [4+2] Annulation of Indoles with Cyclic Azoalkenes.*

***General procedure for the oxidation of compound 1 to 2'(or 2)*:** to a solution of the compound **1** (0.5 mmol) in benzene (1 mL), MnO_2 (10 eq) was added and the reaction was subsequently brought to the temperature of 70 ° C (oil bath) until the reagent disappeared (TLC check, 20 h). The crude mixture was then filtrated and purified by column chromatography on silica gel to afford product **2'** (or **2**).



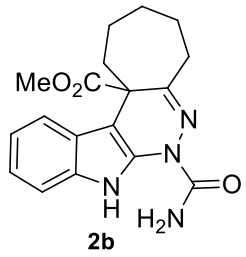
2a

Ethyl 6-carbamoyl-2,3,4,6,7,11c-hexahydro-1*H*-indolo[2,3-*c*]cinnoline-11c-carboxylate: the product **2a** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 17% yield (28.9 mg); whitish solid; mp: 159–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, *J* = 7.2 Hz, 3 H), 1.51–1.89 (m, 4 H), 1.95–2.02 (m, 1 H), 2.48 (dt, J_1 = 13.2 Hz, J_2 = 4.8 Hz, 1 H), 2.62 (d, *J* = 13.2 Hz, 1 H), 3.34 (d, *J* = 13.2 Hz, 1 H), 4.09-4.29 (m, 2 H), 5.26 (br, 1 H), 6.79 (br, 1 H), 7.07-7.14 (m, 2 H), 7.32 (d, *J* = 7.2 Hz, 1 H), 7.63 (d, *J* = 7.2 Hz, 1 H), 10.13 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3, 23.3, 26.8, 34.3, 36.4, 50.4, 61.8, 91.9, 111.1, 119.2, 120.2, 121.1, 123.8, 129.6, 132.7, 151.8, 155.1, 170.6; IR (nujol): ν_{max} = 3455, 3425, 3297, 1720, 1686 cm^{-1}; MS (ESI) *m/z* = 341 [M + H]$^+$; anal. calcd. for $C_{18}H_{20}N_4O_3$ (340.37): C 63.52, H 5.92, N 16.46; found: C 63.69, H 5.85, N 16.34.



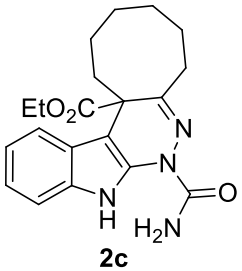
2'a

Ethyl 6-carbamoyl-7-methyl-2,3,4,6,7,11c-hexahydro-1*H*-indolo[2,3-*c*]cinnoline-11c-carboxylate: the product **2'a** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 26% yield (46.1 mg); whitish solid; mp: 179-181 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.18 (t, *J* = 7.2 Hz, 3 H), 1.49-1.89 (m, 4 H), 1.96-2.01 (m, 1 H), 2.47 (dt, J_1 = 14.4 Hz, J_2 = 5.2 Hz, 1 H), 2.69-2.75 (m, 1 H), 3.45-3.52 (m, 1 H), 3.72 (s, 3 H), 4.05-4.20 (m, 2 H), 5.14 (br, 1 H), 6.58 (br, 1 H), 7.09 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1 H), 7.17 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 7.66 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.1, 22.9, 26.0, 33.4, 33.6, 35.4, 50.8, 61.8, 96.5, 109.9, 119.8, 120.1, 121.3, 123.6, 131.3, 136.8, 154.4, 156.2, 170.5; IR (nujol): ν_{max} = 3491, 3363, 1734, 1703 cm^{-1}; MS (ESI) *m/z* = 355 [M + H]$^+$; anal. calcd. for $C_{19}H_{22}N_4O_3$ (354.40): C 64.39, H 6.26, N 15.81; found: C 64.25, H 6.19, N 15.96



2b

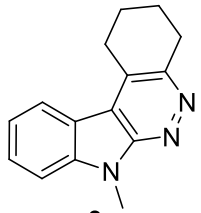
Methyl 7-carbamoyl-1,2,3,4,5,7,8,12c-octahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole-12c-carboxylate: the product **2b** was isolated by column chromatography (ethyl acetate/cyclohexane 30:70) in 55% yield (93.6 mg); white solid; mp: 181–183 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.10–1.23 (m, 1 H), 1.38–1.47 (m, 2 H), 1.65–1.74 (m, 2 H), 1.89–1.93 (m, 1 H), 2.19–2.35 (m, 2 H), 2.65–2.71 (m, 1 H), 2.84–2.90 (m, 1 H), 3.57 (s, 3 H), 6.93-7.01 (m, 2 H), 7.26 (s, 2 H), 7.44–7.50 (m, 2 H), 11.21 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 22.9, 29.2, 29.6, 33.7, 33.8, 51.5, 52.4, 89.9, 112.2, 117.7, 119.5, 120.1, 123.1, 131.0, 133.4, 150.9, 154.1, 171.9; IR (nujol): ν_{max} = 3491, 3430, 3297, 1734, 1707 cm^{-1}; MS (ESI) *m/z* = 341 [M + H]$^+$; anal. calcd. for $C_{18}H_{20}N_4O_3$ (340.38): C 63.52, H 5.92, N 16.46; found: C 63.42, H 6.01, N 16.56.



2c

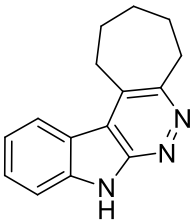
Ethyl 8-carbamoyl-2,3,4,5,6,8,9,13c-octahydro-1*H*-cycloocta[5,6]pyridazino[3,4-*b*]indole-13c-carboxylate: the product **2c** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 45% yield (82.9 mg); white solid; mp: 192–194 °C; ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 1.15 (t, *J* = 7.2 Hz, 3 H), 1.18–1.24 (m, 1 H), 1.35–1.55 (m, 4 H), 1.61–1.81 (m, 2 H), 1.94–2.01 (m, 1 H), 2.33–2.48 (m, 2 H), 2.65–2.71 (m, 1 H), 2.87–2.93 (m, 1 H), 4.01–4.20 (m, 2 H), 5.07 (br, 1 H), 6.76 (br, 1 H), 7.06–7.14 (m, 2 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.60 (d, *J* = 8.0 Hz, 1 H); 10.13 (s, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.2, 23.7, 24.2, 24.9, 28.3, 31.3, 32.9, 52.1, 61.7, 89.6, 111.2, 118.9, 120.3, 121.2, 124.3, 131.1, 132.8, 154.6, 155.0, 171.5; IR (nujol): ν_{max} = 3410, 3276, 3220, 1724, 1698 cm^{-1}; MS (ESI) *m/z* = 369 [M + H]$^+$; anal. calcd. for $C_{20}H_{24}N_4O_3$ (368.43): C 65.20, H 6.57, N 15.21; found: C 65.34, H 6.62, N 15.30.

***General procedure for hydrolysis and oxidation of compound 2 to 3**:* To a suspension of KOH (10 eq.) in alcohol, the compound **2** (0.2 mmol) was added and the mixture was refluxed for the indicate time (TLC check, 7h). The crude mixture was then filtrated and purified by column chromatography on silica gel to afford product (**3**).



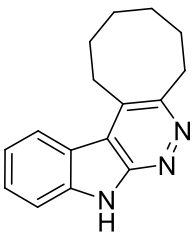
3a

7-Methyl-2,3,4,7-tetrahydro-1*H*-indolo[2,3-*c*]cinnoline: the product **3a** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 43% yield (20.5 mg); yellowish solid; mp: 167–169 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.92–1.96 (m, 3 H), 2.07–2.09 (m, 3 H), 2.13–2.20 (m, 2 H), 3.99 (s, 3 H), 7.31–7.36 (m, 1 H), 7.68–7.74 (m, 2 H), 8.20 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 21.6, 22.5, 25.7, 27.9, 29.8, 109.9, 116.4, 118.3, 120.4, 125.1, 129.4, 130.5, 141.5, 151.1, 152.2; IR (nujol): no significative signals were detected; MS (ESI) *m/z* = 238 [M + H]$^+$; anal. calcd. for $C_{15}H_{15}N_3$ (237.39): C 75.92, H 6.37, N 17.71; found: C 76.01, H 6.45, N 17.82.



3b

1,2,3,4,5,8-Hexahydrocyclohepta[5,6]pyridazino[3,4-*b*]indole: the product **3b** was isolated by column chromatography (ethyl acetate/cyclohexane 40:60) in 52% yield (24.7 mg); yellowish solid; mp: 180–182 °C; ^{1}H NMR (400 MHz[D$_6$]DMSO, 25 °C): δ = 1.66–1.71 (m, 2 H), 1.75–1.81 (m, 2 H), 1.88–1.94 (m, 2 H), 3.30–3.34 (m, 2 H), 3.39–3.43 (m, 2 H), 7.26 (t, *J* = 8.0 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.59 (t, *J* = 8.0 Hz, 1 H), 8.35 (d, *J* = 8.0 Hz, 1 H), 12.10 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 26.8, 26.9, 30.2, 32.2, 34.9, 113.1, 115.3, 119.1, 121.2, 125.0, 130.7, 138.7, 142.4, 153.3, 156.4; IR (nujol): no significative signals were detected; MS (ESI) *m/z* = 238 [M + H]$^+$; anal. calcd. for $C_{15}H_{15}N_3$ (237.29): C 75.92, H 6.37, N 17.71; found: C 76.03, H 6.42, N 17.59.

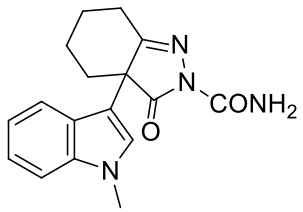


3c

2,3,4,5,6,9-Hexahydro-1*H*-cycloocta[5,6]pyridazino[3,4-*b*]indole: the product **3c** was isolated by column chromatography (ethyl acetate/cyclohexane 60:40) in 68% yield (34.2 mg); yellowish solid; mp: 195–197 °C; ^{1}H NMR (400 MHz[D$_6$]DMSO, 25 °C): δ = 1.18–1.31 (m, 2 H), 1.38–1.44 (m, 2 H), 1.70–1.81 (m, 2 H), 1.83–1.95 (m, 2 H), 3.24–3.29 (m, 2 H), 3.31–3.41 (m, 2 H), 7.29 (t, *J* = 8.0 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.61 (t, *J* = 8.0 Hz, 1 H), 8.21 (d, *J* = 8.0 Hz, 1 H), 12.12 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 25.5, 25.7, 26.5, 28.3, 31.4, 31.7, 111.8, 116.3, 118.5, 120.2, 124.6, 129.2, 133.5, 140.9, 153.8, 154.9; IR (nujol): no significative signals were detected; MS (ESI) *m/z* =

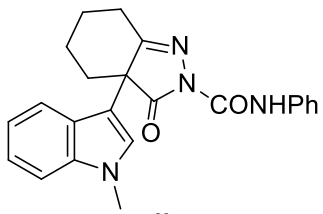
252 $[M + H]^+$; anal. calcd. for $C_{16}H_{17}N_3$ (251.32): C 76.46, H 6.82, N 16.72; found: C 76.58, H 6.87, N 16.60.

General procedure for the synthesis of the indole-pyrazolone derivative 4: to a solution of cycloadduct **1** (0.2 mmol) in methylene chloride (CH_2Cl_2) (2 ml) trifluoroacetic acid (TFA) (2.5 eq) was added at room temperature and then the reaction was refluxed for 2 h. After the disappearance of the reagents (TLC check), CH_2Cl_2 was removed under vacuum. The crude mixture was washed with water and the product was extracted with EtOAc (10 ml). The organic phase was dried with Na_2SO_4 and solvent was removed under vacuum. The compound **4** precipitates as a white solid and was subsequently filtered with ethyl ether.



4a

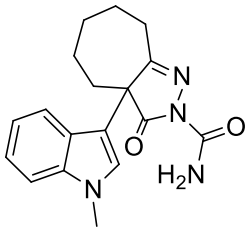
3a-(1-methyl-1*H*-indol-3-yl)-3-oxo-3,3a,4,5,6,7-hexahydro-2*H*-indazole-2-carboxamide: the product **4a** was obtained in 92% yield (57.2 mg); white solid; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.39–1.52 (m, 1 H), 1.58–1.78 (m, 3 H), 1.92–1.99 (m, 1 H), 2.21 (dt, J_1 = 13.2 Hz, J_2 = 5.6 Hz, 1 H), 2.59 (d, J = 12.8 Hz, 1 H), 2.82 (d, J = 12.8 Hz, 1 H), 3.80 (s, 3 H), 7.02 (t, J = 8.0 Hz, 1 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.24 (d, J = 8.0 Hz, 1 H), 7.26 (br, 1 H), 7.45 (d, J = 8.0 Hz, 1 H), 7.53 (br, 1 H), 7.57 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 20.9, 27.0, 28.0, 32.6, 33.5, 54.3, 105.7, 110.3, 117.8, 119.5, 121.7, 125.1, 129.1, 136.9, 149.7, 166.5, 176,8; IR (nujol): ν_{max} =3399, 3251, 1726, 1702 cm^{-1}; anal. calcd. for $C_{17}H_{18}N_4O_2$ (310.35): C 65.79, H 5.85, N 18.05; found: C 65.64, H 5.93, N 17.94.



4b

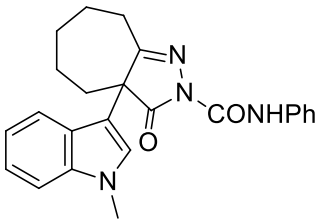
3a-(1-methyl-1*H*-indol-3-yl)-3-oxo-*N*-phenyl-3,3a,4,5,6,7-hexahydro-2*H*-indazole-2-carboxamide: the product **4b** was obtained in 90% yield (69.6 mg); white solid; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.44–1.57 (m, 1 H), 1.59–1.75 (m, 2 H), 1.86 (dt, J_1 = 13.2 Hz, J_2 = 5.6 Hz, 1 H), 1.96–2.01 (m, 1 H), 2.26 (dt, J_1 = 13.2 Hz, J_2 = 5.6 Hz, 1 H), 2.68 (d, J = 12.8 Hz, 1 H), 2.85 (d, J = 12.8 Hz, 1 H), 3.81 (s, 3 H), 7.04 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.09 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.18 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.27–7.38 (m, 3 H), 7.46 (d, J = 8.0 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 2 H), 7.62 (s, 1 H), 9.82 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 20.9, 27.1, 28.0, 32.6, 33.5, 54.5, 105.6, 110.4, 117.9, 119.7, 120.1, 121.7, 123.9, 125.2, 128.9, 129.2, 137.0, 137.4, 147.0, 167.2, 176.6; IR

(nujol): ν_{max} = 3236, 1744, 1709 cm^{-1}; anal. calcd. for $C_{23}H_{22}N_4O_2$ (386.45): C 71.48, H 5.74, N 14.50; found: C 71.36, H 5.83, N 14.62.



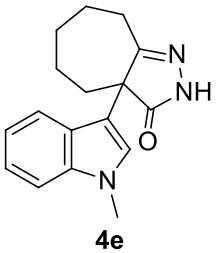
4c

8a-(1-Methyl-1*H*-indol-3-yl)-1-oxo-4,5,6,7,8,8a-hexahydrocyclohepta[*c*]pyrazole-2(1*H*)-carboxamide: the product **4c** was obtained in in 95% yield (61.6 mg); white solid; mp: 131–133 °C; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.28–1.35 (m, 1 H), 1.48–1.69 (m, 4 H), 1.76–1.85 (m, 1 H), 2.15–2.23 (m, 1 H), 2.37–2.46 (m, 2 H), 2.69–2.75 (m, 1 H), 3.78 (s, 3 H), 7.02 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.17 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.24 (br, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.46 (s, 1 H), 7.53 (br, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 24.7, 25.9, 28.5, 29.3, 32.6, 32.8, 58.5, 106.9, 110.3, 118.4, 119.5, 121.7, 124.8, 128.5, 136.9, 149.4, 166.7, 176.6; IR (nujol): ν_{max} = 3425, 3267, 1729, 1683 cm^{-1}; MS (ESI) *m/z* = 325 $[M + H]^+$; anal. calcd. for $C_{18}H_{20}N_4O_2$ (324.38): C 66.65, H 6.21, N 17.27; found: C 66.51, H 6.28, N 17.39; found: C 66.64, H 6.17, N 17.27.



