Exploration of new sustainable synthetic methods for the synthesis of fused pyridines and 4-quinolones based on the domino reaction of chromones and other masked dielectrophiles with nucleophiles.

DISSERTATION

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Satenik Mkrtchyan

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Dekan: Prof. Dr. Martin Köckerling

Gutachter der Dissertation:

1. Prof. Dr. Dr. H.c. mult. Peter Langer, Institut für Chemie, Universität Rostock

2. Prof. Dr. Bernd Schmidt, Institut für Chemie, Universität Postdam

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“In the beginning was the Word, and the Word was with God, and the Word was fully God. The Word was with God in the beginning. All things were created by him and apart from him not one thing was created that has been created”

(John 1:1-3)

Acknowledgments

"Acknowledge the Lord, you heavenly beings, acknowledge the Lord Majesty and power! Acknowledge the Majesty of the Lord's reputation. Worship the Lord in holy attire" (Ps 29:1-2). "You are worthy, our Lord and God, to receive glory and honor and power, since you created all things, and because of your will they existed and were created" (Rev 4:11). Dear Lord I am thankful for your great and unending love and blessings, this work would never be completed without your great and true grace you gave me every day. "If the Lord does not build a house, then those who build it, work in vain" (Ps 127:1).

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Satenik Mkrctyan

June 2014, Rostock

Abstract

The present work aimed to study the big potential of chromone derivatives and 1-(2-fluorophenyl)prop-2-yn-1-ones for the synthesis of purine-like fused pyridines and 4-quinolone derivatives. This includes a facile [3+3] domino cleavage of the chromone ring (that can be considered as masked 1,3-dicarbonyl compound) by electron-excessive aminoheterocycles (which can be considered as an interesting class of 1,3-*CCN*-binucleophiles). In this regard, a wide range of substituents and substitution patterns are tolerated in the reaction. Consequently the synthesis of a wide range of fused pyridines and their further modifications were successfully performed. In addition a new and easy way for synthesis of 4-quinolone derivatives and other fused systems *via* domino cycloaddition reactions of *ortho*-fluorine-substituted benzoylchromones, 1-(2-fluorophenyl)prop-2-yn-1-ones and aliphatic or aromatic amines were developed. The scope and limitations of all reactions were well studied. Some mechanistic explanations of developed transformations, in addition to detailed spectroscopic characterisation of synthesised compounds are presented.

Kurzbeschreibung

Die vorliegende Arbeit untersucht das Potential neuartiger Chromonderivate und 1-(2-Fluorophenyl)prop-2-in-1-one für die Synthese purinanaloger polycyclischer Pyridine und 4-Chinolone. Dies beinhaltet formale [3+3] Cyclisierungen mit elektronenreichen Aminoheterocyclen, einer interessanten Klasse von 1,3-*CCN*-Binucleophilen. Die Umsetzungen verlaufen unter Spaltung des Chromonringes. Das Chromon kann als maskierte 1,3-Dicarbonylverbindung aufgefasst werden. Eine große Bandbreite unterschiedlicher Substitutionsmuster wurde in der Reaktion toleriert. Weiterhin wurde eine neue Synthese von 4-Chinolonen und ähnlichen Verbindungen durch Cyclisierungen von *ortho*-Fluorbenzoylchromonen, 1-(2-Fluorphenyl)prop-2-in-1-onen mit aliphatischen oder aromatischen Aminen entwickelt. Potential und Grenzen aller Reaktionen wurden im Detail untersucht. Basierend auf einigen Untersuchungen konnten auch mechanistische Vorschläge gemacht werden.

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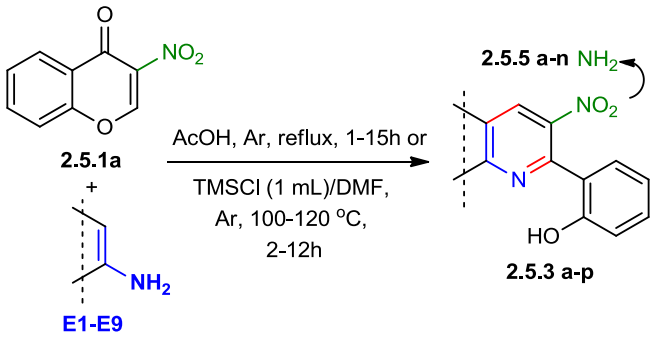
Synthesis of heteroannulated 3-nitro- and 3-aminopyridines by cyclocondensation of electron-excessive aminoheterocycles with 3-nitrochromone



3-Nitrochromone reacts with electron-rich aminoheterocycles and anilines to give a variety of hetero(carbo)annulated 3-nitropyridines. Corresponding amino derivatives were prepared by simple hydration reaction.

Tetrahedron, **2012**, *68*, 2532.

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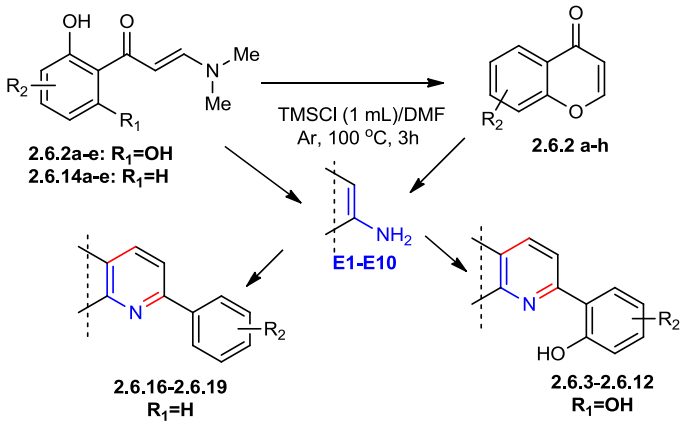

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Org. Biomol. Chem., **2012,** *10*, 890.

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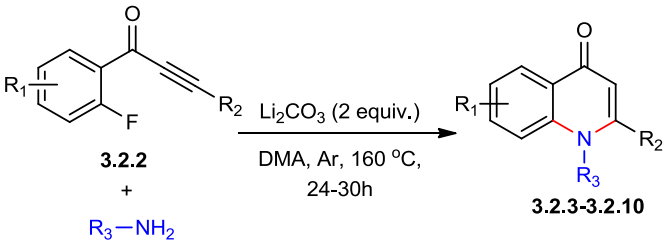

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Synthesis, **2013**, 205.

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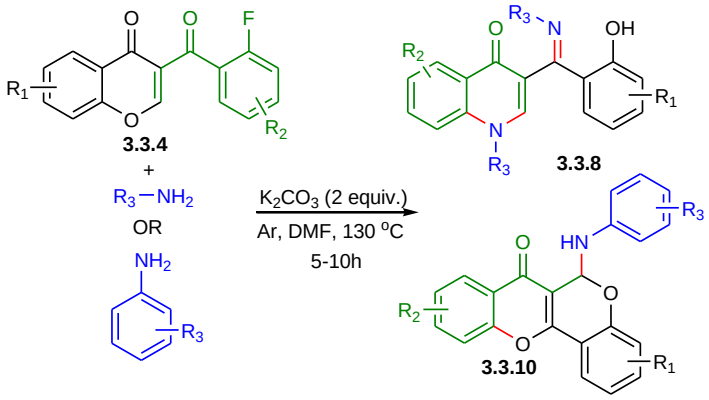


The synthesis of 4-quinolone derivatives *via* [5+1] domino cycloaddition reaction of *ortho*-fluorine-substituted benzoylchromones and aliphatic amines. The method proved to be rather sensitive towards the nature of used amines. Particularly, in case of anilines different unexpected products were prepared.

Content

1.1. General Introduction

Heterocyclic chemistry is one of the important areas of natural sciences and an inseparable part of modern life. Every year the demand of different representatives of the heterocyclic compounds (drugs, dyes, fluorescent compounds, macromolecules etc.) in daily life is getting bigger and the natural sources are not enough to suffice these needs. This became a motivation for chemists to find new and easy synthetic methods toward wide range of new synthetic heterocycles which can be used in different aspects of our everyday life.

In family of natural and synthetic heterocycles nitrogen containing representatives stands out. The simplest representative of this class is pyridine, which is used as a precursor to agrochemicals, pharmaceuticals and in chemical industry as an important solvent and/or base.[1] It is noteworthy that pyridine derivatives[2] are widely used in the medicinal chemistry. For instance, niacin, also known as vitamin B_3,[3] being the precursor of nicotinamide adenine dinucleotide (NAD), and nicotinamide adenine dinucleotide phosphate (NADP) has a great impact on livelihood of live cells. Another example is isoniazid, which was synthesis about hundred years ago and is an important antitubercular drug[4] (Figure 1.1.1).

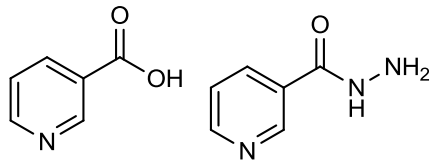


Figure 1.1.1. *Biologically active simple pyridine derivatives.*

Additionally, from nitrogen-containing heterocycles the pyrimidine derivatives represent another important class of compounds which can be found in structures of different natural products, such as antibiotics (bacimethrin,[5] sparsomycin,[6] bleomycin[7] etc), vitamins (thiamine[8]), anticancer agents (heteromine,[9] variolin,[10] meridianine,[11] etc.), toxins (hepatotoxine, ptilocauline[12]) etc. Moreover, all bases from nucleic acids contain a pyrimidine core (Figure 1.1.2).

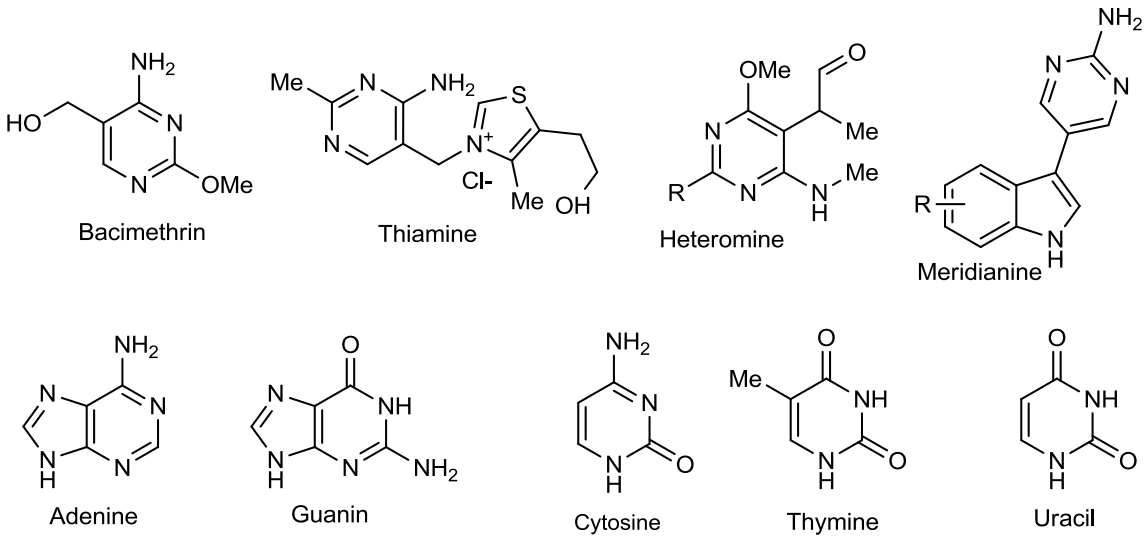


Figure 1.1.2. *Biologically active pyrimidine derivatives.*

More complex molecules like heteroannulated pyridines and pyrimidines, which can be classified as purines, and their deaza analogues also have a great importance, as they are lead structures for drug discovery. They can be found in a variety of medicaments and potential drugs. Purines and purine isosteres show a wide range of biological activities, for instance antiarrhythmic, antihistamine, anticancer, fungicidal, antiviral, anti-inflammatory activities,[13] inhibition of DNA-dependent protein kinesis etc.[14] Some examples are represented in Figure 1.1.3. Valacyclovir is an antiviral drug against herpes simplex, herpes zoster and herpes B,[15] abacavir is a nucleoside which is used against HIV and AIDS,[16] another well known medicament is sildenafil citrate with a trade name Viagra, which is used to treat erectile dysfunction and pulmonary arterial hypertension,[17] thiazolo[5,4-*b*]pyridine derivative, which is an anticoagulant.[18] This list can be continued.

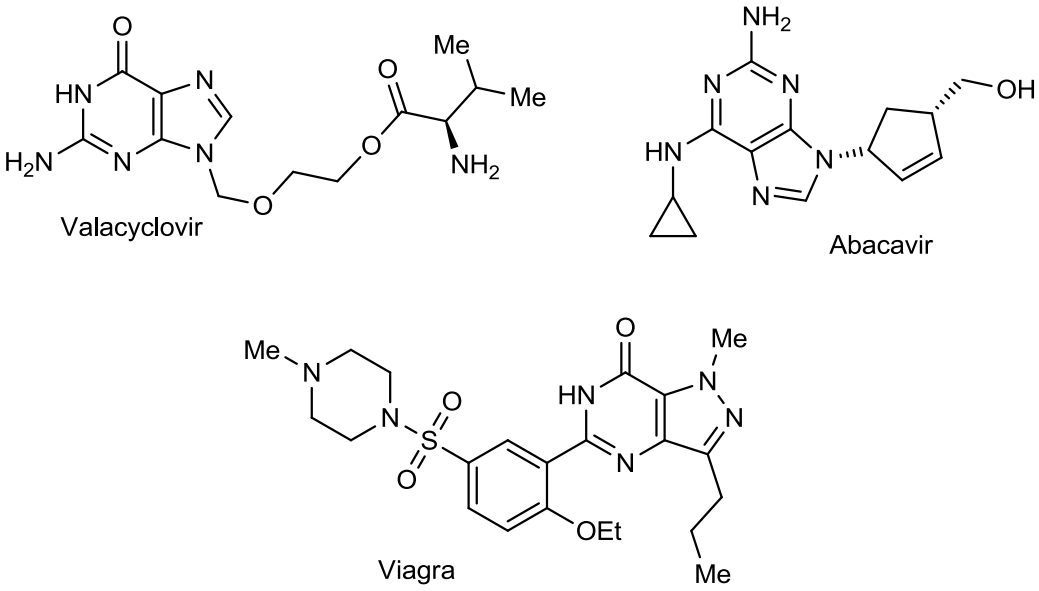
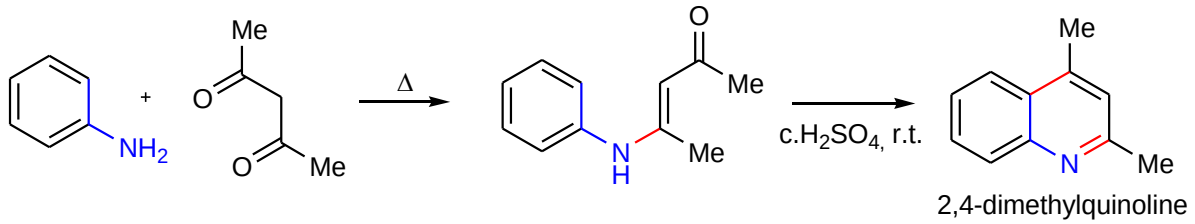


Figure 1.1.3. *Biologically active heteroannulated pyridines and pyrimidines.*

1.2. General methods for the synthesis of fused pyridines

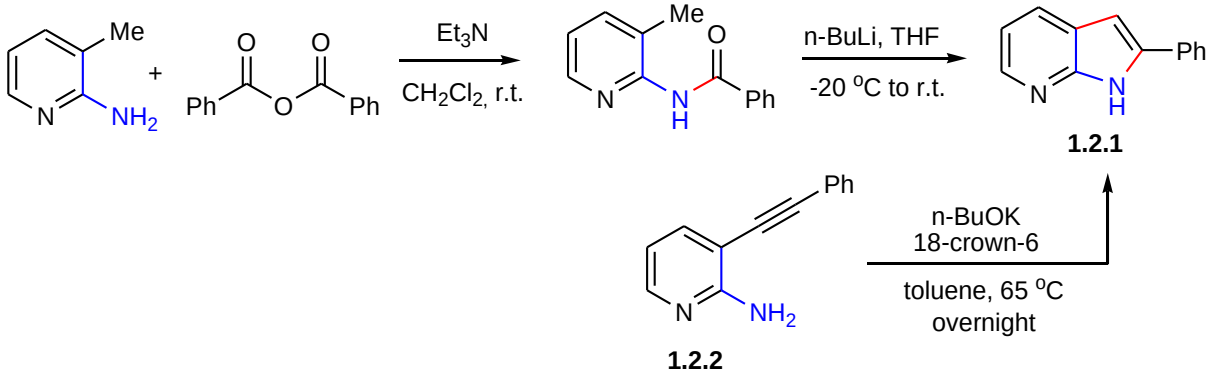
It is obvious that the growing demands of chemical industry dramatically stimulate the development of new synthetic methods for the synthesis of different fused pyridines and/or modifications of existing building blocks. These movements in the field continue to be an urgent area of research that in principle can solve all actual synthetic tasks in the future. My present work is dedicated to development and studying of new and efficient synthetic methods, that will provide an easy way to a wide range of hetero-condensed pyridines. So that for the comparison in the following context some of well known methods for synthesis of heteroannulated pyridines will be discussed.

The first system of choice are quinoline derivatives. Analysis of chemical literature shows that from existing methods for quinoline ring construction the oldest and most frequently used method is the reaction of anilines with 1,3-dicarbonyl compounds. This approach was developed by Combe in 1888 for the first time,[19] then this method was modified in order to increase the substrate scope.[20] Noteworthy the commercial synthesis of chloroquine (synthetic antimalarial drug) is based on this method (Scheme 1.2.1).[21]



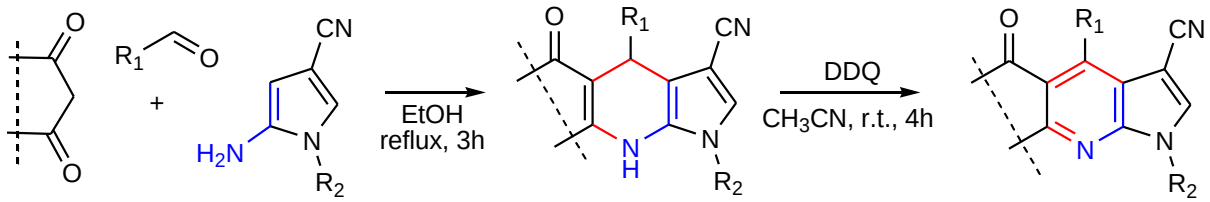
Scheme 1.2.1. *Synthesis of quinolines by method of Combe.*

The next considered heterocyclic systems are 7-azaindole derivatives, also known as pyrrolo[2,3-*b*]pyridines. The prominent synthetic methods for construction of these heterocycles are mostly based on the chemistry of pyridine derivatives. However several synthetic pathways starting from pyrrole derivatives are also known. For instance, it was shown that 2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridines **1.2.1** are easily available from 2-amino-3-methylpyridine and benzoic anhydride in two steps. On the other hand, the same system can be prepared from 2-amino-3-(phenylethynyl)pyridine **1.2.2** in basic media (Scheme 1.2.2).[22]



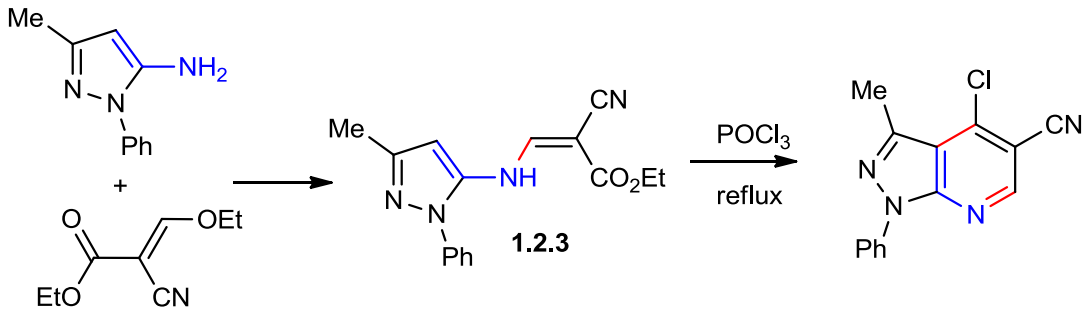
Scheme 1.2.2. *Synthesis of pyrrolo[2,3-b]pyridines **1.2.1** starting from pyridine derivatives.*

As was mentioned there are few approaches for the synthesis of 7-azaindoles starting from pyrrole derivatives. Though, recently a method based on three-component cyclocondensation of *N*-substituted 2-amino-4-cyanopyrroles, various aldehydes, and active methylene compounds in ethanol or acetic acid at reflux was reported (Scheme 1.2.3).[23]



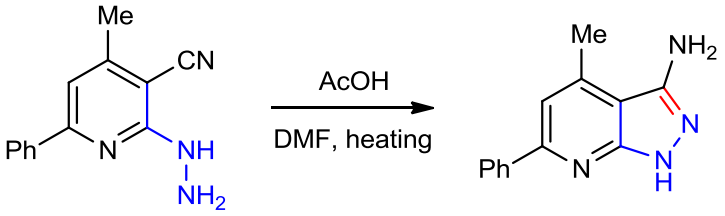
Scheme 1.2.3. *Synthesis of pyrrolo[2,3-b]pyridine starting from 5-aminopyroles.*

Pyrazolo[3,4-*b*]pyridines are also an object of interest, so in the following schemes some approaches towards the synthesis of such systems will be presented. In this field the most applied methods are based on construction of pyridine core starting from pyrazole derivatives. For example, the reaction of 5-amino-3-methyl-1-phenylpyrazole with 2-cyano-3-ethoxyacrylate leads to intermediate ethyl 3-(3-methyl-1-phenyl-1*H*-pyrazol-5-ylamino)-2-cyanoacrylate **1.2.3**, that in the presence of $POCl_3$ subsequently turns to desired heterocyclic system by cyclization (Scheme 1.2.4).[24]



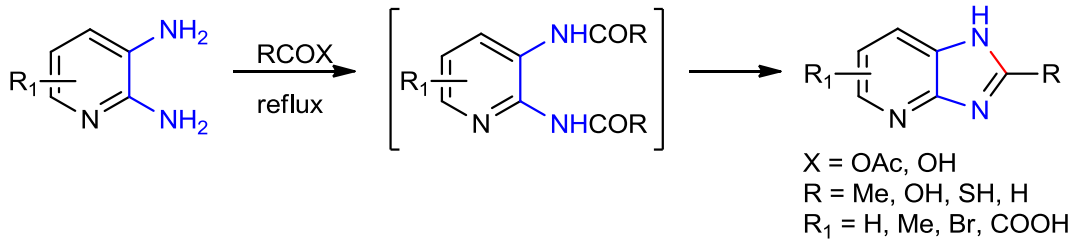
Scheme 1.2.4. *Synthesis of pyrazolo[3,4-b]pyridine starting from 5-aminopyrazole.*

On the other hand, Al-Isa *et al.* proposed an approach that involves pyrazole ring construction on pyridine core. Namely they have found that the synthesis of pyrazolo[3,4-*b*]pyridines can be accomplished by heating 6-hydrazido-4-methyl-2-phenyl-5-pyridinecarbonitrile in acetic acid or DMF (Scheme 1.2.5).[25]



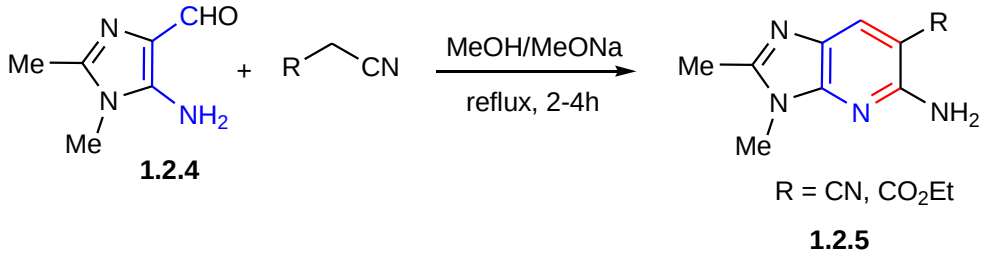
Scheme 1.2.5. *Synthesis of 4-methyl-6-phenyl-1H-pyrazolo[3,4-b]pyridin-3-amine.*

Almost all methods known to date for the synthesis of imidazo[4,5-*b*]pyridines are based on imidazole ring closure on pyridine core. The earliest report in this field appeared in 1927, which represents a reflux of 2,3-diaminopyridine in acetic acid anhydride that was followed by the formation of 2-methylimidiazolo[4,5-*b*]pyridine system. After the initial report this methodology was further developed using other anhydrides. As a result, a number of imidazo[4,5-*b*]pyridine derivatives with different substituents were synthesized (Scheme 1.2.6).[26]



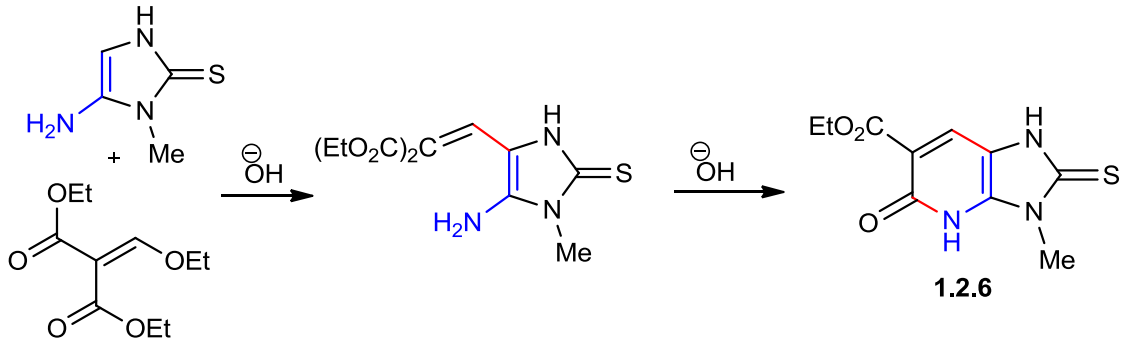
Scheme 1.2.6. *Synthesis of imidiazolo[4,5-b]pyridine starting from 2,3-diaminopyridine.*

Another approach was proposed by Soto *et al.* In order to prepare an imidazo[4,5-*b*]pyridine core **1.2.5**, thay applied the reaction of 5-amino-1-methylimidazol-4-carbaldehydes **1.2.4** with malononitrile or ethyl cyanoacetate in ethanol at basic media under reflux (Scheme 1.2.7).[27]



Scheme 1.2.7. *Synthesis of 5-aminoimidazo[4,5-b]pyridine **1.2.5**.*

Aiming to prepare thio-derivatives of imidazo[4,5-*b*]pyridines, Koga *et al.* showed that the heating of 5-amino-1-methylimidazol-2(3*H*)-thion with diethyl ethoxymethylenmalonate in 10% NaOH water solution leads to corresponding imidazo[4,5-*b*]pyridine-2(3*H*)-thiones **1.2.6** (Scheme 1.2.8).[28]



Scheme 1.2.8. *Synthesis of imidazo[4,5-b]pyridine-2(3H)-thion **1.2.6**.*

Additionally a two-step procedure towards thiazolo[4,5-*b*]pyridines was presented by Bergman *et al.* starting from aminopyridine and appropriate isothiocyanate, following by

cyclization in presence of bromine in acetic acid or chloroform.[29]

Despite the fact, that a number of synthetic approaches for the synthesis of heterocyclic fused pyridine derivatives appear in the literature, however, the overall interest in the chemistry of purine isosters is still very high. Moreover, analysis of the literature shows that the synthesis of fused pyridines bearing a carboxylic, formyl, amino and heteroaryl substituents still remains an actual synthetic task. Having in mind the deficiency, multiple steps and a number of other restrictions of the methods proposed before, the goal of this work was to design and develop new and efficient synthetic methods toward the wide range of fused pyridines starting from simple commercially available building blocks by non-demanding synthetic protocols.

