*Synthetic approaches for the synthesis of 7-azaindole derivatives using 5-amino-1R-1*H*-pyrrole-3-carbonitrile as useful building block*

DISSERTATION

zur

Erlangung des akademischen Grades

doktor rerum naturalium (Dr. rer. nat.)

der Mathematisch-Naturwissenschaftlichen Fakultät

der Universität Rostock

vorgelegt von

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Rostock, October, 2012

urn:nbn:de:gbv:28-diss2013-0034-0

Die vorliegende Arbeit wurde am Institut für Chemie der Universität Rostock von Oktober 2009 bis Oktober 2012 unter der Leitung von Prof. Dr. Dr. h.c. mult. P. Langer und Dr. V.O. Iaroshenko angefertigt.

The present thesis was completed at the University of Rostock, from October 2009 until October 2012, under the guidance of Prof. Dr. Dr. h.c. mult. Peter Langer and Dr. Viktor Iaroshenko.

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Tag der Prüfung: 05.02.2013

Declaration

I hereby declare that this thesis has been written without any assistance from third parties. Furthermore, I confirm that no sources have been used in the preparation of this thesis other than those indicated in the thesis itself.

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Luis Marcelo Vilches Herrera

Rostock, October 2012

Acknowledgements

I would like to thank

Prof. Dr. Dr. h.c. mult. Peter Langer for the opportunity to carry out my Ph.D r.research in his group.

Dr. Viktor Iaroshenko for his support and for involving me in very interesting projects during all my work.

The DAAD, Deutscher Akademischer Austausch Dienst, and CONICYT,Comisión Nacional de Investigaciones Científicas y Tecnnológicas, for supporting my studies in Germany.

The analytical staff of the Institute of Chemistry at the University of Rostock and of the Leibniz Institute for Catalysis.

All the members of the Langer group, especially Anne, Dennis, Franziska, Friedrich, Ingo, Jana, Lutz, Serge and Zahid for the friendly atmosphere in and out of the lab.

Ingo und Anne, für die Hilfe, Geduld und Freundschaft. Danke!

My mother and father, for all their efforts and love to provide me with a good education and all my family members.

My wife Susan, for her love, company and encouragement, not just during this time but always.

Abstract

The structural diversity of organic compounds containing a ring moiety is enormous, and it is known that at least one half of all chemical compounds are heterocyclic.

Heterocycles are extremely important because of their wide range of applications that goes from their use as pharmaceuticals and agrochemicals to dyestuffs and additives, but above all due their fundamental importance for living systems, where they are found as key components in biological processes. For example the purine and pyrimidine systems are of particular importance because of their role in nucleic acid structure. The pyrrole unit is incorporated in the porphyrin rings of chlorophyll and heme, which are the required components for photosynthesis and for oxygen transport in higher plants and animals. Aminoacids and vitamins also contain heterocyclic systems in their structure.

For all these reasons the development of new synthetic methodologies to access new compounds is one of the most important fields in organic chemistry.

The present work is based on the use of different synthetic methodologies using the pyrrole unit as a building block to construct new heterocyclic systems. A variety of fused and non- fused 7-azaindole derivatives were synthesized *via* ring opening of 3-substituted indoles and 3-nitrochromone, condensation with 4-chlorocoumarins, or using three multicomponent reactions. In addition, the azaindole backbone was subjected to typical coupling reactions.

Kurzbeschreibung

Die strukturelle Vielfalt organischer Verbindungen, die ein Ringsystem enthalten, ist herausragend und es wird angenommen, dass mindestens die Hälfte aller chemischen Verbindungen Heterozyklen sind.

Heterozyklen besitzen ein sehr großes Anwendungspotential, z. B. als Pharmazeutika, Agrochemikalien, Farbstoffe oder Additive. Insbesondere haben sie als Schlüsselkomponenten in biologischen Prozessen eine fundamentale Bedeutung für Organismen. So sind z. B. Purin- und Pyrimidin-Systeme wegen ihrer Rolle in Nukleinsäurestrukturen von besonderer Relevanz.

Die Pyrrol-Struktur ist im Porphyrin-Ring von Chlorophyll bzw. Hämoglobin enthalten, die die Grundlage für die Photosynthese in Pflanzen bzw. den Sauerstofftransport in Organismen bilden. Ebenso enthalten die Strukturen von Aminosäuren und Vitaminen heterozyklische Elemente.

Aufgrund dieser Fakten stellt die Entwicklung neuer Methoden zur Darstellung unbekannter (heterozyklischer) Verbindungen eine der wichtigsten Disziplinen der organischen Chemie dar.

In der vorliegenden Arbeit werden verschiedene synthetischen Methoden angewandt, in denen die Pyrroleinheit als Baustein für neue heterozyklische Ringsysteme genutzt wird.

Durch Ringöffnungsreaktionen von 3-substituierten Indolen und 3-Nitrochromon, Kondensationsationsreaktionen von 4-Chlorcumarinen und Drei-Komponenten-Reaktionen wurden verschiedene kondensierte und nicht kondensierte 7-Azaindol-Derivate synthetisiert. Zusätzlich wurde die Azaindol-Struktur in typischen Kupplungsreaktionen eingesetzt.

List of used abbreviations

ADA	Adenosine Deaminase
AIDS	Acquired Immune Deficiency Syndrome
$AlCl_3$	Aluminium trichloride
Bn	Benzyl
COSY	Correlation Spectroscopy
CuBr	Copper (I) bromide
CuI	Copper (I) iodide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DMF	Dimethyl formamide
DNA	Deoxyribonucleic acid
EtOH	Ethanol
GC/MS	Gas Chromatography/Mass Spectrometry
h	Hour
HMBC	Heteronuclear Multiple Bond Correlation
HSQC	Heteronuclear Single Quantum Correlation
Hz	Hertz
IR	Infrared
MCRs	Multicomponent reactions
MeCN	Acetonitrile
MHz	Megahertz
mL	Milliliter
MeOH	Methanol
mp	Melting point
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
Pd/C	Palladium on charcoal
Ph	Phenyl
p-	*para*
t-Bu	*tert*-Butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride
TS	Transition state

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1. Introduction

Indoles are of great relevance because they are ubiquitous motifs in pharmaceuticals as well as in important natural products. Indoles and their derivatives show high affinity for different biological targets, and probably represent the most important of all structural classes in drug discovery.[1][2] The indole ring is a key substructure in a multitude of molecules, including the aminoacid tryptophan, the neurotransmitter serotonin (5-hydroxytryptamine), the hallucinogen D-lysergic acid diethylamide (LSD) and the natural dye indigo, among others (Figure 1).[3]

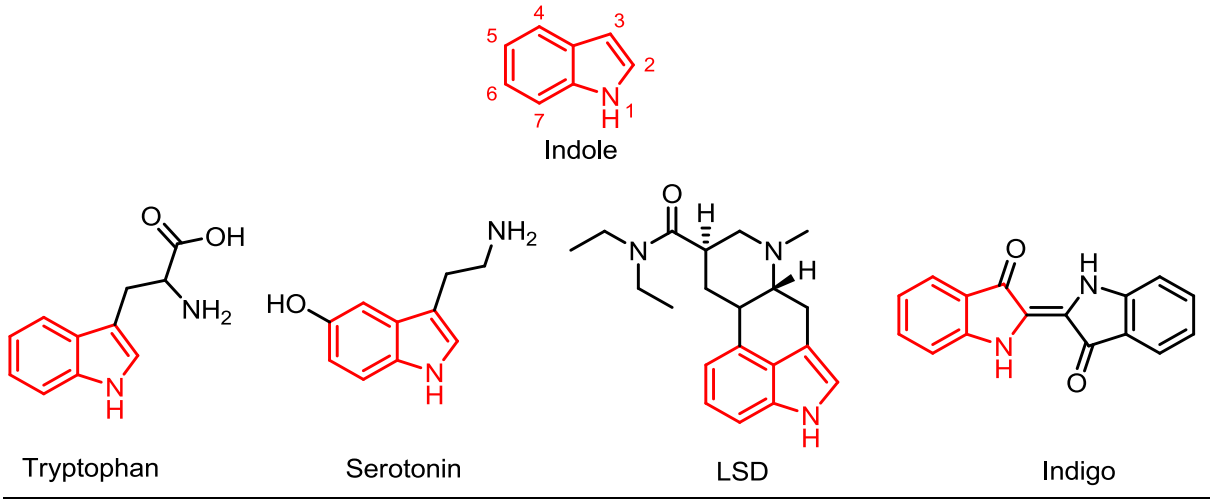


***Figure 1**: Endogenous and other natural compounds containing the indole moiety.*

The widespread usefulness of indoles in life sciences has stimulated the development of numerous methodologies for their synthesis, and a range of well established classical methods is available. Typical examples include the Fischer indole synthesis, the Gassman synthesis, the Madelung cyclization, the Bischler indole synthesis, the Bartoli synthesis and the Batcho-Leimgruber synthesis.[4][5][6]

Replacing one of the carbon atoms at positions 4 to 7 in the indole template with a nitrogen atom gives the so-called azaindoles[7] which are frequently exploited as indole bioisosteres[8] and, although some examples exist in the nature, most of them are synthetic products (Figure 2).[9]

Indoles and Azaindoles belong to the fused [5,6]-member ring systems. They are often classified as purinomimetics or purine isosteres, and exhibit a wide range of biological activities

and pharmacological properties.[10] Among the natural substances where the azaindole core is present, variolin,[11][12] grossularines, and neocryptolepine,[13][14] can be mentioned, and it is also a part of synthetic analogues of naturally occurring alkaloids, such as 7-aza-rebeccamycin[15] and 5-aza-ellipticine.[16] Their biological activities are based mostly on their affinity toward DNA,[17] but also as topoisomerase inhibitors,[18] and as potential multikinase inhibitors.[13]

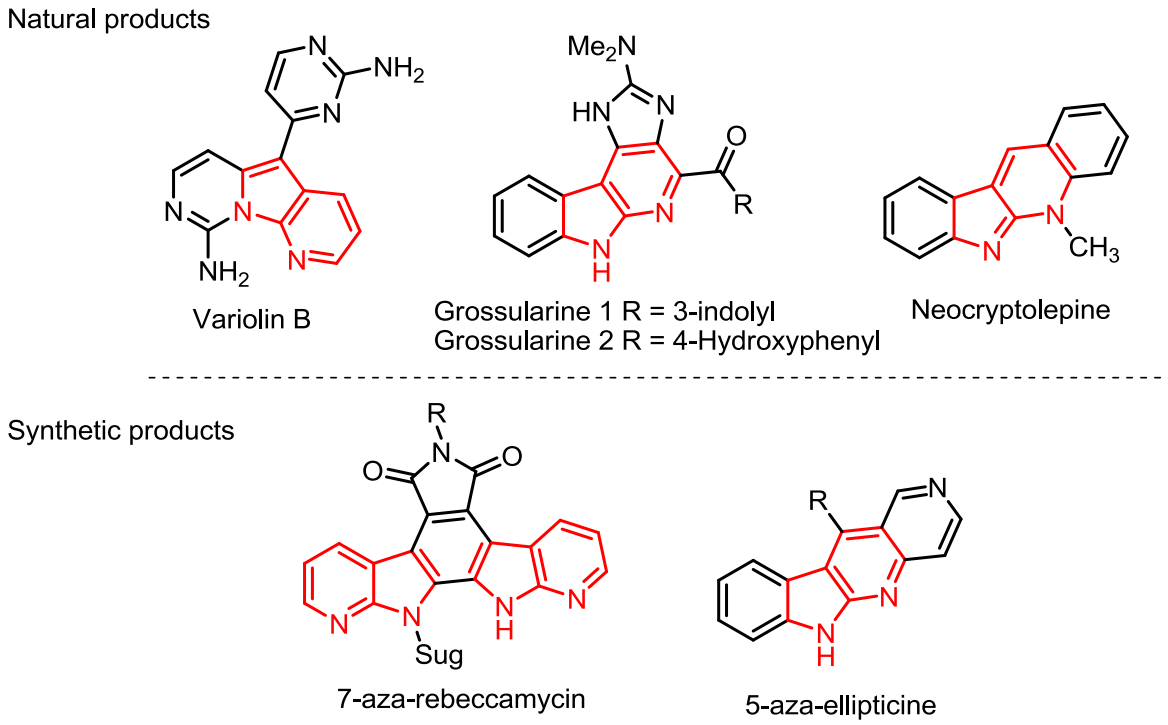


***Figure 2**: Heterocondensed 7-azaindoles present in natural and synthetic compounds.*

In the same way, highly functionalized 7-azaindoles have become major goals for medicinal chemistry studies. Some of them have been shown to be antagonists of the corticotropin-releasing hormone receptor (CRH1-R), which is involved in anxiety and depressive disorders,[19] and the substituted azaindole RWJ 68354 is a potent inhibitor of p38 kinase *in vitro* and *in vivo* and appears to be an attractive candidate for further preclinical evaluation (Figure 3).[20] For all these reasons, they play a crucial role as potential lead compounds for the discovery of biologically active substances. In addition, azaindoles have also found applications in materials science and coordination chemistry.[9]

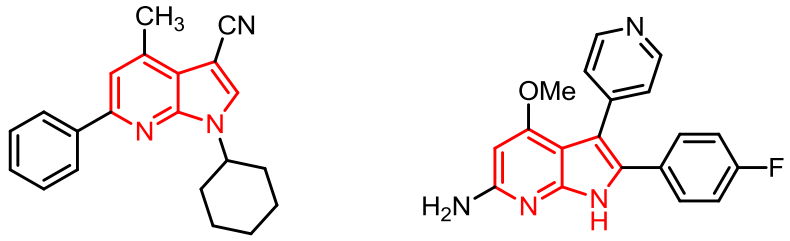
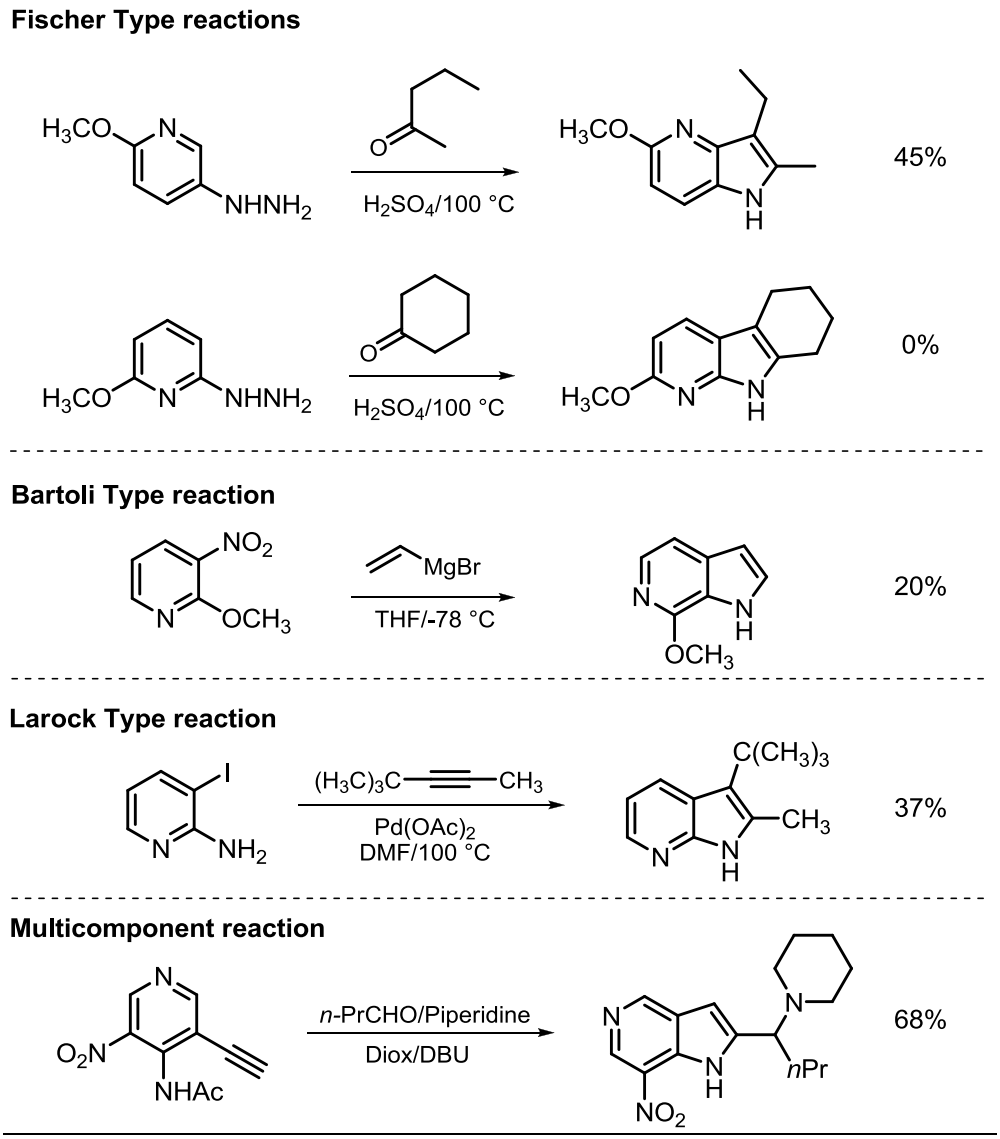


***Figure 3**: Biological compounds containing highly functionalized 7-azaindoles in their structure.*

Despite their usefulness, methods for the synthesis of azaindole scaffolds remain limited with few offering general solutions for the functionalization of the pyridine ring[21] and for the synthesis of heteroannulated azaindoles.

The conventional synthetic strategies for indole formation fail or are less efficient. For example the versatile Fischer indole cyclization is rarely applied because of the unfavorable electron deficient character of the pyridine ring in the [3,3]-sigmatropic rearrangement step of heterocyclization.[22] Using the Bartoli indole synthesis the yields are generally low and a large excess of a vinyl Grignard is necessary (Scheme 1).[23]

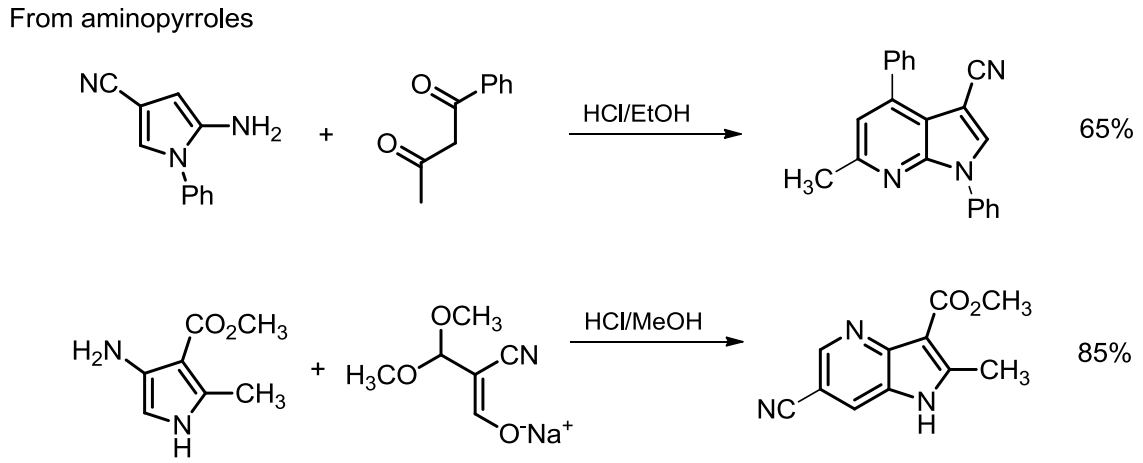
Thanks to developments in the field of organometallic chemistry, particulary transition metal catalysis, a number of new synthetic strategies have been invented for azaindole formation. Most of these methods consist in the cross-coupling of aryl halides with either terminal or internal alkynes. Although these methods offer several advantages such as broader substrate scope and better synthetic efficiencies,[24][25] very limited palladium-mediated coupling reactions for the synthesis of compounds substituted at the 2- and 3-positions have been reported [26][27] and functionalization at positions 4- and 6- are scarce.[28] As an example, the palladium-catalyzed heteroannulation of internal alkynes, originally reported by Larock in 1991 for indole synthesis (Scheme 1),[29] has been applied to the construction of 5-, 6- and 7-azaindoles. However the dependence of the protecting group on the nitrogen group of the pyridine, as well of the alkyne moiety and specific reaction conditions, have only led to moderate yields.[30] Other routes such as azaindole formation via Heck reaction[31] or using a Suzuki coupling strategy [32] have also shown some limitations. Moreover, few methods have been reported for azaindole synthesis based on multiple component reactions (MCRs) (Scheme 1), which provide a divergent approach to functionalized azaindoles in a single step.[33]



Scheme 1*: Synthetic methodologies for the synthesis of 7-azaindole derivatives.*

Other methodologies for the construction of azaindole systems are based on pyrrole derivatives (Scheme 2). These are characterized by the variety of substituents on the pyrrole nucleus. For example a large group of substituted 1-aryl-4-amino-7-azaindoles has been prepared by condensation of 3-cyano-2-aminopyrroles with β-dicarbonyl compounds followed by reductive cyclization. Another interesting approach is to form the pyridine ring by [3+3]-addition of an amino derivative of an electron-rich ring such as 2- or 3-aminopyrroles which provide a nitrogen atom and two carbon atoms for the pyridine ring, and a synthon with three other carbon atoms containing two electrophilic centers. 3,3-Dimethoxy-2-formylpropionic acid, nitromalonic

aldehyde, ethoxymethylenemalonic ester or 1,1,3,3-tetramethoxypropane have been used as synthons.[34-36] Because of the limited availability of suitable substituted substrates or starting materials significant effort is required for the implementation of these procedures.



***Scheme 2**: Synthesis of azaindole derivatives based on amino-pyrroles.*

The purpose of this work is to expand the latter methodology and show the versatility of 5-amino-1-substituted-*1H*-pyrrole-3-carbonitriles as building blocks for the synthesis of 7-azaindole derivatives.

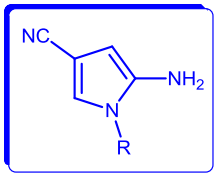


***Figure 4**: 5-Amino-1-substituted-1H-pyrrole-3-carbonitriles.*

In the next chapters different approaches for the synthesis of 7-azaindole derivatives will be described. Their use in one-pot reactions with indoles, chromones and coumarins afforded substituted and heterocondensed azaindole systems. Additionally, their utilization in multicomponent reactions leads not only to azaindole derivatives but also to spiro compounds containing a 1,4-dihydropyridine moiety. Finally, typical cross-coupling reactions were used in order to introduce new substituents in the pyridine ring of the 7-azaindole backbone.

2. Reaction of 5-amino-1-substituted-1H-pyrrole-3-carbonitrile with 3-substituted-indoles

2.1 Introduction

Indole is considered a nucleophile in organic chemistry. It can undergo electrophilic aromatic substitution, C3 being the most nucleophilic site, followed by N1 and C2. However, it is possible to induce it to act as a dielectrophile by introducing an electron deficient group at C3 and reacting it with dinucleophiles. For example, Pravatkar *et al.* reported that the reaction of indole-3-carboxaldehyde with arylamines afforded 6*H*-indolo[2,3-*b*]-quinolines. [37] The reaction proceeds *via* nucleophilic attack of the amine on the aldehyde group followed by annulation with C2 of the indole. Hydrazine derivatives have also been used as nucleophiles instead of anilines. According to Colotta *et al.*, [38] indole-3-oxoacetate reacts with hydrazines leading to pyrazolo[3,4-*c*]quinolin-4-ones. It is very interesting that the reaction proceeds *via* indole ring opening and recyclization leading to the products. The opening of the pyrrole ring of the indole was also observed by Kolotaev's group but without further cyclization, when the reaction was carried out between hydrazine and 3-acetylindole. Nucleophilic attack at C2 of the indole system afforded 4-(2-aminophenyl)-3-methylpyrazole.[39] Scission of the indole ring has been reported by other authors, although not in the reaction with dinucleophiles. Berner observed it as a side reaction while reacting reserpine with TFA in the presence of zinc,[40] and Vecchione in the reaction of indole with aminobenzaldehydes.[41] However, and following a similar approach of indole ring opening, the reaction of electron-rich aminoheterocycles with indole-3-carboxaldehydes has been limited to the use of 1-unsubstituted-5-aminopyrazoles reported by Park *et al.* to afford pyrazolo[3,4-*b*]pyridines.[42]

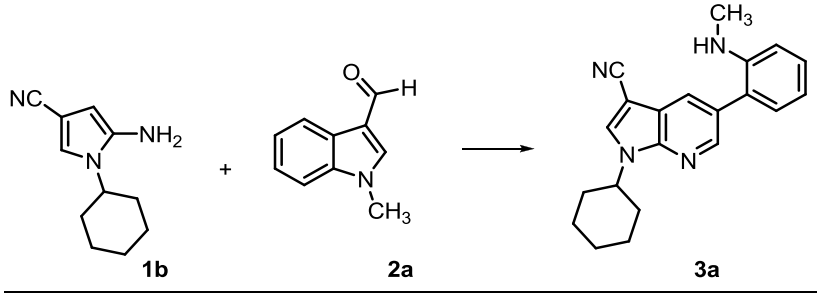
The introduction of an electron-deficient group at C3 of the indole, converts it into a masked bis-electrophile. Reactions using this approach have been reported for the synthesis of purines and purine isosteres by cyclization of electron-rich aminoheterocycles with various 1,3-CCC and 1,3-CNC bis-electrophiles. In this context, cyclocondensations of 3-formylchromone, its thio analogue, and perfluoroalkyl derivatives have been studied.[43]

Considering the potential applications of this reaction, it was decided to explore it using 5-amino-1-substituted-1*H*-pyrrole-3-carbonitriles.

2.2 Results and discussion

2.2.1 Reactions

Several systems were tested in order to find optimal conditions for the reaction of 2-amino-4-cyano-1-cyclohexylpyrrole (**1b**) and *N*-methyl-3-formylindole (**2a**) (Scheme 3).



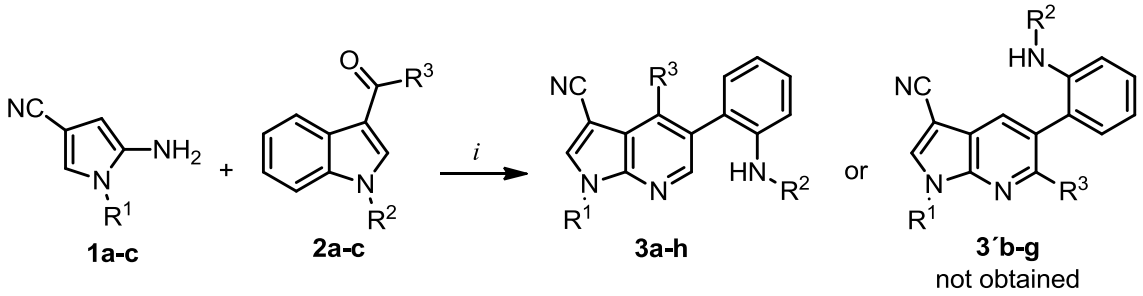
***Scheme 3**: Reaction of **1b** with **2a**.*

It was found that in DMF-TMSCl as water scavenger[44] a mixture of products was formed, whereas in acetic acid the reaction did not proceed. In methanol the yield was only 33% (entry 3) but as observed by Park,[42] the addition of $AlCl_3$ allowed the yield to increase to 65% (entry 4) affording the desired heteroannulated pyridines. Table 1 summarizes these results.

***Table 1**: Screening of conditions for the reaction of **1b** with **2a**.*

Entry	***System***	***Yield %***
1	DMF/TMSCl, 140°C, 6h	21
2	Acetic acid, reflux, 5h	0
3	MeOH	33
4	MeOH/$AlCl_3$, 70°C, 5h	65

Once the optimal conditions were achieved, it was necessary to solve the problem of the regiochemistry of the reaction. Considering that theoretically two regioisomers can be formed, it was envisioned that the use of 3-acetylindole instead of 3-formylindole would allow a better understanding of the mechanism of the reaction due the presence of the methyl group, the location of which could be identified using two-dimensional spectroscopy. Thus, several examples were studied using this approach (Scheme 4).



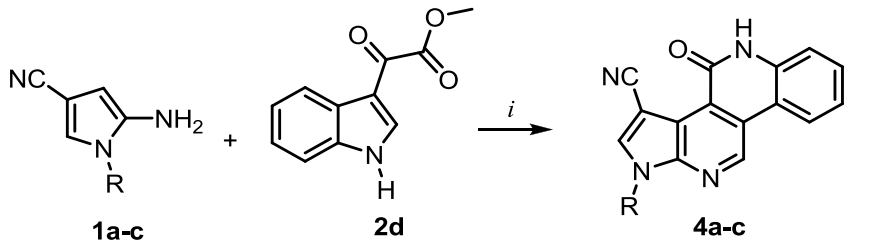
***Scheme 4**: Reaction of 5-aminopyrroles (**1a-c**) with indoles (**2a-c**); i: MeOH/$AlCl_3$ (0.5 eq.), 70 °C, 4 h.*

As shown in Table 2, the reaction afforded exclusively one regioisomer. The best yields were achieved with *N*-methylindoles (entry 2, Table 2). Although the reaction also proceeds with unprotected indoles, their use led to the lowest yields (entries 4, 6, and 7, Table 2). The use of 3-formyl or 3-acetylindoles seems to have no influence on the success of the reaction.

***Table 2**: Yields of the reaction of **1a-c** with **2a-c**.*

Entry	*1*	*R^1*	*2*	*R^2*	*R^3*	*Product*	*Yield %*
1	**b**	Cyclohexyl	**a**	CH_3	H	**3a**	65
2	**c**	*p*-MeO-Bn	**c**	CH_3	CH_3	**3b**	74
3	**b**	Cyclohexyl	**c**	CH_3	CH_3	**3c**	67
4	**b**	Cyclohexyl	**b**	H	CH_3	**3d**	42
5	**a**	*t*-Bu	**c**	CH_3	CH_3	**3e**	55
6	**a**	*t*-Bu	**b**	H	CH_3	**3f**	28
7	**c**	*p*-MeO-Bn	**b**	H	CH_3	**3g**	51
8	**c**	*p*-MeO-Bn	**a**	CH_3	H	**3h**	55

Unexpectedly, the reaction of **1a-c** with methyl 1*H*-indol-3-yl-2-oxoacetates **2d** containing an α-oxoester moiety, afforded new heteroannulated benzo[*c*][2,6]naphthyridin-5(6*H*)-ones **4a-c**. The products were obtained in moderate yield from 40 to 60% (Scheme 5, Table 5).



***Scheme 5**: Reaction of 5-aminopyrroles (**1a-c**) with indole **2d**; i: MeOH/$AlCl_3$ (0.5 eq.), 70 °C, 6 h.*

***Table 3**: Yields of the reactions of **1a-c** with **2d**.*

Entry	*1*	*R*	*Product*	*Yield %*
1	**a**	*t*-Bu	**4a**	44
2	**b**	Cyclohexyl	**4b**	40
3	**c**	*p*-MeO-Bn	**4c**	60

2.2.2 Structure identification

The structures of all products were characterized by ^{1}H- and ^{13}C-NMR spectroscopy as well as IR and HRMS analysis.

As mentioned above, two products might be formed, **3** and **3´**. Formation of **3´** (Scheme 4), with R^3 located at C2 instead of C4 of the pyridine ring, would have only been possible if the reaction had followed the mechanism proposed by Park[42] for the synthesis of heterobiaryl pyrazolo[3,4-*b*]pyridines, where the first step is the formation of the imine of the aminopyrazole and the formyl group of the indole. Two-dimensional spectroscopy, 2D-HMBC, 2D-HSQC, COSY and NOESY for compounds **3c** and **3e**, confirmed the regioselectivity of the reaction (Figure 5).

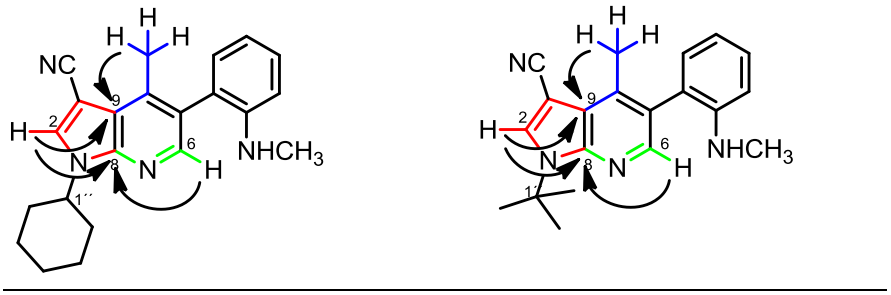


Figure 5*: Analysis of compounds* ***3c*** *and* ***3e*** *using two-dimensional spectroscopy (HSQC and HMBC).*

The 2D-HSQC spectrum, which shows couplings between directly bonded hydrogen and carbon atoms, made it possible to assign the chemical shifts of the protons and carbon atoms at positions 2 and 6. In contrast, the 2D-HMBC spectrum allows assignment of the chemical shifts of carbons positioned, in most cases, three bonds away from hydrogen atoms. Thus, H2 shows 4 couplings (red lines). The first two are easily assigned to C1´´ of the cyclohexyl group at 53.67 ppm and to the nitrile carbon at 83.4 ppm. The other two correspond to carbon nuclei with chemical shifts of 145.3 and 119.4 ppm. H6 shows 3 couplings, denoted in green. One of them relates to a chemical shift of 145.3 ppm, and was assigned to C8. The remaining signal was necessarily assigned to C9 with a chemical shift of 119.4 ppm. Finally the methyl protons showed two couplings (coloured blue). If the methyl group were at C6, a single signal would be expected. In fact, the HMBC spectrum shows two signals, one at 119.4 ppm and the other at 140.3 ppm, proving that the methyl group is bonded to C4, and therefore the regioselectivity of the reaction. A similar analysis was done for **3e**.

2.2.2.1 Crystallographic data

The structures of compounds **3a** and **3b** were independently confirmed by X-Ray diffraction analysis (Figure 6). The structure of **3b** lent definitive proof of the regioselectivity of the reaction. The phenyl group (C(15-20)) or (C(17-22)) of **3a** and **3b**, respectively, is twisted out of the plane of the azaindole system. However the torsion angles are considerably different. Whereas for **3a** (C5-C6-C15-C20) is 53.2°, for **3b** it is 85.7° (C7-C6-C17-C18). The reason appears to be that the methyl group –at C7 in **3b** forces the phenyl group to twist further away from the azaindole plane in order to minimize the repulsive effects between them.

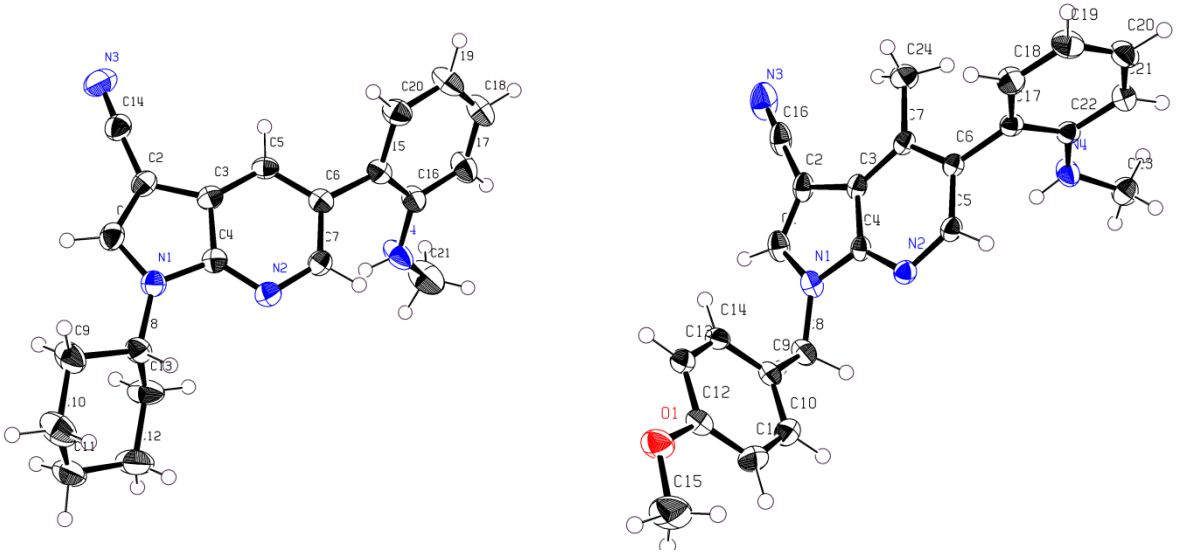
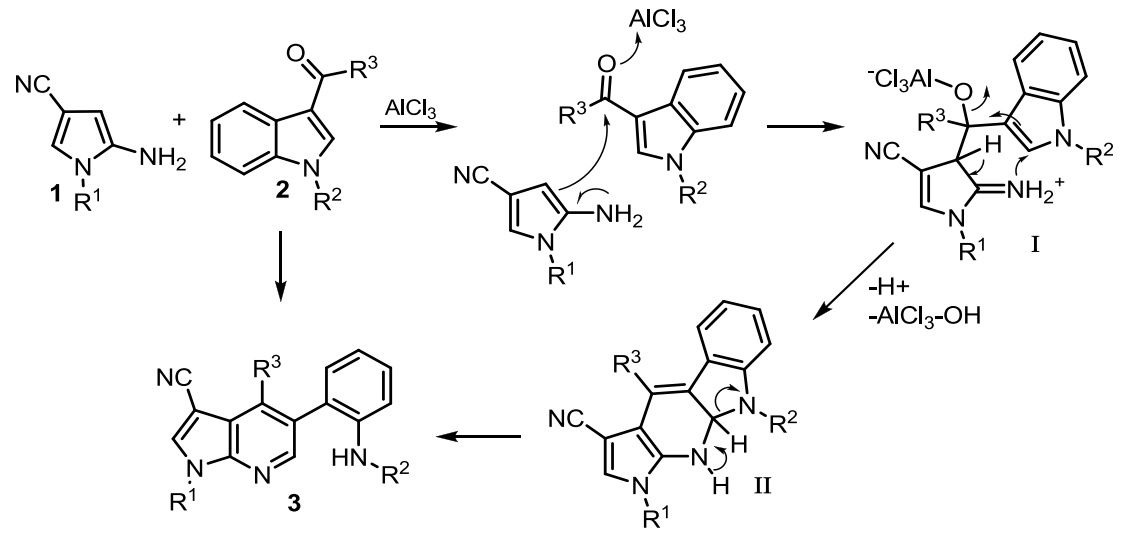


***Figure 6**: Crystallographic structures of compounds **3a** (left) and **3b** (right), oxygen atom red, nitrogen atoms blue.*

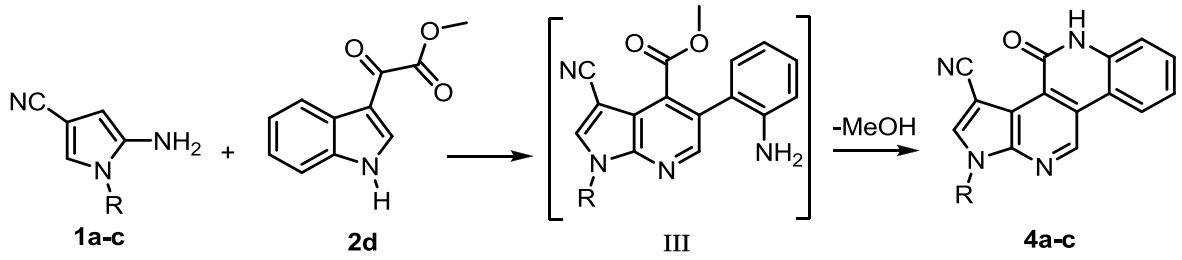
2.2.3 Proposed mechanism

The mechanism of the reaction, and in agreement with that reported by Knepper,[45] can be understood as a nucleophilic attack of C3 of enamine **1** on the carbonyl group of indole **2**. This attack is favoured by the use of $AlCl_3$ which coordinates the Al^{3+} ion to the ketone oxygen atom, leading to intermediate **I**. Subsequent elimination of the aluminium hydroxy species and attack of the amino group on C2 of the indole ring results in formation of the annulated intermediate **II**, which undergoes aromatization and cleavage of the indole ring to give the desired pyridine moiety of **3** (Scheme 6).



***Scheme 6**: Proposed mechanism for the formation of compounds **3**.*

The formation of products **4a-c** (Table 3) can only be explained if the first step also proceeds regioselectively. The mechanism can be viewed as a domino indole-cleavage/cyclocondensation and subsequent lactam formation by attack of the indole-derived amino group on the ester group (Scheme 7).

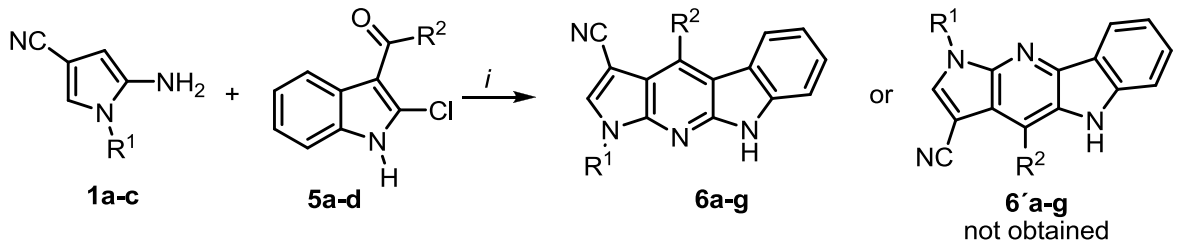


***Scheme 7**: Proposed mechanism for the formation of compounds **4a-c**.*

2.2.4 Annulation reactions

Halovinyl-aldehydes are useful building blocks in organic synthesis. Reactions using this moiety are normally used for the construction of heteroannulated compounds.[46] Thus, 2-chloro-3-formyl- or 3-acetylindole have been used in the reaction with anilines,[14] aminopyridines,[47]

phenylhydrazine[48] and 5-amino-3-methyl-isoxazole,[49] the chlorine atom being fundamental for the annulation process. Because the use of other electron-rich aminoheterocycles has not been reported it was decided to explore the reaction of enamine **1** with 2-chloro-3-substituted indole derivatives **5a-d** (Scheme 8, Table 4).



***Scheme 8**: Synthesis of the heteroannulated 7-azaindoles **6a-g**; i: DMF/TMSCl (5:1), 120 °C, 6-8 h.*

***Table 4**: Yields of the reactions of **1a-c** with **5a-d**.*

Entry	*1*	*R^1*	*5*	*R^2*	*Product*	*Yield %*
1	**a**	*t*-Bu	**a**	H	**6a**	55
2	**a**	*t*-Bu	**b**	CH_3	**6b**	72[a]
3	**b**	Cyclohexyl	**b**	CH_3	**6c**	60
4	**c**	*p*-MeO-Bn	**b**	CH_3	**6d**	52
5	**a**	*t*-Bu	**c**	$CH_3OC(O)$	**6e**	63[a]
6	**b**	Cyclohexyl	**c**	$CH_3OC(O)$	**6f**	54
7	**a**	*t*-Bu	**d**	CF_3	**6g**	40

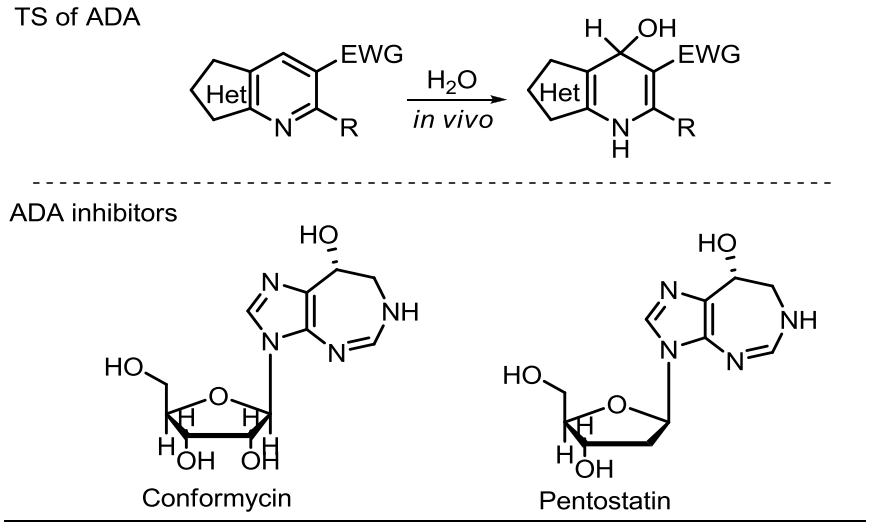
[a] Reactions carried out for Dr. Ingo Knepper

After testing different reaction medias, such as MeOH/$AlCl_3$, EtOH and CH_3COOH, it was found that the best system was DMF/TMSCl. As was expected, the presence of the chlorine atom prevented the ring opening side reacton. Its leaving group character allowed its elimination to occur with preference over the indole ring opening, affording tetracyclic annulated compounds. Similar tetracyclic systems have shown potential biological activity as kinase inhibitors.[50] Additionally, their linear structures make them very attractive as DNA-intercalating agents which mightinhibit DNA replication and transcription as has been shown for the alkaloid neocryptolepine (Figure 2).[51]

3. Reaction of 5-amino-1-substituted-1H-pyrrole-3-carbonitrile with 3-nitrochromone

3.1 Introduction

Heteroannulated pyridines are very attractive because of their pharmacological properties. Within this group 1-deazapurines have proved to be one of the most important scaffolds for the design and synthesis of adenosine deaminase (ADA) inhibitors.[52] ADA abnormalities have been reported in acquired immunodeficiency syndrome (AIDS), in tuberculosis, in Parkinson's disease, in viral hepatitis, in some leukemias, and in many other diseases including cancer. A valuable strategy in drug design is to mimic the transition state (TS) of an enzyme's catalytic mechanism which is believed to be a tetrahedral intermediate.[53] Some potent irreversible ADA transition state analogue inhibitors are coformycin and petostatin (Scheme 9).[54] Molecules that can resemble the tetrahedral intemediate represent promising structures, for example some 3-nitropyridines which are known to undergo hydration at C4 to form stable Meisenheimer-type hydrates.[55] [56] [57]



Scheme 9*: Hydration of pyridine derivatives to form stable Meisenheimer hydrates and ADA inhibitors.*

Chromone is a benzannulated heterocyclic compound which contains a γ-pyrone ring. Its scaffold is widely distributed in plants and shows a range of biological properties including antifungal, antiallergenic, antiviral, antitublin, antihypertensive and anticancer. Additionally, chromone derivatives are active at benzazepine receptors.[58] Some natural examples include flavones and xanthone derivatives (Figure 7).

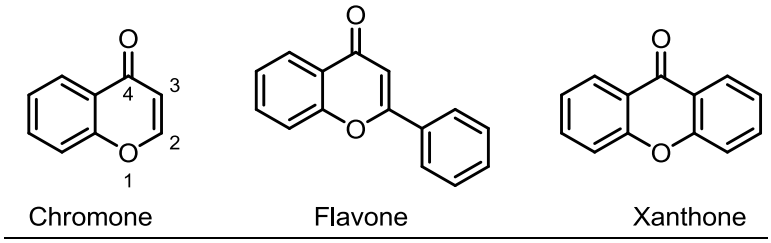


***Figure 7**: Natural compounds containing the chromone moiety.*

The pharmacological and biological activities of chromone derivatives have prompted research into their chemical properties. They show a broad spectrum of reactivity with nucleophiles, electrophiles and other reagents, making them valuable building blocks for the preparation of pharmacologically relevant products and new heterocyclic systems. Nucleophilic attack occurs at the 2- and 4-positions of the heterocyclic ring.[59] Attack at C2 has been found to result in opening of the pyrone ring. Chromones react with hydroxylamine or hydrazine leading to isoxazole or pyrazole derivatives.[60] However, if a substituent attached to the chromone is more electrophilic than C2 or C4, the nucleophile will attack at that position. For example, the reaction of chromone-3-carbaldehyde with 5-aminopyrazole has been shown to afford pyrazolo[1,5-*a*]pyrimidine. This reaction occurrs *via* a conjugate addition of the endocyclic nucleophilic nitrogen of the 5-aminopyrazole, followed by the ring opening of the resulting adduct. Interesting reactions have also been reported using 3-substituted chromones with electron withdrawing groups as 2π components in cycloaddition reactions. For example the Diels-Alder reaction of chromone 3-carboxaldehyde with *ortho*-benzoquino-dimethanes leads to benzo[*b*]xanthones.[61]

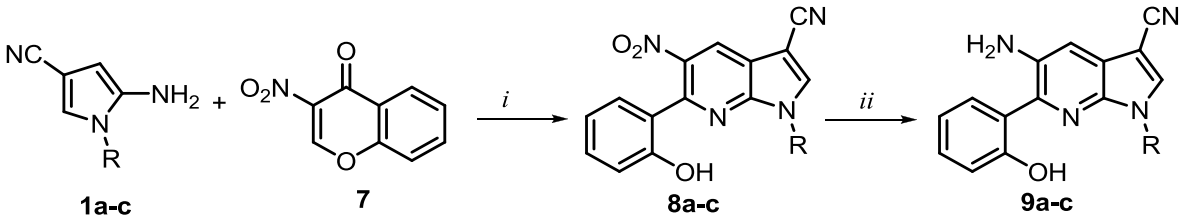
Thus, 3-substituted chromones are versatile compounds that can be used as valuable synthetic intermediates. The most studied classes are 3-acyl-, 3-methyloxalyl-, and 3-cyanochromones.[62] In contrast, 3-nitrochromones have not received much attention even though more than 30 years ago Connor *et al*. reported their potential as building blocks in organic

synthesis.[63] That work described the reaction of 3-nitrochromone with nucleophiles such as amines, enamines and stabilized enolates for the formation of several products, including pyrrolyl, phenyl, pyridyl, pyrimidyl and pyrazolyl nitro derivatives. Similarly, Takasagi reported the use of 2-methyl-3-nitrochromone with various bifunctional nucleophiles such as hydrazines and amidines for the synthesis of a variety of *N*-heterocylic compounds.[64] [65] Since that date no new reports have been found about the use of this versatile compound. For that reason, and based on a previous report where the reaction of 3-nitro-4*H*-chromen-4-one with 5-amino imidazole afforded 6-nitro-3*H*-imidazo[4,5-*b*]pyridines,[52] it was decided to study this reaction, but by using the electron-rich amino heterocycle 5-aminopyrrole (Scheme 10).

3.2 Results and discussion

3.2.1 Reactions

Based on a previous report where the reaction of 3-methoxalylchromone with electron-rich aminoheterocycles was done in acetic acid as solvent, it was decided to test the same reaction conditions.[66] Fortunately the reaction afforded product **8** in excellent yield, making further optimization unnecessary (Table 5).



***Scheme 10**: Reaction of **1a-c** with 7; i: CH_3COOH, reflux, 6-8 h; ii: H_2; Pd/C, CH_3OH, rt, 48 h.*

Actually, and as expected, the methodology represents a rapid route to heteroannulated pyridines bearing a nitro-group located at the β-position of the pyridine core. 3-Nitrochromone acts as an efficient Michael acceptor, C2 and C4 being the sites utilized for the pyridine ring formation. All the attempts to obtain the desired products by react the 3-nitrochromone with a

substituent at C2 failed, due probably to steric hindrance effects. The unsuccessful reaction using 3-nitrothiochromone can be explained in terms of the lower electronegativity of sulphurcompared with oxygen. This difference reduces the electrophilicity of C2 and its susceptibility to nucleophilic attack to cleave the thiopyrone S-C bond. The sulphur atom also enhances the aromaticity of the thiochromone system as compare with chromones. It has been reported that the S1-C2 and C3-C4 bonds in 3-formylthiochromone have some double bond character. [67]

***Table 5**: Yields of the reactions of **1a-c** with **7**.*

Entry	*1*	*R*	*Product*	*Yield%*	*Product*	*Yield%*
1	**a**	*t*-Bu	**8a**	67	**9a**	77
2	**b**	Cyclohexyl	**8b**	81	**9b**	78
3	**c**	*p*-MeO-Bn	**8c**	93	**9c**	64

Because of the importance of 3-amino derivatives as kinase inhibitors,[68] especially 5-amino-7-azaindoles,[69] compounds **8a-c** were reduced by hydrogenation in the presence of 10 mol% Pd/C.

3.2.2 Structure identification

The structures of all products were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as IR and HRMS analysis.

3.2.2.1 Crystallographic data

The structures of compounds **8a** and **8c** were independently confirmed by X-Ray diffraction analysis. In both structures it is possible to observe the planar cores of the heterocyclic framework. In addition, one or two molecules of DMF are present in the crystal structures of **3a** and **3c** respectively. The phenyl groups (C(13-18)) in **8a** and (C(17-22)) in **8c** are slightly twisted out of the azaindole plane, probably to minimize electronic repulsion between the oxygen atoms of the nitro and hydroxyl-groups. The torsion angles are 43.0° for **8a** (C2-C1-C13-C14), and 4.9° for **8c** (C6-C7-C17-C22).

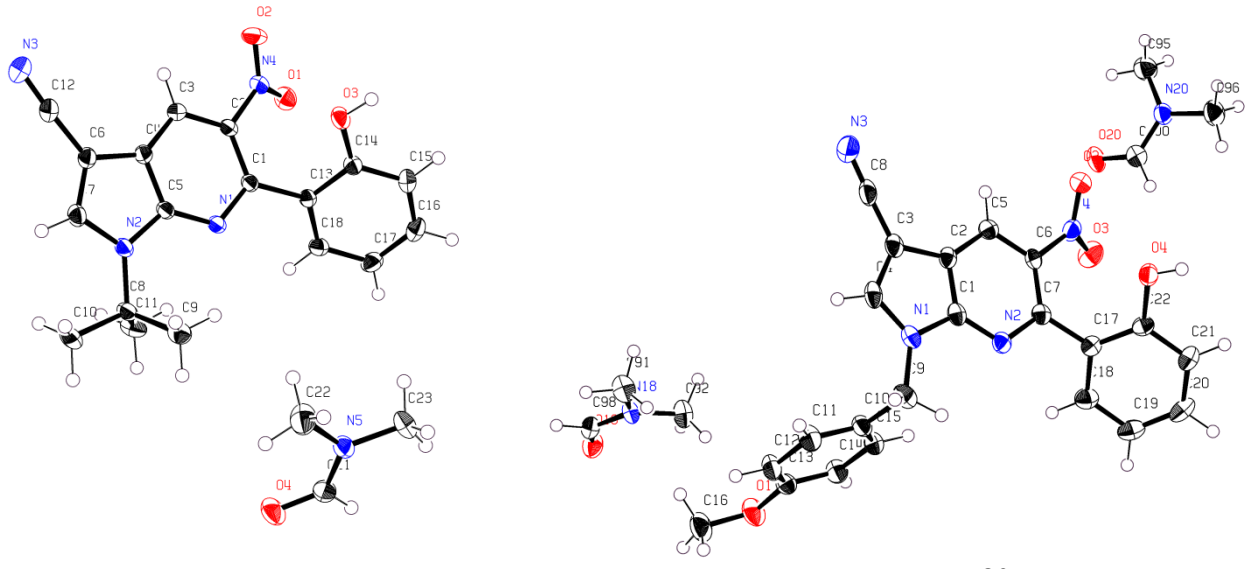
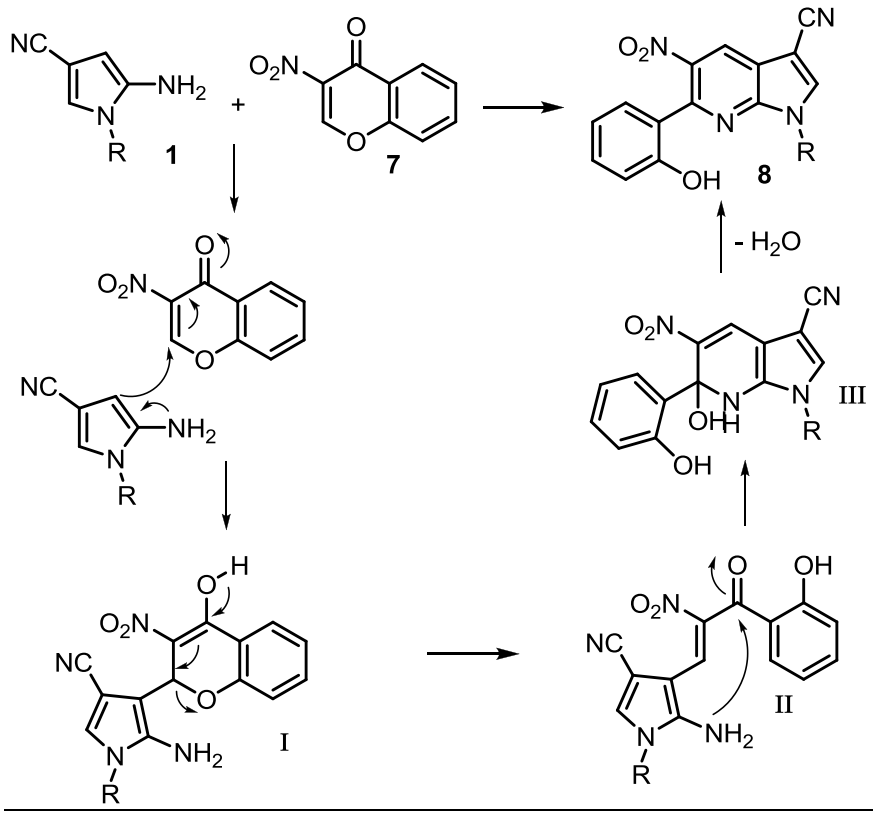


***Figure 8**: Crystallographic structures of compounds **8a** (left) and **8c** (right) oxygen atoms in red, nitrogen atoms in blue.*

3.2.3 Proposed mechanism

In these reactions C2, C3 and the carbonyl carbon C4 served as the source of three carbons for the new *N*-containing aromatic ring. The formation of products **8a-c** can be explained by conjugate addition of the enamine carbon atom of **1** to the double bond of 3-nitrochromone (**7**) to give intermediate **I**. Subsequent pyrone ring opening delivers type **II** intermediates. Intramolecular attack of the amino group on the carbonyl group affords intermediates **III** which undergo elimination of water to give the heteroannulated pyridines **8** (Scheme 11).



***Scheme 11**: Proposed mechanism for the formation of compounds **8**.*

4. Reaction of 5-amino-1-substituted-1H-pyrrole-3-carbonitrile with 4-chloro-3-(trifluoroacetyl)- and 4-chloro-3-(methoxalyl)coumarins

4.1 Introduction

Coumarin, *2H*-chromen-2-one, and its derivatives, constitute an important class of heterocyclic compounds which present a wide variety of properties. Their application can be found in the additive, cosmetic and perfume industries, and also as photographic sensitizers and solar collectors and as fluorescent markers in biochemistry.[70] Because of their therapeutic potential, many natural, seminatural and synthetic coumarins have occupied an important place in drug research, as one of the so-called privileged drug scaffolds.[71] Among their pharmacological properties can be mentioned anticoagulant (*e.g.* warfarin, acenocoumarol), insecticidal (*e.g.* coumaphos), antibacterial (*e.g.* novobiocin, clorobiocin). Additionally, the cytotoxic activities of coumarin and its known metabolite 7-hydroxycoumarin have been tested in several human tumor cell lines (Figure 8).[72]

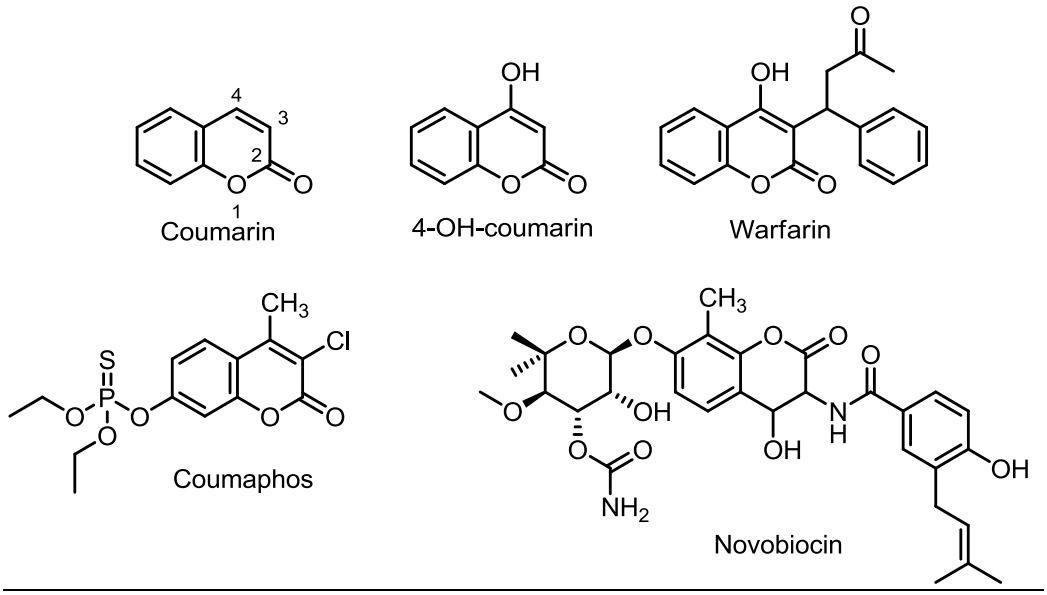
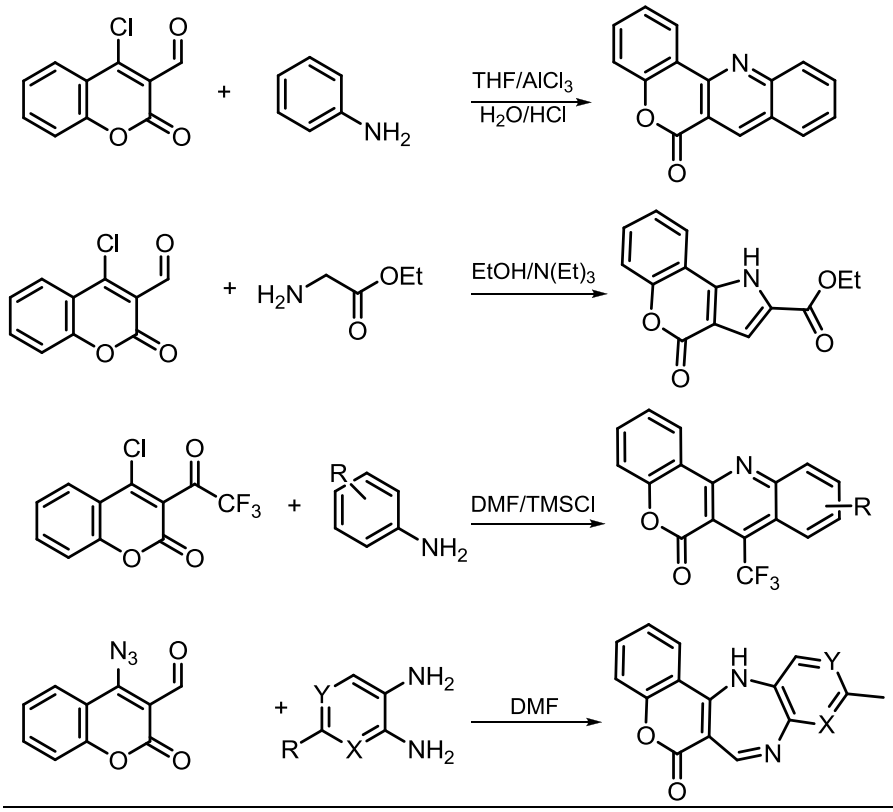


***Figure 9**: Coumarin and coumarin derivatives with pharmacological properties.*

Due to the versatility of the coumarins, one of their most important uses is as building blocks in organic synthesis. Varied biological activity of coumarins fused with other heterocycles in the -3,4 position have been reported and there is a considerable amount of synthetic work in this field.