4d

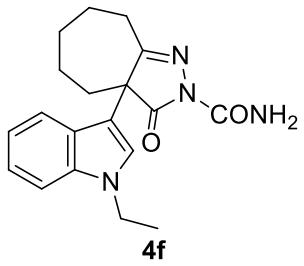
3a-(1-methyl-1*H*-indol-3-yl)-3-oxo-*N*-phenyl-3a,4,5,6,7,8-hexahydrocyclohepta[*c*]pyrazole-2(3*H*)-carboxamide: the product **4d** was obtained in in 90% yield (72.1 mg); white solid; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.35–1.45 (m, 1 H), 1.50–1.71 (m, 4 H), 1.78–1.87 (m, 1 H), 2.23–2.31 (m, 1 H), 2.43–2.55 (m, 2 H), 2.77–2.85 (m, 1 H), 3.79 (s, 3 H), 7.05 (t, J = 7.2 Hz, 1 H), 7.09 (t, J = 7.2 Hz, 1 H), 7.18 (t, J = 7.6 Hz, 1 H), 7.33 (t, J = 8.0 Hz, 2 H), 7.41 (d, J = 8.0 Hz, 1 H), 7.45 (d, J = 8.0 Hz, 1 H), 7.50 (s, 1 H), 7.58 (d, J = 8.0 Hz, 2 H), 9.78 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 24.7, 25.7, 28.4, 29.4, 32.5, 32.8, 58.7, 106.7, 110.3, 118.6, 119.6, 120.1, 121.7, 123.9, 124.9, 128.6, 128.8, 136.9, 137.3, 146.7, 167.4, 176.4; IR (nujol): ν_{max} = 3251, 1739, 1708 cm^{-1}; anal. calcd. for $C_{24}H_{24}N_4O_2$ (400.47): C 71.98, H 6.04, N 13.99; found: C 71.84, H 6.10, N 14.13.



4e

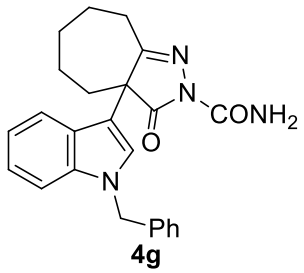
3a-(1-methyl-1*H*-indol-3-yl)-3a,4,5,6,7,8-hexahydrocyclohepta[*c*]pyrazol-3(2*H*)-one: the product **4e** was obtained in 97% yield (54.6 mg); white solid; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.20–1.31 (m, 1 H), 1.41–1.63 (m, 4 H), 1.77–1.85 (m, 1 H), 1.98–2.05 (m, 1 H), 2.25–2.34 (m, 2 H), 2.56–2.63 (m, 1 H), 3.77 (s, 3 H), 6.98 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.14 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.37 (s, 1 H), 7.41 (d, J = 8.0 Hz, 1 H), 11.14 (s,

1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 24.8, 26.3, 28.7, 29.4, 32.4, 32.9, 55.4, 108.3, 109.9, 18.7, 119.0, 121.3, 125.2, 128.1, 136.8, 165.9, 178.9; IR (nujol): ν_{max} = 3165, 1714 cm^{-1}; anal. calcd. for $C_{17}H_{19}N_3O$ (281.35): C 72.57, H 6.81, N 14.94; found: C 72.45, H 6.90, N 15.03.



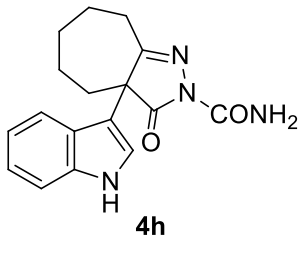
4f

3a-(1-ethyl-1*H*-indol-3-yl)-3-oxo-3a,4,5,6,7,8-hexahydrocyclohepta[*c*]pyrazole-2(3*H*)-carboxamide: the product **4f** was obtained in 93% yield (62.9 mg); white solid; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.27–1.38 (m, 1 H), 1.36 (t, *J* = 7.2 Hz, 3 H), 1.45–1.68 (m, 4 H), 1.77–1.85 (m, 1 H), 2.16–2.24 (m, 1 H), 2.40–2.46 (m, 2 H), 2.68–2.75 (m, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 7.01 (dt, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1 H), 7.16 (dt, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1 H), 7.25 (br, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.51 (s, 1 H), 7.53 (br, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 15.3, 24.7, 25.9, 28.5, 29.3, 32.8, 40.4, 58.5, 107.1, 110.3, 118.5, 119.5, 121.6, 124.9, 126.9, 135.9, 149.4, 166.7, 176.7; IR (nujol): ν_{max} = 3384, 3175, 1734, 1683 cm^{-1}; anal. calcd. for $C_{19}H_{22}N_4O_2$ (338.40): C 67.44, H 6.55, N 16.56.; found: C 67.57, H 6.46, N 16.42.



4g

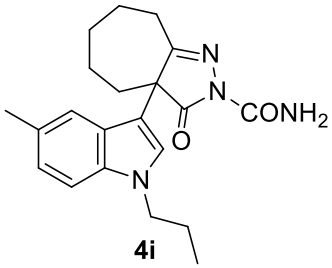
3a-(1-benzyl-1*H*-indol-3-yl)-3-oxo-3a,4,5,6,7,8-hexahydrocyclohepta[*c*]pyrazole-2(3*H*)-carboxamide: the product **4g** was obtained in quant. yield (80.0 mg); white solid; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.30–1.41 (m, 1 H), 1.44–1.67 (m, 4 H), 1.77–1.83 (m, 1 H), 2.14–2.21 (m, 1 H), 2.43–2.49 (m, 2 H), 2.71–2.77 (m, 1 H), 5.44 (s, 2 H), 7.02 (t, *J* = 8.0 Hz, 1 H), 7.12 (t, *J* = 8.0 Hz, 1 H), 7.19–7.33 (m, 6 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.59 (br, 1 H), 7.70 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 24.8, 25.7, 28.4, 29.4, 32.9, 49.2, 58.5, 107.5, 110.8, 118.6, 119.7, 121.8, 125.2, 126.9, 127.4, 128.2, 128.5, 136.3, 137.9, 149.4, 166.7, 176.6; IR (nujol): ν_{max} = 3409, 3257, 1759, 1724 cm^{-1}; anal. calcd. for $C_{24}H_{24}N_4O_2$ (400.47): C 71.98, H 6.04, N 13.99; found: C 72.11, H 5.95, N 13.86.



4h

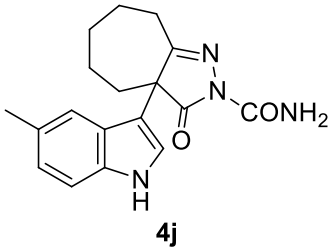
3a-(1*H*-indol-3-yl)-3-oxo-3a,4,5,6,7,8-hexahydrocyclohepta[*c*]pyrazole-2(3*H*)-carboxamide: the product **4h** was obtained in quant. yield (62.1 mg); white solid; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.17–1.81 (m, 6 H), 2.14–2.22 (m, 1 H), 2.30–2.45 (m, 2 H), 2.68–2.82 (m, 1 H), 6.98–7.57 (m, 7 H), 11.35 (s, 1 H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 24.7, 26.0, 28.5, 29.332.7, 58.6, 107.8, 112.0, 118.2, 119.4, 121.6,

124.4, 124.5, 136.6, 149.5, 166.8, 176.8; IR (nujol): ν_{max} = 3404, 3287, 3257, 1734, 1703 cm^{-1}; anal. calcd. for $C_{17}H_{18}N_4O_2$ (310.35): C 65.79, H 5.85, N 18.05; found: C 65.94, H 5.79, N 17.91.



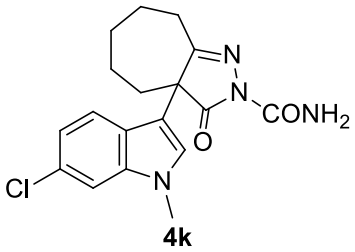
4i

3a-(5-methyl-1-propyl-1*H*-indol-3-yl)-3-oxo-3a,4,5,6,7,8-hexahydrocyclohepta[*c*]pyrazole-2(3*H*)-carboxamide: the product **4i** was obtained in quant. yield (73.3 mg); white solid; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 0.80 (t, *J* = 7.2 Hz, 3 H), 1.30–1.41 (m, 1 H), 1.44–1.63 (m, 4 H), 1.72 (sex, *J* = 7.2 Hz, 2 H), 1.79–1.86 (m, 1 H), 2.10–2.18 (m, 1 H), 2.33 (s, 3 H), 2.38–2.47 (m, 2 H), 2.67–2.78 (m, 1 H), 4.10 (t, *J* = 7.2 Hz, 2 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 7.10 (s, 1 H), 7.28 (br, 1 H), 7.37 (d, *J* = 8.4 Hz, 1 H), 7.43 (s, 1 H), 7.57 (br, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 11.1, 21.3, 22.9, 24.8, 25.7, 28.4, 29.4, 32.9, 47.1, 58.5, 106.2, 110.2, 118.1, 123.1, 125.2, 127.7, 127.9, 134.7, 149.5, 166.7, 176.7; IR (nujol): ν_{max} = 3369, 3175, 1734, 1688 cm^{-1}; anal. calcd. for $C_{21}H_{26}N_4O_2$ (366.45): C 68.83, H 7.15, N 15.29; found: C 68.99, H 7.04, N 15.16.



4j

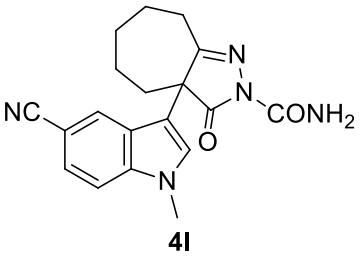
3a-(5-methyl-1*H*-indol-3-yl)-3-oxo-3a,4,5,6,7,8-hexahydrocyclohepta[*c*]pyrazole-2(3*H*)-carboxamide: the product **4j** was obtained in quant. yield (64.9 mg); white solid; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.23–1.37 (m, 1 H), 1.40–1.69 (m, 4 H), 1.73–1.84 (m, 1 H), 2.15–2.23 (m, 1 H), 2.32 (s, 3 H), 2.39–2.45 (m, 2 H), 2.69–2.75 (m, 1 H), 6.93 (d, *J* = 8.4 Hz, 1 H), 7.09 (s, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.31 (br, 1 H), 7.37 (d, *J* = 2.4 Hz, 1 H), 7.56 (br, 1 H), 11.21 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 21.4, 24.7, 25.9, 28.5, 29.3, 32.8, 58.6, 107.2, 111.7, 117.8, 123.1, 124.3, 124.7, 127.8, 134.9, 149.5, 166.8, 176.8; IR (nujol): ν_{max} = 3399, 3328, 3272, 1729, 1714 cm^{-1}; anal. calcd. for $C_{18}H_{20}N_4O_2$ (324.37): C 66.65, H 6.21, N 17.27; found: C 66.53, H 6.33, N 17.38.



4k

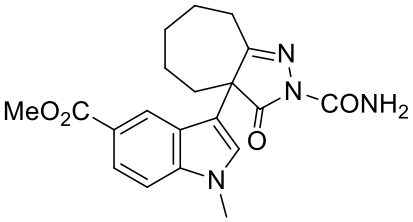
3a-(6-chloro-1-methyl-1*H*-indol-3-yl)-3-oxo-3a,4,5,6,7,8-hexahydrocyclohepta[*c*]pyrazole-2(3*H*)-carboxamide: the product **4k** was obtained in 96% yield (68.9 mg); white solid; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.29–1.35 (m, 1 H), 1.44–1.67 (m, 4 H), 1.72–1.82 (m, 1 H), 2.15–2.23 (m, 1 H), 2.34– 2.48 (m, 2 H), 269–2.76 (m, 1 H), 3.78 (s, 3 H), 7.07 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1 H), 7.23 (br, 1 H), 7.33 (d, *J* = 8.8 Hz, 1 H), 7.51 (s, 1 H), 7.57 (br, 1 H), 7.60 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C):

δ = 24.7, 25.9, 28.4, 29.3, 32.7, 32.8, 58.4, 107.4, 110.3, 119.8, 119.9, 123.5, 126.7, 129.6, 137.4, 149.3, 166.5, 176.3; IR (nujol): ν_{max} = 3420, 3262, 1754, 1724 cm^{-1}; anal. calcd. for $C_{18}H_{19}ClN_4O_2$ (358.82): C 60.25, H 5.34, N 15.61; found: C 60.41, H 5.27, N 15.50.



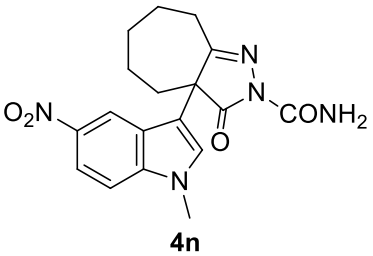
4l

3a-(5-cyano-1-methyl-1*H*-indol-3-yl)-3-oxo-3a,4,5,6,7,8-hexahydrocyclohepta[*c*]pyrazole-2(3*H*)-carboxamide: the product **4l** was obtained in 99% yield (69.2 mg); white solid; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.23–1.38 (m, 1 H), 1.40–1.79 (m, 5 H), 2.26–2.55 (m, 3 H), 2.76–2.82 (m, 1 H), 3.84 (s, 3 H), 7.25 (br, 1 H), 7.54 (d, *J* = 8.4 Hz, 1 H), 7.57 (br, 1 H), 7.65 (s, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.88 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 24.6, 26.0, 28.5, 29.4, 32.7, 32.8, 58.4, 101.7, 108.5, 111.9, 120.3, 124.2, 124.3, 124.4, 131.1, 138.6, 149.3, 166.2, 176.0; IR (nujol): ν_{max} = 3399, 3302, 1739, 1724 cm^{-1}; anal. calcd. for $C_{19}H_{19}N_5O_2$ (349.38): C 65.32, H 5.48, N 20.04; found: C 65.47, H 5.36, N 19.91.



4m

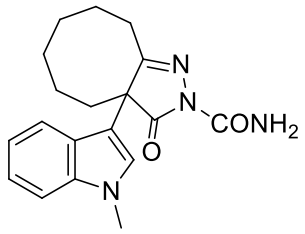
Methyl 3-(2-carbamoyl-3-oxo-2,3,3a,4,5,6,7,8-octahydrocyclohepta[*c*]pyrazol-3a-yl)-1-methyl-1*H*-indole-5-carboxylate: the product **4m** was obtained in 98% yield (74.9 mg); white solid; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.25–1.38 (m, 1 H), 1.45–1.83 (m, 5 H), 2.22–2.43 (m, 2 H), 2.49–2.56 (m, 2 H), 2.73–2.85 (m, 1 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 7.25 (br, 1 H), 7.55 (d, *J* = 8.8 Hz, 1 H), 7.59 (s, 1 H), 7.79 (dd, J_1 = 8.8 Hz, J_2 = 1.2 Hz, 1 H), 8.17 (d, *J* = 1.2 Hz, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 24.7, 26.0, 28.0, 29.4, 32.8, 33.0, 51.8, 58.5, 108.8, 110.4, 120.9, 121.6, 122.5, 124.4, 130.3, 139.3, 149.3, 166.3, 166.9, 176.3; IR (nujol): ν_{max} = 3440, 3343, 1754, 1709 cm^{-1}; anal. calcd. for $C_{20}H_{22}N_4O_4$ (382.41): C 62.82, H 5.80, N 14.65; found: C 62.98, H 5.74, N 14.51.



4n

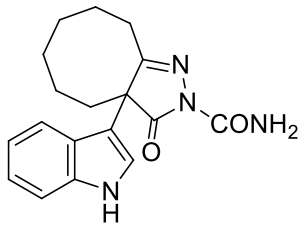
3a-(1-methyl-5-nitro-1*H*-indol-3-yl)-3-oxo-3a,4,5,6,7,8-hexahydrocyclohepta[*c*]pyrazole-2(3*H*)-carboxamide: the product **4n** was obtained in 98% yield (72.4 mg); yellow solid; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.25–1.75 (m, 6 H), 2.27–2.44 (m, 2 H), 2.48–2.58 (m, 1 H), 2.72–2.88 (m, 1 H), 3.87 (s, 3 H), 7.25 (br, 1 H), 7.61 (br, 1 H), 7.68 (d, *J* = 8.4 Hz, 1 H), 7.75 (s, 1 H), 8.07 (d, *J* = 8.4 Hz, 1 H), 8.40 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 24.6, 26.1, 28.5, 29.4, 33.0, 33.2, 58.4, 110.1, 111.2,

115.9, 116.9, 123.8, 132.3, 139.9, 140.9, 149.2, 166.1, 175.9; IR (nujol): ν_{max} = 3399, 3308, 1739, 1719 cm^{-1}; anal. calcd. for $C_{18}H_{19}N_5O_4$ (369.37): C 58.53, H 5.18, N 18.96; found: 58.68, H 5.11, N 18.83.



4o

3a-(1-methyl-1*H*-indol-3-yl)-3-oxo-3,3a,4,5,6,7,8,9-octahydro-2*H*-cycloocta[*d*]pyrazole-2-carboxamide: the product **4o** was obtained in quant. yield (67.7 mg); white solid; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 0.89–1.04 (m, 1 H), 1.36–1.79 (m, 7 H), 2.12–2.26 (m, 1 H), 2.42–2.54 (m, 3 H), 3.79 (s, 3 H), 7.01 (t, *J* = 7.6 Hz, 1 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 7.37 (br, 1 H), 7.44 (d, *J* = 7.6 Hz, 1 H), 7.57 (s, 1 H), 7.68 (br, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 22.4, 25.1, 25.5, 28.0, 28.9, 31.3, 32.6, 57.9, 107.5, 110.3, 117.3, 119.6, 121.7, 124.7, 128.8, 136.9, 149.3, 167.1, 176.9; IR (nujol): ν_{max} = 3404, 3272, 1739, 1698 cm^{-1}; anal. calcd. for $C_{19}H_{22}N_4O_2$ (338.40): C 67.44, H 6.55, N 16.56; found: C 67.58, H 6.47, N 16.42.