2. Synthesis of structurally diverse fused pyridines starting from chromones and electron-excessive aminoheterocycles

As it was discussed in the introduction, our main goal was to develop a new, easy and universal synthetic pathway, which will allow us to build up different purine isosteres starting from low-cost starting materials. In order to construct the desired systems, different approaches were used. Specifically, in this part of work the domino reaction was investigated between chromones and electron-excessive aminoheterocycles.

In current study the retrosynthetic analysis was based on the pathway that includes an enamine-like framework as 1,3-*CCN*-binucleophiles and set of different 1,3-*CCC*-dielectrophiles (Figure 2.1). In following chapters we will use different electron-excessive aminoheterocycles as 1,3-*CCN*-binucleophiles and different chromen-4-ones as 1,3-*CCC*-dielectrophiles. However, more relevant chemical application of electron-excessive aminoheterocycles and chromen-4-ones will be discussed at advance.

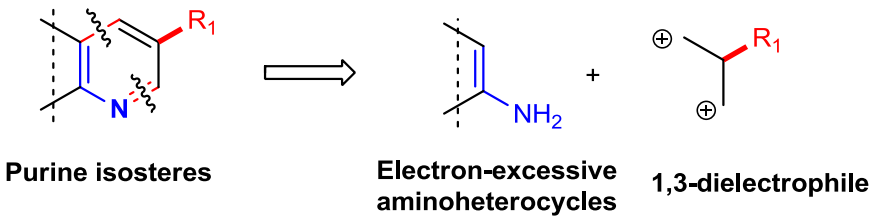


Figure 2.1. *Retrosynthetic analysis of fused pyridines.*

2.1. Chemistry of electron-excessive aminoheterocycles

Electron-excessive aminoheterocycles can be considered to act as enamines. Due to some contribution of enamine resonance structure, these systems usually have more *C*-nucleophile rather than *N*-nucleophile character (Figure 2.1.1). Consequently these systems are an interesting class of 1,3-*CCN*-binucleophiles, which initially react with electrophiles *via* *β*-carbon atom.

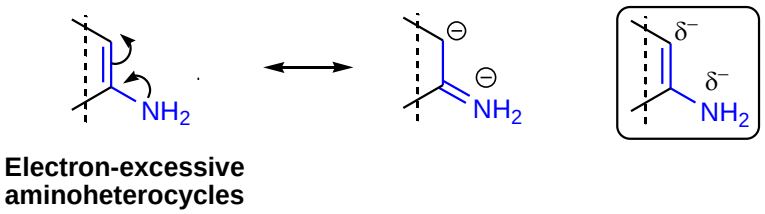
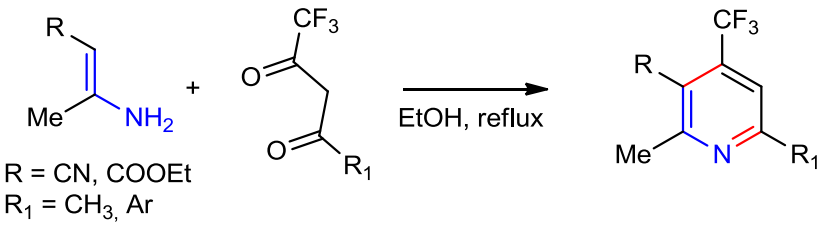


Figure 2.1.1. *Electron-excessive aminoheterocycles as enamines.*

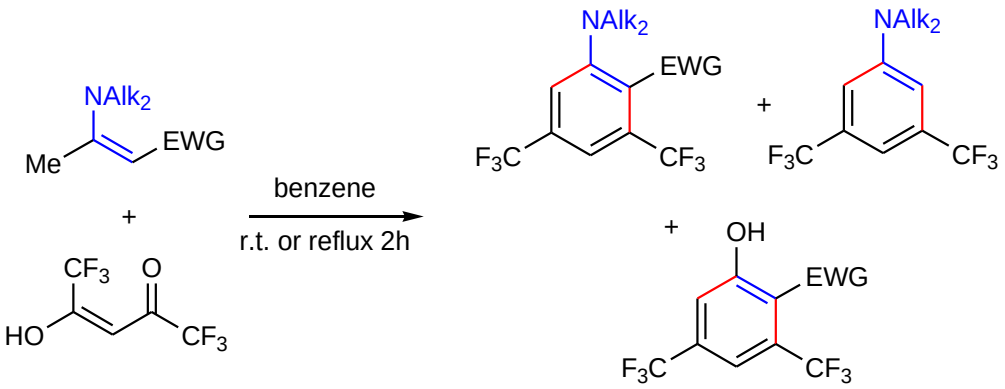
1,3-*CCN*-binucleophiles are widely used in organic chemistry for construction of simple heterocyclic systems, such as pyridines, quinolines, purines and their isosters. In current chapter we would like to summarise previously known methods of the pyridine/pyrimidine syntheses, *via* enamine functionalization by the means of 1,3-*CCC*- and 1,3-*CNC*-bielectrophiles. Simple systems, like pyridine derivatives, can be formed from 1,3-dicarbonyl compounds and 3-aminoacrylate. This approach with its variations is one of the most useful procedures towards the synthesis of unsymmetrically substituted pyridine derivatives.[30] For instance, aminocrotonoethylat and aminoacrylonitriles were applied for the construction of 4-CF_3-pyridines. The reaction was carried out in ethanol under reflux, after 2 hours the desired products were isolated with moderate yields (Scheme 2.1.1).[30]



Scheme 2.1.1. *Synthesis of 4-CF_3-pyridines.*

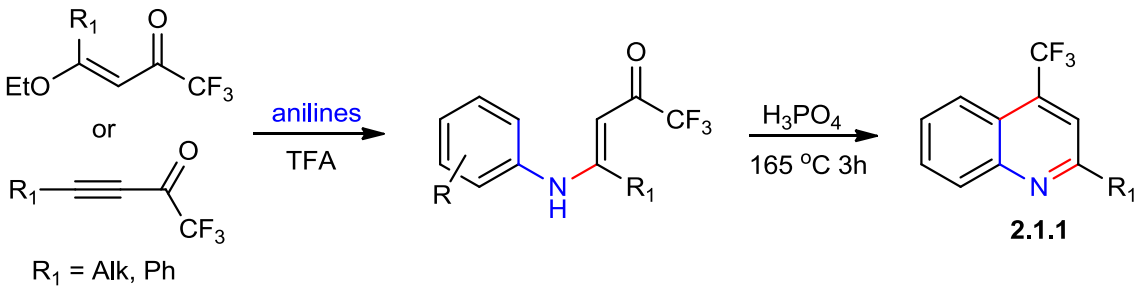
Push-pull enamines appeared to be out of any general regularity: it was shown by authors, that the reaction of 1,1,1,5,5,5-hexafluoroacetylacetone with push-pull enamines (Alk_2N =

pyrrolidino, piperidino, morpholino) having a methyl group at the *α*-position, is sensitive both to the structure of enamines and to reaction conditions. As a result, a set of bis(trifluoromethyl)dialkylanilines and ethyl bis(trifluoromethyl)salicylate were prepared (Scheme 2.1.2).[31]



Scheme 2.1.2. *Synthesis of bis(trifluoromethyl)dialkylanilines and ethyl bis(trifluoromethyl)salicylate.*

Kirollos *et al.* presented the synthesis of 2-CF_3-quinolines starting from TFA-vinyls or TFA-acetylene. The latter were reacted with electron-excessive anilines in neat trifluoroacetic acid.[32] This method was suitable for synthesis of 2-CF_3-benzo[*h*]quinolines **2.1.1**[33] and dihydrobenzo[*c*]acridine[34] using various enaminoketones (Scheme 2.1.3).



Scheme 2.1.3. *Synthesis of 2-CF_3-benzo[h]quinolines* ***2.1.1***.

In this context, electron-excessive anilines, possessing an electron donating group (EDG) in the aromatic ring can behave as enamines and react under mild conditions forming the 4-trifluoromethylquinolines in good yields. Using this concept some androgen receptor modulators and a row of antitumor drugs were synthesised (Figure 2.1.2).[35]

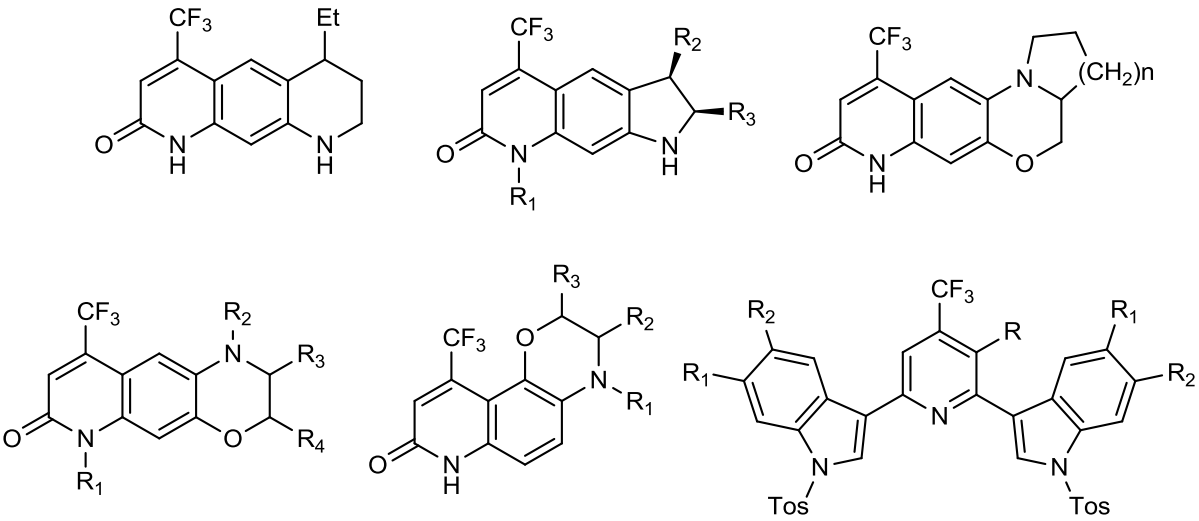
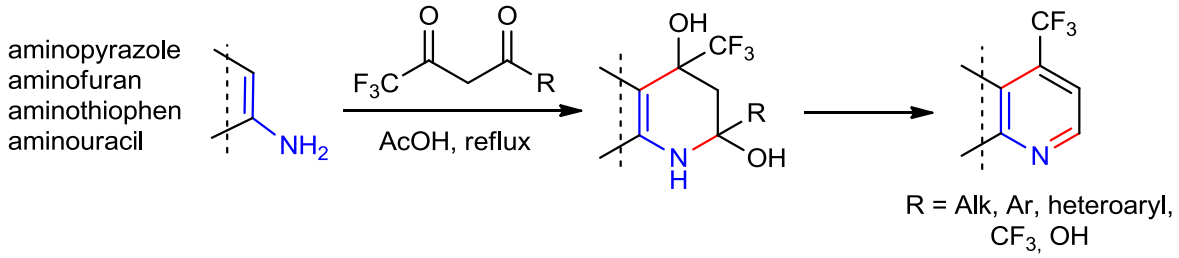


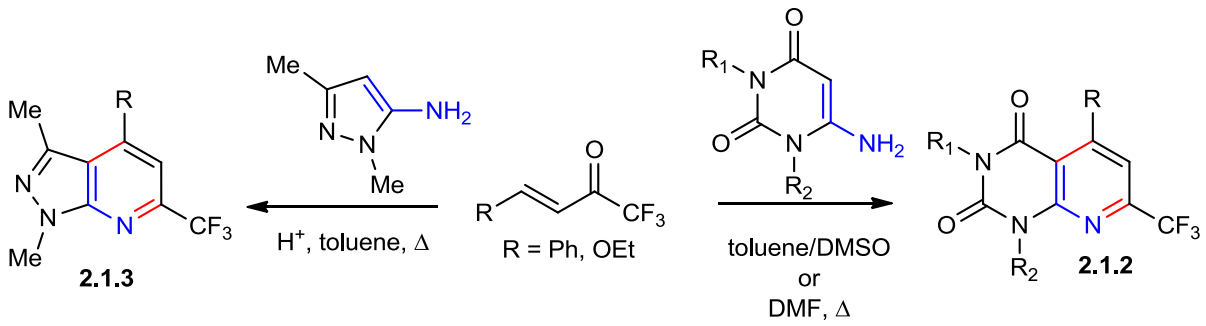
Figure 2.1.2. *Some examples of antitumor drugs with 4-trifluoromethylquinolines moiety.*

Afterwards, it was shown that this approach can be applied also for electron-excessive aminoheterocycles. This approach opened new horizons in the chemistry of fused pyrimidines, hence the reactions of numerous aminoheterocycles with 1,3-dielectrophiles were studied. By this synthetic road the pyridine ring was annulated to the pyrazole, furan, thiophene and uracil. The distinguishing features of this synthetic procedure are almost quantitative yields and the mild reaction conditions (Scheme 2.1.4).[36]



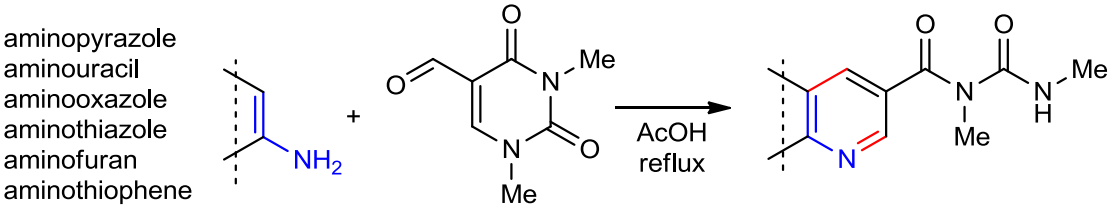
Scheme 2.1.4. *Synthesis of 4-CF_3-substituted fused pyridines.*

Meanwhile, Japanese authors have demonstrated the synthesis of pyrido[2,3-*d*]pyrimidines **2.1.2** and pyrazolo[3,4-*b*]pyridines **2.1.3** by cyclocondensation of corresponding 6-aminouracil or 5-aminopyrazole with CF_3-enones (Scheme 2.1.5).[37]



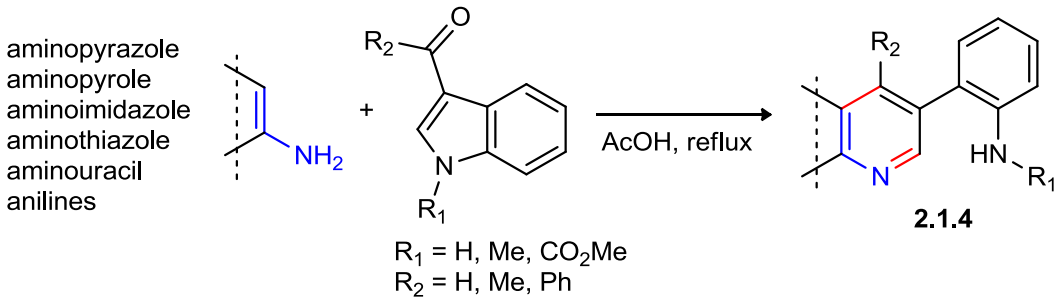
Scheme 2.1.5. *Synthesis of pyrido[2,3-d]pyrimidines* ***2.1.2*** *and pyrazolo[3,4-b]pyridines* ***2.1.3***.

Another group used 5-formyl-1,3-dimethyluracil as 1,3-dielectrophile. The cyclization reactions of the latter, with various electron-excessive aminoheterocycles, lead to the formation of a serie of fused heterocycles containing a unit of nicotinic acid (Scheme 2.1.6).[38]



Scheme 2.1.6. *Synthesis of nicotinic acid substituted fused pyridines.*

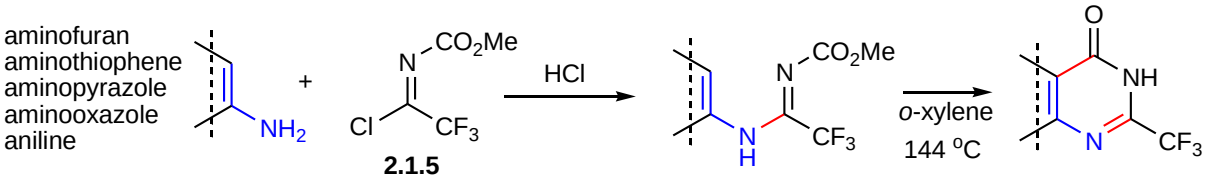
Furthermore, by our colleagues a cyclocondensation reaction of 3-acyl- and 3-formylindoles with aminoheterocycles was presented in order to prepare new heteroannulated 3-(2-aminophenyl)-pyridines **2.1.4**. The reaction starts with opening of indole ring that is followed by subsequent cyclocondensation. The reported transformation represents a rare example of domino reaction, which includes the cleavage of indole moiety (Scheme 2.1.7).[39]



Scheme 2.1.7. *Synthesis of heteroannulated 3-(2-aminophenyl)-pyridines* ***2.1.4***.

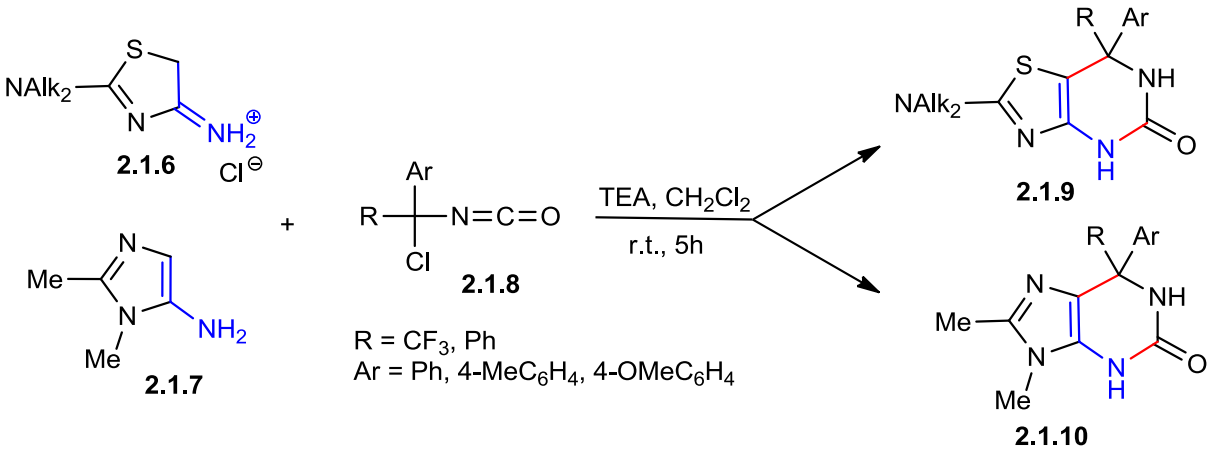
Recently, a variety of 1,3-fluorine-containing dielectrophiles were used for the annulation of

CNC-triade to an electron-excessive systems. The most utilized systems among these 1,3-*CNC*-dielectrophiles are functionalized heterocumulenes. For instance, *N*-(1-chloro-2,2,2-triflouroethylidene)urethane **2.1.5** was coupled with some electron-excessive aminoheterocycles in a two-step process: the first attack was directed by more hard nucleophilic centre; for aminoheterocyles it is the amino function. Formed amidines can undergo a cyclization reaction under harsh conditions (usually in toluene or *o*-xylene) leading to heteroannulated pyrimidines (Scheme 2.1.8).[40]



Scheme 2.1.8. *Synthesis of heteroannulated pyrimidines in two steps starting from* ***2.1.5****.*

Very recently was reported an interesting method for the assembly of fluorine-containing purines and thiazolo[4,5-*d*]pyridimines (7-thiopurines). The method involves cyclization of 5-aminoimidazoles or 4-aminothiazoles with aryl isocyanates as 1,3-*CNC*-dielectrophiles (Scheme 2.1.9).



Scheme 2.1.9. *Synthesis of 2-(dialkylamino)-7-(trifluoromethyl)-6,7-dihydro[1,3]thiazolo[4,5-d]pyrimidones* ***2.1.9*** *6-(trifluoromethyl)-1,3,6,9-tetrahydro-2H-purin-2-one* ***2.1.10.***

Reactions of 2-dialkylamino-thiazole-4-amines **2.1.6** generated *in situ* from their salts and 1,2-dimethyl-imidazole-5-amine **2.1.7** with *α*-chloro-*α*-phenyl-*β,β,β*-trifluoroethyl-isocyanates **2.1.8** leads to 2-(dialkylamino)-7-(trifluoromethyl)-6,7-dihydro[1,3]thiazolo[4,5-

d]pyrimidones **2.1.9** and 6-(trifluoromethyl)-1,3,6,9-tetrahydro-2*H*-purin-2-one **2.1.10** respectively. Moreover, it was found that the reactions of **2.1.8** with 5-aminopyrazole, 5-aminoisoxazole, 2-methoxy-5-aminofuran and 2-methoxy-5-aminothiophene result to a complex mixture of unidentified products. Furthermore, the use of less reactive urethanes leads to trifluoromethyl-containing heteroarylamines.[41]

All discussed methods presented above prompted us to develop the chemistry of fused pyridine derivatives taking advantage of unique properties of electron-excessive aminoheterocyclic (Figure 2.1.3).

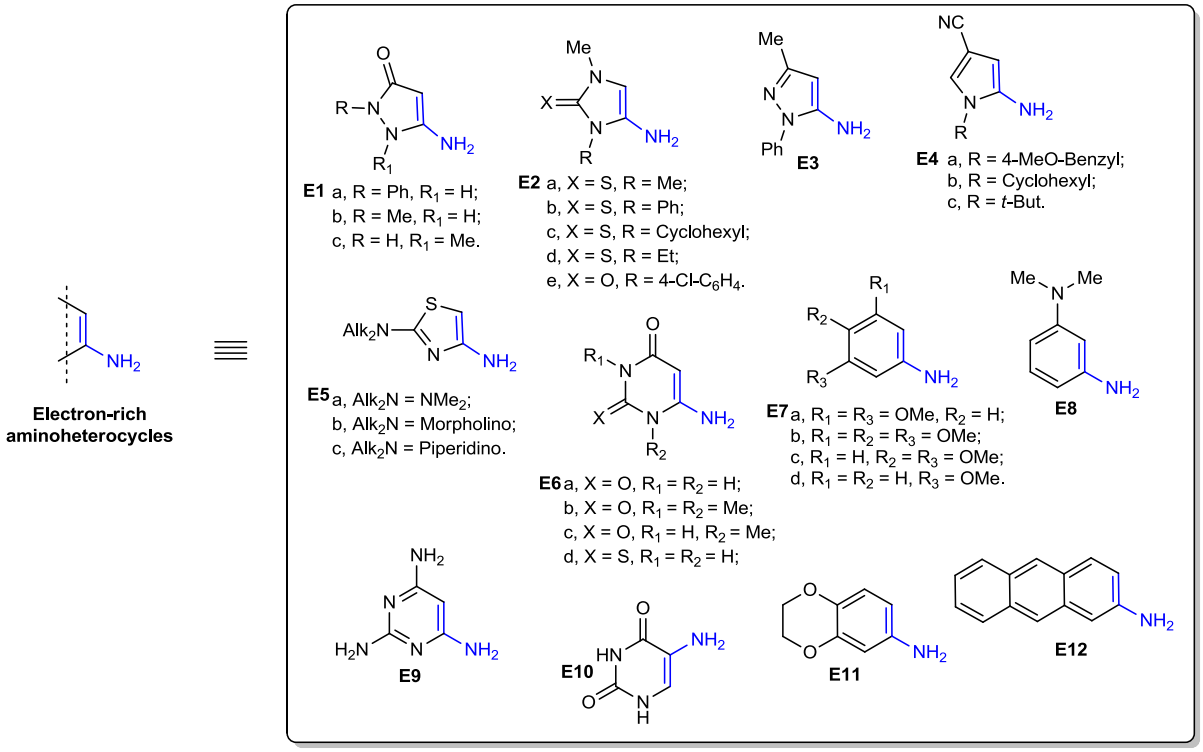


Figure 2.1.3. *List of used electron-excessive aminoheterocycles and anilines.*

Based on the literature data, we chose a library of diverse electron-excessive aminoheterocycles and anilines as main starting binucleophiles for our further study (Figure 2.1.3). In the upcoming chapters the reactions of these enamine-like species with different bielectrophiles will be discussed.

2.2. Chemistry of Chromones

The 2*H*-pyran-2-one ring systems are potential aromatic species, due to the contribution of the pyrylium-2-olate structure, but facile cleavage of the ring by nucleophiles makes it most likely a lactone rather than an aromatic system (Figure 2.2.1). 4*H*-pyran-4-one and its benzo derivatives (chromones) show chemical properties in agreement with substantial π-electron delocalization and consistent with a betaine structure (Figure 2.2.1). Earlier studies suggested that chemical shifts and coupling constants in these systems indicate the presence of a diamagnetic ring current, comparable to the one in benzene. Interestingly, replacement of the oxygen heteroatom with sulfur and/or nitrogen induces downfield shifts of the ring protons, suggesting increased ring currents and therefore increased aromaticity in thiopyrones and quinolones.

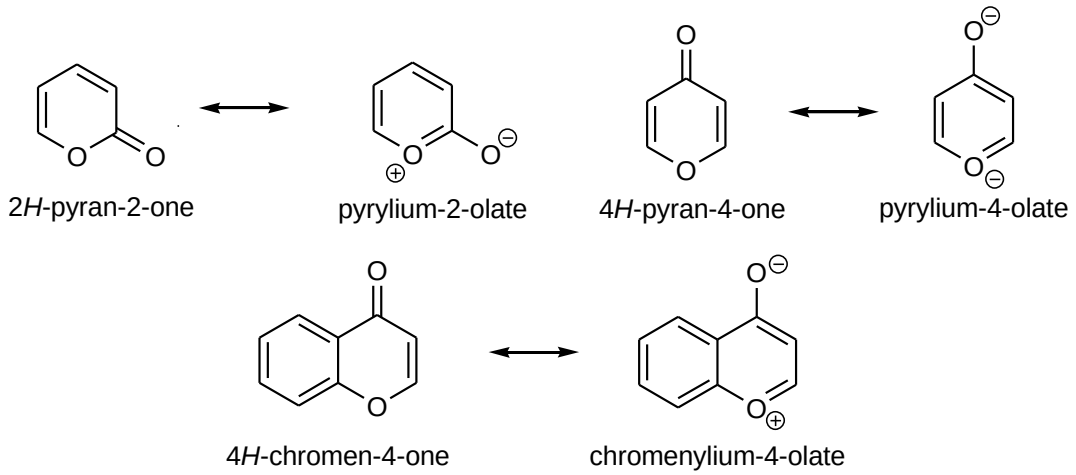


Figure 2.2.1. *π-Electron delocalization and consistent with a betaine structure of pyranones.*

The fact, that chromone ring is also prone to undergo a facile domino cleavage of the ring by nucleophiles makes it most likely a conjugate push-pull system rather than an aromatic system (Figure 2.2.2). Hence, the aromaticity of the heterocyclic ring in pyrones and chromones is still under scrutiny.