Among the already known routes to coumarins [3,4]-fused to five-, six- and seven-membered rings the most commonly used strategy involves the condensation between 3-formyl, 4-hydroxy, 4-chloro, or 4-azidocoumarins with binucleophiles such as hydrazines, hydroxylamine, anilines, α–amino methylenic compounds or 1,3-dicarbonyl compounds. For example the reaction of 4-chlorocoumarin-3-carbaldehyde with substituted anilines afforded 6-oxo-6*H*-[1]benzopyrano[4,3-*b*]quinolines.[73] Similarly, 2-functionalized [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-ones were obtained by reaction of the same precursor with different amino derivatives (*e.g.* glycinonitriles, ethyl glycinates and amino ketones).[74] Also, the reaction of 4-chloro-3-(trifluoroacetyl)coumarin with anilines led to heterocondensed products.[75] Annulated benzodiazepines could also be obtained when 4-azido-3-formylcoumarin was reacted with 1,2-diamines (Scheme 12).[76]



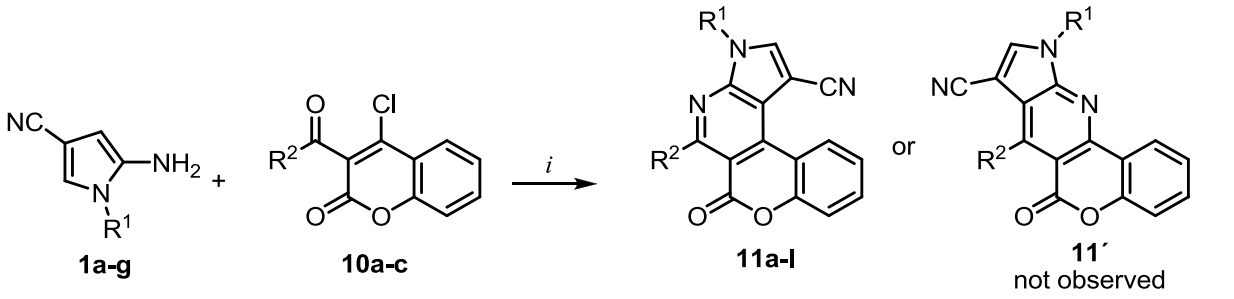
***Scheme 12**: Synthetic methodologies using coumarin derivatives.*

The presence of a good leaving group such as chlorine at C4, and an electron-withdrawing group such as a formyl group at C3 of the coumarin are essential for the addition-elimination conjugated reactions to afford the heteroannulated products. However the use of other 3-substituted derivatives such as 4-chloro-3-(trifluoroacetyl)- and 4-chloro-3-(methoxalyl)coumarin has not been extensively studied, and only the reaction of 4-chloro-3-methoxalylcoumarin with anilines has been reported. Because electron-rich amino heterocycles have proved to be useful dinucleophiles,[77] it was decided to explore this reaction of 4-chloro-3-substituted-coumarins with 5-aminopyrroles.

4.2 Results and discussion

4.2.1 Reactions

The reaction of enamine **1a** with 3-trifluoroacetylcoumarin **10a** was studied. The conditions of choice were DMF and TMS-Cl as water scavenger, which resulted in the formation of heteroannulated chromeno[4,3-*d*]pyrrolo[2,3]pyridines **11** with excellent regioselectivity and in moderate yields (Scheme 13).



***Scheme 13**: Reactions of **1a-g** with coumarins **10a-c**; i: DMF/TMSCl (5:1), reflux, 6-8 h.*

With this result in hand, it was decided to expand the reaction to the use of other *N*-substituted-5-aminopyrroles as well as coumarins with different electron-withdrawing groups –at C3, such as formyl and methoxalyl (Table 6).

Table 6: Yields of the reactions of **1a-g** with **10a-c**.

Entry	*1*	R^1	*10*	R^2	*Product*	*Yield %*
1	**a**	*t*-Bu	**a**	CF_3	**11a**	72
2	**a**	*t*-Bu	**c**	CO_2Me	**11b**	53
3	**b**	Cyclohexyl	**a**	CF_3	**11c**	46
4	**d**	Cyclopentyl	**a**	CF_3	**11d**	58
5	**d**	Cyclopentyl	**c**	CO_2Me	**11e**	38
6	**e**	*p*-Tolyl	**c**	CO_2Me	**11f**	42
7	**f**	*n*-Hexyl	**a**	CF_3	**11g**	45
8	**g**	2-Me-Cyclohexyl	**a**	CF_3	**11h**	44
9	**g**	2-Me-Cyclohexyl	**c**	CO_2Me	**11i**	40
10	**c**	*p*-MeO-Bn	**a**	CF_3	**11j**	41
11	**c**	*p*-MeO-Bn	**c**	CO_2Me	**11k**	55
12	**a**	*t*-Bu	**b**	H	**11l**	40

The results show that all the reactions resulted in the formation of only one regioisomer. The yield seems to depend on the nature of the electron-withdrawing group at C3 of the coumarin. With the same *N*-substituted-5-aminopyrrole, entries 1, 2 and 12, with a *tert*-butyl group, or entries 4 and 5 with a cyclopentyl group, the yield decreases significantly as it goes from 3-trifluoroacetyl to methoxalyl and to an aldehyde group.

4.2.2 Structure identification

The structures of all products were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as IR and HRMS analysis.

The ambident character of the heterocyclic amine could theoretically lead to two products (Scheme 13). The formation of products **11´** (not observed) could be explained if the elimination of the chlorine atom took place due to a nucleophilic attack of the amino group, followed by intramolecular cyclization. Such behaviour has been described with anilines and 5-amino-3-methyl-phenylpyrazole. However, according to the ^{1}H and ^{13}C NMR spectra, only one regioisomer was formed.

4.2.2.1 Crystallographic data

The structures of compounds **11a** and **11b** were independently confirmed by X-Ray crystallographic analysis.

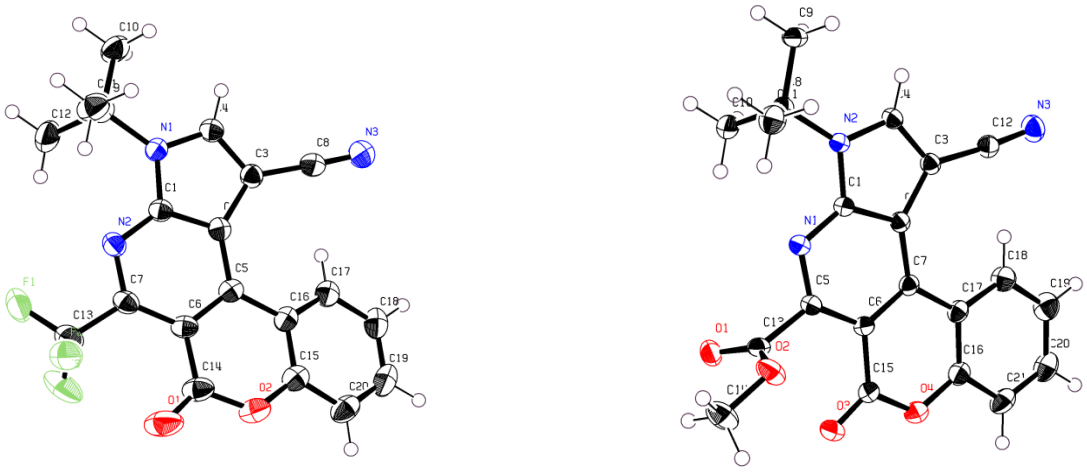


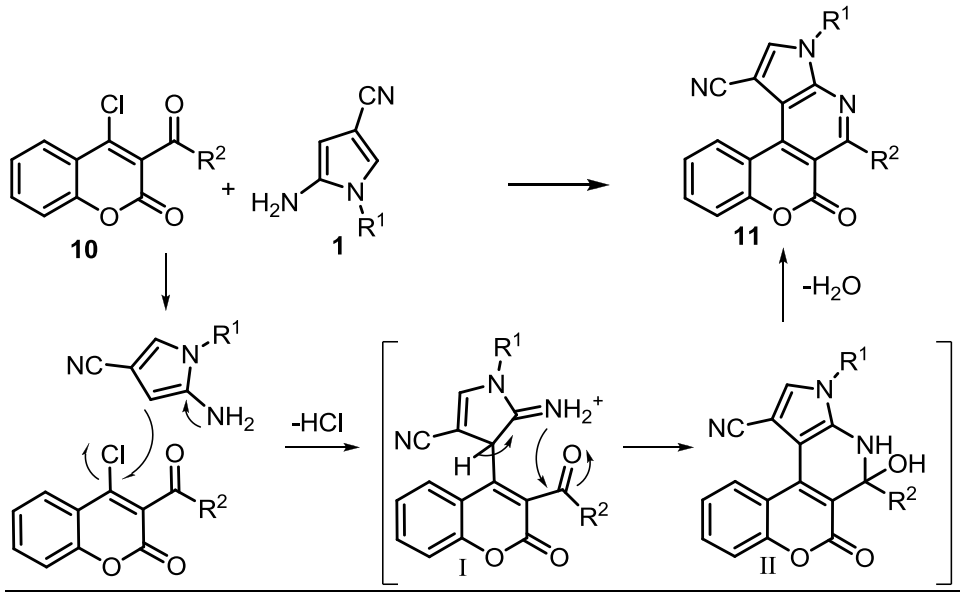
***Figure 10**: Crystallographic structures of compounds **11a** (left) and **11b** (right), oxygen atoms in red, nitrogen atoms in blue, fluorine atoms in green.*

Structure **11a**, unlike **11b** which has a planar core structure, shows a slight distortion of the pyrone ring. Responsible for this phenomenon is the CF_3 group whose van der Waals radius probably overlaps with that of the carbonyl group oxygen triggering a distortion of the planar geometry. The corresponding angles involved are 4.1° (C7-C6-C14-O1); 12.4° (C6-C5-C16-C15), and 13.1° (C14-C6-C7-C13). In the case of **11b,** the carbonyl group lies out of the plane; therefore no repulsion occurs and no distortion is necessary. The N1-C5-C13-O1 angle is 77.0°.

4.2.3 Proposed mechanism

Once the regioselectivity of the reaction was confirmed, a mechanism could be proposed. The first step would be the attack of the internal enamine β-carbon, which is more nucleophilic that the amino group, at C4 of the coumarin with concomitant elimination of HCl to form intermediate **I**. Intramolecular attack of the amino group on the carbonyl group *via* intermediate

II and water elimination, leads to the fused coumarin derivatives **11**.



***Scheme 14**: Proposed mechanism for the formation of compounds **11**.*

5. Three-component reaction of 5-amino-1-substituted-1H-pyrrole-3-carbonitrile with aromatic aldehydes and active methylene compounds.

5.1 Introduction

Multicomponent reactions (MCRs) make it possible to synthesize target molecules with great efficiency and atom economy.[78] Using this approach more than two educts can be converted directly into the product in a one pot reaction and, in contrast with multi-step syntheses, they are more efficient because several bonds are formed in one sequence, without isolation of any intermediates.[79] Even though the first MCRs date back to the middle of 19th century, renewed interest in such reactions has surfaced, not just because of the minimization of waste, but also because solvent, reagent, adsorbent, and energy use are dramatically decreased. Due to the significant therapeutic potential associated with heterocyclic compounds, such reactions coupled with high-throughput biological screening are some of the best tools to generate large compound libraries for evaluation as lead compounds in drug discovery.

The Biginelli condensation is one of the most famous MCRs. Originally the reaction involved the condensation of aldehydes, urea and β-ketoesters to give 3,4-dihydropyrimidin-2-ones. However, the scope of this heterocycle synthesis has been extended considerably by variation of all three building blocks, allowing access to a large number of multifunctionalized pyrimidine derivatives. The aldehyde and the CH-acidic components can be varied to the largest extent. However the urea faces the most restrictions in terms of allowed structural diversity.[80] For that reason, various heterocyclic amines such as 5-aminopyrazoles, 6-aminopyrimidin-4-one, 5-amino-3-methylisoxazole and 6-amino-1,3-dimethyluracil,[81] have been widely used as valuable synthetic intermediates. However, despite their potential interest as building blocks in organic synthesis, 2-aminopyrroles have not been used in multicomponent syntheses for the construction of more complex heterocyclic compounds. Therefore it was decided to develop a simple multicomponent Biginelli-type reaction approach starting with 2-aminopyrrole, active methylene compounds and aromatic aldehydes.

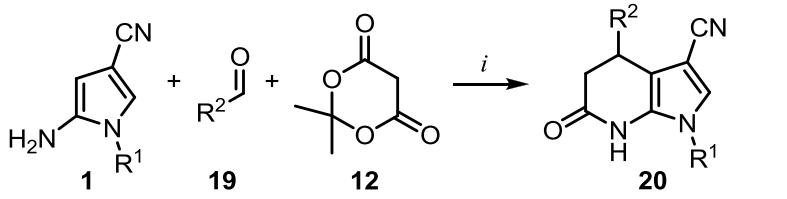
5.2 Results and discussion

It is known that unsubstituted 1*H*-pyrrol-2-amines are hard to access and unstable.[82] For the current study, and based in our previous work, the stable and easily accessible 1-substituted 5-aminopyrrole-3-carbonitriles **1a-c**,**h** were used.[83] The *N*-protective group and the electron-withdrawing cyano functional group maintain the stability of these heterocycles (Figure 10).

5.2.1 Reactions

5.2.1.1 Reactions using Meldrum´s acid

In multicomponent reactions, Meldrum´s acid (**12**) is a useful building block for the construction of a large variety of heterocyclic systems. Its use as a C_2-synthon is based on the addition of electrophiles to the C–H acidic function followed by intermolecular acylation with cleavage of the 1,3-benzodioxane ring and elimination of acetone and carbon dioxide molecules.[84] [85] At least two papers are of interest when Meldrum's acid and aromatic aldehydes are reacted with 5-amino-3-methylisoxazole [86] and 5-amino-3-methylpyrazole [87] to afford the corresponding fused 1,4-dihydropyridin-6-ones. It was thought that aminopyrroles **1** might undergo a similar cycloaddition with **12** and **19** to give 2,3-heteroannulated pyrroles **20** (Scheme 15).



***Scheme 15**: Multicomponent reaction of Meldrum´s acid (**12**), aldehydes (**19**) and 5-aminopyrrole (**1**); i: MeOH, reflux, 6-8 h.*

In fact, it was found that treatment of **12** with aromatic aldehydes (**19**) and pyrroles (**1**) in ethanol at reflux for 5 h resulted in the formation of 6-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitriles **20** in moderate to excellent yields (Table 7).

***Table 7**: Yields of the reactions of **1**, **12** and **19**.*

Entry	***1***	***R^1***	***19***	***R^2***	***Product***	***Yield %***
1	**a**	*t*-Bu	**a**	Ph	**20a**	82
2	**a**	*t*-Bu	**d**	4-OH-Ph	**20b**	71
3	**a**	*t*-Bu	**e**	2-MeO-Ph	**20c**	90
4	**a**	*t*-Bu	**g**	2,3-MeO-Ph	**20d**	87
5	**a**	*t*-Bu	**h**	3-MeO-4-OH-Ph	**20e**	65
6	**a**	*t*-Bu	**k**	3-F-Ph	**20f**	56
7	**a**	*t*-Bu	**l**	C_6F_5	**20g**	44
8	**a**	*t*-Bu	**m**	2-Cl-Ph	**20h**	40
9	**a**	*t*-Bu	**n**	4-Cl-Ph	**20i**	60
10	**a**	*t*-Bu	**o**	2-NO_2-Ph	**20j**	40
11	**a**	*t*-Bu	**p**	4-NO_2-Ph	**20k**	74
12	**a**	*t*-Bu	**q**	CH_3	**20l**	78
13	**b**	Cyclohexyl	**a**	Ph	**20m**	75
14	**b**	Cyclohexyl	**n**	4-Cl-Ph	**20n**	77
15	**c**	*p*-MeO-Bn	**d**	4-OH-Ph	**20o**	57

As shown in Table 7, the same protocol could be applied not only to aromatic aldehydes with either electron-donating (entries 2-5) or electron-withdrawing groups (entries 10 and 11), but also to an aliphatic aldehyde (entry 12). In most cases, the reaction was complete after 3-4 h and the products could be isolated by simple filtration of the precipitate formed, or by column chromatography over silica gel. Interestingly, although the chemistry of the pyrrole system has been well documented,[88] these simple compounds were hitherto unreported.

5.2.1.1.1 Structure identification

The structures of all the products were determined by ^{1}H and ^{13}C NMR spectroscopy as well as IR and HRMS analysis. It is worth noting that for all the compounds three doublets of doublets could be observed corresponding to the CH_2CH fragment in the partially hydrogenated pyridine ring. The appearance of the signals can be understood if the coupling between the methylene protons is considered, resulting in a second-order pair of doublets where the intensities of the inner pair of lines increases at the expense of the outer pair. These original four lines are split again into doublets due to coupling with the CH group, which also appears as a doublet of doublets. The result is an ABX spin system between 2.4 and 4.9 ppm with coupling constants of $^{2}J_{HH}$ = 15.7 Hz, $^{3}J_{HH}$ = 7.5 Hz and $^{3}J_{HH}$ = 5.1 Hz.

5.2.1.1.2 Crystallographic data

Structures **20a**, **20d** and **20g** were established independently by X-ray crystallographic analysis (Figure 12).

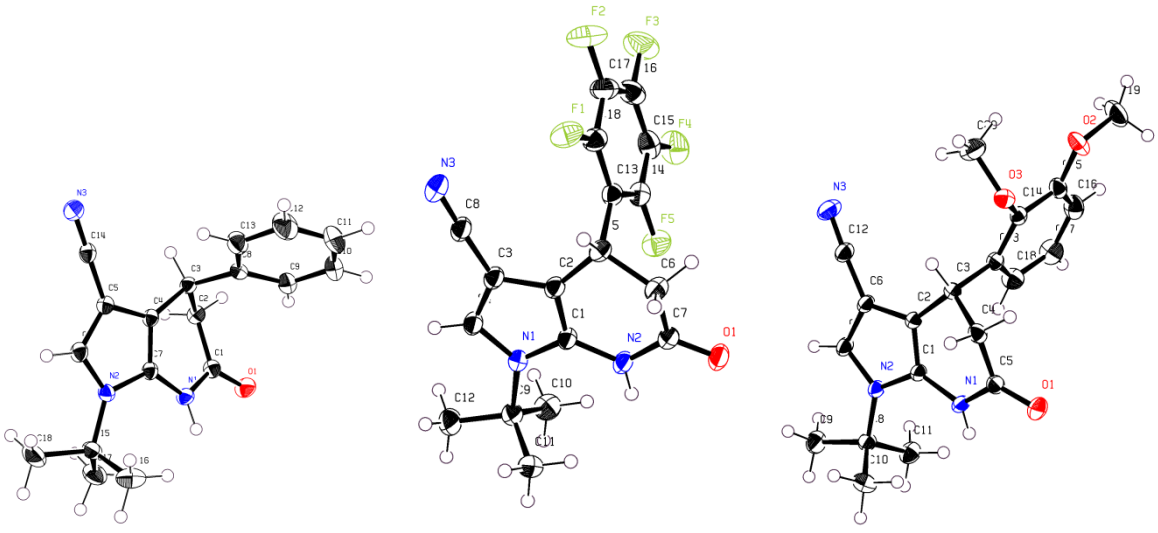


***Figure 11**: Crystallographic structures of compounds* **20a** (left), **20d** (right) and **20g** (centre), *oxygen atoms red, nitrogen atoms blue, fluorine atoms green.*

In all these structures, the aryl substituent occupies a position almost orthogonal to the

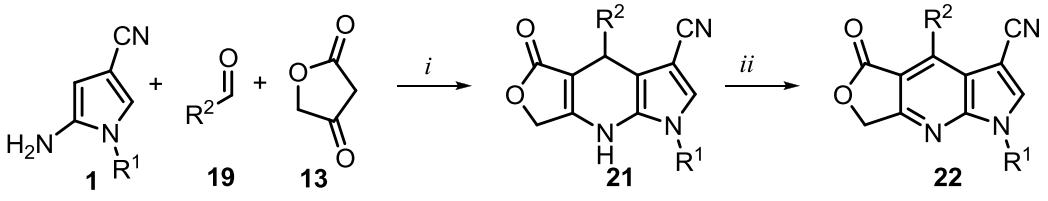
plane of the tetrahydropyridinone ring, which is not absolutely planar due the two sp^3-hybridized carbons. The aromatic ring is twisted, the distortion being more pronounced in **20d** and **20g** than in **20a** because of the two methoxy groups in **20d** which are oriented in opposite directions, or the fluorine atoms in **20g**. This fact can be clearly appreciated from the calculated torsion angles in Table 8.

***Table 8**: Angles and distances in compounds **20a**, **20d** and **20g**.*

Entry	*Compound*	*C_x----C_y*	*Torsion angle°*
1	**20a**	C4-C3-C8-C9	58.3
2	**20a**	C2-C3-C8-C9	2.94
3	**20d**	C4-C3-C13-C14	86.5
4	**20d**	C2-C3-C13-C18	30.4
5	**20g**	C6-C5-C13-C14	54.8
6	**20g**	C2-C5-C13-C14	69.0

5.2.1.2 Reactions using tetronic acid

The chemical versatility of tetronic acid (**13**) makes it a potentially valuable building block in multicomponent reactions because of its intrinsic nucleophilicity and eletrophilicity at C3 and C4, respectively.[89] The use of tetronic acid in MCRs has already been reported in reactions with aldehydes and amino heterocycles such as anilines,[90] naphtylamines,[91] amino-isoxazoles[86] and amino-pyrazoles,[92] but not with 5-aminopyrroles. In collaboration with Knepper,[45] an efficient synthesis of furo[3,4-*b*]pyrrolo[3,2-*e*]pyridines **22** was developed (Scheme 16).



***Scheme 16**: Multicomponent reaction of tetronic acid (**13**), aldehydes (**19**) and 5-aminopyrroles (**1**); i: MeOH, reflux, 6-8 h; DDQ, MeCN, rt, 4 h.*

The reaction proceeded with excellent regioselectivity and in moderate to high yields (35−80%). Performing the reaction in the presence of L-proline led to only slightly higher yields (43−82%). In most cases, the reaction was complete after 3−4 h and the products could be isolated by simple filtration of the precipitate formed or by column chromatography over silica gel (Table 9).

***Table 9**: Yields of the reactions of **1**, **13** and **19**.*

Entry	*1*	*R^1*	*19*	*R^2*	*Product*	*Yield %*	*Product*	*Yield %*
1	**a**	*t*-Bu	**a**	Ph	**21a**[a]	43	**22a**	80
2	**a**	*t*-Bu	**e**	2-MeO-Ph	**21b**[a]	63	**22b**	90
3	**a**	*t*-Bu	**l**	C_6F_5	**21c**[a]	80	**22c**	87
4	**a**	*t*-Bu	**n**	4-Cl-Ph	**21d**[a]	35	**22d**	65
6	**b**	Cyclohexyl	**d**	4-OH-Ph	**21e**	74	-	-
7	**c**	*p*-MeO-Bn	**h**	3-MeO-4-OH-Ph	**21f**	76	-	-

[a] Ref. 45

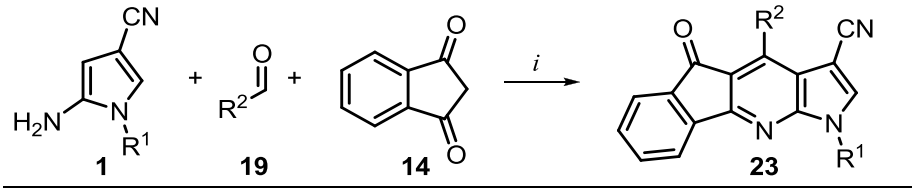
It should be noted that under these reaction conditions, the products are the fused 1,4-dihydropyridines **21a-f**. The oxidation of compounds **21a-d**, carried out by Knepper, with 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ, 1.2 equiv) in acetonitrile at room temperature for 4 h, afforded the corresponding 7-azaindoles **22a-d** in good to excellent yields (Scheme 16, Table 9). Taking into account that the *tert*-butyl and cyano groups could easily be removed from the pyrrolopyridine derivative,[93][35] this is also a method for preparing diverse 7-azaindoles with an unsubstituted pyrrole ring. This new multicomponent reaction provides the first example of a catalyst-free synthesis of compounds **21** and **22**, which can be regarded as heterocyclic analogues of 1-arylnaphthalene lignans and podophyllotoxin.[89]

5.2.1.2.1 Structure identification

The structures of all products were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as IR and HRMS analysis. The regiochemistry of **22c** was unambiguously confirmed by X-ray single crystal diffraction analysis. A complete description can be found in the Dissertation work of Dr. Ingo Knepper.[45]

5.2.1.3 Reactions using indane-1,3-dione

In order to expand the present methodology, another active methylene compound was used, indan-1,3-dione (**14**). This is particulary attractive because heterocycles fused with an indenone ring or indenoquinoline derivatives exhibit a diverse range of biological properties such as 5-HT-receptor binding activity and anti-inflammatory activity. They also act as antitumor agents, steroid reductase inhibitors, acetylcholinesterase inhibitors, antimalarials and new potential topoisomerase I/II inhibitors. The indenopyridine skeleton is present in the 4-azafluorenone group of alkaloids, represented by its simplest member, onychine.[94] Therefore, the synthesis of this type of compounds has attracted considerable attention.



***Scheme 17**: Multicomponent reaction of 1,3-indanedione **14, 5**-aminopyrroles **1**, and aldehydes **19**; i: EtOH, reflux, 6-8 h.*

The reaction of **14**, aromatic aldehydes (**19**) and pyrroles (**1**) under the same conditions (ethanol, reflux, 6 h) afforded only the aromatized products **23** in contrast to that observed with tetronic acid. Variable yields from 27 to 80% were obtained (Scheme 17, Table 10).

***Table 10**: Yields of the reactions of **1**, **14** and **19**.*

Entry	*1*	*R^2*	*19*	*R^2*	*Product*	*Yield %*
1	**a**	*t*-Bu	**a**	Ph	**23a** [a]	67
2	**a**	*t*-Bu	**19**	2-OH-Ph	**23b** [a]	61
3	**a**	*t*-Bu	**19**	3-OH-Ph	**23c** [a]	80
4	**a**	*t*-Bu	**19**	2-MeO-Ph	**23d** [a]	65
5	**a**	*t*-Bu	**19**	4-Cl-Ph	**23e** [a]	44
8	**a**	*t*-Bu	**19**	CH_3	**23f** [a]	27
10	**b**	Cyclohexyl	**19**	4-OH-Ph	**23g**	45
11	**c**	*p*-MeO-Bn	**19**	Ph	**23h**	76

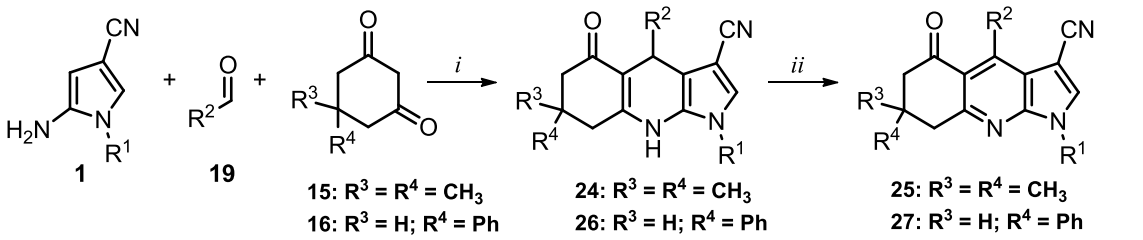
[a] Ref. 45

5.2.1.3.1 Structure identification

The structures of all these products (**23**) were characterized by IR, ^{1}H and ^{13}C NMR spectroscopy as well as HRMS analysis. A complete description can be found in the Dissertation work of Dr. Ingo Knepper.[45]

5.2.1.4 Reactions using 5-substituted-cyclohexane-1,3-dione

Considering the above results, the cycloaddition behavior of two 5-substituted-cyclohexane-1,3-diones, **15** and **16** was studied (Scheme 18). When dimedone (**15**) was used, the addition of L-proline (10 mol %) resulted in improved yields of compounds **24** (entry 3, Table 11). On the other hand, when dimedone was replaced by 5-phenylcyclohexane-1,3-dione (**16**), compounds **26** were obtained in good yields (45−81%) in refluxing ethanol for 6 h and without any catalyst (Scheme 18).



*Scheme 18: Multicomponent reaction of 5-substituted cyclohexane-1,3-diones **15**, **16,** 5-aminopyrroles **1**, and aldehydes **19**; i: EtOH, reflux, 6-8 h; ii: DDQ (1.1 eq.), MeCN, rt, 4 h.*

A variety of aromatic aldehydes with electron-donating or electron-withdrawing groups were employed as reaction substrates. In most cases, the presence of substituents on aromatic aldehydes appeared to have only a slight influence on the reactivity. Similarly to that observed when tetronic acid was used, only the 1,4-dihydropyridine products were obtained. Further treatment with DDQ in acetonitrile at room temperature provided the aromatized carbofused 7-azaindoles **25** and **27** in moderate to good yields (Scheme 18, Table 11).

***Table 11**: Yields of compounds **24-27**.*

Entry	***1***	***R^1***	***19***	***R^2***	***Product***	***Yield %***	***Product***	***Yield %***
1	**a**	*t*-Bu	**d**	4-OH-Ph	**24a**	69	**25a**	86
2	**a**	*t*-Bu	**f**	4-MeO-Ph	**24b**	58	**25b**	85
3	**a**	*t*-Bu	**g**	2,3-MeO-Ph	**24c**	97	**25c**	91
4	**a**	*t*-Bu	**h**	3-MeO-4-OH-Ph	**24d**	67	**25d**	40
5	**a**	*t*-Bu	**i**	3-CH_3-Ph	**24e**	64	**25e**	71
6	**a**	*t*-Bu	**n**	4-Cl-Ph	**24f**	45	**25f**	83
7	**a**	*t*-Bu	**p**	4-NO_2-Ph	**24g**	46	**25g**	83
8	**b**	Cyclohexyl	**j**	4-Me-Ph	**24h**	67	**25h**	--[a]
9	**h**	*m*-CF_3-Ph	**d**	4-OH-Ph	**24i**	63	**25i**	--[a]
10	**a**	*t*-Bu	**d**	4-OH-Ph	**26a**	81	**27a**	56
11	**a**	*t*-Bu	**g**	2,3-MeO-Ph	**26b**	50	**27b**	97
12	**a**	*t*-Bu	**h**	3-MeO-4-OH-Ph	**26c**	77	**27c**	43
13	**a**	*t*-Bu	**n**	4-Cl-Ph	**26d**	72	**27d**	82
14	**b**	Cyclohexyl	**p**	4-NO_2-Ph	**26e**	45	**27e**	--[a]

[a] not oxidized

5.2.1.4.1 Structure identification

The structures of all the products were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as IR and HRMS analysis. In the ^{1}H NMR spectra the differences between the reduced and oxidized products are clearly seen. The NH signal appears as a singlet around 8.5 ppm for the 1,4-dihydropyridine, but disappears after treatment with DDQ. For products **24a-i**, the signals of the methylene protons appear as four doublets, each one with an integral corresponding to 1H, constituting an AB system, likewise for the products **20**, also observable. However this is only valid for the 1,4-dihydropyridine system, because when the molecules were oxidized to compounds **25a-i**, the signals of the two CH_2 groups became two clear singlets integrating for 2H each. A similar phenomenon occurs with the methyl groups. In the oxidized form they appear as only one singlet which integrates for 6H whereas in the reduced form they appear as two singlets for 3H each. In products **26** and **27** a similar behaviour is observed.

5.2.1.4.2 Crystallographic data

The structures of compounds **25b** and **25d** were confirmed by X-ray diffraction analysis. The torsion angles for the fused 1,4-dihydropyridine frameworks confirmed that both tricyclic cores are planar and that the aryl substituent at C3 is twisted to avoid the steric and electronic repulsion of the nitrile group and the carbonyl oxygen. In the case of **25d** one molecule of solvent establishes two hydrogen bonds with the hydroxyl and nitrile groups (Table 12).

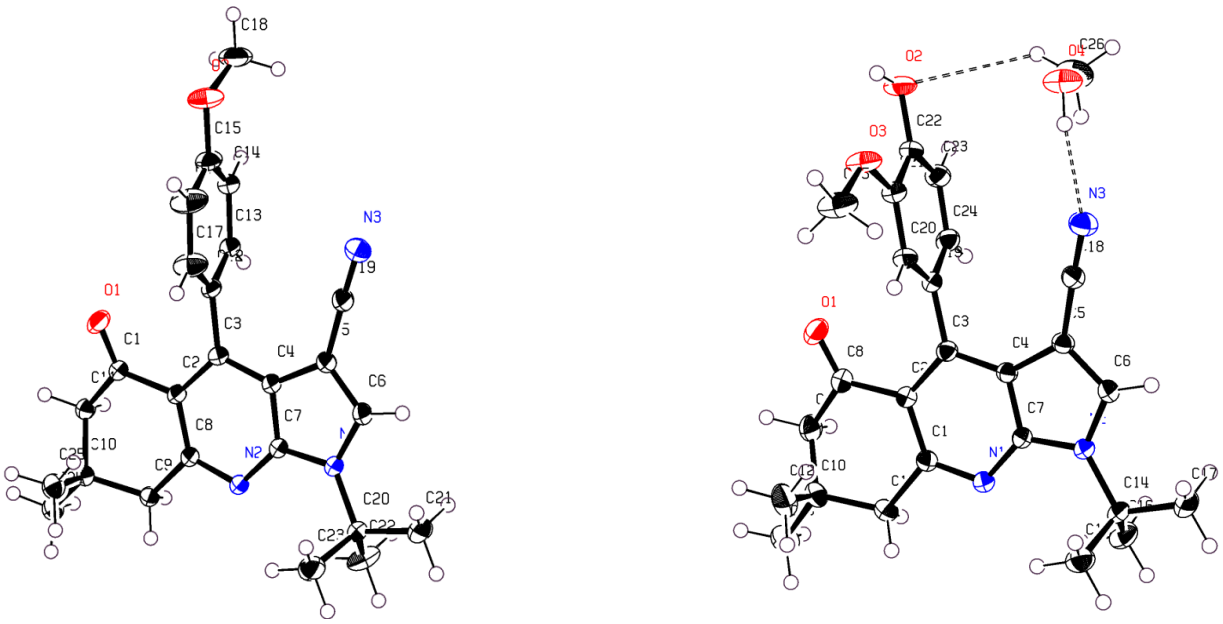


***Figure 12**: Crystallographic structures of compounds **25b** (left) and **25d** (right), oxygen atoms red, nitrogen atoms blue), hydrogen bond dashed line.*

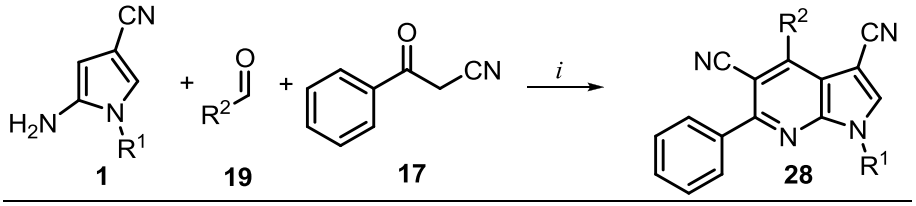
***Table 12**: Angles and distances for compounds **25b** and **25d**.*

Entry	*Comp.*	*C_x---C_y*	*Torsion angle°*	*Comp.*	*C_x---C_y*	*Torsion angle°*
1	**25b**	C3-C2-C8-N2	4.07	**25d**	C3-C2-C1-N1	0.24
2	**25b**	C2-C8-N2-C7	3.28	**25d**	C2-C1-N1-C7	0.51
3	**25b**	C8-N2-C7-C4	0.56	**25d**	C1-N1-C7-C4	0.37
4	**25b**	N2-C7-C4-C3	3.62	**25d**	N1-C7-C4-C3	0.04
5	**25b**	C7-C4-C3-C2	2.67	**25d**	C7-C4-C3-C2	0.32
6	**25b**	C4-C3-C2-C8	0.82	**25d**	C4-C3-C2-C1	0.20
7	**25b**	C2-C3-C12-C17	97.3	**25d**	C4-C3-C19-C24	88.1
8	**25b**	C4-C3-C12-C13	91.1	**25d**	C2-C3-C19-C20	93.1

Entry	*Compound*	*D-H----A*	*D-H/Å*	*H----A/Å*	*D----A/Å*	*D-H----A/°*
1	**25d**	C26-H26b----O2	0.98	2.98	3.62	125.00
2	**25d**	O4-H4----N3	0.89	2.10	2.94	157.49

5.2.1.5 Reactions using cyano derivatives

The utilization of derivatives of malononitrile in multicomponent reactions has been limited until now to the use of 5-aminopyrazoles.[95] For that reason further experiments were conducted to expand the utility of the reaction and substrate scope using two cyano derivatives, namely benzoylacetonitrile (**17**) and malononitrile (**18**). The reaction was carried out in boiling acetic acid in the presence of ammonium acetate as catalyst for 6 h (Scheme 19).



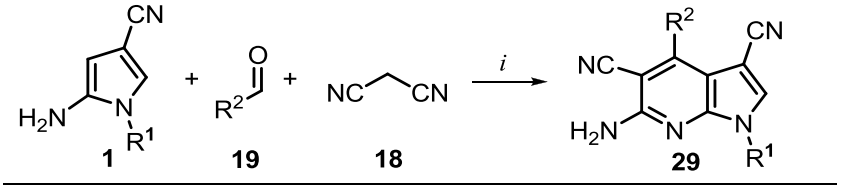
***Scheme 19**: Multicomponent reaction of benzoylacetonitrile (**17**), 5-aminopyrroles (**1**) and aldehydes (**19**); CH_3COOH, reflux, 4-6 h.*

As can be seen in Scheme 19, benzoylacetonitrile underwent pyridine ring annulation with aromatic aldehydes (**19**) and 5-aminopyrroles (**1**) leading to the formation of highly substituted 7-azaindoles (**28**) in moderate to good yields (Table 13, entries 7 and 4).

***Table 13**: Obtained yields for compounds **28a-h**.*

Entry	*1*	*R^1*	*19*	*R^2*	*Product*	*Yield %*
1	**a**	*t*-Bu	**a**	Ph	**28a**	48
2	**a**	*t*-Bu	**d**	4-OH-Ph	**28b**	56
3	**a**	*t*-Bu	**e**	2-MeO-Ph	**28c**	54
4	**a**	*t*-Bu	**g**	2,3-MeO-Ph	**28d**	66
5	**a**	*t*-Bu	**h**	3-MeO-4-OH-Ph	**28e**	60
6	**a**	*t*-Bu	**n**	4-Cl-Ph	**28f**	51
7	**b**	Cyclohexyl	**d**	4-OH-Ph	**28g**	37
8	**c**	*p*-MeO-Bn	**n**	4-Cl-Ph	**28h**	42

Malononitrile exhibits unique reactivity due to activation of the methylene group by the strong electron-withdrawing cyano groups. The cyano groups are suitable for nucleophilic addition and are also good leaving groups for substitution. The methylene group and either one or both of the cyano groups can take part in condensation reactions to give a variety of addition products and heterocyclic compounds. This exceptional behaviour is why malononitrile is used extensively as a reactant or reaction intermediate in a multitude of multicomponent reactions to prepare carbocyclic and heterocyclic compounds.[96]



***Scheme 20**: Multicomponent reaction of malononitrile (**18**), 5-aminopyrroles (**1**) and aldehydes (**19**); i: CH_3COOH, reflux, 4-6 h.*

Thus, the reaction of malononitrile (**18**) with aromatic aldehydes (**19**) and 5-aminopyrroles (**1**) under the same conditions gave the expected aromatized 7-azaindoles (**29**) in moderate yields 40−63% (Scheme 20, Table 14).

***Table 14**: Yields obtained for compounds **29a-h**.*

Entry	***1***	***R^1***	***19***	***R^2***	***Product***	***Yield %***
1	**a**	*t*-Bu	**a**	Ph	**29a**	60
2	**a**	*t*-Bu	**d**	4-OH-Ph	**29b**	50
3	**a**	*t*-Bu	**g**	2,3-MeO-Ph	**29c**	58
4	**a**	*t*-Bu	**h**	3-MeO-4-OH-Ph	**29d**	51
5	**a**	*t*-Bu	**i**	3-Me-Ph	**29e**	50
6	**a**	*t*-Bu	**n**	4-Cl-Ph	**29f**	45
7	**b**	Cyclohexyl	**d**	4-OH-Ph	**29g**	40
8	**c**	*p*-MeO-Bn	**n**	4-Cl-Ph	**29h**	63

Formation of the non-aromatized products was observed neither with malononitrile nor with benzoylacetonitrile. The synthesis of these highly susbtituted azaindoles is particulary interesting if it is considered that dicyanopyridines are important privileged heterocyclic

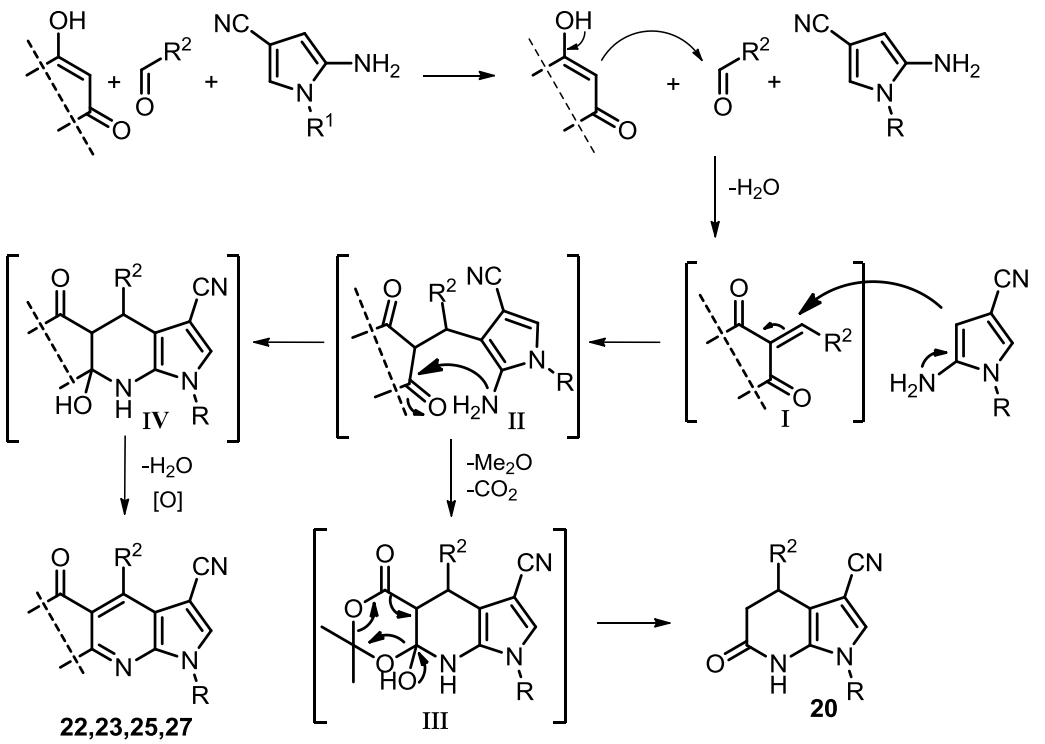
scaffolds.[97]

5.2.1.5.1 Structure identification

The structures of all products were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as IR and HRMS analysis.

5.3 Proposed mechanism

The reaction leading to compounds **24-27** (*5.2.1.4)* might be rationalized proposing the initial formation of conjugated electron-deficient intermediate **I** by Knoevenagel condensation of the aldehyde and a cyclic-1,3-dione. Michael addition of **I** with 5-aminopyrrole would afford intermediate **II**. This step is crucial for the regiochemistry of the reaction due to the ambident character of the heterocyclic amine. A nucleophilic attack of either the nitrogen or the internal enamine β-carbon to **II** is possible. However, the structures of the products obtained, based on the spectroscopic studies as well as the X-ray structures and in accordance with that described in previous chapters, the enamine β-carbon seems to be more nucleophilic than the primary amino group. When the 1,3-dicarbonyl compound is Meldrum's acid, intermediate **III** subsequently undergoes intramolecular cyclization and then releases acetone and carbon dioxide to yield compounds **20**. When the remaining 1,3-dicarbonyl compounds take part in the reactions, intermediate **IV** undergoes dehydration and dehydrogenation to generate the target products.



***Scheme 21**: Proposed mechanism for the synthesis of 7-azaindoles using MCRs.*

With the cyano derivatives the reaction follows a similar mechanism - Knoevenagel condensation and Michael addition as the first steps, followed by nucleophilic attack of the amino group on the carbonyl group, in the case of benzoylacetonitrile, or the cyano group, in the case of malononitrile, aromatization affording the corresponding products.

6. Three-component reaction of 5-amino-1-substituted-1H-pyrrole-3-carbonitrile with 1,2-dicarbonyl and active methylene compounds.

6.1 Introduction

The spiroxindole scaffold is present in many structurally complex natural products such as alstonisine, isolated from *Alstonia muelleriana*, coelurescine isolated from the blue canary grass *Phalaris coerulescens*, horsfiline, an alkaloid found in the plant *Horsfieldia superba*, and spyrotriprostatin A and B found in the fungus *Aspergillus fumigatus*, among others (Figure 14).[98] [99][100][101][102] They represent important naturally occurring substances with interesting conformational features among which the asymmetry of the molecule, due to the chiral spiro C3, and the densely functionalized core are important criteria for the biological activities.[103][104] It has been demonstrated that spyrotriprostatin can act as a new G2/M phase inhibitor of the mamallian cell cycle,[105] and analogues of coerulescine and horsfiline have been shown to possess significant activity against human breast cancer.[106]

On the other hand, the structural features of the 1,4-dihydropyridine ring are associated with calcium entry into cells. Several of them are clinically used in the treatment of cardiovascular disorders, such as hypertension, angina pectoris, and other spastic smooth muscle diseases. They are so-called calcium antagonists or calcium channel blockers and they exert their action through a high affinity binding site in L-type voltage-dependent Ca^{2+} channels.[107][108] [109]Amlodipine, Aranidipine, Nifedipine and Nitrendipine are some examples (Figure 14). Because of the importance of C4 chirality in the pharmacological activity of 1,4-dihydropyridines, new syntheses of these compounds are desirable.

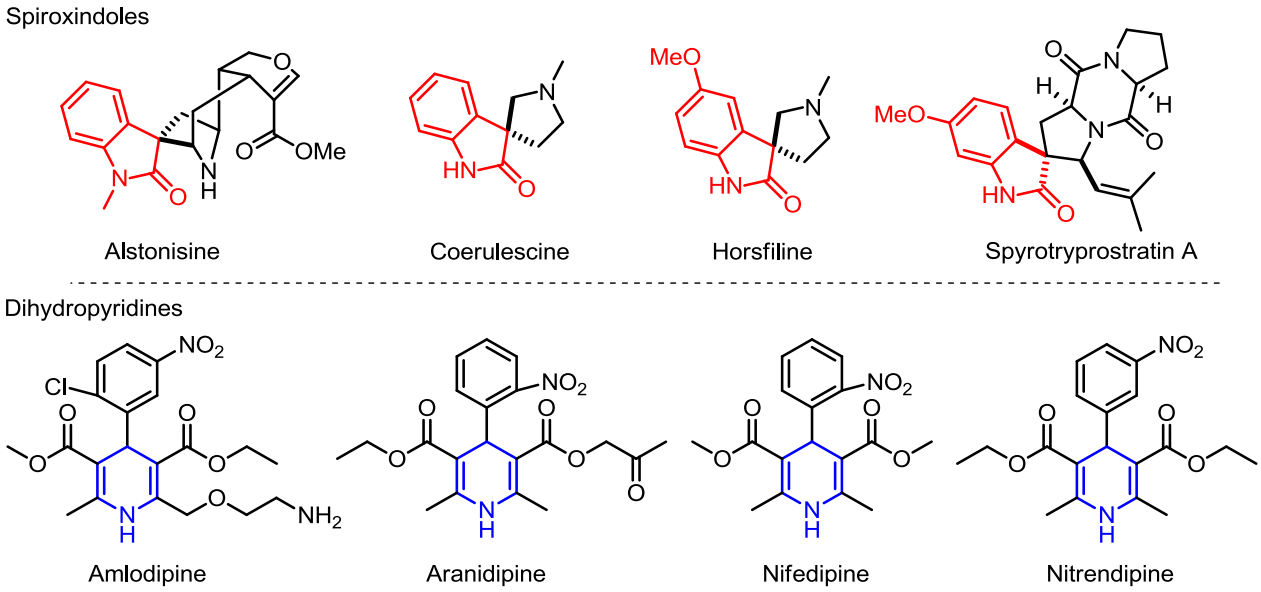


***Figure 13**: Spirooxindoles present in natural products and 1,4-dihydropyridines with pharmacological activities.*

It is known that fused heterocyclic systems that incorporate indole and other heterocycles simultaneously are promising candidates for biological responses. According to our previous work related to the broad utility of 7-azaindoles in medicinal chemistry,[81] and the use of multicomponent reactions to generate interesting heterocyclic compounds, it was decided to carry out a three-component reaction using different isatin derivatives, 5-aminopyrroles and 1,3-dicarbonyl compounds to afford spiro-fused oxindoles with a dihydro-1*H*-pyrrolo[2,3-*b*]pyridine moiety. It is noteworthy that the use of other 1,2-dicarbonyl compounds instead of isatin also led to interesting new heterocyclic systems.

6.2 Results and discussion

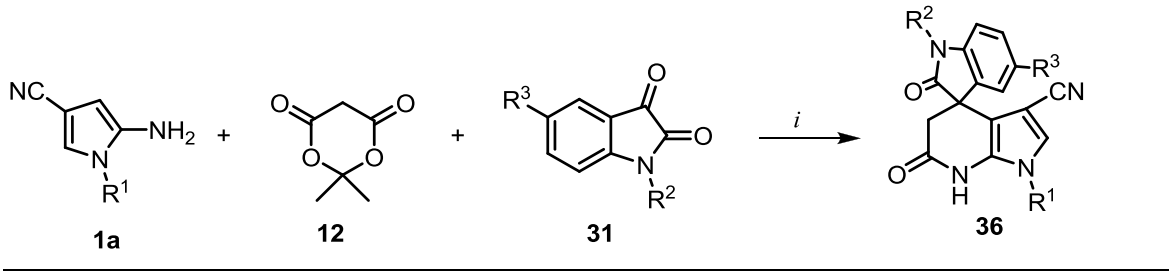
In chapter 5 it was demonstrated that 5-aminopyrroles can be used as valuable synthetic intermediates in multicomponent reactions for the synthesis of 7-azaindoles, *via* oxidation of fused 1,4-dihydropyridines.[81] Previous reports have also shown that interesting spirocyclic compounds can be generated by using 5-amino-3-methyl-pyrazole.[110] However, spiroxindoles

fused with 1,4-dihydropyridine frameworks have not yet been reported. Thus, from a logical point of view, spiroindoline pyrrolo derivatives might be synthesized in a one pot reaction of *N*-substituted-5-amino-3-cyanopyrroles (**1a-c**), commercially isatins (**31a-h**), and an appropriate 1,3-dicarbonyl compound such as Meldrum´s acid (**12**), tetronic acid (**13**), 1,3-dimedone (**14**), and 4-hydroxycoumarin (**30**). To further explore the potential of this protocol, the reaction involving other 1,2-dicarbonyl compounds, *i.e.* acenaphtylene-1,2-dione (**32**), methyl-2-oxophenyl acetate (**33**), ethyl-2-oxopropanoate (**34**), and 3,4-hexadione (**35**) was also investigated.

6.2.1 Reactions

6.2.1.1 Reactions using Meldrum´s acid

In the initial studies, various conditions were evaluated to choice an appropriate reaction medium for the synthesis of spiroxindole derivatives. Initially the reaction of isatin, 5-amino-1-*tert*-butyl-pyrrole-3-carbonitrile and Meldrum´s acid in different solvents, including ethanol, dimethyl formamide, acetic acid, acetic acid/proline, acetic acid/ammonium acetate, and 1,4-dioxane was tested. All the reactions were carried out first at room temperature and increasing temperature until reflux, following the progress of the reaction by thin layer chromatography. Performing the reaction in 1,4-dioxane gave the lowest yield (30%), followed by dimethylformamide and ethanol, 42% and 60%, respectively. Based on our previous work for the synthesis of highly substituted 7-azaindoles, we thought that the use of ethanol/L-proline would again be the best medium for our reaction. However the yield remained unchanged. Surprisingly, when the reaction was carried out in acetic acid the yield rose to 70%. After that we decided to test the acetic acid/L-proline and acetic acid/ammonium acetate systems. The best yield was achieved in acetic acid (entry 1, Table 15), which became the solvent/base of choice to afford the required spiroxindole derivatives **36** (Scheme 22).



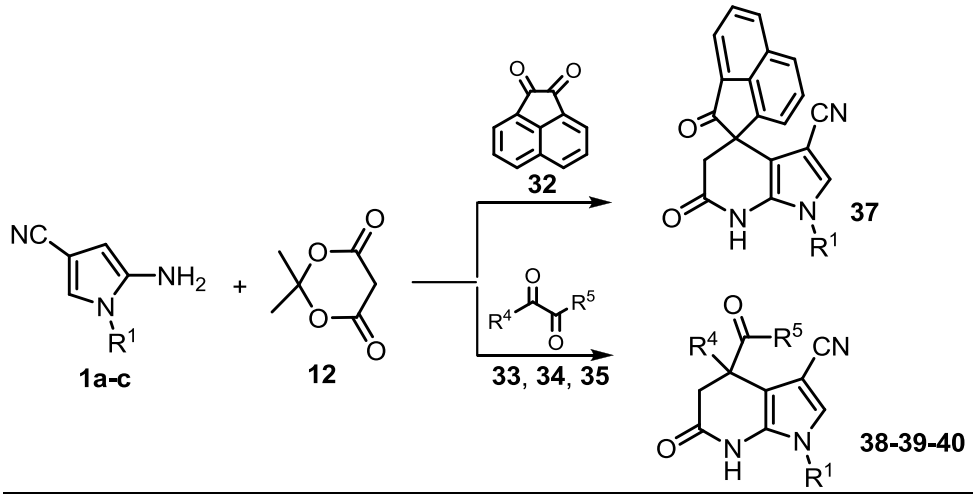
***Scheme 22**: Multicomponent reaction of Meldrum´s acid **(12)**, 5-aminopyrroles **(1)** and isatins **(31)**; i: CH_3COOH, reflux, 6-8 h.*

The procedure was simple and easy to operate. Generally the reaction was complete after 6-8 h and the product formed as a precipitate in almost the cases and was separated by simple filtration. As can be seen in Table 16, the method proved to work with a wide variety of substrates, isatins containing electron withdrawing or electron donating groups such as bromine, chlorine, nitro or trifluoromethoxy. *N*-substituted isatins were also suitable substrates for the reaction (entries 2, 8, and 10, Table 16). In all these cases good yields in the range from 51 to 86 % were obtained. The exceptional feature of Meldrum´s acid (**12**) to regenerate acetone which can be easily removed as a side product,[111] afforded the 1,4-dihydropyridin-6-one ring present in the skeleton of products **36**. Similar results have been reported with 5-aminopyrazoles.[112] Nevertheless, the use of 2-aminopyrroles (**1**) had not been documented in the literature.

***Table 15**: Yields of products **36a-j**.*

Entry	***1***	***R^1***	***31***	***R^2***	***R^3***	***Product***	***Yield %***
1	**a**	*t*-Bu	**a**	H	H	**36a**	81
2	**a**	*t*-Bu	**b**	Me	H	**36b**	73
3	**a**	*t*-Bu	**c**	H	Cl	**36c**	86
4	**a**	*t*-Bu	**d**	H	OCF_3	**36d**	52
5	**a**	*t*-Bu	**e**	H	Br	**36e**	51
6	**a**	*t*-Bu	**f**	H	F	**36f**	75
7	**a**	*t*-Bu	**g**	H	NO_2	**36g**	70
8	**a**	*t*-Bu	**h**	Ph	H	**36h**	55
9	**b**	Cyclohexyl	**g**	H	NO_2	**36i**	37
10	**c**	*p*-MeO-Bn	**b**	Me	H	**36j**	58

To explore the scope of this reaction, the use of acenaphtylene-1,2-dione **32** and aliphatic 1,2-dicarbonyl compounds **33, 34** and **35** was investigated (Table 16, Scheme 23). With compound **32**, it was found that reaction proceeded in moderate to good yields using ethanol as a solvent, whereas with methyl 2-oxo-phenyl-acetate (**33**), acetic acid was the best solvent. When compounds **34** and **35** were used, the solvent of choice was 1,4-dioxane.



***Scheme 23**: Multicomponent reactions of Meldrum´s acid (**12**), 5-aminopyrroles (**1**), and 1,2-dicarbonyl compounds **32-35**.*

***Table 16**: Yields of products **37-40**.*

Entry	*1*	*1,2-dicarbonyl*	R^4	R^5	*Product*	*Yield %*
1	**a**	**32**	--	--	**37a**	71
2	**b**	**32**	--	--	**37b**	55
3	**a**	**33**	Ph	MeO	**38a**	38/70[a]
4	**b**	**33**	Ph	MeO	**38b**	42/77[a]
5	**c**	**33**	Ph	MeO	**38c**	40/65[a]
6	**a**	**34**	Me	EtO	**39a**	73
7	**b**	**34**	Me	EtO	**39b**	57
8	**c**	**34**	Me	EtO	**39c**	68
9	**a**	**35**	Et	Et	**40a**	40

[a]Yields obtained in two steps.

Using **32**, *N*-substituted-2,6'-dioxo-1',5',6',7'-tetrahydro-2*H*-spiro[acenaphthylene-1,4'-pyrrolo[2,3-*b*]pyridine]-3'-carbonitrile was obtained in good yields (entries 1 and 2). However, when **32** was replaced by aliphatic compounds, **33-35**, a decrease in the yields was observed except with ethyl pyruvate (**34**), 3,4-hexanedione being the least reactive. With methyl 2-oxophenyl acetate (**33**), it was found that acetic acid was the best solvent (entry 4, 42% yield) in comparison with ethanol, DMF and 1,4-dioxane. Nevertheless, when the reaction was carried out in 2 steps, first condensing Meldrum´s acid with methyl 2-oxophenyl acetate in the presence of $TiCl_4$, according to a literature procedure,[113] and then cyclizing with **3** in ethanol, the yield rose to 77% (Table 16, entries 3-5[a]).

6.2.1.1.1 Structure identification

The structures of all the products were characterized by ^1H and ^{13}C NMR spectroscopy as well as IR and HRMS analysis. All the compounds synthesized using Meldrum´s acid showed, as in chapter 5, two pairs of doublets as the typical AB spin system with coupling constants $^2J_{HH}$ = 15.5 and 15.9 Hz and chemical shifts between 2.62 ppm and 3.16 ppm.

6.2.1.1.2 Crystallographic data

The structures of compounds **37b** and **39c** were independently confirmed by X-ray diffraction analysis (Scheme 24).