4p

3a-(1*H*-indol-3-yl)-3-oxo-3,3a,4,5,6,7,8,9-octahydro-2*H*-cycloocta[*d*]pyrazole-2-carboxamide: the product **4p** was obtained in quant. 90% (58.4 mg); white solid; ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 0.92–1.03 (m, 1 H), 1.38–1.80 (m, 7 H), 2.10–2.19 (m, 1 H), 2.41–2.51 (m, 2 H), 2.56–2.60 (m, 1 H), 6.96 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.02 (d, *J* = 7.6 Hz, 1 H), 7.09 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1 H), 7.36 (br, 1 H), 7.39 (d, *J* = 7.6 Hz, 1 H), 7.56 (d, *J* = 2.4 Hz, 1 H), 7.65 (br, 1 H), 11.37 (s, 1 H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 22.4, 25.1, 25.5, 28.0, 28.9, 31.2, 58.0, 108.3, 112.1, 117.1, 119.5, 121.6, 124.3, 124.7, 136.5, 1494, 167.3, 177.0; IR (nujol): ν_{max} = 3379, 3297, 3241, 1744, 1714 cm^{-1}; anal. calcd. for $C_{18}H_{20}N_4O_2$ (324.37): C 66.65, H 6.21, N 17.27; found: C 66.43, H 6.30, N 17.41.

CHAPTER 7: Metal and Oxidant-Free Brønsted Acid-Mediated Cascade Reaction to Substituted Benzofurans.

Starting materials

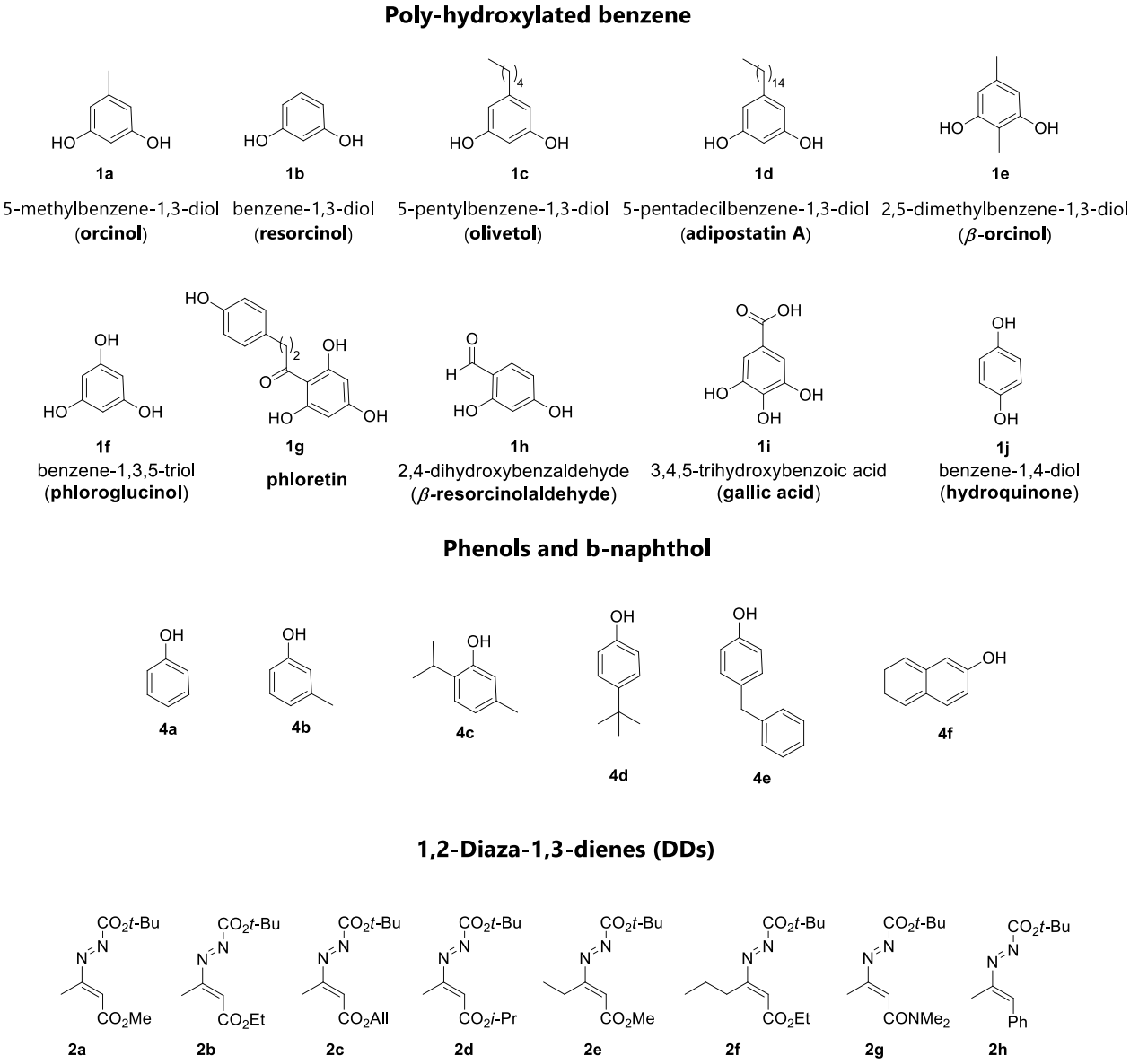


Figure S1.

Reaction of gallic acid with DD 2a

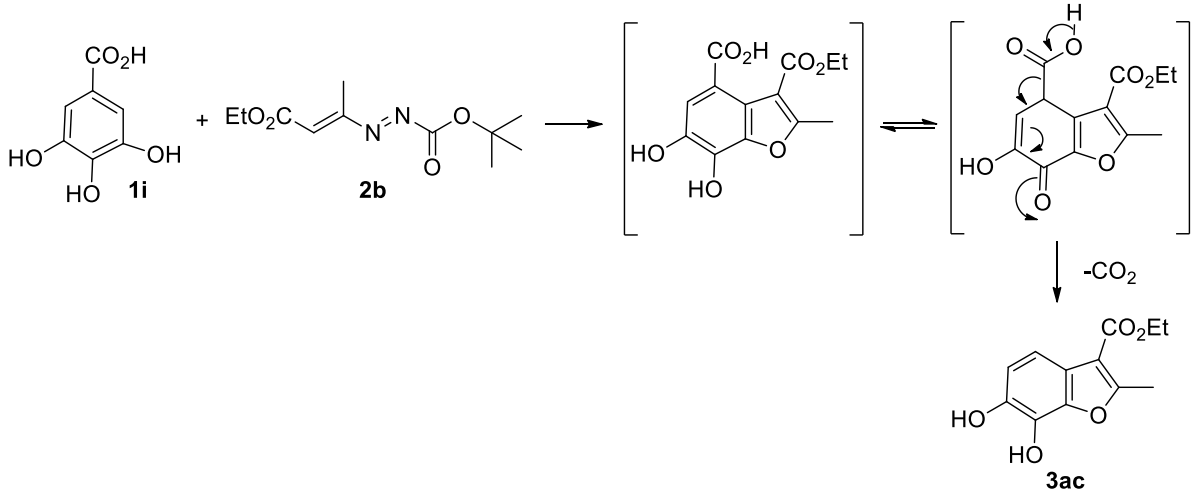
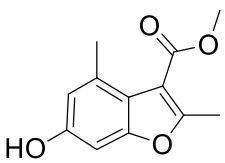


Figure S2

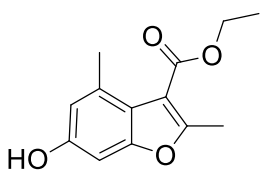
General procedure for the synthesis of hydroxy-benzofuran-3-carboxylates 3a–3ac, alkyl 2-(4-hydroxyphenyl)-3-oxobutanoates 5a–c or napthofuran-3-carboxylates 6a–c: to a solution of resorcinols **1a** · l (1.0 mmol) or phenols **4a** · e (1.0 mmol) or 2-naphthol **4f** (1.0 mmol) in acetonitrile/acetone (95/5, v/v, 5.0 mL), 1,2-diaza-1,3-dienes **2a** · h (0.5 mmol.) and Amberlyst 15H (dry form, 2.0 equiv.) were added and the reaction mixture was softly stirred at room temperature until the disappearance of the limiting reagent **2** (0.5 h). A TLC analysis (elution mixture cyclohexane: ethyl acetate, 70:30) shows the formation of a new intermediate (R*f* = 0.35). At this point, the reaction mixture was refluxed under softly magnetical stirring until the complete disappearance of the intermediate (4.0 h, TLC analysis: elution mixture: cyclohexane : ethyl acetate, 70:30). The reaction mixtures were cooled at room temperature, the Amberlyst 15H was removed by filtration and the solvents was evaporated under reduced pressure. The obtained crude product was then purified by column chromatography on silica gel (elution mixture: cyclohexane:ethyl acetate, 90:10) and the pure products **3a**–**ac**, **5a**–**c**, **6a**–**c** were precipitated in ethyl ether/petrol ether.



3a

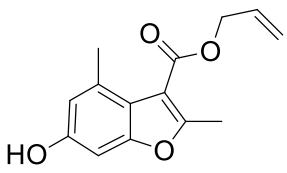
Methyl 6-hydroxy-2,4-dimethylbenzofuran-3-carboxylate 3a: 3a was isolated by column chromatography on silica gel (acetate/cyclohexane) in 72% yield (159 mg). White solid; mp: 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.59 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 3.91 (s, 3H, O*CH*$_3$), 5.27 (br, 1H, *OH*), 6.61 (dd, 1H, *J*= 2.0 Hz, *J*= 0.8 Hz, Ph), 6.76 (dd, 1H, *J*= 2.0 Hz, *J*= 0.4 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.6 (q), 21.4 (q), 51.4 (q), 95.4 (d), 110.0 (s), 114.7 (d), 118.2 (s), 132.9 (s), 153.1 (s), 154.8

(s), 161.1 (s), 165.2 (s); IR (nujol): ν_{max} = 3328, 1678 cm^{-1}; MS *m/z* (ESI): 221 (M + H^+); anal. calcd. for $C_{12}H_{12}O_4$ (220.22): C 65.45, H 5.49, O 29.06; found: C 65.57, H 5.44.



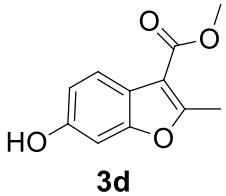
3b

Ethyl 6-hydroxy-2,4-dimethylbenzofuran-3-carboxylate 3b: 3b was isolated by column chromatography on silica gel (acetate/cyclohexane) in 56% yield (132 mg). White solid; mp: 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1,14 (t, 3H, *J*= 6.8 Hz, $OCH_2\mathit{CH_3}$), 2.59 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 4.39 (q, 2H, *J*= 7.2 Hz, $O\mathit{CH_2}CH_3$), 5.73 (br, 1H, *OH*), 6.61 (dd, 1H, *J*= 2.0 Hz, *J*= 0.4 Hz, Ph), 6.76 (d, 1H, *J*= 2.0 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3 (q), 14.6 (q), 21.5 (q), 60.7 (t), 95.4 (d), 110.3 (s), 114.7 (d), 118.1 (s), 132.8 (s), 153.3 (s), 154.8 (s), 161.0 (s), 165.0 (s); IR (nujol): ν_{max} = 3338, 1688 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{14}O_4$ [M + H]$^+$: 235.0970; found: 235.1007.



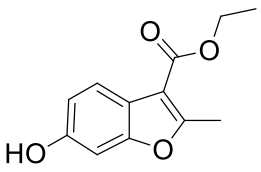
3c

Allyl 6-hydroxy-2,4-dimethylbenzofuran-3-carboxylate 3c: 3c was isolated by column chromatography on silica gel (acetate/cyclohexane) in 61% yield (150 mg). White solid; mp: 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.59 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 4.83 (dt, 2H, *J*= 6.0 Hz, *J*= 0.8 Hz, $O\mathit{CH_2}CHCH_2$), 5.31 (dq, 1H, *J*= 10.4 Hz, *J*= 1.2 Hz, $OCH_2CH\mathit{CH_2}$), 5.37 (br, 1H, *OH*), 5.42 (dq, 1H, *J*= 17.2 Hz, *J*= 1.2 Hz, $OCH_2CH\mathit{CH_2}$), 6.01-6.11 (m, 1H, $OCH_2\mathit{CH}CH_2$), 6.60 (d, 1H, *J*= 2.0 Hz, Hz, Ph), 6.76 (d, 1H, *J*= 2.0 Hz, Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.7 (q), 21.5 (q), 65.4 (t), 95.4 (d), 110.0 (s), 114.7 (d), 118.1 (s), 118.8 (t), 132.1 (d), 132.9 (s), 153.2 (s), 154.8 (s), 161.2 (s), 164.5 (s); IR (nujol): ν_{max} = 3414, 1702, 1672 cm^{-1}; MS *m/z* (ESI): 247 (M + H^+); anal. calcd. for $C_{14}H_{14}O_4$ (246.09): C 68.28, H 5.73, O 25.99; found: C 68.16, H 5.77.



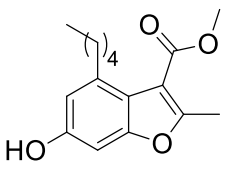
3d

Methyl 6-hydroxy-2-methylbenzofuran-3-carboxylate 3d: 3d was isolated by column chromatography on silica gel (acetate/cyclohexane) in 32% yield (66 mg). Pale yellow solid; mp: 138–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.73 (s, 3H, CH_3), 3.95 (s, 3H, $O\mathit{CH_3}$), 5.46 (br, 1H, *OH*), 6.85 (dd, 1H, *J*= 8.4 Hz, *J*= 2.4 Hz, Ph), 6.95 (d, 1H, *J*= 2.0 Hz, Ph), 7.76 (d, 1H, *J*= 8.8 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3 (q), 51.5 (q), 98.0 (d), 108.7 (s), 112.6 (d), 119.5 (s), 121.9 (d), 153.6 (s), 154.4 (s), 162.9 (s), 165.2 (s); IR (nujol): ν_{max} = 3406, 3328, 1689 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{10}O_4$ [M + H]$^+$: 207.0657; found: 207.0625.



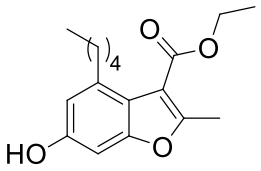
3e

Ethyl 6-hydroxy-2-methylbenzofuran-3-carboxylate 3e: 3e was isolated by column chromatography on silica gel (acetate/cyclohexane) in 61% yield (134 mg). White solid; mp: 140–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.44 (t, 3H, *J*= 7.2 Hz, $OCH_2\mathit{CH_3}$), 2.73 (s, 3H, CH_3), 4.41 (t, 3H, *J*= 7.2 Hz, $OCH_2\mathit{CH_3}$), 5.49 (br, 1H, *OH*), 6.85 (dd, 1H, *J*= 8.4 Hz, *J*= 2.0 Hz, Ph), 6.94 (d, 1H, *J*= 2.0 Hz, Ph), 7.76 (d, 1H, *J*= 8.4 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3 (q), 14.4 (q), 60.3 (t), 97.9 (d), 108.8 (s), 112.6 (d), 119.6 (s), 122.0 (d), 153.6 (s), 154.4 (s), 162.7 (s), 164.7 (s); IR (nujol): ν_{max} = 3312, 1672, cm^{-1}; MS *m/z* (ESI): 221 (M + H^+); anal. calcd. for $C_{12}H_{12}O_4$ (220.07): C 65.45, H 5.49, O 29.06; found: C 65.58, H 5.42.



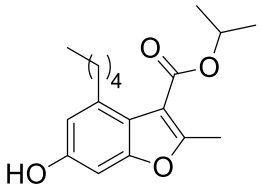
3f

Methyl 6-hydroxy-2-methyl-4-pentylbenzofuran-3-carboxylate 3f: 3f was isolated by column chromatography on silica gel (acetate/cyclohexane) in 62% yield (171 mg). Pale brown solid; mp: 52–54 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.87 (t, 3H, *J*= 6.8 Hz, $CH_2(CH_2)_3\mathit{CH_3}$), 1.29-1.33 (m, 4H, $CH_2CH_2\mathit{(CH_2)_2}CH_3$), 1.48-1.55 (m, 2H, $CH_2\mathit{CH_2}(CH_2)_2CH_3$), 2.62 (s, 3H, CH_3), 2.95 (t, 2H, *J*= 8.0 Hz, $\mathit{CH_2}(CH_2)_3CH_3$), 3.92 (s, 3H, $O\mathit{CH_3}$), 5.87 (br, 1H, *OH*), 6.63 (d, 1H, *J*= 2.4 Hz, Ph), 6.78 (d, 1H, *J*= 2.4 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.0 (q), 14.6 (q), 22.6 (t), 31.1 (t), 31.7 (t), 34.2 (t), 51.6 (q), 95.5 (d), 110.0 (s), 113.8 (d), 117.2 (s), 138.0 (s), 153.4 (s), 155.0 (s), 160.9 (s), 165.6 (s); IR (nujol): · $_{max}$ = 3440, 1709, 1631 cm^{-1}; MS *m/z* (ESI): 277 (M + H^+); anal. calcd. for $C_{16}H_{20}O_4$ (276.14): C 69.54, H 7.30, O 23.16; found: C 69.68, H 7.28.