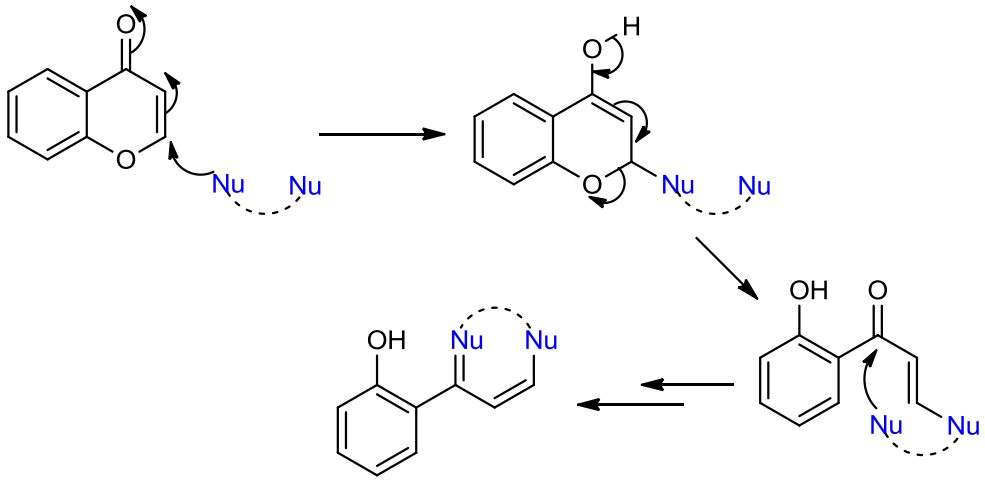


Figure 2.2.2. *Chromones likely a conjugate push-pull system.*

According to our retrosynthetic analysis, the second reaction component to be used are 1,3-dielectrophiles. Particularly 4*H*-chromen-4-ones or simply chromones are prone to react with nucleophiles as 1,3-dielectrophiles (Figure 2.2.3). They can be considered as 1,3-dicarbonyl compounds with masked salicyloyl fragment at the position 2. In addition to their unique chemical properties, chromones are one of the significant classes of oxygen containing compounds, and many natural and synthetic derivatives of chromones possess a variety of biological activities.[42]

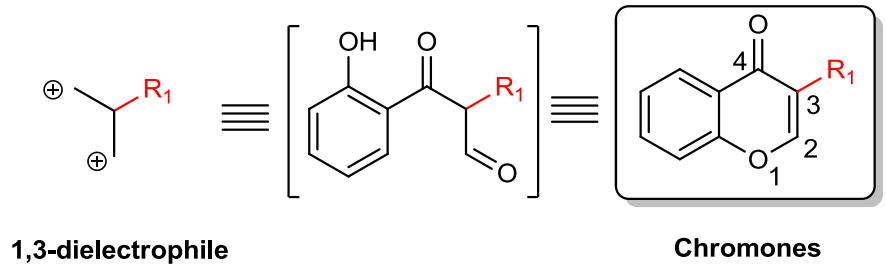


Figure 2.2.3. *3-Substituted chromones as masked 1,3-dielectrophiles.*

The main synthetic interest of these clusters is their ability to react with different nucleophiles leading to assortment of new rearranged heterocyclic systems potentially relevant for drug discovery.[43] Moreover, the reactivity of chromones is well documented in the literature, thereby in this chapter will be discussed readily available derivatives of chromones and their chemistry. In the family of chromone derivatives the most popular one is 3-formylchromone, which was for the first time synthesized on early 1970s. The reason of increased interest is that these types of molecules have three electrophilic centers: the aldehyde moiety, the C-4 atom and the C-2 atom; the latter can be considered as a hidden aldehyde function (Figure

2.2.4). Additionally, it was shown that the reactivity of C-4 atom toward nucleophiles is much lower compared to the formyl group and the C-2 atom.

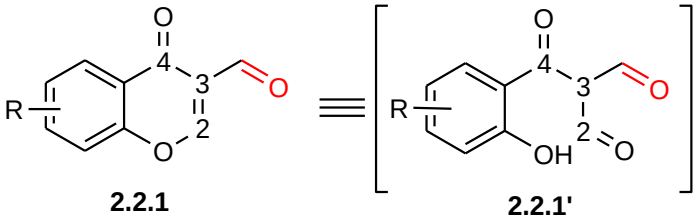
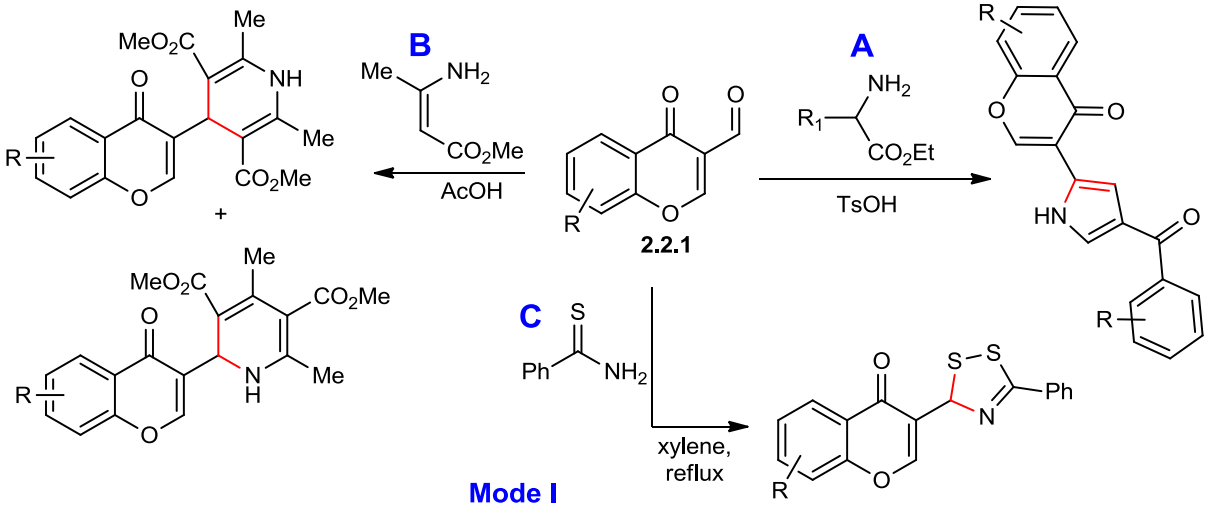


Figure 2.2.4. *3-Substituted chromones **2.2.1** as masked 1,3-dielectrophiles.*

According to detailed analysis of literature concerning the chemistry of 3-formylchromones **2.2.1**, the pathways of transformation of such molecules can be divided on three groups.

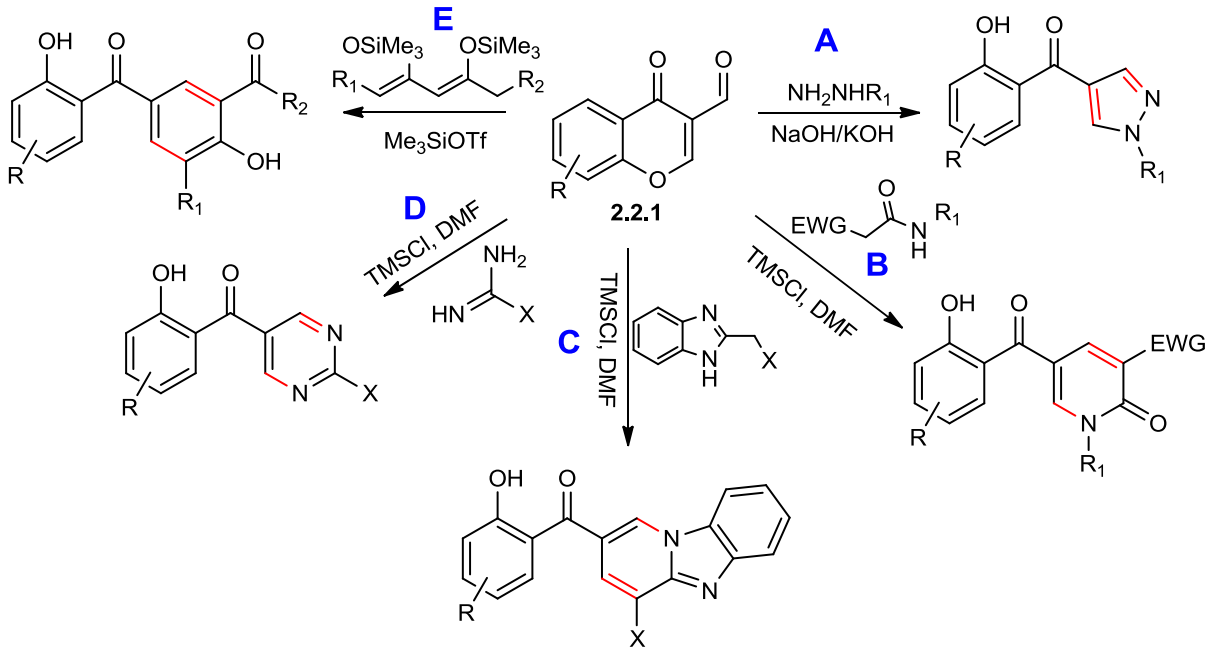
Seldom, the chromone ring stays intact during the reaction, thus only formyl group participates in the reaction, similar to simple aromatic formyl group (**Mode I**, Scheme 2.2.1). For instance, the reaction of 3-formylchromones with alanine or phenylglycine ethyl ester (1,2-*CN*-binucleophile) in toluene in the presence of TsOH leads to pyrrole ring formation (Pathway **A,** Scheme 2.2.1).[44] Another case represents the reaction of 3-formylchromone **2.2.1** with aminocrotonate (1,3-*CCN*-binucleophile) in acetic acid, that delivers to a mixture of dihydropyridines (Pathway **B,** Scheme 2.2.1).[45] Additionally, the authors found that 3-(5-phenyl-3*H*-[1,2,4]-dithiazol-3-yl-chromen-4-ones are formed when **2.2.1** reacts with thiobenzamide (Pathway **C,** Scheme 2.2.1).[46]



Scheme 2.2.1. *The reactivity of the exocyclic formyl moiety of 3-formylchromone **2.2.1**.*

Very often the reaction of **2.2.1** with binucleophiles proceeds *via* aldehyde moiety and C-2

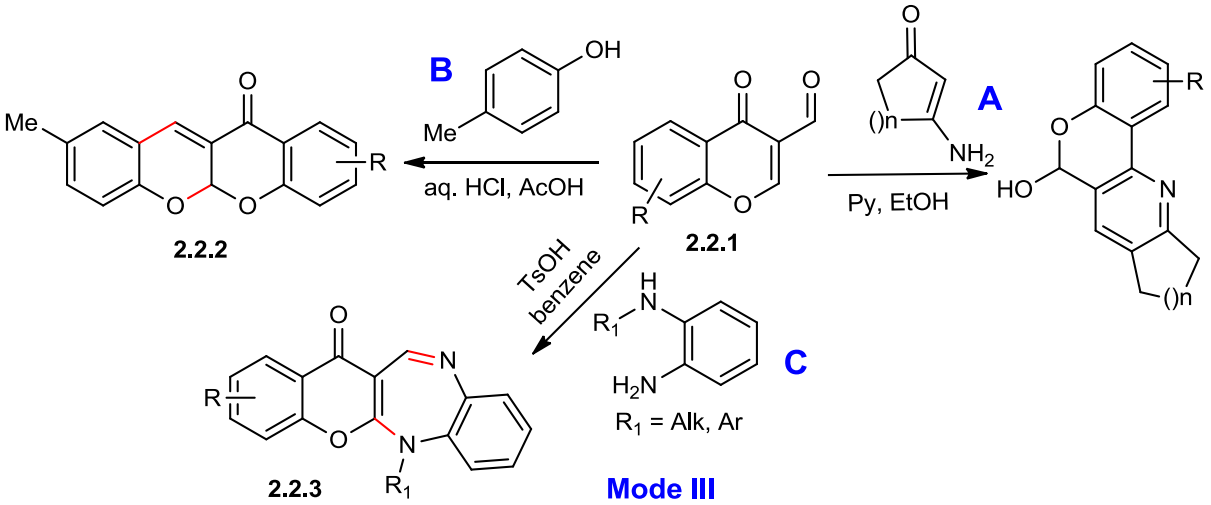
atom of chromone ring, which is usually followed by recyclization and in some cases with various ring annulations (**Mode II**, Scheme 2.2.2). For example the reaction of **2.2.1** with 1,2-*N,N*-binucleophiles, such as hydrazine derivatives provides a new pyrazoles ring formation (Pathway **A**, Scheme 2.2.2).[47] Furthermore, a wide range of reactions with different 1,3-binucleophiles were reported to date. An obvious example is the reaction of **2.2.1** with 1,3-*CCN*-binucleophiles, such as cyanoacetamides or malonodiamides, which provides an interesting pathway to different pyridine derivatives (Pathway **B**, Scheme 2.2.2).[48] Interestingly, heterocyclic 1,3-*CCN*-binucleophiles like 1*H*-benzimidazole derivatives were considered as well. The cyclization takes place in ethylene glycol at 200-210 ^{o}C, or in TMSCl/DMF system resulting pyrido[1,2-*a*]benzimidazoles (Pathway **C**, Scheme 2.2.2).[49] Besides, a convenient synthesis of pyrimidine derivatives was proposed by the reaction of 3-formylchromones **2.2.1** with 1,3-*NCN*-binucleophiles (for instance amidines, guanidines and ureas) (Pathway **D**, Scheme 2.2.2).[50] Finally, by Langer's group the reaction with 1,3-*CCC*-binucleophiles, namely bissylil enol ethers were deeply investigated. According the methodology described by Langer *et al.*, a broad number of benzophenone derivatives were obtained (Pathway **E**, Scheme 2.2.2).[51]



Scheme 2.2.2. *Cyclizations trough formyl moiety and C-2 carbon atom.*

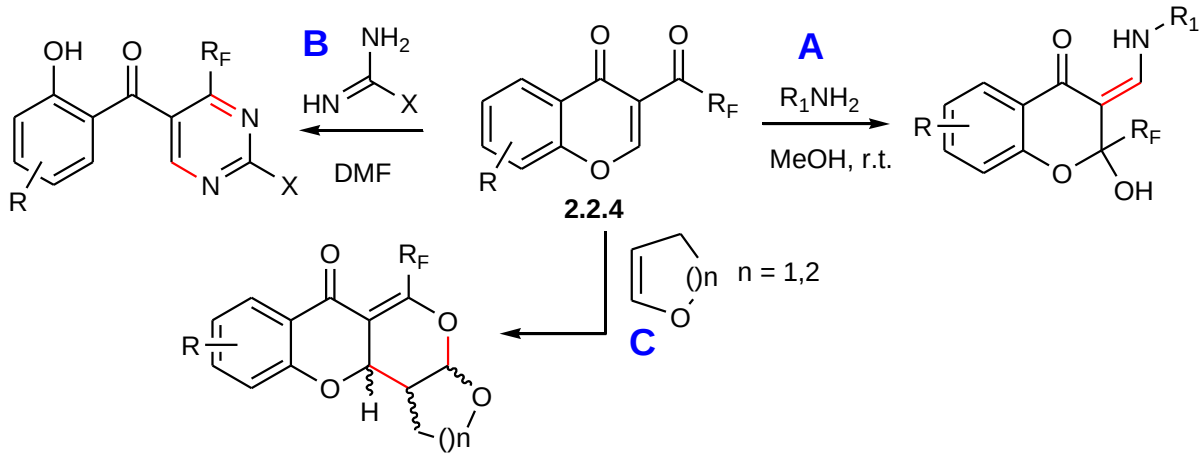
In some transformations of 3-formylchromone **2.2.1** with binucleophiles instead of pyrone ring opening a sort of ring annulation can take place (**Mode III**, Scheme 2.2.3). This type of annulation was observed in the reaction of 3-formylchromone **2.2.1** with heterocyclic amines

(1,3-*CCN*-binucleophiles) that leaded to the formation of fused pyridines (Pathway **A**, Scheme 2.2.3).[52] An interesting results were disclosed with *p*-cresol, that behave as 1,3-*CCO*-binucleophile, namely a subsequent ring annulation product **2.2.2** was obtained (Pathway **B**, Scheme 2.2.3).[53] An annulation product was prepared also, when 3-formylchromone **2.2.1** was treated with 1,4-binucleophiles (for instance *N*-substituted *o*-phenylendiamines) delivering to corresponding chromeno[2,3-*b*][1,5]benzoxazepin-13-ones **2.2.3** from moderate to good yields (Pathway **C**, Scheme 2.2.3).[54]



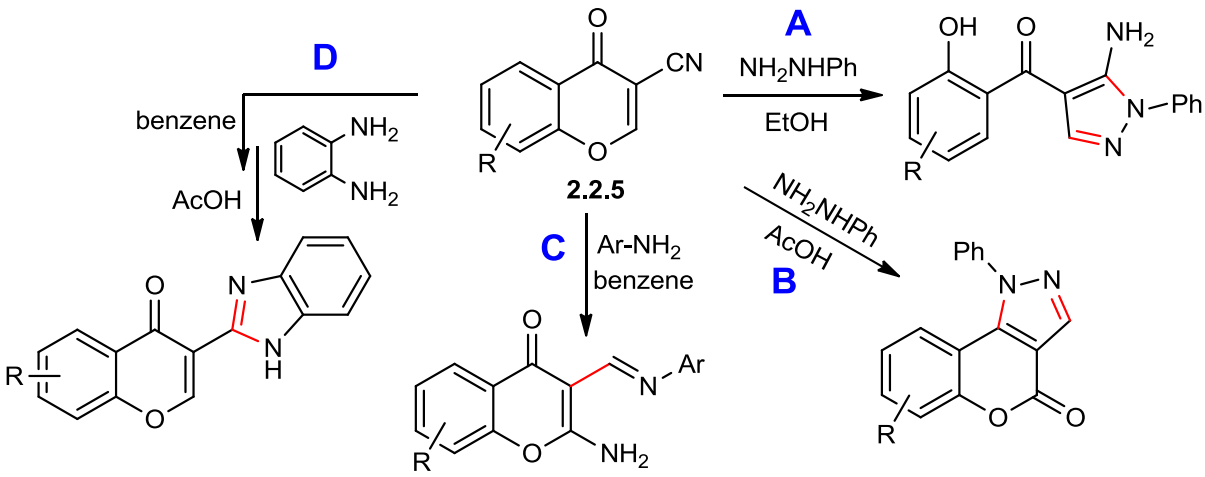
Scheme 2.2.3. *Reactivity of exo-formyl moiety of **2.2.1** without pyrone ring opening.*

Nevertheless, except 3-formylchromone there are some other examples of chromone derivatives which were investigated to date. Recently a reaction of 3-(polyfluoroacyl)-4*H*-chromen-4-ones **2.2.4** with different binucleophiles was performed. This approach provided a new and versatile pathway toward polyfluoroalkyl-substituted fluorinated molecules. For instance the reaction of fluorinated chromones **2.2.4** with aliphatic and aromatic amines in methanol at room temperature for two days afforded 3-(alkyl/arylaminomethylene)-2-hydroxy-2-(polyfluoroalkyl)chroman-4-ones in good yields (Pathway **A**, Scheme 2.2.4).[55] The reactions of 3-COR_F-chromone with amidines or guanidines in the DMF delivers new derivatives of polyfluoroalkyl-pyrimidines (Pathway **B**, Scheme 2.2.4).[56] Interestingly, the cycloaddition of 3-(polyfluoroacyl)-chromones (heterodiene) with 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran under mild conditions produced novel fused pyrones in moderate yields (Pathway **C**, Scheme 2.2.4).[57]



Scheme 2.2.4. *Reactivity of 3-(polyfluororacyl)-chromones* ***2.2.4***.

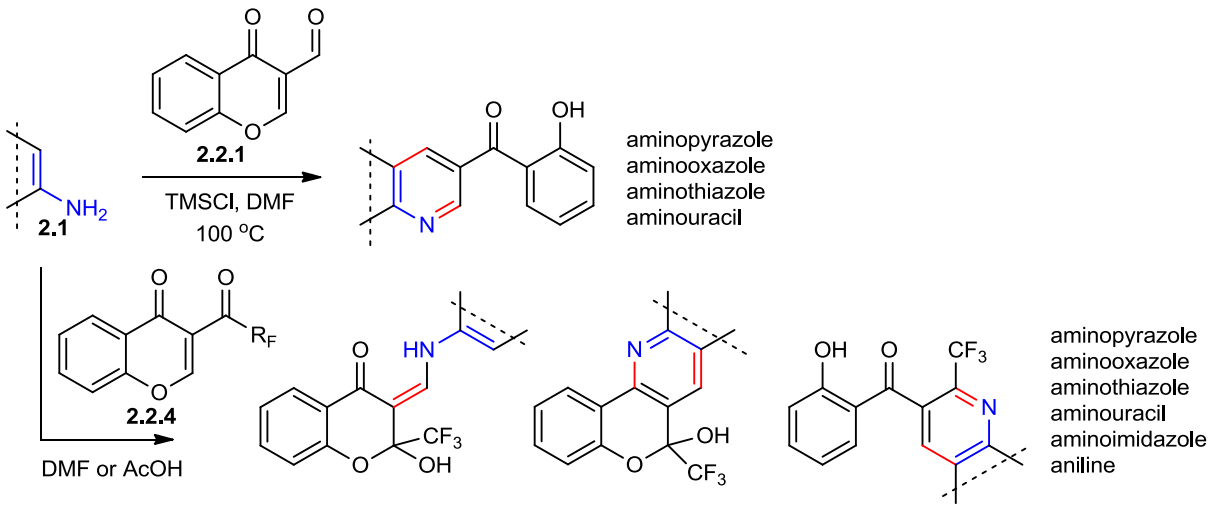
The following chromone derivatives, which were intensively studied, are 4-oxo-4*H*-chromene-3-carbonitriles **2.2.5**. Not surprisingly, introduction of reactive and electron-withdrawing CN group to the position 3 of chromone system initiates crucial changes of reactivity in the pyrone ring towards nucleophiles, that broadens the synthetic potential of 3-cyano chromones. For example, remarkably was found that depending from the solvent the reaction of 3-cyanaochromones and phenyl hydrazine can give different products (Pathway **A**, **B**, Scheme 2.2.5).[58] Moreover, the reaction of cyanochromone **2.2.5** with anilines under reflux in benzene, suddenly leaded to the formation of 2-amino-3-(aryliminomethyl)chromones (Pathway **C**, Scheme 2.2.5).[59] Besides, the mixture of 3-cyanochromone **2.2.5** with different *o*-phenylenediamines in two steps can be converted to benzimidazole-substituted chromones (Pathway **D**, Scheme 2.2.5).[60]



Scheme 2.2.5. *Reactivity of 3-cyanaochromones* ***2.2.5***.

Eventually, it should be noticed, that among the examples of binucleophiles discussed above

recently were published some samples of the reaction between electron-excessive aminoheterocycles **2.1** and 3-formyl **2.2.1** or 3-COR_F-chromones **2.2.4**. In the first case the reaction proceeds *via* pyrone ring opening - other ring closure (**Mode II**, Scheme 2.2.2), so corresponding pyridine derivatives were formed.[61] In contrast to this, the products formed by the reaction of 3-(polyfluoroacyl)chromenones **2.2.4** with aminoheterocycles **2.1** are strongly dependent from the reaction conditions (Scheme 2.2.6).[62]



Scheme 2.2.6. *Electron-excessive aminoheterocycles **2.1** as binucleophiles in the reaction with chromones **2.2.1**, **2.2.4**.*

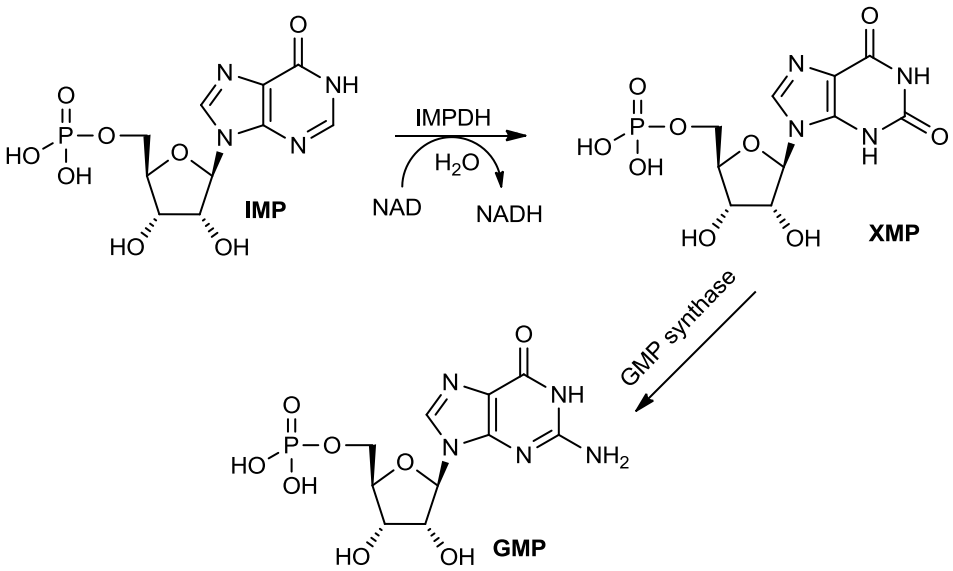
It is obvious that chromone derivatives with electron withdrawing groups (EWG) at the position 3 represent important and flexible starting materials and are intended for cyclization reaction with aminoheterocycles. Being inspired by the great chemical potential of the reaction between chromones and various binucleophiles, we started the present work, in order to develop new and efficient synthetic methods toward the wide range of purine-like compounds. So in the next few chapters the development of convenient procedures for preparation of diverse pyridine derivatives starting from chromones will be discussed.