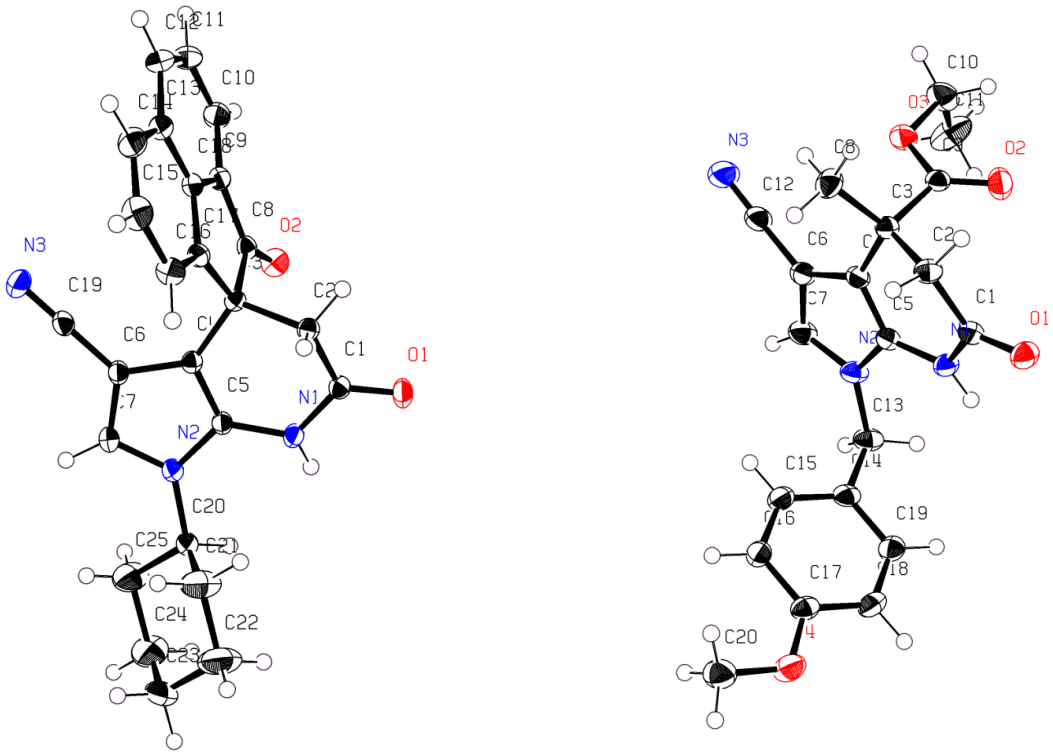
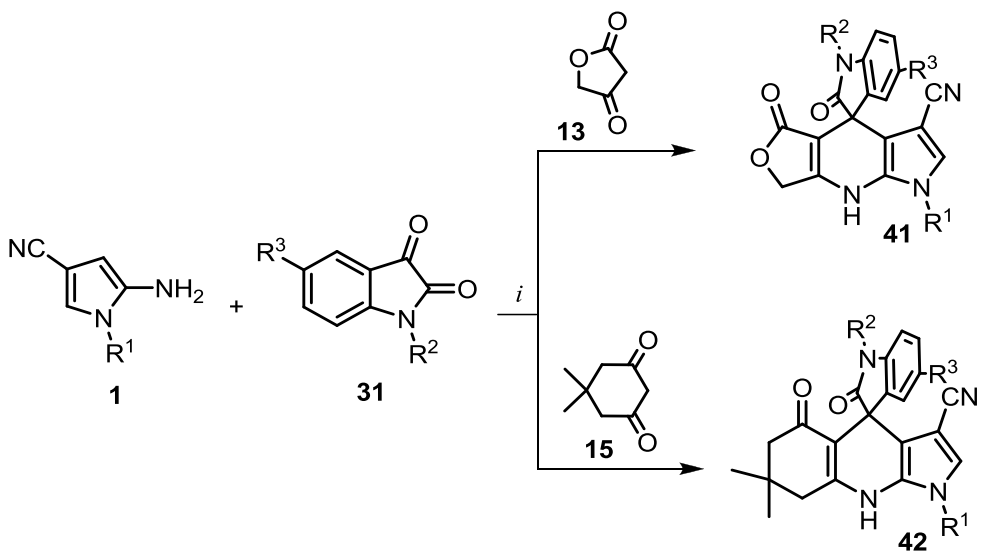


***Figure 14**: Crystallographic structures of compounds **37b** (left) and **39c** (right), oxygen atoms red, nitrogen atoms blue.*

In **37b** and **39c** the 1,4-dihydropyridin-6-one ring is almost planar. In **37b** the aromatic moiety at C3 is found twisted. Other geometric conformation is not possible due the nitrile group at -6 position.

6.2.1.2 Reactions using tetronic acid and dimedone

Under the same conditions used with Meldrum´s acid, the reaction of tetronic acid (**13**) and dimedone (**15**), with substituted isatins, led to fused 1,4-dihydropyridine frameworks **41** and **42**, respectively (Scheme 24). As with Meldrum´s acid, the method worked with a wide variety of substituted isatins. In all these cases moderate yields in the range from 41 to 79 % were obtained (Table 17), except when **1b** was used, giving only 30 % (Table 17, entry 7).



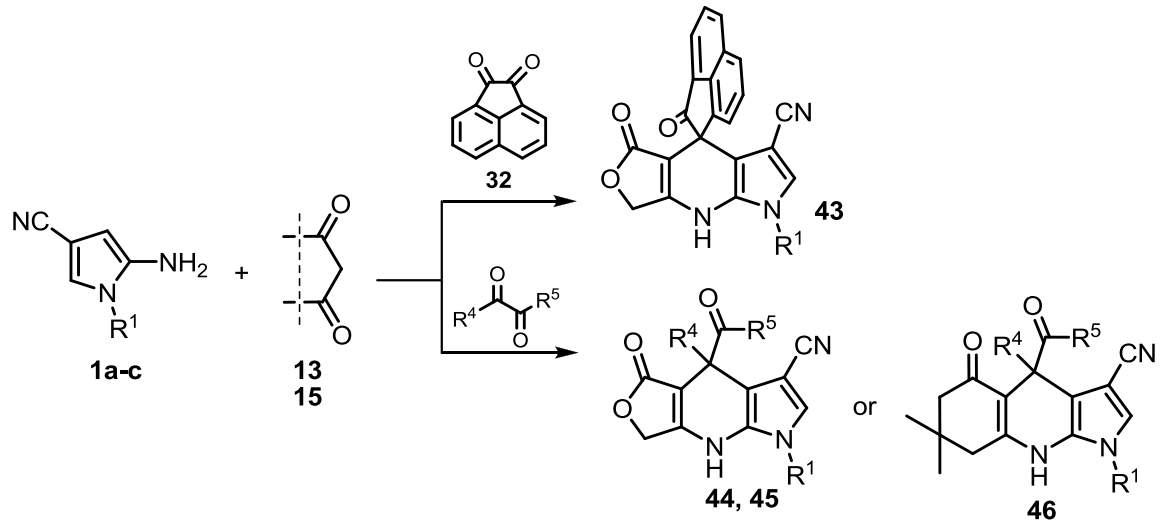
***Scheme 24**: Multicomponent reactions of tetronic acid (**13**) or dimedone (**15**), 5-aminopyrroles (**1**) and isatins (**31**); i: CH_3COOH, reflux, 6-8 h.*

***Table 17**: Yields of products **41a-g** and **42a-f**.*

Entry	*1*	R^1	*31*	R^2	R^3	*Product*	*Yield %*
1	**a**	*t*-Bu	**a**	H	H	**41a**	57
2	**a**	*t*-Bu	**b**	Me	H	**41b**	63
3	**a**	*t*-Bu	**d**	H	OCF_3	**41c**	37
4	**a**	*t*-Bu	**e**	H	Br	**41d**	64
5	**a**	*t*-Bu	**f**	H	F	**41e**	61
6	**a**	*t*-Bu	**h**	Ph	H	**41f**	37
7	**b**	Cyclohexyl	**b**	Me	H	**41g**	30
8	**a**	*t*-Bu	**a**	H	H	**42a**	79
9	**a**	*t*-Bu	**b**	Me	H	**42b**	57
10	**a**	*t*-Bu	**c**	H	Cl	**42c**	65
11	**a**	*t*-Bu	**d**	H	OCF_3	**42d**	64
12	**a**	*t*-Bu	**g**	H	NO_2	**42e**	66
13	**b**	Cyclohexyl	**a**	H	H	**42f**	41

The use of acenaphtylene-1,2-dione **32** afforded spirocompounds **43** (Scheme 25).

However, the reaction failed with dimedone. In the same way methyl-2-oxo-phenyl-acetate **33** only reacted with tetronic acid (**33**) (Table 18, entry 4), and with 3,4-hexanedione (**35**) a complex mixture was obtained. The reaction occurred with ethyl pyruvate affording compounds **45** and **46** in moderate yields (Scheme 25, Table 18, entries 5-9).



***Scheme 25**: Multicomponent reactions of tetronic acid (**13**) or dimedone **(15)**, 5-aminopyrroles (**1**) and dicarbonyl compounds **32**, **33** and **34**.*

***Table 18**: Yields of products **43a-c**, **44a**, **45a-c** and **46a-b**.*

Entry	*1*	*R^1*	*1,2-dicarbonyl*	*R^4*	*R^5*	*Product*	*Yield %*
1	**a**	*t*-Bu	**32**	--	--	**43a**	82
2	**b**	Cyclohexyl	**32**	--	--	**43b**	73
3	**c**	*p*-MeO-Bn	**32**	--	--	**43c**	38
4	**a**	*t*-Bu	**33**	Ph	MeO	**44a**	42
5	**a**	*t*-Bu	**34**	Me	EtO	**45a**	67
6	**b**	Cyclohexyl	**34**	Me	EtO	**45b**	40
7	**c**	*p*-MeO-Bn	**34**	Me	EtO	**45c**	64
8	**a**	*t*-Bu	**34**	Me	EtO	**46a**	55
9	**b**	Cyclohexyl	**34**	Me	EtO	**46b**	58

6.2.1.2.1 Structure identification

The structures of all the products were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as IR and HRMS analysis. Unexpectedly, when tetronic acid was used, the signal for the methylene group of the furanone ring appeared as a singlet at 5.00 ppm for all the spiroderivatives, whereas with ethyl pyruvate a slightly resolved AB system could be observed. With dimedone, four pairs of doublets appeared corresponding to the two AB systems of the cylohexanone ring, one between 2.64 – 2.51 ppm with coupling constants of $^{2}J_{HH}$ = 17.19 and 16.62 Hz, and the other between 2.17 – 1.95 ppm with coupling constants of $^{2}J_{HH}$ = 16.05 and 15.86 Hz.

6.2.1.2.2 Crystallographic data

The structure of compound **43b** was independently confirmed by X-ray diffraction analysis (Figure 15).

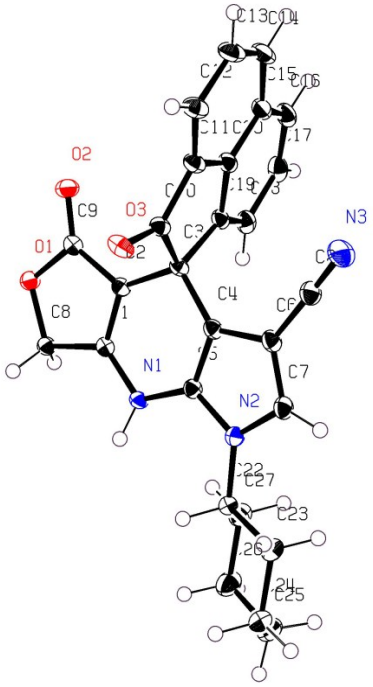
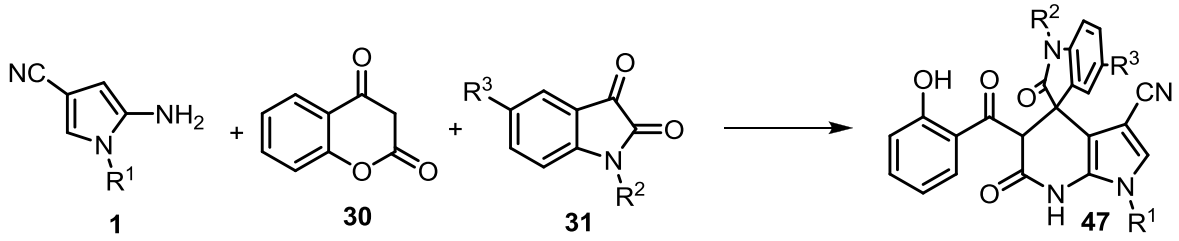


***Figure 15**: Crystallographic structure of compound **43b**, oxygen atoms red, nitrogen atoms blue.*

The 1,4-dihydropyridine framework as well as the acenaphthylene ring are planar and approximately orthogonal.

6.2.1.3 Reactions using 4-hydroxycoumarin

The introduction of 4-hydroxycoumarin (**30**) as an active β-dicarbonyl compound afforded the expected spiroxindoles (**47**) in moderate yields (Table 19, Scheme 26). Previous reports have shown that when 4-hydroxycoumarin is been used, cleavage of the pyrone ring may or may not occur.[114] In this study, the reaction occurs *via* rupture of the C-O bond and subsequent ring opening.

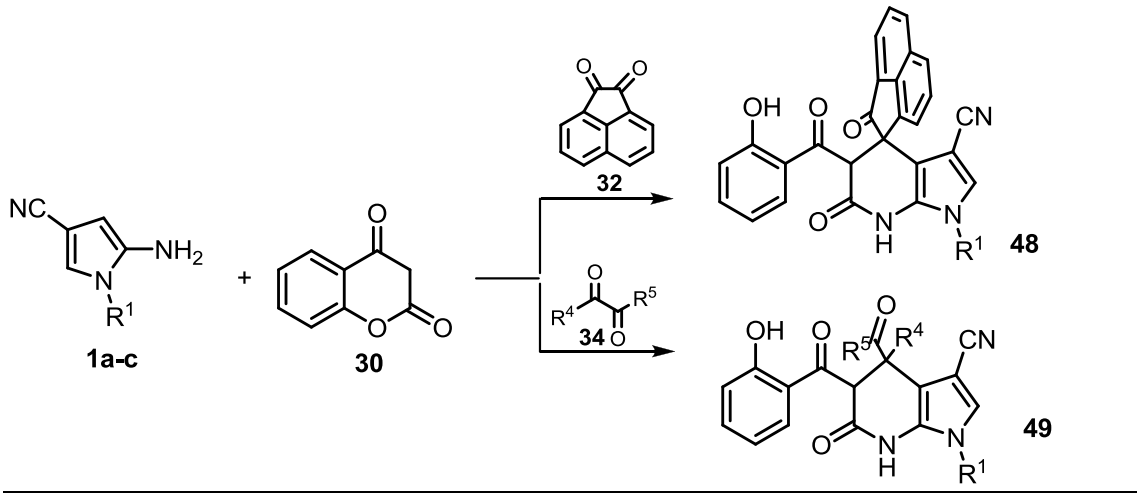


***Scheme 26**: Multicomponent reaction of 4-hydroxycoumarin (**30**), 5-aminopyrroles (**1**) and isatins (**31**).*

***Table 19**: Yields of products **47a-c**.*

Entry	*1*	*R^1*	*31*	*R^2*	*R^3*	*Product*	*Yield %*
1	**a**	*t*-Bu	**d**	H	OCF_3	**47a**	69
2	**a**	*t*-Bu	**g**	H	NO_2	**47b**	38
3	**b**	Cyclohexyl	**a**	H	H	**47c**	59

With acenaphtylene-1,2-dione (**32**), the same pyrone ring opening ocurrs affording spiro-compounds (**48**). Again, using ethyl pyruvate (**34**) products **49** could be isolated, whereas with the other dicarbonyl compounds a complex mixture was obtained (Scheme 27, Table 20).



***Scheme 27**: Multicomponent reaction of 4-hydroxycoumarin (**30**), 5-aminopyrroles (**1**) and 1,2-dicarbonyl compounds **32** and **34**.*

***Table 20**: Yields of the products **48a-c** and **49a-c**.*

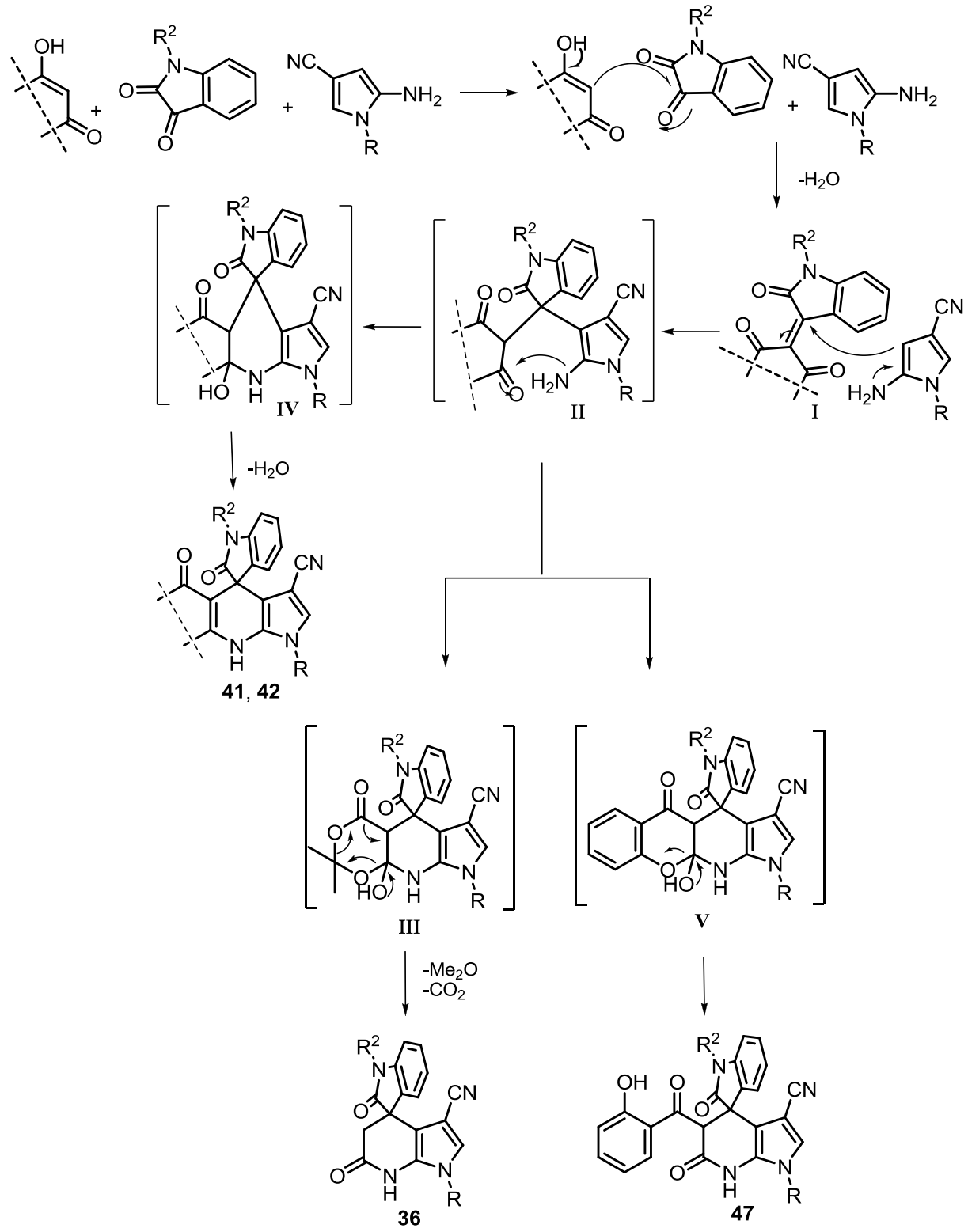
Entry	*1*	*1,2-dicarbonyl*	*R^4*	*R^5*	*Product*	*Yield %*
1	**a**	**32**	--	--	**48a**	65
2	**b**	**32**	--	--	**48b**	56
3	**c**	**32**	--	--	**48c**	35
4	**a**	**34**	Me	EtO	**49a**	67
5	**b**	**34**	Me	EtO	**49b**	64
6	**c**	**34**	Me	EtO	**49c**	47

6.2.1.3.1 Spectroscopy

The structures of all the compounds were deduced from their satisfactory elemental and spectral (IR, ^{1}H and ^{13}C NMR, and MS) studies.

6.3 Proposed mechanism

A plausible mechanism for the formation of the spiro-heterocycles involve a Knoevenagel condensation of the active methylene compounds with the isatin derivatives to form intermediates **I**. It has been proposed for similar reactions using 5-aminopyrazoles that the first step might be the condensation of the enamine and the isatin derivative based on the fact that this intermediate was isolated.[21] However, no product of this type was detected in this work, and a mechanism similar to the one described in the previous chapter is proposed here. The subsequent Michael addition of the β–carbon of the enamine led to intermediates **II**. When the 1,3-dicarbonyl compound is Meldrum's acid (**12**), intermediate **III** undergoes intramolecular cyclization and releases acetone and carbon dioxide giving compounds **36**. When the 1,3-dicarbonyl compound is tetronic acid (**13**) or dimedone (**15**), intermediate **IV** undergoes dehydration to generate the target products **41** and **42**. With 4-hydroxycoumarin (**30**) intermediate **V** undergoes intramolecular cyclization and opening of the pyrone ring to afford products **47**.



***Scheme 28**: Proposed mechanism for the formation of spiro-compounds **36**, **41, 42** and **47**.*

With the rest of the dicarbonyl compounds a similar mechanism should be expected. Other dicarbonyl compounds that were also tested are thioisatin, nihydrin and 2,2,2-trifluoro-1-phenylethanone. In case of thioisatin, even though it can be considered as an analogue of isatin, the reactivity of the carbonyl groups is completely different. The C3 carbonyl group of isatin is the reactive entity of the molecule, because the C2 carbonyl is part of an amide functionality. In contrast, the carbonyl groups in thioisatin are equally susceptible to nucleophilic attacks, leading to a complex mixture that couldnot be separated, even when the reaction was carried out at -10 °C. We wanted to probe the scope of the reaction by using a tricarbonyl compound. For that reason we took nihydrin instead of isatin, but the reaction was unsuccessful. Then we tried the reaction in two steps, first the condensation with tetronic acid [115] and then the cyclization with the 5-aminopyrrole. Unfortunately, the latter step failed probably because the four carbonyl groups formed in the condensation step, sterically hinder the attack of the amino group of the 5-aminopyrrole. Because trifluromethyl groups in the βposition make ketones strongly electron deficient, we thought that such compounds would be appropriate substrates for our reactions,. However the reaction did not work either with 2,2,2-trifluoro-1-phenylethanone or with 1,1,1-trifluoropropan-2-one. Future investigations should be carried out in order to explain this behaviour. Reactions with simple ketones such as 1*H*-inden-2(3*H*)-one, cyclopropyl(phenyl)methanone as well as hydroxyketones such as 2-hydroxy-1,2-diphenylethanone also failed, even when we tested a variety of conditions.

7. 7-Azaindole as a useful substrate for coupling reactions

7.1 Introduction

Some of the most important current synthetic reactions are those involving carbon-carbon bond formation. Among them palladium catalyzed cross coupling reactions are the most prominent. They have impacted multiple areas from the fields of organic synthesis and medicinal chemistry to materials science and polymer chemistry. Key reactions of this type are the Heck reaction, the Suzuki reaction and the Sonogashira reaction. All of them utilize an organohalide compound but they differ in the coupling partner. The Heck reaction uses an alkene, whereas in the Suzuki and Sonogashira reaction this is an organoboron compound and a terminal alkyne, respectively.

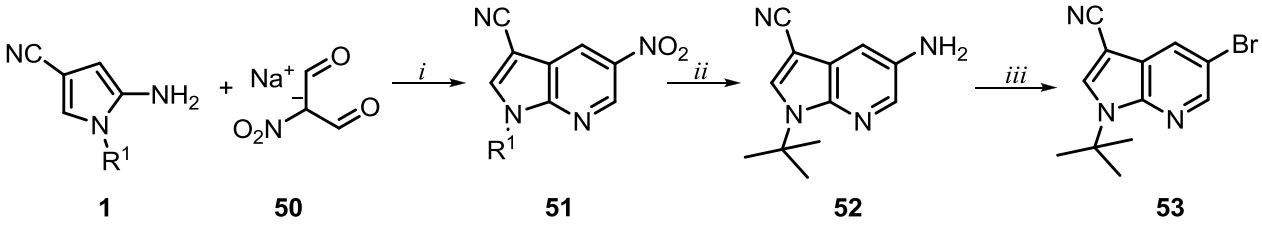
7-Azaindole derivatives bearing an electron-withdrawing group are very attractive because of their potential as ADA inhibitors. In Chapter 3 an interesting synthetic strategy to access to 7-azaindole frameworks containing a nitro group at C5 position was described. At the same time, through appropriate synthetic transformations, the nitro group can be converted into a halogen group, which is ideal to carry out cross coupling reactions, and in that way access a new type of functionalized 7-azaindole moieties.

7.2 Results and discussion

7.2.1 Reactions

Sodium nitro-malonaldehyde (**50**) is a useful reagent for the synthesis of heterocyclic compounds which would be difficult to prepare by any alternative procedure. Synthesis of azaindoles using such an approach has already been reported, but no further reactions have been carried out. Thus, the reaction of nitro-malonaldehyde (**50**) with 5-aminopyrroles (**1**) using DMF/TMSCl as the reaction medium afforded nitro derivatives **51a-c**. Subsequent reduction of **51a** to the corresponding

amine (**52a)** was done under a hydrogen atmosphere in the presence of Pd/C 10% (Scheme 29, Table 21).



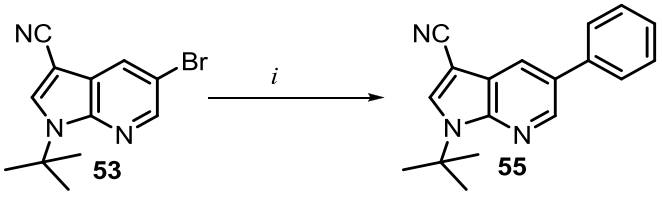
***Scheme 29**: Synthesis of compounds **52**; i: DMF/TMSCl (4:1); ii: H_2-Pd/C; iii: CuBr/DCM.*

***Table 21**: Yields of compounds **51**, **52** and **53**.*

Entry	***1***	***R^1***	***51***	***Yield %***	***52***	***Yield %***	***53***	***Yield %***
1	**a**	*t*-Bu	**a**	63	**52a**	95	**53a**	80
2	**b**	Cyclohexyl	**b**	56	---	---	---	---
3	**c**	*p*-MeO-Bn	**c**	84	---	---	---	---

Compound **52a** was subjected to a brominative deamination in order to obtain a suitable molecule for cross-coupling reactions. Using copper bromide and *tert*-butyl nitrite in acetonitrile compound **53a** was obtained in 80% yield (Table 21, entry 1). With this molecule in hand, a set of aryl boronic acids, aryl styrenes and substituted terminal alkynes were selected.

The Suzuki-Miyaura reaction was used to introduce an Ar-substituent in the γ-position of the heteroannulated pyridine **53a** (Scheme 30). The compound reacted with the set of diverse boronic acids **54a-e** in 1,4-dioxane giving rise to compounds **55** in yields of 60-70% (Table 22).

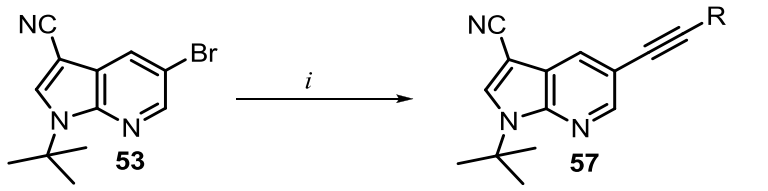


***Scheme 30**: Suzuki-Miyaura reaction; i: Ar-B(OH)$_2$ (1.2 eq.); K_2CO_3 (4 eq.); $PdCl_2(PPh_3)_2$ (4 mol%);1,4-dioxane; 90° C; 4-6 h.*

***Table 22**: Yields of products **55a-e** of the Suzuki-Miyaura reaction.*

Entry	*Ar-B(OH)$_2$*	*Product*	*Yield %*
1	Ar = C_6H_5	**55a**	60
2	Ar = 4-Et-C_6H_5	**55b**	70
3	Ar = 4-MeO-C_6H_5	**55c**	70
4	Ar = 4-Cl-C_6H_5	**55d**	68
5	Ar = 4-CF_3-C_6H_5	**55e**	67

Concerning the Sonogashira coupling, the reaction with commercially available acetylenes **56a-e** took place under standard reaction conditions to deliver the set of derivatives **57a-e** in yields of 60 to 75% (Table 23, Scheme 31).

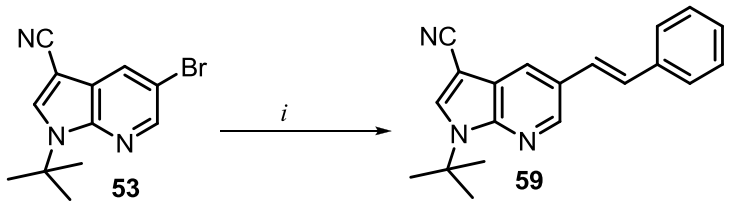


***Scheme 31**: Sonogashira reaction; i: acetylenes **56a-e** (1 eq.); CuI (10 mol%); N(Et)$_3$ (1 eq.); PdCl$_2$(PPh$_3$)$_2$ (2 mol%); DMF; 120° C; 4-6 h.*

***Table 23**: Yields of products of the Sonogashira reaction.*

Entry	≡—R	*Product*	*Yield %*
1	R = C_6H_5	**57a**	70
2	R = 4-Me-C_6H_5	**57b**	65
3	R = 4-MeO-C_6H_5	**57c**	65
4	R = 4-^{t}But-C_6H_5	**57d**	75
5	R = butyl	**57e**	60

The Heck coupling using alkenes **58a-c** was used for the synthesis of the alkenyl-substituted derivatives **59a-c** (Scheme 32). Yields in the 69-72% range were obtained (Table 24).



***Scheme 32**: Heck reaction; i: styrenes **58a-c** (1 eq.); $N(Et)_3$ (4 eq.); $PdCl_2(PPh_3)_2$ (2 mol%); DMF; 140° C; 8 h.*

***Table 24**: Yields of products of the Heck reaction.*

Entry	**Ar**	***Product***	***Yield %***
1	Ar = C_6H_5	**59a**	72
2	Ar = 4-Me-C_6H_5	**59b**	68
3	Ar = 4-^{t}BuO-C_6H_5	**59c**	69

7.2.2 Structure identification

The structures of the products were determined by ^1H and ^{13}C NMR spectroscopy as well as IR and HRMS analysis.

7.2.2.1 Crystallographic data

The structures of compounds **53**, **55d**, **55e**, **57a** and **59a** were confirmed through X-ray diffraction analysis. The framework of the 1,4-dihydropyridine ring (C(1-7)-N(1-2)) of **53** is planar. This is valid for all the rest of the molecules containing this moiety. The *d*(C(1)---Br) distance is 1.894 Å (Figure 16).

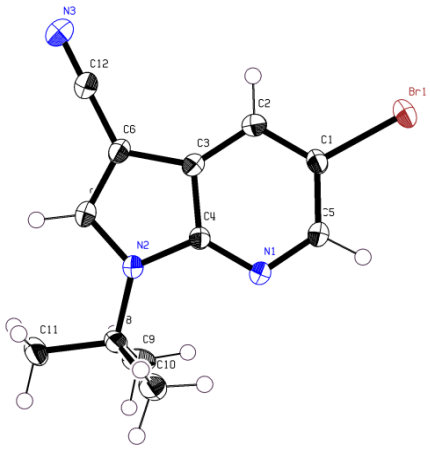


***Figure 16**: Crystallographic structure of compound **53a**, oxygen atom red, nitrogen atoms blue.*

In the products **55d** and **55e** of the Suzuki cross-coupling reactions, the phenyl ring (C13-C18) is twisted out of the azaindole plane. The torsion angles (C4-C5-C13-C14) are 40.6° and 33.3° for **55d** and **55e**, respectively. The distance *d*(C(16)---Cl) is 1.74Å for **55d** and *d*(C(19)---F) is 1.33Å for **55e** (Figure 17).

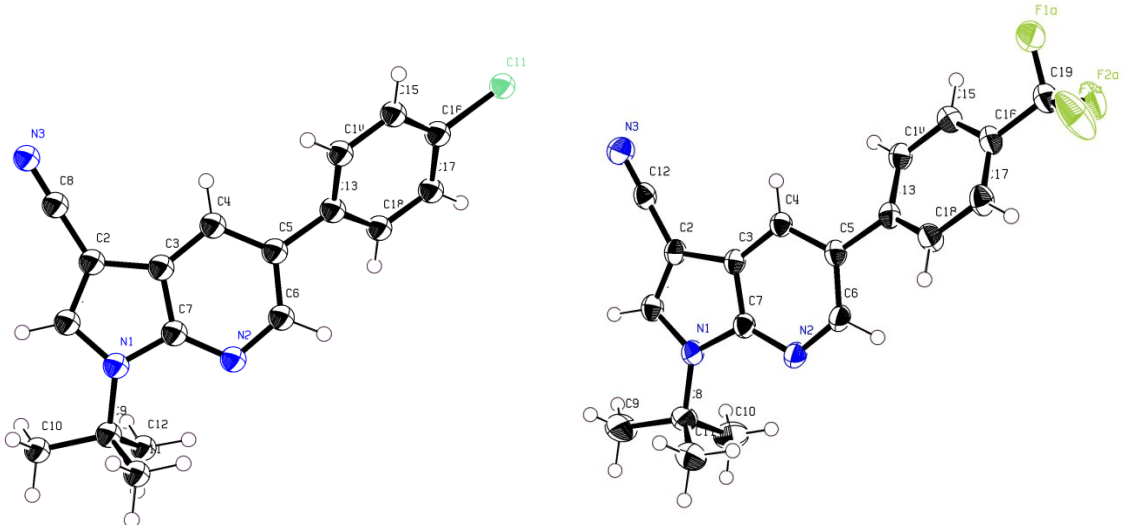


***Figure 17**: Crystallographic structures of compounds **55d** (left) and **55e** (right), nitrogen atoms blue, chlorine atom light green shades, fluorine atom olive green.*

Compound **57a** also presents a planar structure and a hydrogen bond between one of the methyl groups and the nitrogen of the pyridine ring.

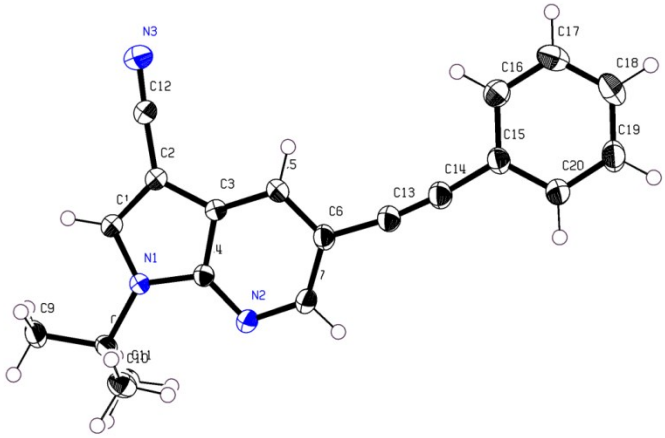


***Figure 18**: Crystallographic structure of compound **57a**, oxygen atoms blue.*

The compound **59b**, product of the Heck cross-coupling reaction, has a planar structure (Figure 19). The phenyl ring (C(15-20)) is in trans relationship with respect to the 1,4-dihydropyridine ring.

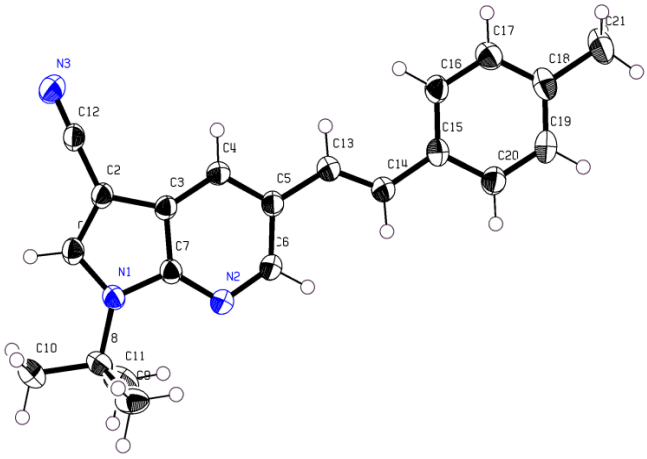


***Figure 19**: Crystallographic structure of compound **59b**, nitrogen atoms blue.*

8. Summary

In the present work the versatility of 5-amino-1*H*-1-substitued-3-carbonitrile as a building block for the synthesis of 7-azaindoles have been developed.

Indole (Chapter 2), chromone (Chapter 3) and coumarin (Chapter 4) were used as starting materials allowing the synthesis in one-pot reactions of substituted as well as heteroannulated compounds containing the pyrrolopyridine framework.

Moreover, the use of 5-aminopyrroles was extended to their use in multicomponent reactions (Chapters 5 and 6), which so far had not been reported. A big library of compounds, including highly functionalized azaindoles and condensed systems was synthesized. Additionally, using this methodology, another library of spiro-compounds with a 1,4-dihydropyridine moiety was obtained.

Finally, the synthesis of a 7-azaindole skeleton suitable for use in coupling reactions (Chapter 7), including Suzuki-Miyaura coupling, Sonogashira coupling and Heck reaction, was developed.

Figure 20 shows the number of structural classes synthesized using different synthetic approaches for the synthesis of 7-azaindole derivatives.

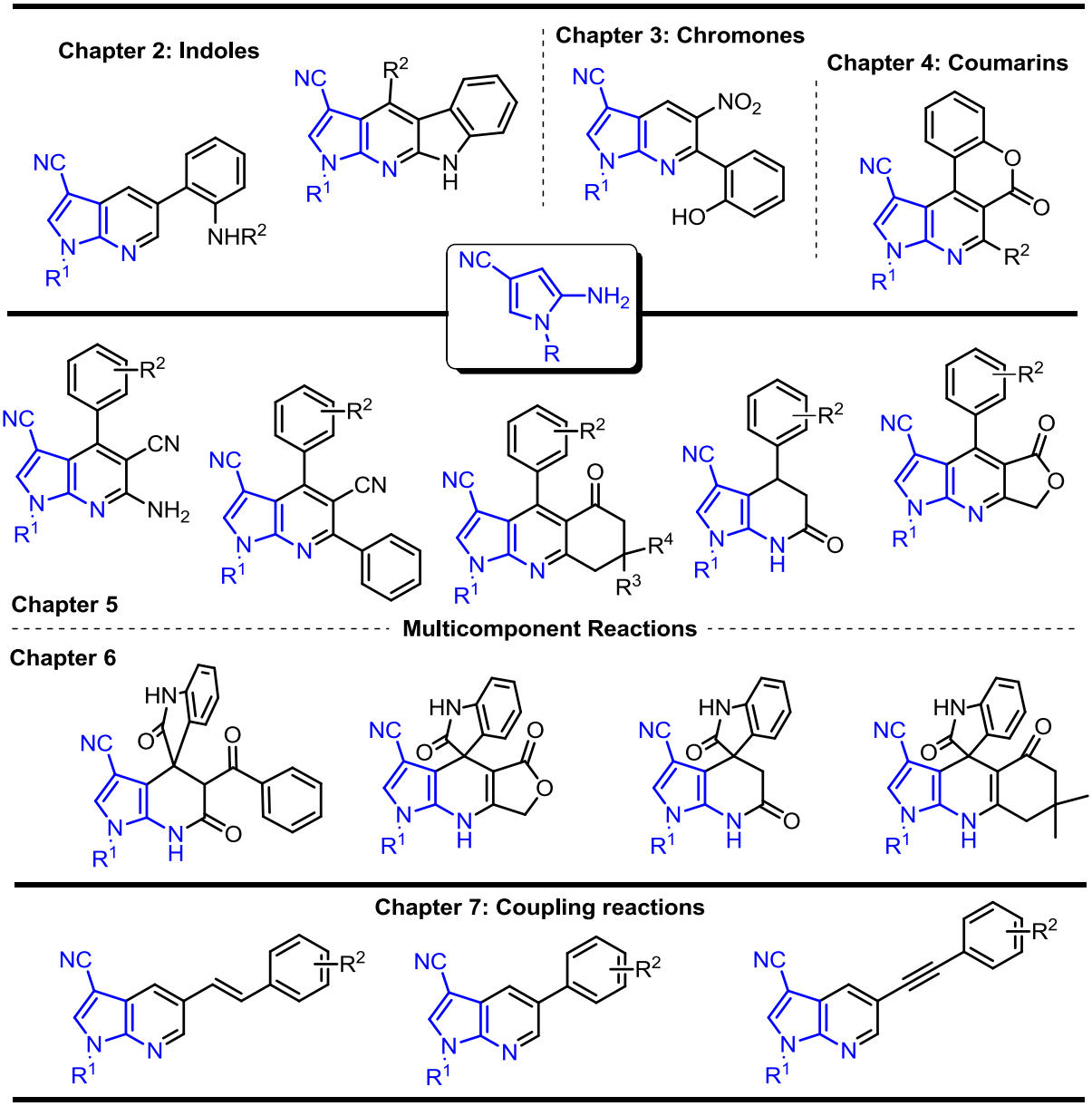


***Figure 20**: General structures of the synthesized compounds*

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Appendix

A.1 Experimental Section

A.1.1 Equipment

^{1}H NMR Spectroscopy: Bruker AM 250, Bruker ARX 300, Bruker ARX 500; δ = 0.00 ppm for Tetramethylsilane; δ = 7.26 ppm for ($CDCl_3$); δ = 2.50 ppm for DMSO-d_6; Characterization of the signals: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, q = quartet, quint = quintet; sext = sextet, sept = septet, m = multiplet, br = broad. Spectra were evaluated according to first order rules. All coupling constants are indicated as (*J*).

^{13}C NMR Spectroscopy: Bruker AM 250, (62.9 MHz); Bruker: ARX 300, (75 MHz), Bruker: ARX 500, (125 MHz) Ref: δ = 77.00 ppm for $CDCl_3$; DMSO-d_6 δ = 39.7 ppm. The multiplicity of the carbon atoms was determined by the DEPT 135 and APT technique (APT = Attached Proton Test) and quoted as CH_3, CH_2, CH and C for primary, secondary, tertiary and quaternary carbon atoms, respectively. Characterization of the signal: quart = quartet- The multiplicity of the signals was determined by the DEPT and/or the APT recording technologies.

Mass Spectroscopy: AMD MS40, AMD 402 (AMD Intectra), Varian MAT CH 7, MAT 731. High Resolution mass spectroscopy: Finnigan MAT 95 or Varian MAT 311; Bruker FT CIR, AMD 402 (AMD Intectra).

Infrared spectroscopy (IR): Bruker IFS 66 (FT IR), Nicolet 205 FT IR; Nicolet Protege 460, Nicolet 360 Smart rbit (ATR); KBr, KAP, Nujol, and ATR; Abbreviations for signal allocations: w = weak, m = medium, s = strong, br = broad

Elementary analysis: LECO CHNS-932, Thermoquest Flash EA 1112.

X-ray crystal structure analysis: Bruker X8Apex Diffractometer with CCD-Kamera (Mo-Kα and graphite monochromator, λ = 0.71073 Å).

***Melting point*s**: Micro heating table HMK 67/1825 Kuestner (Büchi apparatus); Melting points are uncorrected.

Column chromatography*:* Chromatography was performed over Merck silica gel 60 (0,063 - 0,200 mm, 70 - 230 mesh) as normal and/or over silica gel 60 (0,040 - 0,063 mm, 200 -400 mesh) as flash chromatography. All solvents were distilled before use.

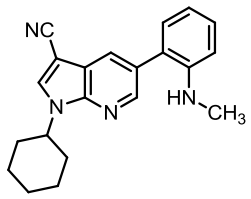
Thin layer chromatography*:* Merck DC finished aluminum foils silica gel 60 F254 and Macherey finished foils Alugram® Sil G/UV254. Detection under UV light at 254 nm and/or 366 nm without dipping reagent, as well as with vanillin-sulfuric acid reagent (1 mL vanillin in 100 mL stock solution of 85% methanol, 14% acetic acid and 1% sulfuric acid).

A.2 Procedures and spectroscopic data

A.2.1 General procedure for the synthesis of compounds 3a-h, 4a-c and 6a-g

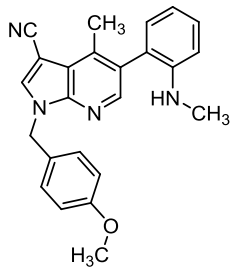
An appropriate indole (1.0 equiv), 1.0 equiv of the corresponding aminoheterocycle and 0.5 equiv of $AlCl_3$ were heated in 20 mL of dry methanol at 70 °C. When the reaction was complete (TLC control), the solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography.

*1-Cyclohexyl-5-(2-(methylamino)phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**3a**)*



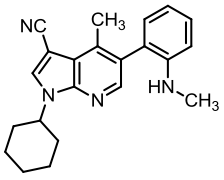
The product was obtained as a white solid, yield: 65 %; mp: 184-185 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.14-1.33 (m, 1H, CH), 1.42-1.80 (m, 5H, CH_2), 1.85-1.95 (m, 2H, CH_2), 2.1-2.2 (m, 2H, CH_2), 2.74 (s, 3H, NCH_3), 4.71-4,83 (m, 1H, CH), 6.71 (d, 1H, ^1J = 8.0 Hz, H_{Ar}), 6.77 (m, 1H), 7.04 (dd, 1H, ^1J = 1.5 Hz, ^3J = 8.0 Hz, H_{Ar}), 7.22-7.30 (m, 1H, H_{Ar}), 7.79 (s, 1H, (CN)C=C*H*), 8.05 (d, 1H, ^1J = 2.1 Hz, H_{Hetar}), 8.39 (d, 1H, ^1J = 2.1 Hz, H_{Hetar}). ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 25.3 (CH_2), 25.6 (CH_2), 30.7 (NCH_3), 33.5 (CH_2), 54.4 (CH), 84.3 (C≡N), 110.0 (CH_{Ar}), 115.3 (CH_{Ar}), 117.1 (CH_{Ar}), 120.2 (C_{Ar}), 124.0 (C_{Ar}), 128.8 (C_{Ar}), 129.5 (C_{Ar}), 129.9 (CH_{Ar}), 130.7 (CH_{Ar}), 132.8 (CH_{Ar}), 145.4 (C_{Ar}), 146.0 (CH_{Ar}), 146.5 (C_{Ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3477 (w), 3385 (w), 3148 (w), 3024 (w), 2975 (w), 2932 (w), 2870 (w), 2221 (m), 1613 (m), 1525 (m), 1501 (m9; 1479 (m), 1447 (m), 1400 (m), 1347 (m), 1282 (m), 1202 (s), 916 (m), 850 (m), 781 (m), 749 (s), 637 (m). *m/z* (%) = 330 (M^+, 100), 248 (62), 232 (16), 164 (2), 143 (2), 130 (5), 55 (5), 41 (4). HRMS (ESI): calcd for $C_{21}H_{22}N_4$ (M^+) 330.18390, found 330.18318.

*1-(4-Methoxybenzyl)-4-methyl-5-(2-(methylamino)phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**3b**)*



The product was obtained as a white solid, yield: 73 %; mp: 154-155 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.47 (s, 3H, CH_3), 2.72 (s, 3H, NCH_3), 3.73 (s, 3H, OCH_3), 5.36 (s, 2H, CH_2), 6.68 (d, 1H, ^3J = 8.2 Hz, H_{Ar}), 6.71-6.78 (m, 1H, H_{Ar}), 6.80 (t, 1H, ^{1}J = 3.0 Hz, H_{Ar}), 6.84 (t, 1H, ^1J = 3.0 Hz, H_{Ar}), 6.94 (dd, 1H, ^1J = 1.58 Hz, ^2J = 8,0 Hz, H_{Ar}), 7.18 (t, 1H, ^1J = 3.0 Hz, H_{Ar}), 7.21 (t, 1H, ^1J = 3.0 Hz, H_{Ar}), 7.24-7,31 (m, 1H, H_{Ar}), 7.59 (s, 1H, H_{Hetar}) 8.58 (s, 1H, (CN)C=C*H*). ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 15.2 (CH_3), 30.7 (NCH_3), 48.3 (CH_2), 55.3 (OCH_3), 84.3 (C≡N), 110.0 (CH_{Ar}), 114.5 (CH_{Ar}), 116.6 (C_{Ar}), 117.0 (CH_{Ar}), 119.2 (C_{Ar}), 122.9 (C_{Ar}), 127.7 (C_{Ar}), 129.3 (C_{Ar}), 129.4 (CH_{Ar}), 129.6 (CH_{Ar}), 130.8 (CH_{Ar}), 135.3 (CH_{Ar}), 140.7 (C_{Ar}), 146.1 (C_{Ar}), 146.8 (C_{Ar}), 147.1 (CH_{Ar}), 159.7 (C_{Ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3353 (w), 3120 (w), 3042 (w), 2978 (w), 2930 (w), 2904 (w), 2862 (w), 2809 (w), 2214 (s), 1606 (m), 1513 (s), 1410 (m), 1394 (m), 1304 (m), 1292 (m), 1255 (m), 1240 (m), 1179 (m), 1035 (m), 845 (m), 831 (m), 820 (m), 808 (m), 738 (m). *m/z* (%) = 382 (M^+, 61), 245 (4), 246 (3), 122 (9), 121 (100), 78 (3), 77 (4). HRMS (ESI): calcd for $C_{24}H_{22}N_4O$ (M^+) 382.17881, found 382.17813.

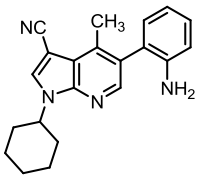
*1-Cyclohexyl-4-methyl-5-(2-(methylamino)phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**3c**)*



The product was obtained as a white solid, yield: 67 %; mp: 159-160 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.17-1.31 (m, 1H, CH), 1.44-1.77 (m, 5H, CH_2), 1.84-1.94 (m, 2H, CH_2), 2.1-2.2 (m, 2H, CH_2), 2.48 (s, 3H, CH_3), 2.72 (s, 3H, NCH_3), 4.77 (m, 1H, CH), 6.68 (d, 1H, ^1J = 8.0 Hz, H_{Ar}), 6.74 (t, 1H, ^1J = 7.37 Hz), 6.94 (dd, 1H, ^1J = 1.5 Hz, ^3J = 8.1 Hz, H_{Ar}), 7.27 (m, 1H, H_{Ar}), 7.78 (s, 1H, H_{Hetar}) 8.15 (s, 1H, (CN)C=C*H*). ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 15.2 (CH_3), 25.3 (CH_2), 25.6 (CH_2), 30.6 (NCH_3), 33.5 (CH_2), 54.1 (CH), 83.7 (C≡N), 109.7 (CH_{Ar}), 116.7 (CH_{Ar}), 117.0 (C_{Ar}), 119.4 (C_{Ar}), 122.8 (C_{Ar}), 129.2 (C_{Ar}), 129.4 (CH_{Ar}), 130.7 (CH_{Ar}), 132.9 (CH_{Ar}), 140.6 (C_{Ar}), 145.6 (C_{Ar}), 146.6 (CH_{Ar}), 147.0 (C_{ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3326 (m), 3130 (w), 2932 (m), 2855 (w), 2809 (w), 2215 (m), 2156 (w), 1575 (m), 1514 (s) 1486 (m), 1452 (m), 1391 (m), 1283 (m), 1184 (m), 1169 (m), 991 (m), 838 (m), 745 (s), 647 (s), 618 (s). *m/z* (%) = 344 (M^+, 100), 289 (5), 262

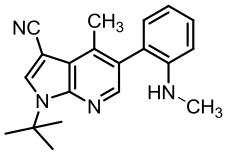
(83), 247 (30), 231 (14), 139 (5), 55 (5), 41 (4). HRMS (ESI): calcd for $C_{22}H_{24}N_4$ (M^+) 344.19955, found 344.19893.

*5-(2-Aminophenyl)-1-cyclohexyl-4-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**3d**)*



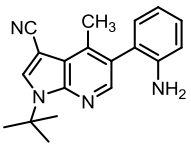
The product was obtained as a white solid, yield: 42 %; mp: 170-171 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.18-1.25 (m, 1H, CH), 1.43-1.76 (m, 5H, CH_2), 1.86-1.91 (m, 2H, CH_2), 2.1-2.1 (m, 2H, CH_2), 2.52 (s, 3H, CH_3), 4.77 (m, 1H, CH), 6.72-6.75 (d, 1H, ^1J = 7.9 Hz, H_{Ar}), 6.77-6.80 (d, 1H, ^1J = 7.4 Hz, H_{Ar}), 6.94-6.97 (dd, 1H, ^1J = 1.3 Hz, ^3J = 7.5 Hz, H_{Ar}), 7.13-7.16 (dd, 1H, ^1J = 1.5 Hz, ^3J = 7.9 Hz, H_{Ar}), 7.77 (s, 1H, H_{Hetar}) 8.17 (s, 1H, (CN)C=C*H*). ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 15.2 (CH_3), 25.3 (CH_2), 25.6 (CH_2), 33.5 (CH_2), 54.1 (CH), 83.8 (C≡N), 115.3 (CH_{Ar}), 117.0 (C_{Ar}), 118.4 (CH_{Ar}), 119.4 (C_{Ar}), 122.8 (C_{Ar}), 129.2 (CH_{Ar}), 129.3 (C_{Ar}), 131.1 (CH_{Ar}), 132.9 (CH_{Ar}), 140.3 (C_{Ar}), 144.5 (C_{Ar}), 145.6 (C_{Ar}), 146.3 (CH_{ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3432 (w), 3349 (w), 2932 (w), 2212 (w), 1617 (m), 1521 (m), 1450 (m), 1389 (m), 1283 (m), 1189 (m), 756 (s), 645 (s), 624 (s). *m/z* (%) = 330 (M^+, 46), 248 (100), 233 (19). HR (EI): calcd for $C_{21}H_{22}N_4$ (M^+) 330.18390, found 330.183723.

*1-Tert-butyl-4-methyl-5-(2-(methylamino)phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**3e**)*



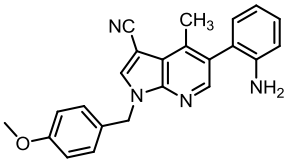
The product was obtained as a white solid, yield: 55 %; mp: 151-152 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.78 (s, 9H, $(CH_3)_3$), 2.45 (s, 3H, CH_3) , 2.72 (s, 3H, NCH_3), 7.05-7.12 (m, 2H, H_{Ar}), 7.23-7.42 (m, 2H, H_{Ar}), 7.84 (s, 1H, (CN)C=C*H*), 8.16 (s, 1H, H_{Hetar}). ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 25.3 (CH_3), 25.6 (CH_3), 30.7 (NCH_3), 33.5 (CH_3), 54.4 (*C*$(CH_3)_3$), 84.3 (C≡N), 110.0 (CH_{Ar}), 115.3 (CH_{Ar}), 117.1 (CH_{Ar}), 120.2 (C_{Ar}), 124.0 (C_{Ar}), 128.8 (C_{Ar}), 129.5 (C_{Ar}), 129.9 (CH_{Ar}), 130.7 (CH_{Ar}), 132.8 (CH_{Ar}), 145.4 (C_{Ar}), 146.0 (CH_{Ar}), 146.5 (C_{Ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3385 (w), 3170 (w), 3039 (w), 2975 (w), 2904 (w), 2863 (w), 2810 (w), 2210 (m), 1593 (m), 1513 (s), 1486 (m), 1392 (m), 1289 (m), 1199 (m), 1167 (m), 753 (m), 743 (s), 650 (m), 622 (m). *m/z* (%) = 318 (M^+, 100), 262 (85), 247 (54), 231 (21), 130 (5), 57 (4), 41 (4). HRMS (ESI): calcd for $C_{20}H_{22}N_4$ (M^+) 318.18390, found 318.18350.

*5-(2-Aminophenyl)-1-tert-butyl-4-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**3f**)*



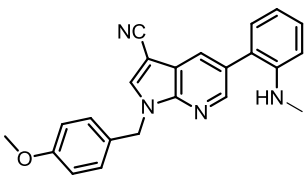
The product was obtained as a white solid, yield: 28 %; mp: 150-151 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.78 (s, 9H, $(CH_3)_3$), 2.52 (s, 3H, CH_3), 6.75-6.81 (m, 2H, H_{Ar}), 6.97-6.98 (dd, 1H, ^{1}J = 1.5 Hz, ^{3}J = 7.7 Hz, H_{Ar}), 7.15-7.19 (m, 1H, H_{Ar}), 7.82 (s, 1H, H_{Hetar}), 8.17 (s, 1H, (CN)C=C*H*). ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 15.2 (CH_3), 29.1 $(CH_3)_3$, 58.5 (CH), 82.6 (C≡N), 115.4 (CH_{Ar}), 117.2 (C_{Ar}), 118.7 (CH_{Ar}), 120.5 (C_{Ar}), 123.5 (C_{Ar}), 128.7 (C_{Ar}), 129.1 (CH_{Ar}), 131.2 (CH_{Ar}), 133.7 (CH_{Ar}), 139.7 (C_{Ar}), 144.2 (C_{ar}), 145.6 (C_{Ar}), 146.6 (CH_{Ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3348 (w), 2216 (m), 1614 (w), 1520 (m), 1393 (m), 1350 (m), 1290 (m), 1206 (m), 745 (s), 649 (s), 630 (s). *m/z* (%) = 304 (M^+, 52), 248 (100), 233 (35). HR (EI): calcd for $C_{19}H_{20}N_4$ (M^+) 304.16825, found 304.169003.

*5-(2-Aminophenyl)-1-(4-methoxybenzyl)-4-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**3g**)*



The product was obtained as a brown solid, yield: 51 %; mp: 72-74 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.52 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.36 (s, 2H, CH_2), 6.72-6.82 (m, 4H, H_{Ar}), 6.94-6.97 (dd, 1H, ^{1}J = 1.5 Hz, ^{3}J = 7.4 Hz, H_{Ar}), 7.1-7.2 (m, 3H, H_{Ar}), 7.59 (s, 1H, H_{Hetar}) 8.21 (s, 1H, (CN)C=C*H*). ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 15.2 (CH_3), 48.3 (CH_2), 55.3 (OCH_3), 84.3 (C≡N), 114.4 (CH_{Ar}), 115.3 (CH_{Ar}), 116.6 (C_{Ar}), 118.4 (CH_{Ar}), 119.2 (C_{Ar}), 123.0 (C_{Ar}), 129.2 (CH_{Ar}), 129.5 (C_{Ar}), 129.6 (CH_{Ar}), 131.1 (CH_{Ar}), 135.3 (CH_{Ar}), 140.4 (C_{Ar}), 144.6 (C_{Ar}), 146.1 (C_{Ar}), 146.9 (CH_{ar}), 159.7 (C_{Ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3361 (w), 2215 (m), 1611 (w), 1512 (s), 1246 (s), 1173 (m), 1097 (m), 748 (s), 630 (s). *m/z* (%) = 368 (M^+, 57), 121 (100). HRMS (ESI): calcd for $C_{23}H_{21}N_4O$ (M^+) 369.171, found 369.1708.

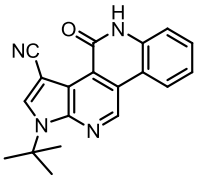
*1-(4-Methoxybenzyl)-4-methyl-5-(2-(methylamino)phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**3h**)*



The product was obtained as a brown solid, yield: 55 %; mp: 64-66 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.74 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 5.38 (s, 2H, CH_2), 6.65-6.84 (m, 4H, H_{Ar}), 7.02-7.04 (dd, 1H, ^{1}J = 1.5 Hz, ^{3}J = 7.6 Hz, H_{Ar}), 7.1-7.3 (m, 4H, H_{Ar}), 8.06 (s, 1H, H_{Hetar})

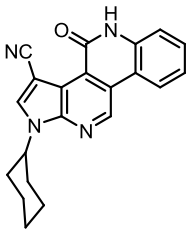
8.43 (s, 1H, (CN)C=C*H*). ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 30.7 (NCH_3), 48.3 (CH_2), 55.3 (OCH_3), 84.8 (C≡N), 110.1 (CH_{Ar}), 114.4 (CH_{Ar}), 117.1 (CH_{Ar}), 120.1 (C_{Ar}), 123.9 (C_{Ar}), 127.5(C_{Ar}), 128.8 (CH_{Ar}), 129.5 (CH_{Ar}), 129.6 (CH_{Ar}), 130.7 (CH_{Ar}), 131.1 (C_{Ar}), 135.2 (CH_{Ar}), 140.4 (C_{Ar}), 144.6 (C_{Ar}), 146.1 (C_{Ar}), 146.6 (CH_{ar}), 159.8 (C_{Ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3393 (w), 2217 (w), 1601 (w), 1510 (s), 1414 (m), 1244 (s), 1168 (s), 1028 (m), 744 (s).

*1-Tert-butyl-4-oxo-4,5-dihydro-1H-benzo[h]pyrrolo[2,3-c][2,6]naphthyridine-3-carbonitrile (**4a**)*



The product was obtained as a white solid, yield: 44 %; mp 356-357 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.83 (s, 9H, $(CH_3)_3$), 7.30-7.37 (m, 1H, H_{Ar}), 7.41-7.47 (m, 1H, H_{Ar}), 7.50-7.57 (m, 1H, H_{Ar}), 8.56-8.62, (m, 2H, H_{Hetar}, (CN)C=C*H*), 9.69 (s, 1H, H_{Hetar}). ^{13}C NMR (DMSO-d_6, 63 MHz): δ = 28.7 $(CH_3)_3$, 59.0 $C(CH_3)_3$, 84.8 (C≡N), 114.8 (C_{Ar}), 115.9 (CH_{Ar}), 116.1 (C_{Ar}), 116.8 (C_{Ar}), 122.8 (CH_{Ar}), 122.9 (CH_{Ar}), 123.2 (C_{Ar}), 124.0 (C_{Ar}), 129.6 (CH_{Ar}), 135.9 (C_{Ar}), 138.9 (CH_{Ar}),140.4 (CH_{Ar}), 145.9 (C_{Ar}), 159.1 (C_{Ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3186 (w), 3151 (w), 3055 (w), 3013 (w), 2967 (w), 2934 (w), 2873 (w), 2223 (m), 1665 (s), 1395 (m), 1381 (m), 1370 (m), 1350 (m), 1329 (m), 1228 (m), 1186 (m), 1111 (s), 879 (m), 826 (m), 743 (s), 657 (s). *m/z* (%) = 316 (M^+, 24), 260 (100), 232 (14), 207 (13), 178 (3), 151 (1), 57 (1), 41 (2). HRMS (ESI): calcd for $C_{19}H_{16}N_4O$ (M^+) 316.13158, found 316.13186.

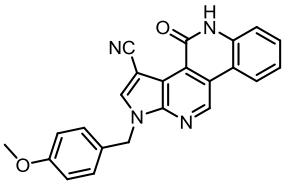
1-Cyclohexyl-4-oxo-4,5-dihydro-1H-benzo[h]pyrrolo[2,3-c][2,6]naphthyridine-3-carbonitrile **(4b)**



The product was obtained as a white solid, yield: 40 %; mp: 311-313 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.21-1.39 (m, 1H, CH), 1.43-1.62 (m, 2H, CH_2), 1.70-2.00 (m, 5H, CH_2), 2.0-2.1 (m, 2H, CH_2), 4.83-4.90 (m, 1H, CH), 7.29-7.37 (m, 1H, H_{Ar}), 7.46 (dd, 1H, ^1J = 1.1 Hz, ^3J = 8.0 Hz, H_{Ar}), 7.51-7.58 (m, 1H, H_{Ar}), 8.61 (d, 1H, ^1J = 8.0 Hz, H_{Hetar}), 8.83 (s, 1H, (CN)C=C*H*), 9.72 (s, 1H, H_{Hetar}), 11.96 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 63 MHz): δ = 24.8 (CH_2), 25.1 (CH_2), 32.4 (CH_2), 54.3 (CH), 85.9 (C≡N), 113.2 (C_{Ar}), 116.1 (CH_{Ar}), 116.3 (C_{Ar}), 116.6 (C_{Ar}), 122.5 (CH_{Ar}), 122.9 (CH_{Ar}), 123.7 (C_{Ar}), 125.0 (C_{Ar}), 129.5 (CH_{Ar}), 136.2 (C_{Ar}), 138.3 (CH_{Ar}),141.4 (CH_{Ar}), 145.2 (C_{Ar}), 160.1 (C_{Ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3140 (w), 3119 (w), 3054 (w), 3002 (w),

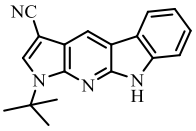
2923 (w), 2857 (w), 2221 (m), 1662 (m), 1651 (m), 1505(m), 1445 (m), 1348 (m), 1292 (m), 1178 (m), 882 (m), 823 (m), 756 (m), 745 (s), 676 (m), 648 (m), 634 (m), 608 (m). HRMS (ESI): calcd for $C_{21}H_{18}N_4O$ (M^+) 344.1553, found 343.1551.