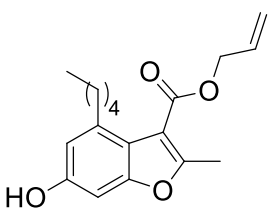
3g

Ethyl 6-hydroxy-2-methyl-4-pentylbenzofuran-3-carboxylate 3g: 3g was isolated by column chromatography on silica gel (acetate/cyclohexane) in 70% yield (202 mg). Pale yellow solid; mp: 56–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.86 (t, 3H, J= 6.8 Hz, $CH_2(CH_2)_3CH_3$), 1.26-1.31 (m, 4H, $CH_2CH_2(CH_2)_2CH_3$), 1.42 (t, 3H, J= 7.2 Hz, OCH_2CH_3), 1.49-1.56 (m, 2H, $CH_2CH_2(CH_2)_2CH_3$), 2.62 (s, 3H, CH_3), 2.99 (t, 2H, J= 8.0 Hz, $CH_2(CH_2)_3CH_3$), 4.40 (q, 2H, J= 7.2 Hz, OCH_2CH_3), 5.78 (br, 1H, OH), 6.63 (d, 1H, J= 2.0 Hz, Ph), 6.77 (d, 1H, J= 2.0 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.0 (q), 14.3 (q), 14.6 (q), 22.6 (t), 31.0 (t), 31.6 (t), 34.1 (t), 60.8 (t), 95.5 (d), 110.3 (s), 113.7 (d), 117.3 (s), 138.0 (s), 153.3 (s), 155.0 (s), 160.6 (s), 165.2 (s); IR (nujol): ν_{max} = 3330, 1674, 1662 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{22}O_4$ $[M + H]^+$: 291.1596; found: 291.1545.



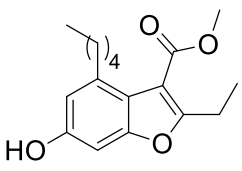
3h

Isopropyl 6-hydroxy-2-methyl-4-pentylbenzofuran-3-carboxylate 3h: 3h was isolated by column chromatography on silica gel (acetate/cyclohexane) in 53% yield (161 mg). Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.87 (t, 3H, *J*= 6.8 Hz, $CH_2(CH_2)_3\mathit{CH_3}$), 1.29-1.33 (m, 4H, $CH_2CH_2\mathit{(CH_2)_2}CH_3$), 1.40 (d, 6H, *J*= 6.4 Hz, $OCH\mathit{(CH_3)_2}$), 1.50-1.57 (m, 2H, $CH_2\mathit{CH_2}(CH_2)_2CH_3$), 2.61 (s, 3H, CH_3), 3.03 (t, 2H, *J*= 8.0 Hz, $\mathit{CH_2}(CH_2)_3CH_3$), 4.83 (br, 1H, *OH*), 5.28 (ept, 1H, *J*= 6.4 Hz, $O\mathit{CH}(CH_3)_2$), 6.61 (d, 1H, *J*= 2.4 Hz, Ph), 6.76 (d, 1H, *J*= 2.0 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.0 (q), 14.6 (q), 22.0 (q), 22.7 (t), 31.0 (t), 31.5 (t), 34.0 (t), 68.2 (d), 95.4 (d), 110.8 (s), 113.4 (d), 117.6 (s), 138.1 (s), 153.0 (s), 154.9 (s), 160.0 (s), 164.4 (s); IR (nujol): ν_{max} = 3409, 1685 cm^{-1}; MS *m/z* (ESI): 305 (M + H$^+$); anal. calcd. for $C_{18}H_{24}O_4$ (304.38): C 71.03, H 7.95, O 21.03; found: C 71.15, H 7.91.



3i

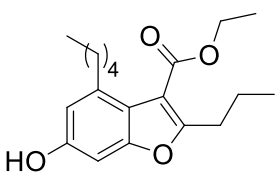
Allyl 6-hydroxy-2-methyl-4-pentylbenzofuran-3-carboxylate 3i: 3i was isolated by column chromatography on silica gel (acetate/cyclohexane) in 60% yield (182 mg). Pale brown oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.85-0.88 (m, 3H, $CH_2(CH_2)_3\mathit{CH_3}$), 1.27-1.32 (m, 4H, $CH_2CH_2\mathit{(CH_2)_2}CH_3$), 1.48-1.58 (m, 2H, $CH_2\mathit{CH_2}(CH_2)_2CH_3$), 2.63 (s, 3H, CH_3), 2.98 (t, 2H, *J*= 8.0 Hz, $\mathit{CH_2}(CH_2)_3CH_3$), 4.84 (dt, 2H, *J*= 5.6 Hz, *J*= 1.6 Hz,$O\mathit{CH_2}CH{=}CH_2$), 5.31 (dq, 1H, *J*= 10.4 Hz, *J*= 1.2 Hz, $OCH_2(CH{=}\mathit{CH_2})$, 5.42 (dq, 1H, *J*= 17.2 Hz, *J*= 1.2 Hz, $OCH_2(CH{=}\mathit{CH_2})$, 5.76 (br, 1H, *OH*), 6.01-6.11 (m, 1H, $OCH_2(\mathit{CH}{=}CH_2)$, 6.63 (d, 1H, *J*= 2.4 Hz, Ph), 6.78 (d, 1H, *J*= 2.4 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.0 (q), 14.7 (q), 22.6 (q), 31.0 (t), 31.6 (t), 34.1 (t), 65.6 (t), 95.5 (d), 110.0 (s), 113.8 (d), 117.1 (s), 118.9 (t), 131.9 (d), 137.9 (s), 153.4 (s), 155.0 (s), 160.8 (s), 164.9 (s); IR (nujol): ν_{max} = 3387, 1702 cm^{-1}; MS *m/z* (ESI): 303 (M + H$^+$); anal. calcd. for $C_{18}H_{22}O_4$ (302.36): C 71.50, H 7.33, O 21.17; found: C 71.59, H 7.28.



3j

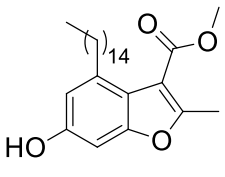
Methyl 2-ethyl-6-hydroxy-4pentylbenzofuran-3-carboxylate 3j: 3j was isolated by column chromatography on silica gel (acetate/cyclohexane) in 48% yield (139 mg). Pale brown oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.88 (t, 3H, *J*= 6.8 Hz,$CH_2(CH_2)_3\mathit{CH_3}$), 1.28-1.33 (m, 7H, $CH_2CH_2\mathit{(CH_2)_2}CH_3$ and $CH_2\mathit{CH_3}$), 1.49-1.56 (m, 2H, $CH_2\mathit{CH_2}(CH_2)_2CH_3$), 2.92-3.04 (m, 4H, $\mathit{CH_2}(CH_2)_3CH_3$ and $\mathit{CH_2}CH_3$), 3.92 (s, 3H, $O\mathit{CH_3}$), 5.93 (br, 1H, *OH*), 6.64 (d, 1H, *J*= 2.4 Hz, Ph), 6.79 (d, 1H, *J*= 2.0 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12. 4 (q), 14.0 (q), 21.8 (t), 22.6 (t), 31.1 (t), 31.7 (t), 34.2 (t), 51.6 (q), 95.6 (d),

109.1 (s), 113.7 (d), 117.3 (s), 138.0 (s), 153.3 (s), 155.0 (s), 165.3 (s), 165.6 (s); IR (nujol): ν_{max} = 3411, 1687 cm^{-1}; MS *m/z* (ESI): 291 (M + H^+); anal. calcd. for $C_{17}H_{22}O_4$ (290.35): C 70.32, H 7.64, O 22.04; found: C 70.19, H 7.68, O 22.13.



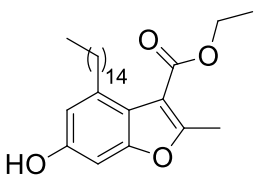
3k

Ethyl 6-hydroxy-4-pentyl-2-propylbenzofuran-3-carboxylate 3k: 3k was isolated by column chromatography on silica gel (acetate/cyclohexane) in 38% yield (121 mg). Pale brown oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.87 (t, 3H, *J*= 7.2 Hz,$CH_2(CH_2)_3$*CH_3*), 0.99 (t, 3H, *J*= 7.6 Hz, CH_2CH_2*CH_3*), 1.29-1.32 (m, 4H, CH_2CH_2*$(CH_2)_2$*CH_3), 1.42 (t, 3H, *J*= 7.2 Hz, OCH_2*CH_3*), 1.49-1.57 (m, 2H, CH_2*CH_2*$(CH_2)_2CH_3$), 1.77 (sex, 2H, *J*= 7.6 Hz, CH_2*CH_2*CH_3), (2.94-2.99 (m, 4H, *CH_2*$(CH_2)_3CH_3$ and *CH_2*CH_2CH_3), 4.40 (q, 2H, *J*= 7.2 Hz, O*CH_2*CH_3), 5.92 (br, 1H, *OH*), 6.64 (d, 1H, *J*= 2.0 Hz, Ph), 6.79 (d, 1H, *J*= 2.0 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13. 8 (q), 14.0 (q), 14.2 (q), 21.6 (t), 22.6 (t), 30.2 (t), 30.9 (t), 31.6 (t), 34.0 (t), 60.8 (t), 95.6 (d), 110.1 (s), 113.6 (d), 117.2 (s), 137.9 (s), 153.4 (s), 155.0 (s), 163.8 (s), 165.4 (s); IR (nujol): ν_{max} = 3394, 1707 cm^{-1}; MS *m/z* (ESI): 319 (M + H^+); anal. calcd. for $C_{19}H_{26}O_4$ (318.41): C 71.67, H 8.23, O 20.10; found: C 71.58, H 8.26.



3l

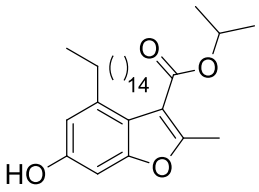
Methyl 6-hydroxy-2-methyl-4-pentadecylbenzofuran-3-carboxylate 3l: 3l was isolated by column chromatography on silica gel (acetate/cyclohexane) in 60% yield (249 mg). White solid; mp: 80–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.89 (t, 3H, *J*= 6.8 Hz, $CH_2(CH_2)_{13}$*CH_3*), 1.25-1.35 (m, 24H, CH_2CH_2*$(CH_2)_{12}$*CH_3), 1.49-1.56 (m, 2H, CH_2*CH_2*$(CH_2)_{12}CH_3$), 2.63 (s, 3H, CH_3), 2.97 (t, 2H, *J*= 8.0 Hz, *CH_2*$(CH_2)_{13}CH_3$), 3.92 (s, 3H, O*CH_3*), 5.40 (br, 1H, *OH*), 6.63 (d, 1H, *J*= 2.0 Hz, Ph), 6.78 (d, 1H, *J*= 2.4 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.1 (q), 14.6 (q), 22.7 (t), 29.4 (t), 29.6 (t), 29.6 (t), 29.6 (t), 29.7 (t), 31.5 (t), 31.9 (t), 34.3 (t), 51.6 (q), 95.5 (d), 110.0 (s), 113.8 (d), 117.3 (s), 138.0 (s), 153.3 (s), 155.0 (s), 160.9 (s), 165.5 (s); IR (nujol): ν_{max} = 3226, 1729, 1703 cm^{-1}; MS *m/z* (ESI): 417 (M + H^+); anal. calcd. for $C_{26}H_{40}O_4$ (416.59): C 74.96, H 9.68, O 15.36; found: C 75.08, H 9.63.



3m

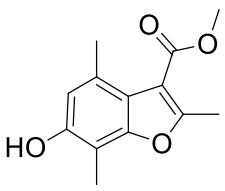
Ethyl 6-hydroxy-2-methyl-4-pentadecylbenzofuran-3-carboxylate 3m: 3m was isolated by column chromatography on silica gel (acetate/cyclohexane) in 76% yield (328 mg). White solid; mp: 65–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.89 (t, 3H, *J*= 7.2 Hz, $CH_2(CH_2)_{13}$*CH_3*), 1.24-1.32 (m, 24H, CH_2CH_2*$(CH_2)_{12}$*CH_3), 1.42 (t, 3H, *J*= 7.2 Hz, OCH_2*CH_3*), 1.49-1.56

(m, 2H, $CH_2CH_2(CH_2)_{12}CH_3$), 2.62 (s, 3H, CH_3), 3.00 (t, 2H, *J*= 8.0 Hz, $CH_2(CH_2)_{13}CH_3$), 4.39 (q, 2H, *J*= 7.2 Hz, OCH_2CH_3), 5.16 (br, 1H, *OH*), 6.62 (d, 1H, *J*= 2.4 Hz, Ph), 6.77 (d, 1H, *J*= 2.4 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.1 (q), 14.4 (q), 14.6 (q), 22.7 (t), 29.3 (t), 29.4 (t), 29.6 (t), 29.7 (t), 29.7 (t), 31.9 (t), 34.2 (t), 60.7 (t), 95.5 (d), 110.4 (s), 113.6 (d), 117.5 (s), 138.1 (s), 153.2 (s), 155.0 (s), 160.5 (s), 165.0 (s); IR (nujol): ν_{max} = 3287, 1698, cm^{-1}; MS *m/z* (ESI): 431. (M + H$^+$); anal. calcd. for $C_{27}H_{42}O_4$ (430.62): C 75.31, H 9.83, O 14.86; found: C 75.16, H 9.89.



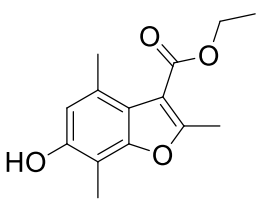
3n

Isopropyl 6-hydroxy-2-methyl-4-pentadecylbenzofuran-3-carboxylate 3n: 3n was isolated by column chromatography on silica gel (acetate/cyclohexane) in 65% yield (289 mg). White solid; mp: 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.89 (t, 3H, *J*= 6.8 Hz, $CH_2(CH_2)_{13}CH_3$), 1.24-1.33 (m, 24H, $CH_2CH_2(CH_2)_{12}CH_3$), 1.40 (d, 6H, *J*= 6.4 Hz, $OCH(CH_3)_2$), 1.49-1.56 (m, 2H, $CH_2CH_2(CH_2)_{12}CH_3$), 2.61 (s, 3H, CH_3), 3.03 (t, 2H, *J*= 8.0 Hz, $CH_2(CH_2)_{13}CH_3$), 4.83 (br, 1H, *OH*), 5.28 (sep, 1H, *J*= 6.4 Hz, $OCH(CH_3)_2$), 6.61 (d, 1H, *J*= 2.4 Hz, Ph), 6.76 (d, 1H, *J*= 2.0 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.1 (q), 14.6 (q), 22.0 (q), 22.7 (t), 29.4 (t), 29.4 (t), 29.6 (t), 29.7 (t), 29.7 (t), 31.3 (t), 31.9 (t), 34.0 (t), 68.2 (d), 95.4 (d), 110.8 (s), 113.4 (d), 117.7 (s), 138.1 (s), 153.1 (s), 155.0 (s), 160.0 (s), 164.4 (s); IR (nujol): ν_{max} = 3353, 1684 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{44}O_4$ [M + H]$^+$: 445.3318; found: 445.3294.



3o

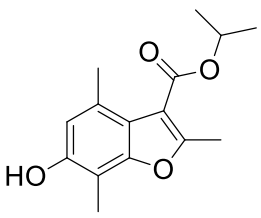
Methyl 6-hydroxy-2,4,7-trimethylbenzofuran-3-carboxylate 3o: 3o was isolated by column chromatography on silica gel (acetate/cyclohexane) in 83% yield (194 mg). White solid; mp: 156–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.33 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.79 (br, 1H, *OH*), 6.58 (s, 1H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 8.0 (q), 14.7 (q), 21.1 (q), 51.3 (q), 104.3 (s), 110.3 (s), 114.4 (d), 117.7 (s), 129.2 (s), 150.8 (s), 153.8 (s), 161.0 (s), 165.3 (s); IR (nujol): ν_{max} = 3364, 1678 cm^{-1}; MS *m/z* (ESI): 235 (M + H$^+$); anal. calcd. for $C_{13}H_{14}O_4$ (234.09): C 66.66, H 6.02, O 27.32; found: C 66.54, H 6.08, O 27.38.