2.3. 3-(Dichloroacetyl)chromone – a new building block for the synthesis of formylated purine isosteres. Design and synthesis of fused α-(formyl)pyridines

2.3.1. Introduction

As it was discussed in previous chapters, purine isosteres and purine-like scaffolds are of substantial attention in medicinal chemistry and drug design.[63] In recent years functionalized derivatives of purine isosteres appear to be of high pharmacological importance as guide structures and synthetic building blocks in medicinal and agricultural chemistry.[64-70] At the same time these building blocks, bearing a carbonyl group, are of special interest because of the potential capability in design of inosine 5'-monophosphate dehydrogenase (IMPDH) inhibitors.[71]

IMPDH is a potential target in antitumor chemotherapy.[72] The reason of extreme popularity of this enzyme among medicinal chemists is the fact, that IMPDH is a NAD-dependent enzyme, which controls *de novo* synthesis of purine nucleotides,[73] namely it catalyzes the oxidation of inosine-5'-monophosphate (IMP) to xanthosine-5'-monophosphate (XMP) that is followed by transformation into guanosine-5'-monophosphate (GMP) (Scheme 2.3.1).



Scheme 2.3.1. *Action of IMPDH.*

The concentration of IMPDH is increased in tumour cells and activated lymphocytes, that is, in the cells with increased activity of synthetic pathways leading to concentration of nucleic

acids. Thus, inhibition of IMPDH should result in anticancer and immunosuppressive activities. Hence IMPDH has received considerable attention in recent years as an important target enzyme, not only for the discovery of anticancer drugs, but also for antiviral, antiparasitic and immunosuppressive chemotherapy (Figure 2.3.1).[74]

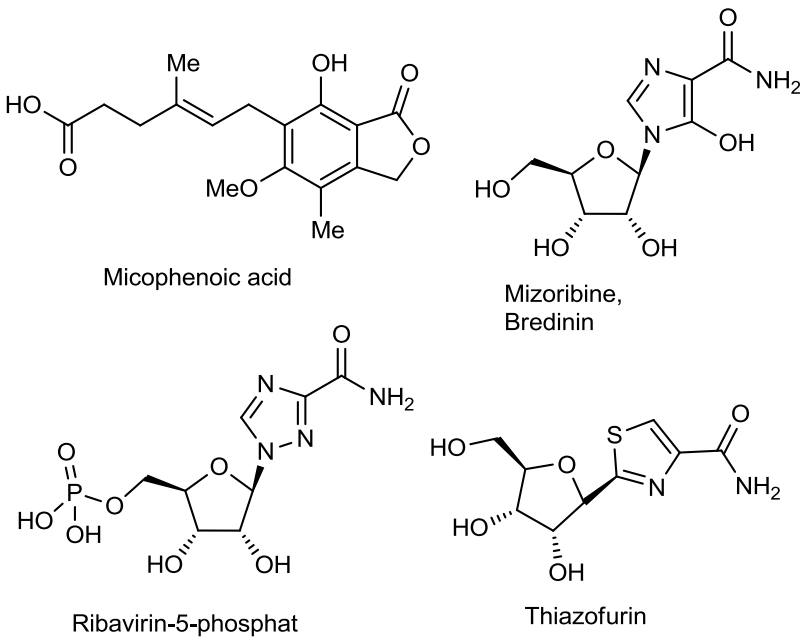


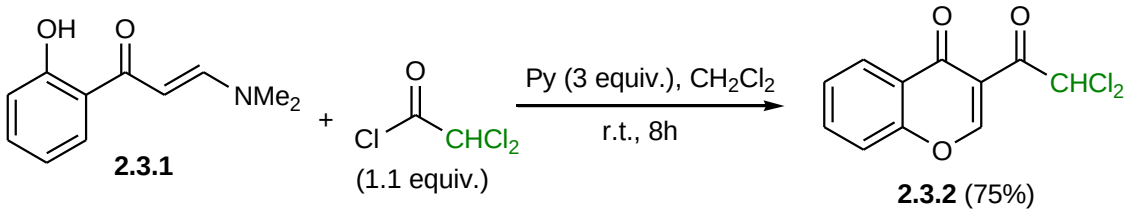
Figure 2.3.1. *Active IMPDH inhibitors.*

Some of IMPDH inhibitors are currently used in the clinic and are released on the market, e.g. ribavirin,[75] mizoribine,[76] tiazofurin TR[77] and mycophenolic acid MPA.[78] However, development of new structures with potential inhibitor activity towards IMPDH continue to be of considerable interest. In this chapter we will discuss a versatile preparative approach for synthesis of purine isosteres bearing a formyl functionality located at the α-position of the purine/pseudo purine core. We consider these scaffolds to be mechanism-based inhibitors of IMPDH.

2.3.2. Synthesis of starting materials

In order to synthesis desired products, as a starting material was chosen 3-(dichloroacetyl)chromone **2.3.2**, which can be considered as a new polydentate electrophilic substrate for the synthesis of dichloromethylated fused pyridines. It is known from the literature, that 3-substituted chromones can be prepared by the reaction of 3-(dimethylamino)-1-(2-hydroxyphenyl)-propen-1-one **2.3.1** with diverse electrophiles.[79] According to the known

general procedure, we were able to prepare 3-(dichloroacetyl)chromone **2.3.2** in 75% yield by reaction of 3-(dimethylamino)-1-(2-hydroxyphenyl)-propen-1-one **2.3.1** with dichloroacetyl chloride in pyridine (Scheme 2.3.2). The product is stable at room temperature (r.t.) for several years.



Scheme 2.3.2. *Preparation of 3-(dichloroacetyl)chromone **2.3.2**.*

It should be noticed, that despite the huge chemical potential of 3-(dichloroacetyl)chromone **2.3.2** as a building block in organic synthesis, no data on the preparation and/or chemical properties of this molecule was reported before us. Another aspect that motivated us to choose 3-(dichloroacetyl)chromone **2.3.2**, is the possibility to have dichloromethyl group in purine isosteres, that can be easily converted into formyl[80] and trichloromethyl[81] groups. Noteworthy, it is difficult to prepare dichloromethylazines by direct chlorination of the corresponding derivatives, since this reaction usually affords a mixture of mono-, di- and trichloromethylazines.[82]

2.3.3. Results and discussion

According to the properties of 3-carbonyl-substituted chromones described in the Chapter 2.2, 3-(dichloroacetyl) chromone **2.3.2** have three electron-deficient centres, namely carbon atoms C-2 and C-4 of the chromone moiety and the carbonyl C atom of $COCCl_2H$ group, in addition to electron deficient dichloromethyl group (Figure 2.3.2).

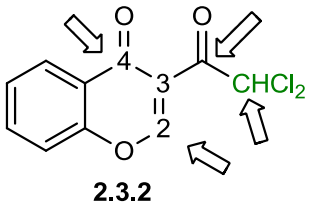
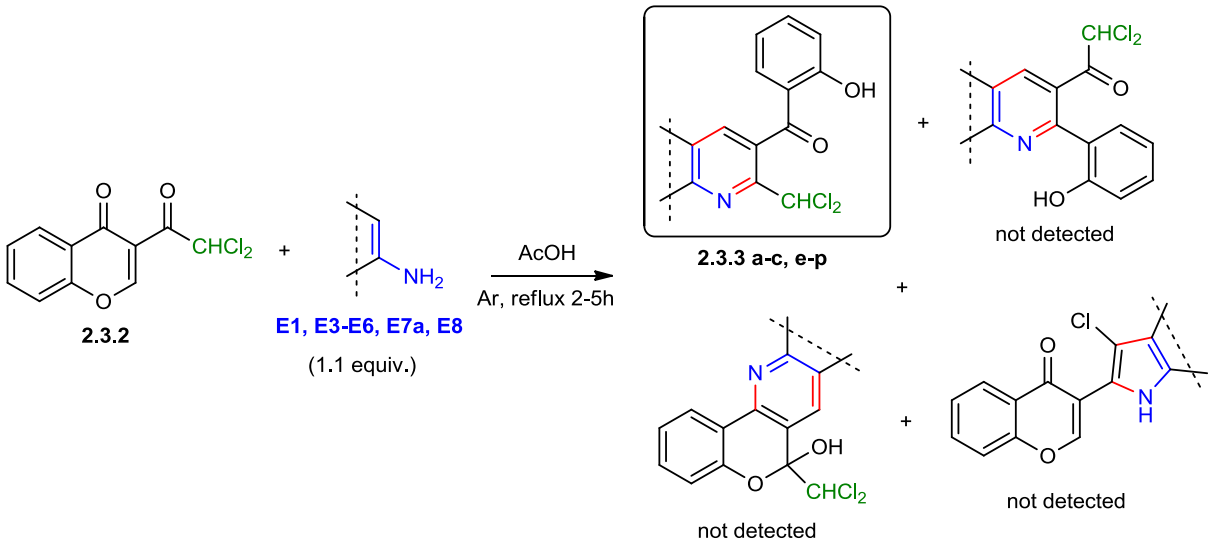


Figure 2.3.2. *Electron-deficient centres of 3-(dichloroacetyl)chromone* **2.3.2.**

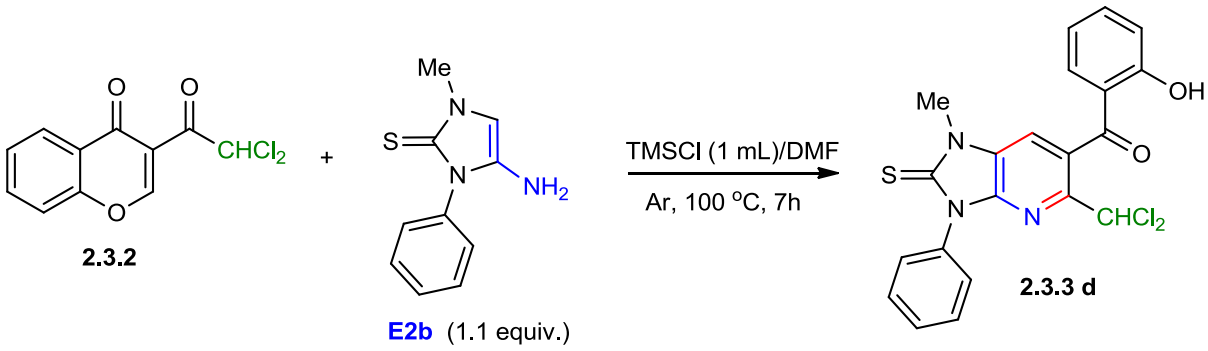
Due to several potentially reactive electrophilic centres, the reaction with binucleophiles in

principle can lead to several isomer products (Scheme 2.3.3). Therefore the development of chemo- and regioselective synthetic method towards the preparation of purine isosteres bearing a dichloromethyl group in position 2 was challenging. Based on the results from the literature, in acidic media the first attack of binucleophile is expecting to be on the position C-2 with following intramoleculare cyclization *via* another electrophilic center. In order to examine the reactivity of **2.3.2,** we started our investigation using electron-excessive aminoheterocycles **E1-E8** described in the Chapter 2.1. The reaction of 3-(dichloroacetyl)chromone **2.3.2** with **E1** (Figure 2.1.2) was performed in acetic acid under reflux. Surprisingly, from a vast number of possible regioisomers 6-(dichloromethyl)-1,2-dihydro-2-phenylpyrazolo[3,4-*b*]pyridin-3-one **2.3.3a** was the only detected product. It was quite easy to control the end of the reaction by TLC, since the starting chromone was totally converted to the product. Having first promising results in hand, the rest of electron-excessive aminoheterocycles **E2-E8** (Figure 2.1.2) were scanned with 3-(dichloroacetyl)chromone **2.3.2** (Scheme 2.3.3). Gratifyingly, corresponding heteroannulated pyridines **2.3.3** were isolated in good to excellent yields (60-93%) (Table 2.3.1).



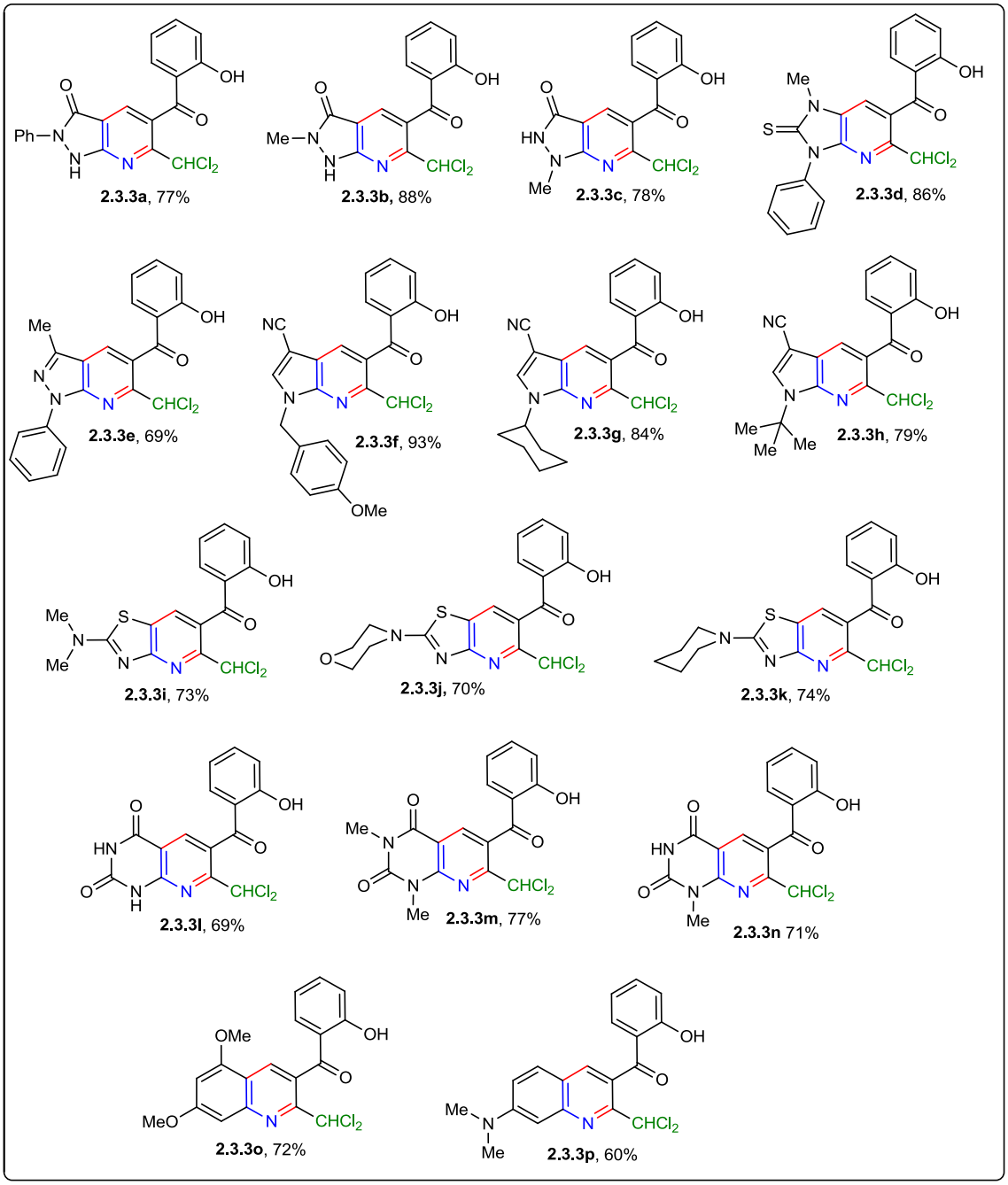
Scheme 2.3.3. *Preparation of α-$CHCl_2$-substituted fused pyridines* ***2.3.3***.

Noteworthy, that in case of 4-amino-1*H*-imidazole-2(3*H*)-thione **E2**, the standard reaction condition in acetic acid was inapplicable, since the starting electron-excessive aminoheterocycle **E2** was not stabile in acidic media. Therefore in this case an alternative TMSCl/DMF system was applied. This system have proved to be a water scavenger; accordingly in recent years it has found numerous applications in synthetic organic chemistry (Scheme 2.3.4).[83]



Scheme 2.3.4. *Preparation of α-$CHCl_2$-substituted imidazopyridine* ***2.3.3d*** *by alternative procedure.*

Table 2.3.1. *List of synthesised α-$CHCl_2$-substituted fused pyridines* ***2.3.3***.



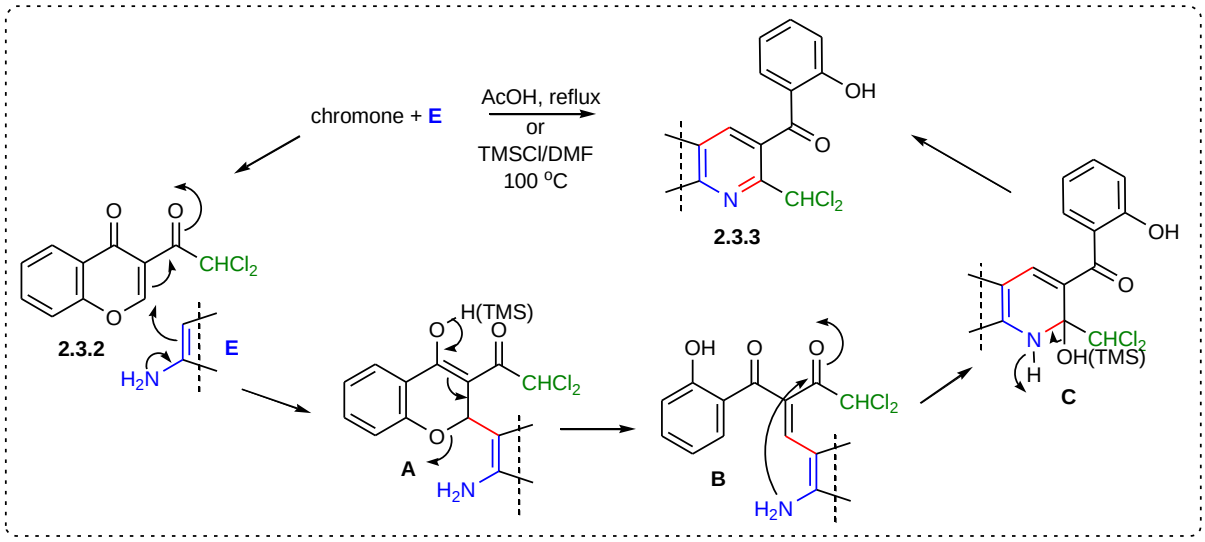
As it was mentioned above, these conditions were successfully applied in the chemistry of 3-formyl **2.2.1** and 3-COR_F **2.2.4** chromones. Namely they were reacted with aminoheterocycles such as aminooxazoles, aminothiazoles, aminouracils etc (see Chapter 2.2). In contrast to 3-COR_F-chromones **2.2.4,** the reaction of 3-(dichloroacetyl)chromone **2.3.2** with electron-excessive aminoheterocycles is more regioselective (see scheme 2.2.6), since in all cases only one regioisomer of fused pyridines was detected. Besides, in most of the cases a simple recrystallisation was enough to purify obtained compounds. Exceptions were few, only in some cases there was a need to purify the crude by column chromatography.

2.3.4. Unsuccessful results

Unfortunately reactions with pyrimidine-2,4,6-triamine **E9**, 5-aminopyrimidine-2,4(1*H*,3*H*)-dione **E10,** as well as with aniline derivatives **E11**, **12** were not successful. Using the both reaction conditions described above resulted in inseparable mixture of compounds.

2.3.5. Mechanistic explanation

We consider that the regioselective formation of annulated pyridines **2.3.3** starts with the attack of internal enamine-like β-carbon at C-2 atom of 3-(dichloroacetyl)chromone **2.3.2**.



Scheme 2.3.5. *Putative mechanism of the reaction of **2.3.2** with electron-excessive aminoheterocycles.*

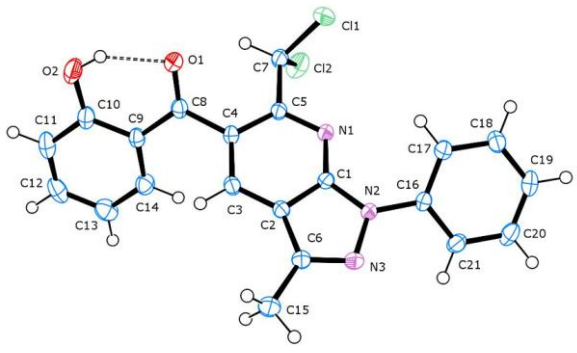
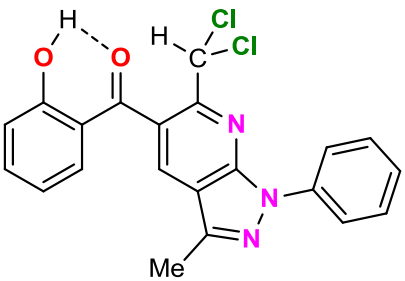
The reason for this is that the *β*-carbon atom in the enamine-like moiety is more nucleophilic than the primary amino group, thus it behaves more like *C*-nucleophile. Following pyrone ring opening delivers the intermediate **B**. Following subsequent intramolecular attack of amino group at the dichloroacetyl group form intermediate **C**. Finally, aromatization of intermediate **C** by fission of H_2O molecule leads to the expected fused pyridines (Scheme 2.3.5).

Neither in AcOH, nor in TMSCl/DMF system no other alternative cyclization product was detected (see Scheme 2.3.3).

2.3.6 Structure identification

All structures obtained during the study were confirmed by ^{1}H and ^{13}C NMR, IR and mass-spectrometry, in addition they are in good correspondence with earlier synthesized heterocyclic compounds. In ^{1}H NMR spectra a typical singlet of the pyridine proton was observed at δ 8.17-8.53 ppm in DMSO-d_6 (7.80-8.00 ppm in $CDCl_3$). The singlet of C*H*Cl_2 proton appears at δ 7.51-7.71 ppm in DMSO-d_6 (7.01-7.50 ppm in $CDCl_3$), additionally the singlet of O*H* was detected at δ 10.51-10.81 ppm in DMSO-d_6 (11.03-11.79 ppm in $CDCl_3$). The peak of O*H* was shifted to 10.50-11.00 ppm, which can be explained by formation of intramolecular hydrogen bond with the neighbouring keto-group. Moreover, all protons of benzene ring are shifted to higher field, which proofs the opening of the pyrone ring. In the ^{13}C NMR spectra the peak of *C*HCl_2 appears at δ 68.8-69.7 ppm. IR spectra show the stretchings of OH group at 3040-3061 cm^{-1} which confirmed the presence of hydrogen bonding.

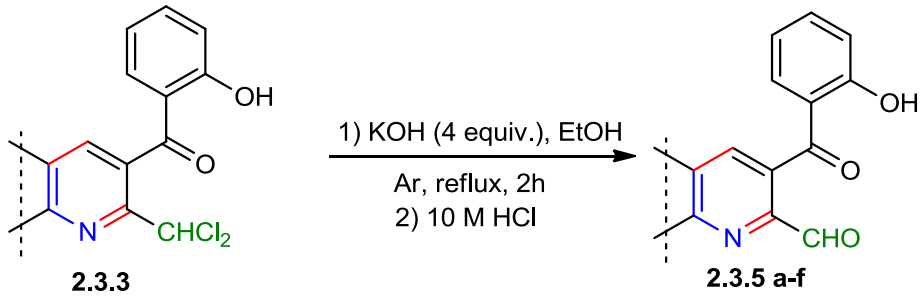
Table 2.3.2. *Crystal structure of* ***2.3.3e***.

Compound	Crystal	Structure
2.3.3e		

Furthermore, the structure of 6-(dichloromethyl)-3-methyl-1-phenyl-5-salicyloyl-1*H*-pyrazolo[3,4-*b*]pyridine **2.3.3e** was established by X-ray single crystal analysis. The presence of hydrogen bond between OH and carbonyl *O*-atom was confirmed by crystal structure (Table 2.3.2). It was possible to see the planar core of heterocyclic fragment. The carbonyl group was slightly twisted out of the pyrazolopyridine plane, probably to minimize the electronic repulsion with the chlorine atoms of dichlomethyl group. The torsion angle for C5-C4-C8-O1 was 45.3°.

2.3.7. Further investigations

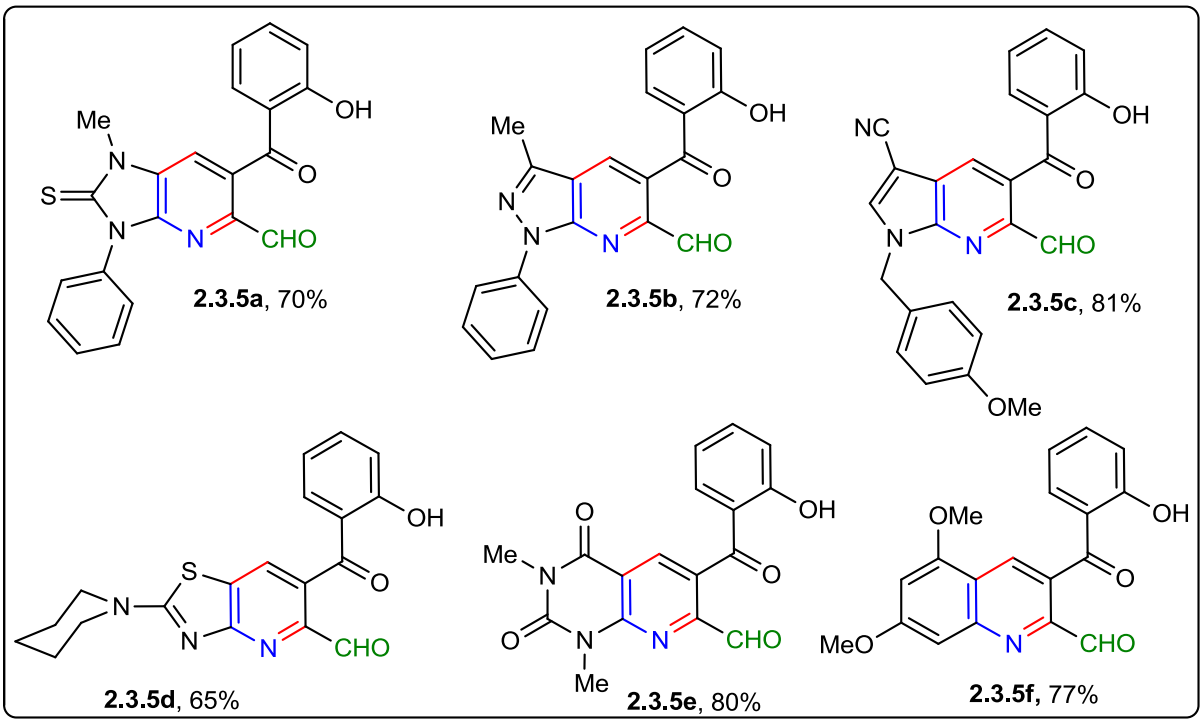
Above already was mentioned that the fused pyridines - purine isosteres bearing formyl group at *α*-position of pyridine core are of special interest for the development of IMPDH inhibitors.[84] Therefore as the next step of the work conversion of $CHCl_2$ group (a masked formyl group) into formyl moiety was performed (Scheme 2.3.6). In overall six examples (one from each type of fused pyridines) **2.3.5** were prepared. The reaction was carried out in the MeOH using 4 equivalents of KOH. After completion of the reaction (TLC control), reaction mixture was worked up with 10 M HCl solution (Table 2.3.3).[85] Proposed method delivers *α*-formyl-substituted imidazolo-, pyrazolo-, pyrrolo-, thiazolopyridine, and quinoline derivatives **2.3.5a-h** in good yields.