*1-(4-Methoxybenzyl)-4-oxo-4,5-dihydro-1H-benzo[h]pyrrolo[2,3-c][2,6]naphthyridine-3-carbonitrile (**4c**)*



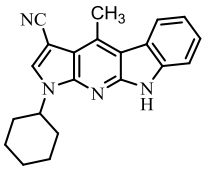
The product was obtained as a white solid, yield: 60 %; mp: 374-375 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 3.65 (s, 3H, OCH_3), 5.52 (s, 2H, CH_2), 6.82-6.85 (d, 1H, ^1J = 8.7 Hz, H_{Ar}), 7.2-7.3 (m, 3H, H_{Ar}), 8.5 (d, 1H, J = 7.7 Hz, H_{Ar}), 8.74 (s, 1H, H_{Ar}), 9.67 (s, 1H, (CN)C=C*H*), 11.94 (s, 1H, NH). ^{13}C NMR ((DMSO-d_6, 300 MHz): sample insoluble was not possible to measure. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3320 (m), 2224 (m), 1665 (s), 1512 (s), 1256 (s), 1170 (m), 1030 (m), 819 (s), 756 (s), 677 (s). HRMS (ESI): calcd for $C_{23}H_{17}N_4O_2$ (M^+) 381.1346, found 381.1339.

*1- Tert-butyl-3-cyano-pyrrolo[3',2':5,6]pyrido[2,3-b]indole (**6a**)*



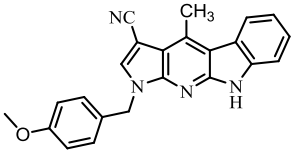
The product was obtained as a white solid, yield: 55 %; mp: 188-190 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.82 (s, 9H, $(CH_3)_3$), 7.20-7.35 (m, 1H, H_{Ar}), 7.36-7.40 (m, 2H, H_{Ar}), 7.74 (s, 1H, (CN)C=C*H*), 8.01-8.04 (d, 1H, J = 7.5 Hz, H_{Ar}), 8,3 (s, 1H, NH), 8.55 (s, 1H, H_{Hetar}). ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 28.4 $(CH_3)_3$, 58.1 ($C(CH_3)_3$), 81.8 (C≡N), 110.7 (CH_{Ar}), 112.6 (C_{Ar}), 114.5 (C_{Ar}), 116.2 (CH_{Ar}), 119.2 (C_{Ar}), 119.7 (CH_{Ar}), 120.5 (CH_{Ar}), 120.9 (CH_{Ar}), 126.2 (CH_{Ar}), 133.2 (CH_{Ar}), 139.4 (C_{Ar}), 145.1 (C_{Ar}), 149.4 (C_{Ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3375 (w), 3170 (w), 3029 (w), 2975 (w), 2863 (w), 2810 (w), 2210 (m), 1593 (m), 1513 (s), 1486 (m), 1392 (m), 1199 (m), 1167 (m), 753 (m), 743 (s), 650 (m), 622 (m). *m/z* (%) = 288 (M^+, 22), 232 (100). HR (EI): calcd for $C_{18}H_{16}N_4$ (M^+) 288.13695, found 288.13683.

1-Cyclohexyl -3-cyano-4-methyl-pyrrolo[3',2':5,6]pyrido[2,3-b]indole ***(6c)***



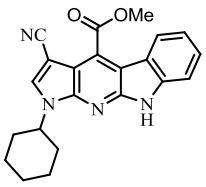
The product was obtained as a white solid, yield: 67 %; mp: 302-303 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.24-1.37 (m, 1H, CH), 1.47-1.58 (m, 2H, CH_2), 1.76-2.08 (m, 7H, CH_2), 3.18 (s, 3H, CH_3), 4.77 (m, 1H, CH), 7.24-7.48 (m, 3H, H_{Ar}), 8.18-8.21 (d, 1H, ^{1}J = 7.7 Hz, H_{Ar}), 8.49 (s, 1H, (CN)C=C*H*), 11.84 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 300 MHz): δ = 14.9 (CH_3), 24.9 (CH_2), 25.3 (CH_2), 32.2 (CH_2), 53.7 (CH), 81.8 (C≡N), 110.6 (CH_{Ar}), 111.8 (C_{Ar}), 112.6 (C_{Ar}), 117.7 (C_{Ar}), 119.3 (CH_{Ar}), 121.1 (C_{Ar}), 122.2 (CH_{Ar}), 125.5 (CH_{Ar}), 132.9 (CH_{Ar}), 135.1 (C_{Ar}), 139.1 (C_{Ar}), 144.3 (C_{Ar}), 150.1 (C_{Ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3326 (m), 3130 (w), 2932 (m), 2855 (w), 2809 (w), 2215 (m), 2156 (w), 1575 (m), 1514 (s) 1486 (m), 1452 (m), 1391 (m), 1283 (m), 1184 (m), 1169 (m), 991 (m), 838 (m), 745 (s), 647 (s), 618 (s). *m/z* (%) = 328 (M^+, 44), 246 (100)**.** HR (EI): calcd for $C_{20}H_{20}N_4$ (M^+) 328.16825, found 316.16814.

*1- (4-Methoxybenzyl)-3-cyano-4-methyl-pyrrolo[3',2':5,6]pyrido[2,3-b]indole (****6d****)*



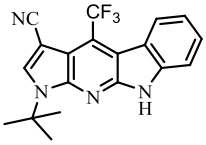
The product was obtained as a white solid, yield: 52 %; mp: 270-272 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 3.17 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.48 (s, 2H, CH_2), 6.89-6.92 (d, 1H, ^{1}J = 8.9 Hz, H_{Ar}), 7.22-7.32 (m, 3H, H_{Ar}), 7.42-7.50 (m, 2H, H_{Ar}), 8.17-8.19 (d, 1H, J = 7.7 Hz, H_{Hetar}), 8.42 (s, 1H, (CN)C=C*H*), 11.83 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 300 MHz): δ = 14.9 (CH_3), 47.5 (CH_2), 55.1 (OCH_3), 82.1 (C≡N), 110.7 (CH_{Ar}), 11.8 (C_{Ar}), 112.5(C_{Ar}), 113.9 (CH_{Ar}), 117.4 (C_{Ar}), 119.4 (CH_{Ar}), 121.0 (C_{Ar}), 122.3 (CH_{Ar}), 125.5 (CH_{Ar}), 128.8 (CH_{Ar}), 129.1 (C_{Ar}), 135.1 (C_{Ar}), 135.3 (CH_{Ar}), 139.1 (C_{Ar}), 144.7 (C_{Ar}), 150.3 (C_{Ar}), 158.8 (C_{Ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3326 (m), 3130 (w), 2932 (m), 2855 (w), 2809 (w), 2215 (m), 2156 (w), 1575 (m), 1514 (s) 1486 (m), 1452 (m), 1391 (m), 1283 (m), 1184 (m), 1169 (m), 991 (m), 838 (m), 745 (s), 647 (s), 618 (s). *m/z* (%) = 366 (M^+, 24), 245 (13), 121 (100). HR (EI): calcd for $C_{23}H_{18}N_4$ (M^+) 366.14739, found 366.14751.

1- Cyclohexyl-3-cyano-4-(methylcarboxylat)-pyrrolo[3',2':5,6]pyrido[2,3-b]indole ***(6f)***



The product was obtained as a white solid, yield: 54 %; mp: 229-230 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.21-1.30 (m, 1H, CH), 1.42-1.76 (m, 5H, CH_2), 1.86-1.91 (m, 2H, CH_2), 2.0-2.1 (m, 2H, CH_2), 4.17 (s, 3H, OCH_3), 4.68-4.77 (m, 1H, CH), 7.17-7.22 (m, 1H, H_{Ar}), 7.34-7.43 (m, 2H, H_{Ar}), 7.79 (s, 1H, H_{Ar}), 8.33-8.36 (d, 1H, ^{1}J = 8.0 Hz, H_{Hetar}), 8.55 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 63 MHz): δ = 25.4 (CH_2), 25.6 (CH_2), 32.3 (CH_2), 52.1 (OCH_3), 54.3 (CH), 84.7 (C≡N), 110.5 (CH_{Ar}), 111.5 (C_{Ar}), 111.7 (C_{Ar}), 116.3 (C_{Ar}), 119.9 (C_{Ar}), 120.5 (CH_{Ar}), 124.2 (CH_{Ar}), 125.7 (C_{Ar}), 127.4 (CH_{Ar}), 132.9 (CH_{Ar}), 139.3 (C_{Ar}), 145.1 (C_{Ar}), 150.3 (C_{Ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3140 (w), 3119 (w), 3054 (w), 3002 (w), 2923 (w), 2857 (w), 2221 (m), 1662 (m), 1651 (m), 1505(m), 1445 (m), 1348 (m), 1292 (m), 1178 (m), 882 (m), 823 (m), 756 (m), 745 (s), 676 (m), 648 (m), 634 (m), 608 (m). *m/z* (%) = 372 (M^+, 86), 290 (100), 231 (49). HR (EI): calcd for $C_{22}H_{20}N_4O_2$ (M^+) 372.15808, found 372.15814.

*1- Tert-butyl-3-cyano-4-trifluoromethyl-pyrrolo[3',2':5,6]pyrido[2,3-b]indole (****6g****)*

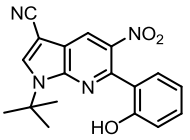


The product was obtained as a yellow solid, yield: 40 %; mp: 313-314 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.88 (s, 1H, $CH_3)_3$), 7.28-7.34 (m, 1H, H_{Ar}), 7.54-7.61 (m, 2H, H_{Ar}), 8.2-8.3 (d, 1H, ^{3}J = 8.1 Hz, H_{Ar}), 8.69 (s, 1H, (CN)C=C*H*), 12.39 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 28.3 $(CH_3)_3$, 58.8 (C_{Ar}), 81.2 (C≡N), 108.7 (q, $^{4}J_{C,F}$ = 2.75 Hz), 109.4 (q, $^{4}J_{C,F}$ = 2.2 Hz), 111.5 (CH_{Ar}), 116.2 (q, $^{4}J_{C,F}$ = 1.7 Hz), 117.3 (C_{Ar}), 120.1 (CH_{Ar}), 120.6 (q, $^{2}J_{C,F}$ = 35.8 Hz), 124.3 (q, $^{1}J_{C,F}$ = 275.1 Hz), 127.2 (CH_{Ar}), 129.9 (C_{Ar}), 138.2 (CH_{Ar}), 140.5 (C_{Ar}), 145.8 (C_{Ar}), 149.2 (C_{Ar}). ^{19}F NMR ($CDCl_3$, 282 MHz): δ -55.48. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3326 (m), 3130 (w), 2932 (m), 2855 (w), 2809 (w), 2215 (m), 2156 (w), 1575 (m), 1514 (s) 1486 (m), 1452 (m), 1391 (m), 1283 (m), 1184 (m), 1169 (m), 991 (m), 838 (m), 745 (s), 647 (s), 618 (s). *m/z* (%) = 344 (M^+, 100), 289 (5), 262 (83), 247 (30), 231 (14), 139 (5), 55 (5), 41 (4). *m/z* (%) = 356 (M^+, 18), 300 (100). HR (EI): calcd for $C_{19}H_{15}N_4F_3$ (M^+) 356.12433, found 356.12414.

A.2.2 General procedure for the synthesis of compounds 8a-c

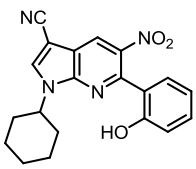
3-Nitrochromone (2 mmol, 0.38 g) and the corresponding amine **(**2.2 mmol) were dissolved in acetic acid (20 mL) and heated under reflux in an inert atmosphere during 1–5 h (controlled by TLC, Table 1). Then this solution was concentrated under reduced pressure,the residue treated with water, filtereed and air-dried and recrystallized from an appropriate solvent, or was subjected to column chromatography over silica gel.

1-Tert-butyl-6-(2-hydroxyphenyl)-5-nitro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**8a**)



The product was obtained as a colorless solid, yield 67 %; mp 244–245 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.78 (s, 9H, *t*-Bu), 6.86 (dd, 1H, ^{3}J = 8.0 Hz, ^{4}J = 0.8 Hz), 7.00 (td, 1H, ^{3}J = 7.5 Hz, ^{4}J = 0.9 Hz), 7.29 (m, 1H), 7.56 (dd, 1H, ^{3}J = 7.6 Hz, ^{4}J = 1.6 Hz), 8.72 (s, 1H), 8.78 (s, 1H), 10.01 (s, 1H, OH). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 28.6, 59.4, 83.5, 114.5, 115.1, 118.3, 119.6, 124.6, 125.2, 130.3, 130.5, 139.6, 142.7, 145.1, 146.3, 154.7; MS (GC, 70 eV) *m/z* (%) 336 (M+, 96), 306 (15), 280 (100), 263 (10), 250 (47), 234 (84), 206 (34), 195 (16), 180 (13), 152 (10), 57 (68), 41 (33); HRMS (ESI): calcd for $C_{18}H_{16}N_4O_3$ (M+1) 337.1295, found 337.1292; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3293 (w), 2980 (w), 2240 (m), 1671 (w), 1605 (w), 1595 (w), 1567 (m), 1522 (s), 1450 (m), 1412 (m), 1400 (w), 1372 (m), 1352 (s), 1341 (s), 1295 (m), 1255 (m), 1197 (s), 1123 (m), 1101 (m), 1092 (m), 1043 (s), 1007 (w), 945 (w), 920 (m), 852 (w), 838 (m), 819 (w), 784 (s), 761 (s), 700 (m), 667 (s), 625 (s), 615 (s), 600 (m), 557 (m), 532 (m).

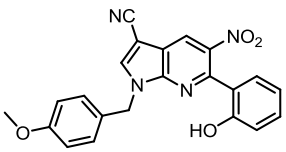
1-Cyclohexyl-6-(2-hydroxyphenyl)-5-nitro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**8b**)



The product was obtained as a yellow solid, yield: 93 %; mp 226–227 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23–2.06 (m, 10H, 5 CH_2), 4.78 (m, 1H, CHN), 6.87 (d, 1H, ^{3}J = 8.0 Hz), 7.01 (t, 1H, ^{3}J = 7.5 Hz), 7.31 (td, 1H, ^{3}J = 8.0 Hz, ^{4}J = 1.6 Hz), 7.56 (dd, 1H, ^{3}J = 7.6 Hz, ^{4}J = 1.5 Hz), 8.78 (s, 1H), 8.92 (s, 1H), 9.97 (s, 1H, OH). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 24.7, 25.0, 32.2, 54.5, 84.5, 114.4, 115.0, 116.9, 119.3, 124.9, 125.1, 130.4, 138.9, 143.1, 145.6, 146.3, 154.6; MS (GC, 70 eV) *m/z* (%)

362 (M+, 96), 280 (100), 234 (58), 206 (17), 55 (19); HRMS (ESI): calcd for $C_{20}H_{18}N_4O_3$ (M+1) 363.1452, found 363.1446; IR (ATR, cm^{-1}): $\tilde{\nu}$ 3117 (w), 2942 (w), 2856 (w), 2227 (m), 1607 (m), 1580 (w), 1563 (w), 1531 (s), 1496 (w), 1478 (m), 1450 (w), 1431 (s), 1395 (m), 1311 (w), 1289 (w), 1263 (m), 1230 (w), 1202 (m), 1161 (w), 1142 (w), 1114 (w), 1094 (w), 1034 (w), 995 (w), 948 (w), 921 (w), 891 (w), 875 (w), 822 (w), 788 (m), 766 (s), 756 (m), 703 (w), 641 (m), 623 (m), 543 (w).

1-(4-Methoxybenzyl)-6-(2-hydroxyphenyl)-5-nitro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**8c**)



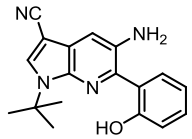
The product was obtained as a colorless solid, yield 81 %; mp: 166–167 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.71 (s, 3H, MeO), 5.50 (s, 2H, CH_2), 6.85–6.92 (m, 3H), 7.01 (td, 1H, ^3J = 7.5 Hz, ^4J = 0.9 Hz), 7.27–7.37 (m, 3H), 7.56 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.6 Hz), 8.77 (s, 1H), 8.83 (s, 1H), 10.00 (s, 1H, OH).^{13}C NMR (62.9 MHz, DMSO-d_6) δ 48.1, 55.1, 84.7, 114.1, 114.2, 115.1, 116. 9, 119.5, 125.0, 125.1, 128.2, 129.5, 130.5, 130.6, 140.9, 143.2, 145.9, 146.7, 154.6, 159.0; MS (EI, 70 eV) *m/z* (%) 400 (M+, 27 121 (100), 91 (13), 77 (20); HRMS (ESI): calcd for $C_{22}H_{16}N_4O_4$ (M+1) 401.1244, found 401.1242; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3116 (w), 3020 (w), 2841 (w), 1609 (m), 1581 (w), 1573 (w), 1515 (s), 1475 (w), 1462 (w), 1437 (s), 1389 (m), 1361 (w), 1341 (s), 1324 (m), 1305 (w), 1282 (m), 1252 (s), 1216 (m), 1174 (s), 1160 (m), 1121 (w), 1094 (w), 1029 (m), 953 (w), 910 (w), 884 (w), 868 (w), 845 (m), 817 (m), 790 (m), 766 (s), 727 (m), 700 (w), 686 (w), 666 (w), 644 (m), 627 (w), 609 (m), 569 (w), 554 (m), 528 (w).

A.2.3 General procedure for the synthesis of compounds 9a-c

In a 50 mL Schlenk flask under a flow of dry argon were placed the corresponding 3-nitro-pyridine (1.0 mmol) and 0.05 g of Pd/C (10%). Afterwards, 25 mL of degassed methanol was added. The system was flushed three times with hydrogen. The hydrogenation was conducted with the help of a glass burette under atmospheric pressure. After 3 equiv. of hydrogen were consumed, the mixture was stirred for 2 days at 20 °C (controlled by TLC). The reaction mixture was filtered through a Celite pad (2–3 cm). The Celite was washed 3 times with methanol. The

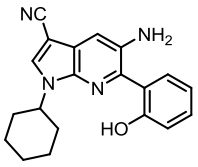
solvent of the filtrate was removed under reduced pressure. In many cases, the compounds isolated did not demand further purification; however, some of substances were purified by column chromatography (silica gel, heptane/EtOAc) or recrystallized from an appropriate solvent.

5-Amino-1-tert-butyl-6-(2-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**9a**)



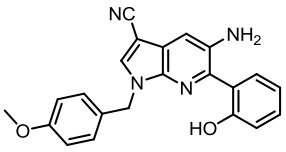
The product was obtained as a colorless solid, yield 77 %; mp 191–193 °C (from heptane:*i*-PrOH/1:3); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.73 (s, 9H, *t*-Bu), 4.91 (br s, 2H, NH_2), 6.93–7.00 (m, 2H), 7.25–7.30 (m, 1H), 7.38 (dd, 1H, ^{3}J = 7.6 Hz, ^{4}J = 1.5 Hz), 7.43 (s, 1H, Py), 8.29 (s, 1H, =CHN), 10.09 (br s, 1H, OH). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 28.7, 57.8, 79.4, 112.0, 116.3, 116.4, 119.5, 120.9, 126.8, 129.3, 131.6, 134.7, 138.1, 140.6, 141.1, 154.6; MS (GC, 70 eV) *m/z* (%) 306 (M+, 50), 249 (100), 233 (13); HRMS (ESI): calcd for $C_{18}H_{18}N_4O$ (M+1) 307.1553, found 307.1554; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3376 (w), 3305 (w), 3128 (w), 1607 (w), 1575 (w), 1519 (m), 1484 (w), 1462 (w), 1407 (m), 1368 (m), 1350 (m), 1304 (w), 1270 (m), 1231 (m), 1211 (s), 1154 (m), 1097 (m), 1046 (w), 1012 (w), 941 (w), 881 (m), 858 (m), 753 (s), 695 (m), 675 (m), 624 (s).

4.3.7. 5-Amino-1-cyclohexyl-6-(2-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**9b**)



The product was obtained as a yellow solid, yield 64 %; mp 206–208 °C (from heptane:*i*-PrOH/1:3); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.2–2.0 (m, 10H, $5CH_2$), 4.58 (m, 1H, CHN), 4.82 (br s, 2H, NH_2), 6.92–6.98 (m, 2H), 7.25–7.35 (m, 2H), 7.42 (s, 1H, Py), 8.41 (s, 1H, =CHN), 9.89 (br s, 1H, OH). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 24.9, 25.1, 32.5, 53.5, 80.2, 111.8, 115.8, 116.2, 119.4, 119.6, 126.3, 129.4, 131.6, 134.0, 138.9, 139.7, 141.8, 154.7; MS (GC, 70 eV) *m/z* (%) 332 (M+, 47), 250 (100); HRMS (ESI): calcd for $C_{20}H_{20}N_4O$ (M+1) 333.1710, found 333.1711; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3329 (w), 3131 (w), 2931 (w), 2853 (w), 1607 (w), 1575 (w), 1523 (m), 1435 (s), 1395 (m), 1374 (m), 1300 (m), 1260 (m), 1232 (m), 1175 (m), 1147 (m), 1121 (w), 1052 (w), 989 (m), 935 (m), 887 (m), 859 (m), 808 (m), 747 (s), 697 (m), 666 (m), 627 (m), 613 (s).

5-Amino-1-(4-methoxybenzyl)-6-(2-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**9b**).

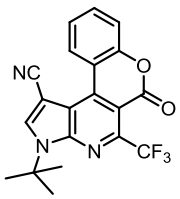


The product was obtained as a yellow solid, yield 78 %; mp 78–80 °C (from heptane:*i*-PrOH/1:3); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.70 (s, 3H, MeO), 4.90 (br s, 2H, NH_2), 5.35 (s, 2H, CH_2), 6.87–6.90 (m, 2H), 6.94–7.01 (m, 2H), 7.26–7.32 (m, 3H), 7.38 (dd, 1H, ^{3}J = 7.6 Hz, ^{4}J = 1.0 Hz), 7.46 (s, 1H, Py), 8.36 (s, 1H, =CHN), 9.5–10.5 (br s, 1H, OH). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 47.0, 55.0, 80.5, 112.1, 114.0, 115.9, 116.4, 119.4, 119.5, 126.2, 129.1, 129.2, 129.5, 131.5, 136.3, 138.9, 140.0, 142.2, 154.7, 158.8; MS (EI, 70 eV) *m/z* (%) 370 (M+, 46), 121 (100); HRMS (ESI): calcd for $C_{22}H_{18}N_4O_2$ (M+1) 371.1431, found 371.1430; IR (ATR, cm^{-1}) $\tilde{\nu}$ 3348 (w), 3114 (w), 2929 (w), 2215 (m), 1609 (w), 1581 (w), 1512 (m), 1484 (w), 1428 (m), 1372 (m), 1303 (m), 1276 (m), 1244 (s), 1172 (s), 1124 (m), 1026 (m), 819 (m), 757 (s), 675 (m), 652 (m), 626 (m), 608 (s).

A.2.4 General procedure for the synthesis of compounds 11a-l

An appropiate coumarin (2 mmol) and the corresponding aminoheterocycle (2.2 mmol) were placed in a pressure tube under a flow of dry argon and dissolved in dry DMF (10 mL) containing 1 mL of TMSCl. The mixture was heated at 100 to 120 °C during 6 h (controlled by TLC). Then this solution was concentrated under reduced pressure, the residue treated with water, filtered, and air-dried and recrystallized from an appropriate solvent, or subjected to column chromatography over silica gel.

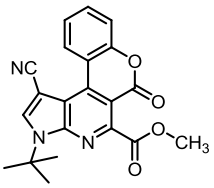
*3-Tert-butyl-6-oxo-5-(trifluoromethyl)-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**11a**)*



The product was obtained as a white solid, yield 72 %; mp 267-269 °C (from heptane: ethyl acetate/ 2:1); ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.70 (1H, dd, ^{1}J = 8.1, ^{2}J= 1.2 Hz, Ar-H), 8.32 (1H, s, Ar-H), 7.65 - 7.72 (1H, m, Ar-H), 7.43 - 7.56 (2H, m, Ar-H), 1.93 (9H, s, $(CH_3)_3$). ^{13}C NMR($CDCl_3$, 250MHz): δ 156.5 (C=O), 152.0 (CH_{Ar}), 146.5 (C_{Ar}), 143.5 (q, $^{2}J_{C,F}$ = 36.6 Hz), 140.7 (C_{Ar}), 139.5 (CH_{Ar}), 133.4 (CH_{Ar}), 129.2

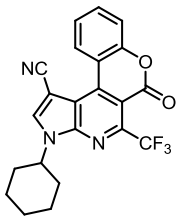
(CH_{Ar}), 124.4 (CH_{Ar}), 121.3 (q, $^1J_{C,F}$ = 275.1 Hz), 117.3 (CH_{Ar}), 116.0 (C_{Ar}), 115.8 (C_{Ar}), 114.6 (C_{Ar}), 110.6 (C_{Ar}), 86.1 (CN), 60.7 ($C(CH_3)_3$), 29.2 (CH_3). ^{19}F NMR ($CDCl_3$, 282 MHz): -61.2. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3472 (w), 2981 (w), 2215 (m), 1747 (m), 1545 (m), 1362 (m), 1147 (s), 1008 (s), 757 (m), 747 (s). MS (EI, 180 ev): *m/z* (%) = 385 (M^+, 17), 330 (19), 329 (100), 309 (23). HRMS (ESI): calcd for $C_{20}H_{15}F_3N_3O_2$ (M^+) 386.11109, found 386.11134.

*Methyl-3-tert-butyl-1-cyano-6-oxo-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-5-carboxylate (**11b**)*



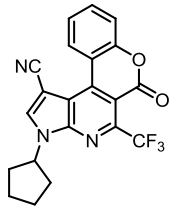
The product was obtained as a white solid, yield 53 % (from heptane: ethyl acetate/ 2:1); mp 245-247 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 8.79 (1H, dd, ^1J=8.1, ^2J=1.7 Hz, Ar-H), 8.18 (1H, s, Ar-H), 7.54 - 7.61 (1H, m, Ar-H), 7.40 - 7.46 (1H, m, Ar-H), 7.36 (1H, dd, ^1J=8.1, ^2J = 1.6 Hz,Ar-H), 4.01 (3H, s, OCH_3), 1.81 (9H, s, $(CH_3)_3$).^{13}C NMR($CDCl_3$, 250MHz): δ 167.2 (C=O), 159.2 (C=O), 152.1 (CH_{Ar}), 149.3 (C_{Ar}), 148.4 (C_{Ar}), 138.9 (CH_{Ar}), 138.6 (C_{Ar}), 133.1 (CH_{Ar}), 129.1 (CH_{Ar}), 124.6 (CH_{Ar}), 117.7 (CH_{Ar}),116.7 (C_{Ar}), 116.2 (C_{Ar}), 113.3 (C_{Ar}), 109.2 (C_{Ar}), 85.6 (CN), 60.5 ($C(CH_3)_3$), 53.4 (OCH_3), 29.2 (CH_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3438 (w), 2210 (m), 1728 (s), 1544 (s), 1159 (s), 1058 (s), 748 (m), 734 (s). MS (EI, 180 ev) *m/z* (%) = 375 (M^+, 27), 319 (50), 288 (46), 287 (100), 259 (25). HRMS (ESI): calcd for $C_{21}H_{18}N_3O_4$ (M^+) 376.12918, found 376.12883.

*3-Cyclohexyl-6-oxo-5-(trifluoromethyl)-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**11c**)*



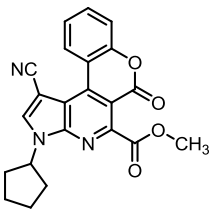
The product was obtained as a white solid, yield 46 %, (from heptane: ethyl acetate/ 2:1) mp 288-290 ºC. ^{1}H NMR (DMSO-d_6, 250 MHz): δ 9.28 (1H, s, Ar-H), 8.60 (1H, dd, ^1J = 8.1, ^2J= 1.6 Hz, Ar-H), 7.61 - 7.80 (1H, m, Ar-H), 7.34 - 7.61 (2H, m, Ar-H), 4.79 - 5.26 (1H, m, CH), 1.33 -2.17 (10H, m, CH_2). ^{13}C NMR insoluble sample, measuring was not possible. ^{19}F NMR ($CDCl_3$, 282 MHz): δ -58.85. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3124 (w), 2228 (m), 1736 (s), 1586 (s), 1180 (s), 1145 (s), 754 (m), 730 (s).MS (EI, 180 ev) *m/z* (%) = 411 (M^+, 39), 330 (24), 329 (100). HRMS (ESI): calcd for $C_{22}H_{17}F_3N_3O_2$ (M^+) 412.12674, found 412.12743.

*3-Cyclopentyl-6-oxo-5-(trifluoromethyl)-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**11d**)*



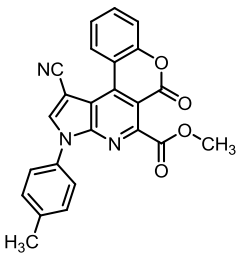
The product was obtained as a white solid, yield 58 % (from heptane: ethyl acetate/ 2:1); mp 256-258 ºC. ^{1}H NMR (DMSO-d_6, 250 MHz): δ 9.24 (1H, s, Ar), 8.59 (1H, dd, ^{1}J = 8.1, ^{2}J = 1.1 Hz, Ar-H), 7.68 - 7.82 (1H, m, Ar-H), 7.41 - 7.60 (2H, m, Ar-H), 5.23 - 5.41 (1H, m, CH), 2.18 -2.37 (2H, m, CH_2), 1.84 - 2.10 (4H, m, CH_2), 1.63 - 1.82 (2H, m, CH_2). ^{13}C NMR (DMSO-d_6, 250 MHz) δ 156.1 (C=O), 151.5 (C_{Ar}), 145.8 (C_{Ar}), 142.6 (q, $^{1}J_{C,F}$ = 36.5 Hz), 139.9 (C_{Ar}), 133.5 (CH_{Ar}), 129.02 (C_{Ar}), 129.0 (C_{Ar}), 128.0 (CH_{Ar}), 124.0 (CH_{Ar}), 121,4 (q, $^{1}J_{C,F}$ = 275.0 Hz), 119.2 (C_{Ar}), 116.9 (CH_{Ar}), 116.1 (C_{Ar}), 115.6 (C_{Ar}), 113.5 (C_{Ar}), 110.6 (CH_{Ar}), 85.8 (CN), 57.1 (CH), 32.2 (CH_2), 23.6 (CH_2). ^{19}F NMR ($CDCl_3$, 282 MHz): δ -62.21. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3142 (w), 2217 (m), 1746 (s), 1552 (s), 1453 (m), 1359 (m), 1154 (s), 757 (s), 609 (m). MS (EI, 180 ev) *m/z* (%) = 397 (M^+, 25), 329 (100), 309 (42). HRMS (ESI): calcd for $C_{21}H_{14}N_3F_3O_2$ (M^+) 397.10326, found 397.103256.

*Methyl--1-cyano-3-cyclopentyl-6-oxo-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-5-carboxylate (**11e**)*



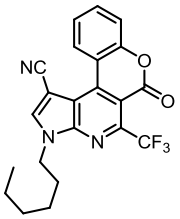
The product was obtained as a white solid, yield 38 % (from heptane: ethyl acetate/ 2:1) mp 225-227 ºC. ^{1}H NMR ($CDCl_3$, 300MHz):δ 8.87 (1H, dd, ^{1}J = 8.1 Hz ^{2}J = 1.0 Hz, Ar-H), 8.12 (1H, s, Ar-H), 7.55 - 7.64 (1H, m, Ar-H), 7.30 - 7.51 (2H, m, Ar-H), 5.34 - 5.48 (1H, m, CH), 4.02 (3H, s, OCH_3), 2.23 - 2.40 (2H, m, CH_2), 1.77 - 1.95 (6H, m, CH_2).^{13}C NMR($CDCl_3$, 250MHz): δ 167.3 (C=O), 159.2 (C=O), 152.3 (C_{Ar}), 150.6 (C_{Ar}), 148.2 (C_{Ar}), 139.1 (C_{Ar}), 138.0 (CH_{Ar}), 133.2 (CH_{Ar}), 129.2 (CH_{Ar}), 124.7 (CH_{Ar}), 117.8 (CH_{Ar}),116.7 (C_{Ar}), 116.3 (C_{Ar}), 112.1 (C_{Ar}), 109.8 (C_{Ar}), 87.0 (CN), 56.9 (OCH_3), 53.4 (CH), 33.1 (CH_2), 24.0 (CH_2). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3114 (w), 2218 (w), 1729 (s), 1549 (s), 1398 (m), 1216 (s), 763 (s). (HRMS (ESI): calcd for $C_{22}H_{18}N_3O_4$ (M^+) 388.12918, found 388.12886.

*Methyl-1-cyano-6-oxo-3-p-tolyl-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-5-carboxylate (**11f**)*



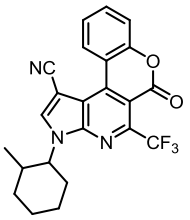
The product was obtained as a yellow solid, yield 42 % (heptane: ethyl acetate/ 2:1); mp 245 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 8.96 (1H, dd, ^{1}J= 8.1 ^{2}J = 1.1 Hz, Ar-H), 8.34 (1H, s, Ar-H), 7.66 - 7.75 (1H, m, Ar-H), 7.37 - 7.59 (6H, m, Ar-H), 4.04 (3H, s, OCH_3), 2.47 (3H, s, CH_3). ^{13}C NMR($CDCl_3$, 250MHz): δ 166.9 (C=O), 158.9 (C=O), 152.3 (C_{Ar}), 151.4 (C_{Ar}), 148.0 (C_{Ar}), 140.5 (CH_{Ar}), 139.4 (C_{Ar}), 139.3 (C_{Ar}), 133.4 (CH_{Ar}), 133.0 (C_{Ar}), 130.3 (CH_{Ar}),129.2 (CH_{Ar}), 125.0 (CH_{Ar}), 124.7 (CH_{Ar}), 124.4 (C_{Ar}), 117.8 (CH_{Ar}), 116.1 (C_{Ar}), 112.3 (C_{Ar}), 110.2 (C_{Ar}), 88.1 (CN), 53.3 (OCH_3), 21.2 (CH_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3136 (w), 2215 (m), 1727 (s), 1544 (s), 1415 (m), 1225 (s), 756 (m), 660 (s). *m/z* (%) = 409 (100), 378 (44), 350 (59), 349 (30), 322 (18). HRMS (ESI): calcd for $C_{24}H_{15}N_3O_4$ (M^+) 409.10571, found 409.105966.

*3-Hexyl-6-oxo-5-(trifluoromethyl)-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**11g**)*



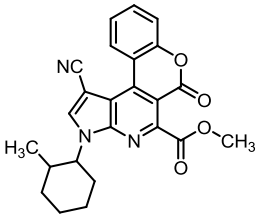
The product was obtained as a white solid, yield 45 % (from heptane: ethyl acetate/ 2:1); mp 177 ºC. ^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ 9.15 (1H, s, Ar-H), 8.51 (1H, d, *J* = 8.1 Hz, Ar-H), 7.62 - 7.72 (1H, m, Ar-H), 7.37 - 7.56 (2H, m, Ar-H), 4.45 - 4.54 (2H, m, CH_2), 1.90 – 1.99 (2H, m, CH_2), 1.24 - 1.37 (6H, m, CH_2), 0.86 (3H, t, CH_3). ^{13}C NMR (DMSO-*d*$_6$, 250 MHz) δ 156.9 (C=O), 151.4 (C_{Ar}), 149.8 (C_{Ar}), 147.9 (C_{Ar}), 146.4 (q, $^{2}J_{C,F}$ = 36.5 Hz), 132.6 (CH_{Ar}), 128.9 (C_{Ar}), 124.7 (C_{Ar}), 124.4 (CH_{Ar}), 122.8 (q, $^{1}J_{C,F}$ = 275.1 Hz), 118.1 (C_{Ar}), 116.3 (CH_{Ar}), 115.5 (C_{Ar}), 114.6 (C_{Ar}), 109.8 (CH_{Ar}), 84.7 (CN), 45.3 (CH_2), 30.6 (CH_2), 28.8 (CH_2), 25.5 (CH_2), 21.9 (CH_2), 13.8 (CH_3). ^{19}F NMR (DMSO-*d*$_6$, 282 MHz): δ -53.67. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2229 (m), 1727 (s), 1589 (s), 1389 (m), 1365 (m), 1145 (s), 755 (s). MS (EI, 180 ev) *m/z* (%) = 413 (M^+, 100), 384 (22), 329 (83). HRMS (ESI): calcd for $C_{22}H_{18}N_3F_3O_2$ (M) 413.13456, found 413.134465.

*3-(2-Methylcyclohexyl)-6-oxo-5-(trifluoromethyl)-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**11h**)*



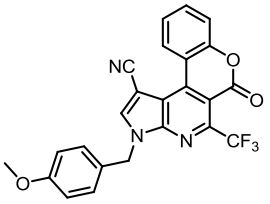
The product was obtained as a white solid, yield 44 % (heptane: ethyl acetate/ 2:1); mp 259-261 ºC. ^{1}H NMR (DMSO-*d6*, 300 MHz) : δ 9.30 (1H, s, Ar-H), 8.65 (1H, dd, ^{1}J = 8 ^{2}J = 1 Hz, Ar-H), 7.66 - 7.78 (1H, m, Ar-H), 7.43 - 7.55 (2H, m, Ar-H), 4.59 - 4.88 (1H, m, CH), 1.77-2.05 (6H, m, CH_2), 1.34 - 1.63 (3H, m, CH_2), 0.64 (3H, d, J = 6 Hz, CH_3). ^{13}C NMR (DMSO-*d6*, 300 MHz) δ 157.0 (C=O), 151.5 (C_{Ar}), 150.1 (C-), 148.1 (CH_{Ar}), 144.7 (q, $^{2}J_{C,F}$ = 35.1 Hz), 132.7 (CH_{Ar}), 124.9 (CH_{Ar}), 124.8 (CH_{Ar}), 124.7 (C_{Ar}), 122.8 (q, $^{1}J_{C,F}$ = 275.0 Hz), 118.3 (C_{Ar}), 116.4 (CH_{Ar}),116.2 (C_{Ar}), 114.8 (C_{Ar}), 110.2 (CF_3), 85.4 (CN), 57.7 (CH), 33.9 (CH_2), 32.2 (CH_2), 25.3 (CH_2), 25.1 (CH_2), 18.6 (CH_3), 12.0 (CH). ^{19}F NMR (DMSO-*d6*, 282 MHz): δ -53.60. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2228 (m), 1746 (s), 1586 (s), 1397 (m), 1367 (m), 1161 (s), 754 (s). MS (EI, 180 ev) *m/z* (%) = 425 (M^+, 33), 330 (72), 329 (100). HRMS (ESI): calcd for $C_{23}H_{18}N_3F_3O_2$ (M^+) 425.13456, found 425.134253.

*3-(2-Methylcyclohexyl)-6-oxo-5-(trifluoromethyl)-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**11i**)*



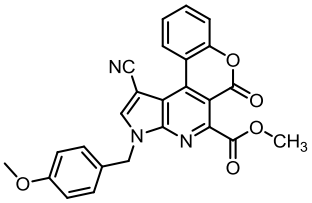
The product was obtained as a white solid, yield 40 % (from heptane: ethyl acetate/ 2:1) mp 259-261 ºC. ^{1}H NMR (DMSO-*d6*, 300 MHz): δ 9.08 (1H, s, Ar-H), 8.62 (1H, d, J = 7 Hz, Ar-H), 7.61 - 7.71 (1H, m, Ar-H), 7.41 - 7.56 (2H, m, Ar-H), 4.68 (1H, br. s., CH), 4.05 (3H, s, OCH_3), 3.36 (3H, s, CH_3), 1.67 - 2.18 (6H, m, CH_2), 1.30 - 1.60 (3H, m, CH_2), 0.63 (3H, d, J = 6 Hz, CH_3). ^{13}C NMR (DMSO-*d6*, 250 MHz) δ 164.9 (C=O), 159.2 (C=O), 151.6 (C_{Ar}), 149.1 (C_{Ar}), 147.4 (C_{Ar}), 136.2 (C_{Ar}), 132.4 (CH_{Ar}), 124.9 (CH_{Ar}), 124.4 (CH_{Ar}), 124.2 (CH_{Ar}), 118.7 (C_{Ar}), 116.9 (CH_{Ar}),115.8 (C_{Ar}), 113.4 (C_{Ar}), 108.1 (C_{Ar}), 83.7 (CN), 52.5 (OCH_3), 33.9 (CH_2), 32.3 (CH_2), 30.8 (CH), 25.3 (CH_2), 25.1 (CH_2), 18.5 (CH_3), 12.0 (CH). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3093 (w), 2930 (w), 2221 (m), 1739 (s), 1582 (m), 1398 (m), 1210 (s), 1053 (s), 754 (s).

*3-(4-Methoxybenzyl)-6-oxo-5-(trifluoromethyl)-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**11j**)*



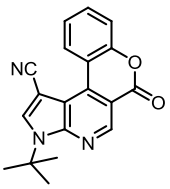
The product was obtained as a white solid, yield 41 % (from heptane: Ethyl acetate/ 2:1) mp 264-266 ºC. ^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ 9.28 (1H, s, Ar-H), 8.63 - 8.71 (1H, m, Ar-H), 7.67 - 7.85 (1H, m, Ar-H), 7.45 - 7.59 (2H, m, Ar-H), 6.93 - 7.00 (2H, m, Ar-H), 5.70 (2H, s,CH_2), 3.74 (3H, s, CH_3). ^{13}C NMR insoluble sample, measuring was not possible.^{19}F NMR ($CDCl_3$, 282 MHz): δ -56.67 .IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3461 (w), 2220 (m), 1736 (s), 153 (s), 1145 (s), 1008 (s), 762 (m), 757 (s). MS (EI, 180 ev) *m/z* (%) = 449 (M^+, 25), 122 (16), 121 (100), 63 (18), 44 (11). HRMS (ESI): calcd for $C_{24}H_{14}F_3N_3O_3$ (M) 449.09818, found 449.09833.

*Methyl-1-cyano-3-(4-methoxybenzyl)-6-oxo-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-5-carboxylate (**11k**)*



The product was obtained as a white solid, yield 55 % (from heptane: ethyl acetate/ 2:1) mp 227-229 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 8.55 (1H, dd, ^{1}J=8.1, ^{2}J=1.7 Hz, Ar-H), 7.78 (1H, s, Ar-H), 7.43 - 7.51 (1H, m, Ar-H), 7.18 - 7.29 (4H, m, Ar-H), 6.79 - 6.84 (2H, m,Ar-H), 5.50 (2H, s, CH_2), 4.10 (3H, s, OCH_3), 3.72 (3H, s, OCH_3). ^{13}C NMR (DMSO-*d*$_6$, 250MHz): δ 164.8 (C=O), 159.1 (C=O), 151.5 (C_{Ar}), 148.5 (C_{Ar}), 147.5 (C_{Ar}), 142.6 (CH_{Ar}), 136.2 (C_{Ar}), 132.3 (CH_{Ar}), 129.7 (CH_{Ar}), 129.4 (C_{Ar}), 127.9 (C_{Ar}), 124.9 (CH_{Ar}),124.2 (CH_{Ar}), 118.6 (C_{Ar}), 116.8 (CH_{Ar}), 115.8 (C_{Ar}), 114.1 (CH_{Ar}), 113.2 (C_{Ar}), 108.1 (C_{Ar}), 83.5 (CN), 55.0 (OCH_3), 52.5 (OCH_3), 48.3 (CH_2). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3131 (w), 2217 (m), 1730 (s), 1514 (s), 1224 (s), 1168 (s), 753 (s). HRMS (ESI): calcd for $C_{25}H_{17}N_3O_5$ (M^+) 439.11627, found 439.1164.

*3-Tert-butyl-6-oxo-3,6-dihydrochromeno[4,3-d]pyrrolo[2,3-b]pyridine-1-carbonitrile (**11l**)*



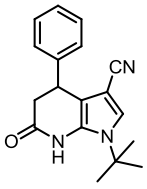
The product was obtained as a yellow solid, yield 40 % (from heptane: ethyl acetate/ 2:1) mp 252-254 ºC. ^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ 9.18 (1H, s, Ar-H), 8.93 (1H, s, Ar-H), 8.76 (1H, dd, ^{1}J = 8.1 ^{2}J= 1.1 Hz, Ar-H), 7.65 - 7.80 (1H,

m, Ar-H), 7.41 - 7.56 (2H, m, Ar-H), 1.86 (9H, s, $(CH_3)_3$). ^{13}C NMR (DMSO-*d*$_6$, 250MHz): δ 159.9 (C=O), 151.9 (C_{Ar}), 149.6 (C_{Ar}), 145.8 (CH_{Ar}), 140.9 (CH_{Ar}), 136.2 (C_{Ar}), 132.8 (CH_{Ar}), 132.0 (C_{Ar}), 128.5 (CH_{Ar}), 124.1 (CH_{Ar}), 117.6 (CH_{Ar}), 116.4 (C_{Ar}),112.1 (C_{Ar}), 111.6 (C_{Ar}), 83.6 (CN), 59.9 ($C(CH_3)_3$), 28.6 (CH_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3132 (w), 2216 (w), 1726 (s), 1592 (m), 1364 (m), 1181 (s), 1081 (m), 758 (s), 745 (s). HRMS (ESI): calcd for $C_{19}H_{15}N_3O_2$ (M^+) 317.11588, found 317.116008.

A.2.5 General procedure for the synthesis of compounds 20 a-o

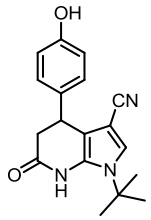
A mixture of Meldrum's acid (1 equiv.), the corresponding aldehyde (1 equiv.) and 5-amino-1-R-pyrrole-3-carbonitrile (1 equiv.) was refluxed in ethanol for 5 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent: n-heptane/ethylacetate).

*1-Tert-butyl-6-oxo-4-phenyl-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**20a**)*



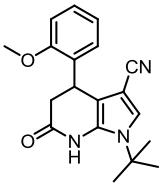
The product was obtained as a white solid, yield 82 %; mp 230-231 ºC. ^1H NMR (300 MHz, $CDCl_3$): δ 8.44 (1H, br. s., NH), 7.12 - 7.27 (5H, m, Ar-H), 6.91 (1H, s, Ar-H), 4.18 (1H, dd, ^1J = 7.2 ^2J = 5.1 Hz, CH), 2.96 (1H, dd, ^1J = 16.1 ^2J = 7.2 Hz, CH_2), 2.80 (1H, dd, ^1J = 15.9 ^2J = 5.1 Hz, CH_2), 1.53 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 170.7 (C-), 141.8 (C-), 128.9 (CH-), 128.6 (C-), 127.2 (CH-), 127.0 (CH-), 121.4 (CH-), 115.6 (C-), 108.2 (C-), 89.1 (C-), 57.3 (C-), 39.6(CH_2), 35.7 (CH), 29.7 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 293 (M+, 77), 237 (100), 194 (87); HRMS (ESI): calcd for $C_{18}H_{20}N_3O$ (M + 1) 294.16009, found 294.15997; IR (ATR, cm^{-1}) ũ 3150 (w), 2217 (m), 1668 (s), 1524 (m), 1492 (m), 1358 (m), 1190 (s), 1031 (w), 983 (w), 767 (s), 685 (s), 631 (s), 561 (s). calcd for $C_{18}H_{19}N_3O$: C: 73.69, H: 6.53, N: 14.32, found: C: 73.25, H: 6.61, N: 13.86 . The structure was independently confirmed by X-Ray analysis.

*1-Tert-butyl-4-(4-hydroxyphenyl)-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**20b**)*



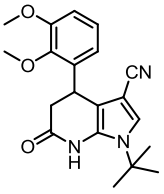
The product was obtained as a white solid, yield 71 %, mp 290-291 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.98 (1H, br. s., OH), 9.30 (1H, s, NH), 7.40 (1H, s, Ar-H), 6.96 (2H, d, J = 8.5 Hz, Ar-H), 6.70 (2H, d, J = 8.3 Hz, Ar-H), 4.06 (1H, m,CH), 2.93 (1H, dd, ^{1}J = 7.2Hz, ^{2}J = 15.7 Hz, CH_2), 2.58 (1H, d, J = 3.9 Hz, CH_2), 1.57 (9H, s, $(CH_3)_3$).^{13}C NMR (62.9 MHz, DMSO-d_6): δ 169.7 (C-), 156.1 (C-), 132.7 (C-), 129.5 (C-), 127.7 (CH) 122.3 (CH-), 116.1 (C-), 115.3 (CH-), 107.6 (C-), 87.4 (C-), 57.4 (C-), 40.2 (CH_2-), 33.9(CH), 29.2 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 309 (M+, 86), 253 (83), 210 (100); HRMS (ESI): calcd for $C_{18}H_{20}N_3O_2$ (M + 1) 310.155 found 310.15534; IR (ATR, cm^{-1}) ũ 3286 (w), 2217 (m), 1662 (s), 1512 (m), 1493 (m), 1271 (m), 1192 (s), 1163 (m), 938 (m), 837 (s), 772 (s), 623 (m).

*1-Tert-butyl-4-(2-methoxyphenyl)-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**20c**)*



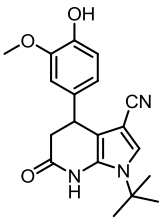
The product was obtained as a white solid, yield 90 %, mp 280-281 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (1H, br. s., NH), 7.11 - 7.17 (1H, m, Ar-H), 6.91 (1H, s, Ar-H), 6.75 - 6.87 (3H, m, Ar-H), 4.49 (1H, dd, ^{1}J= 8 ^{2}J = 4 Hz, CH), 3.76 (3H, s, OCH_3), 2.89 (1H, dd, ^{1}J= 16 ^{2}J 8 Hz, CH_2), 2.77 (1H, dd, ^{1}J= 16 ^{2}J = 4 Hz, CH_2), 1.52 (9H, s, $(CH_3)_3$). δ ^{13}C NMR (62.9 MHz, DMSO-d_6): 169.8 (C-), 156.3 (C-), 130.5 (C-), 129.5 (C-), 128.2 (CH-), 127.0 (CH-), 122.5 (CH-), 120.2 (CH-), 116.0 (C-), 111.0 (CH-), 105.9 (C-), 87.3 (C-),57.4 (C-), 55.2 (OCH_3), 38.3 (CH_2-), 29.2 $(CH_3)_3$, 29.0 (CH-). MS (GC, 70 eV) m/z (%) 323 (M+, 100), 267 (62), 266 (55), 224 (38); HRMS (ESI): calcd for $C_{19}H_{22}N_3O_2$ (M + 1) 324.17065, found 324.17015; IR (ATR, cm^{-1}) ũ 3225 (w), 2221 (m), 1667 (s), 1489 (s), 1358 (w), 1194 (m), 1026 (m), 934 (w), 759 (s).

*1-Tert-butyl-4-(2,3-dimethoxyphenyl)-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**20d**)*



The product was obtained as a white solid, yield 87 %, mp 252-253 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.05 (1H, br. s, NH), 7.42 (1H, s, Ar-H), 6.94 - 7.03 (2H, m, Ar-H), 6.46 (1H, dd, ^{1}J = 5.97 Hz, ^{2}J = 2.87 Hz, Ar-H), 4.42 (1H, dd, ^{1}J = 8.1 ^{2}J= 2.89 Hz, CH), 3.83 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.01 (1H, dd, ^{1}J = 16 ^{2}J = 8.1 Hz, CH_2), 2.43 (1H, dd, ^{1}J =16 ^{2}J = 2.89 Hz, CH_2), 1.59 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 169.4 (C-), 152.5 (C-), 145.8 (C-), 135.5 (C-), 130.4 (C-), 123.9 (CH-), 122.4 (CH-),119.2 (CH-),115.9 (C-), 111.7 (CH-), 106.3 (C-), 87.3 (C-), 60.0 (OCH_3-), 57.4 (C-), 55.6 (OCH_3-), 39.4 (CH_2), 29.2 $(CH_3)_3$, 29.0 (CH-). MS (GC, 70 eV) m/z (%) 353 (M+, 100), 296 (34), 282 (68), 266 (82), 138 (34); HRMS (ESI): calcd for $C_{20}H_{24}N_3O_3$ (M + 1) 354.18122, found 354.18092; IR (ATR, cm^{-1}) ũ 3307 (w), 2222 (m), 1689 (s), 1596 (w), 1495 (w), 1471 (s), 1338 (w), 1270 (m), 1208 (m), 1191 (s), 1075 (s), 1001 (s), 987 (s), 773 (w), 746 (m), 601 (w), 558 (s). calcd for $C_{20}H_{23}N_3O_3$: C: 67.97, H: 6.56, N: 11.89, found: C: 67.41, H: 6.67, N: 11.64. The structure was independently confirmed by X-Ray analysis.

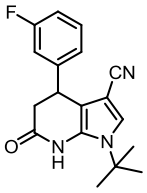
*1-Tert-butyl-4-(4-hydroxy-3-methoxyphenyl)-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**20e**)*



The product was obtained as a white solid, yield 65 %, mp 234-235 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (1H, br. s., OH), 6.99 (1H, s, Ar-H), 6.77 - 6.86 (2H, m, Ar_H), 6.68 (1H, dd, J = 8.1 and 1.89 Hz, Ar_H), 5.64 (1H, br. s., NH), 4.20(1H, dd, J = 7.2 and 4.7 Hz, CH), 3.86 (3H, s, OCH_3), 3.02 (1H, dd, ^{1}J = 15.9 ^{2}J = 7.2 Hz, CH_2), 2.87 (1H, dd, ^{1}J = 15.9 ^{2}J = 4.7 Hz, CH_2), 1.61 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 170.7 (C-), 146.8 (C-), 144.7 (C-), 133.7 (C-), 128.3 (C-), 121.3 (CH-), 119.0 (CH-), 115.8 (C-), 114.6 (CH-), 109.9 (CH-), 108.8 (C-), 89.0(C-), 57.3 (C-), 55.9 (OCH_3-), 39.4 (CH_2-), 35.2 (CH-), 29.8 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 339 (M+, 100), 283 (70), 240 (68), 124 (53), 57 (40); HRMS (ESI): calcd for $C_{19}H_{22}N_3O_3$ (M + 1) 340.16557, found 340.16493; IR (ATR, cm^{-1}) ũ 3268 (w), 2221 (m), 1658 (s), 1651 (s), 1511 (s), 1490 (m), 1364 (m), 1282 (m), 1260 (m), 1230 (m), 1206 (s), 1195 (s), 11140 (m), 1120 (m), 1037 (m), 993 (w),

833 (m), 813 (m), 756 (m), 689 (m), 552 (m).

*1-Tert-butyl-4-(3-fluorophenyl)-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**20f***

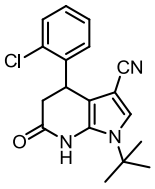


The product was obtained as a white solid, yield 56 %, mp 231-232 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.07 (1H, s, NH), 7.45 (1H, s, Ar-H), 7.35 - 7.43 (1H, m, Ar-H), 6.93 - 7.13 (3H, m, Ar-H), 4.15 - 4.32 (1H, dd, ^{1}J= 4.3 ^{2}J = 7.2 Hz, CH), 3.00 (1H, dd, ^{1}J = 15.7 ^{2}J= 7.2 Hz, CH_2), 2.65 (1H, dd, ^{1}J = 15.7 ^{2}J= 4.3 Hz, CH_2), 1.58 (9H, s, $(CH_3)_3$). ^{19}F NMR ($CDCl_3$): δ -112.86 (Ar-F). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 169.4 (C-), 163.9 (C-), 160.7 (C-), 145.5(C-, ^{1}J= 6.6 Hz), 130.7 (CH, ^{1}J = 8.25 Hz), 129.8 (C-), 123.0 (CH, J = 2.75 Hz), 122.7 (CH-), 115.9 (C-), 113.7 (CH, J = 3.3 Hz), 113.5 113.5 (CH, J = 3.85 Hz), 106.4 (C-), 87.3 (C-), 57.5 (C-), 39.6 (CH_2-), 34.4 (CH-), 29.2 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 311 (M+, 60), 255 (100), 212 (61), 57 (66); HRMS (ESI): calcd for $C_{18}H_{19}FN_3O$ (M + 1) 312.15067 found 312.15108; IR (ATR, cm^{-1}) ῦ 3148 (w), 2215 (m), 1672 (s), 1586 (m), 1487 (m), 1355 (m), 1192 (s), 1135 (m), 905 (w), 778 (m), 680 (m). calcd for $C_{18}H_{18}FN_3O$: C: 69.44, H: 5.83, N: 13.50, found: C:68.84, H: 5.73, N: 13.16

*1-Tert-butyl-6-oxo-4-(pentafluorophenyl)-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**20g**)*

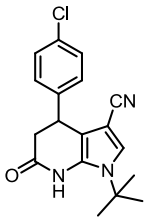
The product was obtained as a yellow solid, yield 44 %, mp 226-227 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (1H, s, NH), 6.92 (1H, s, Ar-H), 4.69 (1H, t, ^{1}J = 8.1 Hz, CH), 2.80 - 2.99 (2H, m, CH_2), 1.56 (9H, s, $(CH_3)_3$). ^{19}F NMR ($CDCl_3$): δ -141.81 (Ar-F), -141.86 (Ar-F), -154 (Ar-F), -161.10 (Ar-F), -161.13 (Ar-F). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 169.0 (C-), 147.0 (C-), 143.7 (C-), 139.5 (C-), 136.1 (C-), 128.9 (C-), 121.6 (CH-), 114.6 (C-), 114.4 (C-), 103.4 (C-), 88.6 (C-), 57.6 (C-), 36.5 (CH_2-), 29.7 $(CH_3)_3$, 25.9 (CH-). MS (GC, 70 eV) m/z (%) 383 (M+, 34), 327 (100), 265 (25); HRMS (ESI): calcd for $C_{18}H_{15}F_5N_3O$ (M + 1) 384.11298, found 384.11307; IR (ATR, cm^{-1}) ῦ 3137 (w), 2222 (m), 1672 (s), 1499 (s), 1369 (w), 1338 (w), 1195 (m), 1116 (m), 1004 (m), 884 (m), 777 (m), 624 (m), 607 (m). calcd for $C_{18}H_{14}F_5N_3O$: C: 56.40, H: 3.68, N: 10.96, found: C:56.45, H: 3.96, N: 10.58. The structure was independently confirmed by X-Ray analysis.

*1-Tert-butyl-4-(2-chlorophenyl)-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**20h**)*



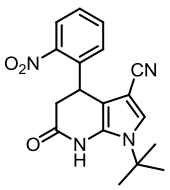
The product was obtained as a white solid, yield 40 %, mp 271-272 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.77 (1H, br. s., NH), 7.30 - 7.36 (1H, m, Ar-H), 7.05 - 7.16 (2H, m, Ar-H), 6.95 (1H, s, Ar-H), 6.84 (1H, dd, ^{1}J = 7.2 ^{2}J = 2.1 Hz, Ar-H),4.66 (1H, dd, ^{1}J = 7.3 ^{2}J= 5.4 Hz, CH), 2.94 (1H, dd, ^{1}J =16.1Hz ^{2}J = 7.4Hz, CH_2), 2.76 (1H, dd ^{1}J =16.1Hz ^{2}J = 5.3Hz, CH_2), 1.52 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 170.1 (C-), 138.2 (C-), 133.4 (C-), 130.1 (CH-), 129.7 (C-), 128.7 (CH-), 128.3 (CH-), 127.2 (CH-), 121.7 (CH-), 115.2 (C-), 106.4 (C-), 89.2(C-), 57.4 (C-), 38.5 (CH_2-), 32.6 (CH-), 29.7 $(CH_3)_3$.MS (GC, 70 eV) m/z (%) 327 (M+, 50), 271 (100), 228 (27); HRMS (ESI): calcd for $C_{18}H_{19}ClN_3O$ (M + 1) 328.12112, found 328.12164; IR (ATR, cm^{-1}) ũ 3224 (w), 2220 (m), 1666 (s), 1494 (m), 1352 (m), 1195 (s), 1034 (m), 980 (w), 758 (s), 625 (m).