3p

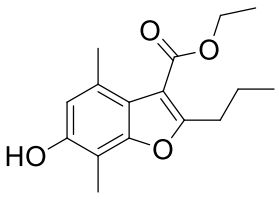
Ethyl 6-hydroxy-2,4,7-trimethylbenzofuran-3-carboxylate 3p: 3p was isolated by column chromatography on silica gel (acetate/cyclohexane) in 81% yield (202 mg). White solid; mp: 129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.41 (t, 3H, *J*= 7.2 Hz, OCH_2CH_3), 2.33 (s, 3H, CH_3), 2.55 (s, 3H,

CH_3), 2.66 (s, 3H, CH_3), 4.39 (q, 2H, *J*= 7.2 Hz, OCH_2CH_3), 5.22 (br, 1H, *OH*), 6.57 (s, 1H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 8.0 (q), 14.3 (q), 14.7 (q), 21.2 (q), 60.5 (t), 104.3 (s), 110.6 (s), 114.4 (d), 117.6 (s), 129.1 (s), 150.9 (s), 153.8 (s), 160.9 (s), 165.1 (s); IR (nujol): ν_{max} = 3358, 1668 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}O_4$ $[M + H]^+$: 249.1127; found: 249.1151.



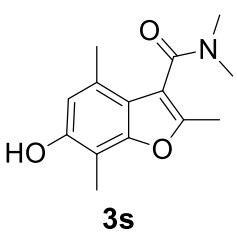
3q

Isopropyl 6-hydroxy-2,4,7-trimethylbenzofuran-3-carboxylate 3q: 3q was isolated by column chromatography on silica gel (acetate/cyclohexane) in 74% yield (194 mg). White solid; mp: 122–124 °C; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.40 (d, 6H, *J*= 6.4 Hz, $OCH(CH_3)_2$), 2.33 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 4.97 (br, 1H, *OH*), 5.29 (sep, 1H, *J*= 6.4 Hz, $OCH(CH_3)_2$), 6.56 (s, 1H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 8.0 (q), 14.6 (q), 21.3 (q), 22.0 (q), 68.2 (d), 104.3 (s), 111.0 (s), 114.3 (d), 117.7 (s), 129.0 (s), 150.9 (s), 153.8 (s), 160.6 (s), 164.6 (s); IR (nujol): ν_{max} = 3430 cm^{-1}; MS *m/z* (ESI): 263 ($M + H^+$); anal. calcd. for $C_{15}H_{18}O_4$ (262.30): C 68.68, H 6.92, O 24.40; found: C 68.77, H 6.88.



3r

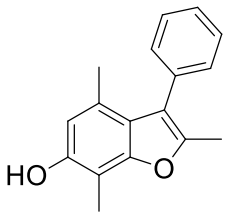
Ethyl 6-hydroxy-4,7-dimethyl-2-propylbenzofuran-3-carboxylate 3r: 3r was isolated by column chromatography on silica gel (acetate/cyclohexane) in 91% yield (251 mg). White solid; mp: 87–88 °C; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.01 (t, 3H, *J*= 7.2 Hz, $CH_2CH_2CH_3$), 1.42 (t, 3H, *J*= 7.2 Hz, OCH_2CH_3), 1.80 (sex, 2H, *J*= 7.2 Hz, $CH_2CH_2CH_3$), 2.34 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.02 (t, 2H, *J*= 7.6 Hz, $CH_2CH_2CH_3$), 4.40 (q, 2H, *J*= 7.2 Hz, OCH_2CH_3), 5.49 (br, 1H, *OH*), 6.58 (s, 1H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 8.0 (q), 13.8 (q), 14.2 (q), 21.1 (q), 21.6 (t), 30.2 (t), 60.6 (t), 104.5 (s), 110.3 (s), 114.4 (d), 117.6 (s), 129.1 (s), 151.0 (s), 153.8 (s), 164.3 (s), 165.2 (s); IR (nujol): ν_{max} = 3379, cm^{-1}; MS *m/z* (ESI): 277 ($M + H^+$); anal. calcd. for $C_{16}H_{20}O_4$ (276.14): C 69.54, H 7.30, O 23.16; found: C 69.43, H 7.35.



3s

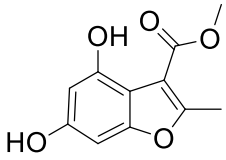
6-Hydroxy-*N,N*,2,4,7-pentamethylbenzofuran-3-carboxamide 3s: 3s was isolated by column chromatography on silica gel (acetate/cyclohexane) in 48% yield (118 mg). Pale brown solid; mp: 188–190 °C; ^1H NMR (400 MHz, $DMSO_{d6}$, 25 °C): δ = 2.17 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.87 (s, 3H, NCH_3), 3.02 (s, 3H, NCH_3), 6.55 (s, 1H, Ph), 9.21 (s, 1H, *OH*); ^{13}C NMR (100 MHz,

DMSO$_{d6}$, 25 °C): δ = 8.3 (q), 12.4 (q), 17.4 (q), 34.1 (q), 37.7 (q), 103.8 (s), 112.8 (d), 117.1 (s), 126.3 (s), 149.2 (s), 152.4 (s), 153.4 (s), 165.4 (s); IR (nujol): ν_{max} = 3287, 1636 cm^{-1}; MS *m/z* (ESI): 248 (M + H$^+$); anal. calcd. for $C_{14}H_{17}NO_3$ (247.29): C 68.00, H 6.93, N 5.66; found: C 67.86, H 6.98, N 5.73.



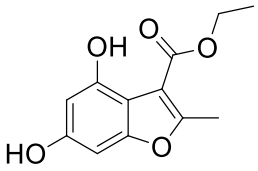
3t

2,4,7-trimethyl-3-phenylbenzofuran-6-ol 3t: 3t was isolated by column chromatography on silica gel (acetate/cyclohexane) in 69% yield (174 mg). Pale yellow solid; mp: 119–120 °C; ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 2.04 (s, 3H, CH$_3$), 2.32 (s, 3H, CH$_3$), 2.40 (s, 3H, CH$_3$), 4.30 (br, 1H, *OH*), 6.48 (s, 1H, Ph), 7.34-7.45 (m, 5H, Ph); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 8.0 (q), 12.2 (q), 19.0 (q), 104.3 (s), 112.8 (d), 118.0 (s), 121.0 (s), 127.1 (d), 128.0 (d), 128.1 (s), 130.7 (d), 134.4 (s), 150.3 (s), 150.4 (s), 153.7 (s); IR (nujol): ν_{max} = 3262 cm^{-1}; MS *m/z* (ESI): 253 (M + H$^+$); anal. calcd. for $C_{17}H_{16}O_2$ (252.31): C 80.93.54, H 6.39, O 12.68; found: C 81.06, H 6.33.



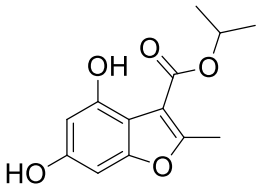
3u

Methyl 4,6-dihydroxy-2-methylbenzofuran-3-carboxylate 3u: 3u was isolated by column chromatography on silica gel (acetate/cyclohexane) in 84% yield (187 mg) or in 82% (1.452 g starting from 8.0 mmol of **1a**). White solid; mp: 186–188 °C; ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 2.60 (s, 3H, CH$_3$), 3.92 (s, 3H, O*CH$_3$*), 6.16 (d, 1H, *J*= 2.0 Hz, Ph), 6.41 (d, 1H, *J*= 2.0 Hz, Ph), 9.61 (s, 1H, OH), 10.26 (s, 1H, OH); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 14.4 (q), 53.0 (q), 89.4 (d), 98.7 (d), 105.4 (s), 108.0 (s), 150.3 (s), 155.2 (s), 157.3 (s), 160.8 (s), 167.7 (s); IR (nujol): ν_{max} = 3399, 3081, 1663 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{10}O_5$ [M + H]$^+$: 223.0606; found: 223.0650.



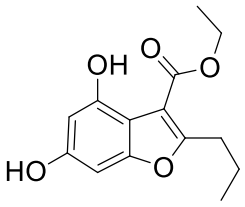
3v

Ethyl 4,6-dihydroxy-2-methylbenzofuran-3-carboxylate 3v: 3v was isolated by column chromatography on silica gel (acetate/cyclohexane) in 56% yield (133 mg). White solid; mp: 194–196 °C; ^{1}H NMR (400 MHz, DMSO$_{d6}$, 25 °C): δ = 1.36 (t, 3H, *J*= 7.2 Hz, OCH$_2$*CH$_3$*), 2.63 (s, 3H, CH$_3$), 4.39 (q, 2H, *J*= 7.2 Hz, O*CH$_2$*CH$_3$), 6.16 (d, 1H, *J*= 1.6 Hz, Ph), 6.42 (d, 1H, *J*= 2.0 Hz, Ph), 9.61 (s, 1H, OH), 10.30 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO$_{d6}$, 25 °C): δ = 13.9 (q), 14.5 (q), 62.1 (t), 89.4 (d), 98.7 (d), 105.4 (s), 108.2 (s), 150.3 (s), 155.2 (s), 157.3 (s), 160.8 (s), 167.3 (s); IR (nujol): ν_{max} = 3398, 3393, 1651 cm^{-1}; MS *m/z* (ESI): 237 (M + H$^+$); anal. calcd. for $C_{12}H_{12}O_5$ (236.22): C 61.01, H 5.12, O 33.87; found: C 59.94, H 5.08.



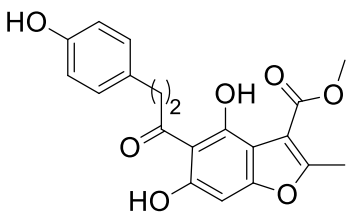
3w

Isopropyl 4,6-dihydroxy-2-methylbenzofuran-3-carboxylate 3w: 3w was isolated by column chromatography on silica gel (acetate/cyclohexane) in 77% yield (192 mg). White solid; mp: 158–160 °C; ^{1}H NMR (400 MHz, DMSO$_{d6}$, 25 °C): δ = 1.36 (d, 6H, *J*= 6.4 Hz, OCH(*CH*$_3$)$_2$), 2.62 (s, 3H, CH$_3$), 5.19 (sep, 1H, *J*= 6.4 Hz, O*CH*(CH$_3$)$_2$), 6.15 (d, 1H, *J*= 1.6 Hz, Ph), 6.41 (d, 1H, *J*= 2.0 Hz, Ph), 9.57 (s, 1H, OH), 10.32 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO$_{d6}$, 25 °C): δ = 14.5 (q), 21.5 (q), 70.2 (d), 89.4 (d), 98.6 (d), 105.4 (s), 108.4 (s), 150.3 (s), 155.2 (s), 157.3 (s), 160.6 (s), 167.8 (s); IR (nujol): ν_{max} = 3418, 3066, 1650 cm^{-1}; MS *m/z* (ESI): 251 (M + H$^+$); anal. calcd. for $C_{13}H_{14}O_5$ (250.25): C 62.39, H 5.64, O 31.97; found: C 62.35, H 5.60.



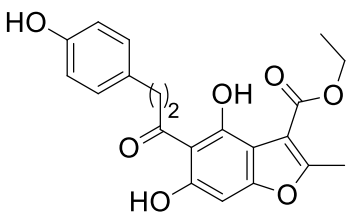
3x

Ethyl 4,6-dihydroxy-2-propylbenzofuran-3-carboxylate 3x: 3x was isolated by column chromatography on silica gel (acetate/cyclohexane) in 69% yield (182 mg). White solid; mp: 136–138 °C; ^{1}H NMR (400 MHz, DMSO$_{d6}$, 25 °C): δ = 0.93 (t, 3H, *J*= 7.2 Hz, CH$_2$CH$_2$*CH*$_3$), 1.35 (t, 3H, *J*= 7.2 Hz, OCH$_2$*CH*$_3$), 1.70 (sex, 2H, *J*= 7.2 Hz, CH$_2$*CH*$_2$CH$_3$), 3.00 (t, 2H, *J*= 7.2 Hz, *CH*$_2$CH$_2$CH$_3$), 4.39 (q, 2H, *J*= 7.2 Hz, O*CH*$_2$CH$_3$), 6.16 (d, 1H, *J*= 2.0 Hz, Ph), 6.43 (d, 1H, *J*= 2.0 Hz, Ph), 9.62 (s, 1H, OH), 10.35 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO$_{d6}$, 25 °C): δ = 13.6 (q), 13.8 (q), 21.2 (t), 29.8 (t), 62.1 (t), 89.5 (d), 98.7 (d), 105.3 (s), 108.1 (s), 150.5 (s), 155.3 (s), 157.4 (s), 164.1 (s), 167.2 (s); IR (nujol): ν_{max} = 3407, 3080, 1668 cm^{-1}; MS *m/z* (ESI): 265 (M + H$^+$); anal. calcd. for $C_{14}H_{16}O_5$ (264.27): C 63.63, H 6.10, O 30.27; found: C 63.54, H 6.12.



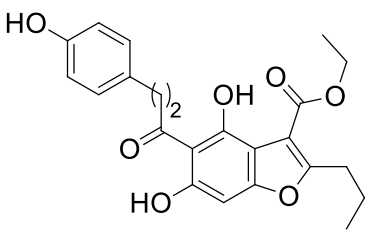
3y

Methyl 4,6-dihydroxy-5-(3-(4-hydroxyphenyl) propanoyl)-2-methylbenzofuran-3-carboxylate 3y: 3y was isolated by column chromatography on silica gel (acetate/cyclohexane) in 53% yield (196 mg). White solid; mp: 176–178 °C; ^{1}H NMR (400 MHz, DMSO$_{d6}$, 25 °C): δ = 2.66 (s, 3H, *CH*$_3$), 2.86 (t, 2H, *J*= 7.6 Hz, CH$_2$*CH*$_2$), 3.34 (t, 2H, *J*= 7.6 Hz, *CH*$_2$CH$_2$), 3.96 (s, 3H, OCH$_3$), 6.22 (s, 1H, Ph), 6.88 (d, 2H, *J*= 7.6 Hz, Ph), 7.06 (d, 2H, *J*= 7.6 Hz, Ph), 9.15 (s, 1H, OH), 11.44 (s, 1H, OH), 13.18 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO$_{d6}$, 25 °C): δ = 14.4 (q), 28.8 (q), 43.3 (t), 53.4 (q), 99.0 (d), 100.6 (s), 106.9 (s), 108.4 (s), 115.0 (d), 129.0 (d), 130.9 (s), 153.7 (s), 155.4 (s), 156.8 (s), 161.2 (s), 164.0 (s), 167.5 (s), 201.6 (s); IR (nujol): ν_{max} = 3430, 1663 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{18}O_7$ [M + H]$^+$: 371.1113; found: 371.1064.



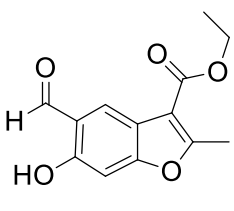
3z

Ethyl 4,6-dihydroxy-5-(3-(4-hydroxyphenyl) propanoyl)-2-methylbenzofuran-3-carboxylate 3z: 3z was isolated by column chromatography on silica gel (acetate/cyclohexane) in 30% yield (115 mg). White solid; mp: 166–168 °C; ^{1}H NMR (400 MHz, DMSO$_{d6}$, 25 °C): δ = 1.37 (t, 3H, *J*= 7.2 Hz, OCH$_2$*CH$_3$*), 2.65 (s, 3H, *CH$_3$*), 2.85 (t, 2H, *J*= 7.6 Hz, CH$_2$*CH$_2$*), 3.33 (t, 2H, *J*= 7.6 Hz, *CH$_2$*CH$_2$), 4.41 (q, 2H, *J*= 7.2 Hz, O*CH$_2$*CH$_3$), 6.20 (s, 1H, Ph), 6.67 (d, 2H, *J*= 8.8 Hz, Ph), 7.06 (d, 2H, *J*= 8.4 Hz, Ph), 9.16 (s, 1H, OH), 11.48 (s, 1H, OH), 13.18 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO$_{d6}$, 25 °C): δ = 13.8 (q), 14.5 (q), 28.8 (t), 43.9 (t), 62.6 (t), 99.0 (d), 100.5 (s), 106.9 (s), 108.5 (s), 115.1 (d), 129.1 (d), 130.9 (s), 153.6 (s), 155.5 (s), 156.8 (s), 161.2 (s), 164.1 (s), 167.1 (s), 201.6 (s); IR (nujol): ν_{max} = 3443, 1689 cm^{-1}; MS *m/z* (ESI): 385 (M + H$^+$); anal. calcd. for $C_{21}H_{20}O_7$ (384.38): C 65.62, H 5.24, O 29.14; found: C 65.74, H 5.20.