Scheme 2.3.6. *Conversion of $CHCl_2$ group to the CHO* ***2.3.5****.*

The conversion of $CHCl_2$ group to formyl was proved by NMR spectroscopy. In ^{1}H NMR spectra the singlet of C*H*Cl_2 moiety at δ 7.51-7.71 ppm disappeared, and a new singlet corresponding to CO*H* appeared at δ 10.55-11.81 ppm (DMSO-d_6). Moreover, in the ^{13}C NMR at 191.6-192.7 ppm (DMSO-d_6) a peak for formyl carbon atom was detected.

Table 2.3.3. *List of prepared 2-formyl fused pyridine derivatives* ***2.3.5***.



2.3.8 Conclusion

In summary of presented chapter, for the first time was reported the synthesis of 3-(dichloroacetyl)chromone **2.3.2**. An efficient cyclocondensation reaction of 3-(dichloroacetyl)chromone **2.3.2** as a new building block with diversity of electron-excessive aminoheterocycles **E1-E8** was reported. The reflux in acidic condition was applied for most cases, or alternatively TMSCl/DMF system was used. The proposed methods were easy and simple ensuring good regioselectivity. Corresponding fused pyridines were formed in good yields. The dichlormethyl group was easily transferred into formyl group leading to formation of α-formyl-substituted fused pyridines **2.3.5**. This approach gives a possibility to prepare new fused pyridines which could be IMPDH inhibitors.

2.4. 3-Methoxyalylchromone – a new building block for the synthesis of carboxylated purine isosteres. Design and synthesis of fused α-carboxymethyl pyridines

2.4.1. Introduction

Having initial successful results in preparation of α-formyl-substituted purine isosteres, we continued the study on synthetic utility of 2-unsubstituted 3-acylchromones as starting materials towards α-substituted fused pyridines. As it was previously mentioned, purine derivatives bearing carbonyl or carboxyl functional groups are of special interest in the design of IMPDH inhibitors. Moreover, fused pyridines with a carboxyl functional group in the α-position can be considered as derivatives of picolinic acid, an isomer of nicotinic acid. Picolinic acid acts as a chelating agent for some biogene metals, such as chromium, zinc, manganese etc in human body. It is involved in biological synthetic pathways of phenylalanine, tryptophan and number of alkaloids (Figure 2.4.1).[86]

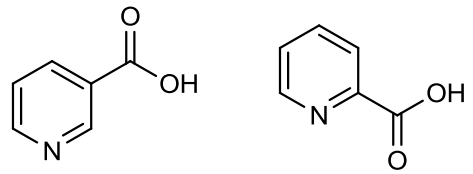
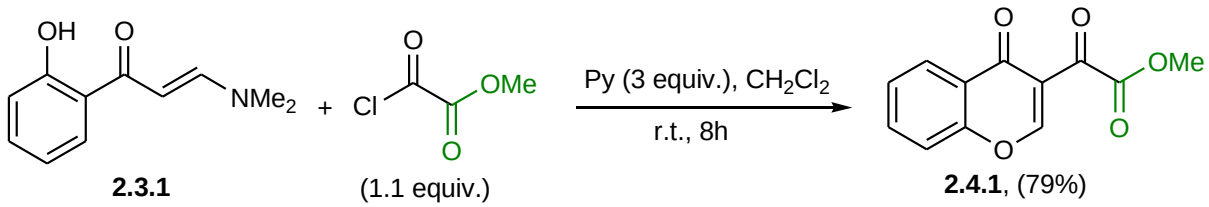


Figure 2.4.1. *Biologically active pyridines with carboxyl substituent.*

In order to prepare α-carboxyl-substituted fused pyridines 3-methoxyalyl chromone was set as the main subject for the following study. We believed that it can have similar reactivity toward electron-excessive aminoheterocycles like other 3-carbonyl-substituted chromones, thereby giving an opportunity to construct a list of fused pyridines with carboxyl functionality.

2.4.2. Synthesis of starting materials

3-Methoxyalyl chromone **2.4.1** can be prepared from 3-(dimethylamino)-1-(2-hydroxyphenyl)-propen-1-one **2.3.1** using the same procedure proposed for 3-(dichloroacetyl)chromone **2.3.2**.[87]



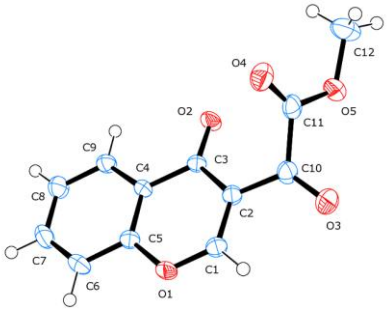
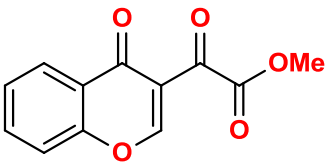
2.3.1 (1.1 equiv.) **2.4.1**, (79%)

Scheme 2.4.1. *Preparation of 3-methoxyalyl chromone **2.4.1**.*

That is, treatment of 1 equivalent of enaminone **2.3.1** with 1.1 equivalents of methoxyoxalyl chloride in diclormethane in the presence of pyridine as a base delivered desired 3-methoxyalyl chromone in 79 % yield (Scheme 2.4.1).

To the best of our knowledge so far exists only a single report related to the synthesis of such molecules. In the beginning of 1950s by Whalley *et al.* was presented the synthesis of 6,7-dimethoxy-3-ethoxalyl-2-methylchromone, which was prepared from 2-hydroxyacetophenone, diethyl oxalate and acetic anhydride.[88] The chemistry of this molecule was not previously studied. Additionally, the structure of our starting chromone **2.4.1** was also confirmed by X-ray crystal structure analysis (Table 2.4.1).

Table 2.4.1. *Crystal structure of 3-methoxyalyl chromone **2.4.1**.*

Compound	Crystal	Structure
2.4.1		

2.4.3. Results and discussions

Obviously, 3-methoxyalyl chromone **2.4.1** has analogous properties with 3-(dichloroacetyl)chromone **2.3.2**. Therefore the regioselectivity of reaction between this chromone as dielectrophile and aminoheterocycles as binucleophiles is interesting in its own right.

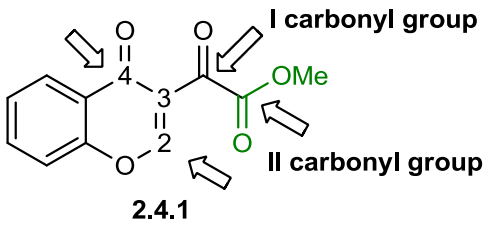
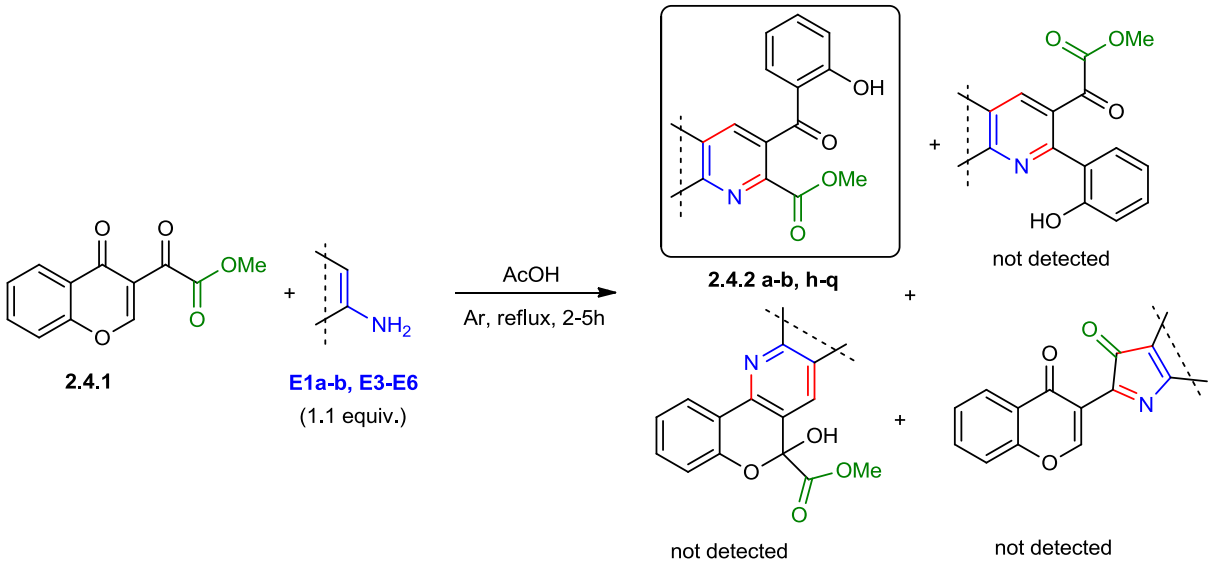
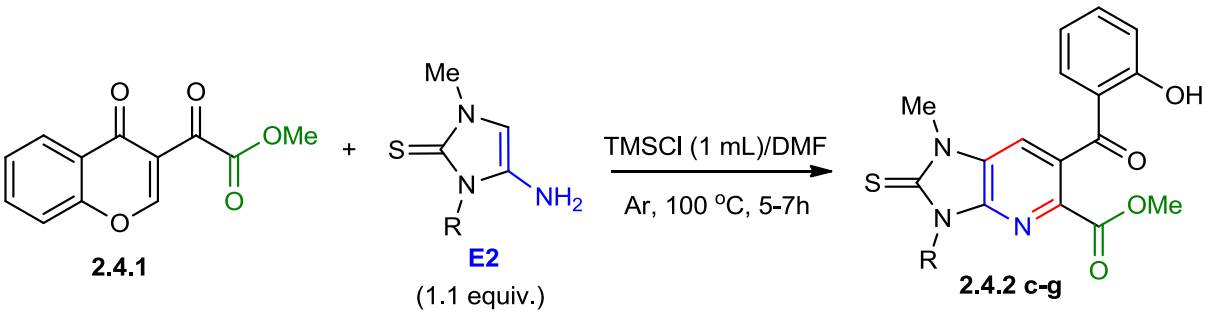


Figure 2.4.2. *Possible reaction centers of 3-methoxyalyl chromone* ***2.4.1.***

Starting chromone **2.4.1** has four electron-deficient centres, i.e. carbon atoms C-2 and C-4 of chromone moiety and two carbonyl groups of $COCO_2Me$ moiety attached to carbon C-3 (Figure 2.4.2). From the analysis of literature it is evident that the majority of previously described reactions of these compounds are nucleophilic additions with concomitant opening of pyrone ring, leading to various heterocyclic compounds. Our goal was to develop a convenient reaction condition for the reaction of **2.4.1** with different electron-excessive aminoheterocycles, with succeeding study of regioselectivity of the method. The sufficient results, which were obtained by the domino cyclocondensation reactions of 3-(dichloroacetyl)chromone **2.3.2** with set of amioheterocycles, have motivated us to use similar conditions also for present investigation. Therefore, a test reaction of **2.4.1** with **E1a** was performed in acetic acid under reflux for 3 h (Scheme 2.4.2). Gratifyingly, starting from initial trials we were successful to obtain the desired fused pyrazolopyridine **2.4.2a** in 57% yield. It is noteworthy that the product was formed with excellent regioselectivity.

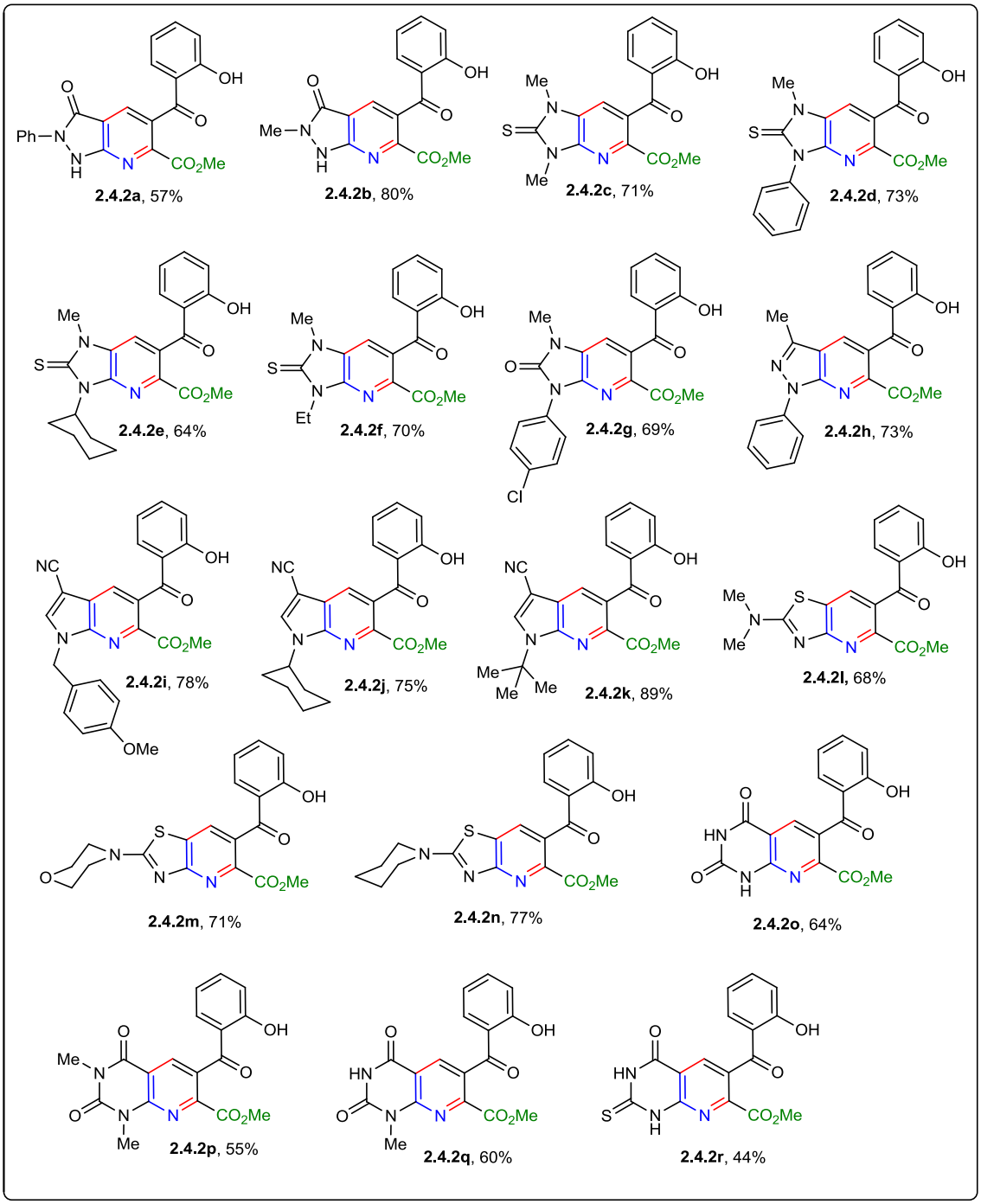


Scheme 2.4.2. *Preparation of α-CO_2Me-substituted fused pyridines* ***2.4.2.***



Scheme 2.4.3. *Preparation of α-CO_2Me-substituted imidazo[4,5-b]pyridine-2(3H)-thiones* ***2.4.2d-g***.

Table 2.4.2. *Synthesised α-CO_2Me-substituted fused pyridines* ***2.4.2***.



Encouraged by these findings, on the next step of our work we tested the scope and limitations of proposed methodology towards various electron-excessive aminoheterocycles and anilines **E2-E8**. Gratifyingly, almost in all cases corresponding fused pyridines **2.4.2** with carboxymethyl group in α-position of pyridine core were prepared in good yields and exclusive regioselectivity (Scheme 2.4.2, Table 2.4.2). However, as it was observed previously (see scheme 2.3.4), the reaction of 3-methoxyalyl chromone **2.4.1** with 4-amino-1*H*-imidazole-2(3*H*)-thione **E2** was not successful in acetic acid. Nevertheless, the alternative reaction condition, namely TMSCl/DMF system was successfully applied for this reaction leading to corresponding imidazo[4,5-*b*]pyridine-2(3*H*)-thiones **2.4.2d-g** with good yields (Table 2.4.2).

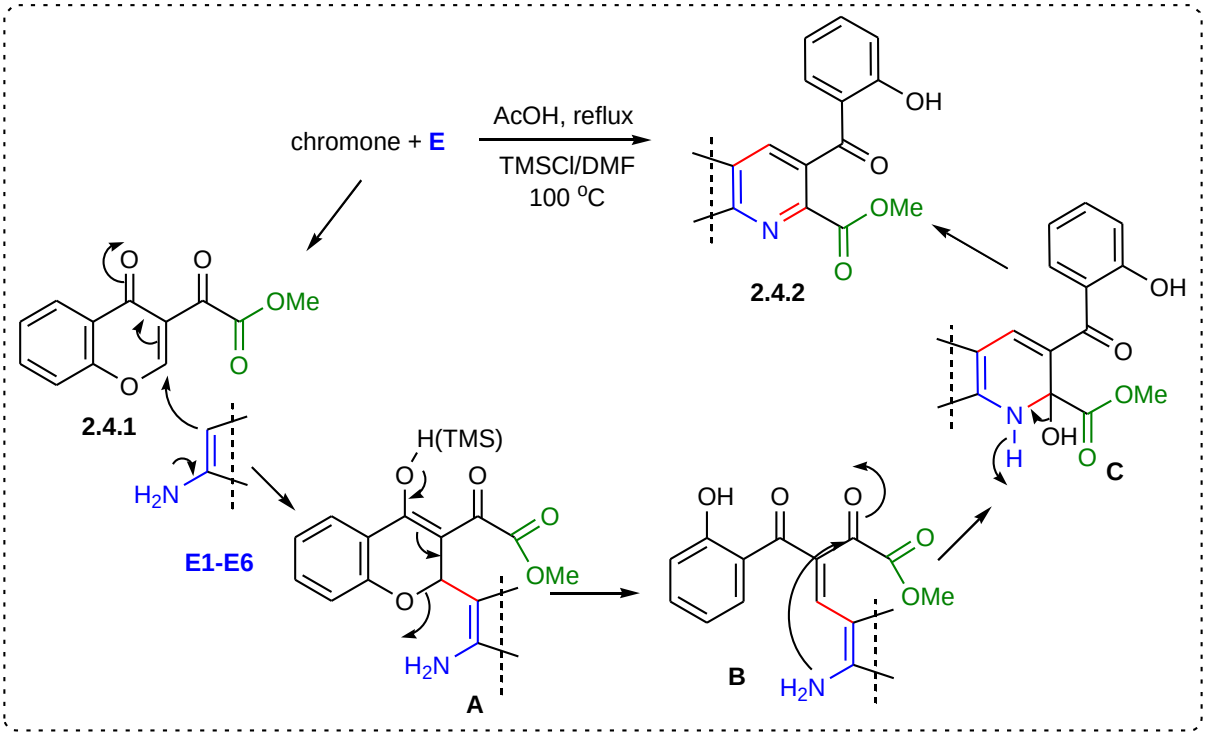
Interestingly, the reactivity of 3-methoxyalyl chromone **2.4.1** toward electron-excessive aminoheterocycles is comparable to those for 3-(dichloroacetyl)chromone **2.3.2**, however the yields of compounds obtained from methoxyalyl chromone were in general lower (see Table 2.4.2).

2.4.4. Unsuccessful results

Unfortunately the reactions of 3-methoxyalyl chromone **2.4.1** with anilines **E7-8, 11, 12** as well as with pyrimidine-2,4,6-triamine **E9** and 5-aminopyrimidine-2,4(1*H*,3*H*)-dione **E10** were not successful. In all cases a complex mixture of many unidentified products in addition to low quantities of two possible regioisomers were formed (detected by HPLC). Our numerous attempts to isolate and separate mentioned products experienced a failure. The reactions were repeated also in DMF/TMSCl system, though without any success.

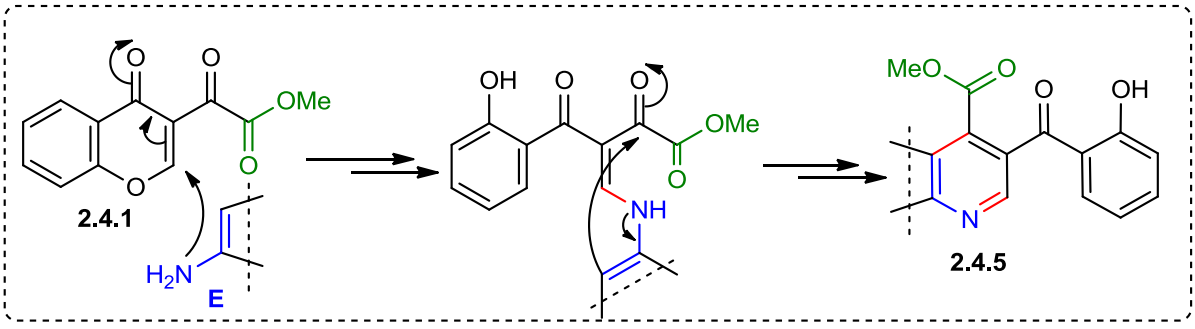
2.4.5. Mechanistic explanation

Since the structure of **2.4.2** is in good correspondence with **2.3.3**, this prompted us to consider that the regioselective formation of annulated α-CO_2Me pyridines **2.4.2** starts with attack of internal enamine-like β-carbon at C-2 atom of the chromone forming intermediate **A** (Scheme 2.4.4). Following pyrone ring opening leads to formation of intermediate **B** (1,4-addition). Afterwards subsequent intramolecular attack of amino group to the first carbonyl group attached at position 3 of pyrone ring, leads to intermediate **C**. Finally, the cleavage of water molecule delivers desired fused pyridine.



Scheme 2.4.4. *Putative mechanism of the reaction.*

During the reaction other products of alternative cyclization of intermediate **A**, involving an attack of amino group to the carbonyl group connected to the benzene ring, were not detected (for some possible by-products see Scheme 2.4.2). All reactions were repeated also in TMSCl/DMF system in order to detect alternative cyclization products. Nevertheless, only expected products were formed similar to those obtained in acetic acid. It is important mentioning, that the product, which could have been formed *via* alternative *N*-nucleophilic attack, was not detected either (Scheme 2.4.5). This was established based on the crystal structure analysis and 2D NMR (see below).

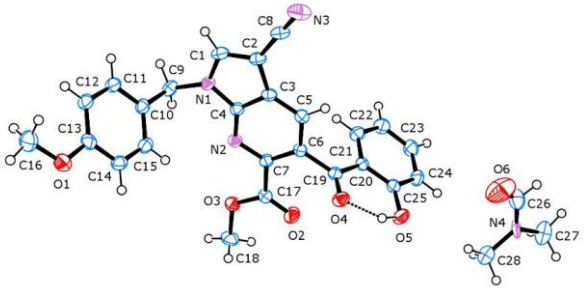
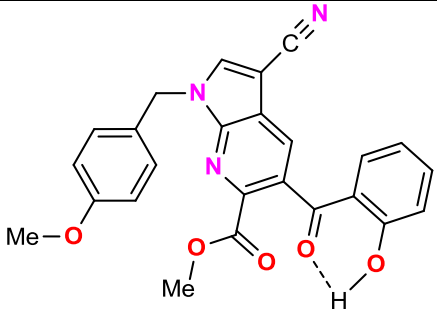
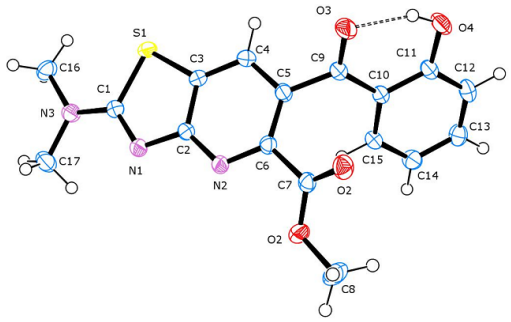
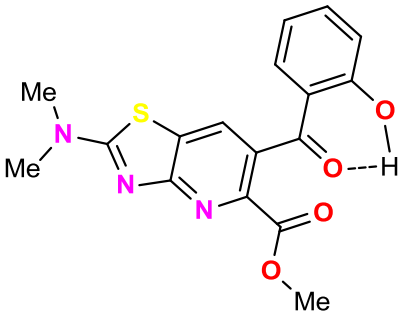


Scheme 2.4.5. *Mechanism of N-nucleophile attack.*

2.4.6. Structure identification

Structures of all obtained compounds were confirmed by ^{1}H and ^{13}C NMR, 2D NMR spectroscopy, IR and mass-spectrometry. Not surprisingly they were similar to earlier synthesized heterocyclic compounds. In ^{1}H NMR spectra a typical singlet of the pyridine γ-position proton was observed at δ 7.88-8.65 ppm in DMSO-d_6. The singlet of COO*Me* moiety was at δ 3.60-3.81 ppm in DMSO-d_6, additionally O*H* singlet appeared at δ 10.66-11.82 ppm in DMSO-d_6. Moreover, all protons of the benzene ring were shifted to higher field. This may be accepted as an evidence for the opening of pyrone ring. In ^{13}C NMR spectra was possible to see the peak of O*Me* at δ 52.1-53.0 ppm. The presence of hydrogen bonding was seen in the IR spectrums as well (O*H*-strech at 3049-3113 cm^{-1}).

Table 2.4.3. *Crystal structure of* ***2.4.2i,l.***

Compound	Crystal	Structure
2.4.2i		
2.4.2l		

The structures of **2.4.2i** and **2.4.2l** were independently confirmed by X-ray crystal structure analysis (Table 2.4.3). The spectral similarities of α-CO_2Me-substituted fused pyridines **2.4.2** with the products obtained in Chapter 2.3 can be considered as an evidence for similar regioselectivity. In the molecule **2.4.2i** was seen the planner structure of indolopyridine system. Obviously, the carbonyl group was perpendicular to the plane of pyridine core, probably to minimise the energy of molecule (the torsion angle for C5-C6-C19-O4 was

91.8°). In contrast to this thiazolo[4,5-*b*]pyridin **2.4.2l** does not have an excellent plannar form, since the sulfur atom was slightly out of the plane of pyridine. Moreover, in this structure the CO_2Me group and the carbonyl group are both out of the plane of pyridine (torsion angles for C6-C5-C9-O3 and C5-C6-C7-O2 are -126.8° and 28.3° respectively). Furthermore, hydrogen bonds between OH group and carbonyl moiety is present in both structures.

We measured also a NOESY spectra for **2.4.2h** in order to examine the possibility of alternative regioselectivity *via N*-nucleophilic attack (Figure 2.4.3). Not surprisingly, only a week correlation between γ-proton of pyridine ring and α-proton of benzoyl moiety with the methyl group of pyrazole ring was detected. The correlation between methyl group and O*Me* of the ester group was not observed. In case of second possible regioisomer corresponding correlation of methyl group from pyrazole ring with the ester moiety in γ-position of pyridine ring would be detected. However no correlation of this type was seen. This can be considered as an additional verification of regioselectivity of the product formed by *C*-nuclophilic attack.