*1-Tert-butyl-4-(4-chlorophenyl)-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**20i**)*



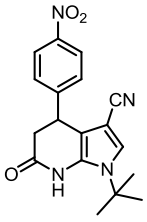
The product was obtained as a white solid, yield 60 %; mp 218-220 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (1H, br. s., NH), 7.20 (2H, d, ^{1}J= 8 Hz, Ar-H), 7.08 (2H, d, ^{1}J= 8 Hz, Ar-H), 6.93 (1H, s, Ar-H), 4.08 - 4.20 (1H, m, CH), 2.74 (1H,dd, ^{1}J= 16 ^{2}J= 5 Hz, CH_2), 1.53 (9H, s,$(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 170.2 (C-), 140.2 (C-), 133.0 (C-), 129.0 (CH-), 128.6 (C-), 128.3 (CH-), 121.5 (CH-), 115.5 (C-), 107.6 (C-), 89.1 (C-), 57.4 (C-), 39.5(CH_2-), 35.1 (CH-), 29.7 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 327 (M+, 63), 271 (100), 228 (57); HRMS (ESI): calcd for $C_{18}H_{19}ClN_3O$ (M + 1) 328.12112, found 328.1207; IR (ATR, cm^{-1}) ũ 3146 (w), 2214 (m), 1668 (s), 1491 (s), 1359 (m), 1199 (m), 1189 (m), 1146 (m), 1095 (m), 985 (m), 821 (s), 775 (s), 637 (m). calcd for $C_{18}H_{18}ClN_3O$: C: 65.95, H: 5.53, N: 12.82, found: C:65.57, H: 5.67, N: 12.55

1-Tert-butyl-4-(2-nitrophenyl)-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile ***(20j)***



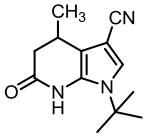
The product was obtained as a yellow solid, yield 40 %; mp 268-269 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (1H, br. s., NH), 7.86 - 7.95 (1H, m, Ar-H), 7.44 - 7.52 (1H, m, Ar-H), 7.32 - 7.41 (1H, m, Ar-H), 7.10 - 7.18 (1H, m, Ar-H),6.96 (1H, s, Ar-H), 4.85 (1H, t, ^{1}J = 7 Hz, CH), 3.10 (1H, dd, ^{1}J = 16.2 ^{2}J = 7.4 Hz, CH_2), 2.79 (1H, dd, ^{1}J = 16.3 ^{2}J = 6.5 Hz, CH_2), 1.55 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 169.7 (C-), 149.0 (C-), 136.1 (C-), 133.6 (CH-), 129.8 (C-), 129.5 (CH-), 128.5 (CH-), 125.3 (CH-), 121.9 (CH-), 114.8 (C-), 106.0 (C-), 89.1(C-), 57.6 (C-), 39.6 (CH_2-), 31.5 (CH-), 29.8 $(CH_3)_3$. MS (GC, 70 eV) 338 (M+, 20), 320 (30), 264 (82), 248 (100), 195 (65); HRMS (ESI) calcd for $C_{18}H_{19}N_4O_3$ (M + 1) 339.14517, found 339.14535;IR (ATR, cm^{-1}) ũ 3151 (w), 2220 (m), 1665 (s), 1522 (m), 1494 (m), 1344 (m), 1195 (s), 786 (s), 627 (m). calcd for $C_{18}H_{18}N_4O_3$: C: 63.89, H: 5.36, N: 16.56, found: C:63.73, H: 5.50, N: 16.57

1-Tert-butyl-4-(4-nitrophenyl)-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile ***(20k)***



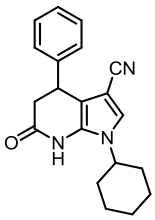
The product was obtained as a yellow solid, yield 74 %; mp 219-221 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (1H, br. s., NH), 8.12 (2H, d, ^{1}J = 8.7 Hz, Ar-H), 7.34 (2H, d, ^{1}J = 8.7 Hz, Ar-H), 6.96 (1H, s, Ar-H), 4.17 - 4.40 (1H, m, CH), 3.01 (1H,dd, ^{1}J = 7.4 ^{2}J = 16.1 Hz, CH_2), 2.79 (1H, dd, ^{1}J = 5.1 ^{2}J = 16.1 Hz, CH_2), 1.55 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 169.0 (C-), 148.9 (C-), 147.2 (C-), 128.8 (C-), 128.0 (CH), 124.3 (CH-), 121.7 (CH-), 115.2 (C-), 106.5 (C-), 89.3 (C-), 57.6 (C-), 39.1 (CH_2-), 35.7 (CH-), 29.9 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 338 (M+, 35), 282 (100), 57 (42); HRMS (ESI): calcd for $C_{18}H_{19}N_4O_3$ (M + 1) 339.14517 found 339.14517; IR (ATR, cm^{-1}) ũ 3219 (w), 3145 (w), 2217 (m), 1666 (m), 1512 (m), 1493 (m), 1341 (s), 1190 (m), 1145 (m), 983 (w), 846 (m), 773 (m), 634 (m).calcd for $C_{18}H_{18}N_4O_3$: C: 63.89, H: 5.36, N: 16.56, found: C:63.64, H: 5.54, N: 16.53

*1-Tert-butyl-4-methyl-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**20l**)*



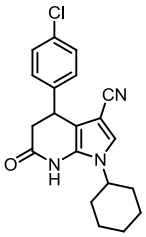
The product was obtained as a white solid, yield 78 %; mp 233-235 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.88 (1H, s, NH), 7.35 (1H, s, Ar-H), 2.91 - 3.06 (1H, m, CH), 2.61 (1H, dd, ^{1}J = 15.5 ^{2}J = 6.1 Hz, CH_2), 2.26 (1H, dd, ^{1}J = 15.7 ^{2}J = 7.4 Hz, CH_2), 1.53 (9H, s,$(CH_3)_3$), 1.20 (3H, d, ^{1}J = 7 Hz, CH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 170.1 (C-), 128.7 (C-), 121.9 (CH-), 116.7 (C-), 109.1 (C-), 86.4 (C-), 57.2 (C-), 39.7 (CH_2) 29.2 $(CH_3)_3$, 24.6 (CH), 19.5 (CH_3). MS (GC, 70 eV) m/z (%) 231 (M+, 33), 175 (49), 160 (100); HRMS (ESI): calcd for $C_{13}H_{18}N_3O$ (M + 1) 232.14444 found 232.14475; IR (ATR, cm^{-1}) ũ 3153 (w), 2961 (w), 2215 (m), 1668 (s), 1525 (m), 1495 (m), 1359 (s), 1196 (s), 1082 (wm), 950 (w), 811 (w), 774 (m), 624 (s).

*1-Cyclohexyl-6-oxo-4-phenyl-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**20m**)*



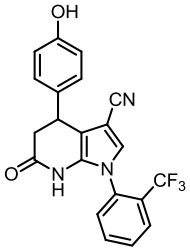
The product was obtained as a white solid, yield 75 %; mp 281-283 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.63 (1H, br. s., NH), 7.45 (1H, s, Ar-H), 7.04 - 7.40 (6H, m, Ar-H), 4.21 (1H, dd, J = 7 J = 4 Hz, CH), 3.97 - 4.17 (1H, m, CH), 3.04 (1H, dd, ^{1}J =15.8 ^{2}J = 7.6 Hz, CH_2), 2.59 (1H, dd, ^{1}J =15.8 ^{2}J = 3.9 Hz, CH_2), 1.09 - 2.00 (10H, m, $(CH_2)_5$). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 169.3 (C-), 143.1 (C-), 129.7 (C-), 128.6 (CH-), 126.7 (CH-), 126.6 (CH-), 121.1 (CH-), 116.1 (C-), 103.5 (C-), 88.5 (C-), 53.9 (CH-), 34.9 (CH-), 33.0 (CH_2-), 32.8 (CH_2-), 24.9 (CH_2-), 24.5 (CH_2-). MS (GC, 70 eV) m/z (%) 319 (M+, 100), 237 (48), 194 (52); HR (EI): calcd for $C_{20}H_{21}N_3O$ (M + 1) 319.16791, found 319.16721; IR (ATR, cm^{-1}) ũ 3136 (w), 2937 (w), 2220 (s), 1665 (s), 1539 (w), 1357 (m), 1184 (m), 768 (m), 698 (s). calcd for $C_{20}H_{21}N_3O$: C: 75.21, H: 6.63, N: 13.16, found: C: 74.70, H: 6.64, N: 13.08.

*4-(4-Chlorophenyl)-1-cyclohexyl-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**20n**)*



The product was obtained as a white solid, yield 77 %; mp 278-280 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.66 (1H, s, NH), 7.45 (1H, s, Ar-H), 7.40 (2H, d, J = 8.5 Hz, Ar-H), 7.19 (2H, d, J = 8.5Hz, Ar-H), 4.24 (1H, dd, J = 7 and 5 Hz, CH), 4.03 – 4.17 (1H, m, CH), 3.00 (1H, dd, ^{1}J =15.8 ^{2}J = 7.4 Hz, CH_2), 2.59 (1H, dd, ^{1}J =16.1 ^{2}J = 4.9 Hz, CH_2), 1.12 - 1.95 (10H, m, $(CH_2)_5$). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 169.0 (C-), 141.9 (C-), 131.3 (C-), 129.8 (C-), 128.7 (CH-), 128.6 (CH-), 121.2 (CH-), 115.9 (C-), 102.9 (C-), 88.4 (C-), 53.9 (CH-), 34.4 (CH-), 33.0 (CH_2-), 32.8 (CH_2-), 24.9 (CH_2-), 24.5 (CH_2-). MS (GC, 70 eV) m/z (%) 353 (M+, 100), 271 (58), 228 (38); HR (EI): calcd for $C_{20}H_{20}ClN_3O$ (M + 1) 353.12894, found 353.12880; IR (ATR, cm^{-1}) ῡ 3113 (w), 2939 (w), 2217 (s), 1664 (s), 1597 (m), 1503 (m), 1490 (m), 1357 (m), 1174 (m), 1088 (m), 1014 (m), 832 (m), 737 (m), 603 (m), 551 (m). calcd for $C_{20}H_{20}ClN_3O$: C: 67.89, H: 5.70, N: 11.88, found: C: 67.33, H: 5.80, N: 11.77.

*4-(4-Hydroxyphenyl)-6-oxo-1-(2-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**20o**)*

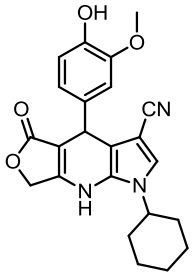


The product was obtained as a white solid, yield 57 %; mp 250 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.38 (1H, s, NH), 9.34 (1H, s, Ar-H), 7.78 - 7.91 (4H, m, Ar-H), 7.69 (1H, s, Ar-H), 7.00 - 7.05 (2H, m, Ar-H), 6.71 - 6.75 (2H, m, Ar-H), 4.20 (1H, dd, ^{1}J = 4.3 ^{2}J = 7.0 Hz, CH), 3.04 (1H, dd, ^{1}J = 15.5 ^{2}J = 7.2 Hz, CH_2), 2.61 (1H, dd, ^{1}J = 15.6 ^{2}J = 4.3 Hz, CH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 169.6 (C-), 156.2 (C-), 136.6 (C-), 132.7 (C-), 130.9 (CH-), 130.4 (C-), 129.6 - 130.5 (CF_3, q, J_{CF3} = 32.5 Hz), 129.2 (CH-), 127.8 (CH-), 125.5 (C-), 125.2 (CH-), 124.9 – 125.0 (CH, q, J_{C-F} = 3.3 Hz), 121.9 - 122.1 (CH, q, J_{C-F} = 3.3 Hz), 121.8 (C-), 115.4 (CH-), 106.3 (C-), 91.0 (C-), 40.4 (CH_2-), 34.3 (CH-). ^{19}F NMR (300 MHz, DMSO-d_6) -60-99 Hz.MS (GC, 70 eV) m/z (%) 397 (M+, 100), 354 (87 ;HR (EI): calcd for $C_{21}H_{14}F_3N_3O_2$ (M + 1) 397.10326, found 397.10309 IR (ATR, cm^{-1}) ῡ 3384 (w), 2229 (s), 1671 (s), 1528 (m), 1508 (s), 1464 (s), 1328 (m), 1314 (m), 1262 (m), 1198 (m), 1163 (m), 1112 (s), 1100 (s), 1073 (m), 968 (m), 905 (m), 837 (s), 798 (s), 750 (s), 694 (s), 656 (m), 563 (m).

A.2.6 General procedure for the synthesis of compounds 21e and 21f

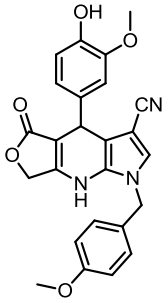
A mixture of tetronic acid (1 equiv.), the corresponding aldehyde (1 equiv.) and 5-amino-1-R-pyrrole-3-carbonitrile (1 equiv.) was refluxed in ethanol for 3 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent: n-heptane/ethylacetate).

*1-Cyclohexyl-4-(4-hydroxyphenyl)-5-oxo-4,5,7,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,2-e]pyridine-3-carbonitrile (**21e**)*



The product was obtained as a white solid, yield 74 %; mp 308-310 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.23 (1H, s, OH), 9.20 (1H, s, NH), 7.42 (1H, s, Ar-H), 6.99 (2H, d, J = 8.5 Hz, Ar-H), 6.66 (2H, d, J = 8.5 Hz, Ar-H), 4.84 – 4.92 (2H, dd, J = 15.8 Hz, CH_2), 4.85 (1H, s, CH), 3.86 - 4.07 (1H, m, CH), 1.79 - 2.02 (4H, m, CH_2), 1.51 - 1.74 (3H, m, CH_2), 1.40 (2H, s, CH_2), 1.13 - 1.28 (1H, m, CH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 171.7 (C-), 157.2 (C-), 155.7 (C-), 135.5 (C-), 128.6 (CH-), 122.0 (CH-), 115.9 (C-), 114.7 (CH-), 104.1 (C-), 97.7 (C-), 89.1 (C-), 64.8 (CH_2), 54.4 (CH-), 35.4 (CH-), 32.7 (C-), 32.6 (CH_2), 25.0 (CH_2), 24.5 (CH_2). MS (GC, 70 eV) m/z (%) 375 (M+, 69), 332 (39), 291 (100); HRMS (ESI): calcd for $C_{22}H_{20}N_3O_3$ (M + 1) 374.14992, found 374.14906; IR (ATR, cm^{-1}) ῦ 3244 (w), 2933 (w), 2235 (s), 1716 (m), 1633 (m), 1547 (s), 1512 (s), 1451 (m), 1332 (m), 1220 (m), 1025 (s), 848 (m), 592 (m), 556 (m). calcd for $C_{22}H_{21}N_3O_3$: C: 70.38, H: 5.64, N: 11.19, found: C: 69.79, H: 5.80, N: 11.08.

*4-(4-Hydroxy-3-methoxyphenyl)-1-(4-methoxybenzyl)-5-oxo-4,5,7,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,2-e]pyridine-3-carbonitrile (**21f**)*

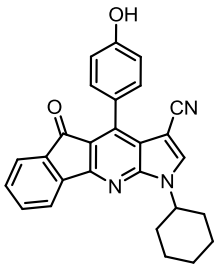


The product was obtained as a white solid, yield 76 %, mp 215-217 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.35 (1H, s, OH), 8.77 (1H, s, NH), 7.40 (1H, s, Ar-H), 7.18 (2H, d, *J* = 8.3 Hz, Ar-H), 6.96 (2H, d, *J* = 8.5 Hz, Ar-H), 6.82 (1H, s, Ar-H), 6.68 (1H, d, *J* = 8.1 Hz, Ar-H), 6.53 (1H, d, *J* = 8.1 Hz, Ar-H), 5.10 (2H, s, CH_2), 4.76 - 5.02 (3H, m, CH, CH_2), 3.75 (6H, s, OCH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 171.8 (C-), 158.9 (C-), 157.5 (C-), 147.0 (C-), 144.9 (C-), 136.1 (C-), 129.1 (C-), 128.5 (C-), 128.4 (CH-), 125.4 (CH-), 119.7 (CH-),115.8 (C-), 115.2 (CH-), 114.1 (CH-), 112.2 (CH-), 104.6 (C-), 97.5 (C-), 89.4 (C-), 64.9 (CH_2-), 55.3 (OCH_3-), 55.1 (OCH_3-), 48.3 (CH_2-), 35.8 (CH-). MS (GC, 70 eV) m/z (%) 443 (M+, 15), 121 (100); HRMS (ESI): calcd for $C_{25}H_{20}N_3O_5$ (M + 1) 442.13892, found 442.13975; IR (ATR, cm^{-1}) ῦ 3232 (w), 2218 (m), 1713 (s), 1613 (m), 1548 (s), 1510 (s), 1343 (m), 1248 (s), 1023 (s), 813 (w), 680 (m), 576 (m).

A.2.7 General procedure for the synthesis of compounds 23g and 23h

A mixture of 1,3-indanedione (1 equiv.), the corresponding aldehyde (1 equiv.) and 5-amino-1-R-pyrrole-3-carbonitrile (1 equiv.) was refluxed in ethanol for 3 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent: n-heptane/ethylacetate)

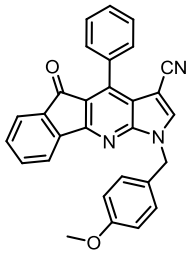
*1-Cyclohexyl-4-(4-hydroxyphenyl)-5-oxo-1,5-dihydroindeno[2,1-e]pyrrolo[2,3-b]pyridine-3-carbonitrile (**23g**)*



The product was obtained as a yellow solid, yield 45 %, mp 242 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.80 (1H, br. s., OH), 8.60 (1H, s, Ar-H), 7.85 (1H, d, *J* = 7.4 Hz, Ar-H), 7.66 (1H, t, *J* = 7.2 Hz, Ar-H), 7.44 - 7.56 (2H, m, Ar-H), 7.39 (2H, d, *J* = 8.3 Hz, Ar-H), 6.90 (2H, d, *J* = 8.3 Hz, Ar-H), 4.85 (1H, m, CH), 2.03 - 2.10 (2H, m, CH_2), 1.76 - 1.96 (5H, m, CH_2), 1.48 - 1.61 (2H, m, CH_2), 1.25 - 1.39(1H, m, CH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 206.5 (C-), 189.5 (C-), 160.8 (C-), 158.5 (C-), 148.0 (C-), 143.4 (C-), 141.9 (C-), 136.9 (CH-), 135.8

(C-), 134.9 (CH-), 131.3 (CH-), 130.9 (CH-), 123.0 (CH-), 121.8 (C-), 120.3 (CH-), 119.4 (C-), 117.6 (C-), 114.3 (CH-), 86.1 (C-), 54.2 (CH-), 32.2 (CH_2-), 25.1 (CH_2-), 24.7 (CH_2-). MS (GC, 70 eV) m/z (%) 419 (M+, 39), 337 (100); HR (EI): calcd for $C_{27}H_{21}N_3O_2$ (M + 1) 419.16283, found 419.16275; IR (ATR, cm^{-1}) ũ 3375 (w), 2932 (w), 2222 (s), 1682 (s), 1555 (m), 1514 (s), 1398 (w), 1225 (m), 1172 (m), 768 (s), 730 (s), 607 (m), 548 (m). calcd for $C_{27}H_{21}N_3O_2$: C: 77.31, H: 5.05, N: 10.02, found: C: 76.94, H: 5.14, N: 10.05.

*1-(4-Methoxybenzyl)-5-oxo-4-phenyl-1,5-dihydroindeno[1,2-b]pyrrolo[3,2-e]pyridine-3-carbonitrile (**23h**)*

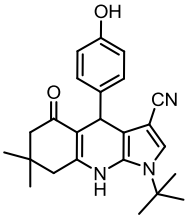


The product was obtained as an orange solid, yield 45 %, mp 252 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.63 (1H, s, Ar-H), 7.96 (1H, d, *J* = 7.2 Hz, Ar-H), 7.74 (1H, m, Ar-H), 7.46 - 7.62 (9H, m, Ar-H), 6.97 (2H, d, *J* = 8.5 Hz, Ar-H), 5.55 (2H, s, CH_2), 3.75 (3H, s, CH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 189.5 (C-), 161.1 (C-), 159.1 (C-), 148.4 (C-), 142.9 (C-), 142.0 (C-), 141.6 (C-), 141.3 (C-), 139.3 (CH-), 135.8 (C-), 135.4 (C-),132.7 (CH-), 131.5 (C-), 131.3 (CH-), 129.7 (CH-), 129.4 (CH-), 129.2 (CH-), 128.4 (C-), 127.6 (CH-), 123.3 (CH-), 120.6 (CH-), 114.1 (CH-), 86.0 (C-), 55.1(OCH_3-), 48.1 (CH_2-); MS (GC, 70 eV) m/z (%) 441 (M+, 76), 320 (18), 121 (100); ; HR (EI): calcd for $C_{29}H_{19}N_3O_2$ (M + 1) 441.14718, found 441.14704; IR (ATR, cm^{-1}) ũ 3109 (w), 2222 (m), 1704 (s), 1562 (s), 1512 (s), 1412 (m), 1331 (m), 1298 (s), 1249 (s), 1175 (s), 1018 (m), 821 (w), 754 (m), 728 (m), 698 (m), 536 (m).

A.2.8 General procedure for the synthesis of compounds 24a-i

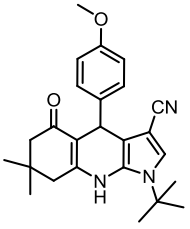
A mixture of dimedone (1 equiv.), the corresponding aldehyde (1 equiv.) and 5-amino-1-R-pyrrole-3-carbonitrile (1 equiv.) was refluxed in ethanol with proline as catalyst or in acetic acid for 6 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent: n-heptane/ethylacetate).

*1-Tert-butyl-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**24a**)*



The product was isolated as a white solid, yield 69 %, mp 247-248 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.06 (1H, s, OH), 8.56 (1H, s, NH), 7.29 (1H, s, Ar-H), 6.93 (2H, d, ^{1}J = 8.5 Hz, Ar-H), 6.59 (2H, d, ^{1}J = 8.5 Hz, Ar-H), 4.92 (1H, s, CH), 2.69 (1H,d, ^{1}J = 17 Hz, CH_2), 2.56 (1H, s, CH_2), 2.18 (1H, d, ^{1}J=16.1 Hz, CH_2), 1.98 (1H, d, ^{1}J = 16.1 Hz, CH_2), 1.58 (9H, s, $(CH_3)_3$), 1.04 (3H, s, CH_3), 0.94 (3H, s, CH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.9 (C-), 155.2 (C-), 150.4 (C-), 138.3 (C-), 127.9 (CH-), 127.2 (C-), 122.4 (CH) 116.2 (C-), 114.5 (CH-), 108.3 (C-), 107.9 (C-), 87.1 (C-), 56.9 (C-), 50.3 (CH_2-), 40.6 (CH_2-), 35.2 (CH-), 31.8 (C-), 29.3 (CH_3), 29.1 $(CH_3)_3$, 26.4 (CH_3). MS (GC, 70 eV) m/z (%) 387 (M+, 45), 331 (100) 275 (38); HRMS (ESI): calcd for $C_{24}H_{28}N_3O_2$(M + 1) 390.2176 found 390.21842; IR (ATR, cm^{-1}) ῡ 3341 (w), 3164 (w), 2956 (w), 2217 (w), 1608 (m), 1524 (s), 1494 (s), 1422 (m), 1343 (m), 1268 (m), 1248 (m), 1226 (m), 1191 (s), 1168 (m), 1153 (m), 766 (m), 596 (m), 546 (m). calcd for $C_{24}H_{27}N_3O_2$: C: 74.01, H: 6.99, N: 10.79, found: C:73.80, H: 7.16, N: 10.79

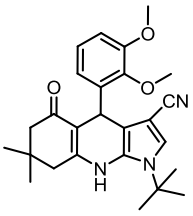
*1-Tert-butyl-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**24b**)*



The product was isolated as a white solid, yield 58 %, mp 229-230 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.60 (1H, s, NH), 7.30 (1H, s, Ar-H), 7.04 (2H, d, J = 8.7 Hz, Ar-H), 6.78 (2H, d, J = 8.5 Hz, Ar-H), 4.96 (1H, s, CH), 3.69 (3H, s, OCH_3), 2.70(1H, d, J = 17 Hz, CH_2), 2.57 (1H, s, CH_2), 2.19 (1H, d, J = 16.1 Hz, CH_2), 1.98 (1H, d, J = 16.2 Hz, CH_2), 1.04 (3H, s, CH_3), 0.94 (3H, s, CH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.9 (C-), 157.2 (C-), 150.5 (C-), 139.9 (C-), 128.0 (CH-), 127.3 (C-), 122.5 (CH-), 116.2 (C-), 113.2 (CH-), 108.0 (C-), 107.7 (C-), 87.1 (C-),56.9 (C-), 54.8 (OCH_3), 50.2 (CH_2-), 40.6 (CH_2-), 35.4 (CH-), 31.8 (C-), 29.1 $(CH_3)_3$, 26.4 (CH_3). MS (GC, 70 eV) m/z (%) 403 (M+, 40), 388 (100), 347 (73); HRMS (ESI): calcd for $C_{25}H_{30}N_3O_2$ (M + 1) 404.23325 found 404.233; IR (ATR, cm^{-1}) ῡ 3306 (w), 2954 (w), 2221 (w), 1595 (m), 1524 (s), 1498 (s), 1431 (m), 1392 (m), 1333 (m), 1249 (m), 1226 (m), 1188 (m), 1117 (m), 1028 (m), 847

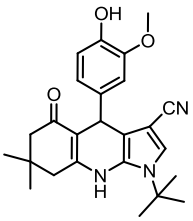
(w), 802 (w), 543 (w). calcd for $C_{25}H_{29}N_3O$: C: 74.41, H: 7.24, N: 10.41, found: C:74.31, H: 7.51, N: 10.36. The aromatized structure was independently confirmed by X-Ray analysis.

*1-Tert-butyl-4-(2,3-dimethoxyphenyl)-7,7-dimethyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**24c**)*



The product was isolated as a white solid, yield 97 %, mp 201-202 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.52 (1H, s, NH), 7.24 (1H, s, Ar-H), 6.82 - 6.90 (1H, m, Ar-H), 6.77 (1H, dd, ^1J = 1.7 ^2J = 8.3 Hz, Ar-H), 6.69 (1H, dd, ^1J=1.5 ^2J = 7.6 Hz, Ar-H), 5.29 (1H, s, CH),3.75 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 2.68 (1H, d, ^1J = 17 Hz, CH_2), 2.56 (1H, d, ^1J = 16.1 Hz, CH_2), 2.16 (1H, d, ^1J = 16.1 Hz, CH_2), 1.94 (1H, d, ^1J = 16.1 Hz, CH_2), 1.58 (9H,s, $(CH_3)_3$), 1.04 (3H, s, CH_3), 0.95 (3H, s, CH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.6 (C-), 152.2 (C-), 151.2 (C-), 145.9 (C-), 140.4 (C-), 127.7 (C-), 122.7 (CH-), 122.4 (CH-), 121.6 (CH-), 115.9 (C-), 110.4 (CH-), 107.6 (C-),107.3 (C-), 87.4 (C-), 59.3 (OCH_3-), 56.9 (C-), 55.4 (OCH_3-), 50.4 (CH_2-), 40.7 (CH_2-), 31.8 (C-), 31.5 (CH-), 29.2 $(CH_3)_3$, 26.5 (CH_3). MS (GC, 70 eV) m/z (%) 433 (M+, 8), 402 (100), 346 (98); HRMS (ESI): calcd for $C_{26}H_{32}N_3O_3$ (M + 1) 434.24382 found 434.24428; IR (ATR, cm^{-1}) ῦ 3371 (w), 3164 (w), 2215 (m), 1622 (s), 1525 (s), 1503 (s), 1470 (m), 1426 (m), 1332 (m), 1260 (m), 1245 (m), 1198 (m), 1070 (s), 1002 (s), 928 (w), 820 (w), 750 (s), 582 (m). calcd for $C_{26}H_{31}N_3O_3$: C: 72.03, H: 7.21, N: 9.69, found: C:71.85, H: 7.41, N: 9.72

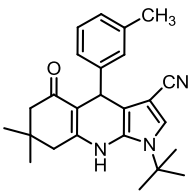
*1-Tert-butyl-4-(4-hydroxy-3-methoxyphenyl)-7,7-dimethyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**24d**)*



The product was isolated as a white solid, yield 67 %, mp 214-215 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.63 (1H, s, OH), 8.57 (1H, s, NH), 7.30 (1H, s, Ar-H), 6.74 - 6.80 (1H, m, Ar-H), 6.61 (1H, d, ^1J = 8.1 Hz, Ar-H), 6.45 - 6.52 (1H, m, Ar-H),4.93 (1H, s, CH), 3.71 (3H, s, OCH_3), 2.66 - 2.78 (1H, m, CH_2), 2.58 (1H, s, CH_2), 2.21 (1H, d, ^1J=16.1 Hz, CH_2), 2.01 (1H, d, ^1J = 16.1 Hz, CH_2), 1.57 (9H, s,$(CH_3)_3$), 1.06 (3H, s, CH_3), 1.00 (3H, s, CH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 194.0 (C-), 150.8 (C-), 146.8 (C-), 144.4 (C-), 139.1 (C-), 127.1 (C-), 122.4 (CH-), 118.9 (CH-), 116.4 (C-), 115.0 (CH-),

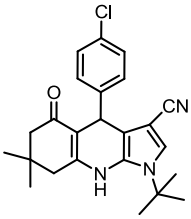
111.5 (CH-), 108.3 (C-),107.5 (C-), 87.1 (C-), 56.9 (C-), 55.3 (OCH_3-), 50.3 (CH_2-), 40.6 (CH_2-), 35.6 (CH-), 31.7 (C-), 29.4 (CH_3) 29.1 $(CH_3)_3$, 26.4 (CH_3). MS (GC, 70 eV) m/z (%) 417 (M+, 100), 361 (81); HRMS (ESI): calcd for $C_{25}H_{28}N_3O_3$ (M + 1) 428.21252 found 428.21258; IR (ATR, cm^{-1}) ũ 3536 (w), 3290 (w), 2220 (w), 1597 (s), 1575 (m), 1526 (m), 1500 (s), 1385 (m), 1332 (m), 1265 (m), 1232 (m), 1189 (s), 1027 (m), 753 (m), 598 (m), 575 (m). calcd for $C_{25}H_{27}N_3O_3$: C: 71.57, H: 6.97, N: 10.02, found: C:71.52, H: 7.16, N: 10.09. The aromatized structure was independently confirmed by X-Ray analysis.

*1-Tert-butyl-7,7-dimethyl-5-oxo-4-m-tolyl-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**24e**)*



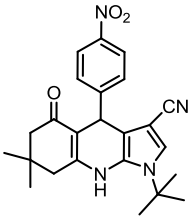
The product was isolated as a yellow solid, yield 64 %, mp 222-223 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.61 (1H, s, NH), 7.30 (1H, s, Ar-H), 7.06 - 7.14 (1H, m, Ar-H), 6.88 - 7.00 (3H, m, Ar-H), 4.98 (1H, s, CH), 2.73 (1H, d, ^1J = 17 Hz, CH_2), 2.59(1H, br. s., M08), 2.23 (3H, s, OCH_3), 2.14 (1H, d, ^1J = 20.21 Hz, CH_2), 2.00 (1H, d, ^1J = 16.1 Hz, CH_2), 1.58 (9H, s, $(CH_3)_3$), 1.05 (3H, s, CH_3), 0.97 (3H, s, CH_3).^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.9 (C-), 151.0 (C-), 147.6 (C-), 136.6 (C-), 127.8 (CH-), 127.3 (C-), 126.3 (CH-), 124.3 (CH-), 122.6 (CH-), 116.2 (C-), 107.8 (C-), 107.4 (C-),87.2 (C-), 57.0 (C-), 50.2 (CH_2-), 40.6 (CH_2-), 36.3 (CH-), 31.8 (C-), 29.3 (CH_3-), 29.2 $(CH_3)_3$, 26.4 (CH_3-), 21.2 (CH_3).MS (GC, 70 eV) m/z (%) 387 (M+, 38), 331 (100), 275 (40); HRMS (ESI): calcd for $C_{25}H_{28}N_3O$ (M + 1) 386.22269 found 386.22384; IR (ATR, cm^{-1}) ũ 3268 (w), 2217 (w), 1599 (m), 1576 (m), 1526 (s), 1504 (s),1385 (m), 1336 (m), 1248 (m), 1188 (s), 1151 (w), 757 (w), 594 (m). calcd for $C_{25}H_{29}N_3O$: C:77.48, H: 7.54, N: 10.84, found: C:77.37, H: 7.66, N: 10.83

*1-Tert-butyl-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**24f**)*



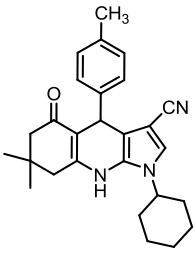
The product was isolated as a white solid, yield 45 %, mp 239-240 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.69 (1H, br. s., NH), 7.24 - 7.37 (3H, m, Ar-H), 7.16 (2H, d, ^{1}J = 7.9 Hz, Ar-H), 5.04 (1H, s, CH), 2.72 (1H, d, ^{1}J = 17 Hz, CH_2), 2.55 (1H, d, ^{1}J = 19Hz, CH_2), 2.20 (1H, d, ^{1}J = 16.1 Hz, CH_2), 2.00 (1H, d, ^{1}J = 16.1 Hz, CH_2), 1.60 (9H, s, $(CH_3)_3$), 1.05 (3H, br. s., CH_3), 0.94 (3H, br. s., CH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.9 (C-), 150.9 (C-), 146.4 (C-), 130.1 (C-), 129.0 (CH-), 127.8 (CH-), 127.4 (C-), 122.8 (CH-), 116.0 (C-), 107.1 (C-), 107.0 (C-), 87.1 (C-),57.1 (C-), 50.1 (CH_2), 40.6 (CH_2-), 36.0 (CH), 31.8 (C-), 29.1 $(CH_3)_3$, 26.4 (CH_3-)MS (GC, 70 eV) m/z (%) 405 (M+, 33), 349 (100), 258 (49); HRMS (ESI): calcd for $C_{24}H_{25}ClN_3O$ (M + 1) 406.16807 found 406.16796; IR (ATR, cm^{-1}) ῡ 3330 (w), 2216 (m), 1638 (m), 1617 (s), 1525 (s), 1503 (s), 1380 (m), 1334 (m), 1192 (s), 1013 (m), 850 (m), 770 (m), 595 (m), 543 (m).

*1-Tert-butyl-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**24g**)*



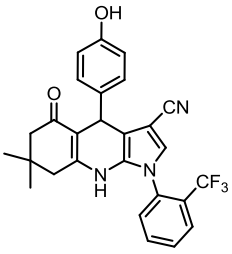
The product was isolated as a yellow solid, yield 46 %, mp 230-231 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.78 (4H, s, NH), 8.13 (2H, d, J = 8.7 Hz, Ar-H), 7.40 (2H, d, J = 8.7 Hz, Ar-H), 7.36 (1H, s, Ar-H), 5.17 (1H, s, CH), 2.73 (1H, d, J = 17 Hz, CH_2), 2.59 (1H, d, J = 17 Hz, CH_2), 2.20 (1H, d, J = 16 Hz, CH_2), 1.99 (1H, d, J = 16 Hz, CH_2), 1.60 (9H, s, $(CH_3)_3$), 1.04 (3H, s, OCH_3), 0.93 (3H, s, OCH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.9 (C-), 154.7 (C-), 151.3 (C-), 145.6 (C-), 128.5 (CH-), 127.5 (C-), 123.3 (CH-), 123.2 (CH-), 115.8 (C-), 106.5 (C-), 106.0 (C-), 87.2 (C-),57.2 (C-), 50.0 (CH_2-), 40.6 (CH_2-), 36.9 (CH-), 31.8 (C-), 29.1 $(CH_3)_3$, 26.5 (CH_3).MS (GC, 70 eV) m/z (%) 416 (M+, 22), 360 (100), 304 (33); HRMS (ESI): calcd for $C_{24}H_{27}N_4O_3$ (M + 1) 419.20777 found 419.20858; IR (ATR, cm^{-1}) ῡ 3442 (w), 2974 (w), 2214 (m), 1637 (m), 1620 (m), 1526 (m), 1502 (s), 1340 (s), 1332 (s), 1191 (m), 829 (m), 627 (m), 616 (m), 544 (m).calcd for $C_{24}H_{26}N_4O_3$: C: 68.88, H: 6.26, N: 13.39, found: C:66.92, H: 6.26, N: 12.67

*1-Cyclohexyl-7,7-dimethyl-5-oxo-4-p-tolyl-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**24h**)*



The product was isolated as a white solid, yield 67 %, mp 247-249 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.43 (1H, s, NH), 7.34 (1H, s, Ar-H), 6.98 - 7.06 (4H, m, Ar-H), 4.99 (1H, s, CH), 4.07 - 4.20 (1H, m, CH), 2.56 (1H, d, J = 16.6 Hz, CH_2), 2.48 (1H, d, J = 16.8 Hz, CH_2), 2.22 (3H, s, CH_3), 2.18 (1H, d, J = 16.1 Hz, CH_2), 2.00 (1H, d, J = 16.2 Hz, CH_2), 1.79 - 1.93 (4H, m, CH_2), 1.35 - 1.72 (5H, m, CH_2), 1.14 - 1.28 (1H, m, CH_2), 1.05 (3H, s, CH_3), 0.98 (3H, s, CH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.5 (C-), 150.4 (C-), 145.0 (C-), 134.4 (C-), 128.3 (CH-), 127.3 (C-), 127.0 (CH-), 121.2 (CH-), 116.2 (C-), 107.5 (C-), 105.0 (C-), 88.5 (C-), 53.8 (CH-), 50.3 (CH_2-), 36.2 (CH-), 33.0 (CH_2-), 32.7 (CH_2-), 31.8 (C-), 29.0 (CH_3-), 26.6 (CH_3-), 25.0 (CH_2-), 24.5 (CH_2-), 20.5 (CH_3-). MS (GC, 70 eV) m/z (%) 413 (M+, 33), 331 (100), 316 (29); HRMS (ESI): calcd for $C_{27}H_{32}N_3O$ (M + 1) 414.254, found 414.2542; IR (ATR, cm^{-1}) ῡ 3217 (w), 2935 (w), 2217 (s), 1602 (m), 1585 (m), 1522 (s), 1505 (s), 1439 (m), 1360 (m), 1239 (m), 1151 (m), 538 (m). calcd for $C_{27}H_{31}N_3O$: C: 78.42, H: 7.56, N: 10.16, found: C: 77.52, H: 7.57, N: 10.05.

*4-(4-Hydroxyphenyl)-7,7-dimethyl-5-oxo-1-(2-(trifluoromethyl)phenyl)-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**24i**)*



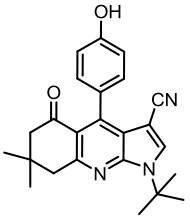
The product was isolated as a white solid, yield 63 %, mp 260-262ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.25 (1H, s, OH), 9.11 (1H, s, NH), 7.87 - 7.94 (2H, m, Ar-H), 7.80 - 7.86 (2H, m, Ar-H), 7.57 (1H, s, Ar-H), 7.03 (2H, d, J = 8.5 Hz, Ar-H), 6.63 (2H, d, J = 8.5 Hz, Ar-H), 5.01 (1H, s, CH), 2.44 (2H, s, CH_2), 2.11 - 2.21 (1H, m, CH_2), 1.97 - 2.05 (1H, m, CH_2), 1.01 (3H, s, CH_3), 0.94 (3H, s, CH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.9 (C-), 155.3 (C-), 150.6 (C-), 138.1 (C-), 136.7 (C-), 131.0 (CH-), 129.8 -130.6 (CF_3,q, J_{CF3} = 32.5 Hz),129.7 (CH-), 128.3 (CH-), 128.2 (C-),125.6 (CH-), 125.1 -125.4 (CH, q, J_{C-F} = 3.3 Hz), 122.4 -122.6 (CH, q, J_{C-F} = 3.8 Hz-), 121.8 (C-), 115.4 (C-), 114.6 (CH-), 108.2 (C-), 106.6 (C-), 91.1 (C-), 50.4 (CH_2-), 40.5 (CH_2) 35.7 (CH-), 31.8 (C-), 29.0 (CH_3), 26.6 (CH_3-). ^{19}F NMR (300 MHz, DMSO-d_6) δ -60-99. MS (GC, 70 eV) m/z (%) 383 (M+, 99), 327 (100), 230 (42); HRMS (ESI): calcd for

$C_{27}H_{21}F_3N_3O_2$ (M + 1) 498.15804, found 498.1579; IR (ATR, cm^{-1}) ũ 3258 (w), 2227 (m), 1620 (m), 1526 (s), 1510 (s), 1505 (s), 1433 (m), 1367 (m), 1326 (m), 1221 (m), 1120 (s), 692 (m). calcd for $C_{27}H_{22}F_3N_3O_2$: C: 67.92, H: 4.64, N: 8.80, found: C: 67.82, H: 4.53, N: 8.55.

A.2.9 General procedure for the synthesis of compounds 25a-i

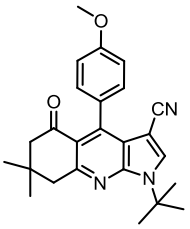
A mixture of the corresponding 1,4-dihydropyridine ***24a-i*** (1 equiv.) and 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ) (1.2 equiv.) was stirred at room temperature in acetonitrile (10mL) for 4 h. The crude product was purified by column chromatography (eluent: n-heptane/ethylacetate).

*1-Tert-butyl-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**25a**)*



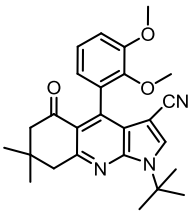
The product was isolated as a white solid, yield 86 %, mp 285 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (1H, s, Ar-H), 7.04 (2H, d, *J* = 8.5 Hz, Ar-H), 6.82 (2H, d, *J* = 8.3 Hz, Ar-H), 5.93 (1H, br. s., OH), 3.11 (2H, s, CH_2), 2.46 (2H, s,CH_2), 1.77 (9H, s, $(CH_3)_3$), 1.07 (6H, s, $(CH_3)_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 197.4 (C-), 157.5 (C-), 155.3 (C-), 146.7 (C-), 145.0 (C-), 139.1 (C-), 134.5 (CH-), 128.3 (CH-), 127.2 (C-), 119.4 (C-), 119.4 (C-), 114.1 (CH-), 84.1 (C-), 57.9 (C-), 53.2 (CH_2), 47.3 (CH_2), 31.5 (C-), 28.1 $(CH_3)_3$, 27.3 $(CH_3)_2$ MS (GC, 70 eV) m/z (%) 387 (M+, 42), 331 (100), 274 (39); HR (EI): calcd for $C_{24}H_{25}N_3O_2$ (M + 1) 387.19413, found 387.19392; IR (ATR, cm^{-1}) ũ 3266 (w), 2955 (w), 2221 (s), 1663 (s), 1565 (m), 1518 (m), 1463 (m), 1393 (m), 1305 (m), 1233 (m), 1225 (m), 1168 (m), 1119 (m), 830 (m), 811 (m), 794 (m), 633 (m), 565 (m).

*1-Tert-butyl-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**25b**)*



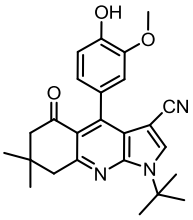
The product was isolated as a white solid, yield 83 %, mp 274-276 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7,74 (1H, s, Ar-H), 7.07 - 7.14 (2H, d, *J* = 8.7 Hz, Ar-H), 6.93 (2H, d, *J* = 8.7 Hz, Ar-H), 3.79 (3H, s, OCH_3), 3.11 (2H, s, CH_2), 2.44 (2H, s, CH_2), 1.77 (9H, s, $(CH_3)_3$), 1.06 (6H, s, $(CH_3)_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 197.9 (C-), 159.6 (C-), 158.4 (C-), 147.6 (C-), 145.7 (C-), 135.4 (CH-), 129.3 (CH-), 128.7 (C-), 120.4 (C-), 120.3 (C-), 114.5 (C-), 113.4 (CH-), 85.2 (C-), 58.9 (C-), 55.2 (OCH_3), 54.1 (CH_2), 48.3 (CH_2), 32.5 (C-), 29.1 $(CH_3)_3$, 28.3 $(CH_3)_2$. MS (GC, 70 eV) m/z (%) 401 (M+, 66), 345 (100), 289 (27); HR (EI): calcd for $C_{25}H_{27}N_3O_2$ (M + 1) 401.20978, found 401.20956; IR (ATR, cm^{-1}) ῡ 3120 (w), 2956 (w), 2222 (s), 1681 (s), 1574 (m), 1510 (m), 1465 (m), 1390 (m), 1365 (m), 1230 (s), 1205 (s), 1172 (m), 1026 (m), 818 (m), 632 (m), 559 (m). calcd for $C_{25}H_{27}N_3O_2$: C: 74.79, H: 6.78, N: 10.47, found: C: 73.39, H: 6.76, N: 10.22.

*1-Tert-butyl-4-(2,3-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**25c**)*



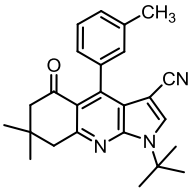
The product was isolated as a white solid, yield 91 %, mp 202-204 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (1H, s, Ar-H), 7.09 (1H, t, *J* = 8 Hz, Ar-H), 6.98 (1H, dd, ^{1}J = 8.1 ^{2}J = 1.5 Hz, Ar-H), 6.63 (1H, dd, ^{1}J = 7.5 ^{2}J =1.55 Hz, Ar-H), 3.85 (3H, s,OCH_3), 3.50 (3H, s, OCH_3), 3.11 (2H, s, CH_2), 2.44 (2H, s, CH_2), 1.77 (9H, s, $(CH_3)_3$), 1.07 (3H, s, CH_3), 1.06 (3H, s, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 197.5 (C-), 158.1 (C-), 152.4 (C-), 147.7 (C-), 145.8 (C-), 142.0 (C-), 135.2 (CH), 131.1 (C-), 123.8 (CH), 120.8 (CH), 120.5 (C-),120.0 (C-), 114.0 (C-), 112.9 (CH), 85.1 (C-), 60.4 (OCH_3), 58.9 (C-), 55.8 (OCH_3), 53.7 (CH_2), 48.2 (CH_2), 32.4 (C-), 29.1 $(CH_3)_3$, 28.5 (CH_3), 28.0 (CH_3); MS (GC, 70 eV) m/z (%) 431 (M+, 21), 400 (67), 344 (100); HR (EI): calcd for $C_{26}H_{29}N_3O_3$ (M + 1) 431.22034, found 431.220102; IR (ATR, cm^{-1}) ῡ 3121 (w), 2952 (w), 2218 (s), 1676 (m), 1573 (m), 1521 (m), 1463 (m), 1397 (s), 1307 (m), 1307 (m), 1258 (s), 1291 (s), 1199 (s), 1079 (m), 1008 (m), 782 (m), 758 (m), 632 (m), 546 (m). calcd for $C_{26}H_{29}N_3O_3$: C: 72.37, H: 6.77, N: 9.74, found: C: 72.20, H: 6.84, N: 9.74.

*1-Tert-butyl-4-(4-hydroxy-3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**25d**)*



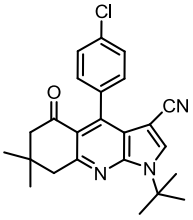
The product was isolated as a white solid, yield 40 %, mp 232-234 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (1H, s, OH), 6.92 (1H, d, *J* = 7.9 Hz, Ar-H), 6.71 - 6.74 (1H, m, Ar-H), 6.61 - 6.66 (1H, m, Ar-H), 3.82 (3H, s, OCH_3), 3.11 (2H, s, CH_2), 2.45 (2H, d, *J* = 6.2 Hz, CH_2), 1.77 (9H, s, $(CH_3)_3$), 1.07 (6H, s, $(CH_3)_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 197.8 (C-), 158.4 (C-), 147.6 (C-), 146.1 (C-), 145.7 (C-), 145.6 (C-), 135.5 (CH-), 128.3 (C-), 121.4 (CH-), 120.4 (C-), 120.3 (C-), 114.6 (C-), 114.1 (CH-), 111.4 (CH-), 85.2 (C-), 58.9 (C-), 55.9 (OCH_3-), 54.2 (CH_2-), 48.3 (CH_2-), 32.5 (C-), 29.1 $(CH_3)_3$, 28.4 (CH_3-), 28.2 (CH_3-) MS (GC, 70 eV) m/z (%) 417 (M+, 100), 361 (85); HR (EI): calcd for $C_{25}H_{27}N_3O_3$ (M + 1) 417.20469, found 417.20466; IR (ATR, cm^{-1}) ῦ 3390 (w), 2956 (w), 2220 (s), 1681 (m), 1573 (m), 1513 (m), 1467 (m), 1395 (m), 1254 (m), 1227 (m), 1202 (s), 1032 (m), 768 (m), 547 (w).

*1-Tert-butyl-7,7-dimethyl-5-oxo-4-m-tolyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**25e**)*



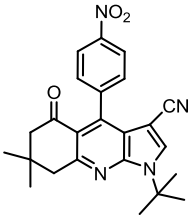
The product was isolated as a white solid, yield 71 %, mp 217-219 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (1H, s, Ar-H), 7.25 - 7.31 (1H, m, Ar-H), 7.20 (1H, d, *J* = 8.3 Hz, Ar-H), 6.94 - 6.99 (2H, m, Ar-H), 3.11 (2H, s, CH_2), 2.44 (2H, s, CH_2), 2.34 (3H, s, CH_3), 1.76 (9H, s, $(CH_3)_3$), 1.07 (6H, s, $(CH_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 197.7 (C-), 158.4 (C-), 147.6 (C-), 146.0 (C-), 137.4 (C-), 136.5 (C-), 135.4 (CH-), 128.8 (CH-), 128.5 (CH-), 127.7 (CH-), 124.9 (CH-), 120.0 (C-), 120.0 (C-), 114.2 (C-), 85.3 (C-), 58.9 (C-), 54.0 (CH_2-), 48.3 (CH_2-), 32.5 (C-), 29.1 $(CH_3)_3$, 28.3 $(CH_3)_2$, 21.7 (CH_3).MS (GC, 70 eV) m/z (%) 385 (M+, 42), 328 (100), 314 (33); HR (EI): calcd for $C_{25}H_{27}N_3O$ (M + 1) 385.21486, found 385.214578; IR (ATR, cm^{-1}) ῦ 3112 (w), 2217 (s), 1681 (s), 1571 (m), 1466 (w), 1395 (m), 1306 (m), 1262 (m), 1208 (s), 778 (m), 712 (m), 648 (w), 567 (m). calcd for $C_{25}H_{27}N_3O$: C: 77.89, H: 7.06, N: 10.90, found: C: 73.68, H: 7.02, N: 10.90.

*1-Tert-butyl-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**25f**)*



The product was isolated as a white solid, yield 83 %, mp 166 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (1H, s, Ar-H), 7.37 (2H, d, *J* = 8.5 Hz, Ar-H), 7.10 (2H, d, *J* = 8.3 Hz, Ar-H), 3.12 (2H, s, CH_2), 2.44 (2H, s, CH_2), 1.77 (9H, s,$(CH_3)_3$), 1.07 (6H, s, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 197.8 (C-), 158.5 (C-), 147.7 (C-), 144.3 (C-), 135.7 (CH-), 135.0 (C-), 134.1 (C-), 129.3 (CH-), 128.2 (CH-), 120.0 (C-), 119.7 (C-),114.1 (C-), 85.0 (C-), 59.0 (C-), 54.0 (CH_2-), 48.2 (CH_2-), 32.5 (C-), 29.1 $(CH_3)_3$, 28.2 $(CH_3)_2$; MS (GC, 70 eV) m/z (%) 405 (M+, 31), 349 (100), 258 (55); HR (EI): calcd for $C_{24}H_{24}ClN_3O$ (M + 1) 405.16024, found 405.160251; IR (ATR, cm^{-1}) ῦ 3149 (w), 2962 (w), 2221 (s), 1689 (m), 1574 (m), 1524 (m), 1492 (m), 1395 (m), 1370 (m), 1302 (m), 1257 (m), 1202 (s), 1087 (m), 1015 (m), 812 (m), 749 (m), 626 (m), 555 (m). calcd for $C_{24}H_{24}ClN_3O$: C: 71.01, H: 5.96, N: 10.35, found: C: 70.13, H: 5.96, N: 10.25.

*1-Tert-butyl-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**25g**)*

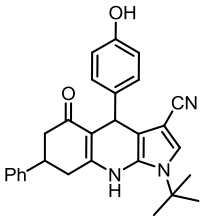


The product was isolated as a white solid, yield 83 %, mp 291 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (2H, d, *J* = 8.5 Hz, Ar-H), 7.79 (1H, s, Ar-H), 7.33 (2H, d, *J* = 8.7 Hz, Ar-H), 3.15 (2H, s, CH_2), 2.45 (2H, s, CH_2), 1.78 (9H, s, $(CH_3)_3$), 1.08 (6H, s, CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 197.7 (C-), 158.6 (C-), 147.8 (C-), 147.5 (C-), 143.8 (C-), 142.8 (C-), 136.1 (CH-), 128.9 (CH-), 123.3 (CH-), 119.5 (C-), 119.0 (C-), 113.8 (C-), 84.6 (C-), 59.3 (C-), 53.7 (CH_2-), 48.1 (CH_2-), 32.6 (C-), 29.1 $(CH_3)_3$, 28.2 $(CH_3)_2$. MS (GC, 70 eV) m/z (%) 416 (M+, 23), 360 (100), 304 (32); HR (EI): calcd for $C_{24}H_{24}N_4O_3$ (M + 1) 416.18429, found 416.184269; IR (ATR, cm^{-1}) ῦ 3149 (w), 2959 (w), 2219 (s), 1682 (m), 1577 (m), 1513 (s), 1397 (m), 1341 (m), 1307 (m), 1198 (m), 843 (m), 831 (m), 749 (m), 624 (m), 555 (m). calcd for $C_{24}H_{24}N_4O_3$: C: 69.21, H: 5.81, N: 13.45, found: C: 66.33, H: 5.73, N: 12.75.

A.2.10 General procedure for the synthesis of compounds 26a-e

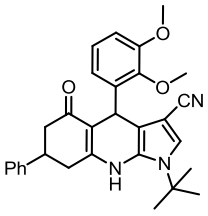
A mixture of 5-phenyl-1,3-cyclohexanedione (equiv.), the corresponding aldehyde (1 equiv.) and 5-amino-1-R-pyrrole-3-carbonitrile (1 equiv.) was refluxed in ethanol for 6 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent: n-heptane/ethylacetate).

*1-Tert-butyl-4-(4-hydroxyphenyl)-5-oxo-7-phenyl-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**26a**)*



The product was isolated as a white solid, yield 81 %, mp 241-242 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.02 (1H, s, OH), 8.61 (1H, s, NH), 7.16 - 7.37 (6H, m, Ar-H), 6.85 (2H, d, J = 8.2 Hz, Ar-H), 6.53 (2H, d, ^{1}J = 8.0 Hz, Ar-H), 4.94 (1H, s, CH), 3.36- 3.51 (1H, m, CH), 2.93 - 3.14 (2H, m, CH_2), 2.52 - 2.65 (2H, m, CH_2), 1.55 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.2 (C-), 155.1 (C-), 151.2 (C-), 143.6 (C-), 138.0 (C-), 128.3 (CH-), 128.1 (CH-), 127.0 (C-), 126.9 (CH-), 126.4 (CH-), 122.5 (CH-), 116.3 (C-), 114.4 (CH-), 108.6 (C-), 108.1 (C-), 87.1 (C-), 56.9 (C-), 43.6 (CH_2-), 38.4 (CH-), 35.4 (CH-), 34.2 (CH_2-), 29.2 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 435 (M+, 79), 379 (100), 275 (88); HRMS (ESI): calcd for $C_{28}H_{26}N_3O_2$ (M + 1) 436.20195 found 436.20257; IR (ATR, cm^{-1}) ῦ 3312 (w), 2220 (m), 1603 (m), 1572 (m), 1522 (s), 1495 (s), 1421 (m), 1392 (m), 1374 (w), 1342 (m), 1210 (s), 1192 (m), 1177 (m), 1157 (m), 981 (m), 883 (m), 855 (m), 819 (m), 758 (m), 698 (m), 548 (m). calcd for $C_{28}H_{27}N_3O_2$: C: 76.86, H: 6.22, N: 9.60, found: C: 76.06, H: 6.31, N: 9.81

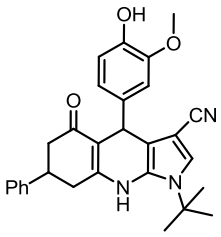
*1-Tert-butyl-4-(2,3-dimethoxyphenyl)-5-oxo-7-phenyl-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**26b**)*



The product was isolated as a white solid. Yield 50 %, mp 229-231 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.59 (1H, s, NH), 7.20 - 7.34 (6H, m, Ar-H), 6.71 - 6.85 (2H, m, Ar-H), 6.63 (1H, dd, ^{1}J = 7 ^{2}J = 2 Hz, Ar-H), 5.28 (1H, s, CH), 3.74 (3H, s,OCH_3), 3.69 (3H, s, OCH_3), 3.35 - 3.49 (1H, m, CH), 2.86 - 3.08 (2H, m, CH_2), 2.36 - 2.47 (2H, m, CH_2), 1.56 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, DMSO-

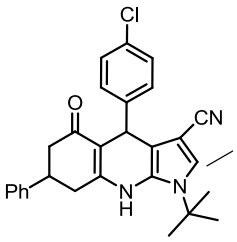
d_6): δ 193.0 (C-), 152.1 (C-), 151.9 (C-), 146.0 (C-), 143.7 (C-), 140.1 (C-), 128.3 (CH-), 127.6 (C-), 126.9 (CH-), 126.4 (CH-), 122.6 (CH-), 122.4 (CH-),121.8 (CH-), 115.9 (C-), 110.3 (CH-), 108.3 (C-), 107.0 (C-), 87.5 (C-), 59.3 (OCH_3-), 56.9 (C-), 55.4 (OCH_3-), 43.9 (CH_2-), , 38.7 (CH-), 34.6 (CH_2-), 32.1 (CH-), 29.2 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 479 (M+, 28), 448 (77), 392 (100); HRMS (ESI): calcd for $C_{30}H_{30}N_3O_3$ (M + 1) 480.22927 found; 480.22898. IR (ATR, cm^{-1}) ũ 3404 (w), 3143 (w), 2216 (m), 1630 (m), 1608 (m), 1522 (s), 1502 (s), 1478 (m), 1422 (m), 1331 (m), 1210 (m), 1193 (m), 1060 (m), 1000 (m), 758 (s), 748 (s), 701 (m). calcd for $C_{30}H_{31}N_3O_3$: C: 74.82, H: 6.49, N: 8.73, found: C: 74.49, H: 6.47, N: 8.76

*1-Tert-butyl-4-(4-hydroxy-3-methoxyphenyl)-5-oxo-7-phenyl-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**26c**)*



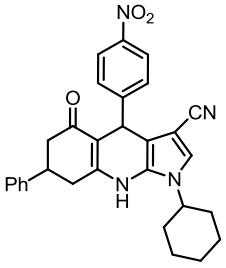
The product was isolated as a white solid, yield 77 %, mp 230-231 ºC. ^{1}H NMR (300 MHz, DMSO-*d_6*): δ 8.65 (1H, s, OH), 8.60 (1H, s, NH), 7.23 - 7.37 (6H, m, Ar-H), 6.80 (1H, s, Ar-H), 6.55 (1H, d, *J* = 7.9 Hz, Ar-H), 6.35 (1H, d, *J* = 7.7 Hz, Ar-H),4.99 (1H, s, CH), 3.70 (3H, s, OCH_3), 3.41 - 3.51 (1H, m, CH), 2.99 - 3.19 (2H, m, CH_2), 2.53 - 2.69 (2H, m, CH_2), 1.58 (9H, s, $(CH_3)_3$).^{13}C NMR (62.9 MHz, DMSO-*d_6*): δ 193.3 (C-), 151.4 (C-), 146.8 (C-), 144.3 (C-), 143.6 (C-), 138.6 (C-), 128.2 (CH-), 126.9 (CH-), 126.8 (C-), 126.4 (CH-), 122.5 (CH-), 118.9 (CH-),116.6 (C-), 114.9 (CH-), 111.6 (CH-), 108.2 (C-), 108.1 (C-), 87.1 (C-), 56.9 (C-), 55.2 (OCH_3-), 43.5 (CH_2-), 38.3 (CH-), 35.8 (CH-), 34.2 (CH_2-), 29.1 $(CH_3)_3$.MS (GC, 70 eV) m/z (%) 465 (M+, 89), 409 (100), 273 (36); HRMS (ESI): calcd for $C_{29}H_{28}N_3O_3$ (M + 1) 466.21211 found 466.21252; IR (ATR, cm^{-1}) ũ 3330 (w), 2211 (m), 1607 (m), 1597 (m), 1573 (m), 1495 (s), 1423 (m), 1390 (m), 1270 (m), 1247 (m),1228 (m), 1247 (m), 1228 (m), 1187 (m), 1161 (m), 1125 (m), 1036 (m), 743 (s), 696 (m), 596 (m).

*1-Tert-butyl-4-(4-chlorophenyl)-5-oxo-7-phenyl-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**26d**)*



The product was isolated as a white solid. Yield 72 %, mp 239-241 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.72 (1H, s, NH), 7.17 - 7.34 (8H, m, Ar-H), 7.01 - 7.12 (2H, m, Ar-H), 5.04 (1H, s, CH), 3.34 - 3.49 (1H, m, CH), 2.96 - 3.16 (2H, m, CH_2),2.52 - 2.57 (2H, m, CH_2), 1.56 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.3 (C-), 151.7 (C-), 146.1 (C-), 143.4 (C-), 130.1 (C-), 129.1 (CH-), 128.3 (CH-), 127.6 (CH-), 127.2 (C-), 126.9 (CH-), 126.4 (CH-), 123.0 (CH-),116.1 (C-), 107.8 (C-), 106.9 (C-), 87.2 (C-), 57.1 (C-), 43.4 (CH_2-), 38.2 (CH-), 36.2 (CH-), 34.2 (CH_2), 29.1 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 453 (M+, 48), 397 (100) 293 (30), 258 (76); HRMS (ESI): calcd for $C_{28}H_{24}ClN_3O$ (M + 1) 454.16807 found 454.16867; IR (ATR, cm^{-1}) ũ 3318 (w), 2217 (m), 1603 (m), 1574 (m), 1525 (s), 1502 (s), 1487 (s), 1428 (m), 1392 (m), 1372 (m), 1343 (m), 1314 (m), 1275 (w), 1234 (m), 1191 (m), 1177 (s), 1156 (m), 1085 (m), 1012 (m), 981 (m), 882 (w), 840 (m), 819 (m), 796 (s), 757 (s), 700 (s), 550 (s). calcd for $C_{28}H_{26}ClN_3O$: C: 73.75, H: 5.75, N: 9.22, found: C:73.32, H: 5.88, N: 9.41

*1-Cyclohexyl-4-(4-nitrophenyl)-5-oxo-7-phenyl-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**26e**)*

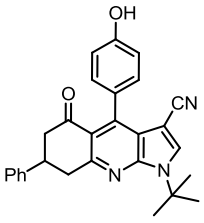


The product was isolated as a yellow solid, yield 57 %, mp 237-239 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.72 (1H, s, NH), 8.06 (2H, d, J = 8.8 Hz, Ar-H), 7.42 (1H, s, Ar-H), 7.26 - 7.37 (7H, m, Ar-H), 5.22 (1H, s, CH), 4.10 - 4.21 (1H, m, CH), 3.44 - 3.51 (1H, m, CH), 3.05 (1H, dd, ^{1}J = 16.2 ^{2}J = 8.7 Hz, CH_2), 2.95 (1H, dd, ^{1}J = 16.1 ^{2}J= 6.1 Hz, CH_2), 2.56 (2H, s, CH_2), 1.80 - 1.95 (4H, m,CH_2), 1.35 - 1.70 (5H, m, CH_2), 1.14 - 1.26 (1H, m, CH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.0 (C-), 154.5 (C-), 151.9 (C-), 145.5 (C-), 143.2 (C-), 128.5 (CH-), 128.3 (CH-), 127.5 (C-), 126.8 (CH-), 126.4 (CH-), 123.0 (CH-), 122.0 (CH-), 115.9 (C-), 107.3 (C-), 103.2 (C-), 88.6 (C-), 54.0 (C-), 43.3 (CH_2-), 38.0 (CH-), 37.4 (CH-), 34.0 (CH_2-), 32.9 (CH_2-), 25.0 (CH_2-), 24.5 (CH_2-). MS (GC, 70 eV) m/z (%); HRMS (ESI): calcd for $C_{30}H_{29}N_4O_3$ (M + 1) 493.22287, found 493.22342; IR (ATR, cm^{-1}) ũ 3241 (w), 2218 (m), 1598 (m), 1517 (s), 1344 (s), 1172 (m), 1153 (m), 695 (m).