3aa

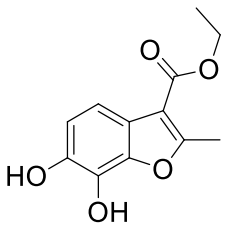
Ethyl 4,6-dihydroxy-5-(3-(4-hydroxyphenyl) propanoyl)-2-propylbenzofuran-3-carboxylate 3aa: 3aa was isolated by column chromatography on silica gel (acetate/cyclohexane) in 48% yield (198 mg). White solid; mp: 166–168 °C; ^{1}H NMR (400 MHz, DMSO$_{d6}$, 25 °C): δ = 0.91 (t, 3H, *J*= 7.6 Hz, CH$_2$*CH$_2$CH$_3$*), 1.36 (t, 3H, *J*= 7.2 Hz, OCH$_2$*CH$_3$*), 1.70 (sex, 2H, *J*= 7.2 Hz, CH$_2$*CH$_2$*CH$_3$), 2.85 (t, 2H, *J*= 7.6 Hz, CH$_2$*CH$_2$*), 3.02 (t, 2H, *J*= 7.6 Hz, *CH$_2$*CH$_2$CH$_3$), 3.34 (t, 2H, *J*= 7.6 Hz, *CH$_2$*CH$_2$), 4.41 (q, 2H, *J*= 7.2 Hz, O*CH$_2$*CH$_3$), 6.21 (s, 1H, Ph), 6.67 (d, 2H, *J*= 8.4 Hz, Ph), 7.05 (d, 2H, *J*= 8.4 Hz, Ph), 9.18 (s, 1H, OH), 11.53 (s, 1H, OH), 13.20 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO$_{d6}$, 25 °C): δ = 13.6 (q), 13.8 (q), 20.6 (t), 28.8 (t), 29.7 (t), 43.9 (t), 62.7 (t), 99.0 (d), 100.5 (s), 106.9 (s), 108.5 (s), 115.1 (d), 129.0 (d), 130.9 (s), 153.8 (s), 155.5 (s), 157.1 (s), 164.2 (s), 164.3 (s), 167.1 (s), 201.7(s); IR (nujol): ν_{max} = 3430, 1658 cm^{-1}; MS *m/z* (ESI): 413 (M + H$^+$); anal. calcd. for $C_{23}H_{24}O_7$ (412.43): C 66.98, H 5.87, O 27.15; found: C 66.85, H 5.94.



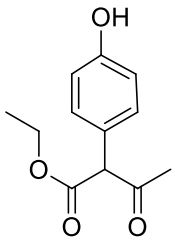
3ab

Ethyl 5-formyl-6-hydroxy-2-methylbenzofuran-3-carboxylate 3ab: 3ab was isolated by column chromatography on silica gel (acetate/cyclohexane) in 16% yield (40 mg). White solid; mp: 136–138 °C; ^{1}H NMR (400 MHz, DMSO$_{d6}$, 25 °C): δ = 1.46 (t, 3H, *J*= 7.2 Hz, OCH$_2$*CH$_3$*), 2.75 (s, 3H, *CH$_3$*), 4.44 (q, 2H, *J*= 7.2 Hz, O*CH$_2$*CH$_3$), 6.99 (s, 1H, Ph), 8.13 (s, 1H, Ph), 9.98 (s, 1H, COH), 11.22 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO$_{d6}$, 25 °C): δ = 14.4 (q), 14.4 (q), 60.6 (t), 99.2 (d), 109.0 (s), 118.5 (s),

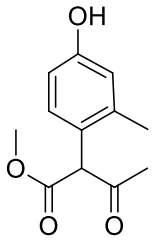
119.9 (s), 128.1 (d), 158.3 (s), 160.2 (s), 163.7 (s), 164.4 (s), 196.4 (s); IR (nujol): ν_{max} = 3413, 1738 cm^{-1}; MS *m/z* (ESI): 249 (M + H^+); anal. calcd. for $C_{13}H_{12}O_5$ (248.23): C 62.90, H 4.87, O 32.23; found: C 63.01, H 4.84.


3ac

Ethyl 6,7-dihydroxy-2-methylbenzofuran-3-carboxylate 3ac: 3ac was isolated by column chromatography on silica gel (acetate/cyclohexane) in 66% yield (156 mg). Pale yellow solid; mp: 120–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.44 (t, 3H, *J*= 7.2 Hz, $OCH_2\mathit{CH_3}$), 2.74 (s, 3H, CH_3), 4.40 (q, 2H, *J*= 7.2 Hz, $O\mathit{CH_2}CH_3$), 5.45 (br, 2H, 2 OH), 6.90 (d, 1H, *J*= 8.4 Hz, Ph), 7.36 (d, 1H, *J*= 8.4 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3 (q), 29.7 (q), 60.4 (t), 109.5 (s), 112.8 (d), 112.9 (d), 121.0 (s), 128.5 (s), 141.0 (s), 142.3 (s), 163.0 (s), 164.6 (s); IR (nujol): ν_{max} = 3375, 3231, 1742 cm^{-1}; MS *m/z* (ESI): 237 (M + H^+); anal. calcd. for $C_{12}H_{12}O_5$ (236.22): C 61.01, H 5.12, O 33.87; found: C 60.89, H 5.19.

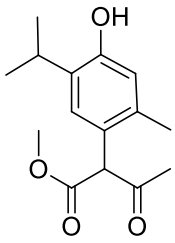

5a

Ethyl 2-(4-hydroxyphenyl)-3-oxobutanoate 5:[145] **5a** was isolated by column chromatography on silica gel (acetate/cyclohexane) in 42% yield (93 mg) The enolic form (E) constitutes the 76% of the mixture and the ketonic form (K) the remaining 24% (determined by ^{1}H-NMR) Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.0 (q, 3H, *J*= 7.2 Hz, $OCH_2\mathit{CH_3}$, E), 1.28 (q, 3H, *J*= 7.2 Hz, $OCH_2\mathit{CH_3}$, K), 1.86 (s, 3H, CH_3, E), 2.18 (s, 3H, CH_3, K), 4.15-4.27 (m, 2H, $OCH_2\mathit{CH_3}$, E, K), 4,63 (s, 1H, CH, K), 5.37 (br, 1H, *OH,* E), 5.68 (br, 1H, *OH,* K), 6.62 (s, 1H, Ph, K), 6.80 (d, 1H, *J*= 8.4 Hz, Ph, E), 6.81 (d, 1H, *J*= 8.4 Hz, Ph, K), 7.01 (d, 1H, *J*= 8.4 Hz, Ph, E), 7.19 (d, 1H, *J*= 8.4 Hz, Ph, K), 13.1 (s, 1H, OH, E); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.0, 14.2, 19.8, 28.7, 60.6, 61.8, 64.8, 103.7, 115.0, 116.0, 124.3, 127.4, 130.5, 130.6, 132.4, 154.6, 156,0, 169.2, 172.8, 173.9, 202.6.


5b

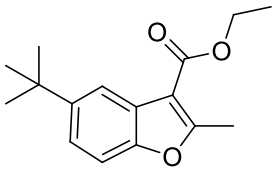
Methyl 2-(4-hydroxy-2-methylphenyl)-3-oxobutanoate 5b: 5b was isolated by column chromatography on silica gel (acetate/cyclohexane) in 50% yield (111 mg). The enolic form (E) constitutes the 63% of the mixture and the ketonic form (K) the remaining 37% (determined by ^{1}H-NMR) Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.77 (s, 3H, CH_3, E), 2.10 (s, 3H, CH_3, E), 2.17 (s, 3H, CH_3, K), 2.28 (s, 3H, CH_3, K), 3.68 (s, 3H, $O\mathit{CH_3}$, E), 3.77 (s, 3H, $O\mathit{CH_3}$, K), 4,86 (s, 1H, CH, K), 5.34 (br, 1H, *OH,* E), 5.57 (br, 1H, *OH,* K), 6.64-6.73 (m, 2H, Ph, E, K), 6.91 (d, 1H, *J*= 8.0 Hz, Ph, E), 7.13 (d, 1H, *J*= 8.4 Hz, Ph, K), 12.9 (s, 1H, OH, E); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 19.4, 19.7, 19.8, 28.7, 51.7, 52.6, 61.4,

102.1, 112.8, 113.7, 116.7, 117.7, 123.3, 126.8, 130.2, 132.6, 138.4, 139.7, 155.1, 155.7, 169.8, 173.1, 174.0, 202.8.



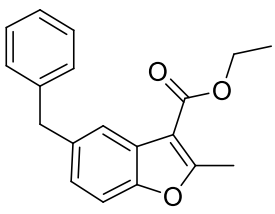
5c

Methyl 2-(4-hydroxy-5-isopropyl-2-methylphenyl)-3-oxobutanoate 5c: 5c was isolated by column chromatography on silica gel (acetate/cyclohexane) in 67% yield (261 mg). The enolic form (E) constitutes the 76% of the mixture and the ketonic form (K) the remaining 24% (determined by ^{1}H-NMR) Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.22-1.26 (m, 6H, CH*(CH$_3$)$_2$*, E, K), 1.77 (d, 3H, CH_3, *J*= 0.8 Hz, E), 2.07 (s, 3H, CH_3, E), 2.17 (s, 3H, CH_3, K), 2.26 (s, 3H, CH_3, K), 3.13-3.20 (m, 1H, CH*(CH$_3$)$_2$*, E, K), 3.70 (s, 3H, OCH_3, E), 3.77 (s, 3H, OCH_3, K), 4,84 (s, 1H, CH, K), 5.00 (br, 1H, *OH,* E), 5.15 (br, 1H, *OH,* K), 6.62 (s, 1H, Ph, K), 6.63 (s, 1H, Ph, E), 6.87 (s, 1H, Ph, E), 7.08 (s, 1H, Ph, K), 13.0 (d, 1H, *J*= 0.4 Hz, OH, E); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 19.2, 19.3, 19.5, 22.5, 22.5, 22.8, 26.7, 26.9, 28.6, 51.8,52.5, 61.7, 102.4, 116.6, 117.6, 123.4, 126.7, 127.3, 129.5, 131.8, 132.7, 135.2, 136.4, 152.1, 152.7, 169.8, 173.2, 174.0, 202.8.



6a

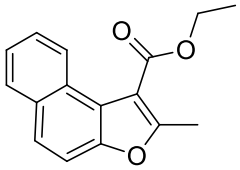
Ethyl 5-(*tert*-butyl)-2methylbenzofuran-3-carboxylate 6a: 6a was isolated by column chromatography on silica gel (acetate/cyclohexane) in 13% yield (34 mg). Pale yellow solid; mp: 50–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.39, (s, 9H, $C(CH_3)_3$), 1.47 (t, 3H, *J*= 7.2 Hz, OCH_2*CH$_3$*), 2.76 (s, 3H, CH_3), 4.43 (q, 2H, *J*= 7.2 Hz, O*CH$_2$*CH_3), 7.35 (s, 1H, Ph), 7.35 (s, 1H, Ph), 8.01 (s, 1H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.4 (q), 14.5 (q), 31.8 (q), 60.2 (t), 109.0 (s), 110.0 (d), 117.9 (d), 122.1 (d), 125.9 (s), 146.8 (s), 151.8 (s), 163.6 (s), 164.7 (s); IR (nujol): ν_{max} = 1720, cm^{-1}; MS *m/z* (ESI): 261 (M + H^{+}); anal. calcd. for $C_{16}H_{20}O_3$ (260.33): C 73.82, H 7.74, O 18.44; found: C 73.69, H 7.80.



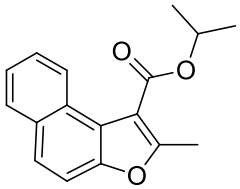
6b

Ethyl 5-benzyl)-2methylbenzofuran-3-carboxylate 6b: 6b was isolated by column chromatography on silica gel (acetate/cyclohexane) in 19% yield (56 mg). Pale yellow solid; mp: 74–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.41 (t, 3H, *J*= 7.2 Hz, OCH_2*CH$_3$*), 2.76 (s, 3H, CH_3), 4.10 (s, 2H, CH_2Ph), 4.39 (q, 2H, *J*= 7.2 Hz, O*CH$_2$*CH_3), 7.11 (dd, 1H, *J*= 8.4 Hz, *J*= 1.6 Hz, Ph), 7.18-7.23 (m, 3H, Ph), 7.28-7.34 (m, 3H, Ph), 7.79 (d, 1H, *J*= 1.2 Hz, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.4 (q), 14.5 (q), 41.9 (t), 60.2 (t), 109.0 (s), 110.6 (d), 121.7 (d), 125.3 (d), 126.0 (d), 126.4 (s), 128.4 (d), 128.9(d), 136.7 (s), 141.5 (s), 152.4 (s), 163.8 (s), 164.5 (s); IR (nujol): ν_{max} = 1743 cm^{-1}; MS *m/z*

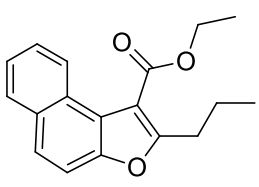
(ESI): 295 (M + H^+); anal. calcd. for $C_{19}H_{18}O_3$ (294.34): C 77.53, H 6.16, O 16.31; found: C 77.69, H 6.09.


6c

Ethyl 2-methylnaphtho[2,1-*b*]furan-1-carboxylate 6c: 6c was isolated by column chromatography on silica gel (acetate/cyclohexane) in 74% yield (188 mg). White solid; mp: 84–86 °C; ^{1}H NMR (400 MHz, DMSO$_{d6}$, 25 °C): δ = 1.50 (t, 3H, *J*= 7.2 Hz, OCH$_2$*CH$_3$*), 2.79 (s, 3H, CH$_3$), 4.52 (q, 2H, *J*= 7.2 Hz, O*CH$_2$*CH$_3$), 7.51 (ddd, 1H, *J*= 8.0 Hz, *J*= 6.8 Hz, *J*= 1.2 Hz, H$_e$), 7.59 (d, 1H, *J*= 8.0 Hz, H$_a$), 7.61 (ddd, 1H, *J*= 8.4 Hz, *J*= 6.8 Hz, *J*= 1.6 Hz, H$_d$), 7.74 (d, 1H, *J*= 8.8 Hz, H$_c$), 7.93 (d, 1H, *J*= 9.2 Hz, H$_b$), 9.22 (d, 1H, *J*= 8.4 Hz, H$_f$); ^{13}C NMR (100 MHz, DMSO$_{d6}$, 25 °C): δ = 14.4 (q), 15.3 (q), 60.8 (t), 111.6 (d), 111.8 (s), 120.4 (s), 124.6 (d), 126.0 (d), 126.2(d), 126.3 (d), 127.8 (s), 128.7 (d), 131.3 (s), 151.4 (s), 161.3 (s), 165.0 (s); IR (nujol): ν_{max} = 1724, 1703 cm^{-1}; MS *m/z* (ESI): 255 (M + H^+); anal. calcd. for $C_{16}H_{14}O_3$ (254.28): C 75.57, H 5.55, O 18.88; found: C 75.48, H 5.59.


6d

Isopropyl 2-methylnaphtho[2,1-*b*]furan-1-carboxylate 6d: 6d was isolated by column chromatography on silica gel (acetate/cyclohexane) in 68% yield (182 mg). White solid; mp: 79–80 °C; ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 1.49 (d, 6H, *J*= 6.4 Hz, OCH*(CH$_3$)$_2$*), 2.79 (s, 3H, CH$_3$), 5.43 (sep, 1H, *J*= 6.4 Hz, O*CH*(CH$_3$)$_2$), 7.51 (ddd, 1H, *J*= 8.0 Hz, *J*= 6.8 Hz, *J*= 1.2 Hz, H$_e$), 7.59 (d, 1H, *J*= 8.8 Hz, H$_a$), 7.61 (ddd, 1H, *J*= 8.4 Hz, *J*= 6.8 Hz, *J*= 1.6 Hz, H$_d$), 7.74 (d, 1H, *J*= 9.2 Hz, H$_c$), 7.93 (d, 1H, *J*= 8.0 Hz, H$_b$), 9.24 (d, 1H, *J*= 8.4 Hz, H$_f$); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 15.3 (q), 22.1 (q), 68.4 (d), 111.6 (d), 112.2 (s), 120.5 (s), 124.6 (d), 126.1 (d), 126.2(d), 126.2 (d), 127.9 (s), 128.7 (d), 131.3 (s), 151.5 (s), 161.1 (s), 164.6 (s); IR (nujol): ν_{max} = 1705 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{16}O_3$ [M + H]$^+$: 269.1178; found: 269.1178.


6e

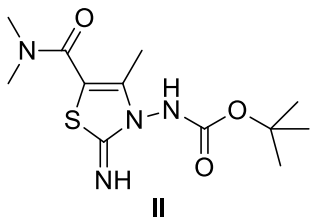
Ethyl 2-propylnaphtho[2,1-*b*]furan-1-carboxylate 6e: 6e was isolated by column chromatography on silica gel (acetate/cyclohexane) in 72% yield (203 mg). Pale yellow solid; mp: 48–50 °C; ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 1.05 (t, 3H, *J*= 7.6 Hz, (CH$_2$)$_2$*CH$_3$*), 1.50 (t, 3H, *J*= 7.2 Hz, OCH$_2$*CH$_3$*), 1.87 (sex, 2H, *J*= 7.6 Hz, CH$_2$*CH$_2$*CH$_3$), 3.15 (t, 2H, *CH$_2$*CH$_2$CH$_3$), 4.52 (q, 2H, *J*= 7.2 Hz, O*CH$_2$*CH$_3$), 7.51 (ddd, 1H, *J*= 8.0 Hz, *J*= 6.8 Hz, *J*= 1.2 Hz, Ar), 7.62 (d, 1H, *J*= 9.2 Hz, Ar), 7.61 (ddd, 1H, *J*= 8.4 Hz, *J*= 6.8 Hz, *J*= 1.6 Hz, Ar), 7.75 (d, 1H, *J*= 8.8 Hz, Ar), 7.94 (d, 1H, *J*= 8.0 Hz, Ar), 9.15 (d, 1H, *J*= 8.8 Hz, Ar); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 13.9 (q), 14.3 (q), 21.8 (t), 30.8 (t), 60.8 (t),

111.5 (s), 111.7 (d), 120.3 (s), 124.6 (d), 125.9 (d), 126.2(d), 126.3 (d), 127.8 (s), 128.7 (d), 131.2 (s), 151.5 (s), 164.8 (s), 165.1 (s); IR (nujol): ν_{max} = 1709 cm^{-1}; MS *m/z* (ESI): 283 (M + H^+); anal. calcd. for $C_{18}H_{18}O_3$ (282.33): C 76.57, H 6.43, O 17.00; found: C 75.61, H 6.38.