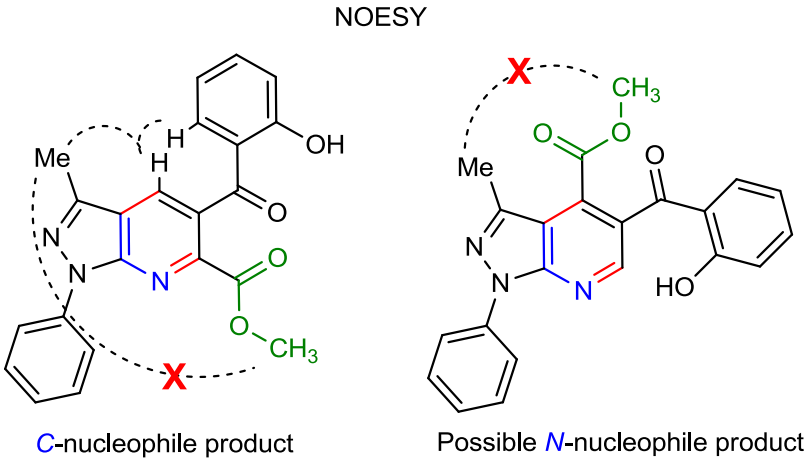
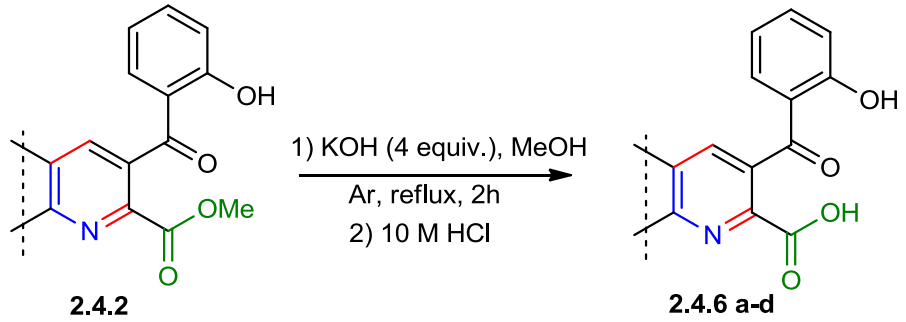


Figure 2.4.3. *The correlations observed in NOESY spectra of compound* ***2.4.2h.***

2.4.7. Further investigations

The next step of our study was the preparation of corresponding carboxylic derivatives of fused pyridines **2.4.6**. As it was mentioned, α-carboxyl-substituted pyridines are of considerable interest.[86]

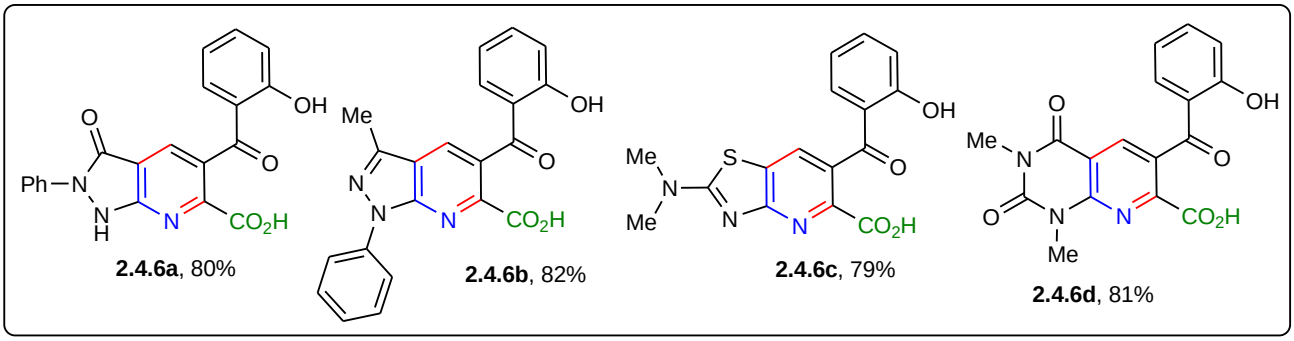
The treatment of corresponding ester derivatives **2.4.2** with KOH in methanol under reflux delivered to desired products **2.4.6a-d** in excellent yields (Scheme 2.4.6).



Scheme 2.4.6. *The hydrolysis reaction α-CO_2Me fused pyridines* ***2.4.6***.

By this method four examples of *α*-CO_2H-substituted fused pyridines **2.4.6** were prepared (Table 2.4.4). The structures of all compounds were identified by NMR spectroscopy. Particularly for all four examples in ^{1}H NMR spectra the singlet of O*Me* group disappeared, instead respective broad peak of COO*H* emerged on 13.71-13.98 ppm in DMSO-d_6.

Table 2.4.4. *List of synthesised α-CO_2H-substituted fused pyridines* ***2.4.6***.



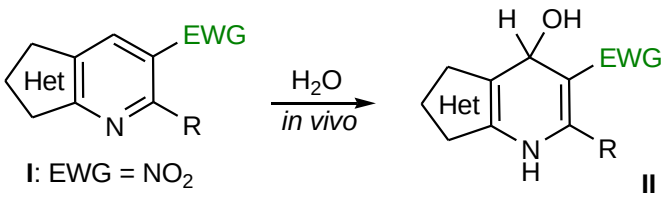
2.4.8. Conclusion

As the conclusion of this chapter should be noted that the synthesis and further transformations of 3-methoxyalylchromone **2.4.1** as masked dielectrophile was reported. We have showcased that 3-methoxyalylchromone **2.4.1** is a novel versatile reagent for the synthesis of fused pyridines - purine isosters bearing *α*-CO_2H substituent. The scope and limitations of the method was examined. Namely cyclocondensation reaction of 3-methoxyalylchromone **2.4.1** with different electron-excessive aminoheterocycles was performed. Corresponding fused pyridines **2.4.2** were prepared in good yields with excellent regioselectivity. For some exemples of **2.4.2** was possible to hydrolyse the ester group to appropriate *α*-CO_2H-substituted fused pyridines **2.4.6**. The possible biological relevance of new compounds is under investigation.

2.5. Synthesis of heteroannulated 3-nitro- and 3-aminopyridines by cyclocondensation of electron-excessive aminoheterocycles with 3-nitrochromone

2.5.1. Introduction

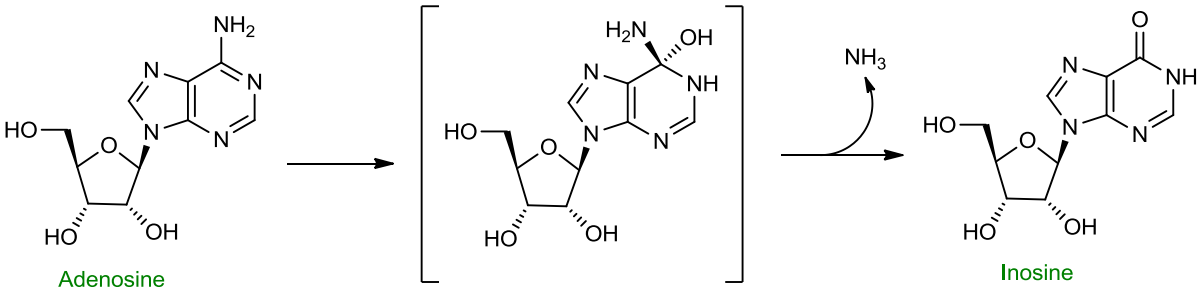
Going on with our study towards the development of new and simple methods for the synthesis of diverse fused pyridines, we switched our attention on purine-like scaffolds containing an electron withdrawing group (EWG) at the *β*-position of the fused pyridine core (Scheme 2.5.1). It is known from the literature that 3-nitropyridines can form a stable Meisenheimer type hydrate **II** at the 4-position.[89] Structures of this type represent promising patterns for the development of potential inhibitors for Adenosine Deaminase (ADA) (Scheme 2.5.1).



I: EWG = NO_2 **II**

Scheme 2.5.1. *The hydrate formation of 3-nitropyridines **I**.*

Adenosine Deaminase (ADA) is a cytosolic enzyme. ADA is an object of considerable interest; first of all, due to the fact that congenital defects of the enzyme in human cells causes severe combined immunodeficiency disease (SCID).[90] Additionally, human ADAR (Adenosine Deaminase that acts on RNA) was specified as one of few unambiguously up-regulated genes in solid tumours and liver cancer.[91] The dysfunction of ADAR was related to cancer progression in mammals. ADA participates in the purine metabolism, particularly it degrades adenosine to produce inosine (Scheme 2.5.2).



Scheme 2.5.2. *Action of ADA.*

Because of its importance for drug design, the mechanism of deamination reaction catalysed by ADAs and ADARs was recently studied in details.[92] Notably, it was found that transition state of inosine production proceeds with a complete pro-*S*-face hydroxyl addition to adenosine in S_NAr transition state (Figure 2.5.1). The formation of tetrahedral Meisenheimer intermediate during deamination reaction was well established and proved (Figure 2.5.1).[92]

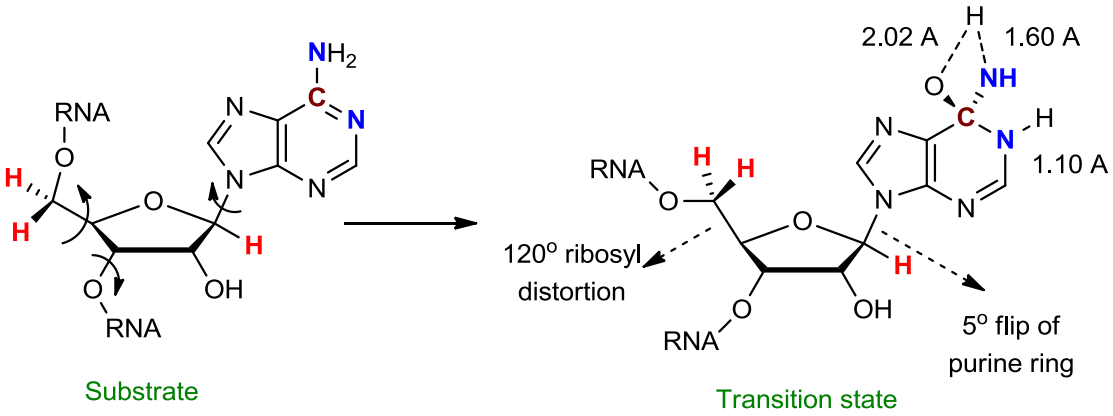


Figure 2.5.1. *Formation of tetrahedral Meisenheimer intermediate.*

Moreover, known potent ADA inhibitors could be summarised into two big groups: 1) purine ribosides or 2'-deoxyribosides, containing the hydrated heterobase, which resembles the putative transition state (e.g. well known commercially available anticancer drugs conformicin and pentostatin);[93] 2) (+)-EHNA (erythro-9-(2-hydroxy-3-nonyl)adenine) and related compounds.[94] The main disadvantage of these compounds is the fact that they are prone to be rapidly metabolized,[95] which results in shorter duration of the action allowing faster recovery of enzymatic activity. Noteworthy, recently were reported some other highly potent non-nucleoside ADA inhibitors[96], for instance 6-aminocarbovir[97] (Figure 2.5.2).

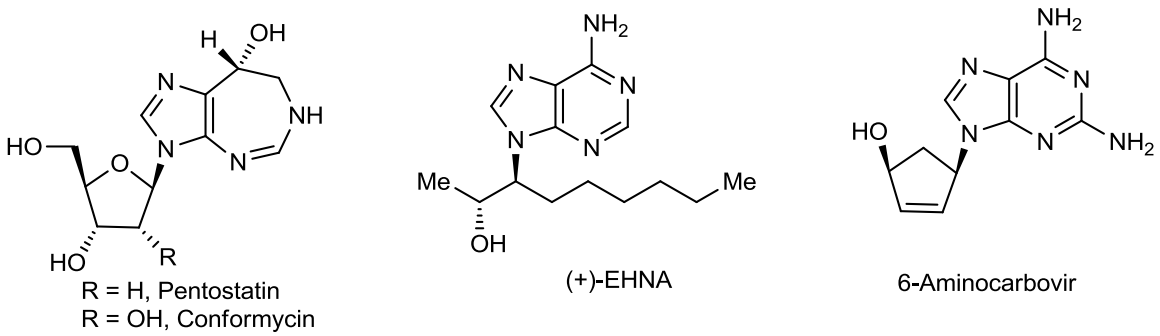
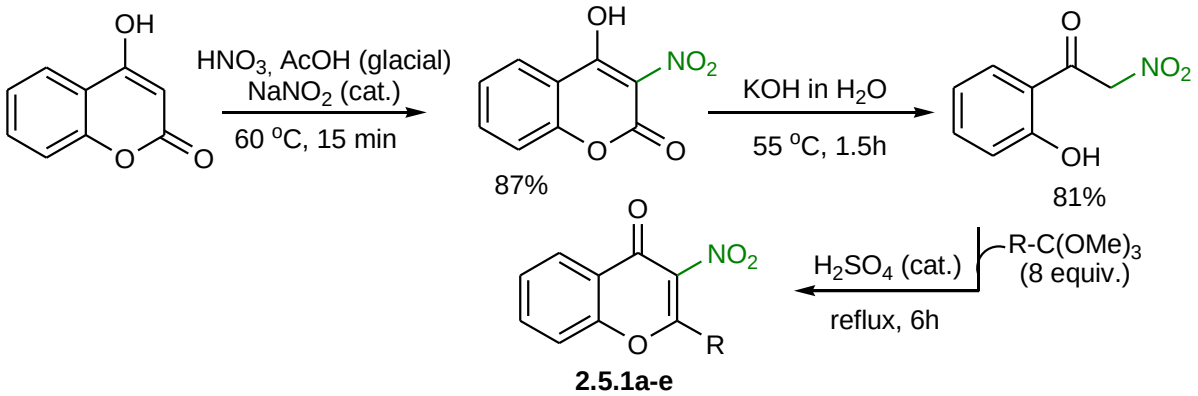


Figure 2.5.2. *Potential ADA inhibitors.*

According to the importance of ADA inhibitors in cancer research, we were interested in elaboration of principally new synthetic strategy giving possibility to prepare diverse libraries of bicyclic fused pyridines with nitro or amino group at the *β*-position. In principle they can also form a hydrate intermediate being a promising scaffolds towards the development of ADA transition state mimetics.

2.5.2. Synthesis of starting materials

Based on the retrosynthetic analysis and our previous results on development of new cyclocondensation reactions of chromones, we envisaged that 3-nitro(thio)chromones can be suitable starting dielectrophiles for the synthesis of heteroannulated 3-nitropyridines.



Scheme 2.5.3. *Preparation of 3-nitrochromones* ***2.5.1*** *from 4-hydroxycumarin; for R see Table 2.5.1.*

There are only two methods available in the literature describing the synthesis of 2-unsubstituted 3-nitrochromones. The simplest represents a four step process, starting from 4-hydroxycoumarin.[98] Notably, in some cases it was possible to prepare 3-nitrochromone by

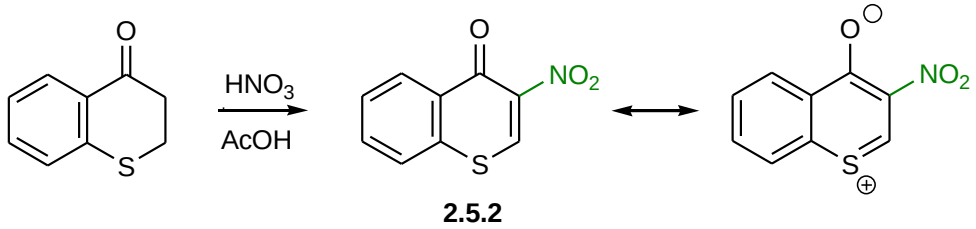
direct nitration of corresponding 3-hydroxymethyl- or 3-formylchromones.[99] However, in this work the first method was used with some alternations in order to prepare 2-unsubstituted and 2-substituted 3-nitrochomones.

The nitration of 4-hydroxycoumarin was carried out in the mixture of glacial acetic acid and 65% nitric acid, using catalytic amounts of sodium nitrite (Scheme 2.5.3). The following hydrolysis of 4-hydroxy-3-nitrocoumarin proceeds in aqueous solution of KOH at 55 °C for 90 min. Subsequently the neutralization was done with 1.3 equivalents of acetic acid in ice bath (instead of HCl used in initial report). In this conditions 2'-hydroxy-2-nitroacetophenone was formed with up to 81% yield. Noteworthy, in strong acidic conditions the nitro group can be hydrolyzed to an aldehyde. Another optimization was the use of orthoesters (previously carboxylic acid anhydrides were used in the reaction) in the presence of sulphuric acid in order to obtain 3-nitrochromones **2.5.1** with improved yields. Applied changes were especially useful for R = H, since in this case formic anhydride was necessary as substrate. Thus we were able to prepare five different 3-nitrochromones **2.5.1** in 82-88 % yields (Table 2.5.1).

Table 2.5.1. *List of synthesised 3-nitrochromones **2.5.1***.

2.5.1	R	Reaction time of last step (h)	Yields (%)
a	H	6	82
b	Me	3	84
c	Et	4	83
d	Ph	5	88
e	*p*-Tol	5	85

It should be noticed that compounds **2.5.1d** and **2.5.1e** were also possible to synthesise by nitration of appropriate flavones, using ammonium nitrate and trifluoroacetic anhydride.[100] In order to study the scope and limitations of the method 3-nitrothiochromone **2.5.2** was prepared as well, as a thio- analogue of nitrochromones **2.5.1**. The later can be obtained by nitration of thiochroman-4-one with 65% nitric acid in acetic acid (Scheme 2.5.4).[101]



Scheme 2.5.4. *Preparation of 3-nitrothiochromone* ***2.5.2***.

Finally, it was not possible to prepare 3-nitro-2-(trifluoromethyl)chromone and methyl 3-nitrochromone-2-carboxylate using the reaction of 2'-hydroxy-2-nitroacetophenone with trifluoroacetic anhydride and methyl 2-chloro-2-oxoacetate respectively.

2.4.3. Results and discussions

3-Nitrochromone **2.5.1** is a type of masked 1,3-dielectrophile as well, so it can be an interesting starting material toward binucleophiles (Figure 2.5.3). To date only few works are known in the literature describing the reaction of 3-nitrochromone **2.5.1** with amines, benzamidine, phenylhydrazine,[102] amidines, guanidine, acid hydrazides, *S*-methylisothiourea and hydroxylamine.[103] In addition, recently one of our colleagues have prepared a range of 1-substituted 6-nitro-3*H*-imidazo[4,5-*b*]pyridines starting from 1-substituted 5-amino-1*H*-imidazoles generated *in situ*.[104]

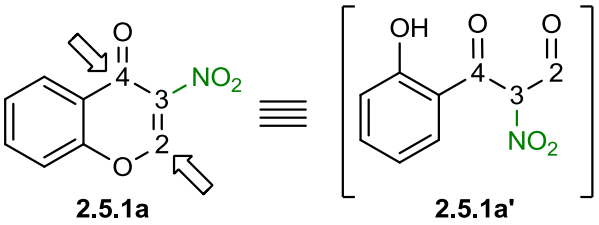
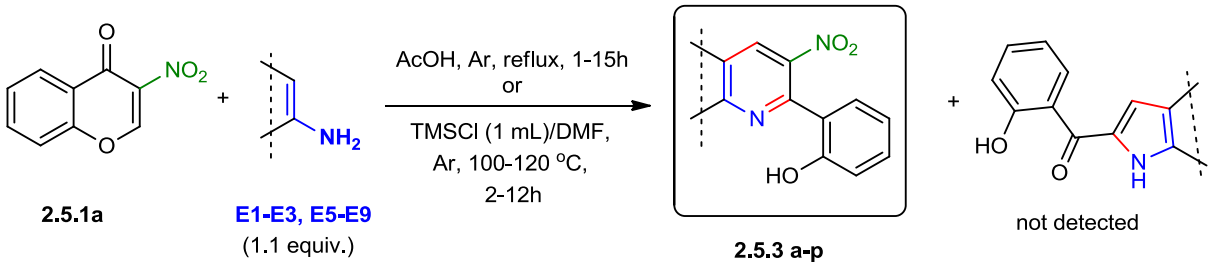


Figure 2.5.3. *3-Nitrochromone* ***2.5.1*** *as 1,3-dielectrophile.*

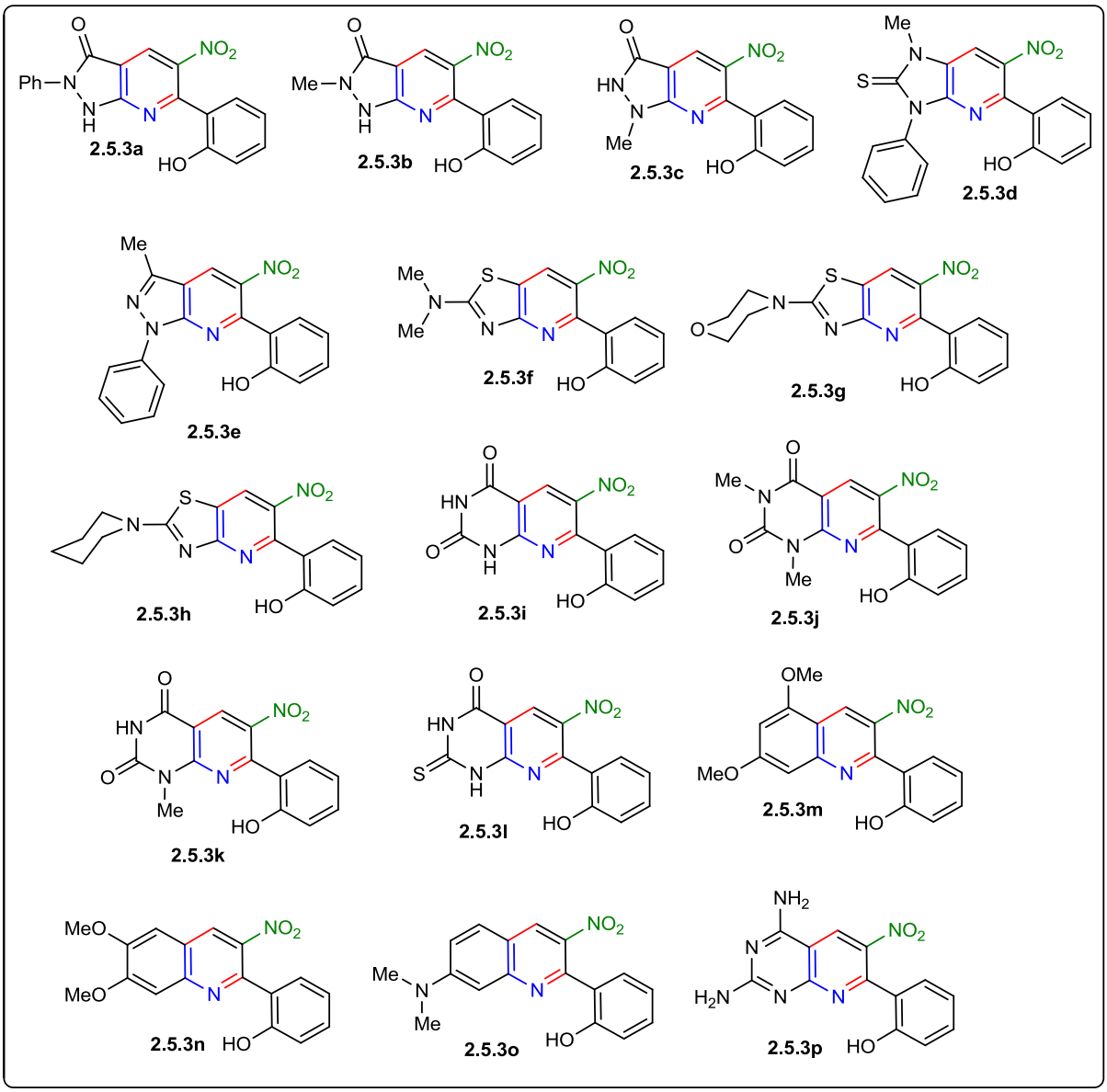
Analogically to other chromones described above the domino reaction should be started with nucleophilic attack onto the position 2 with subsequent pyrone ring opening that can be followed by a cyclization with the second electrophilic centre. Using the general procedures developed in the last two chapters (see Chapter 2.2, 2.3), the test reaction of the 2-unsubstituted chromone **2.5.1a** with **E1** proved to be successful, corresponding fused pyridine **2.5.3a** was isolated in 98% yields. We got the product with excellent regioselectivity; the other possible isomer that can be formed by nucleophilic substitution of nitro group was not

detected.



Scheme 2.5.5. *Preparation of library of 3-nitro-substituted fused pyridines* ***2.5.3****.*

Table 2.5.2. *List of obtained compounds* ***2.5.3*** *(see the yields in Table 2.5.3).*



Following the initial sufficient results, a set of other aminoheterocycles **E1-E9** were tested.

Fortunately, corresponding 3-nitro-substituted fused pyridines **2.5.3a-p** were successfully prepared in 62-98% yields (Scheme 2.5.5). It is worth mentioning that all reactions proceed with an excellent regioselectivity, in all cases only one product was formed. Besides, since 3-nitrochromone **2.5.1a** has only two electrophilic carbonyl centres, the regioselectivity in this case is different from the regioselectivity of two previously discussed chromones (see Chapter 2.5.6). Additionally, the isolation of products was quite easy, as long as in most cases after completion of the reaction (TLC control) precipitation of the product occurred, therefore a simple filtration and washing was enough to get pure products (Table 2.5.2).

Like encountered in previous chapters the 4-amino-1*H*-imidazole-2(3*H*)-thione **E2** as well as 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one **E9** were not stable in acetic acid, therefore corresponding products were prepared using the alternative reaction conditions (TMSCl/DMF), the yields were 95% and 65% respectively. In this context we were interested in comparison of 3-nitrochromones reactivity **2.5.1a** towards aminoheterocycles **E1**-**E9** in both conditions. For this reason the same reaction was runned in both conditions for majority of aminoheterocycles. One can see that in acetic acid reaction yields are higher, although in some cases the starting materials were not stable (**E2**, **E9**, Entry **d**,**p,** Table 2.5.3), or mixture of inseparable compounds (for instance in case of anilines) were formed (Entry **m-o**, Table 2.5.3). Alternative methodology (TMSCl/DMF) was effective for all aminoheterocycles, though in some cases the duration of reactions was increased. For more active aminoheterocycles (Entry **a**,**b**,**e,** Table 2.5.3) the yields were comparable to those for Method A. Additionally, in TMSCl/DMF system the reaction with anilines emerged with good 62-91% yields (Entry **m-p,** Table 2.5.3). Thereby these methods are complement to each other, thus together they offer an easy and comfortable route for preparing various types of hetero(carbo)annulated pyridines with NO_2 group located at the β-position of pyridine core.