A.2.11 General procedure for the synthesis of compounds 27a-e

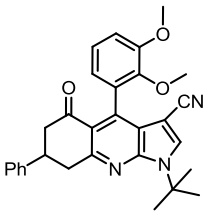
A mixture of the corresponding 1,4-dihydropyridine ***26a-e*** (1 equiv.) and 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ) (1.2 equiv.) was stirred in acetonitrile (10 mL) at room temperature for 4 h. The crude product was purified by column chromatography (eluent: n-heptane/ethylacetate).

*1-Tert-butyl-4-(4-hydroxyphenyl)-5-oxo-7-phenyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**27a**)*



The product was isolated as a white solid, yield 56 %, mp 328-330 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ ^{1}H NMR (300 MHz, DMSO-d_6): 9.53 (1H, s, OH), 8.55 (1H, s, Ar-H), 7.27 - 7.53 (5H, m, Ar-H), 7.10 (2H, d, J = 8.3 Hz, Ar-H), 6.86 (2H, d, J = 8.3 Hz, Ar-H), 3.55 - 3.65 (3H, m, CH, CH_2), 3.04 (1H, s, CH_2), 2.81 (1H, br. s., CH_2), 1.85 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 196.3 (C-), 158.2 (C-), 156.9 (C-), 146.7 (C-), 145.3 (C-), 143.4 (C-), 138.3 (CH-), 129.4 (CH-), 128.5 (CH-), 127.0 (C-), 126.8 (CH-),126.6 (CH-), 120.5 (C-), 119.6 (C-), 114.4 (CH-), 114.3 (C-), 83.7 (C-), 58.8 (C-), 46.9 (CH_2), 41.4 (CH_2), 38.5 (CH-), 28.5 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 435 (M+, 61), 379 (100), 275 (79); HR (EI): calcd for $C_{28}H_{25}N_3O_2$ (M + 1) 435.19413, found 435.19443; IR (ATR, cm^{-1}) ῡ 3252 (w), 2965 (w), 2218 (s), 1667 (s), 1574 (m), 1511 (m), 1453 (m), 1399 (m), 1266 (m), 1198 (s), 818 (m), 698 (s), 569 (m).

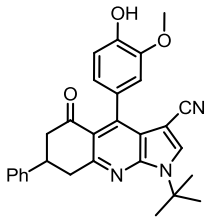
*1-Tert-butyl-4-(2,3-dimethoxyphenyl)-5-oxo-7-phenyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**27b**)*



The product was isolated as a white solid, yield 97 %, mp 116-118 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (1H, s, Ar-H), 7.18 - 7.32 (5H, m, Ar-H), 7.06 - 7.14 (1H, m, Ar-H), 6.96 - 7.04 (1H, m, Ar-H), 6.56 - 6.69 (1H, m, Ar-H), 3.86 (3H, s, OCH_3), 3.47 - 3.54 (4H, m, CH, OCH_3), 2.85 (2H, d, J = 6.2 Hz, CH_2), 1.97 (2H, s, CH_2), 1.76 (9H, s, $(CH_3)_3$).^{13}C NMR (62.9 MHz, $CDCl_3$): δ 196.7 (C-), 171.1 (C-), 158.5 (C-), 152.5 (C-), 147.5 (C-), 146.0 (C-), 143.1 (C-), 142.7 (C-), 135.5 (CH-), 131.0 (C-), 128.8 (CH-), 127.0 (CH-), 126.7 (C-), 126.6 (CH-), 123.9 (CH-), 120.7 (CH-), 113.9 (C-), 113.0 (CH-),

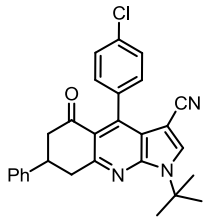
85.2 (C-), 60.5 (OCH_3-), 58.9 (C-), 55.9 (OCH_3-), 47.2 (CH_2-), 42.1 (CH_2-), 39.6 (CH-), 29.1 (CH_3)3. MS (GC, 70 eV) m/z (%) 479 (M+, 25), 448 (78), 392 (100); HR (EI): calcd for $C_{30}H_{29}N_3O_3$ (M + 1) 479.22034, found 479.220087; IR (ATR, cm^{-1}) ũ 3029(w), 2968 (w), 2221 (s), 1732 (m), 1686 (m), 1573 (m), 1472 (m), 1396 (m), 1308 (m), 1227 (s), 1056 (w), 753 (m), 700 (s).

*1-Tert-butyl-4-(4-hydroxy-3-methoxyphenyl)-5-oxo-7-phenyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**27c**)*



The product was isolated as a white solid, yield 43 %, mp 265-267 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (1H, s, Ar-H), 7.17 - 7.31 (5H, m, Ar-H), 6.93 (1H, d, *J* = 8 Hz, Ar-H), 6.75 (1H, d, *J* = 2 Hz, Ar-H), 6.64 - 6.70 (1H, m, Ar-H), 3.82 (3H, s, OCH_3), 3.38 - 3.55 (3H, m, CH;CH_2), 2.86 (2H, d, *J* = 5.7 Hz, CH_2), 1.75 (9H, s, $(CH_3)_3$).^{13}C NMR (62.9 MHz, $CDCl_3$): δ 196.0 (C-), 157.7 (C-), 146.5 (C-), 145.1 (C-), 144.8 (C-), 142.0 (C-), 141.2 (C-), 134.8 (CH-), 127.8 (CH-), 127.2 (C-), 126.0 (CH-), 125.7 (CH-), 120.7 (CH-), 120.3 (C-), 119.7 (C-), 119.6 (C-), 113.2 (CH-), 110.3 (CH-), 84.4 (C-), 58.0 (OCH_3-), 54.9 (C-), 46.6 (CH_2-), 41.2 (CH_2-), 38.6 (CH-), 28.0 $(CH_3)_3$;MS (GC, 70 eV) m/z (%) 465 (M+, 100), 409 (64), 273 (21); HR (EI): calcd for $C_{29}H_{27}N_3O_3$ (M+) 465.20469, found 465.20498; IR (ATR, cm^{-1}) ũ 3402 (w), 2962 (w), 2224 (s), 1681 (s), 1573 (m), 1516 (m), 1396 (m), 1301 (m), 1261 (m), 1202 (s), 1136 (w), 1031 (w), 760 (m), 697 (m), 560 (w).

*1-Tert-butyl-4-(4-chlorophenyl)-5-oxo-7-phenyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-b]quinoline-3-carbonitrile (**27d**)*

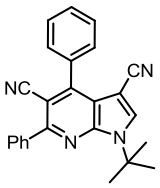


The product was isolated as a white solid, yield 82%, mp 235-237 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (1H, s, Ar-H), 7.07 - 7.44 (9H, m, Ar-H), 3.33 - 3.60 (3H, m, CH; CH_2), 2.72 - 2.93 (2H, m, CH_2), 1.76 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 195.9 (C-), 157.8 (C-), 146.5 (C-), 143.8 (C-), 141.8 (C-), 135.0 (CH-), 133.9 (C-), 133.2 (C-), 128.2 (CH-), 127.8 (CH-), 127.3 (CH-),126.1 (CH-), 125.6 (CH-), 119.3 (C-), 119.0 (C-), 113.0 (C-), 84.1 (C-), 58.1 (C-), 46.4 (CH_2-), 41.1 (CH_2-), 38.5 (CH-), 28.0 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 453 (M+, 44), 397 (100), 258 (83); HR (EI): calcd for $C_{28}H_{24}ClN_3O$ (M + 1) 453.16024, found 453.160152; IR (ATR, cm^{-1}) ῡ 3147 (w), 2971 (w), 2219 (s), 1683 (s), 1576 (s), 1490 (w), 1396 (s), 1203 (s), 1084 (m), 1012 (m), 811 (m), 698 (s), 570 (m).

A.2.12 General procedure for the synthesis of compounds 28a-h

A mixture of benzoylacetonitrile (1 equiv.), the corresponding aldehyde (1 equiv.) and 5-amino-1-R-pyrrole-3-carbonitrile (1 equiv.) was refluxed in acetic acid with 6 equiv. of ammonium acetate as base for 6 h. The product was purified by column chromatography (eluent: n-heptane/ethylacetate).

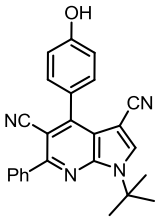
*1-Tert-butyl-4,6-diphenyl-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**28a**)*



The product was isolated as a brown solid, yield 48 %, mp 260-261°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.80 (1H, s, Ar-H), 7.91 - 8.01 (2H, m, Ar-H), 7.56 - 7.71 (8H, m, Ar-H), 1.85 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 155.2 (C-), 148.5 (C-), 146.7 (C-), 140.2 (CH-), 138.0 (C-), 133.1 (C-), 129.9 (CH-), 129.7 (CH-), 129.5 (CH-), 129.3 (CH-), 128.5 (CH-), 128.3 (CH-),117.7 (C-), 117.0 (C-), 114.2 (C-), 101.2 (C-), 83.1 (C-), 59.6 (C-), 28.6 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 376 (M+, 24), 320 (100), 319 (85); HRMS (ESI): calcd for $C_{25}H_{21}N_4$ (M + 1) 377.1607 found 377.17552; IR (ATR, cm^{-1}) ῡ 3140 (w), 2986 (w), 2230 (m), 1585 (m), 1571 (m), 1516 (m), 1401 (s), 1371 (m), 1359 (m),

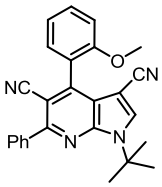
1305 (s), 1209 (s), 756 (s), 707 (s), 697 (s), 644 (m).

*1-Tert-butyl-4-(4-hydroxyphenyl)-6-phenyl-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**28b**)*



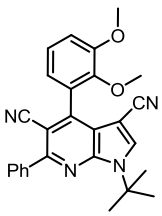
The product was isolated as a brown solid, yield 56 %, mp 256-258 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.98 (1H, s, OH), 8.76 (1H, s, Ar-H), 7.90 - 8.02 (2H, m, Ar-H), 7.56 - 7.66 (3H, m, Ar-H), 7.51 (2H, d, J = 8.5 Hz, Ar-H), 6.99 (2H, d, J = 8.5 Hz, Ar-H), 1.84 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, DMSO- d_6): δ 158.9 (C-), 155.3 (C-), 148.9 (C-), 146.7 (C-), 139.9 (CH-), 138.1 (C-), 131.2 (CH-), 129.6 (CH-), 129.2 (CH-), 128.4 (CH-), 123.7 (C-), 118.0 (C-),117.1 (C-), 115.1 (CH-), 114.5 (C-), 101.2 (C-), 83.2 (C-), 59.4 (C-), 28.6 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 392 (M+, 25), 336 (100); HRMS (ESI): calcd for $C_{25}H_{21}N_4O$ (M + 1) 393.17099; 393.17136 IR (ATR, cm^{-1}) ũ 3409 (w), 3356 (w), 2220 (w), 1612 (m), 1593 (m), 1515 (s), 1434 (m), 1399 (m), 1370 (m), 1273 (m), 1208 (s), 1175 (m), 839 (m), 785 (m), 776 (m), 710 (s), 614 (w), 541 (m).

*1-Tert-butyl-4-(2-methoxyphenyl)-6-phenyl-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**28c**)*



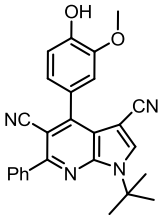
The product was isolated as a brown solid, yield 54 %, mp 234-235 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.76 (1H, s, Ar-H), 7.97 (2H, d, J = 5.3 Hz, Ar-H), 7.57 - 7.68 (4H, m, Ar-H), 7.52 (1H, d, J = 7.2 Hz, Ar-H), 7.29 (1H, d, J = 8.3 Hz, Ar-H), 7.14 -7.22 (1H, m, Ar-H), 3.83 (3H, s, OCH_3), 1.86 (9H, s, $(CH_3)_3$).^{13}C NMR (62.9 MHz, DMSO- d_6): δ 156.5 (C-), 154.9 (C-), 146.4 (C-), 145.8 (C-), 139.6 (CH-), 137.9 (C-), 131.7 (CH-), 130.9 (CH-), 129.6 (C-), 129.2 (CH-), 128.5 (CH-), 121.4 (C-),120.3 (CH-), 117.5 (C-), 117.4 (C-), 114.1 (C-), 111.5 (CH-), 101.9 (C-), 83.4 (C-), 59.4 (C-), 55.4 (CH-), 28.6 $(CH_3)_3$. MS (GC, 70 eV) m/z (%), 406 (M+, 50), 350 (100), 319 (35); HRMS (ESI):calcd for $C_{26}H_{23}N_4O$ (M + 1) 407.18664 found 407.18706; IR (ATR, cm^{-1}) ũ 3153 (w), 2220 (w), 1600 (w), 1515 (m), 1493 (m), 1402 (m), 1367 (m), 1308 (m), 1244 (m), 1211 (m), 1022 (m), 751 (s), 744 (m), 712 (s), 694 (m), 641 (m), 621 (m), 581 (m). calcd for $C_{26}H_{22}N_4O$: C: 76.83, H: 5.46, N: 13.78, found: C: 76.51, H: 5.35, N: 13.71

1-Tert-butyl-4-(2,3-dimethoxyphenyl)-6-phenyl-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile ***(28d)***



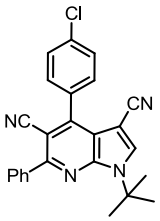
The product was isolated as a brown solid, yield 66 %, mp 191-192 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.74 (1H, s, Ar-H), 7.86 - 8.03 (2H, m, Ar-H), 7.55 - 7.67 (3H, m, Ar-H), 7.21 - 7.34 (2H, m, Ar-H), 7.00 (1H, dd, ^{1}J = 7.4 ^{2}J = 1.9 Hz, Ar-H), 3.92 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 1.84 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 154.6 (C-), 152.0 (C-), 146.4 (C-), 146.1 (C-), 145.9 (C-), 139.7 (CH-), 137.8 (C-), 129.7 (CH-), 129.1 (CH-), 128.5 (CH-), 127.1 (C-), 124.0 (CH-),121.8 (CH-), 117.8 (C-), 117.4 (C-), 114.9 (CH-), 113.7 (C-), 101.7 (C-), 83.2 (C-), 60.5 (OCH_3-), 59.5 (C-), 55.8 (OCH_3-), 28.6 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 436 (M+, 100), 380 (88); HRMS (ESI): calcd for $C_{27}H_{25}N_4O_2$ (M + 1) 437.1972 found 437.1978; IR (ATR, cm^{-1}) ũ 3144 (w), 2967 (w), 2222 (m), 1588 (m), 1574 (m), 1515 (m), 1471 (m), 1402 (m), 1368 (m), 1310 (m), 1264 (m), 1202 (m), 1170 (m), 1087 (m), 999 (m), 937 (w), 772 (s), 755 (s), 708 (s), 622 (m). Anal. Calcd. for $C_{27}H_{24}N_4O_2$: C: 74.29, H: 5.54, N: 12.84, found: C:73.90, H: 5.68, N: 12.77

1-Tert-butyl-4-(4-hydroxy-3-methoxyphenyl)-6-phenyl-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile ***(28e)***



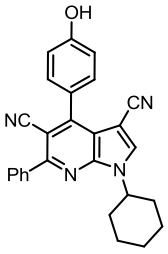
The product was isolated as a brown solid, yield 60 %, mp 258-259 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.54 (1H, s, OH), 8.77 (1H, s, Ar-H), 7.95 (2H, dd, ^{1}J= 7.9 ^{2}J= 2.3 Hz, Ar-H), 7.54 - 7.67 (3H, m, Ar-H), 7.29 (1H, d, ^{1}J =1.9 Hz, Ar-H), 7.12 (1H, dd, ^{1}J =7.9 ^{2}J = 2.1 Hz, Ar-H), 6.99 (1H, d, ^{1}J = 8.1 Hz, Ar-H), 3.87 (3H, s, OCH_3), 1.83 (9H, s, $(CH_3)_3$).^{13}C NMR (62.9 MHz, DMSO-d_6): δ 155.3 (C-), 148.7 (C-), 148.2 (C-), 147.0 (C-), 146.7 (C-), 139.9 (CH-), 138.1 (C-), 129.6 (CH-), 129.2 (CH-), 128.4 (CH-), 123.8 (C-), 122.7 (CH-),118.0 (C-), 116.9 (C-), 115.3 (CH-), 114.7 (C-), 114.1 (CH-), 101.1 (C-), 83.3 (C-), 59.4 (C-), 55.5 (OCH_3-), 28.6 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 422 (M+, 48), 366 (100), 319 (11); HRMS (ESI): calcd for $C_{26}H_{23}N_4O_2$ 423.18155 found 423.18221; IR (ATR, cm^{-1}) ũ 3380 (w), 2224 (m), 1594 (m), 1583 (m), 1514 (s), 1461 (w), 1403 (m), 1311 (m), 1280 (m), 1270 (m), 1166 (m), 1146 (m), 1117 (m), 874 (m), 777 (s), 708 (s).

*1-Tert-butyl-4-(4-chlorophenyl)-6-phenyl-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**28f**)*



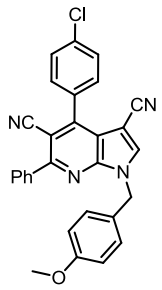
The product was isolated as a brown solid, yield 51 %, mp 223-225 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.87 (1H, s, Ar-H), 7.66 (9H, m, Ar-H), 1.89 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, DMSO- d_6): δ 155.0 (C-), 147.1 (C-), 146.6 (C-), 140.2 (CH-), 137.8 (C-), 134.8 (C-), 131.9 (C-), 131.4 (CH-), 129.8 (CH-), 129.2 (CH-), 128.5 (CH-), 128.4 (CH-),117.5 (C-), 116.9 (C-), 114.1 (C-), 82.9 (C-), 59.5 (C-), 28.6 $(CH_3)_3$.MS (GC, 70 eV) m/z (%) 410 (M+, 25), 354 (100), 319 (43); HR (EI): calcd for $C_{24}H_{19}ClN_4$ 410.12932 found 410.12928; IR (ATR, cm-1) ũ 3257 (w), 2221 (s), 2188 (s), 1585 (w), 1485 (m), 1410 (m) 1371 (m), 1200 (m), 1086 (m), 1014 (m), 836 (m), 773(s), 704 (m), 580 (m).

1-*Cyclohexyl-4-(4-hydroxyphenyl)-6-phenyl-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**28g**)*



The product was isolated as a white solid, yield 37 %, mp 292 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.96 (1H, s, OH), 8.91 (1H, s, Ar-H), 7.91 (2H, m, Ar-H), 7.61 (3H, m, Ar-H), 7.53 (2H, d, J = 8.5 Hz, Ar-H), 7.00 (2H, d, J = 8.5 Hz, Ar-H), 4.81 - 4.91 (1H, m, CH), 2.03 - 2.11 (2H, m, CH_2), 1.85 - 1.96 (4H, m, CH_2), 1.75 (1H, d, J = 11.7 Hz, CH_2), 1.52 (4H, s, CH_2), 1.30 -1.37 (1H, m, CH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 159.0 (C-), 156.6 (C-), 148.9 (C-), 146.0 (C-), 139.1 (CH-), 138.0 (C-), 131.2 (CH-), 129.6 (CH-), 129.3 (CH-), 128.3 (CH-), 123.5 (C-), 117.9 (C-), 115.8 (C-), 115.1 (CH-), 114.4 (C-), 101.7 (C-), 84.2 (C-), 54.4 (CH-), 32.2 (CH_2-), 25.1 (CH_2-), 24.7 (CH_2-). MS (GC, 70 eV) m/z (%) 418 (M+, 28), 336 (100); HR (EI): calcd for $C_{27}H_{22}N_4O$ (M + 1) 418.17881, found 418.17868; IR (ATR, cm^{-1}) ũ 3383 (w), 2935 (w), 2222 (m), 1611 (m), 1519 (m), 1418 (m), 1397 (m), 1277 (m), 1171 (m), 702 (s).

*4-(4-Chlorophenyl)-1-(4-methoxybenzyl)-6-phenyl-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**28h**)*

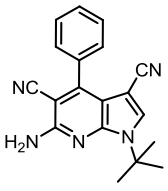


The product was isolated as a beige solid, yield 42 %, mp 206-208 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 - 8.07 (2H, m, Ar-H), 7.83 (1H, s, Ar-H), 7.55 - 7.63 (7H, m, Ar-H), 7.33 (2H, d, *J* = 8.7 Hz, Ar-H), 6.95 (2H, d, *J* = 8.7 Hz, Ar-H), 5.54 (2H, s, CH_2), 3.84 (3H, s, OCH_3). ^{13}C NMR (300 MHz, $CDCl_3$): δ 160.1 (C-), 158.1 (C-), 148.7 (C-), 147.5 (C-), 147.0 (C-), 138.3 (CH-), 137.7 (C-), 136.8 (C-),130.9 (CH-), 130.0 (CH-), 129.5 (CH-), 129.0 (CH-), 128.6 (CH-), 127.5 (CH-), 126.7 (C-), 117.5 (C-), 115.9 (C-), 114.7 (CH-), 113.7 (C-), 102.5 (C-), 86.0 (C-), 55.4 (OCH_3-), 48.8 (CH_2-).MS (GC, 70 eV) m/z (%) 474 (M+, 14), 393 (25), 282 (100); IR (ATR, cm^{-1}) ũ 3212 (w), 2219 (w), 2196 (m), 1643 (w), 1581 (m), 1504 (s), 1493 (s), 1248 (s), 1176 (m), 1090 (m), 1015 (m), 833 (m), 774 (m), 702 (s), 692 (m). Anal.calcd for $C_{29}H_{19}ClN_4O$: C: 73.34, H: 4.03, N: 11.80, found: C: 72.92, H: 4.28, N: 11.53

A.2.13 General procedure for the synthesis of compounds 29a-h

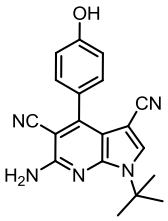
A mixture of malononitrile (1 equiv.), the corresponding aldehyde (1 equiv.) and 5-amino-1-R-pyrrole-3-carbonitrile (1 equiv.) was refluxed in acetic acid with 6 equiv. of ammonium acetate as base for 6 h. The product was purified by column chromatography (eluent: n-heptane/ethylacetate).

*6-Amino-1-tert-butyl-4-phenyl-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**29a**)*



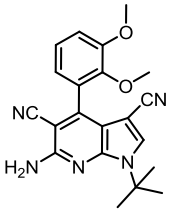
The product was isolated as a brown solid, yield 60 %, mp 194-196 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (1H, s, Ar-H), 7.47 (5H, s, Ar-H), 5.12 (2H, s, NH_2), 1.69 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 155.8 (C-), 149.6 (C-), 147.8 (C-), 133.6 (CH-), 133.1 (C-), 130.2 (CH-), 129.2 (CH-), 128.5 (CH-), 117.0 (C-), 114.8 (C-), 111.8 (C-), 88.1 (C-), 84.5 (C-), 58.7 (C-), 28.9 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 315 (M+, 19), 259 (100); HRMS (ESI): calcd for $C_{19}H_{18}N_5$ (M + 1) 316.15567 found 316.15526; IR (ATR, cm^{-1}) ũ 3355 (m), 2216 (m), 2205 (m), 1610 (s), 1592 (m), 1555 (m), 1525 (m), 1484 (m), 1397 (s), 1367 (m), 1305 (s), 1207 (m), 759 (s), 709 (m), 700 (m), 651 (m).

*6-Amino-1-tert-butyl-4-(4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**29b**)*



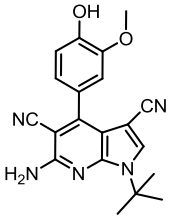
The product was isolated as a brown solid, yield 50 %, mp 129-130 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.85 (1H, s, OH), 8.18 (1H, s, Ar-H), 7.33 (2H, d, ^{1}J = 8.5 Hz, Ar-H), 6.89 (2H, d, ^{1}J = 8.5 Hz, Ar-H), 6.70 (2H, s, NH_2), 1.70 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, DMSO- d_6): δ 158.6 (C-), 156.8 (C-), 149.1 (C-), 147.7 (C-), 135.2 (CH-), 130.6 (CH-), 124.0 (C-), 117.1 (C-), 115.1 (C-), 114.9 (CH-), 109.9 (C-), 86.8 (C-), 82.8 (C-), 58.2 28.3 $(CH_3)_3$.. MS (GC, 70 eV) m/z (%); 331 (M+, 22), 275 (100), 247 (15), HRMS (ESI): calcd for $C_{19}H_{18}N_5O$ (M + 1) 332.15059, found 332.1504; IR (ATR, cm^{-1}) ũ 3343 (w), 2215 (m), 1607 (s), 1595 (s), 1516 (s), 1393 (s), 1370 (m), 1306 (m), 1207 (m), 1169 (m), 833 (m), 786 (m), 602 (m). calcd for $C_{19}H_{17}N_5O$: C: 68.87, H: 5.7, N: 21.13, found: C: 68.89, H: 5.25, N: 20.58

*6-Amino-1-tert-butyl-4-(2,3-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**29c**)*



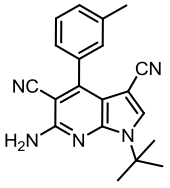
The product was isolated as a brown solid, yield 58 %, mp 103-105 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (1H, s, Ar-H), 7.21 (1H, d, ^{1}J = 7.7 Hz, Ar-H), 7.10 - 7.15 (1H, dd, ^{1}J = 1.5, ^{2}J = 8.3 Hz), 6.87-6.90 (1H, dd, ^{1}J = 1.5, ^{2}J = 7.6 Hz) 5.18 (2H, s, NH_2), 3.96 (3H, s, OCH_3), 3.78 (3H, s,OCH_3), 1.80 (9H, s, $(CH_3)_3$. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 155.5 (C-), 152.6 (C-), 147.4 (C-), 146.8 (C-), 132.9 (CH-), 127.3 (C-), 124.0 (CH-), 121.8 (CH-), 116.8 (C-), 114.7 (CH-), 114.3 (C-),112.9 (C-), 89.1 (C-), 84.7 (C-), 61.3 (OCH_3-), 58.6 (C-), 56.0 (OCH_3-), 28.9 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 375 (M+, 48), 319 (100), 304 (33); HRMS (ESI): calcd for $C_{21}H_{22}N_5O_2$ (M + 1) 376.1768 found 376.17638; IR (ATR, cm^{-1}) ũ 3350 (w), 2216 (m), 1594 (m), 1530 (m), 1471 (m), 1396 (m), 1309 (m), 1264 (m), 1201 (m), 1070 (m), 1001 (m), 782 (m), 751 (m), 616 (m).

*6-Amino-1-tert-butyl-4-(4-hydroxy-3-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**29d**)*



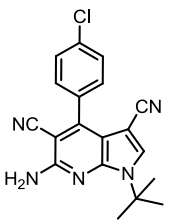
The product was isolated as a brown solid, yield 51 %, mp 225-227 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (1H, s, Ar-H), 6.93 - 7.10 (3H, m, Ar-H), 5.87 (1H, br. s., OH), 5.12 (2H, s, NH_2), 3.90 (3H, s, OCH_3), 1.69 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 156.0 (C-), 149.5 (C-), 147.9 (C-), 147.5 (C-), 146.2 (C-), 133.7 (CH-), 124.9 (C-), 123.0 (CH-), 117.5 (C-), 115.4 (C-), 114.7 (CH-), 112.3 (CH-), 111.7 (C-), 88.0 (C-), 84.5 (C-), 58.7 (C-), 56.0 (OCH_3-), 28.9 $(CH_3)_3$; MS (GC, 70 eV) m/z (%); 361 (M+, 35), 305 (100), HR(EI): calcd for $C_{20}H_{19}N_5O_2$ (M) 361.15333, found 361.15317; IR (ATR, cm-1) ῡ 3440 (m), 3344 (m), 2210 (m), 1582 (m), 1556 (m), 1513 (m), 1394 (m), 1311 (s), 1268 (m), 1168 (m), 1122 (m), 1026 (m), 820 (m), 786 (m), 763 (m), 619 (m).

*6-Amino-1-tert-butyl-4-m-tolyl-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**29e**)*



The product was isolated as a brown solid, yield 50 %, mp 222-224 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.21 (1H, s, Ar-H), 7.26 - 7.46 (4H, m, Ar-H), 6.78 (2H, s, NH_2), 2.38 (3H, s, CH_3), 1.71 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 156.7 (C-), 148.8 (C-), 147.7 (C-), 137.3 (C-), 135.5 (CH-), 133.3 (C-), 130.1 (CH-), 129.7 (CH-), 128.1 (CH-), 126.0 (CH-), 116.9 (C-), 114.9 (C-), 109.8 (C-), 86.6 (C-), 82.8 (C-), 58.3 (C-), 28.3 $(CH_3)_3$, 21.0 (CH_3-). MS (GC, 70 eV) m/z (%) 329 (M+, 36), 273 (100) 272 (84); HR (EI): calcd for $C_{20}H_{19}N_5$ 329.16350 found 329.163678; IR (ATR, cm^{-1}) ῡ 3480 (w), 3357 (m), 2968 (w), 1608 (s), 1591 (m), 1553 (m), 1482 (w), 1396 (s), 1367 (m), 1308 (s), 1214 (m), 1168 (m), 791 (m), 774 (m), 700 (s), 615 (m). calcd for $C_{20}H_{19}N_5$: C: 72.93, H: 5.81, N: 21.26, found: C: 72.52, H: 6.00, N: 20.77

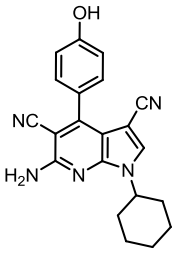
*6-Amino-1-tert-butyl-4-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**29f**)*



The product was isolated as a brown solid, yield 45 %, mp 202-204 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.27 (1H, s, Ar-H), 7.51 - 7.72 (4H, m, Ar-H), 6.89 (2H, br. s., NH_2), 1.75 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 156.7 (C-),

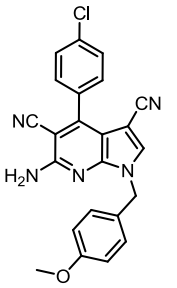
147.8 (C-), 147.5 (C-), 135.6 (CH-), 134.4 (C-), 132.4 (C-), 131.0 (CH-), 128.4 (CH-), 116.6 (C-), 114.9 (C-), 109.9 (C-), 86.8 (C-), 82.5 (C-), 58.4 (C-), 28.4 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 349 (M+, 19), 293 (100); HR (EI): calcd for $C_{19}H_{16}ClN_5$ 349.10887 found 349.10903; IR (ATR, cm-1) ũ 3388 (w), 3155 (w), 2215 (s), 1610 (m), 1589 (m), 1552 (m), 1477 (w), 1391 (s), 1368 (m), 1305 (s), 1210 (m), 1091(m), 1014 (m), 829 (s), 783 (m), 608 (m). calcd for $C_{19}H_{16}ClN_5$: C: 65.24, H: 4.61, N: 20.02, found: C: 64.90, H: 4.68, N: 18.38

*6-Amino-1-cyclohexyl-4-(4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**29g**)*



The product was isolated as a brown solid. Yield 40 %, mp 242-244 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.91 (1H, s, OH), 8.37 (1H, s, Ar-H), 7.39 (2H, d, J = 8.5 Hz, Ar-H), 6.93 (2H, d, J = 8.5 Hz, Ar-H), 6.82 (2H, s, NH_2), 4.49 - 4.66 (1H, m, CH), 1.73 - 1.96 (7H, m, CH_2), 1.22 - 1.46 (3H, m, CH_2). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 158.6 (C-), 157.8 (C-), 149.4 (C-), 147.0 (C-), 134.5 (CH-), 130.6 (CH-), 123.9 (C-), 117.1 (C-), 115.1 (C-), 115.0 (CH-), 108.5 (C-), 87.2 (C-), 84.0 (C-), 53.2 (CH-), 32.1 (CH_2-), 25.2 (CH_2-), 24.6 (CH_2-). MS (GC, 70 eV) m/z (%) 357 (M+, 58), 275 (100), 247 (16); HR (EI): calcd for $C_{21}H_{19}N_5O$ (M + 1) 357.15841, found 357.15815; IR (ATR, cm^{-1}) ũ 3354 (w), 2933 (w), 2215 (s), 1738 (m), 1595 (m), 1517 (m), 1444 (m), 1394 (m), 1281 (m), 1231 (m), 832 (m), 787 (m), 598 (m).

*6-Amino-4-(4-chlorophenyl)-1-(4-methoxybenzyl)-1H-pyrrolo[2,3-b]pyridine-3,5-dicarbonitrile (**29h**)*



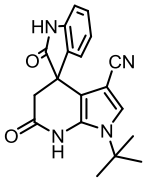
The product was isolated as a beige solid, yield 60 %, mp 222-224 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.31 (1H, s, Ar-H), 7.57 - 7.66 (4H, m, Ar-H), 7.33 (2H, d, J = 8.7 Hz, Ar-H), 7.00 (2H, s, NH_2), 6.92 (2H, d, J = 8.8 Hz, Ar-H), 5.30(2H, s, CH_2), 3.74 (3H, s, OCH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 158.9 (C-), 157.9 (C-), 147.9 (C-), 147.5 (C-), 137.0 (CH-), 134.5 (C-), 132.1 (C-), 130.9 (CH-), 129.2 (CH-), 128.5 (C-), 128.3 (CH-), 116.6 (C-), 114.5 (C-), 114.0 (CH-), 108.3 (C-), 87.2 (C-), 83.7 (C-), 55.0 (OCH_3-), 47.2 (CH_2-).MS (GC, 70 eV) m/z (%) 413 (M+, 11), 121 (100); HRMS (ESI): calcd for $C_{23}H_{17}ClN_5O$ (M + 1) 414.11161, found 414.11086; IR (ATR, cm^{-1}) ũ 3443 (w), 3323 (w), 2225 (m), 2209 (m), 1626 (m), 1562 (m), 1512 (m), 1415 (m), 1381

(m), 1299 (m), 1253 (m), 1174 (m), 1091 (m), 813 (s), 608 (m). calcd for $C_{23}H_{16}ClN_5O$: C: 66.75, H: 3.90, N: 16.92, found: C: 66.59, H: 3.91, N: 16.67.

A.2.14 General procedure for the synthesis of compounds 36a-j

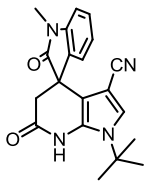
A mixture of Meldrum´s acid (1 equiv.), the corresponding isatin (1 equiv.), 5-amino-1R-pyrrole-3-carbonitrile (1 equiv.) and ammonium acetate (5 equiv.) was refluxed in acetic acid for 4-6 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent: *n*-heptane/ethylacetate).

*1'-Tert-butyl-2,6'-dioxo-1',5',6',7'-tetrahydrospiro[indoline-3,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**36a**)*



The product was isolated as a light yellow solid, yield 81 %, mp 291–293 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.56 (9H, s, $(CH_3)_3$), 2.61 - 2.85 (2H, dd, J = 15.76 Hz, CH_2), 6.84 - 7.03 (2H, m, Ar-H), 7.08 - 7.28 (2H, m, Ar-H), 7.35 (1H, s, Ar-H), 10.14 (1H, s, NH), 10.61 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 177.7 (C-), 168.4 (C-), 141.5 (C-), 131.4 (C-), 131.2 (C-), 128.8 (CH-), 123.6 (CH-), 123.1 (CH-), 122.0 (CH-), 114.6 (C-), 109.8 (CH-), 103.5 (C-), 86.1 (C-), 57.8 (C-), 46.2 (C-), 40.3 (CH_2), 29.2 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 334 (M^+, 49), 277 (89), 250 (68); HRMS (ESI): calcd for $C_{19}H_{19}N_4O_2$(M + 1) 335.15025, found 335.15072; IR (ATR, cm^{-1}): 3172 (w), 2230 (w), 1715 (s), 1672 (s), 1471 (m), 1208 (m), 748 (s), 606 (s).

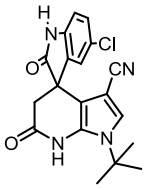
*1'-Tert-butyl-1-methyl-2,6'-dioxo-1',5',6',7'-tetrahydrospiro[indoline-3,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**36b**)*



The product was isolated as a white solid, yield 73 %, mp 326 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.59 (9H, s, $(CH_3)_3$), 2.81 (2H, dd, ^1J = 22.3 ^2J = 15.7 Hz, CH_2), 3.19 (3H, s, OCH_3), 7.04 - 7.16 (2H, m, Ar-H), 7.20 (1H, d, J = 7 Hz, Ar-H), 7.32 - 7.41 (2H, m, Ar-H),10.23 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 175.9 (C-), 168.4 (C-), 142.8 (C-), 131.2 (C-), 130.8 (C-), 128.9 (CH-), 123.2 (CH-), 123.0 (CH-

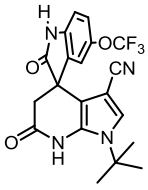
), 122.7 (CH-), 114.5 (C-), 108.9 (CH), 103.5 (C-), 86.0 (C-), 57.8 (C-), 45.8 (C-), 39.9 (CH_2), 29.2 $(CH_3)_3$, 26.1 (CH_3); MS (GC, 70 eV): *m/z* (%) 348 (M^+, 44), 291 (100), 250 (36); HRMS (ESI): calcd for $C_{20}H_{21}N_4O_2$(M + 1) 349.1659, found 349.1664; IR (ATR, cm^{-1}): 3140 (w), 2220 (w), 1704 (s), 1668 (s), 1614 (w), 1469 (m), 1347 (s), 1208 (m), 1008 (w), 742 (s), 626 (w).

*1'-Tert-butyl-5-chloro-2,6'-dioxo-1',5',6',7'-tetrahydrospiro[indoline-3,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**36c**)*



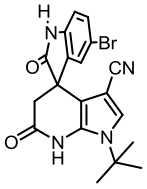
The product was isolated as a white solid, yield 86 %, mp 334 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.59 (9H, s, $(CH_3)_3$), 2.68 (1H, d, J = 15.7 Hz, CH_2), 3.03 (1H, d, J = 15.7 Hz, CH_2), 6.93 (1H, d, J = 8.3 Hz, Ar-H), 7.27 - 7.34 (2H, m, Ar-H), 7.41 (1H, s, Ar-H), 10.15 (1H, s, NH),10.75 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 177.5 (C-), 168.3 (C-), 140.7 (C-), 133.1 (C-), 131.4 (C-), 128.8 (CH-), 125.9 (C-), 124.0 (CH-), 123.2 (CH-), 114.5 (C-), 111.2 (CH-), 102.8 (C-),86.0 (C-), 57.9 (C-), 46.4 (C-), 39.6 (CH_2), 29.2 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 368 (M+, 34), 311 (64), 284 (34); HRMS (ESI): calcd for $C_{19}H_{18}N_4O_2Cl$(M + 1) 369.1113, found 369.1114; IR (ATR, cm–1): 3280 (w), 2229 (w), 1727 (s), 1698 (s), 1614 (w), 1471 (m), 1199 (m), 821 (s), 615 (w).

*1'-Tert-butyl-2,6'-dioxo-5-(trifluoromethoxy)-1',5',6',7'-tetrahydrospiro[indoline-3,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**36d**)*



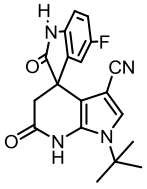
The product was isolated as white a solid, yield 52 %, mp 299 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.61 (9H, s, $(CH_3)_3$), 2.66 (1H, d, J=15.9 Hz, CH_2), 3.14 (1H, d, J = 15.7 Hz, CH_2), 7.01 (1H, d, J = 8.3 Hz, Ar-H), 7.24 - 7.35 (2H, m, Ar-H), 7.41 (1H, s, Ar-H), 10.17 (1H, s, NH), 10.78 (1H, s, NH); ^{19}F NMR (DMSO-d_6) δ -57.19; ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 177.9 (C-), 168.3 (C-), 143.5 -143.4 (C-F, q, $^3J_{C\text{-}F}$ = 1.8 Hz), 141.2 (C-), 132.6 (C-), 131.5 (C-), 123.1 (CH-), 122.2 (CH-), 117.9 (CH-), 114.3 (C-), 114.0-126.2 (C-F, q, $^1J_{C\text{-}F}$ = 255.4 Hz) 110.6 (CH-), 102.6 (C-), 86.1 (C-), 57.9 (C-), 46.6 (C-), 39.4 (CH_2), 29.2 $(CH_3)_3$; MS (GC, 70 eV): m/z (%) 418 (M^+, 28), 361 (46), 334 (24); HRMS (ESI): calcd for $C_{20}H_{18}F_3N_4O_3$(M + 1) 419.13255, found 419.13294; IR (ATR, cm^{-1}): 3202 (w), 2225 (w), 1714 (m), 1681 (s), 1482 (m), 1247 (m), 1206 (s), 1166 (s), 614 (w).

*5-Bromo-1'-tert-butyl-2,6'-dioxo-1',5',6',7'-tetrahydrospiro[indoline-3,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**36e**)*



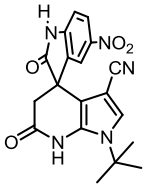
The product was isolated as a white solid, yield 51 %, mp 309 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.59 (9H, s, $(CH_3)_3$), 2.72 (1H, d, J = 15.9 Hz, CH_2), 2.97 (1H, d, J = 15.9 Hz, CH_2) , 6.97 (1H, t, J = 8.1 Hz,Ar-H), 7.20 (1H, d, J = 7.0 Hz, Ar-H), 7.41 (1H, s, Ar-H), 7.46 (1H, dd, J_1 = 8.1 J_2 = 1 Hz, Ar-H), 10.20 (1H, s, NH),10.94 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 177.6 (C-), 168.2 (C-), 141.1 (C-), 132.9 (C-), 131.8 (CH-), 131.4 (C-), 123.7 (CH-), 123.2 (CH-), 122.9 (CH-), 114.5 (C-), 102.8 (C-), 102.1 (C-), 86.1 (C-), 57.9 (C-), 47.3 (C-), 40.0 (CH_2), 29.2 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 412 (M^+, 22), 357 (38), 314 (25); HRMS (ESI): calcd for $C_{19}H_{18}BrN_4O_2$(M + 1) 413.06077, found 430.06122; IR (ATR, cm^{-1}): 3152 (w), 2227 (w), 1727 (s), 1677 (s), 1469 (m), 1321 (m), 1201 (m), 736 (s).

*1'-Tert-butyl-5-fluoro-2,6'-dioxo-1',5',6',7'-tetrahydrospiro[indoline-3,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**36f**)*



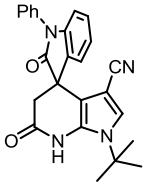
The product was isolated as a brown solid, yield 75 %, mp 277–279 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.59 (9H, s, $(CH_3)_3$), 2.64 (1H, d, J = 15.7 Hz, CH_2), 3.04 (1H, d, J = 15.7 Hz, CH_2), 6.90 (1H, dd, ^{1}J = 8.3 ^{2}J = 4.3 Hz, Ar-H),7.06 - 7.17 (2H, m, Ar-H), 7.40 (1H, s, Ar-H), 10.14 (1H, s, NH) 10.62 (1H, s, NH); ^{19}F NMR (DMSO-d_6) δ ; ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 177.8 (C-), 168.3 (C-), 156.3-160.1 (C-F, d, $^{1}J_{C\text{-}F}$ = 237 Hz), 138.0-138.1 (C-F, d, $^{4}J_{C\text{-}F}$ = 1.83 Hz), 132.6 -132.7 (C-F, d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 131.4 (C-), 123.2 (CH-), 115.0 -115.4 (C-F, d, $^{2}J_{C\text{-}F}$ = 23.4 Hz),114.5 (C-), 111.7 - 111.9 (C-F, d, $^{2'}J_{C\text{-}F}$ = 24.7 Hz), 110.6 - 110.7 (C-F, d, $^{3'}J_{C\text{-}F}$ = 7.8 Hz), 102.9 (C-), 86.1 (C-), 57.9 (C-), 46.6-46.7 (C-F, d, $^{4'}J_{C\text{-}F}$ = 1.8 Hz), 39.7 (CH_2-), 29.2 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 352 (M^+, 44), 295 (67), 268 (40); HRMS (ESI): calcd for $C_{19}H_{18}FN_4O_2$(M + 1) 353.14083, found 353.14122; IR (ATR, cm^{-1}): 3207 (w), 2220 (w), 1657 (s), 1651 (s), 1486 (m), 1200 (m), 821 (w), 612 (w).

*1'-Tert-butyl-5-nitro-2,6'-dioxo-1',5',6',7'-tetrahydrospiro[indoline-3,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**36g**)*



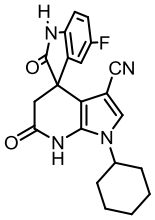
The product was isolated as a brown solid, yield 70 %, mp 331 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.33 (1H, s, NH), 10.25 (1H, s, NH), 8.27 (1H, dd, ^{1}J= 8.7 Hz ^{2}J = 2.3 Hz, Ar-H), 8.18 (1H, d, J = 2.3 Hz, Ar-H), 7.43 (1H, s, Ar-H), 7.13 (1H, d, J = 8.7 Hz, Ar-H), 3.27 (1H, d, J = 15.7 Hz, CH_2), 2.73 (1H, d, J=15.7 Hz, CH_2), 1.60 (9H, s, $(CH_3)_3$); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 178.3 (C-), 168.2 (C-), 148.6 (C-), 142.4 (C-), 132.0 (C-), 131.7 (C-), 126.3 (CH-), 123.4 (CH-), 119.9 (CH-), 114.5 (C-), 110.1 (CH-), 102.1 (C-), 85.8 (C-), 58.0 (C-), 46.2 (C-), 38.9 (CH_2-), 29.2 $(CH_3)_3$; HRMS (ESI): calcd for $C_{19}H_{18}N_5O_4$(M + 1) 380.13533, found 380.13579; IR (ATR, cm^{-1}): 3212 (w), 2227 (w), 1748 (m), 1690 (s), 1326 (s), 1202 (s), 1079 (w).

*1'-Tert-butyl-2,6'-dioxo-1-phenyl-1',5',6',7'-tetrahydrospiro[indoline-3,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**36h**)*



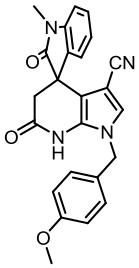
The product was isolated as a white solid, yield 55 %, mp 310 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.62 (9H, s, $(CH_3)_3$), 3.00 (2H, dd, ^{1}J = 15.7 Hz ^{2}J = 2.5 Hz, CH_2), 6.78 (1H, d, J = 7.7 Hz, Ar-H),7.09 - 7.18 (1H, m,Ar-H), 7.26 - 7.34 (2H, m, Ar-H), 7.45 (1H, s, Ar-H), 7.48 - 7.56 (3H, m, Ar-H), 7.59 - 7.66 (2H, m, Ar-H), 10.31 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 175.5 (C-), 168.3 (C-), 142.7 (C-), 134.1 (C-), 131.2 (C-), 130.8 (C-), 129.6 (CH-), 129.0 (CH-), 128.3 (CH-), 126.9 (CH-), 123.6 (CH-), 123.3 (CH-),123.2 (CH-), 114.9 (C-), 109.3 (CH-), 103.7 (C-), 85.9 (C-), 57.9 (C-), 46.1 (C-), 40.1 (CH_2-), 29.2 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 410 (M^+, 45), 353 (100), 325 (64); HRMS (ESI): calcd for $C_{25}H_{23}N_4O_2$(M + 1) 411.18155, found 411.18188; IR (ATR, cm^{-1}): 3149 (w), 2220 (w), 1725 (s), 1678 (s), 1605 (m), 1495 (m), 1327 (m), 1204 (m), 752 (s), 693 (m).

*1'-Cyclohexyl-5-fluoro-2,6'-dioxo-1',5',6',7'-tetrahydrospiro[indoline-3,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**36i**)*



The product was isolated as a white solid, yield 55 %, mp 235-237 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.16 - 1.28 (1H, m, CH_2), 1.33 - 1.49 (2H, m, CH_2), 1.54 - 1.73 (3H, m, CH_2), 1.77 - 2.00 (4H, m, CH_2), 2.63 (1H, d, J = 15.9 Hz, CH_2), 3.08 (1H, d, J = 15.9 Hz, CH_2), 4.08 - 4.22 (1H, m, CH), 6.91 (1H, dd, ^{1}J = 8.21 Hz, ^{2}J = 4.25 Hz, Ar-H), 7.07 - 7.22 (2H, m, Ar-H), 7.44 (1H, s, Ar-H), 10.60 (1H, s, NH), 10.77 (1H, s, OH); ^{19}F NMR (DMSO-d_6) δ -121.3; ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 178.1 (C-), 168.1 (C-), 160.1 - 156.3 (C-F, d, $^{1}J_{C\text{-}F}$ = 237.1 Hz), 138.08 - 138.1 (C-F, d, $^{4}J_{C\text{-}F}$ = 1.4 Hz), 132.9 - 132.7 (C-F, d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 131.5 (C-), 121.7 (CH-), 115.3 - 114.9 (C-F, d, $^{2'}J_{C\text{-}F}$ = 23.4 Hz), 114.5 (C-), 111.9 - 111.6 (C-F, d, $^{2}J_{C\text{-}F}$ = 24.7 Hz), 110.6 -110.5 (C-F, d, $^{3'}J_{C\text{-}F}$ = 8.2 Hz), 99.6 (C-), 87.2 (C-), 54.1 (CH_2), 46.9 - 47.0 (C-F, d, $^{4'}J_{C\text{-}F}$ = 1.4 Hz), 32.9 (CH_2), 32.8 (CH_2), 24.9 (CH_2), 24.9 (CH_2), 24.5 (CH_2-); MS (GC, 70 eV): *m/z* (%) 378 (M^+, 100), 295 (44), 268 (45); HR (EI): calcd for $C_{21}H_{19}N_4FO_2$(M + 1) 378.14866, found 378.14867; IR (ATR, cm^{-1}): 3220 (w), 2220 (w), 1720 (s), 1705 (s), 1486 (s), 1175 (m), 600 (s). Anal calcd for $C_{21}H_{19}FN_4O_2$; C: 66.66, H: 5.06, N: 14.81, found C: 66.27, H: 5.07, N: 14.84.

1'-(4-Methoxybenzyl)-1-methyl-2,6'-dioxo-1',5',6',7'-tetrahydrospiro[indoline-3,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (***36j***)



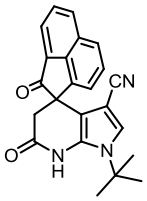
The product was isolated as a white solid, yield 58 %, mp 224-226 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.69 - 2.75 (1 H, dd, ^{1}J=16.05 Hz, CH_2), 2.88 -2.94 (1 H, dd, ^{1}J=15.9 Hz, CH_2), 3.18 (3H, s, NCH_3), 3.77 (3H, s, OCH_3), 5.14 (2H, s, CH_2), 6.98 (2H, d, J = 8.50 Hz, Ar-H), 7.03 - 7.16 (2H, m, Ar-H), 7.18 - 7.31 (3H, m, Ar-H), 7.31 - 7.43 (2H, m, Ar-H), 10.96 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 176.1 (C-), 168.2 (C-), 158.9 (C-), 143.0 (C-), 131.9 (C-), 130.7 (C-), 129.0 (CH-), 128.9 (CH-), 128.4 (C-), 124.8 (CH-), 123.2 (CH-), 122.7 (CH-), 114.2 (C-), 114.1 (CH-), 108.8 (C-), 100.8 (CH-), 87.3 (C-), 55.1 (OCH_3-), 48.3 (CH_2), 46.1 (C-), 39.9 (CH_2), 26.1 (CH_3); MS (GC, 70 eV): *m/z* (%) 412 (M^+, 10), 121 (100); HRMS (ESI): calcd for $C_{24}H_{20}N_4O_3$(M + 1) 413.16082, found 413.16003; IR (ATR, cm^{-1}): 3102 (w), 2217 (w), 1688 (s), 1682 (s), 1606 (M), 1515 (M), 1288 (m), 1256 (m), 1173 (m), 1131 (m), 757 (s). Anal calcd for $C_{24}H_{20}N_4O_3$; C: 69.89, H: 4.89, N:

13.58, found C: 69.59, H: 4.84, N: 13.51.

A.2.15 General procedure for the synthesis of compounds 37a-b, 38a-c, 39a-c and 40a

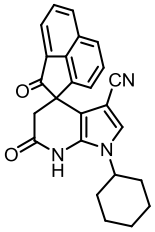
A mixture of Meldrum´s acid (1 equiv.), the corresponding 1,2-dicarbonyl compound (1 equiv.) and 5-amino-1R-pyrrole-3-carbonitrile (1equiv.) was refluxed in ethanol (**37a-b**), acetic acid (**38a-c**) or 1,4 dioxane (**39a-c**, **40a**) for 4-6 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent: *n*-heptane/ethylacetate).

*1'-Tert-butyl-2,6'-dioxo-1',5',6',7'-tetrahydro-2H-spiro[acenaphthylene-1,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**37a**)*



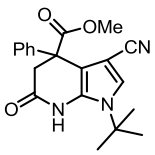
The product was isolated as a yellow solid, yield 71 %, mp 330 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.61 (9H, s, $(CH_3)_3$), 2.83 (1H, d, J = 15.7 Hz, CH_2), 3.13 (1H, d, J = 15.7 Hz, CH_2),7.35 (1H, s, Ar-H), 7.57 (1H, d, J = 7 Hz, Ar-H), 7.75 (1H, m, Ar-H), 7.86 - 7.95 (1H, m, Ar-H), 8.04 (2H, m, Ar-H), 8.37 (1H, d, J = 7.9 Hz, Ar-H), 10.28 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 203.3 (C-), 168.6 (C-), 140.6 (C-), 140.2 (C-), 132.5 (CH-), 131.2 (C-), 130.8 (C-), 130.3 (C-), 128.9 (CH-), 128.8 (CH-), 125.0 (CH-),123.1 (CH-), 122.4 (CH-), 120.6 (CH-), 114.5 (C-), 104.5 (C-), 86.1 (C-), 57.9 (C-), 51.0 (C-), 39.9 (CH_2), 29.2 ($(CH_3)_3$); MS (GC, 70 eV): *m/z* (%) 369 (M^+, 75), 313 (50), 284 (100); HRMS (EI): calcd for $C_{23}H_{19}N_3O_2$(M + 1) 369.14718, found 369.14745; IR (ATR, cm^{-1}): 3153 (w), 2221 (w), 1710 (s), 1673 (s), 1341 (s), 1204 (m), 776 (s).

*1'-Cyclohexyl-2,6'-dioxo-1',5',6',7'-tetrahydro-2H-spiro[acenaphthylene-1,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**37b**)*



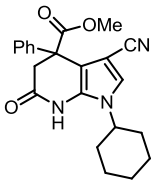
The product was isolated as a yellow solid, yield 55 %, mp 335-337 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.13 - 1.31 (1H, m, CH_2), 1.34 - 1.55 (2H, m, CH_2), 1.55 - 1.76 (3H, m, CH_2), 1.83 - 1.98 (4H, m, CH_2), 2.85 (1H, dd, J = 15.9 Hz, CH_2), 3.19(1H, dd, J = 15.9 Hz, CH_2), 4.21 (1H, m, CH), 7.40 (1H, br. s., Ar-H), 7.62 (1H, d, J = 6.4 Hz, Ar-H), 7.79 (1H, m, Ar-H), 7.85 - 7.98 (1H, m, Ar-H), 7.98 - 8.17 (2H, m, Ar-H), 8.40 (1H, d, J = 7.9 Hz, Ar-H), 10.91 (1H, br. s., NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 203.5 (C-), 168.4 (C-), 140.7 (C-), 140.2 (C-), 132.4 (CH-), 131.3 (C-), 130.6 (C-), 130.3 (C-), 128.9 (CH-), 128.8 (CH-), 125.0 (CH-),122.4 (CH-), 121.6 (CH-), 120.6 (CH-), 114.5 (C-), 101.3 (C-), 87.3 (C-), 54.1 (CH-), 51.2 (C-), 40.1 (CH_2), 32.8 (CH_2), 24.9 (CH_2), 24.5 (CH_2); MS (GC, 70 eV): *m/z* (%) 395 (M^+, 100), 366 (28), 284 (59); HRMS (ESI): calcd for $C_{25}H_{21}N_3O_2$(M + 1) 395.16283, found 395.16299; IR (ATR, cm^{-1}): 3280 (w), 2218 (w), 1713 (s), 1683 (s), 1494 (m), 1326 (s), 1178 (m), 784 (s).

*Methyl-1-tert-butyl-3-cyano-6-oxo-4-phenyl-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-4-carboxylate (**38a**)*



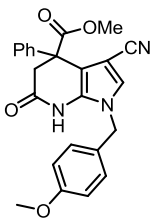
The product was isolated as a yellow solid, yield 70 %, mp 85 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.57 (9H, s, $(CH_3)_3$), 3.22 - 3.00 (2H, dd, J = 15.5 Hz, CH_2), 3.70 (3H, s, OCH_3), 7.14 - 7.22 (2H, m, Ar-H), 7.26 - 7.41 (3H, m, Ar-H), 7.54 (1H, s, Ar-H), 10.07 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 172.5 (C-), 168.0 (C-), 140.2 (C-), 130.2 (C-), 128.3 (CH-), 127.3 (CH-), 126.9 (CH-), 124.0 (CH-), 115.6 (C-), 104.6 (C-), 88.0 (C-), 57.8 (C-), 52.4 (OCH_3-), 50.5 (C-), 43.5 (CH_2), 29.1 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 351 (M^+, 18), 292 (27), 236 (100); HRMS (EI): calcd for $C_{20}H_{21}N_3O_3$(M + 1) 351.15800, found 351.15774; IR (ATR, cm^{-1}): 3231 (w), 2222 (w), 1731 (m), 1681 (s), 1674 (s), 1494 (m), 1199 (m), 698 (m).

*Methyl-3-cyano-1-cyclohexyl-6-oxo-4-phenyl-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-4-carboxylate (**38b**)*



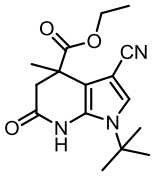
The product was isolated as a white solid, yield 77 %, mp 310 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.22 (1H, m, CH_2), 1.39 (2H, m, CH_2), 1.52 - 1.74 (3H, m, CH_2), 1.75 - 1.99 (4H, m, CH_2), 2.94 (1H, d, J = 15.86 Hz, CH_2), 3.20 (1H, d, J = 15.86 Hz, CH_2), 3.70 (3H, s, OCH_3), 3.99 - 4.23 (1H, m, CH), 7.18 (2H, d, J = 7.36 Hz, Ar-H), 7.26 - 7.45 (3H, m, Ar-H), 7.58 (1H, s, Ar-H), 10.73, (1H, br. s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 172.6 (C-), 167.8 (C-), 140.7 (C-), 130.5 (C-), 128.4 (CH-), 127.3 (CH-), 126.6 (CH-), 122.7 (CH-), 115.8 (C-), 100.8 (C-), 89.4 (C-), 54.1(CH-), 52.4 (OCH_3-), 50.9 (C-), 44.0 (CH_2), 32.7 (CH_2), 24.9 (CH_2), 24.5 (CH_2); MS (GC, 70 eV): *m/z* (%) 377 (M^+, 15), 318 (100), 236 (41);HR (EI): calcd for $C_{22}H_{23}N_3O_3$(M + 1) 377.17339, found 377.17367; IR (ATR, cm^{-1}): 3253 (w), 2940 (w), 2224 (w), 1724 (s), 1692 (s), 1529 (m), 1500 (m), 1290 (w), 1231 (m), 1175 (m), 1065 (m), 759 (s), 702 (s), 607 (s). Anal calcd for $C_{22}H_{23}N_3O_3$; C: 70.01, H: 6.14, N: 11.13, found C: 69.81, H: 6.08, N: 11.27.

*Methyl-3-cyano-1-(4-methoxybenzyl)-6-oxo-4-phenyl-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-4-carboxylate (**38c**)*



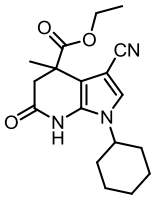
The product was isolated as a yellow solid, yield 65%, mp 102-104 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.87 (1H, d, ^{1}J = 15.9 Hz, CH_2), 3.12 (1H, d, ^{1}J = 15.9 Hz, CH_2), 3.66 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 5.09 (2H, s), 6.84 -7.03 (2H, m, Ar-H), 7.06 - 7.23 (4H, m, Ar-H), 7.24 - 7.42 (3H, m, Ar-H), 7.48 (1H, s, Ar-H), 10.81 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 172.5 (C-), 167.7 (C-), 158.9 (C-), 140.6 (C-), 131.1 (C-), 128.9 (CH-), 128.5 (CH-), 128.3 (C-), 127.4 (CH-), 126.6 (CH-), 126.0 (CH-), 115.5 (C-), 114.2 (C-), 101.4 (C-), 89.7 (C-), 55.1 (C-), 52.5 (OCH_3), 51.1 (OCH_3), 48.3 (CH_2), 44.0 (CH_2); MS (GC, 70 eV): *m/z* (%) 415 (M^+, 6), 121 (100); HRMS (EI): calcd for $C_{24}H_{21}N_3O_4$(M + 1) 415.15266, found 415.15251; IR (ATR, cm^{-1}): 3126 (w), 2224 (w), 1728 (m), 1513 (s), 1245 (s), 1175 (m), 699 (m). Anal calcd for $C_{24}H_{21}N_3O_4$; C: 69.39, H: 5.10, N: 10.11, found C: 69.54, H: 5.45, N: 9.85.