CHAPTER 8: Sequential MCR via Staudinger/aza-Wittig versus cycloaddition reaction to access diversely functionalized 1-amino-1H-imidazole-2(3H)-thiones.

Procedure referred to Scheme 2.

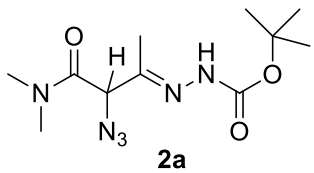
To a stirred solution of 2-chloro-*N*,*N*-dimethyl-3-oxobutanamide (**A**) (1 mmol) in AcOH (4 mL) finely crashed potassium thiocyanate (**B**) (1.5 mmol) was added at room temperature. After 1 hour, *tert*-butyl hydrazinecarboxylate (**C**) (1 mmol) was added portionwise quickly. In a short time the reaction mixture turned yellow and was left to stirr until the disappeareance of **A** (TLC check, 2 hrs). The crude reaction mixture was then treated with a diluted solution of 5% NaOH until neutrality, extracted with EtOAc (50 mL) and washed with water (3 x 10 mL). The combined organic phases were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography eluting with cyclohexane:EtOAc mixture (from 1:1 to pure EtOAc) to afford **II** as major product.



II

***tert*-Butyl (5-((dimethylamino)carbonyl)-2-imino-4-methyl-1,3-thiazol-3(2*H*)-yl)carbamate** (**II**): Yield 48% (144.2 mg) white powder from EtOAc/light petroleum ether; mp 157–161 °C (dec.); ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 1.34 and 1.43 (2 s, 9 H, OBu^t), 1.90 (s, 3 H, CH_3), 2.94 [s, 6 H, $N(CH_3)_2$], 8.21 (br s, 1 H, NH), 9.48 (br s, 1 H, NH); ^{13}C-NMR (100 MHz, [D6]DMSO, 25 °C) δ = 12.7, 27.6, 27.8, 36.7, 80.5, 98.5, 137.0, 154.6, 158.0, 162.8; IR (Nujol, v, cm^{-1}): 3320, 3254, 3200, 1736, 1633, 1607; MS *m/z* (ESI): 301.15 $(M + H)^+$; calcd. for $C_{12}H_{20}N_4O_3S$ (300.38): C, 47.98; H, 6.71; N, 18.65; found: C, 48.07; H, 6.75; N, 18.69.[146]

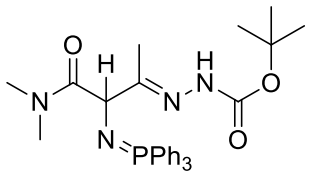
Step by step Synthetic Method for 5a



2a

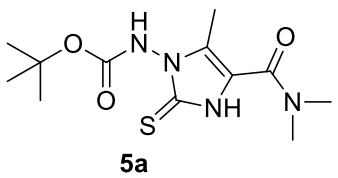
Synthesis of tert-butyl 2-(3-azido-4-(dimethylamino)-4-oxobutan-2-ylidene)hydrazinecarboxylate (**2a**): to the α-halohydrazone **1a** (555.5 mg, 2.0 mmol) solved in THF (9.0 mL) an ice-cooled aqueous solution (1.0 mL, T = 4 °C) of NaN_3 (2.0 mmol, 130.02 mg) was added. The reaction mixture was stirred at room temperature until the disappearance of the starting **1a** (TLC check). THF was removed under reduced pressure and the residue was diluted with water and extracted with CH_2Cl_2 (3 x 15.0 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction was purified by

crystallization from Et_2O affording the α-azido derivative **2a**. Yield 70.0% (398.0 mg) as a white solid; mp 120–124 °C (dec); ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 1.44 (s, 9H, OBu^t), 1.84 (s, 3H, CH_3), 2.86 (s, 3H, NCH_3), 2.92 (s, 3H, NCH_3), 4.99 (s, 1H, CH), 9.82 (br s, 1H, NH, D_2O exch.); ^{13}C-NMR (100 MHz, [D6]DMSO, 25 °C) δ = 13.8, 28.0, 35.5, 36.6, 64.6, 79.5, 146.2, 152.9, 166.5; IR (Nujol, ν, cm^{-1}): 3239, 3150, 2982, 2172, 2098, 1706, 1686, 1664; MS m/z (ESI): 285.07 $(M + H)^+$; anal. calcd. for $C_{11}H_{20}N_6O_3$ (284.31): 46.47; H, 7.09; N, 29.56; found: C, 46.36; H, 7.15; N, 29.65.



3a

Synthesis of tert-butyl 2-(4-(dimethylamino)-4-oxo-3-((triphenylphosphoranylidene)amino)butan-2-ylidene)hydrazinecarboxylate (3a): 1.0 mmol of **2a** (284.31 mg) was solved in CH_2Cl_2 (5.0 mL). The reaction flask was then immersed in an ice bath (T = 0 °C), and a cooled solution of PPh_3 (262.3 mg, 1.0 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise. The reaction was brought back to room temperature and stirred until the disappeareance of organic azide **2a** (monitored by TLC). The formation of phosphazene **3a** was accompanied by the development of N_2. After partial removal of the solvent under reduced pressure, **3a** was isolated by precipitation from a solution of CH_2Cl_2/EtOAc as white powder; yield 66% (342.3 mg); mp 127–131 °C (dec.); ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 42 (s, 9H, OBu^t), 1.81 (s, 3H, CH_3), 2.59 (s, 3H, NCH_3), 2.73 (s, 3H, NCH_3), 4.62 (t, J_{H-P} = 9.2 Hz, 1H, CH), 7.57-7.90 (m, 15H, Ar), 9.64 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, [D6]DMSO, 25 °C) δ = 13.0, 28.0, 35.6, 36.1, 59.3, 79.5, 120.9 ($^1J_{C-P}$ = 102.0 Hz), 129.7 ($^2J_{C-P}$ = 14.0 Hz), 133.7 ($^3J_{C-P}$ = 11.0 Hz), 133.8 ($^3J_{CP}$ = 12.0 Hz), 134.9 ($^4J_{C-P}$ = 2.0 Hz), 150.7, 167.0 ppm; IR (Nujol, ν, cm^{-1}): 3543, 3377, 3211, 1722, 1664; MS m/z (ESI): 519.31 $(M + H)^+$; anal. calcd. for $C_{29}H_{35}N_4O_3P$ (518.59): C, 67.17; H, 6.80; N, 10.80; found: C, 67.31; H, 6.86; N, 10.72.

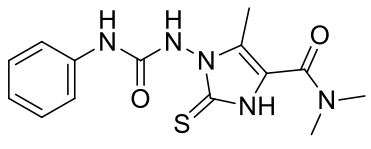


5a

Synthesis of tert-butyl (4-(dimethylcarbamoyl)-5-methyl-2-thioxo-2,3-dihydro-1H-imidazol-1-yl)carbamate (**5a**): 0.65 mmol of **3a** (337.0 mg,) was solved in a mixture of THF:MeOH (4:1, 5.0 mL) heating. Then, 0.5 mL of CS_2 was added and the reaction was refluxed. The end of the reaction was defined (4.0 hrs) by the disappearance of **3a** together with the formation of Ph_3P=S as byproduct (monitored by TLC). Removed the reaction solvents under reduced pressure, a first crop of **5a** was obtained as white powder from a solution of THF / light petroleum ether. A further amount was be gained by column chromatography eluting with CH_2Cl_2/EtOAc mixtures.

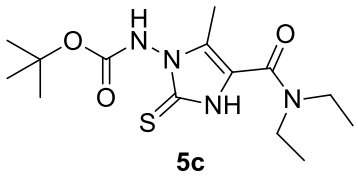
White powder from THF/light petroleum ether ; yield 53% (103.4 mg); mp 172–173°C (dec.); ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 1.32 and 1.45 (2 s, 9H, OBu^{t}), 1.99 (s, 3H, CH_3), 2.94 [s, 6H, $N(CH_3)_2$], 9.69 and 10.15 (2 br s, 1H, NH, D_2O exch.), 12.50 (br s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, [D6]DMSO, 25 °C) δ = 8.9, 27.6, 27.8, 35.9, 80.8, 116.2, 128.2, 153.8, 160.2, 162.9 ppm; IR (Nujol, ν, cm^{-1}): 3188, 3115, 1741, 1645, 1607; MS m/z (ESI): 301.15 $(M + H)^+$; calcd. for $C_{12}H_{20}N_4O_3S$ (300.38): C, 47.98; H, 6.71; N, 18.65; found: C, 48.11; H, 6.63; N, 18.57.

***Typical MCR procedure for the synthesis of N-substituted 1-amino-1H-imidazole-2(3H)-thione derivatives 5a–k*:** to a round flask equipped with a magnetic stirring bar containing ice-cooled solution of NaN_3 (1.0 mmol, 65.01 mg) dissolved in 0.5 mL of H_2O, the corresponding α-halohydrazone **1a**-**k** (1.0 mmol) dissolved in THF (4.5 mL) was added. The mixture was stirred at room temperature until the disappearance of **1** (monitored by TLC). Upon completion, Na_2SO_4 (0.5 g), a solution of PPh_3 (1.1 mmol, 288.5 mg) in THF (1.0 mL) and CS_2 (1.0 mL) were added in sequence and the mixture was refluxed for the appropriate reaction time (3.0-20.0 hrs). The formation of the final products **5a**-**k** was revealed by the complete disappearance of the spot corresponding to the α-azidohydrazone **2a**-**k** as well as the detection of the byproduct $Ph_3P{=}S$. The Na_2SO_4 was filtered in vacuo and washed with THF (10.0 mL). The filtrate was concentrated under reduced pressure and the residue was purified by crystallization and/or by chromatography eluting with cyclohexane:EtOAc or CH_2Cl_2:EtOAc mixtures. The resulting products **5a**-**k** were isolated by crystallization from the specific solvents (see below). According to this procedure, **5a** was obtained in 79% (237.3 mg).



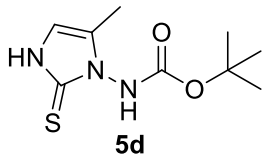
5b

***N,N*,5-trimethyl-1-(3-phenylureido)-2-thioxo-2,3-dihydro-1*H*-imidazole-4-carboxamide** (**5b**): yield 53% (169.3 mg), pink powder from CH_2Cl_2/Et_2O; mp 247–248°C (dec.); ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 2.06 (s, 3H, CH_3), 2.97 [s, 6H, $N(CH_3)_2$], 7.01 (t, J = 8.0 Hz, 1H, Ar), 7.29 (t, J = 8.0 Hz, 2H, Ar), 7.46 (d, J = 8.0 Hz, 2H, Ar), 9.00 (s, 1H, NH, D_2O exch.), 9.33 (br s, 1H, NH, D_2O exch.), 12.56 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, [D6]DMSO, 25 °C) δ = 9.3, 36.8, 116.1, 118.3, 122.3, 128.7, 129.0, 139.1, 153.6, 160.3, 162.6 ppm; IR (Nujol, ν, cm−1): 3323, 3248, 3195, 3136, 1713, 1638, 1605; MS m/z (ESI): 320.40 $(M + H)^+$; calcd. for; $C_{14}H_{17}N_5O_2S$ (319.38): C, 52.65; H, 5.37; N, 21.93; calcd. for; $C_{14}H_{17}N_5O_2S$ (319.38): C, 52.65; H, 5.37; N, 21.93; found: C, 52.79; H, 5.44; N, 21.84.



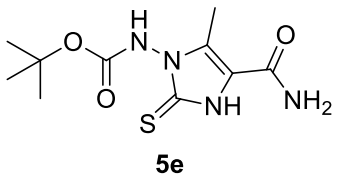
5c

***tert*-Butyl (4-(diethylcarbamoyl)-5-methyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate** (**5c**): yield 72% (236.3 mg), white powder from EtOAc/THF/light petroleum ether; mp 168–169 °C (dec.); ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 1.06–1.10 (m, 6H, 2xNCH$_2$CH$_3$), 1.32 and 1.45 (2s, 9H, OBu^t), 1.94 and 1.97 (2s, 3H, CH$_3$), 3.26-3.37 (m, 4H, 2xNCH$_2$CH$_3$), 9.68 and 10.07 (2 br s, 1H, NH, D$_2$O exch.), 12.49 (br s, 1H, NH, D$_2$O exch.) ppm; ^{13}C-NMR (100 MHz, [D6]DMSO, 25 °C) δ = 8.6, 13.4, 27.5, 27.8, 34.8, 80.6, 117.0, 126.6, 153.8, 159.8, 162.7 ppm; IR (Nujol, ν, cm^{-1}): 3169, 3120, 1748, 1642, 1634; MS m/z (ESI): 329.23 (M + H)$^+$;calcd. for C$_{14}$H$_{24}$N$_4$O$_3$S (328.16): C, 51.20; H, 7.37; N, 17.06; found: C, 51.09; H, 7.42; N, 16.95.



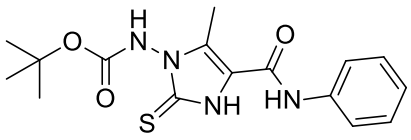
5d

***tert*-Butyl (5-methyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate** (**5d**): yield 69% (158.1 mg), white powder from EtOAc/THF/light petroleum ether; mp 168–169 °C (dec.); ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 1.32 and 1.45 (2s, 9H, OBu^t), 1.93 (s, 3H, CH$_3$), 6.60 (s, 1H, CH), 9.51 and 9.94 (2 br s, 1H, NH, D$_2$O exch.), 11.97 (br s, 1H, NH, D$_2$O exch.) ppm; ^{13}C-NMR (100 MHz, [D6]DMSO, 25 °C) δ = 8.9, 27.9, 80.5, 108.9, 126.9, 153.9, 162.4 ppm; IR (Nujol, ν, cm^{-1}): 3271, 3144, 3098, 1744, 1732, 1640; MS m/z (ESI): 229.96 (M + H)$^+$; calcd. for C$_9$H$_{15}$N$_3$O$_2$S (229.09): C, 47.14; H, 6.59; N, 18.33; found: C, 47.01; H, 6.65; N, 18.41.



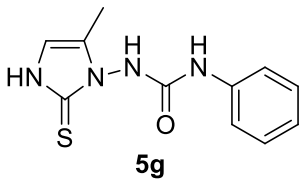
5e

***tert*-Butyl (4-carbamoyl-5-methyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate** (**5e**): yield 58% (157.8 mg), white powder from CH$_2$Cl$_2$ /light petroleum ether; mp 270°C (dec.); ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 1.32 and 1.45 (2s, 9H, OBu^t), 2.23 and 2.26 (2s, 3H, CH$_3$), 7.23 and 7.53 (2 br s, 2H, NH$_2$, D$_2$O exch.), 9.71 and 10.17 (2s, 1H, NH, D$_2$O exch.), 12.42 (s, 1H, NH, D$_2$O exch.) ppm; ^{13}C-NMR (100 MHz, [D6]DMSO, 25 °C) δ = 8.9, 10.1, 27.6, 27.8, 80.9, 115.8, 133.1, 153.7, 159.6, 162.9 ppm; IR (Nujol, ν, cm^{-1}): 3395, 3354, 3182, 3137, 1754, 1717, 1676, 1594; MS m/z (ESI): 273.04 (M + H)$^+$; calcd. for C$_{10}$H$_{16}$N$_4$O$_3$S (272.09): C, 44.10; H, 5.92; N, 20.57; found: C, 44.23; H, 5.96; N, 20.45.



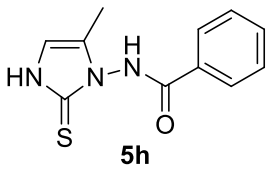
5f

***tert*-Butyl (5-methyl-4-(phenylcarbamoyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate** (**5f**): yield 67% (233.2 mg), white powder from EtOAc; mp 170–171 °C (dec.); ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 1.34 and 1.46 (2s, 9H, OBu^{t}), 2.28 (s, 3H, CH_3), 7.11 (t, J = 8.0 Hz, 1H, Ar), 7.35 (t, J = 8.0 Hz, 2H, Ar), 7.65 (d, J = 8.0 Hz, 2H, Ar), 9.68 (s, 1H, NH, D_2O exch.), 10.28 (s, 1H, NH, D_2O exch.), 12.69 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, [D6]DMSO, 25 °C) δ = 9.2, 27.8, 81.0, 116.0, 119.7, 123.8, 128.8, 133.9, 138.4, 153.7, 156.3, 163.2 ppm; IR (Nujol, ν, cm^{-1}): 3375, 3243, 3066, 1752, 1659, 1630, 1598, 1545; MS m/z (ESI): 349.22 (M + H)$^{+}$; calcd. for $C_{16}H_{20}N_4O_3S$ (348.13): C, 55.16; H, 5.79; N, 16.08; found: C, 55.01; H, 5.72; N, 16.16.