Table 2.5.3. *Method A (Acetic acid, reflux), Method B (TMSCl/DMF, 100 °C, 140 °C for **2.5.3n**).*

2.5.3	Method *A*	T (h)	Method *B*	T (h)	**2.5.3**	Method *A*	T (h)	Method *B*	T (h)
a	98	5	77	5	**i**	84	2	40	2
b	87	2	63	2	**j**	97	4	44	4
c	78	4	54	4	**k**	73	6	32	6
d	Mix	2	95	10	**l**	79	3	35	3
e	97	1	88	1	**m**	Mix	2	62	18
f	65	4	43	4	**n**	Mix	2	83	2

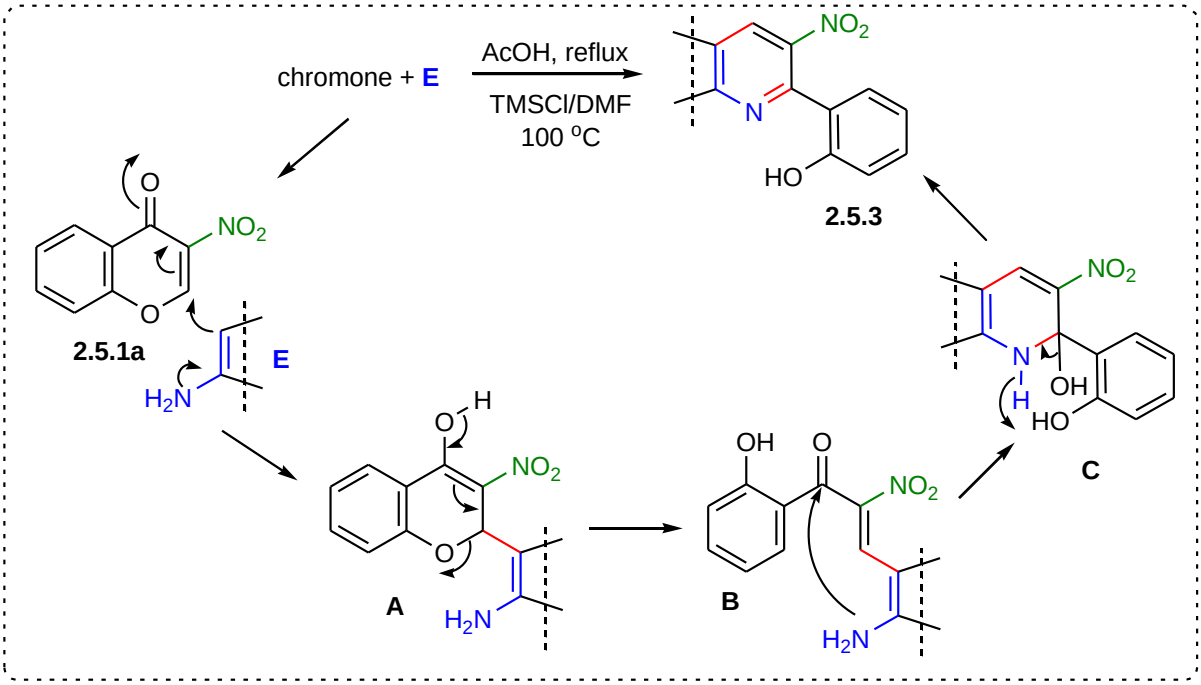
g	90	1	44	1	**o**	Mix	2	91	10
h	71	15	32	15	**p**	Mix	2	65	4

2.5.4 Unsuccessful results

Having successful results with the range of aminoheterocycles **E1-E9**, next we tried to apply this methodology for 2-methyl-, 2-ethyl-3-nitrochromones **2.5.1b,c** and 3-nitroflavones **2.5.1d,e**. Unfortunately, all trials to perform a domino cyclocondensation between 2-substituted chromones and aminoheterocycles failed, only starting materials were recovered (by Method A and B). For some examples the reaction gave multicomponent mixtures, from which we could not isolated any fused pyridines. We supposed that cyclocondensation reaction of 3-nitrochromones **2.5.1** with electron-excessive aminoherecycles is rather sensitive to the nature of the substituent at the C-2 atom, hereby in order to obtain pyridines it is necessary to use chromones without any substitution at position 2. This can be a result of steric and conjugation factors. Furthermore, the reaction of 3-nitrothiochromone **2.5.2** with amines was also ineffective and only starting thiochromone was recovered from the reaction mixture. The reaction was carried out in standard conditions developed as well as under harsher conditions (dimethylacetamide, TMSCl, 170 °C), however no product was observed. This can be explained with the thought that 3-nitrothiochromone **2.5.2** is much less reactive than 3-nitrochromone **2.5.1**. The differences in reactivity between **2.5.1** and **2.5.2** may be connected with the difficulties met by the nucleophile in attacking position 2 of thiopyrone, since the sulphur atom is less electronegative therefore the electrophilicity of the C-2 is strongly reduces. Therewith, it was shown before that the aromaticity of thiochromone system is much higher than in simple chromones.[105]

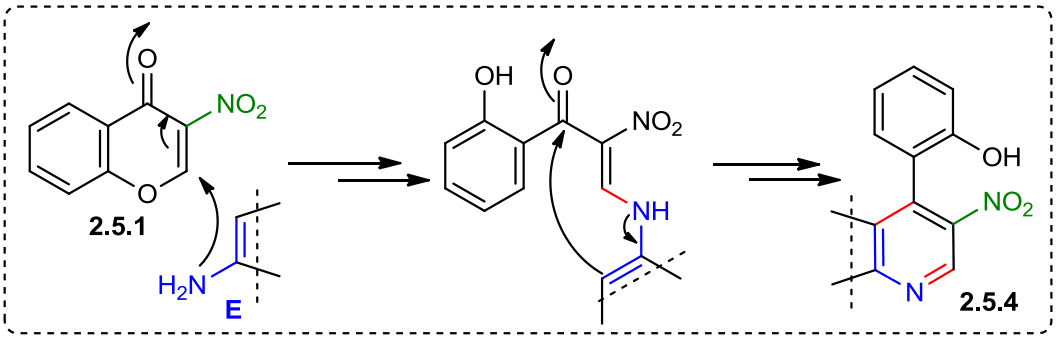
2.4.5 Mechanistic explanation

Likely the condensation reaction proceeds very similar two previous chromones. We believe that the reaction starts by conjugate addition of enamine-like carbon atom of **E** onto the 2nd position of **2.5.1a** to give intermediate **A**. Afterwards the pyrone ring opening takes place delivering intermediate **B** (Scheme 2.5.6).



Scheme 2.5.6. *Putative mechanism of the cyclocondensation reation.*

Following intramolecular attack of amino group onto the carbonyl group affords intermediate **C**, later on the elimination of water molecule gives corresponding fused pyridines **2.5.3** with nitro group at the *β*-position.



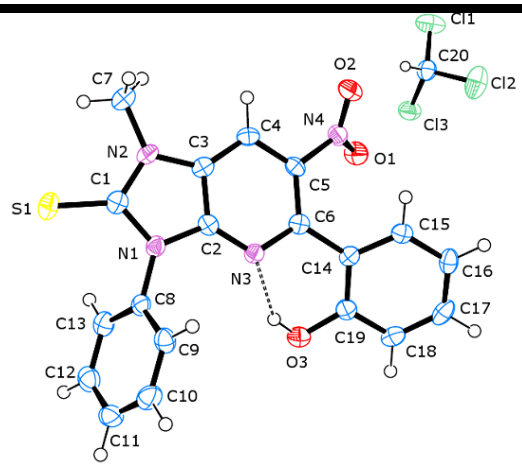
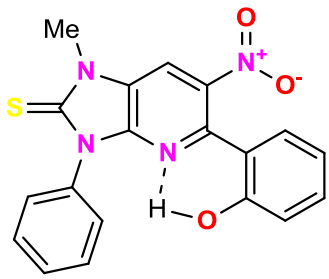
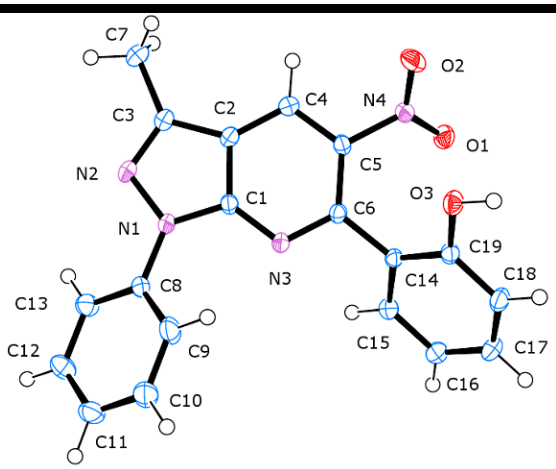
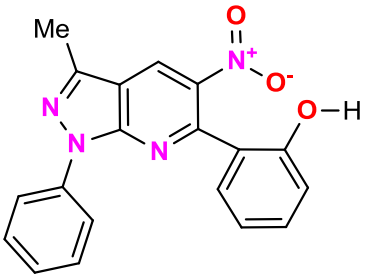
Scheme 2.5.7. *Putative formation of the product by N-nucleophile attack.*

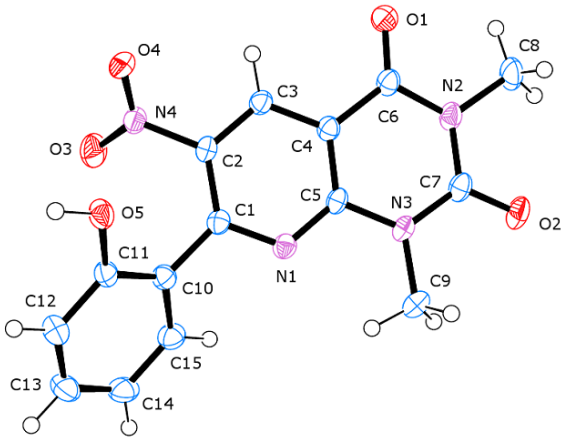
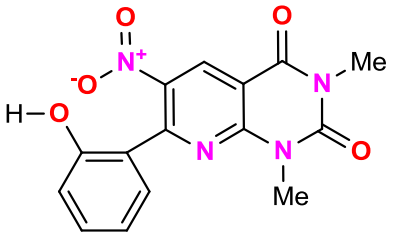
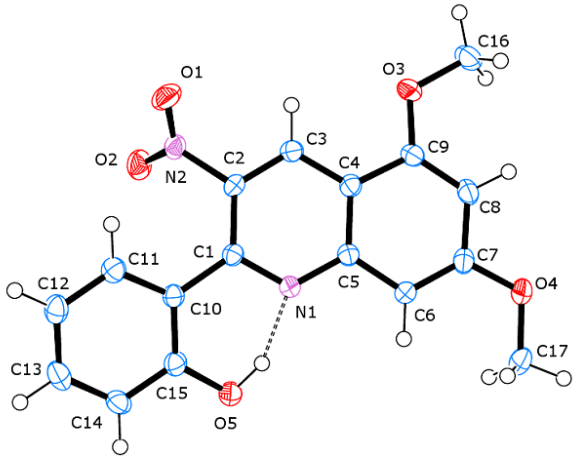
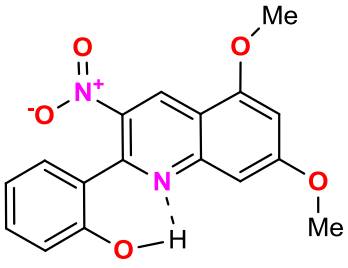
In fact we conducted all reactions using both methods (Method A and B); interestingly in all cases we got the same regioisomer so we were interested to detect any type of intermediate or alternative product, for instance product of *N*-nucleophile attack of the enamine-like moiety **2.5.4** (Scheme 2.5.7). However, product of this type or any others were not detected (see next chapter). This fact makes our proposed method a versatile approach towards the regioselective synthesis of 3-nitro-substituted fused pyridines.

2.5.6. Structure identification

All structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy, as well as IR and mass-spectrometry. In all cases obtained products were similar to the formerly prepared fused pyridines. In ^{1}H NMR spectra the typical singlet of pyridine proton was observed at δ 8.15-9.13 ppm in DMSO-d_6 (7.93-8.82 ppm in $CDCl_3$). In addition a broad O*H* singlet appeared at δ 9.84-10.41 ppm in DMSO-d_6 (8.50-11.7 ppm in $CDCl_3$). A slight interaction (hydrogen bond) was detected between O*H* and the nitrogen of pyridine, although not for all cases. Moreover, the protons of benzene appear in higher field proving the opening of pyrone ring.

Table 2.5.4. *Crystal structure of* ***2.5.3d,e,j,m.***

Compound	Crystal	Structure
2.5.3d		
2.5.3e		

2.5.3j		
2.5.3m		

The structures of **2.5.3d,e,j,m** were independently confirmed by X-ray crystal structure analysis (Table 2.5.4). In all structures appears planar structure of fused pyridine core. Moreover, in all cases the *N*-atom of NO_2 group is almost in the same plane with fused pyridine core, though oxygens were perpendicular to the pyridine surface (in **d** the torsion angle H4-C4-C5-N4 is 38.76^{o}). Since the α-hydroxyphenyl group in the fused pyridine is in free rotation, in some cases the OH group can be on the side of nitrogen atom (**2.5.3d** and **m**), in other cases the OH group is turned towards the opposite side (**2.5.3e** and **j**). Furthermore, the hydrogen bonds were observed in the first type of structures (**2.5.3d** and **m**).

The structural identification of the rest of fused pyridines was based on the date obtained from crystal structures. It is worth mentioning that all structures are in correspondence to the mode of proposed general mechanism. The product of *N*-nucleophile cyclocondensation was not observed.

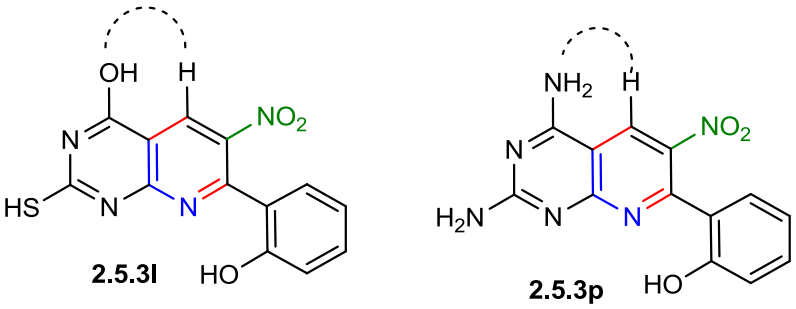
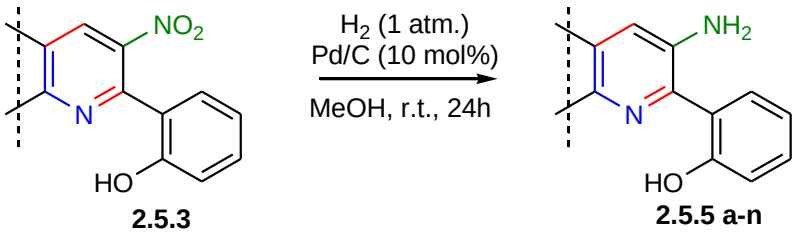


Figure 2.5.4. *NOESY analysis of compounds **2.5.3l** and **p**.*

In addition to this argument the NOESY analysis shows a week interaction between pyridine γ-H with OH and NH_2 in the structures of **2.5.3l** and **2.5.3p** respectively. This is an additional evidence for proposed regioselectivity (Figure 2.5.4).

2.4.7. Further investigations

Having access to the fused 3-nitropyridines **2.5.3** and due to the biological importance of 3-aminopyridine derivatives, we studied their synthesis by hydrogenation of fused 3-nitropyridines **2.5.3** using Pd/C (10 mol%) in MeOH. We found that the reaction proceeds with excellent yields leading to appropriate 3-amino-substituted fused pyridines **2.5.5** (Scheme 2.5.8).

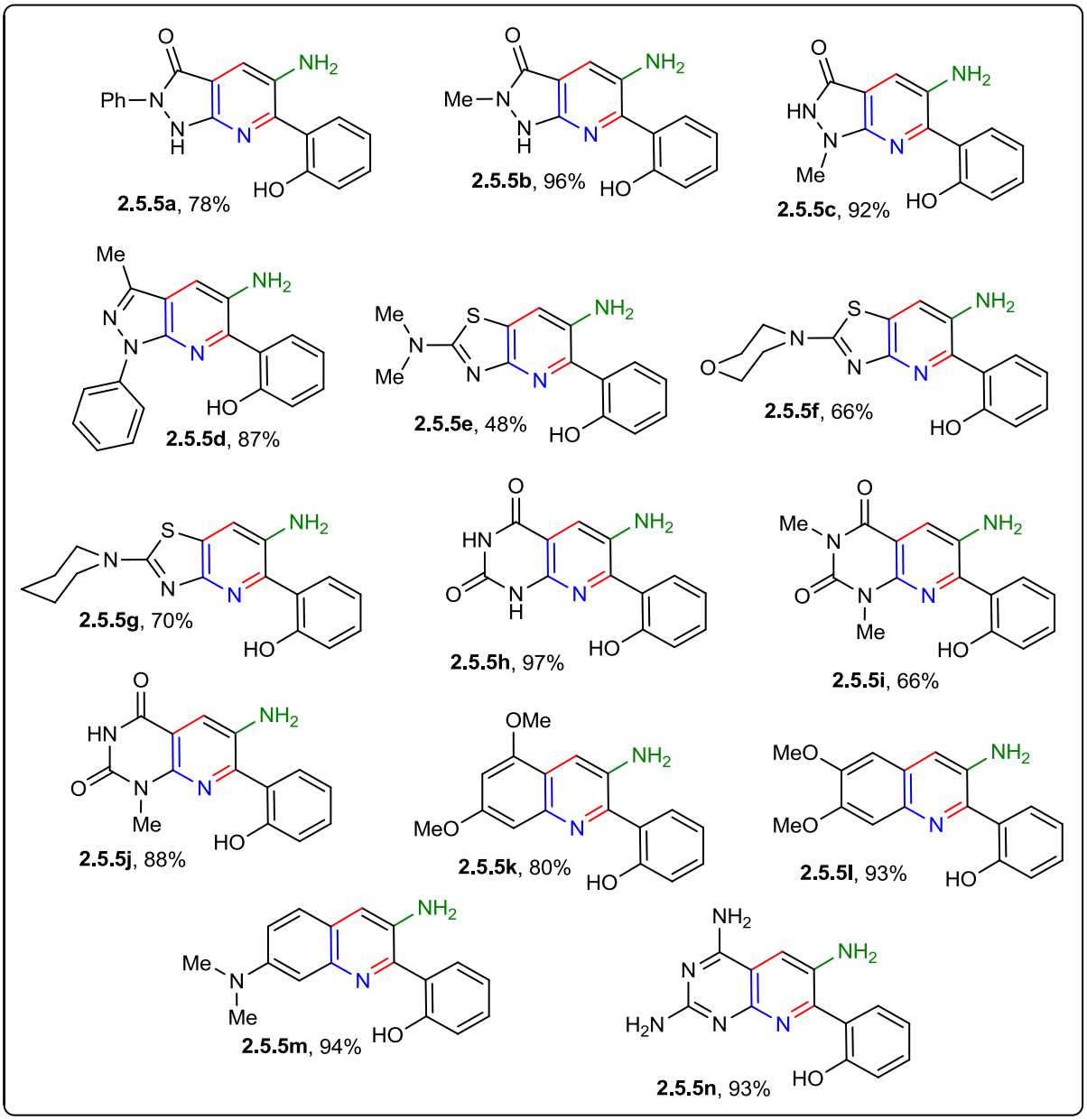


Scheme 2.5.8. *Hydration of the 3-nitropyridines **2.5.3**.*

The structures of corresponding products were established by ^{1}H NMR spectroscopy. In all spectras a large singlet of N*H*$_2$ appears at δ 4.00-6.00 ppm in DMSO-d_6. Furthermore, in IR spectrums appears a broad signal at 3392-3226 cm^{-1} that also corresponds to NH_2 group (Table 2.5.5).

The reduction of compounds **2.5.3d** and **2.5.3l** was not effective, this can be explained by the property of sulphur atom to poison the Pd-catalyst. Obtained products can be used further to prepare novel 3-unsubstituted pyridines by using of synthetic combinatorial means.

Table 2.5.5. *Prepared 3-aminopyridines* ***2.5.5***.



2.5.8. Conclusion

In conclusion of this chapter should be mentioned that the regioselective cyclocondensation reaction of 3-nitrochromone **2.5.1a** and electron-excessive aminoheterocycles **2.1** was studied in detail. Corresponding fused 3-nitropyrdines **2.5.3** and 3-aminopyridines **2.5.5** were prepared in good to excellent yields. The scope and limitations of the method towards 2-substituted 3-nitrochromones **2.5.1b-e** and aminoheterocycles **2.1** was well investigated. The presence of NO_2 group gave a possibility to perform further operations, namely appropriate aminopyridines were synthesised by simple hydration. All prepared compounds can be

biologically active, thus the biological evaluation of these compounds is currently in study.

2.6. 2,3-Unsubstituted chromones as versatile reagents for the synthesis of fused pyridines

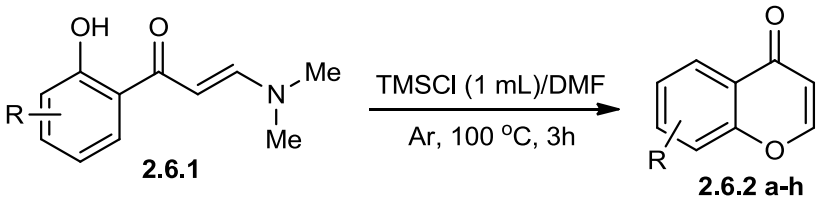
2.6.1. Introduction

The proposed methods in Chapters 2.3, 2.4, 2.5 allowed us to synthesise a variety of fused pyridines and quinolines bearing different functional groups such as $CHCl_2$ and CHO (Chapter 2.3), COOMe and COOH (Chapter 2.4), NO_2 and NH_2 (Chapter 2.5). In described procedures were applied cheap and easily available starting materials. The next step of the present work was the preparation of α-aryl and/or hetreoaryl-substituted fused pyridine derivatives. This type of compounds is of special interest, since they can be considered as purine isosteres. Such compounds are widely used in medicinal chemistry, in the engineering of drug-like scaffolds.[106]

According to the retrosynthetic analysis and our previous experience we have assumed that 2,3-unsubstituted chromones could be an ideal starting materials for preparation of β,γ-unsubstituted fused pyridines. It is worth mentioning that to date there are only few papers presenting the reactivity of 2,3-unsubstituted chromones towards binucleophiles. This can be explained by the low reactivity of this type of chromones in comparison to similar structures having an EWG at the position 3. In this chapter the properties of different 2,3-unsubstituted chromones towards electron-excessive aminoheterocycles and aromatic amines will be discussed.

2.6.2. Synthesis of starting materials

According to the literature data 2,3-unsubstituted chromones **2.6.2a-h** can be prepared in 2 steps starting from *o*-hydroxyacetophenone. The first step is the preparation of (*E*)-3-(dimethylamino)-1-(2-hydroxyaryl)prop-2-en-1-ones **2.6.1** by reaction of *o*-hydroxyacetophenones with DMFDMA (*N*,*N*-dimethylformamide dimethyl acetal).[107] On the second step subsequent treatment of (*E*)-3-(dimethylamino)-1-(2-hydroxyaryl)prop-2-en-1-ones **2.6.1** with perchloric acid leads to chromone ring formation. Nevertheless, we have found that corresponding chromones can be easily prepared starting from **2.6.1** in TMSCl/DMF system at 100 ^{o}C under argon atmosphere (Scheme 2.6.1).



Scheme 2.6.1. *Preparation of 2,3-unsubstituted chromones **2.6.2**.*

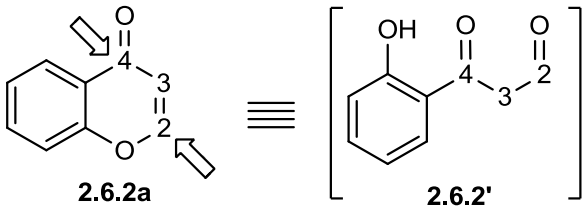
Proposed methodology allowed us to prepare desired 2,3-unsubstituted chromone derivatives in almost quantitative yields (90-97%). Following this procedure eight examples of different 2,3-unsubstituted chromones **2.6.2** were synthesized, however only first five chromones were tested during the next studies (Table 2.6.1).

Table 2.6.1. *List of prepared chromones **2.6.2**.*

2.6.2	R	Yields (%)
a	H	93
b	6-Me	97
c	6-Br	94
d	6-Cl	97
e	7,8-Benzo	90
f	6-OMe	95
g	6-Cl-7-Me	95
h	7-OMe	94

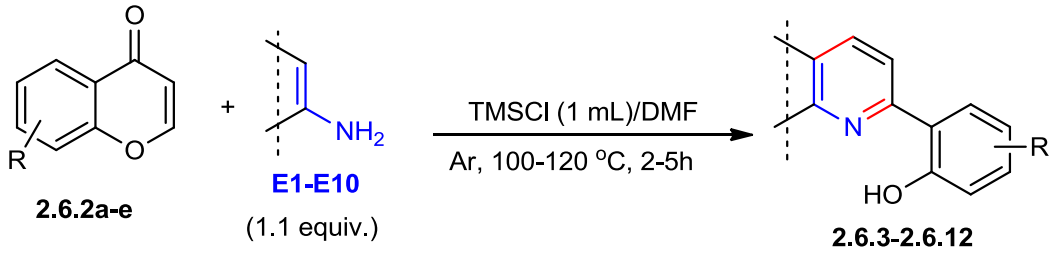
2.6.3. Results and discussions

2,3-Unsubstituted chromones can be considered as 1,3-*CCC*-dielecrophiles possessing a masked 1,3-dicarbonyl fragment in the structure (Scheme 2.6.2). Actually 2,3-unsubstituted chromones appeared to be less reactive in comparison to the other representatives. So far only few reactiones with pyrone ring opening of 2,3-unsubstituted chromones are known, for instance, the reaction with dimethyl acetonedicarboxylate[108] or *N*-iminopyrimidine ylide.[109] Recently, in our laboratory TMSOTf mediated reaction of 2,3-unsubstituted chromones with 1,3-bissilyl enol ethers were investigated, as a result number of functionalized 6*H*-benzo[*c*]chromen-6-one derivatives were synthesized.[110] In all cases the reaction proceeded by nucleophilic 1,4-addition, that was accompanied by pyrone ring opening.