*Ethyl-1-tert-butyl-3-cyano-4-methyl-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-4-carboxylate (**39a**)*



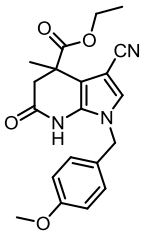
The product was isolated as a white solid, yield 73 %, mp 210-212 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19 (3H, t, J = 6 Hz, CH_3), 1.57 (9H, s, $(CH_3)_3$), 1.62 (3H, s, CH_3), 2.82 - 2.59 (2H, dd, J = 15.5 Hz, CH_2), 4.11 (2H, q, CH_2), 7.46 (1H, s, Ar-H), 9.98 (1H, br. s., NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 173.2 (C-), 168.7 (C-), 129.7 (C-), 123.3 (CH-), 116.5 (C-), 105.4 (C-), 86.5 (C-), 60.7 (CH_2), 57.5 (C-), 42.1 (CH_2), 41.0 (C-), 29.1 $(CH_3)_3$, 22.3 (CH_3), 13.7 (CH_3); MS (GC, 70 eV): *m/z* (%) 305 (M^+, 51), 249 (100), 174 (86); HRMS (ESI): calcd for $C_{21}H_{19}N_4O_3$(M + 1) 304.16557, found 304.1655; IR (ATR, cm^{-1}): 3219 (w), 2216 (w), 1722 (s), 1674 (s), 1352 (m), 1209 (m), 1156 (m), 1131 (m), 629 (s).

*Ethyl-3-cyano-1-cyclohexyl-4-methyl-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-4-carboxylate (**39b**)*



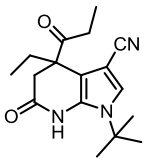
The product was isolated as a white solid, yield 57 %, mp 263 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (3H, t, J = 7.08 Hz, CH_3), 1.17 - 1.45 (3H, m, CH_2), 1.46 - 1.73 (6 H, m, CH_2), 1.73 - 2.03 (4 H, m, CH_2), 2.62 (3 H, s, CH_3), 2.57 (2 H, dd, ^{1}J = 15.9 Hz, ^{2}J = 49.1 Hz, CH_2), 3.91 - 4.24 (m, 3 H, $CHCH_2$), 7.45 (1 H, s, Ar-H), 10.55 (1 H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 173.3 (C-), 168.6 (C-), 129.8 (C-), 121.9 (CH), 116.5 (C-), 102.2 (C-), 87.9 (C-), 60.7 (CH_2), 53.9 (CH), 42.4 (CH_2), 41.3 (C-), 32.9 (CH_2), 24.8 (CH_2), 24.5 (CH_2), 22.3 (CH_3), 13.7 (CH_3); MS (GC, 70 eV): *m/z* (%) 329 (M^+, 15), 256 (100), 174 (57); HR (EI): calcd for $C_{18}H_{23}N_3O_3$(M + 1) 329.17339, found 329.17359; IR (ATR, cm^{-1}): 3131 (w), 2938 (w), 2217 (w), 1723 (s), 1673 (s), 1544 (s), 1351 (s), 1187 (m), 1098 (m), 1015 (m), 773 (s), 621 (s). Anal calcd for $C_{18}H_{23}N_3O_3$; C: 65.63, H: 7.04, N: 12.76, found C: 65.74, H: 6.98, N: 12.97.

*Ethyl-3-cyano-1-(4-methoxybenzyl)-4-methyl-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-4-carboxylate (**39c**)*



The product was isolated as a white solid, yield 68 %, mp 139-142 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (3H, t, J = 7.08 Hz, CH_3), 1.59 (3H, s, CH_3), 2.55 - 2.61 (1H, d, J = 15.9 Hz , CH_2), 2.72 - 2.77 (1H, d, J = 15.9 Hz , CH_2), 3.75 (3H, s, OCH_3), 4.06 (2H, m, CH_2), 4.94 - 5.20 (2H, dd, ^{1}J = 15.3, ^{2}J = 34.6 Hz, CH_2), 6.94 (2H, d, J = 8.69 Hz, Ar-H), 7.20 (2H, d, J=8.69 Hz, Ar-H), 7.41 (1H, s, Ar-H), 10.66 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 173.3 (C-), 168.6 (C-), 158.9 (C-), 130.4 (C-), 128.9 (CH-), 128.4 (C-), 125.2 (CH-), 116.2 (C-), 114.1 (CH-), 102.7 (C-), 88.0 (C-), 60.8 (CH_2-), 55.0 (OCH_3-), 48.1 (CH_2-), 42.2 (CH_2-), 41.4 (C-), 22.1 (CH_3-), 13.7 (CH_3-); MS (GC, 70 eV): *m/z* (%) 367 (M^+, 5), 121 (100); HRMS (ESI): calcd for $C_{20}H_{21}N_3O_4$(M +1) 367.15266, found 367.15270; IR (ATR, cm^{-1}): 3286 (w), 2222 (w), 1695 (s), 1511 (s), 1460 (m), 1251 (s), 810 (s). Anal calcd for $C_{20}H_{21}N_3O_4$; C: 65.38, H: 5.76, N: 11.44, found C: 65.57, H: 5.78, N: 11.55.

*1-Tert-butyl-4-ethyl-6-oxo-4-propionyl-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**40a**)*

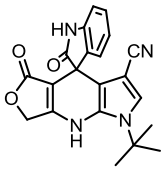


The product was isolated as a white solid, yield 40 %, mp 257-259 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.86 (4H, s, NH), 7.52 (1H, s, Ar-H), 2.75 (1H, d, J = 15.7 Hz, CH_2), 2.48 (2H, q, 7.4 Hz), 2.42 (1H, d, J = 15.5 Hz, CH_2), 2.24 (1H, m, CH_2), 1.97 (1H, m, CH_2), 1.53 (9H, s, $(CH_3)_3$), 0.85 (6H, m, J = 7.6 Hz, J = 7.2 Hz, CH_3); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 209.3 (C-), 169.4 (C-), 130.6 (C-), 124.1 (CH-), 117.1 (C-), 103.5 (C-), 86.5 (C-), 57.7 (C-), 51.4 (C-), 37.8 (CH_2), 29.2 (CH_2), 29.0 $(CH_3)_3$, 26.4 (CH_2), 8.4 (CH_3), 8.3 (CH_3); MS (GC, 70 eV): *m/z* (%) 301 (M^+, 2), 244 (34), 188 (100); HRMS (ESI): calcd for $C_{17}H_{23}N_3O_2$(M + 1) 301.17873, found 301.17848; IR (ATR, cm^{-1}): 3149 (w), 2215 (w), 1705 (s), 1668 (s), 1346 (s), 1207 (s).

A.2.16 General procedure for the synthesis of compounds 41a-g and 42a-f

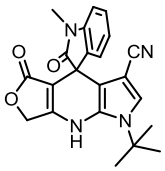
A mixture of tetronic acid (1 equiv.) or dimedone (1 equiv.), the corresponding isatin (1 equiv.), 5-amino-1R-pyrrole-3-carbonitrile (1 equiv.) and ammonium acetate (5 equiv.) was refluxed in acetic acid for 4-6 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent: *n*-heptane/ethylacetate).

*1-Tert-butyl-2',5-dioxo-1,5,7,8-tetrahydrospiro[furo[3,4-b]pyrrolo[3,2-e]pyridine-4,3'-indoline]-3-carbonitrile (**41a**)*



The product was isolated as a white solid, yield 57 %, mp 302-304 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ s, $(CH_3)_3$), 5.00 (2H, s, CH) 6.82 - 6.95 (3H, m, Ar-H), 7.15 - 7.24 (1H, m, Ar-H), 7.40 (1H, s, Ar-H), 10.06 (1H, s, NH), 10.54 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 177.7 (C-), 170.2 (C-), 158.1 (C-), 141.8 (C-), 134.6 (C-), 129.6 (C-), 128.4 (CH-), 124.4 (CH-), 124.1 (CH-), 121.7 (CH-), 114.3 (C-), 109.3 (CH-),103.5 (C-), 95.5 (C-), 86.5 (C-), 65.9 (CH_2), 57.5 (C-), 47.7 (C-), 28.9 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 372 (M^+, 36), 316 (100), 274 (64); HRMS (ESI): calcd for $C_{21}H_{19}N_4O_3$(M + 1) 375.14517, found 375.14512; IR (ATR, cm^{-1}): 3265 (w), 2224 (w), 1710 (s), 1638 (s), 1536 (s), 1512 (s), 1469 (m), 1332 (s), 1199 (m), 1056 (m), 759 (s). Anal calcd for $C_{21}H_{18}N_4O_3$; C: 67.37, H: 4.85, N: 14.88, found C: 67.07, H: 4.85, N: 15.04.

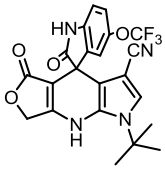
*1-Tert-butyl-1'-methyl-2',5-dioxo-1,5,7,8-tetrahydrospiro[furo[3,4-b]pyrrolo[3,2-e]pyridine-4,3'-indoline]-3-carbonitrile (**41b**)*



The product was isolated as a white solid, yield 63 %, mp 327-329 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.58 (9H,s, $(CH_3)_3$), 3.16 (3H, s, CH_3), 4.99 (2H, s, CH_2), 6.91 - 7.06 (3H, m, Ar-H), 7.22 - 7.31 (1H, m, Ar-H), 7.36 (1H, s, Ar-H), 10.10 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 176.1 (C-), 170.2 (C-), 158.4 (C-), 143.0 (C-), 133.9 (C-), 129.4 (C-), 128.6 (CH-), 124.0 (CH-), 122.5 (CH-), 114.3 (C-), 108.2 (CH-), 103.8 (C-), 95.0 (C-), 86.2 (C-), 66.0 (CH_2-), 57.5 (C-), 47.2 (C-), 28.9 $(CH_3)_3$, 26.1 (CH_3-); MS (GC, 70 eV): *m/z* (%) 388 (M^+, 68), 360 (37), 304 (67); HRMS (ESI): calcd for $C_{22}H_{21}N_4O_3$(M + 1) 389.16114, found 389.16082; IR (ATR, cm^{-1}): 3260 (w), 2230 (w), 1738 (s),

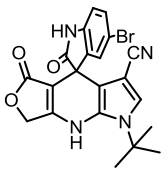
1687 (s), 1641 (s), 1539 (m), 1514 (m), 1029 (m), 752 (s). Anal calcd for $C_{21}H_{18}N_4O_3$; C: 68.03, H: 5,34 N: 14.42, found C: 67.60, H: 5.34, N: 14.23.

*1-Tert-butyl-2',5-dioxo-5'-(trifluoromethoxy)-1,5,7,8-tetrahydrospiro[furo[3,4-b]pyrrolo[3,2-e]pyridine-4,3'-indoline]-3-carbonitrile (**41c**)*



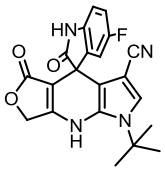
The product was isolated as a white solid, yield 37 %, mp 303-305 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ1.63 (9H, s, $(CH_3)_3$), 5.02 (2H, s,CH_2), 6.90 - 7.00 (2H, m, Ar-H), 7.23 (1H, dd, *J*=8 and 1 Hz, Ar-H), 7.44 (1H, s, Ar-H), 10.14 (1H, br. s., NH), 10.76 (1H, s, NH); ^{19}F NMR (DMSO-d_6) δ -57.13; ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 177.8 (C-), 170.2 (C-), 158.5 (C-), 143.4 - 143.5 (C-F, q, $^3J_{C\text{-}F}$ = 1.8 Hz), 141.1 (C-), 135.8 (C-), 129.7 (C-),124.3 (CH-), 121.7 (CH-), 118.0 (CH-), 114.1 (C-), 114.0- 126.2(C-F, q, $^1J_{C\text{-}F}$ = 251.7 Hz), 110.1 (CH-), 102.6 (C-), 94.7 (C-), 86.2 (C-), 66.0 (CH_2-), 57.5 (C-), 48.1 (C-), 28.8 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 456 (M^+, 27), 400 (100), 358 (44); HRMS (ESI): calcd for $C_{22}H_{18}N_4O_4F_4$(M + 1) 459.12747, found 459.1272; IR (ATR, cm^{-1}): 3271 (w), 2224 (w), 1714 (s), 1639 (s), 1537 (m), 1515 (m), 1199 (s), 1053 (m), 1024 (m), 803 (m). Anal calcd for $C_{22}H_{17}N_4O_4F_4$; C: 57.64, H: 3.74, N: 12.22, found C: 57.35, H: 3.67, N: 11.82.

*5'-Bromo-1-tert-butyl-2',5-dioxo-1,5,7,8-tetrahydrospiro[furo[3,4-b]pyrrolo[3,2-e]pyridine-4,3'-indoline]-3-carbonitrile (**41d**)*



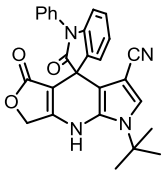
The product was isolated as a yellow solid, yield 64 %, mp 287-289 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.62 (9H, s, $(CH_3)_3$), 5.00 (2H, s, CH_2), 6.82 (1H, d, *J* = 8.3 Hz, Ar-H), 7.10 (1H, d, *J* = 2.1 Hz, Ar-H), 7.38 (1H, dd, J_1 = 8.1 Hz, J_2 = 2.1 Hz, Ar-H), 7.43 (1H, s, Ar-H), 10.12 (1H, s, NH), 10.70 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 177.3 (C-), 170.2 (C-), 158.4 (C-), 141.1 (C-), 136.7 (C-), 131.3 (CH-), 129.7 (C-), 127.2 (CH-), 124.3 (CH-), 114.3 (C-), 113.4 (C-),111.3 (CH-), 102.7 (C-), 94.8 (C-), 86.2 (C-), 66.0 (CH_2), 57.5 (C-), 47.8 (C-), 28.8 $(CH_3)_3$); MS (GC, 70 eV): *m/z* (%) 452 (M^+, 33), 394 (100), 352 (38); IR (ATR, cm^{-1}): 3163 (w), 2227 (w), 1711 (s), 1632 (s), 1537 (s), 1516 (s), 1199 (m), 813 (m).

*1-Tert-butyl-5'-fluoro-2',5-dioxo-1,5,7,8-tetrahydrospiro[furo[3,4-b]pyrrolo[3,2-e]pyridine-4,3'-indoline]-3-carbonitrile (**41e**)*



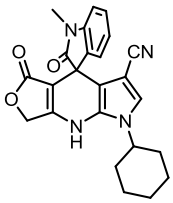
The product was isolated as a white solid, yield 61 %, mp 274-276 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.63 (9H,s, $(CH_3)_3$), 5.01 (2H, s, CH_2),6.83 - 6.87 (2H, m, Ar-H), 7.01 - 7.02 (1H, m, Ar-H), 7.43 (1H, s, Ar-H), 10.11 (1H, s, NH), 10.53 (1H, s, NH); ^{19}F NMR (DMSO-d_6) δ -122.01; ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 183.0 (C-), 175.4 (C-), 163.6 (C-), 161.6 - 165.4 (C-F, d, $^{1}J_{C\text{-}F}$ = 237.1 Hz), 143.3 - 143.2 (C-F, d, $^{4}J_{C\text{-}F}$ = 1.8 Hz), 141.3 -141.1 (C-F, d, $^{3'}J_{C\text{-}F}$ = 7.3 Hz), 134.9 (C-), 129.5 (CH), 120.2 - 119.8 (C-F, d, $^{2'}J_{C\text{-}F}$ = 23.4 Hz), 119.5 (C-), 117.5 - 117.1 (C-F, d, $^{2}J_{C\text{-}F}$ = 24.3 Hz), 115.3-115.2 (C-F, d, $^{3}J_{C\text{-}F}$ = 7.8 Hz), 108.1 (C-), 100.2 (C-), 91.5 (C-), 71.2 (CH_2), 62.7 (C-), 53.3-53.4 (C-F, d, $^{4'}J_{C\text{-}F}$ = 1.8 Hz), 53.4 (C-), 34.1 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 390 (M^+, 36), 334 (100), 292 (51); HRMS (ESI): calcd for $C_{21}H_{18}FN_4O_3$(M + 1) 393.13575, found 393.13531; IR (ATR, cm^{-1}): 3169 (w), 2229 (w), 1712 (s), 1630 (s), 1537 (s), 1486 (s), 1198 (m), 1026 (m), 800 (m).

*1-Tert-butyl-2',5-dioxo-1'-phenyl-1,5,7,8-tetrahydrospiro[furo[3,4-b]pyrrolo[3,2-e]pyridine-4,3'-indoline]-3-carbonitrile (**41f**)*



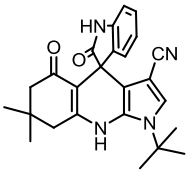
The product was isolated as a light yellow solid, yield 37 %, mp 327-329 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.64 (9H, s, $(CH_3)_3$), 5.06 (2H, s, CH_2), 6.68 (1H, d, *J*=7.7 Hz, Ar-H), 7.02 - 7.11 (2H, m, Ar-H), 7.20 - 7.28 (1H, m, Ar-H), 7.44 - 7.54 (4H, m, Ar-H), 7.59 - 7.67 (2H, m, Ar-H), 10.19 (5H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 175.6 (C-), 170.3 (C-), 158.2 (C-), 142.9 (C-), 134.6 (C-), 133.5 (C-), 129.7 (C-), 129.6 (CH-), 128.7 (CH-), 128.2 (CH-), 126.9 (CH-), 124.7 (CH-), 124.3 (CH-), 123.1 (CH-), 114.7 (C-), 108.5 (CH-), 103.6 (C-), 95.5 (C-), 86.3 (C-), 66.2 (CH_2), 57.6 (C-), 47.5 (C-), 28.9 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 3450 (M^+, 85), 422 (96), 366 (100); HRMS (ESI): calcd for $C_{27}H_{22}N_4O_3$(M) 450.16864, found 450.16881; IR (ATR, cm^{-1}): 3273 (w), 2224 (w), 1747 (m), 1690 (s), 1655 (s), 1533 (m), 1513 (m), 1197 (m), 1030 (s), 765 (m). Anal calcd for $C_{27}H_{22}N_4O_3$; C: 71.99, H: 4.92, N: 12.44, found C: 71.61, H: 5.06, N: 12.14.

*1-Cyclohexyl-1'-methyl-2',5-dioxo-1,5,7,8-tetrahydrospiro[furo[3,4-b]pyrrolo[3,2-e]pyridine-4,3'-indoline]-3-carbonitrile (**41g**)*



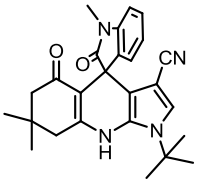
The product was isolated as a light yellow solid, yield 30 %, mp 352-355 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 - 1.29 (1H, m, CH), 1.33 - 1.49 (2H, m, CH), 1.56 - 1.75 (3H, m, CH), 1.83 - 1.93 (4H, m, CH), 3.19 (3H, s, CH_3), 3.86 - 4.22 (1H, m, CH), 5.05 (2H, s, CH_2), 6.95 - 7.09 (3H, m, Ar-H), 7.24 - 7.35 (1H, m, Ar-H), 7.45 (1H, s, Ar-H), 10.75 (1H, br. s., NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 176.1 (C-), 170.2 (C-), 158.6 (C-), 142.9 (C-), 133.8 (C-), 129.7 (C-), 128.6 (CH-), 124.0 (CH-), 122.7 (CH-), 122.5 (CH-), 114.3 (C-), 108.2 (CH-), 101.7 (C-), 95.3 (C-), 87.4 (C-), 65.4 (CH_2), 54.8 (CH), 47.2 (C-), 32.6 (CH_2), 26.0 (CH_3), 25.0 (CH_2), 24.5 (CH_2); MS (GC, 70 eV): *m/z* (%) 414 (M^+, 83), 386 (100), 370 (48); HRMS (ESI): calcd for $C_{24}H_{22}N_4O_3$(M + 1) 414.16864, found 414.16961; IR (ATR, cm^{-1}): 3136 (w), 2229 (w), 1744 (m), 1725 (m), 1681 (s), 1647 (s), 1551 (s), 1334 (m), 1222 (m), 1027 (m), 757 (s).

*1'-Tert-butyl-7',7'-dimethyl-2,5'-dioxo-1',5',6',7',8',9'-hexahydrospiro[indoline-3,4'-pyrrolo[2,3-b]quinoline]-3'-carbonitrile (**42a**)*



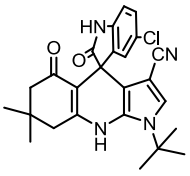
The product was isolated as a orange solid, yield 79 %, mp 304-305 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.04 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.63 (9H, s, $(CH_3)_3$), 1.97 - 2.20 (2H, m, CH_2), 2.72 (2H, d, J = 16.1 Hz, CH_2), 6.75 - 6.86 (3H, m, Ar-H), 7.05 - 7.15 (1H, m, Ar-H), 7.32 (1H, s, Ar-H), 8.77 (1H, br. s., NH), 10.26 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.1 (C-), 179.3 (C-), 151.8 (C-), 142.0 (C-), 137.2 (C-), 127.9 (C-), 127.2 (CH) 123.8 (CH-), 122.7 (CH-), 120.9 (CH-), 114.5 (C-), 108.7 (CH-), 106.1 (C-), 104.1 (C-), 86.1 (C-), 57.3 (C-), 50.3 (C-), 49.3 (CH_2-), 41.0 (CH_2-), 32.0 (C-), 29.2 $(CH_3)_3$, 28.4 (CH_3-), 26.7 (CH_3-); MS (GC, 70 eV): *m/z* (%) 412 (M^+, 14), 370 (42), 314 (100); HRMS (ESI): calcd for $C_{25}H_{27}N_4O_2$(M + 1) 415.21285, found 415.21218; IR (ATR, cm^{-1}): 3314 (w), 3115 (w), 2219 (w), 1708 (s), 1613 (s), 1524 (s), 1505 (s), 1469 (m), 1329 (m), 1209 (m), 747 (m).

*1'-Tert-butyl-1,7',7'-trimethyl-2,5'-dioxo-1',5',6',7',8',9'-hexahydrospiro[indoline-3,4'-pyrrolo[2,3-b]quinoline]-3'-carbonitrile (**42b**)*



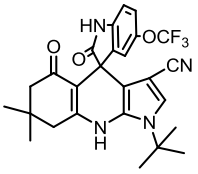
The product was isolated as a light yellow solid, yield 57 %, mp 300-307 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02 (3H, s, CH_3)1.08 (3H, s, CH_3),1.61 (9H, s, $(CH_3)_3$), 2.05 -1.99 (2H, dd, ^{1}J = 34.5 Hz, ^{2}J = 13 Hz, CH_2), 2.79-2.65 (2H, dd, ^{1}J = 17 Hz, ^{2}J = 7.55 Hz, CH_2), 3.16 (3H, s, CH_3), 6.76 - 6.97 (3H, m, Ar-H), 7.14 - 7.26 (1H, m, Ar-H), 7.30 (1H, s, Ar-H), 8.83 (1H, br. s., NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.1 (C-), 177.8 (C-), 152.1 (C-), 143.0 (C-), 136.4 (C-), 127.9 (C-), 127.4 (CH-), 123.7 (CH-), 122.4 (CH-), 121.7 (CH-), 114.7 (C-), 107.5 (CH-), 105.7 (C-), 104.5 (C-), 85.8 (C-), 57.3 (C-), 50.2 (CH_2), 48.9 (C-), 40.9 (CH_2), 32.0 (C-), 29.1 $(CH_3)_3$, 28.5 (CH_3), 26.6 (CH_3), 25.6 (CH_3); MS (GC, 70 eV): *m/z* (%) 428 (M^+, 58), 344 (72), 288 (100); HRMS (ESI): calcd for $C_{26}H_{29}N_4O_2$(M + 1) 429.2285, found 429.22867; IR (ATR, cm^{-1}): 3301 (w), 2220 (w), 1693 (s), 1606 (s), 1525 (s), 1504 (s), 1327 (m), 1207 (s), 746 (s).

*1'-Tert-butyl-5-chloro-7',7'-dimethyl-2,5'-dioxo-1',5',6',7',8',9'-hexahydrospiro[indoline-3,4'-pyrrolo[2,3-b]quinoline]-3'-carbonitrile (**42c**)*



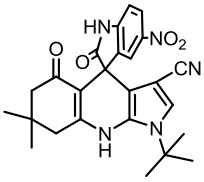
The product was isolated as a white solid, yield 65 %, mp 312-315 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.61 (9H, s, $(CH_3)_3$), 2.07 (2H, dd, *J* = 1 Hz, CH_2), 2.70 (9H, dd, *J* = 1 Hz, CH_2), 6.72 - 6.79 (2H, m, Ar-H), 7.14 (1H, dd, *J* = 8 and 2 Hz, Ar-H), 7.33 (1H, s, Ar-H), 8.82 (1H, br. s., NH) 10.41 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.3 (C-), 179.0 (C-), 152.3 (C-), 141.2 (C-), 139.0 (C-), 128.0 (C-), 127.1 (CH-), 124.8 (C-), 124.1 (CH-), 122.7 (CH-), 114.4 (C-),110.1 (CH-), 105.6 (C-), 103.2 (C-), 85.9 (C-), 57.4 (C-), 50.2 (CH_2-), 49.7 (C-), 40.9 (CH_2-), 32.0 (C-), 29.1 $(CH_3)_3$, 28.0 (CH_3-), 27.1 (CH_3-); MS (GC, 70 eV): *m/z* (%) 446 (M^+, 16), 404 (41), 348 (100); HRMS (ESI): calcd for $C_{25}H_{26}ClN_4O_2$(M + 1) 449.1740, found 449.1746; IR (ATR, cm^{-1}): 3311 (w), 2216 (w), 1711 (s), 1614 (s), 1525 (s), 1506 (s), 1208 (m), 811 (m), 559 (s).

*1'-Tert-butyl-7',7'-dimethyl-5'-methylene-2-oxo-5-(trifluoromethoxy)-1',5',6',7',8',9'-hexahydrospiro[indoline-3,4'-pyrrolo[2,3-b]quinoline]-3'-carbonitrile (**42d**)*



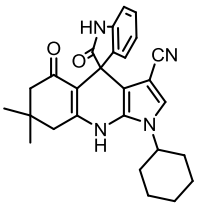
The product was isolated as a yellow solid, yield 64 %, mp 230-232 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.00 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.62 (9H, s, $(CH_3)_3$),2.14 - 1.99 (2H, dd, ^{1}J = 17.2 ^{2}J = 22.5 Hz, CH_2), 2.61 - 2.80 (2H, dd, ^{1}J = 16.5 ^{2}J = 45.5 Hz CH_2), 6.73 (1H, s, Ar-H) , 6.84 (1H, d, J=8.3 Hz, Ar-H),7.10 (1H, d, J = 7.4 Hz, Ar-H), 7.34 (1H, s, Ar-H), 8.91 (1H, br. s., NH), 10.47 (1H, s, NH); ^{19}F NMR (DMSO-d_6) δ -57.27; ^{13}C NMR (62.9 MHz, DMSO-d_6): δ193.1 (C-), 179.4 (C-), 152.4 (C-), 142.9-142.8 (C-F, q, $^{3}J_{C-F}$ = 1.9 Hz), 141.3 (C-), 138.6 (C-), 128.4 (C-),124.0 (CH-), 120.3 (CH-), 116.2 (CH-), 114.4 -126.2 (C-F, q, J_{C-F} = 254.9 Hz), 114.0 (C-), 109.3 (CH-), 105.4 (C-), 103.1 (C-), 85.9(C-), 57.4 (C-), 50.2 (CH_2), 49.8 (C-), 41.1 (CH_2), 32.0 (C-), 29.1 (CH_3), 28.4 (CH_3), 26.4 (CH_3); MS (GC, 70 eV): *m/z* (%) 496 (M^+, 15), 454 (27), 398 (100); IR (ATR, cm^{-1}): 3290 (w), 2224 (w), 1710 (s), 1608 (s), 1526 (s), 1504 (s), 1486 (m), 1262 (s), 1191 (m).

*1'-Tert-butyl-7',7'-dimethyl-5-nitro-2,5'-dioxo-1',5',6',7',8',9'-hexahydrospiro[indoline-3,4'-pyrrolo[2,3-b]quinoline]-3'-carbonitrile (**42e**)*



The product was isolated as a yellow solid, yield 66 %, mp 273 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.04 (3H, s, CH_3), 1.07 (3H, s, CH_3),1.63 (9H, s, $(CH_3)_3$), 2.09 (2H, dd, J_1=16.2, J_2 = 20.1 Hz, CH_2), 2.76 (2H, dd, J_1 = 26.5, J_2 = 17.2 Hz, CH_2), 7.00 (1H, d, J = 8.7 Hz, Ar-H), 7.38 (1H, s, Ar-H), 7.62 (1H, d, J = 1.9 Hz, Ar-H), 8.13 (1H, dd, J_1=8.5, J_2 = 2.1 Hz, Ar-H), 11.10 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.6 (C-), 179.8 (C-), 171.9 (C-), 152.8 (C-), 149.0 (C-), 141.8 (C-), 137.9 (C-), 128.2 (C-), 125.1 (CH-), 124.4 (CH-), 118.0 (CH-), 114.4 (C-), 108.9 (CH-), 105.2 (C-), 102.4 (C-), 85.7 (C-), 57.6 (C-), 50.0 (CH_2), 40.8 (CH_2), 32.1 (C-), 29.1 $(CH_3)_3$, 27.8 (CH_3), 27.2 (CH_3); MS (GC, 70 eV): *m/z* (%) 459 (M^+, 29), 401 (42), 319 (100); HRMS (ESI): calcd for $C_{25}H_{26}N_5O_4$(M + 1) 460.19793, found 460.19888; IR (ATR, cm^{-1}): 3324 (w), 2216 (w), 1722 (s), 1614 (s), 1526 (s), 1512 (s), 1335 (s), 1209 (m), 1189 (m).

*1'-Cyclohexyl-7',7'-dimethyl-2,5'-dioxo-1',5',6',7',8',9'-hexahydrospiro[indoline-3,4'-pyrrolo[2,3-b]quinoline]-3'-carbonitrile (**42f**)*

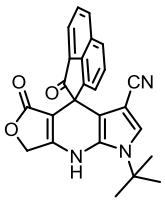


The product was isolated as a white solid, yield 41 %, mp 274-277 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.20 (1H, m, CH),1.35 - 1.74 (5H, m, CH), 1.80 - 1.95 (4H, m, CH), 2.01 – 2.18 (2H, m, CH_2), 2.55 - 2.66 (2H, m, CH_2), 4.17 - 4.22 (1H, m, CH), 6.71 - 6.85 (3H, m, Ar_H), 7.00 - 7.14 (1H, m, Ar-H), 7.36 (1H, s, Ar-H), 9.67 (1H, s, NH), 10.2 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 192.9 (C-), 179.4 (C-), 151.7 (C-), 142.0 (C-), 137.3 (C-), 128.1 (C-), 127.1 (CH-), 122.7 (CH-), 122.4 (CH-), 121.0 (CH-), 114.6 (C-), 108.7 (CH-), 106.3 (C-), 101.6 (C-), 87.5 (C-), 53.9 (CH-), 50.4 (CH_2), 49.5 (C-), 40.9 (CH_2), 32.8 (CH_2), 32.1 (C-), 28.3 (CH_3), 26.8 (CH_3), 25.1 (CH_2), 24.6 (CH_2); MS (GC, 70 eV): *m/z* (%) 440 (M^+, 51), 396 71), 348 (88); HRMS (ESI): calcd for $C_{27}H_{28}N_4O_2$(M + 1) 440.22068, found 440.22013; IR (ATR, cm^{-1}): 3276 (w), 2224 (w), 1693 (s), 1616 (s), 1532 (s), 1326 (m), 1217 (m), 744 (s).

A.2.17 General procedure for the synthesis of compounds 43a-c, 44a, 45a-c and 46a-b

A mixture of Meldrum´s acid (1 equiv.), the corresponding 1,2-dicarbonyl compound (1 equiv.) and 5-amino-1R-pyrrole-3-carbonitrile (1equiv.) was refluxed in ethanol (**43a-c**), acetic acid (**44a**) or 1,4 dioxane (**45a-c**, **46a-b**) for 4-6 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent: *n*-heptane/ethylacetate).

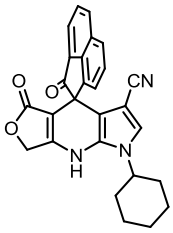
*1'-Tert-butyl-2,5'-dioxo-1',5',7',8'-tetrahydro-2H-spiro[acenaphthylene-1,4'-furo[3,4-b]pyrrolo[3,2-e]pyridine]-3'-carbonitrile (**43a**)*



The product was isolated as a yellow solid, yield 82 %, mp 259-263 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.65 (9H, s, $(CH_3)_3$), 5.08 (2H, br. s., CH_2), 7.25 - 7.46 (2H, m, Ar-H), 7.68 - 8.08 (4H, m, Ar-H), 8.34 (1H, d, *J* = 7.9 Hz, Ar-H), 10.17 (1H, br. s., NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 203.6 (C-), 170.5 (C-), 158.5 (C-), 142.6 (C-), 141.5 (C-), 132.1 (C-), 131.8 (CH-), 129.6 (C-), 129.6 (C-), 129.0 (CH-), 128.6 (CH-), 124.7 (CH-), 124.2 (CH-), 122.1 (CH-), 121.1 (CH-), 114.2 (C-), 104.6 (C-), 96.4 (C-),

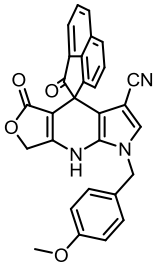
86.3 (C-), 66.2 (CH_2), 57.5 (C-), 52.4 (C-), 28.9 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 365 (M^+, 24), 309 (100), 280 (16); IR (ATR, cm^{-1}): 3270 (w), 2220 (w), 1713 (s), 1640 (s), 1532 (s), 1513 (s), 1328 (m), 1201 (m), 1048 (m), 784 (s). Anal calcd for $C_{25}H_{19}N_3O_3$; C: 73.34, H: 4.68, N: 10.26, found C: 73.49, H: 4.87, N: 9.85.

*1'-Cyclohexyl-2,5'-dioxo-1',5',7',8'-tetrahydro-2H-spiro[acenaphthylene-1,4'-furo[3,4-b]pyrrolo[3,2-e]pyridine]-3'-carbonitrile (**43b**)*



The product was isolated as a yellow solid, yield 73 %, 295-297 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.16 - 1.33 (1 H, m, CH_2), 1.45 (2 H, q, *J* = 11.46 Hz, CH_2), 1.55 - 1.81 (3H, m, CH_2), 1.91 - 2.12 (4H, m, CH_2), 4.10 (1H, m, CH), 5.12 (2H, s, CH_2), 7.34 (1 H, d, *J* = 6.61 Hz, Ar-H), 7.44 (1H, s, Ar-H), 7.71 (1H, t, *J* = 7.55 Hz, Ar-H), 7.82 - 7.94 (1H, m, Ar-H), 7.94 - 8.11 (2H, m, Ar-H), 8.35 (1H, d, *J* = 7.93 Hz, Ar-H), 10.82 (1H, s, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 203.5 (C-), 170.5 (C-), 158.6 (C-), 142.5 (C-), 141.4 (C-), 132.0 (C-), 131.8 (CH), 129.8 (C-), 129.6 (C-), 128.9 (CH), 128.6 (CH), 124.6 (CH), 122.9 (CH), 122.0 (CH), 121.0 (CH), 114.2 (C-), 102.5 (C-), 96.7 (C-), 87.5 (C-), 65.5 (CH_2), 54.8 (CH), 52.3 (C-), 32.6 (CH_2), 25.1 (CH_2), 24.5 (CH_2); MS (GC, 70 eV): *m/z* (%) 435 (M^+, 30), 391 (71), 309 (100); HRMS (EI): calcd for $C_{27}H_{21}N_3O_3$(M+1) 435.15774, found 435.15755; IR (ATR, cm^{-1}): 3136 (w), 2220 (w), 1750 (s), 1682 (s), 1651 (s), 1545 (s), 1330 (s), 1210 (m), 1023 (m), 780 (s).

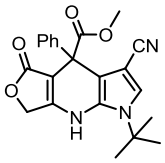
*1'-(4-Methoxybenzyl)-2,5'-dioxo-1',5',7',8'-tetrahydro-2H-spiro[acenaphthylene-1,4'-furo[3,4-b]pyrrolo[3,2-e]pyridine]-3'-carbonitrile (**43c**)*



The product was isolated as a yellow solid, yield 38 %, mp 275-278 □C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.79 (3H, s, OCH_3), 5.10 ((2H, s, CH_2), 5.17 (2H, s, CH_2), 7.01 (2H, d, *J* = 8.50 Hz, Ar-H), 7.21 - 7.44 (4 H, m, Ar-H), 7.71 (1H, m, Ar-H), 7.83 - 7.94 (1H, m,Ar-H), 7.96 - 8.11 (2H, m, Ar-H), 8.34 (1H, d, *J* = 8.12 Hz, Ar-H), 10.93 (1H, s, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 203.4 (C-), 170.5 (C-), 159.0 (C-), 158.7 (C-), 142.4 (C-), 141.4 (C-), 131.9 (C-), 131.8 (CH), 130.5 (C-), 129.6 (C-), 129.0 (CH), 128.7 (C-), 128.6 (C-), 128.1 (CH), 126.0 (CH), 124.7 (CH), 122.1 (CH), 121.0 (CH), 114.2 (CH), 113.8 (C-), 103.0 (C-), 96.8 (C-), 87.8 (C-), 65.5 (CH_2), 55.1(OCH_3),

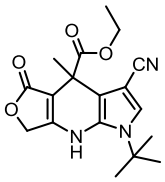
52.4 (C-), 48.5 (CH_2); MS (GC, 70 eV): *m/z* (%) 473 (M^+, 14), 429 (21), 121 (100); HRMS (EI): calcd for $C_{29}H_{19}N_3O_4$(M + 1) 473.13701, found 473.13642; IR (ATR, cm^{-1}): 3026 (w), 2220 (w), 1739 (s), 1694(s), 1650 (s), 1548 (s), 1514 (s), 1325 (m), 1250 (s), 1173 (m), 1026 (m), 782 (s).

*Methyl -1-tert-butyl-3-cyano-5-oxo-4-phenyl-4,5,7,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,2-e]pyridine-4-carboxylate (**44a**)*



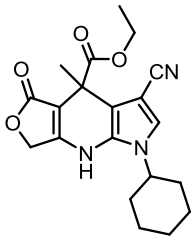
The product was isolated as a white solid, yield 42 %, mp 225-227 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.63 (9H, s, $(CH_3)_3$), 4.91 (2H, dd, J = 16.4 Hz, CH_2), 7.16 - 7.34 (5H, m, Ar-H), 7.53 (1H, s, Ar-H), 10.00 (1H, s, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 171.4 (C-), 170.5 (C-), 156.0 (C-), 142.5 (C-), 129.5 (C-), 127.9 (CH-), 127.4 (CH-), 126.4 (CH-), 125.0 (CH-), 115.4 (C-), 102.9 (C-), 97.5 (C-), 88.4 (C-), 65.1 (CH_2), 57.4 (C-), 52.2 (OCH_3), 51.3 (C-), 28.8 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 331 (32), 275 (100), 246 (59); HRMS (ESI): calcd for $C_{22}H_{22}N_3O_4$(M + 1) 392.16048, found 392.16055; IR (ATR, cm^{-1}): 3296 (w), 2227 (w), 1754 (s), 1727 (s), 1658 (s), 1531 (s), 1506 (s), 1224 (m), 1197 (s), 1031 (s), 1010 (s), 693 (s).

*Ethyl-1-tert-butyl-3-cyano-4-methyl-5-oxo-4,5,7,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,2-e]pyridine-4-carboxylate (**45a**)*



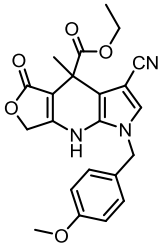
The product was isolated as a white solid, yield 67 %, mp 248-251 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17 (3H, t, J = 7.1 Hz, CH_3), 1.58 (9H, s, $(CH_3)_3$), 1.72 (3H, s, CH_3), 4.00 - 4.19 (2H, m, CH_2), 4.90 (2H, s, CH_2), 7.45 (1H, s, Ar-H), 9.78 (1H, br. s., NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 172.0 (C-), 171.1 (C-), 156.8 (C-), 128.1 (C-), 124.2 (CH-), 115.8 (C-), 105.4 (C-), 97.7 (C-), 86.7 (C-), 65.4 (CH_2), 60.8 (CH_2), 57.3 (C-), 41.8 (C-), 28.8 $(CH_3)_3$, 24.1 (CH_3), 13.9 (CH_3); MS (GC, 70 eV): *m/z* (%) 269 (M+,25), 213 (100), 184 (67); HRMS (ESI): calcd for $C_{18}H_{21}N_3O_4$(M + 1) 344.16048, found 344.16032; IR (ATR, cm^{-1}): 3382 (m), 2979 (w), 2221 (m), 1727 (w), 1703 (s), 1643 (s), 1533 (s), 1515 (s), 1205 (s), 999 (s).

*Ethyl-3-cyano-1-cyclohexyl-4-methyl-5-oxo-4,5,7,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,2-e]pyridine-4-carboxylate (**45b**)*



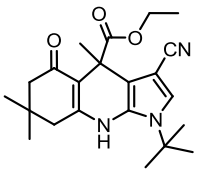
The product was isolated as a white solid, yield 40 %, mp 298-300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (3H, t, J = 7 Hz, CH_3), 1.17 - 1.44 (3H, m, CH_2), 1.44 - 1.66 (3H, m, CH_2), 1.68 (3H, s, CH_3), 1.75 - 1.94 (4H, m, CH_2), 3.87 - 4.00 (1H, m, CH), 4.06 (2H, q, J = 6.8 Hz, CH_2), 4.88 (2H, dd, ^{1}J = 16.4 Hz ^{2}J =18.7 Hz, CH_2), 7.47 (1H, s, Ar-H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 172.1 (C-), 171.3 (C-), 157.6 (C-), 129.2 (C-), 122.8 (CH), 115.9 (C-), 103.1 (C-), 97.6 (C-), 88.0 (C-), 64.9 (CH_2), 60.7 (CH_2), 54.4 (CH), 42.0 (C-), 32.7 (CH_2), 25.0 (CH_2), 24.5 (CH_2), 24.1 (CH_3), 13.9 (CH_3); MS (GC, 70 eV): *m/z* (%) 295 (32), 213 (100), 184 (30); HRMS (ESI): calcd for $C_{20}H_{24}N_3O_4$(M + 1) 370.17613, found 370.17584; IR (ATR, cm^{-1}): 3217 (w), 2221 (w), 1748 (s), 1691 (s), 1652 (s), 1551 (s), 1452 (m), 1332 (m), 1278 (m), 990 (s), 575 (m).

*Ethyl-3-cyano-1-(4-methoxybenzyl)-4-methyl-5-oxo-4,5,7,8-tetrahydro-1H-furo[3,4-b]pyrrolo[3,2-e]pyridine-4-carboxylate (**45c**)*



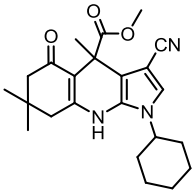
The product was isolated as a yellow solid, yield 64 %, mp 221-223 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17 (3H, t, J = 6.99 Hz, CH_3), 1.74 (3H, s, CH_3), 3.77(3H, s, OCH_3), 4.11 (2H, q, J = 6.92 Hz, CH_2), 4.69 - 5.01 (2H, dd, $^{1}J_{=}$ 16.4 Hz, $^{2}J_{=}$ 19.2 Hz CH_2), 5.09 (2H, s, CH_2), 6.97 (2H, d, J = 8.31 Hz, Ar-H), 7.22 (2H, d, J = 8.31 Hz,Ar-H), 7.49 (1H, s, Ar-H), 10.53 (1H, br. s.,NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 171.9 (C-), 171.1 (C-), 159.0 (C-), 157.1 (C-), 129.1 (C-), 128.7 (CH), 128.1 (C-), 126.1 (CH), 115.5 (C-), 114.2 (CH), 103.8 (C-), 98.1 (C-), 88.3 (C-), 64.8 (CH_2), 60.8 (CH_2), 55.1 (OCH_3), 48.4 (CH_2), 42.0 (C-), 24.0 (CH_3), 13.9 (CH_3); MS (GC, 70 eV): *m/z* (%) 407 (M^+, 2), 334 (25), 121 (100); HRMS (ESI): calcd for $C_{22}H_{22}N_3O_5$(M + 1) 408.1554, found 408.15499; IR (ATR, cm^{-1}): 3203 (w), 2223 (w), 1712 (s), 1625 (s), 1541 (s), 1513 (s), 1328 (m), 1254 (m), 1027 (m), 1009 (m), 611 (m). Anal calcd for $C_{22}H_{21}N_3O_5$; C: 64.86, H: 5.20, N: 10.31, found C: 65.00, H: 5.20, N: 10.46.

*Ethyl-1-tert-butyl-3-cyano-4,7,7-trimethyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-4-carboxylate (**46a**)*



The product was isolated as a white solid, yield 55 %, mp 201-204 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.04 (3H, s, CH_3), 1.05 (3H, s, CH_3), 1.13 (3H, t, J = 7.1 Hz, CH_3), 1.55 (3H, s, CH_3),1.57 (9H, s, $(CH_3)_3$), 2.12 (2H, dd, J = 15.9 Hz, CH_2), 2.60 (2H, dd, J = 17 Hz, CH_2), 3.82 - 4.14 (2H, m, CH_2), 7.35 (1H, s, Ar-H), 8.47 (1H, s, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 194.1 (C-), 173.1 (C-), 150.3 (C-), 126.9 (C-), 123.7 (CH-), 115.6 (C-), 109.3 (C-), 106.2 (C-), 86.1 (C-), 59.8 (CH_2), 57.2 (C-), 50.6 (CH_2), 42.9 (C-), 40.8 (CH_2), 32.0 (C-), 29.1 $(CH_3)_3$, 27.6 (CH_3), 27.4 (CH_3), 25.9 (CH_3), 13.9 (CH_3); MS (GC, 70 eV): *m/z* (%) 383 (M^+, 3), 310 (73), 254 (100); HRMS (ESI): calcd for $C_{22}H_{30}N_3O_3$(M + 1) 384.22817, found 384.22847; IR (ATR, cm^{-1}): 3307 (w), 2220 (w), 1731 (s), 1617 (s), 1523 (s), 1504 (s), 1326 (m), 1098 (m).

*Ethyl-3-cyano-1-cyclohexyl-4,7,7-trimethyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrrolo[2,3-b]quinoline-4-carboxylate (**46b**)*

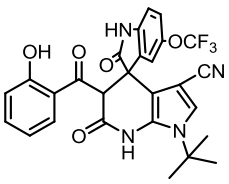


The product was isolated as a yellow solid, yield 58 %, mp 246-248 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02 (6H, br. s., CH_3), 1.09 (3H, t, J = 7 Hz, CH_3), 1.14 - 1.25 (1H, m, CH_2), 1.26 - 1.51 (3H, m, CH_2), 1.54 (3H, s, CH_3), 1.57 - 1.71 (2H, m, CH_2), 1.73 - 1.92 (4H, m, CH_2), 2.10 (2H, dd, ^{1}J = 15.7 Hz ^{2}J = 29.7 Hz, CH_2), 2.41 (2H, dd, ^{1}J = 16.2 Hz ^{2}J = 29.8 Hz, CH_2), 3.83 - 4.18 (3H, m, CH), 7.38 (1H, s, Ar-H), 9.35 (1H, br. s., NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 193.8 (C-), 173.2 (C-), 150.3 (C-), 127.2 (C-), 122.3 (CH), 115.7 (C-), 109.5 (C-), 103.7 (C-), 87.6 (C-), 59.8 (CH_2), 53.8 (CH), 50.7(CH_2), 43.2 (C-), 40.8 (CH_2), 32.6 (C-), 32.2 (CH_2), 27.9 (CH_3), 27.2 (CH_3), 25.9 (CH_3), 25.0 (CH_2), 24.6 (CH_2), 14.0 (CH_3); MS (GC, 70 eV): *m/z* (%) 409 (M^+, 9), 336 (100), 254 (77); HRMS (ESI): calcd for $C_{24}H_{31}N_3O_3$(M + 1) 409.23599, found 409.23646; IR (ATR, cm^{-1}): 3302 (w), 2942 (w), 2224 (m), 1725 (s), 1642 (m), 1628 (m), 1531 (s), 1508 (m), 1423 (m), 1327 (m), 1222 (m), 1102 (m).

A.2.18 General procedure for the synthesis of compounds 43a-c, 44a, 45a-c and 46a-b

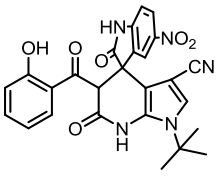
A mixture of 4-hydroxycoumarin (1 equiv.), the corresponding isatin (1 equiv.), 5-amino-1R-pyrrole-3-carbonitrile (1 equiv.) and ammonium acetate (5 equiv.) was refluxed in acetic acid for 4-6 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent: *n*-heptane/ethylacetate).

*1'-Tert-butyl-5'-(2-hydroxybenzoyl)-2,6'-dioxo-5-(trifluoromethoxy)-1',5',6',7'-tetrahydrospiro-indoline-3,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**47a**)*



The product was isolated as a white solid, yield 69 %, mp 234-236 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.61 (9H, s, $(CH_3)_3$), 6.04 (1H, s, CH), 6.87 - 6.99 (3H, m, Ar-H), 7.15 - 7.26 (1H, m, Ar-H), 7.35 - 7.55 (3H, m, Ar-H), 7.80 - 7.97 (1H, m, Ar-H), 10.43 (1H, s, NH), 10.60 (1H, s, NH), 11.17 (1H, s, OH); ^{19}F NMR (DMSO-d_6) δ -57.35. ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 198.0 (C-), 177.4 (C-), 167.1 (C-), 159.8 (C-), 143.0-143.1 (C-F, q, $^{3}J_{C\text{-}F}$ = 1.9 Hz), 142.9 (C-), 136.1 (CH-), 131.2 (CH-), 130.6 (C-), 130.4 (C-), 123.4 (CH-), 122.4 (CH-), 122.0 (C-), 119.2 (CH-), 117.7 (CH-), 117.5 (CH-), 114.0-126.2 (C-F, q, $J_{C\text{-}F}$ = 255.4 Hz), 113.7 (C-), 110.2 (CH-), 104.7 (C-), 86.2 (C-), 58.2 (CH-), 56.1 (C-), 48.2 (C-), 29.3 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 538 (M^+, 17), 121 (100); HRMS (ESI): calcd for $C_{27}H_{22}F_3N_4O_5$(M + 1) 539.15368, found 539.15348; IR (ATR, cm^{-1}): 3163 (w), 2224 (w), 1714 (s), 1682 (m), 1487 (m), 1253 (m), 615 (m).

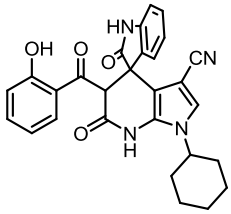
*1'-Tert-butyl-5'-(2-hydroxybenzoyl)-5-nitro-2,6'-dioxo-1',5',6',7'-tetrahydrospiro[indoline-3,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**47b**)*



The product was isolated as a brown solid, yield 38 %, mp 310 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.63 (9H, s, $(CH_3)_3$), 6.23 (1H, s, CH), 6.95 (2H, m, Ar-H), 7.11 (1H, d, J = 8.7 Hz, Ar-H), 7.51 (2H, m, Ar-H), 7.87 (2H, d, J = 7.7 Hz, Ar-H), 8.24 (2H, dd, ^{1}J = 8.5, ^{2}J = 1.7 Hz, Ar-H), 8.28 - 8.42 (1H, m, Ar-H), 10.50 (1H, br. s., OH), 11.15 (1H, s, NH), 11.22 (1H, br. s., NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 197.7 (C-), 177.9 (C-), 166.9 (C-), 159.8 (C-), 150.4 (C-), 142.0 (C-), 136.2 (CH-), 131.3 (CH-), 130.8 (C-), 130.1 (C-), 126.6 (CH-),123.8 (CH-), 122.0 (C-), 119.8 (CH-), 119.2

(CH-), 117.6 (CH-), 113.9 (C-), 109.7 (CH-), 104.1 (C-), 86.0 (C-), 58.3 (CH-), 56.0 (C-), 47.7 (C-), 29.3 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 499 (M^+, 15), 162 (35), 121 (100); HRMS (ESI): calcd for $C_{26}H_{22}N_5O_6$(M + 1) 500.15646, found 500.15615; IR (ATR, cm^{-1}): 3155 (w), 2226 (w), 1726(s), 1682 (s), 1525 (m), 1332 (s), 1194 (m), 1157 (m), 709 (s) 555 (s).

*1'-Cyclohexyl-5'-(2-hydroxybenzoyl)-2,6'-dioxo-1',5',6',7'-tetrahydrospiro[indoline-3,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**47c**)*

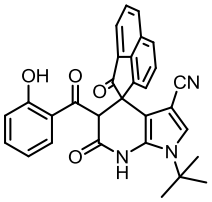


The product was isolated as a yellow solid, yield 59 %, mp 297-299 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.25 (1H, m, CH_2), 1.44 (2H, m, CH_2), 1.57 - 1.76 (3H, m, CH_2), 1.89-1.98 (4H, m, CH_2), 4.02 - 4.29 (1H, m, CH), 6.03 (1H, br. s., CH), 6.91 - 6.94 (4H, s, Ar-H), 7.23 - 7.31 (2H, m, Ar-H), 7.43 - 7.60 (2H, m, Ar-H), 7.97 – 7.99 (1H, m, Ar-H), 10.42 (1H, br. s., OH), 11.00 (1H, br. s., NH), 11.29 (1H, br. s., NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 198.2 (C-), 177.6 (C-), 167.3 (C-), 159.9 (C-), 143.6 (C-), 136.1 (CH-), 131.3 (CH-), 130.6 (C-), 128.9 (CH-), 128.8 (C-), 123.3 (CH-),122.0 (C-), 121.7 (CH-), 121.4 (CH-), 119.2 (CH-), 117.5 (CH-), 114.0 (C-), 109.4 (CH-), 102.3 (C-), 87.5 (C-), 56.4 (CH-), 54.4 (CH-), 48.2 (C-), 32.7 (CH_2), 25.0 (CH_2), 24.5 (CH_2); MS (GC, 70 eV): *m/z* (%) 480 (M^+, 47), 359 (81), 121 (100); HRMS (ESI): calcd for $C_{28}H_{25}N_4O_4$(M + 1) 481.18703, found 481.18799; IR (ATR, cm^{-1}): 3137 (w), 2222 (w), 1713 (s), 1682 (s), 1471 (m), 1191 (m), 744 (s). Anal calcd for $C_{28}H_{24}N_4O_4$; C: 69.99, H: 5.03, N: 11.66, found C: 70.27, H: 5.20, N: 11.41.

A.2.19 General procedure for the synthesis of compounds 48a-c and 49a-c

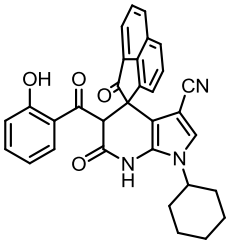
A mixture of 4-hydroxycoumarin (1 equiv.), the corresponding 1,2-dicarbonyl compound (1 equiv.) and 5-amino-1R-pyrrole-3-carbonitrile (1equiv.) was refluxed in ethanol (**48a-c**), or 1,4 dioxane (**49a-c**) for 4-6 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent: *n*-heptane/ethylacetate).

*1'-Tert-butyl-5'-(2-hydroxybenzoyl)-2,6'-dioxo-1',5',6',7'-tetrahydro-2H-spiro[acenaphthylene-1,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**48a**)*



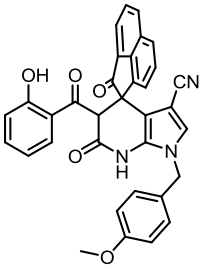
The product was isolated as a yellow solid, yield 65 %, mp 270-272 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.64 (9H, s, $(CH_3)_3$), 6.29 (1H, s, CH), 6.91 (2H, d, J = 8.31 Hz, Ar-H), 7.38 (1H, s, Ar-H), 7.42 - 7.52 (1H, m, Ar-H), 7.60 - 7.67 (2H, m, Ar-H), 7.81 - 7.94 (2H, m, Ar-H), 7.95 - 8.05 (2H, m, Ar-H), 8.29 (1H, d, J = 8.12 Hz, Ar-H), 10.55 (1H, s, NH), 11.01 (1H, s, OH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 201.4 (C-), 197.4 (C-), 167.6 (C-), 159.7 (C-), 141.7 (C-), 138.1 (C-), 136.1 (CH-), 131.9 (C-), 131.4 (CH-), 131.2 (CH-), 130.3 (C-),130.1 (C-), 128.6 (CH-), 128.5 (CH-), 125.3 (CH-), 123.4 (CH-), 121.9 (C-), 121.7 (CH-), 120.5 (CH-), 119.2 (CH-), 117.6 (CH-), 113.6 (C-), 106.1 (C-), 86.6 (C-), 58.2 (C-), 58.0 (CH-), 52.4 (C-), 29.3 $(CH_3)_3$; MS (GC, 70 eV): *m/z* (%) 489 (M^+, 35), 368 (6), 312 (100); HR (EI): calcd for $C_{30}H_{23}N_3O_4$(M + 1) 489.16831, found 489.16779; IR (ATR, cm^{-1}): 3153 (w), 2220 (w), 1673 (s), 1634 (s), 1493 (s), 1343 (m), 1469 (m), 1194 (m), 1160 (m), 782 (s).

*1'-Cyclohexyl-5'-(2-hydroxybenzoyl)-2,6'-dioxo-1',5',6',7'-tetrahydro-2H-spiro[acenaphthylene-1,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**48b**)*



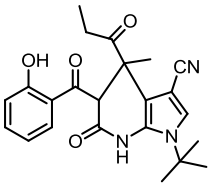
The product was isolated as a yellow solid, yield 56 %, mp 290-292 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 - 1.27 (1H, m, CH_2), 1.34 - 1.48 (2H, m, CH_2),1.57 - 1.73 (3H, m, CH_2), 1.80 - 2.01 (4H, m, CH_2), 4.11 - 4.23 (1H, m, CH) , 6.35 (1H, s, CH), 6.91 (2H, m, Ar-H), 7.40 (1H, s, Ar-H), 7.44 - 7.53 (1H, m, Ar-H), 7.60 - 7.72 (2H, m, Ar-H), 7.83 - 7.95 (2H, m, Ar-H), 8.01 (2H, m, Ar-H), 8.29 (1H, d, J = 7.9 Hz, Ar-H), 11.02 (1H, s, NH), 11.13 (1H, s, OH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 201.6 (C-), 197.7 (C-), 167.4 (C-), 159.8 (C-), 141.7 (C-), 138.0 (C-), 136.1 (CH-), 131.8 (C-), 131.4 (CH-), 131.3 (CH-), 130.3 (C-), 130.1 (C-), 128.6 (CH-), 128.5 (CH-), 125.3 (CH-), 121.9 (CH-), 121.8 (CH-), 120.4 (CH-), 119.2 (CH-), 117.5 (CH-), 113.7 (C-), 103.0 (C-), 87.6 (C-), 58.1 (CH), 54.5 (CH), 52.7 (C-), 32.8 (CH_2), 25.0 (CH_2), 24.5 (CH_2); MS (GC, 70 eV): *m/z* (%) 515 (M^+, 31), 394 (100), 312 (55); HRMS (ESI): calcd for $C_{32}H_{26}N_3O_4$ (M + 1) 516.19178, found 516.19154; IR (ATR, cm^{-1}): 3125 (w), 2220 (w), 1722 (s), 1670 (s), 1634 (s), 1340 (w), 1155 (m), 755 (s).

*5'-(2-Hydroxybenzoyl)-1'-(4-methoxybenzyl)-2,6'-dioxo-1',5',6',7'-tetrahydro-2H-spiro[acenaphthylene-1,4'-pyrrolo[2,3-b]pyridine]-3'-carbonitrile (**48c**)*



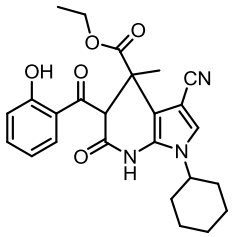
The product was isolated as a yellow solid, yield 35 %, mp 248-250 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.88 (3H, br. s, OCH_3), 4.96 - 5.53 (2H, m, CH_2), 6.40 (1H, br. s., CH), 6.97 (4H, m, Ar-H), 7.41- 8.1 (10 H,m, Ar-H), 8.37 (1H, br. s., Ar-H), 11.03 (1H, br. s., NH), 11.35 (1H, br. s., OH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 201.6 (C-), 197.4 (C-), 167.3 (C-), 159.6 (C-), 159.0 (C-), 141.7 (C-), 137.9 (C-), 136.1 (C-), 131.8 (C-), 131.4 (CH-), 131.2 (CH-),130.9 (C-), 130.8 (C-), 130.1 (C-), 129.3 (CH-), 128.6 (CH-), 128.5 (CH-), 128.2 (C-), 125.3 (CH-), 124.9 (CH-), 122.0 (C-), 121.8 (CH-), 120.4 (CH-), 119.2 (CH-), 117.5 (CH-), 114.2 (CH-), 113.4 (C-), 103.4 (C-), 87.7 (C-), 58.1 (CH-), 55.1 (OCH_3-), 52.9 (C-), 48.5 (CH_2); MS (GC, 70 eV): *m/z* (%) 253 (100), 226 (16); HRMS (ESI): calcd for $C_{34}H_{24}N_3O_5$(M + 1) 554.17105, found 554.17188; IR (ATR, cm^{-1}): 3182 (w), 2224 (w), 1712 (s), 1699 (s), 1638 (s), 1515 (m), 1239 (m), 1176 (m), 1153 (m), 748 (m).