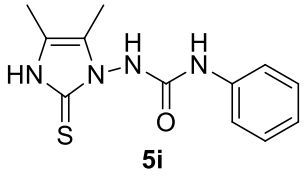
5g

1-(5-Methyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)-3-phenylurea (**5g**): yield 82% (203.4 mg), white powder from THF/EtOAc; mp 245–248 °C (dec.); ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 2.01 (s, 3H, CH_3), 6.64 (s, 1H, CH), 6.99 (t, J = 8.0 Hz, 1H, Ar), 7.28 (t, J = 8.0 Hz, 2H, Ar), 7.46 (d, J = 8.0 Hz, 2H, Ar), 8.91 (s, 1H, NH, D_2O exch.), 9.25 (s, 1H, NH, D_2O exch.), 12.05 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz [D6]DMSO, 25 °C) δ = 9.1, 108.8, 118.3, 122.3, 127.6, 128.8, 139,1, 153.8, 161.9 ppm; IR (Nujol, ν, cm^{-1}): 3305, 3154, 3119, 3097, 1714, 1681, 1637, 1602; MS m/z (ESI): 249.07 (M + H)$^{+}$; calcd. for $C_{11}H_{12}N_4OS$ (248.07): C, 53.21; H, 4.87; N, 22.56; found: C, 53.08; H, 4.94; N, 22.65.



5h

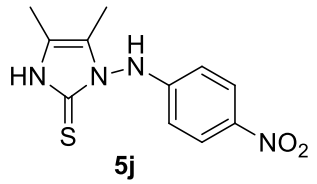
***N*-(5-methyl-2-thioxoimidazolidin-1-yl)benzamide** (**5h**): yield 59% (137.6 mg) white powder from MeOH; mp 240–242 °C (dec.); ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 1.97 (s, 3H, CH_3), 6.72 (s, 1H, CH), 7.56 (t, J = 8.0 Hz, 2H, Ar), 7.65 (t, J = 8.0 Hz, 1H, Ar), 7.99 (d, J = 8.0 Hz, 2H, Ar), 11.44 (s, 1H, NH, D_2O exch.), 12.15 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, [D6]DMSO, 25 °C) δ = 8.9, 109.3, 127.0, 127.7, 128.6, 131.5, 132.5, 162.0, 165.4 ppm; IR (Nujol, ν, cm^{-1}): 3168, 3106, 1666, 1631; MS m/z (ESI): 234.04 (M + H)$^{+}$; calcd. for $C_{11}H_{11}N_3OS$ (233.29): C, 56.63; H, 4.75; N, 18.01; found: C, 56.76; H, 4.82; N, 17.89.



5i

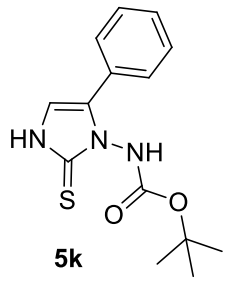
1-(4,5-Dimethyl-2.thioxo-2,3-dihydro-1*H*-imidazol-1-yl)-3-phenylurea (**5i**): yield 85% (223.0 mg), white powder from THF/Et_2O; mp 245–250 °C (dec.); ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 1.94 (s, 3H,

CH_3), 1.99 (s, 3H, CH_3), 6.99 (t, J = 8.0 Hz, 2H, Ar), 7.28 (t, J = 8.0 Hz, 1H, Ar), 7.46 (d, J= 8.0 Hz, 2H, Ar), 8.89 (s, 1H, NH, D_2O exch.), 9.19 (s, 1H, NH, D_2O exch.), 12.00 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, [D6]DMSO, 25 °C) δ = 7.8, 8.9, 116.6, 118.3, 122.2, 122.5, 128.7, 139.1, 153.9, 160.7 ppm; IR (Nujol, ν, cm^{-1}): 3271, 3172, 3095, 1719, 1691, 1665, 1603; MS m/z (ESI): 263.11 $(M + H)^+$; calcd. for $C_{12}H_{14}N_4OS$ (262.33): C, 54.94; H, 5.38; N, 21.36; found: C, 54.87; H, 5.46; N, 21.23.



5j

4,5-Dimethyl-1-[(4-nitrophenyl)amino]-1*H*-imidazole-2(3*H*)-thione (**5j**): yield 84% (222.0 mg), beige powder from THF/EtOAc/Et_2O; mp 279–282 °C (dec.); ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 1.90 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 6.59 (d, J = 8.0 Hz, 2H, Ar), 8.10 (d, J= 8.0 Hz, 2H, Ar), 10.09 (s, 1H, NH, D_2O exch.), 12.19 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, [D6]DMSO, 25 °C) δ = 7.6, 9.0, 111.3, 117.8, 121.7, 125.8, 139.3, 153.0, 160.8 ppm; IR (Nujol, ν, cm^{-1}): 3199, 3094, 1673, 1594; HRMS m/z calcd. for $[M + H]^+$ $C_{11}H_{13}N_4O_2S$ 265.0759; found 265.0774.



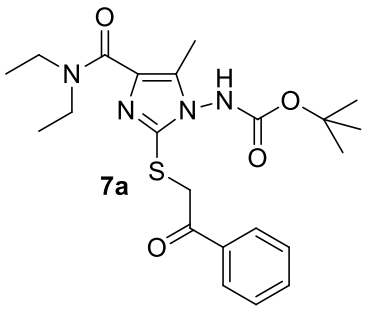
5k

***tert*-Butyl (5-phenyl-2-thioxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate** (**5k**): yield 66% (192.3 mg), light yellow powder from THF/EtOAc/light petroleum ether; mp 172–174 °C (dec.); ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 1.17 and 1.39 (2s, 9H, OBu^t), 7.18 (s, 1H, CH), 7.35-7.49 (m, 5H, Ar), 9.79 and 10.12 (2s, 1H, NH, D_2O exch.), 12.51 (br s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, [D6]DMSO, 25 °C) δ = 27.5, 27.9, 80.2, 80.5, 110.7, 110.8, 126.9, 127.0, 127.7, 127.9, 128.1, 128.5, 130.6, 130.8, 153.2, 153.9, 162.0, 164.2 ppm; IR (Nujol, ν, cm^{-1}): 3275, 3120, 3093, 1726, 1618, 1600; MS m/z (ESI): 292.18 $(M + H)^+$; calcd. for $C_{14}H_{17}N_3O_2S$ (291.37); C, 57.71; H, 5.88; N, 14.42; found: C, 57.83; H, 5.82; N, 14.37.

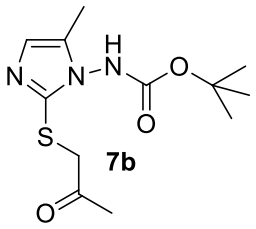
General procedure for the synthesis of α-(imidazol-2-ylthio) carbonyl compounds 7a-c.

To a suspension of the N-Boc-protected 1-amino-1H-imidazole-2(3H)-thione derivatives **5c,d**,**f** (1.0 mmol) and K_2CO_3 (1.0 mmol, 138 mg) in 10.0 mL of acetone was added the corresponding α-halocarbonyl derivative **6a-c** (1.0 mmol). The reaction mixture was kept under magnetic stirring at room temperatures. Upon completion (monitored by TLC) the solvent was removed and the crude reaction mixture was quenched to neutrality with a solution of HCl 1N and extracted with EtOAc (30.0 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuum and the crude extract was purified by crystallization or by column

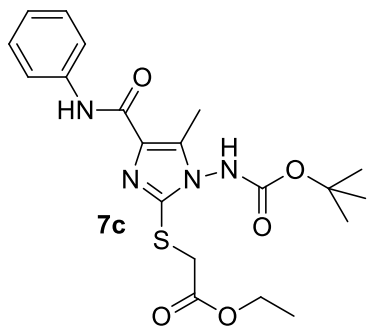
chromatography eluting with cyclohexane:ethyl acetate mixtures to furnish **7a**-**c** derivatives in good yields (84-93%).



***tert*-Butyl (4-(diethylcarbamoyl)-5-methyl-2-((2-oxo-2-phenylethyl)thio)-1*H*-imidazol-1-yl)carbamate** (**7a**): yield 84% (375.1 mg); white solid from Et_2O; mp 123–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.14-1.23 (m, 6H, 2xNCH_2CH_3), 1.48 (s, 9H, OBu^t), 1.98 (s, 3H, CH_3), 3.37-3.64 (m, 4H, 2xNCH_2CH_3), 4.50 (br s, 1H, SCH_aH_b), 4.69 (br s, 1H, SCH_aH_b), 7.46 (t, J = 8.0 Hz, 2H, Ar), 7.58 (t, J = 8.0 Hz, 1H, Ar), 7.97 (d, J = 8.0 Hz, 2H, Ar), 9.45 (br s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz $CDCl_3$, 25 °C) δ = 8.7, 12.9, 14.5, 28.0, 40.6, 41.6, 43.4, 82.5, 128.4, 128.5, 128.7, 130.9, 133.7, 135.3, 135.4, 139.9, 153.8, 164.5, 193.7 ppm; IR (Nujol, ν, cm^{-1}): 3114, 3059, 1741, 1726, 1700, 1681, 1597, 1584; MS m/z (ESI): 447.35 $(M + H)^+$; calcd. for $C_{22}H_{30}N_4O_4S$ (446.56): C, 59.17; H, 6.77; N, 12.55; found: C, 59.02; H, 6.84; N, 11.67.



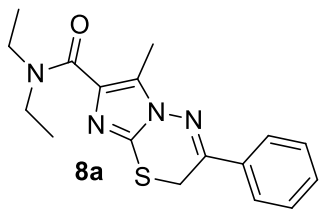
***tert*-Butyl (5-methyl-2-((2-oxopropyl)thio)-1*H*-imidazol-1-yl)carbamate** (**7b**): yield 93% (265.4 mg); ocher solid from EtOAc/cyclohexane; mp 103–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.50 (s, 9H, OBu^t), 2.14 (s, 3H, CH_3), 2.24 (s, 3H, $COCH_3$), 3.81 (br s, 1H, SCH_aH_b), 3.94 (br s, 1H, SCH_aH_b), 6.77 (s, 1H, CH), 8.26 (br s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ = 8.9, 28.0, 28.8, 44.8, 82.8, 125.1, 131.5, 139.5, 154.1, 203.5 ppm; IR (Nujol, ν, cm−1): 3125, 1725, 1714; MS m/z (ESI): 286.17 $(M + H)^+$; calcd. for $C_{12}H_{19}N_3O_3S$ (285.36): C, 50.51; H, 6.71; N, 14.73; found: C, 50.40; H, 6.78; N, 14.86.



Ethyl 2-((1-((tert-Butoxycarbonyl)amino)-5-methyl-4-(phenylcarbamoyl)-1*H*-imidazol-2-yl)thio)acetate (**7c**): yield 92% (399.7 mg), white solid from EtOAc/cyclohexane; mp 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.27 (t, J = 8.0 Hz, 3H, OCH_2CH_3), 1.51 (s, 9H, OBu^t), 2.55 (s, 3H, CH_3), 3.66 (d, J = 16.0 Hz, 1H, SCH_aH_b), 3.90 (d, J = 16.0 Hz, 1H, SCH_aH_b), 4.17-4.24 (m, 2H, OCH_2CH_3), 7.10 (t, J = 8.0 Hz, 1H, Ar), 7.34 (t, J = 8.0 Hz, 2H, Ar), 7.67 (d, J = 8.0 Hz, 2H, Ar), 8.18 (br s, 1H, NH, D_2O exch.), 8.96 (s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ = 9.4, 14.0, 28.0, 36.7, 62.7, 83.4, 119.5, 123.8, 128.9, 129.9, 137.3, 138.0, 139.0, 153.6, 160.6, 169.9 ppm; IR (Nujol, ν, cm−1): 3315, 3182, 1733, 1647, 1601; MS m/z (ESI): 435.20 $(M + H)^+$; calcd. for $C_{20}H_{26}N_4O_5S$ (434.51): C, 55.28; H, 6.03; N, 12.89; found: C, 55.39; H, 5.97; N, 12.81.

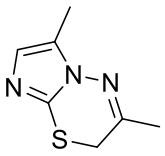
General procedure for the synthesis of N-bridgeheaded heterobicyclic derivatives 8a-c.

Derivative **7a,b** (1.0 mmol) was solved in 5.0 mL of a solution of trifluoroacetic acid (TFA) and CH_2Cl_2 (1:1). The reaction mixture has been left at room temperature until the disappeareance of the starting **7a**,**b** (TLC check). Then, the solvent was removed under reduced pressure and the crude reaction mixture was quenced to neutrality with a satured solution of Na_2CO_3 and extracted with EtOAc (20.0 mL x 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After the removal of the solvent, the crude extract was purified by crystallization or by column chromatography eluting with cyclohexane:ethyl acetate mixtures to furnish **8a**,**b** derivatives. For obtaining **8c**, the best condition found was to treat **7c** (1.0 mmol) with Amberlyst 15H (500 mg) in refluxing dioxane (15.0 mL) for 12.0 hrs. Upon completion (monitored by TLC) the resin was filtered off in vacuo and washed with THF (20.0 mL). The filtrate was evaporated under reduced pressure and the crude reaction mixture was purified by cristallization.



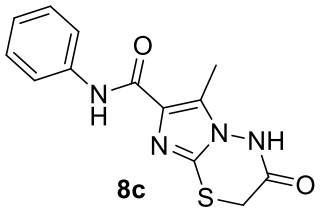
***N,N*-diethyl-6-methyl-3-phenyl-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine-7-carboxamide** (**8a**): yield 82% (269.3 mg) white powder from EtOAc/ yclohexane; mp 125–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, J = 8.0 Hz, 6H, 2·NCH_2CH_3), 2.56 (s, 3H, CH_3), 3.53 (br s, 2H, NCH_2CH_3), 3.74 (br s, 2H, NCH_2CH_3), 3.97 (s, 2H, SCH_2), 7.50-7.52 (m, 3H, Ar), 7.90 (d, J = 8.0 Hz, 2H, Ar) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ = 9.7, 13.0, 14.5, 23.9, 40.3, 43.0, 127.0, 128.9, 129.7, 131.1, 131.3, 133.5, 134.2, 150.8, 164.1 ppm; IR (Nujol, ν, cm^{-1}): 1611, 1574, 1562, 1557;

MS m/z (ESI): 329.28 $(M + H)^+$; calcd. for $C_{17}H_{20}N_4OS$ (328.43): C, 62.17; H, 6.14; N, 17.06; found: C, 62.04; H, 6.19; N, 17.15.



8b

3,6-Dimethyl-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine (**8b**): yield 65% (108.7 mg); white needles from $CHCl_3$/cyclohexane; mp 57–58 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.42 (s, 2H, SCH_2), 6.70 (s, 1H, CH), ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 8.8, 23.5, 26.1, 123.7, 128.6, 130.1, 152.0 ppm; IR (Nujol, ν, cm^{-1}): 1640. 1582; MS m/z (ESI): 168.06 $(M + H)^+$; calcd. for $C_7H_9N_3S$ (167.23): C, 50.27; H, 5.42; N, 25.13; found: C, 50.39; H, 5.39 N, 25.06.



8c

6-Methyl-3-oxo-N-phenyl-3,4-dihydro-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine-7-carboxamide (**8c**): yield 74% (213.3 mg), light yellow powder from EtOAc/light petroleum ether; mp 229–232 °C; ^{1}H NMR (400 MHz, [D6]DMSO, 25 °C): δ = 2.53 (s, 3H, CH_3), 3.81 (s, 2H, SCH_2), 7.04 (t, J = 8.0 Hz, 1H, Ar), 7.29 (t, J = 8.0 Hz, 2H, Ar), 7.81 (d, J = 8.0 Hz, 2H, Ar), 9.80 (s, 1H, NH, D_2O exch.), 12.27 (br s, 1H, NH, D_2O exch.) ppm; ^{13}C-NMR (100 MHz, [D6]DMSO, 25 °C) δ = 9.2, 29.7, 119.8, 123.0, 128.3, 128.4, 130.6, 132.2, 138.8, 160.8, 164.6 ppm; IR (Nujol, ν, cm^{-1}): 1679, 1666, 1595, 1582; MS m/z (ESI): 288.97 $(M + H)^+$; calcd. for $C_{13}H_{12}N_4O_2S$ (288.32): C, 54.15; H, 4.20; N, 19.43; found: C, 54.08; H, 4.27; N, 19.31.

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