*Ethyl-1-tert-butyl-3-cyano-5-(2-hydroxybenzoyl)-4-methyl-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-4-carboxylate (**49a**)*



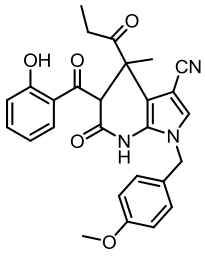
The product was isolated as a white solid, yield 67 %, mp 258-260 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.10 (3H, t, J = 7 Hz, CH_3), 1.59 (12H, s, CH_3), 3.93 - 4.21 (2H, m, CH_2), 5.25 (1H, s, CH), 6.87 - 7.09 (2H, m, Ar-H), 7.43 - 7.60 (2H, m, Ar-H), 7.93 (1H, d, J = 7.7 Hz, Ar-H), 10.26 (1H, br. s., NH), 11.38 (1H, br. s., OH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 198.8 (C-), 172.3 (C-), 167.6 (C-), 159.9 (C-), 136.0 (CH-), 131.3 (CH-), 130.0 (C-), 123.8 (CH-), 122.7 (C-), 119.2 (CH-), 117.6 (CH-),116.5 (C-), 105.6 (C-), 86.1 (C-), 60.3 (CH_2), 58.6 (CH-), 57.9 (C-), 42.9 (C-), 29.1 (CH_3), 19.6 (CH_3), 13.6 (CH_3); MS (GC, 70 eV): *m/z* (%) 331 (M^+, 35), 275 (100), 246 (59); IR (ATR, cm^{-1}): 3218 (w), 2227 (w), 1725 (s), 1674 (s), 1634 (s), 1349 (m), 1219 (m), 1188 (m), 1158 (m), 752 (s), 619 (s). Anal calcd for $C_{23}H_{25}N_3O_5$; C: 65.24, H: 5.95, N: 9.92, found C: 64.99, H: 5.97, N: 9.81

*Ethyl-3-cyano-1-cyclohexyl-5-(2-hydroxybenzoyl)-4-methyl-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-4-carboxylate (**49b**)*



The product was isolated as a white solid, yield 34 %, mp 252-255 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.09 (3 H, t, J = 7.08 Hz,), 1.16 - 1.47 (3 H, m, CH_2), 1.53 - 1.71 (6H, m, CH), 1.77 - 1.96 (4H, m, CH), 3.96 - 4.13 (3H, m, CH), 5.26 (1H, s, CH), 6.91 - 7.02 (2H, m, Ar-H), 7.48 - 7.58 (2H, m, Ar-H), 7.93 (1H, dd, ^{1}J = 8.12 Hz, ^{2}J = 1.32 Hz, Ar-H), 10.86 (1H, s, OH), 11.39 (1H, s, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 199.1 (C-), 172.5(C-) , 167.5 (C-), 160.0 (C-), 136.1(CH), 131.4 (CH), 130.0 (C-), 122.6 (C-), 122.3 (CH), 119.1 (CH), 117.6 (CH), 116.5 (C-), 102.6 (C-), 87.3(C-), 60.3 (CH_2), 59.0 (CH), 54.2 (CH), 43.3 (C-), 32.9 (C-), 32.7 (CH_2), 24.8 (CH_2), 24.5 (CH_2), 19.5 (CH_3), 13.6 (CH_3); MS (GC, 70 eV): *m/z* (%) 449 (M^+, 17), 256 (100), 121 (50); HRMS (ESI): calcd for $C_{25}H_{28}N_3O_5$ (M + 1) 450.20235, found 450.20237; IR (ATR, cm^{-1}): 2931 (w), 2219 (w), 1723 (m), 1687 (s), 1634 (m), 1444 (w), 1339 (m), 1215 (m), 751 (s). Anal calcd for $C_{25}H_{27}N_3O_5$; C: 66.80, H: 6.05, N: 9.35, found C: 66.78, H: 6.04, N: 9.54.

*Ethyl-3-cyano-5-(2-hydroxybenzoyl)-1-(4-methoxybenzyl)-4-methyl-6-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridine-4-carboxylate (**49c**)*

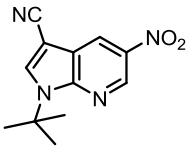


The product was isolated as a white solid, yield 47 %, mp 199-201 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11 (3H, t, J = 7.08 Hz, CH_3), 1.60 (3H, s, CH_3), 3.78 (3H, s, OCH_3), 4.00 - 4.15 (2H, m, CH_2), 5.05 (1H, d, J = 15.30 Hz, CH_2), 5.20(1H, d, J = 15.30 Hz, CH_2), 5.27 (1H, s, CH), 6.93 - 7.00 (4H, m, Ar-H), 7.19 - 7.28 (2H, m, Ar-H), 7.47 (1H, s, Ar-H), 7.48 - 7.56 (1H, m, Ar-H), 7.89 (1H, dd, ^{1}J = 8.03 Hz, ^{2}J = 1.42 Hz, Ar-H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 198.7 (C-), 172.5 (C-), 167.4 (C-), 159.8 (C-), 158.9 (C-), 136.0 (CH-), 131.3 (CH-), 130.5 (C-), 129.0 (CH-), 128.3 (C-), 125.5 (CH-),122.8 (C-), 119.2 (CH-), 117.5 (CH-), 116.1 (C-), 114.1 (CH-), 103.1 (C-), 87.5 (C-), 60.4 (CH_2), 58.9 (CH), 55.1 (OCH_3), 48.3 (CH_2), 43.4 (C-), 19.4 (CH_3), 13.6 (CH_3); MS (GC, 70 eV): *m/z* (%) 487 (M^+,1), 260 (6), 121 (100); HRMS (ESI): calcd for $C_{27}H_{26}N_3O_6$(M + 1) 488.18161, found 488.18027; IR (ATR, cm^{-1}): 3030 (w), 2222 (w), 1679 (s), 1635 (m),1246 (s), 1208 (s), 1153 (s), 1029 (m), 750 (s). Anal calcd for $C_{27}H_{25}N_3O_6$; C: 66.52, H: 5.17, N: 8.62, found C: 66.56, H: 5.14, N: 8.85.

A.2.20 General procedure for the synthesis of compounds 51a-c

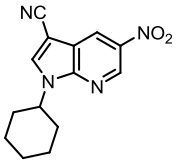
Nitromalonaldehyde (1 equiv.) and 5-amino-1R-pyrrole-3-carbonitrile (1 equiv.) were placed in pressure tube under a flow of dry argon and dissolved in dry DMF (10 mL) containing 1 mL of TMSCl. The mixture was heated at 100 ^{o}C during 2–12 h (controlled by TLC). Then this solution was concentrated under reduced pressure, the residue treated with water, filtered and air-dried and recrystallized from an appropriate solvent, or was subjected to column chromatography over silica gel.

*1-Tert-butyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**51a**)*



The product was isolated as a orange solid, yield 63 %, mp 218-220 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.24 (1H, d, *J* = 2.5 Hz, Ar-H), 8.82 (1H, d, *J* = 2.6 Hz, Ar-H), 8.00 (1H, s, Ar-H), 1.79 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 148.7 (C-), 140.1 (CH-), 140.0 (C-), 136.6 (CH-), 124.1 (CH-), 120.3 (C-), 113.7 (C-), 86.0 (C-), 59.9 (C-), 29.1 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 244 (M+, 24), 188 (100), 142 (28); HRMS (ESI): calcd for $C_{12}H_{13}N_4O_2$ (M + 1) 245.1033, found 245.1032; IR (ATR, cm^{-1}) ῡ 3167 (w), 2974 (w), 2222 (s), 1604 (m), 1575 (m), 1515 (s), 1414 (m), 1333 (s), 1292 (s), 1196 (s), 1119 (m), 912 (m), 776 (m), 744 (m), 660 (m), 619 (m). Anal. Calcd for $C_{12}H_{12}N_4O_2$: C: 59.01, H: 4.95, N: 22.94, found: C: 58.83, H: 5.03, N: 22.55.

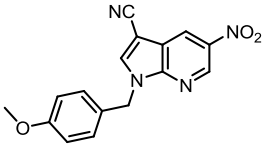
*1-Cyclohexyl-5-nitro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**51b**)*



The product was isolated as a brown solid, yield 56 %, mp 211-213 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.24 (1H, d, *J* = 2.3 Hz, Ar-H), 8.86 (1H, d, *J* = 2.3 Hz, Ar-H), 7.94 (1H, s, Ar-H), 1.88 - 2.15 (4H, m, CH), 1.45 - 1.81 (5H, m, CH_2), 1.18-1.33 (1H, m, CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 147.9 (C-), 141.1 (CH-), 140.5 (C-), 135.9 (CH-), 124.5 (CH-), 119.0 (C-), 113.6 (C-), 87.0 (C-), 55.4 (CH), 33.3 (CH_2), 25.5 (CH_2), 25.1 (CH_2). MS (GC, 70 eV) m/z (%) 270 (M+, 46), 189 (61), 188 (100); HR (EI): calcd for $C_{14}H_{14}N_4O_2$ (M) 270.11113, found 270.11097; IR (ATR, cm^{-1}) ῡ 3151 (w), 2938 (m), 2226 (s), 1604 (m), 1578 (m), 1521 (m), 1509 (s), 1428 (m), 1327 (s), 1197 (m), 1077 (m), 915 (m), 785 (m), 746 (m), 615 (s). calcd for $C_{14}H_{14}N_4O_2$: C: 62.21, H: 5.22, N: 20.73, found: C: 60.33, H:

5.30, N: 19.68.

*1-(4-Methoxybenzyl)-5-nitro-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**51c**)*

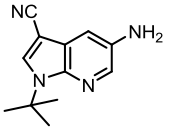


The product was isolated as a yellow solid, yield 84 %, mp 130-132 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.30 (1H, d, *J* = 2.5 Hz, Ar-H), 8.95 (1H, d, *J* = 2.5 Hz, Ar-H), 8.90 (1H, s, Ar-H), 7.33 (2H, d, *J* = 8.7 Hz, Ar-H), 6.89 (2H, d, *J* = 8.7 Hz, Ar-H), 5.54 (2H, s, CH_2), 3.71 (3H, s, OCH_3). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 159.0 (C-), 147.6 (C-), 141.4 (CH-), 141.0 (CH-), 140.3 (C-), 129.3 (CH-), 128.0 (C-), 124.5 (CH-), 118.2 (C-), 114.1 (CH-), 113.8 (C-), 85.5 (C-), 55.0 (OCH_3), 48.2 (CH_2). MS (GC, 70 eV) m/z (%) 121 (M+, 100), 77 (6); HR (EI): calcd for $C_{18}H_{12}N_4O_3$ (M) 308.09039, found 308.09124; IR (ATR, cm^{-1}) ῡ 3104 (w), 2221 (s), 1734 (s), 1603 (m), 1579 (m), 1513 (s), 1342 (s), 1240 (s), 1171 (s), 1027 (m), 948 (w), 795 (m). calcd for $C_{16}H_{12}N_4O_3$: C: 62.33, H: 3.92, N: 18.17, found: C: 61.75, H: 4.25, N: 17.25.

A.2.21 Procedure for the synthesis of compound 52a

In a 50 mL Schlenk flask under a flow of dry argon were placed the corresponding nitro-compound (1.0 mmol) and 0.05 g of Pd/C (10%). Afterwards, 25 mL of degassed methanol was added. The system was flushed three times with hydrogen. The hydrogenation was conducted with the help of a glass burette under atmospheric pressure. After 3 equiv. of hydrogen were consumed, the mixture was stirred for a day at 20 ^{o}C (controlled by TLC). The reaction mixture was filtered through a Celite pad (2–3 cm). The Celite was washed 3 times with methanol. The compound isolated did not demand further purification. However, some of them were purified by preparative chromatography (silica gel, heptane/EtOAc) or recrystallized from an appropriate solvent.

*5-Amino-1-tert-butyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**52a**)*



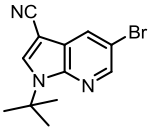
The product was isolated as a brown solid, yield 95 %, mp 129-131 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (1H, d, *J* = 2.6 Hz, Ar-H), 7.65 (1H, s, Ar-H), 7.22

(1H, d, J = 2.6 Hz, Ar-H), 3.60 (2H, br. s., NH_2), 1.71 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 140.8 (C-), 140.0 (C-), 134.0 (CH-), 133.6 (CH-), 121.7 (C-), 116.2 (C-), 108.7 (CH-), 79.4 (C-), 57.6 (C-), 28.6 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 214 (M+, 20), 158 (100), 130 (10); HR (EI): calcd for $C_{12}H_{14}N_4$ (M+) 214.12130, found 214.12134; IR (ATR, cm^{-1}) ũ 3349 (w), 2202 (s), 1613 (w), 1519 (m), 1417 (s), 1305 (m), 1087 (m), 862 (w), 725 (m), 692 (m), 620 (s). calcd for $C_{12}H_{14}N_4$: C: 67.27, H: 6.59, N: 26.15, found: C: 66.09: 6.63, N: 25.36.

A.2.22 Procedure for the synthesis of compound 53a

Anhydrous copper bromide (1.2 mmol), *tert*-butyl nitrite (1.5mmol), and anhydrous acetonitrile (40 mL) were placed in a three-necked round bottom flask that was equipped with a reflux condenser, addition funnel or solid inlet tube, and a gas outlet tube. Amine **52a** (1 mmol) in 5 mL of acetonitrile was slowly added over a period of 5 min to the reaction solution. During this addition, the reaction solution turned completely black from the initial green color as nitrogen was evolved. After complete gas evolution, the reaction was poured into 200 mL of 20% aqueous hydrochloric acid and extracted with 200 mL of ether and the organic layer was washed once with 200 mL of 20% aqueous hydrochloric acid. The resulting ether solution was dried over anhydrous magnesium sulfate and the ether was removed under reduced pressure.

*5-Bromo-1-tert-butyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**53a**)*

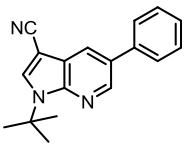


The product was isolated as a white solid, yield 80 %, mp 183 ºC. ^1H NMR (300 MHz, $CDCl_3$): δ 8.36 (1H, d, J = 2.3 Hz, Ar-H), 8.08 (1H, d, J = 2.3 Hz, Ar-H), 7.78 (1H, s, Ar-H), 1.73 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 145.4 (C-), 144.9 (CH-), 134.1 (CH-), 129.9 (CH-), 122.8 (C-), 114.8 (C-), 114.1 (C-), 82.9 (C-), 58.9 (C-), 29.0 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 279 (M+, 16), 223 (100), 142 (28); HRMS (ESI): calcd for $C_{12}H_{13}BrN_3$ (M + 1) 278.02866, found 278.02874; IR (ATR, cm^{-1}) ũ 2972 (w), 2217 (s), 1519 (s), 1407 (m), 1372 (m), 1271 (s), 1190 (s), 1073 (w), 881 (m), 832 (m), 617 (s). calcd for $C_{12}H_{12}BrN_3$: C: 51.82, H: 4.35, N: 15.11, found: C: 53.12, H: 4.79, N: 15.10. The structure was independently confirmed by X-Ray analysis.

A.2.23 General procedure for the synthesis of compounds 55a-e

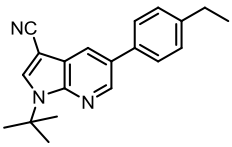
Under an argon atmosphere, an appropriate boronic acid (1.2 equiv.), compound **53a** (1 equiv.), potassium carbonate (2 equiv.) and $PdCl_2(PPh_3)_2$ (2 mol %) were placed in a pressure tube and 4 mL of dry 1,4 dioxane were added. Once the tube was sealed the mixture was heated at 90 ^oC for 4-6 hours. The product was then purified by column chromatography (eluent: *n*-heptane/ethylacetate).

*1-Tert-butyl-5-phenyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**55a**)*



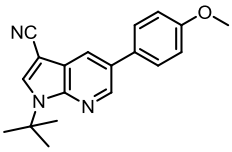
The product was isolated as a white solid, yield 60%, mp 182 ºC. ^1H NMR (300 MHz, DMSO-d_6): δ 8.80 (1H, s, Ar-H), 8.60 (1H, s, Ar-H), 8.36 (1H, s, Ar-H), 7.85 (2H, d, J = 7.4 Hz, Ar-H), 7.42 - 7.58 (3H, m, Ar-H), 1.84 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, DMSO- d_6): δ 146.1 (C-), 143.0 (CH-), 137.7 (C-), 136.7 (CH-), 130.4 (C-), 129.1 (CH-), 127.7 (CH-), 127.3 (CH-), 125.4 (CH), 120.9 (C-), 115.6 (C-), 82.0 (C-), 58.6 (C-), 28.7 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 275 (M+, 17), 219 (100); HR (EI): calcd for $C_{18}H_{17}N_3$ (M) 275.14170, found 275.14181; IR (ATR, cm^{-1}) ῡ 3138 (w), 2212 (m), 1603 (w), 1523(m), 1407 (m), 1396 (m), 1208 (s), 891 (m), 760 (s), 702 (s). calcd for $C_{18}H_{17}N_3$: C: 78.52, H: 6.22, N: 15.26, found: C: 78.04, H: 6.33, N: 15.08.

*1-Tert-butyl-5-(4-ethylphenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**55b**)*



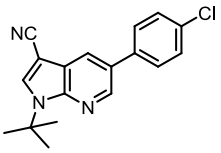
The product was isolated as a white solid, yield 70%, mp196 ºC. ^{1}H NMR (300 MHz, DMSO- d_6): δ 8.74 (1H, d, J = 2.1 Hz, Ar-H), 8.57 (1H, s, Ar-H), 8.29 (1H, d, J = 2.3 Hz, Ar-H), 7.72 (2H, d, J = 8.1 Hz, Ar-H), 7.35 (2H, d, J = 8.1 Hz, Ar-H), 2.68 (2H, q, J = 7.4 Hz, CH_2), 1.81 (9H, s, $(CH_3)_3$), 1.24 (3H, t, J = 7.6Hz, CH_3). ^{13}C NMR (62.9 MHz, DMSO- d_6): δ 145.9 (C-), 143.2 (C-), 142.7 (CH-), 136.4 (CH-), 134.9 (C-), 130.3 (C-), 128.4 (CH-), 127.1 (CH-), 124.9 (CH-), 120.8 (C-), 115.5 (C-), 81.8 (C-), 58.4 (C-), 28.5 $(CH_3)_3$, 27.8 (CH_2), 15.5 (CH_3). MS (GC, 70 eV) m/z (%) 303 (M+, 29), 247 (100), 232 (62); HR (EI): calcd for $C_{20}H_{21}N_3$ (M) 303.1730, found 303.1732; IR (ATR, cm^{-1}) ũ 3150 (w), 2216 (m), 1526 (w), 1366 (w), 1208 (m), 903 (w), 833 (s), 777 (m). calcd for $C_{20}H_{21}N_3$: C: 79.17, H: 6.98, N: 13.85, found: C: 78.95, H: 7.10, N: 13.74.

*1-Tert-butyl-5-(4-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**55c**)*



The product was isolated as a white solid, yield 70%, mp 130 ºC. ^{1}H NMR (300 MHz,($CDCl_3$): δ 8.55 (2H, d, J = 2 Hz, Ar-H), 8.07 (2H, d, J = 2 Hz, Ar-H), 7.79 (1H, s, Ar-H), 7.49 (2H, d, J = 9 Hz, Ar-H), 6.95 (2H, d, J = 9 Hz, Ar-H), 3.79 (3H, s, OCH_3), 1.77 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 159.4 (C-), 146.2 (C-), 143.2 (CH-), 133.4 (CH-), 131.1 (C-), 130.8 (C-), 128.5 (CH-), 125.4 (CH-), 121.5 (C-), 115.6 (C-), 114.6 (CH-), 83.1 (C-), 58.5 (C-), 55.4 (OCH_3-), 29.1 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 305 (M+, 36), 249 (100), 234 (29); HR (EI): calcd for $C_{19}H_{19}N_3O$ (M) 305.15226, found 305.15261; IR (ATR, cm^{-1}) ũ 3145 (w), 2213 (m), 1606 (m), 1519 (m), 1399 (m), 1295 (m), 1246 (m), 830 (s). calcd for $C_{19}H_{19}N_3O$: C: 74.73, H: 6.27, N: 13.76, found: C: 74.51, H: 6.36, N: 13.64.

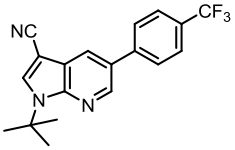
*1-Tert-butyl-5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**55d**)*



The product was isolated as a white solid, yield 58%, mp 189-190 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.54 (1H, d, J = 2 Hz, Ar-H), 8.08 (1H, d, J = 2 Hz, Ar-H), 7.82 (1H, s, Ar-H), 7.45 - 7.50 (2H, m, Ar-H), 7.36 - 7.41 (2H, m,

Ar-H), 1.78 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 146.6 (C-), 143.1 (CH-), 136.9 (C-), 133.9 (C-), 133.8 (CH-), 130.2 (C-), 129.3 (CH-), 128.6 (CH-), 125.8 (CH-), 121.5 (C-), 115.4 (C-), 83.4 (C-), 58.7 (C-), 29.1 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 309 (M+, 17), 253 (100); HR (EI): calcd for $C_{18}H_{16}N_3Cl$ (M) 309.10273, found 309.10261; IR (ATR, cm^{-1}) ῡ 3145 (w), 2217 (m), 1608 (w), 1524 (m), 1469 (m), 1414 (m), 1368 (m), 1207 (s), 1089 (m), 830 (s). calcd for $C_{18}H_{16}N_3Cl$: C: 69.79, H: 5.21, N: 13.56, found: C: 68.98, H: 5.34, N: 13.38.

*1-Tert-butyl-5-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**55e**)*

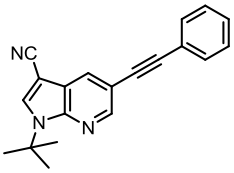


The product was isolated as a white solid, yield 67%, mp 177-179 ºC. ^1H NMR (300 MHz, $CDCl_3$): δ 8.60 (1H, d, J = 2 Hz, Ar-H), 8.15 (1H, d, J = 2 Hz, Ar-H), 7.85 (1H, s, Ar-H), 7.68 (4H, s, Ar-H), 1.79 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 146.9 (C-), 144.0 (C-), 143.3 (CH-), 142.0 (C-), 134.0 (CH-), 129.9 (C-), 129.5 (C-), 127.7 (CH-), 126.2 (C-), 126.1 (CF_3, q, J_1 = 3.36 J_2= 7.78 Hz),, 121.5 (C-), 115.3 (C-), 83.5 (C-), 58.8 (C-), 29.1 $(CH_3)_3$; ^{19}F NMR (300 MHz,($CDCl_3$): δ -62.48 Hz; MS (GC, 70 eV) m/z (%) 343 (M+, 11), 287 (100); HR (EI): calcd for $C_{19}H_{16}N_3F_3$ (M) 343.1290, found 343.1289; IR (ATR, cm^{-1}) ῡ 3143 (w), 2218 (m), 1608 (m), 1523 (m), 1399 (m), 1322 (s), 1208 (m), 1164 (m), 1111 (s), 1070 (m), 835 (m). calcd for $C_{19}H_{16}F_3N_3$: C: 66.46, H: 4.70, N: 12.24, found: C: 66.37, H: 4.66, N: 11.87.

A.2.24 General procedure for the synthesis of compounds 57a-e

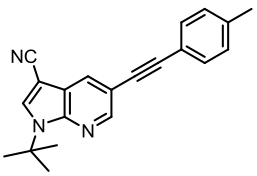
Under an argon atmosphere, copper iodide (5 mol %), an appropriate acetylene (1.2 equiv.), compound **53a** (1 equiv.), triethylamine (1,5 equiv.) and $PdCl_2(PPh_3)_2$ (2 mol %), were placed in a pressure tube and 4 mL of dry DMF were added. Once the tube was sealed the mixture was heated at 120 °C for 4-6 hours. The product was then purified by column chromatography (eluent: *n*-heptane/ethylacetate).

*1-Tert-butyl-5-(phenylethynyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**57a**)*



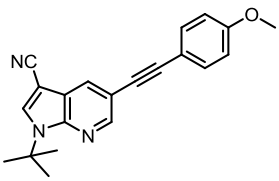
The product was isolated as a brown solid, yield 70 %, mp 136-138 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (1H, d, *J* = 2.1 Hz, Ar-H), 8.11 (1H, d, *J* = 1.9 Hz, Ar-H), 7.80 (1H, s, Ar-H), 7.47 - 7.52 (2H, m, Ar-H), 7.27 - 7.33 (3H, m, Ar-H), 1.76 (9H, s, $(CH_3)_3$).^{13}C NMR (62.9 MHz, $CDCl_3$): δ 146.9 (CH-), 145.9 (C-), 133.9 (CH-), 131.6 (CH-), 130.4 (CH-), 128.5 (CH-), 128.4 (CH-), 122.9 (C-), 120.8 (C-), 115.0 (C-), 114.3 (C-), 91.3 (C-), 86.7 (C-), 83.4 (C-), 58.8 (C-), 29.1 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 299 (M+, 23), 243 (100); HR (EI): calcd for $C_{20}H_{17}N_3$ (M) 299.1417, found 299.14203; IR (ATR, cm-1) ῡ 3144 (w), 2217 (m), 1610 (w), 1491 (m), 1407 (m), 1208 (s), 896 (m), 753 (s), 688 (s), 634 (m), 584 (m). calcd for $C_{20}H_{17}N_3$: C: 80.24, H: 5.72, N: 14.04, found: C: 79.92, H: 5.96, N: 13.69. The structure was independently confirmed by X-Ray analysis.

*1-Tert-butyl-5-(p-tolylethynyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**57b**)*



The product was isolated as an orange solid, yield 65 %, mp185 -187 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (1H, d, *J* = 1.9 Hz, Ar-H), 8.09 (1H, d, *J* = 2.1 Hz, Ar-H), 7.78 (1H, s, Ar-H), 7.38 (2H, d, *J* = 8.1 Hz, Ar-H), 7.10 (2H, d, *J*=7.9 Hz, Ar-H), 2.30 (3H, s, CH_3), 1.74 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 146.9 (CH-), 145.8 (C-), 138.7 (C-), 133.9 (CH-), 131.5 (CH-), 130.3 (CH-), 129.2 (CH-), 120.8 (C-), 119.8 (C-), 115.1 (C-), 114.5 (C-), 91.5 (C-), 86.0 (C-), 83.4 (C-), 58.8 (C-), 29.1 $(CH_3)_3$, 21.6 (CH_3). MS (GC, 70 eV) m/z (%) 313 (M+, 31), 257 (100); HR (EI): calcd for $C_{21}H_{19}N_3$ (M) 313.15735, found 313.15732; IR (ATR, cm^{-1}) ῡ 3149 (w), 2219 (m), 1609 (w), 1509(w), 1407 (s), 1361 (m), 1206 (s), 894 (m), 812 (s), 774 (m), 634 (m). calcd for $C_{21}H_{19}N_3$: C: 80.48, H: 6.11, N: 13.41, found: C: 80.27, H: 6.29, N: 12.90.

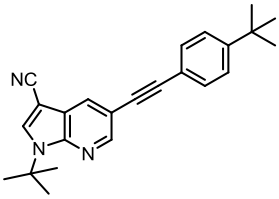
*1-Tert-butyl-5-((4-methoxyphenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**57c**)*



The product was isolated as a white solid, yield 65 %, mp 202 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (1H, d, *J* = 2 Hz, Ar-H), 8.08 (1H, d, *J* = 2 Hz, Ar-H), 7.78 (1H, s, Ar-H), 7.42 (2H, d, *J* = 9 Hz, Ar-H), 6.82 (2H,

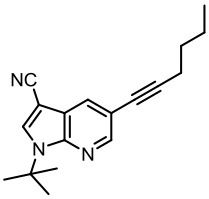
d, *J* = 9 Hz, Ar-H), 3.76 (3H, s, OCH_3), 1.75 (9H, s, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 159.8 (C-), 146.8 (CH-), 145.7 (C-), 133.8 (CH-), 133.1 (CH-), 130.1 (CH-), 120.8 (C-), 115.1 (C-), 114.9 (CH-), 114.7 (C-), 114.1 (C-), 91.3 (C-), 85.4 (C-), 83.3 (C-), 58.8 (C-), 55.3 (OCH_3-), 29.1 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 329 (M+, 49), 273 (100), 258 (35); HR (EI): calcd for $C_{21}H_{19}N_3O$ (M) 329.15226, found 329.15221; IR (ATR, cm^{-1}) ũ 3119 (w), 2212 (m), 1738 (w), 1511(s), 1406 (w), 1242 (m), 1211 (m), 1033 (m), 821 (s), 636 (m). calcd for $C_{21}H_{19}N_3O$: C: 76.57, H: 5.81, N: 12.76, found: C: 76.1, H: 5.76, N: 12.72.

*1-Tert-butyl-5-((4-tert-butylphenyl)ethynyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**57d**)*



The product was isolated as an orange solid, yield 75 %, mp 143-145 ºC. ^1H NMR (300 MHz, $CDCl_3$): δ 8.48 (1H, d, *J* = 1.9 Hz, Ar-H), 8.09 (1H, d, *J* = 1.9 Hz, Ar-H), 7.79 (1H, s, Ar-H), 7.39 - 7.46 (2H, m, Ar-H), 7.29 - 7.35 (2H, m, Ar-H), 1.75 (9H, s, $(CH_3)_3$), 1.26 (9H, s, $(CH_3)_3$). δ ^{13}C NMR (62.9 MHz, $CDCl_3$): 151.9 (C-), 146.9 (CH-), 145.8 (C-), 133.8 (CH-), 131.4 (CH-), 130.3 (CH-), 125.5 (CH-), 120.8 (C-), 119.9 (C-), 115.1 (C-), 114.6 (C-), 91.5(C-), 86.0 (C-), 83.4 (C-), 58.8 (C-), 34.8 (C-), 31.2 $(CH_3)_3$, 29.1 $(CH_3)_3$. MS (GC, 70 eV) m/z (%) 355 (M+, 47), 299 (32), 284 (100); HR (EI): calcd for $C_{24}H_{25}N_3$ (M) 355.2043, found 355.2042; IR (ATR, cm^{-1}) ũ 3143 (w), 2218 (m), 1604 (w), 1520 (w), 1405 (s), 1347 (m), 1266 (m), 1205 (s), 894 (m), 831 (s), 775 (m), 635 (m). calcd for $C_{24}H_{25}N_3$: C: 81.09, H: 7.09, N: 11.82, found: C: 81.21, H: 7.41, N: 11.14.

*1-Tert-butyl-5-(hex-1-ynyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**57e**)*



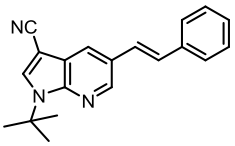
The product was isolated as a white solid, yield 60 %, mp 102-104 ºC. ^1H NMR (300 MHz, $CDCl_3$): δ 8.35 (1H, d, *J* = 2.1 Hz, Ar-H), 7.96 (1H, d, *J* = 1.9 Hz, Ar-H), 7.76 (1H, s, Ar-H), 2.37 (2H, t, *J* = 6.9 Hz, CH_2), 1.73 (9H, s, $(CH_3)_3$), 1.39 -1.57 (4H, m, CH_2), 0.89 (3H, t, *J* = 7.2 Hz, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 146.9 (CH-), 145.5 (C-), 138.2 (C-), 133.6 (CH) 130.3 (CH-), 120.7 (C-), 115.2 (C-), 115.1 (C-), 92.4 (C-), 83.1 (C-), 58.6 (C-), 30.7(CH_2-), 29.0 $(CH_3)_3$, 22.0 (CH_2-), 19.1 (CH_2-), 13.6 (CH_3). MS (GC, 70 eV) m/z (%) 279 (M+, 49), 223 (100), 208 (89), 194 (58) ; HR (EI): calcd for $C_{18}H_{21}N_3$ (M) 279.17300, found 279.17307; IR (ATR, cm^{-1}) ũ 2975 (w), 2225 (s),

1545 (s), 1398 (m), 1372 (m), 1268 (s), 1183 (s), 880 (m), 825 (m), 612 (s).

A.2.25 General procedure for the synthesis of compounds 59a-c

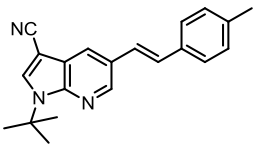
Under an argon atmosphere, an appropriate styrene (3 equiv.), **53a** (1 equiv.), triethylamine (4 equiv.) and $PdCl_2(PPh_3)_2$ (4 mol %), were placed in a pressure tube and 4 mL of dry dimethylformamide were added. Once the tube was sealed the mixture was heated at 140 ^oC for 8 hours. The product was then purified by column chromatography (eluent: *n*-heptane/ethylacetate).

*(E)-1-Tert-butyl-5-styryl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**59a**)*



The product was isolated as a yelllow solid, yield 72%, mp 146-148 ºC. ^1H NMR (300 MHz,($CDCl_3$): δ 8.43 (1H, d, *J* = 2 Hz, Ar-H), 8.03 (1H, d, *J* = 2 Hz, Ar-H), 7.73 (1H, s, Ar-H), 7.42 - 7.47 (2H, m, Ar-H), 7.24 - 7.32 (2H, m, Ar-H),7.15 - 7.22 (1H, m, Ar-H), 7.08 (2H, s, Ar-H), 1.72 (9H, s, $(CH_3)_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 145.6 (C-), 142.8 (CH-), 135.9 (C-), 132.6 (CH-), 128.5 (CH-), 127.8 (CH-), 126.9 (CH-), 126.6 (C-), 125.5 (CH-), 124.2 (CH-), 123.1 (CH-),120.6 (C-), 114.6 (C-), 82.2 (C-), 57.6 (C-), 28.1 $(CH_3)_3$; MS (GC, 70 eV) m/z (%) 301 (M+, 38), 244 (100); HR (EI): calcd for $C_{20}H_{19}N_3$ (M) 301.15735, found 301.1577; IR (ATR, cm^{-1}) ῦ 3155 (w),2979 (m), 2214 (m), 1520 (m), 1397 (m), 1371 (m), 1363 (m), 1204 (s), 1083 (w), 949 (s), 746 (s), 687 (s), 631 (s). calcd for $C_{20}H_{19}N_3$: C: 79.70, H: 6.35, N: 13.94, found: C: 78.22, H: 6.41, N: 13.55.

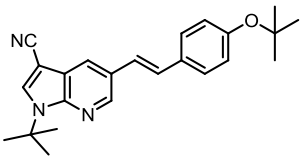
*(E)-1-Tert-butyl-5-(4-methylstyryl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**59b**)*



The product was isolated as a yellow solid, yield 58%, mp 179-181 ºC. ^1H NMR (300 Mhz,($CDCl_3$): δ 8.46 (1H, d, *J* = 2 Hz, Ar-H), 8.07 (1H, d, *J* = 2 Hz, Ar-H), 7.76 (1H, s, Ar-H), 7.37 (2H, d, *J* = 8 Hz, Ar-H), 7.12 (2H, d, *J* = 8 Hz, Ar-H),7.08 (2H, s, Ar-H), 2.30 (3H, s, CH_3), 1.75 (9H, s, $(CH_3)_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 146.5 (C-), 143.8 (CH-), 137.9 (C-), 134.2 (C-), 133.5 (CH-), 129.6 (CH-), 129.5 (CH-

), 127.9 (C-), 126.5 (CH-), 124.3 (CH-), 124.0 (CH-),121.6 (C-), 115.6 (C-), 83.1 (C-), 58.6 (C-), 29.1 $(CH_3)_3$, 21.3 (CH_3); MS (GC, 70 eV) m/z (%) 315 (M+, 64), 258 (100), 244 (45); HR (EI): calcd for $C_{21}H_{21}N_3$ (M) 315.17300, found 315.1728; IR (ATR, cm^{-1}) ũ 3142 (w),2976 (m), 2214 (m), 1522 (m), 1414 (m), 1366 (m), 1206 (s), 1089 (w), 972 (m), 854 (m), 806 (m), 744 (m), 633 (s). calcd for $C_{21}H_{21}N_3$: C: 79.97, H: 6.71, N: 13.32, found: C: 78.79, H: 6.73, N: 12.91.

*(E)-5-(4-Tert-butoxystyryl)-1-tert-butyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (**59c**)*



The product was isolated as a yellow solid, yield 58%, mp 143-145 ºC. ^{1}H NMR (300 MHz,($CDCl_3$): δ 8.46 (1H, s, Ar-H), 8.07 (1H, s, Ar-H), 7.77 (1H, s, Ar-H), 7.39 (2H, d, *J* = 8 Hz, Ar-H), 7.06 (2H, d, *J* = 8 Hz, Ar-H), 6.94 (2H, d, *J* = 8 Hz, Ar-H), 1.76 (9H, s, $O(CH_3)_3$), 1.31 (9H, s, $(CH_3)_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 154.4 (C-), 145.5 (C-), 142.7 (CH-), 132.5 (CH-), 131.1 (C-), 128.1 (CH-), 126.9 (C-), 126.1 (CH-), 123.3 (CH-), 123.0 (CH-), 122.9 (CH-), 120.6 (C-), 114.6 (C-), 82.1 (C-), 77.9 (C-), 57.5 (C-), 28.1 $(CH_3)_3$, 27.9 $(OCH_3)_3$; MS (GC, 70 eV) m/z (%) 373 (M+, 6), 317 (60), 261 (100); HR (EI): calcd for $C_{24}H_{27}N_3O$ (M) 373.21486, found 373.21453; IR (ATR, cm^{-1}) ũ 3134 (w), 2963 (m), 2210 (m), 1504 (m), 1406 (m), 1364 (m), 1257 (s), 893 (m), 859 (m), 796 (s), 633 (m). calcd for $C_{24}H_{27}N_3O$: C: 77.18, H: 7.29, N: 11.25, found: C: 70.61, H: 7.41, N: 9.29.

A.3 Crystallographic data

A.3.1 Crystal data and structure refinement for 3a

Identification code	mv049
Empirical formula	C_{21} H_{22} N_4
Formula weight	330.43
Temperature	173 (2)
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group (H.-M.)	C c
Space group (Hall)	C -2yc
Unit cell dimensions	a = 35.7558(8) Å α = 90.00°
	b = 12.2448(3) Å β = 104.9230(10)°
	c = 17.1301(4) Å γ = 90.00°
Volume	7247.0(3) $Å^3$
Z	16
Density (calculated)	1.211 Mg/m^3
Absorption coefficient	0.074
F (000)	2816
Crystal size	0.69x0.44x0.11
Θ range for data collection	2.43 to 30.0°
Index ranges	$-50 \leq h \leq 50$, $-17 \leq k \leq 15$, $-21 \leq l \leq 24$
Reflections collected	40459
Independent reflections	17575[R(int) = 0.0266]
Completeness to Θ = 30.00°	99.6 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9653 and 0.9961
Refinement	Full-matrix least-squares on F^2
Data / restraints / parameters	13936/3/940
Goodness-of-fit on F^2	1.036
Final R indices [$I>2\sigma(I)$]	R1 = 0.0440, wR2 = 0.0931
R indices (all data)	R1 = 0.0633, wR2 = 0.0995
Largest diff. peak and hole	0.236 and -0.237 $e.Å^{-3}$

A.3.2 Crystal data and structure refinement for 3b

Identification code	mv047
Empirical formula	C_{24} H_{22} N_4 O
Formula weight	382.46
Temperature	173 (2)
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group (H.-M.)	P -1
Space group (Hall)	-P 1
Unit cell dimensions	a = 8.4594(2) Å α = 94.503(2)°
	b = 14.0748(4) Å β = 99.926(2)°
	c = 17.3726(5) Å γ = 93.7380(10)°
Volume	2024.67(9) $Å^3$
Z	4
Density (calculated)	1.255 Mg/m^3
Absorption coefficient	0.079
F (000)	808
Crystal size	0.45x0.21x0.05
Θ range for data collection	2.39 to 29.98°
Index ranges	-17≤ h ≤17, -23≤ k ≤23, -24≤ l ≤25
Reflections collected	42450
Independent reflections	11668[R(int) = 0.0389]
Completeness to Θ = 29.98°	99 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9509 and 0.9919
Refinement	Full-matrix least-squares on F^2
Data / restraints / parameters	7336/0/537
Goodness-of-fit on F^2	1.050
Final R indices [I>2σ(I)]	R1 = 0.0538, wR2 = 0.1212
R indices (all data)	R1 = 0.1012, wR2 = 0.1347
Largest diff. peak and hole	0.303 and -0.271 e.$Å^{-3}$

A.3.3 Crystal data and structure refinement for 8a

Identification code	ag47
Empirical formula	C_{18} H_{16} N_4 O_3, C_3H_7NO
Formula weight	409.44
Temperature	173 (2)
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group (H.-M.)	P 21/c
Space group (Hall)	-P 2ybc
Unit cell dimensions	a = 7.5705(2) Å α = 90.0°
	b = 24.5164(6) Å β = 94.9310(10)°
	c = 11.0462(3) Å γ = 90.0°
Volume	2042.60(9) $Å^3$
Z	4
Density (calculated)	1.331 Mg/m^3
Absorption coefficient	0.095
F (000)	864
Crystal size	0.54x0.51x0.27
Θ range for data collection	2.49 to 30.0°
Index ranges	$-10\leq h \leq 10$, $-19\leq k \leq 34$, $-15\leq l \leq 15$
Reflections collected	24039
Independent reflections	5951[R(int) = 0.0193]
Completeness to Θ = 30.00°	99.9 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9506 and 0.9749
Refinement	Full-matrix least-squares on F^2
Data / restraints / parameters	5152/0/280
Goodness-of-fit on F^2	1.027
Final R indices [$I>2\sigma(I)$]	R1 = 0.0413, wR2 = 0.1099
R indices (all data)	R1 = 0.0482, wR2 = 0.1135
Largest diff. peak and hole	0.358 and -0.256 $e.Å^{-3}$

A.3.4 Crystal data and structure refinement for 8b

Identification code	ag48
Empirical formula	$C_{22}\ H_{16}\ N_4\ O_4,\ C_3H_7NO$
Formula weight	473.48
Temperature	173 (2)
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group (H.-M.)	P -1
Space group (Hall)	-P 1
Unit cell dimensions	a = 11.9485(10) Å α = 91.289(4)°
	b = 18.2795(16) Å β = 100.953(3)°
	c = 21.9039(19) Å γ = 97.208(3)°
Volume	4654.5(7) $Å^3$
Z	8
Density (calculated)	1.351 Mg/m^3
Absorption coefficient	0.097
F (000)	1984
Crystal size	0.49x0.23x0.07
Θ range for data collection	0.95 to 27.0°
Index ranges	$-15\leq h\leq 13,\ -23\leq k\leq 23,\ -27\leq l\leq 27$
Reflections collected	70846
Independent reflections	19921[R(int) = 0.0600]
Completeness to Θ = 27.00°	98.0 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9542 and 0.9933
Refinement	Full-matrix least-squares on F^2
Data / restraints / parameters	10725/0/1277
Goodness-of-fit on F^2	0.912
Final R indices [$I>2\sigma(I)$]	R1 = 0.0473, wR2 = 0.0945
R indices (all data)	R1 = 0.1200, wR2 = 0.1097
Largest diff. peak and hole	0.301 and -0.279 $e.Å^{-3}$

A.3.5 Crystal data and structure refinement for 11a

Identification code	mv068	
Empirical formula	$C_{20}H_{14}F_3N_3O_2$	
Formula weight	385.34	
Temperature	173 (2)	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	C 2/c	
Space group (Hall)	-C 2yc	
Unit cell dimensions	a = 53.4181(13) Å	α = 90.0°
	b = 7.4393(2) Å	β = 99.5500(10)°
	c = 17.9543(4) Å	γ = 90.0°
Volume	7036.0(3) $Å^3$	
Z	16	
Density (calculated)	1.455 Mg/m^3	
Absorption coefficient	0.118	
F (000)	3168	
Crystal size	0.43x0.25x0.10	
Θ range for data collection	2.55 to 29.98°	
Index ranges	$-73 \leq h \leq 73$, $-10 \leq k \leq 6$, $-25 \leq l \leq 24$	
Reflections collected	38412	
Independent reflections	10221[R(int) = 0.0356]	
Completeness to Θ = 29.98°	99.7 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9512 and 0.9883	
Refinement	Full-matrix least-squares on F^2	
Data / restraints / parameters	6143/0/511	
Goodness-of-fit on F^2	1.027	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0475, wR2 = 0.1098	
R indices (all data)	R1 = 0.0946, wR2 = 0.1248	
Largest diff. peak and hole	0.241 and -0.266 $e.Å^{-3}$	

A.3.6 Crystal data and structure refinement for 11b

Identification code	mv071
Empirical formula	$C_{21}H_{17}N_3O_4$
Formula weight	375.38
Temperature	173 (2)
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group (H.-M.)	P -1
Space group (Hall)	-P 1
Unit cell dimensions	a = 8.2384(6) Å α = 102.476(5)°
	b = 8.6786(7) Å β = 102.749(5)°
	c = 13.7950(11) Å γ = 105.512(4)°
Volume	886.37(12) $Å^3$
Z	2
Density (calculated)	1.406 Mg/m^3
Absorption coefficient	0.099
F (000)	392
Crystal size	0.30x0.20x0.11
Θ range for data collection	2.55 to 29.99°
Index ranges	$-11 \leq h \leq 11$, $-10 \leq k \leq 12$, $-19 \leq l \leq 19$
Reflections collected	18241
Independent reflections	5113 [R(int) = 0.0209]
Completeness to Θ = 29.99°	99.0 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9708 and 0.9891
Refinement	Full-matrix least-squares on F^2
Data / restraints / parameters	3868/0/257
Goodness-of-fit on F^2	1.056
Final R indices [$I>2\sigma(I)$]	R1 = 0.0437, wR2 = 0.1134
R indices (all data)	R1 = 0.0638, wR2 = 0.1224
Largest diff. peak and hole	0.337 and -0.281e.$Å^{-3}$

A.3.7 Crystal data and structure refinement for 20a

Identification code	mv0114-2	
Empirical formula	$C_{18}H_{18}N_3O$	
Formula weight	293.36	
Temperature	173 (2)	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	P -1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 6.52990(10) Å	α = 90.3730(10)°
	b = 13.1171(3) Å	β = 93.7910(10)°
	c = 18.7821(4) Å	γ = 95.7440(10)°
Volume	1597.03(6) $Å^3$	
Z	4	
Density (calculated)	1.220 Mg/m^3	
Absorption coefficient	0.078	
F (000)	624	
Crystal size	0.62x0.21x0.07	
Θ range for data collection	2.69 to 29.0°	
Index ranges	$-8 \leq h \leq 8, -17 \leq k \leq 17, -25 \leq l \leq 25$	
Reflections collected	35067	
Independent reflections	8467 [R(int) = 0.0307]	
Completeness to Θ = 29.00°	99.8 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9534 and 0.9946	
Refinement	Full-matrix least-squares on F^2	
Data / restraints / parameters	6561/0/411	
Goodness-of-fit on F^2	1.037	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0462, wR2 = 0.1059	
R indices (all data)	R1 = 0.0645, wR2 = 0.1151	
Largest diff. peak and hole	0.289 and -0.223e.$Å^{-3}$	

A.3.8 Crystal data and structure refinement for 20d

Identification code	mv0134
Empirical formula	$C_{20}H_{23}N_3O_3$
Formula weight	353.41
Temperature	173 (2)
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group (H.-M.)	P 21/n
Space group (Hall)	-P 2yn
Unit cell dimensions	a = 9.8678(2) Å α = 90.0°
	b = 8.8954(2) Å β = 99.1650(10)°
	c = 21.2833(3) Å γ = 95.0°
Volume	1844.36(6) $Å^3$
Z	4
Density (calculated)	1.273 Mg/m^3
Absorption coefficient	0.087
F (000)	752
Crystal size	0.35x0.28x0.19
Θ range for data collection	2.49 to 30.0°
Index ranges	$-13\leq h\leq 12$, $-12\leq k\leq 12$, $-29\leq l\leq 29$
Reflections collected	22136
Independent reflections	5367 [R(int) = 0.0224]
Completeness to Θ = 30.00°	99.8 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9702 and 0.9837
Refinement	Full-matrix least-squares on F^2
Data / restraints / parameters	4497/0/244
Goodness-of-fit on F^2	1.040
Final R indices [$I>2\sigma(I)$]	R1 = 0.0424, wR2 = 0.1058
R indices (all data)	R1 = 0.0527, wR2 = 0.1117
Largest diff. peak and hole	0.323 and -0.246e.$Å^{-3}$

A.3.9 Crystal data and structure refinement for 20g

Identification code	mv0138
Empirical formula	$C_{18}H_{14}F_5N_3O$
Formula weight	383.32
Temperature	173 (2)
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group (H.-M.)	C 2/c
Space group (Hall)	-C 2yc
Unit cell dimensions	a = 14.4779(9) Å α = 90.0°
	b = 22.7122(14) Å β = 118.714(3)°
	c = 12.2120(8) Å ã = 90.0°
Volume	3521.8(4) $Å^3$
Z	8
Density (calculated)	1.446 Mg/m^3
Absorption coefficient	0.128
F (000)	1568
Crystal size	0.44x0.28x0.21
Θ range for data collection	1.79 to 29.99°
Index ranges	$-20\leq h\leq 20$, $-31\leq k\leq 31$, $-17\leq l\leq 15$
Reflections collected	20787
Independent reflections	5134 [R(int) = 0.0306]
Completeness to Θ = 29.99°	99.8 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9457 and 0.9736
Refinement	Full-matrix least-squares on F^2
Data / restraints / parameters	4006/0/251
Goodness-of-fit on F^2	1.069
Final R indices [$I>2\sigma(I)$]	R1 = 0.0393, wR2 = 0.1061
R indices (all data)	R1 = 0.0532, wR2 = 0.1131
Largest diff. peak and hole	0.309 and -0.236e.$Å^{-3}$

A.3.10 Crystal data and structure refinement for 25b

Identification code	mv0178A	
Empirical formula	$C_{25}H_{27}N_3O_2$	
Formula weight	401.50	
Temperature	173 (2)	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	P 21/c	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 9.7443(2) Å	α = 90.0°
	b = 18.5350(5) Å	β = 98.1520(10)°
	c = 12.0498(3) Å	γ = 90.0°
Volume	2154.33(9) $Å^3$	
Z	4	
Density (calculated)	1.238 Mg/m^3	
Absorption coefficient	0.079	
F (000)	856	
Crystal size	0.40x0.31x0.18	
Θ range for data collection	1.79 to 29.99°	
Index ranges	-13≤ h ≤11, -25≤ k ≤26, -10≤ l ≤17	
Reflections collected	25042	
Independent reflections	6580 [R(int) = 0.0219]	
Completeness to Θ = 29.99°	99.5 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9689 and 0.9858	
Refinement	Full-matrix least-squares on F^2	
Data / restraints / parameters	5295/0/277	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2σ(I)]	R1 = 0.0470, wR2 = 0.1211	
R indices (all data)	R1 = 0.0608, wR2 = 0.1291	
Largest diff. peak and hole	0.377 and -0.223e.$Å^{-3}$	

A.3.11 Crystal data and structure refinement for 25d

Identification code	mv0172pk
Empirical formula	$C_{25}H_{27}N_3O_3$, CH_4O
Formula weight	449.54
Temperature	173 (2)
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group (H.-M.)	P 21/c
Space group (Hall)	-P 2ybc
Unit cell dimensions	a = 6.9633(3) Å α = 90.0°
	b = 18.9564(7) Å β = 96.999(2)°
	c = 18.7028(8) Å γ = 90.0°
Volume	2450.36(17) $Å^3$
Z	4
Density (calculated)	1.219 Mg/m^3
Absorption coefficient	0.083
F (000)	960
Crystal size	0.25x0.24x0.12
Θ range for data collection	2.95 to 30.0°
Index ranges	$-9 \leq h \leq 9$, $-26 \leq k \leq 26$, $-26 \leq l \leq 23$
Reflections collected	27451
Independent reflections	7136 [R(int) = 0.0375]
Completeness to Θ = 30.00°	99.8 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9796 and 0.9901
Refinement	Full-matrix least-squares on F^2
Data / restraints / parameters	4968/0/ 312
Goodness-of-fit on F^2	1.027
Final R indices [$I>2\sigma(I)$]	R1 = 0.0571, wR2 = 0.1223
R indices (all data)	R1 = 0.0917, wR2 = 0.1386
Largest diff. peak and hole	0.275 and -0.262e.$Å^{-3}$

A.3.12 Crystal data and structure refinement for 37b

Identification code	ax0234	
Empirical formula	$C_{25}H_{21}N_3O_2$	
Formula weight	395.45	
Temperature	150 (2)	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group (H.-M.)	P2(1)2(1)2(1)	
Unit cell dimensions	a = 10.9355(2) Å	α = 90.0°
	b = 11.6654(3) Å	β = 90.0°
	c = 15.9623(3) Å	γ = 90.0°
Volume	2036.26(7) $Å^3$	
Z	4	
Density (calculated)	1.290 Mg/m^3	
Absorption coefficient	0.083	
F (000)	960	
Crystal size	0.36x0.30x0.23	
Θ range for data collection	2.16 to 28.0°	
Index ranges	$-13 \leq h \leq 14$, $-14 \leq k \leq 15$, $-21 \leq l \leq 21$	
Reflections collected	38287	
Independent reflections	4914 [R(int) = 0.0368]	
Completeness to Θ = 28.00°	100.0 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.93 and 1.00	
Refinement	Full-matrix least-squares on F^2	
Data / restraints / parameters	4452/0/275	
Goodness-of-fit on F^2	1.015	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0381, wR2 = 0.0896	
R indices (all data)	R1 = 0.0443, wR2 = 0.0936	
Largest diff. peak and hole	0.272 and -0.226e.$Å^{-3}$	

A.3.13 Crystal data and structure refinement for 39c

Identification code	ax0208	
Empirical formula	$C_{20}H_{21}N_3O_4$	
Formula weight	367.40	
Temperature	150 (2)	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group (H.-M.)	P-1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 6.4228(1) Å	α = 64.501(1)°
	b = 12.7292(2) Å	β = 76.127(1)°
	c = 12.9928(2) Å	γ = 76.590(1)°
Volume	920.72(2) $Å^3$	
Z	2	
Density (calculated)	1.325 Mg/m^3	
Absorption coefficient	0.094	
F (000)	388	
Crystal size	0.58x0.35x0.29	
Θ range for data collection	1.76 to 27.5°	
Index ranges	$-8 \leq h \leq 8$, $-16 \leq k \leq 16$, $-16 \leq l \leq 16$	
Reflections collected	21180	
Independent reflections	4236 [R(int) = 0.0222]	
Completeness to Θ = 27.50°	100.0 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.95 and 1.00	
Refinement	Full-matrix least-squares on F^2	
Data / restraints / parameters	3647/0/251	
Goodness-of-fit on F^2	1.034	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0371, wR2 = 0.0914	
R indices (all data)	R1 = 0.0443, wR2 = 0.0971	
Largest diff. peak and hole	0.311 and -0.222e.$Å^{-3}$	

A.3.14 Crystal data and structure refinement for 43b

Identification code	ax0232	
Empirical formula	$C_{27}H_{21}N_3O_3$	
Formula weight	435.47	
Temperature	150 (2)	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group (H.-M.)	P-1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 7.7675(2) Å	α = 78.310(1)°
	b = 11.2712(2) Å	β = 81.848(1)°
	c = 13.0114(3) Å	γ = 80.530(1)°
Volume	1093.35(4) $Å^3$	
Z	2	
Density (calculated)	1.323 Mg/m^3	
Absorption coefficient	0.088	
F (000)	456	
Crystal size	0.47x0.29x0.20	
Θ range for data collection	1.61 to 27.5°	
Index ranges	$-10\leq h\leq 10$, $-14\leq k\leq 14$, $-16\leq l\leq 16$	
Reflections collected	31717	
Independent reflections	5022 [R(int) = 0.0278]	
Completeness to Θ = 27.5°	100.0 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.96 and 1.00	
Refinement	Full-matrix least-squares on F^2	
Data / restraints / parameters	4350/0/302	
Goodness-of-fit on F^2	1.031	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0383, wR2 = 0.0929	
R indices (all data)	R1 = 0.0449, wR2 = 0.0985	
Largest diff. peak and hole	0.294 and -0.240.$Å^{-3}$	

A.3.15 Crystal data and structure refinement for 53

Identification code	mv0253
Empirical formula	$C_{12}H_{12}BrN_3$
Formula weight	278.16
Temperature	173(2)
Wavelength	0.71073 Å
Crystal system	triclinic
Space group (H.-M.)	P-1
Space group (Hall)	-P 1
Unit cell dimensions	a = 6.05460(10) Å α = 112.5570(10)°
	b = 9.5968(2) Å β = 96.1820(10)°
	c = 11.2829(3) Å γ = 96.8800(10)°
Volume	592.58(2) $Å^3$
Z	2
Density (calculated)	1.559 Mg/m^3
Absorption coefficient	3.444
F (000)	280
Crystal size	0.41x0.24x0.11
Θ range for data collection	3.44 to 30.0°
Index ranges	$-7\leq h\leq 8$, $-12\leq k\leq 13$, $-15\leq l\leq 15$
Reflections collected	13104
Independent reflections	3438 [R(int) = 0.0179]
Completeness to Θ = 30.00°	99.3 %
Absorption correction	Multi-scan
Max. and min. transmission	0.3325 and 0.7032
Refinement	Full-matrix least-squares on F^2
Data / restraints / parameters	3099/0/ 148
Goodness-of-fit on F^2	1.083
Final R indices [$I>2\sigma(I)$]	R1 = 0.0223, wR2 = 0.0544
R indices (all data)	R1 = 0.0270, wR2 = 0.0554
Largest diff. peak and hole	0.350 and -0.359e.$Å^{-3}$

A.3.16 Crystal data and structure refinement for 55d

Identification code	mv0317	
Empirical formula	$C_{18}H_{16}ClN_3$	
Formula weight	309.79	
Temperature	173(2)	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group (H.-M.)	P-1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 9.2518(2) Å	α = 66.9290(10)°
	b = 13.4360(3) Å	β = 83.9480(10)°
	c = 14.0853(3) Å	γ = 82.9020(10)°
Volume	1595.40(6) $Å^3$	
Z	4	
Density (calculated)	1.290 Mg/m^3	
Absorption coefficient	0.239	
F (000)	648	
Crystal size	0.51x0.28x0.24	
Θ range for data collection	2.64 to 31.0°	
Index ranges	$-13\leq h\leq 13$, $-18\leq k\leq 19$, $-20\leq l\leq 20$	
Reflections collected	37163	
Independent reflections	10069 [R(int) = 0.0187]	
Completeness to Θ = 31.00°	98.8 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.8878 and 0.9448	
Refinement	Full-matrix least-squares on F^2	
Data / restraints / parameters	8167/0/403	
Goodness-of-fit on F^2	1.014	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0429, wR2 = 0.1140	
R indices (all data)	R1 = 0.0558, wR2 = 0.1248	
Largest diff. peak and hole	0.911 and -0.348e.$Å^{-3}$	

A.3.17 Crystal data and structure refinement for 55e

Identification code	mv0321
Empirical formula	$C_{19}H_{16}F_3N_3$
Formula weight	343.35
Temperature	173(2)
Wavelength	0.71073 Å
Crystal system	triclinic
Space group (H.-M.)	P-1
Space group (Hall)	-P 1
Unit cell dimensions	a = 9.5367(6) Å α = 67.393(3)°
	b = 13.8889(9) Å β = 83.669(3)°
	c = 14.0401(9) Å γ = 80.588(3)°
Volume	1691.37(19) $Å^3$
Z	4
Density (calculated)	1.348 Mg/m^3
Absorption coefficient	0.104
F (000)	712
Crystal size	0.47x0.23x0.15
Θ range for data collection	1.78 to 29.0°
Index ranges	$-13\leq h\leq 11$, $-18\leq k\leq 18$, $-19\leq l\leq 16$
Reflections collected	34907
Independent reflections	8949 [R(int) = 0.0215]
Completeness to Θ = 29.00°	99.6 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9525 and 0.9845
Refinement	Full-matrix least-squares on F^2
Data / restraints / parameters	6874/6/483
Goodness-of-fit on F^2	1.030
Final R indices [$I>2\sigma(I)$]	R1 = 0.0489, wR2 = 0.1241
R indices (all data)	R1 = 0.0663, wR2 = 0.1375
Largest diff. peak and hole	0.450 and -0.469e.$Å^{-3}$

A.3.18 Crystal data and structure refinement for 57a

Identification code	mv0266	
Empirical formula	$C_{20}H_{17}N_3$	
Formula weight	299.37	
Temperature	173(2)	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group (H.-M.)	P 21/n	
Space group (Hall)	-P 2yn	
Unit cell dimensions	a = 14.0025(3) Å	α = 90.0°
	b = 14.8182(2) Å	β = 108.1520(10)°
	c = 16.6026(3) Å	γ = 90.0°
Volume	3273.46(10) $Å^3$	
Z	8	
Density (calculated)	1.215 Mg/m^3	
Absorption coefficient	0.073	
F (000)	1264	
Crystal size	0.67x0.37x0.22	
Θ range for data collection	2.58 to 30.5°	
Index ranges	$-19 \leq h \leq 19$, $-18 \leq k \leq 21$, $-23 \leq l \leq 23$	
Reflections collected	38831	
Independent reflections	9960 [R(int) = 0.0269]	
Completeness to Θ = 30.5°	99.0 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9526 and 0.9841	
Refinement	Full-matrix least-squares on F^2	
Data / restraints / parameters	7144/0/421	
Goodness-of-fit on F^2	1.098	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0459, wR2 = 0.1276	
R indices (all data)	R1 = 0.0703, wR2 = 0.1388	
Largest diff. peak and hole	0.334 and -0.220e.$Å^{-3}$	

A.3.19 Crystal data and structure refinement for 59b

Identification code	mv0330
Empirical formula	$C_{21}H_{21}N_3$
Formula weight	315.41
Temperature	173(2)
Wavelength	0.71073 Å
Crystal system	triclinic
Space group (H.-M.)	P -1
Space group (Hall)	-P 1
Unit cell dimensions	a = 10.1605(5) Å α = 63.931(2)°
	b = 13.8784(6) Å β = 82.043(2)°
	c = 14.4302(6) Å γ = 81.099(2)°
Volume	1800.10(14) $Å^3$
Z	4
Density (calculated)	1.164 Mg/m^3
Absorption coefficient	0.070
F (000)	672
Crystal size	0.41x0.17x0.09
Θ range for data collection	2.67 to 28.0°
Index ranges	$-13 \leq h \leq 13$, $-18 \leq k \leq 18$, $-19 \leq l \leq 19$
Reflections collected	35457
Independent reflections	8632 [R(int) = 0.0282]
Completeness to Θ = 28.0°	99.4 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9720 and 0.9938
Refinement	Full-matrix least-squares on F^2
Data / restraints / parameters	6158/0/443
Goodness-of-fit on F^2	1.017
Final R indices [$I>2\sigma(I)$]	R1 = 0.0449, wR2 = 0.1059
R indices (all data)	R1 = 0.0708, wR2 = 0.1208
Largest diff. peak and hole	0.226 and -0.217e.$Å^{-3}$