Scheme 2.6.2. *2,3-Unsubstituted chromones as 1,3-dielectrophile.*

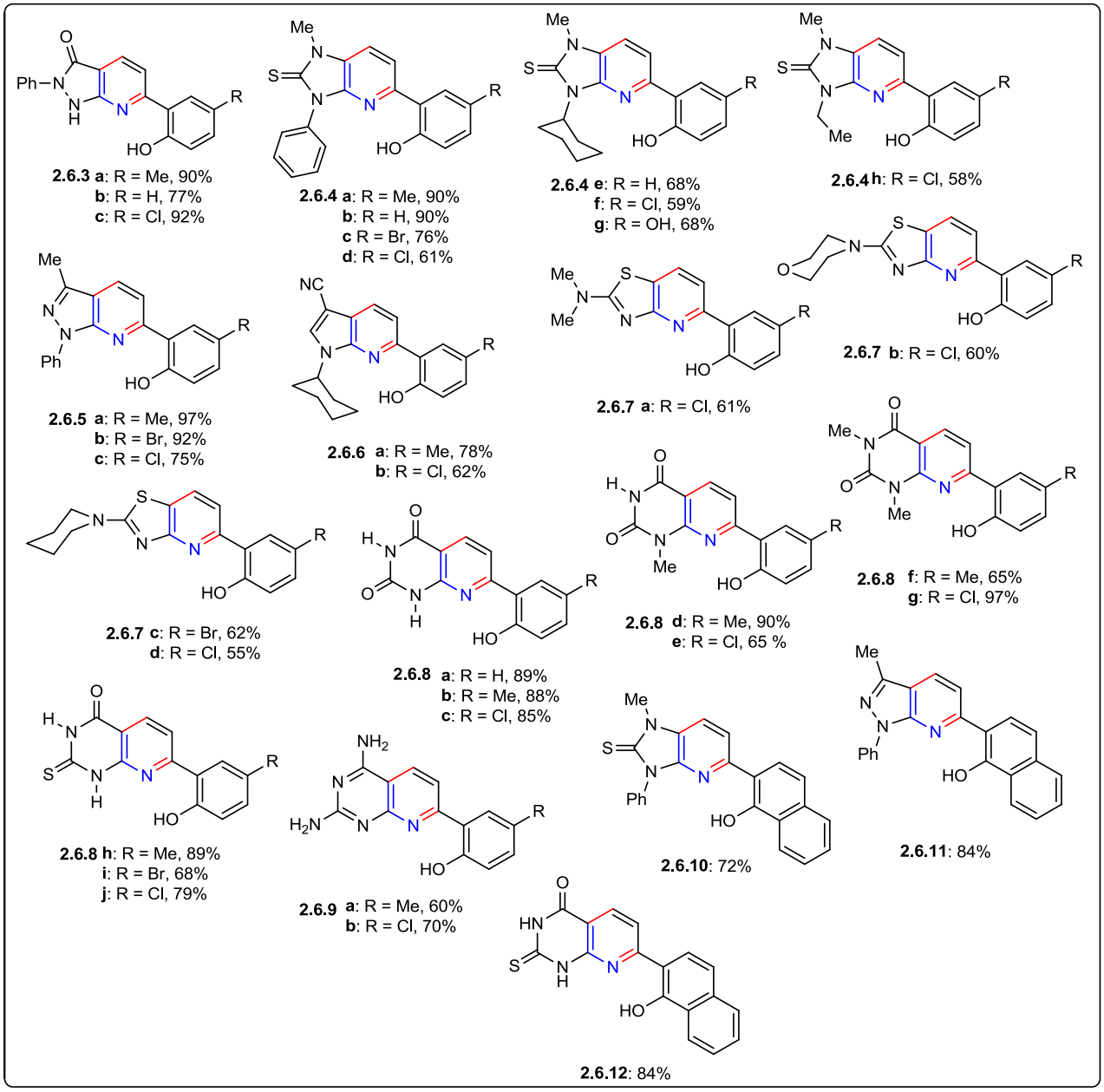
Continuing our research program dedicated to the design and synthesis of novel fused pyridines, the reaction of 2,3-unsubstituted chromones with set of electron-excessive aminoheterocycles was examined. The initial experiments of **2.6.2a** with **E1** were carried out in AcOH under reflux, but unfortunately the desired product was not detected. However, when the alternative reaction condition was used (TMSCl/DMF system), luckily we could isolate corresponding 2-phenylpyrazolo[3,4-*b*]pyridin-3-one **2.6.3a** in 90% yield (Scheme 2.6.3).



Scheme 2.6.3. *Synthesis of β,γ-unsubstituted fused pyridines* ***2.6.3-2.6.12***.

Having primary successful results in hand the scope and limitations of the reaction was studied. Initial chromones **2.6.2a-e** were reacted with a set of electron-excessive aminoheterocycles and anilines **E1-E10**. As a result a number of *β,γ*-unsubstituted fused pyridines **2.6.3-2.6.12** were prepared in good yields (Table 2.6.2).

Table 2.6.2. *List of synthesised β,γ-unsubstituted fused pyridines* ***2.6.3-2.6.12***.



Encouraged with successful results we have considered (*E*)-3-(dimethylamino)-1-(2-hydroxyaryl)prop-2-en-1-one **2.6.1** to be a starting material for the synthesis of *β,γ*-unsubstituted fused pyridines. As it was shown in the chapter preparation of 2,3-unsubstituted chromones **2.6.2** and further cyclocondensation with aminheterocycles runs at similar conditions (Scheme 2.6.1, 2.6.2). In this context we were interested in shortening the process by skipping one step. Therefore, we tried to start the cyclization reaction from enaminones **2.6.1**, keeping in mind the possibility to synthesize corresponding chromone *in situ*. As a model the reaction of enaminone **2.6.1a** with electron-excessive aminoheterocycle **E1a** was chosen (Figure 2.6.1). The state and direction of the reaction in the period of full conversion

of reactants was controlled by TLC (Heptane : Ethyl acetate 1:2). In the first TLC one can see starting materials (**2.6.1a** and **E1a)**, corresponding chromone **2.6.2a** along with the reaction mixture in the beginning of reaction (Figure 2.6.1). Half an hour later the second TLC showed an interesting picture, namely the spot of **2.6.1a** vanished and a spot similar to chromone **2.6.2a** in addition to a spot corresponding to fused pyridine appeared. After 3 hours third TLC showed full conversion of staring materials with a spot corresponding to the product **2.6.3a**.

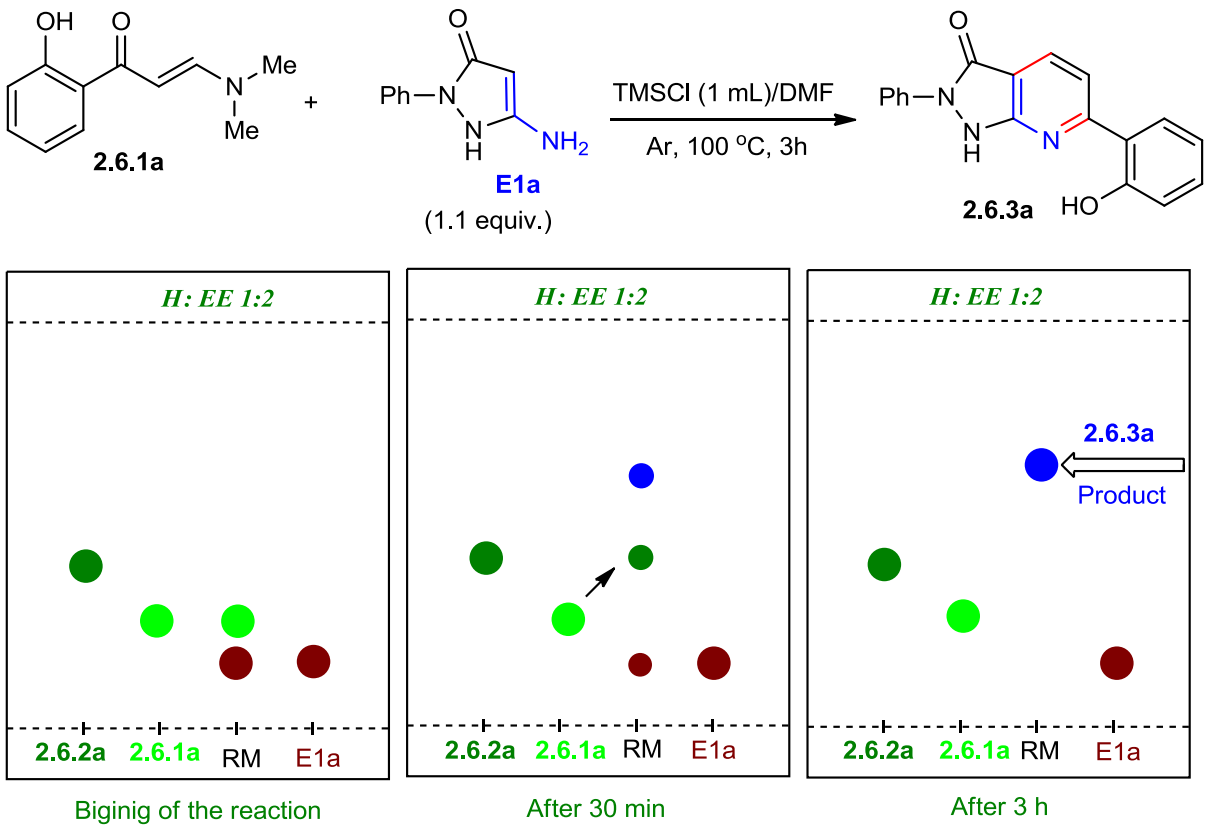
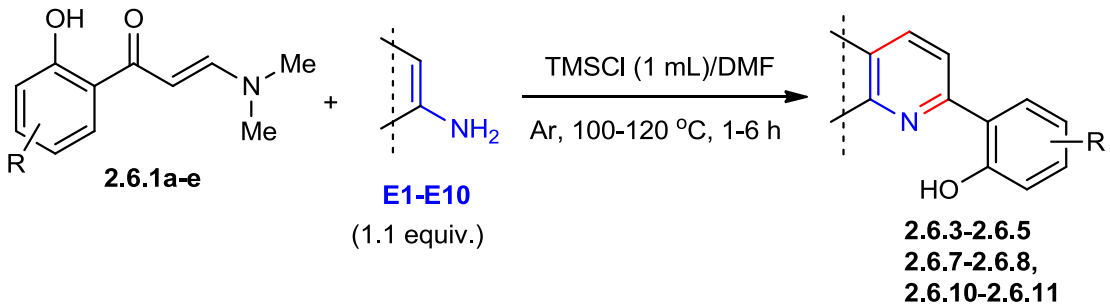


Figure 2.6.1. *TLC control of the reaction (**2.6.2a**-Chromone (R_f = 0.4), **2.6.1a**- Enamine (R_f = 0.26), RM-Reaction mixture (R_f = 0.62), **E1a**- enaminone (R_f = 0.16)).*

Once the reaction successfully delivered the corresponding products (**2.6.3a**, Figure 2.6.1), the same set of electron-excessive aminoheterocycles were tested in the reaction. In addition yields of prepared *β,γ*-unsubstituted fused pyridines were compared to those, which were synthesized using 2,3-unsubstituted chromones (Scheme 2.6.4, Table 2.6.3).

The data of Table 2.6.3 indicates that the yields are resemble for both starting materials. However, the privilege of enones is that it gives an opportunity to reach desired fused pyridines in one step, skipping the synthesis of chromones. It can be concluded that the starting enaminones **2.6.1a-e** can also be versatile starting compounds toward synthesis of diverse fused pyridines. This can represent an interesting approach for synthesis of other

heterocyclic systems in the future.



Scheme 2.6.4. *Synthesis of β,γ-unsubstituted fused pyridines* ***2.6.3-2.6.5, 2.6.7-2.6.8, 2.6.10-2.6.11*** *starting from enones* ***2.6.1***.

Table 2.6.3. *List of yields of prepared fused pyridine.*

Product	Yileds (%)[a]	Yileds (%)[b]	Product	Yileds (%)[a]	Yileds (%)[b]
2.6.3a	90	86	**2.6.7b**	60	54
2.6.3b	77	78	**2.6.7c**	62	60
2.6.3c	92	90	**2.6.7d**	55	50
2.6.4a	90	89	**2.6.8a**	88	87
2.6.4b	90	86	**2.6.8b**	89	87
2.6.4c	76	74	**2.6.8c**	85	85
2.6.4d	61	60	**2.6.8d**	90	88
2.6.4h	58	60	**2.6.8e**	65	66
2.6.5a	97	93	**2.6.8f**	65	60
2.6.5b	92	92	**2.6.8g**	97	90
2.6.5c	75	74	**2.6.10**	72	77
2.6.7a	61	61	**2.6.11**	84	82

(a) Starting from **2.6.2**, (b) starting from **2.6.1**.

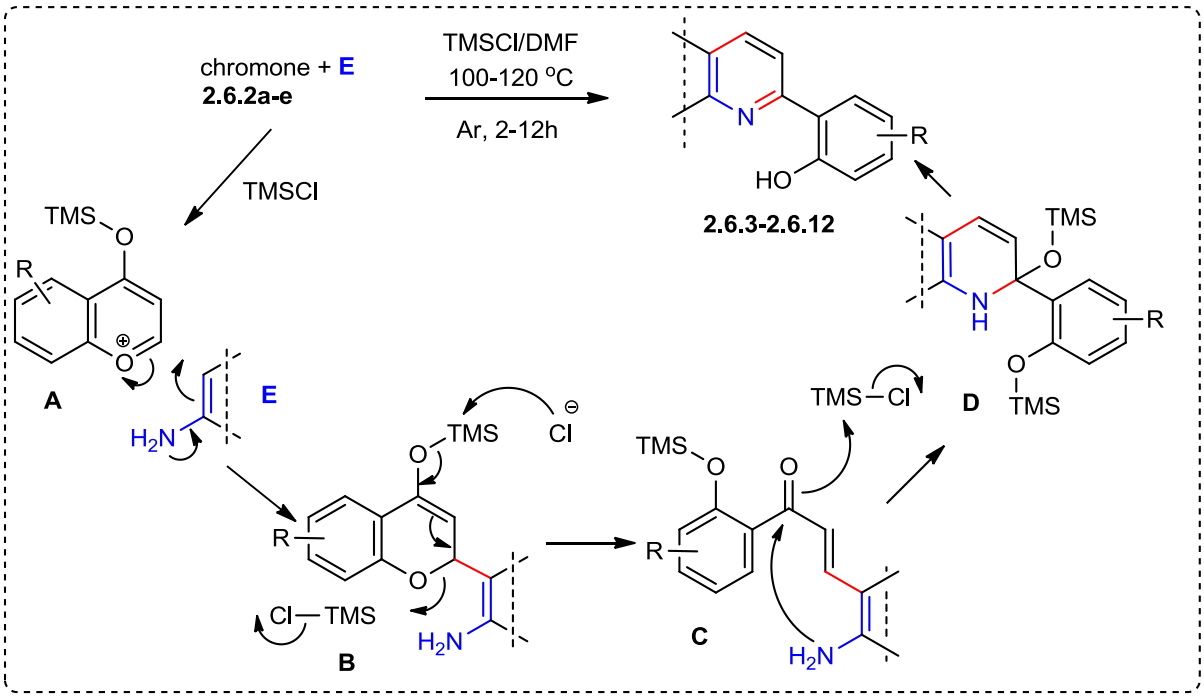
2.6.4. Unsuccessful results

Summarising unsuccessful results it must be noticed that the reaction of chromones **2.6.2** and corresponding enaminones **2.6.1** with anilines failed, more precisely no product was detected at all. Additionally, the reaction of enaminones **2.6.1** and **E12** delivered to the formation of naphtho[2,3-*f*]quinolone framework (GC/MS data). However, due to low solubility in common solvents it was not possible to measure a ^{1}H NMR spectra, in order to see which of

possible isomers were formed. Nevertheless, the mass-spectrometry as well as elemental analysis data confirm the formation of naphtho[2,3-*f*]quinolone skeleton (See Chapter 2.6.6).

2.6.5. Mechanistic explanation

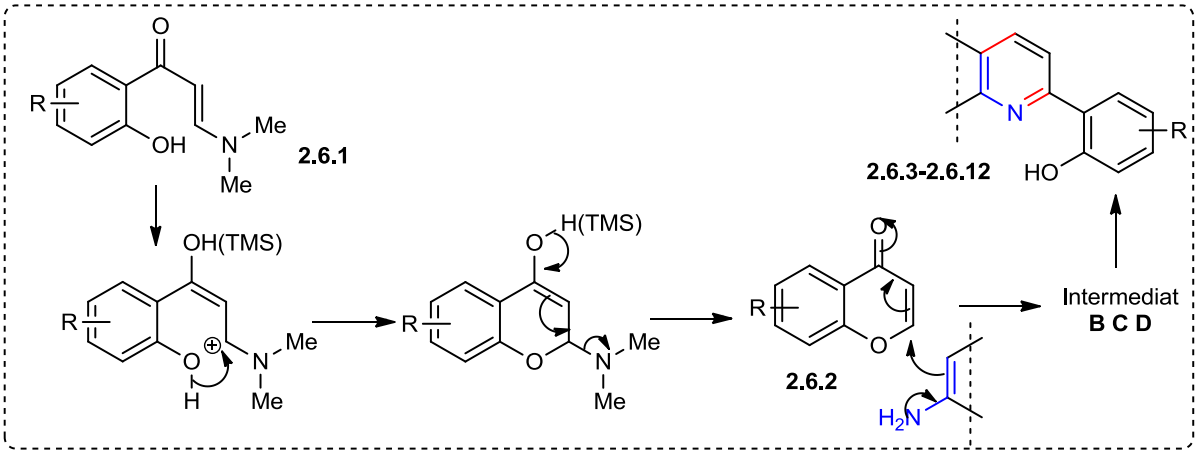
2,3-Unsabtituted chromones in terms of active reaction centres are similar to 3-nitrochromone **2.5.1**. The only difference is that NO_2 group being a strong EWG makes the position 2 more electron deficient, in other words they should react with binucleophiles following the same reaction pathway. Therefore, the proposed mechanism is similar to the one presented in Chapter 2.5.5 (Scheme 2.6.5).



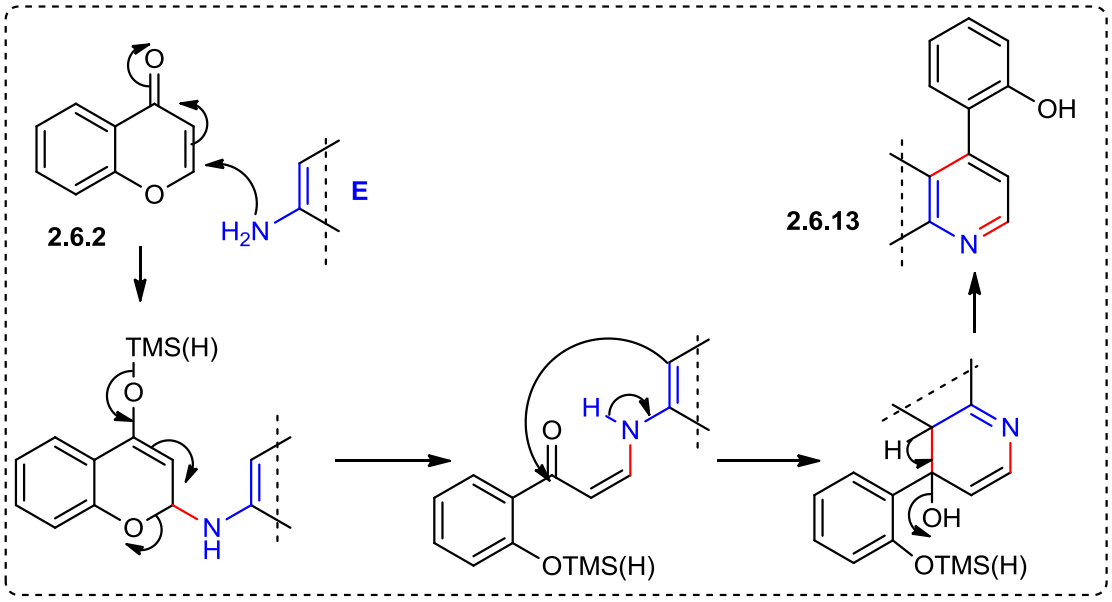
Scheme 2.6.5. *Putative mechanism of the annulation reaction of* ***2.6.2***.

We suppose that the reaction starts with formation of benzopyrylium salt **A** by initial silylation. This makes position 2 of chromone framework more favourable for nucleophilic attack. Subsequent nucleophilic attack of *β*-carbon atom of aminoheterocycles to the position 2 gives the first intermediate **B** in this cascade. The *γ*-pyrone ring opening delivers second intermediate **C**. Additionally, it should be noticed that such type intermediates (intermediate **C)** are quite stable, thus in some cases it can be isolated and characterized. [111] In the next step amino group attacks the carbonyl moiety forming silylated pyridine hydrate **D**. Further, the elimination of Me_3SiOH forms desired product.

Concerning the reaction starting from enaminones **2.6.1**, we assume that first corresponding chromone **2.6.2** formation takes place (based on the TLC study and structure identification, see next chapter), that is followed by cyclocondensation (Scheme 2.6.6).



Scheme 2.6.6. *Putative mechanism of the annulations reaction of **2.6.1** and electron-excessive aminoheterocycles.*



Scheme 2.6.7. *Putative mechanism of the annulation reactions, where the aminoheteocycles behave as N-nucleophiles.*

The reaction starts with activation of C-2 atom of enamine fragment, that is followed by the attack of oxygen atom to the electrophilic centre. Subsequent cyclization leads to the formation of chromone, so further steps of the reaction proceeds as was shown in Scheme 2.6.4. This mechanism is more reasonable, since obtained products are similar to the ones

obtained from corresponding chromones **2.6.3**-**2.6.12** (Scheme 2.6.6).

It should be noticed that during the study of these reactions other regioisomers **2.6.13** were not detected. The latter would have been formed by initial *N*-nucleophile attack of electron-excessive aminoheterocycle (Scheme 2.6.7). Herein we can affirm that proposed methodology is absolutely regioselective for the range of used starting materials (See Chapter 2.6.6).

2.6.6. Structure identification

Structures of all synthesised compounds were confirmed by 1D and 2D NMR, mass and IR spectroscopy. Despite the fact that we have different 5,6-bicyclic systems and different initial chromones, still was possible to follow some general peaks in ^{1}H and ^{13}C NMR spectra. In all cases the peak of O*H* group was observed in ^{1}H NMR at 11.46-14.88 ppm (DMSO-d_6). In a case of 6-methylchromone the singlet of methyl group was seen in ^{1}H NMR at 2.25-2.35 ppm and in ^{13}C NMR at 20.0-21.0 ppm (DMSO-d_6) (Table 2.6.2, compounds **2.6.3a**, **2.6.4b**, **2.6.5b**, **2.6.6a**, **2.6.8b**,**d**,**f**,**h**, **2.6.9a**). The presence of Br was easily detected by GC/MS spectromethry, since the mass peaks for both isotopes of Br were presented in almost equal intensity (Table 2.6.2, compounds **2.6.4b**, **2.6.5b**, **2.6.7c**, **2.6.8i**). The same was with compounds bearing Cl (Table 2.6.2, compounds **2.6.3c**, **2.6.4g**,**i**,**h**, **2.6.5c**, **2.6.6b**, **2.6.7a**,**d**,**j**, **2.6.8c**,**e**, **2.6.9b**), namely in all cases about 30% of M+2 peak was detected. In IR spectra a broad peak of OH group appears at 3140-2764 cm^{-1} indicate the hydrogen bonding between the pyridine nitrogen and OH group.

In NOESY spectra of compound **2.6.4b** we observed an interaction between N-*Ph* protons and O*H* of the α-aryl moiety, in addition to a very week correlation between methyl group of aryl and N-*Ph* protons (Figure 2.6.2). Another week correlation was detected between N-*Me* and γ-proton of the fused pyridine. However, there were no interaction between two methyl groups or N-*Me* and O*H* group of the aryl moiety. These interactions could have been observed if we would have another regioisomer. This could be taken as an evidence for the regioselectivity of the reaction.

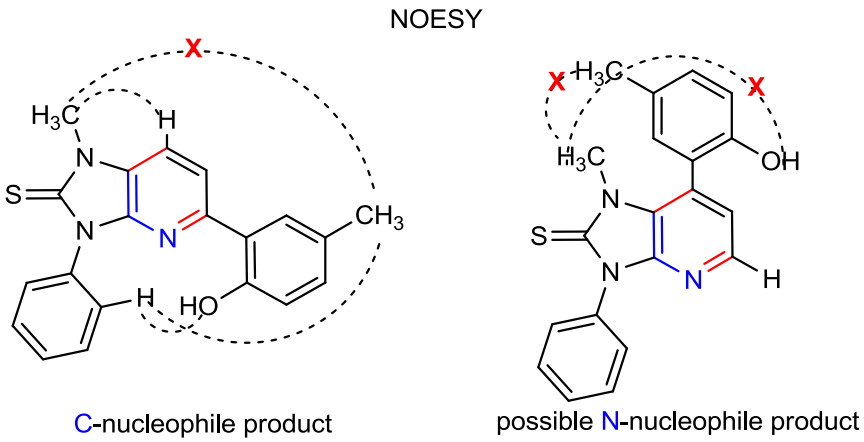
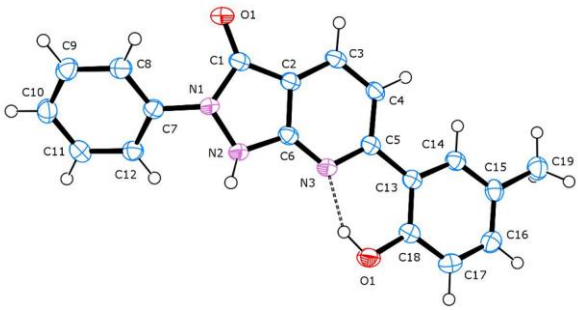
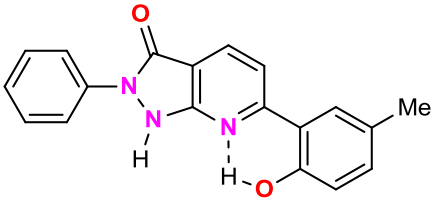
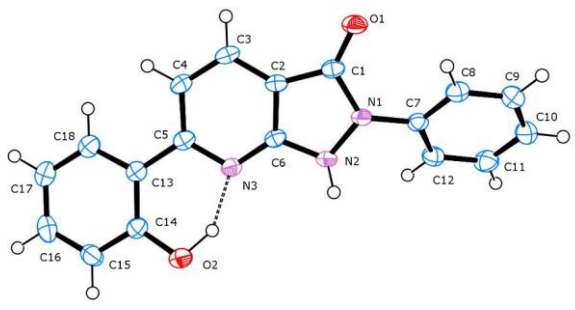
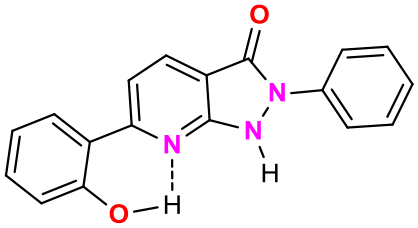
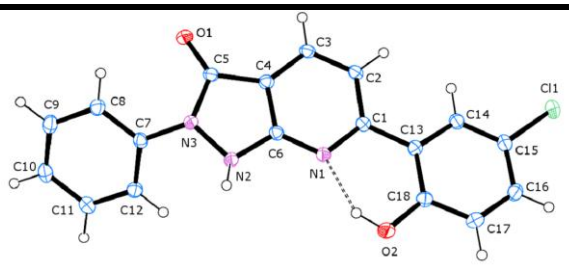
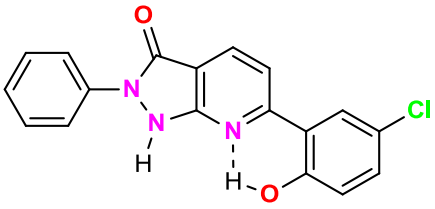
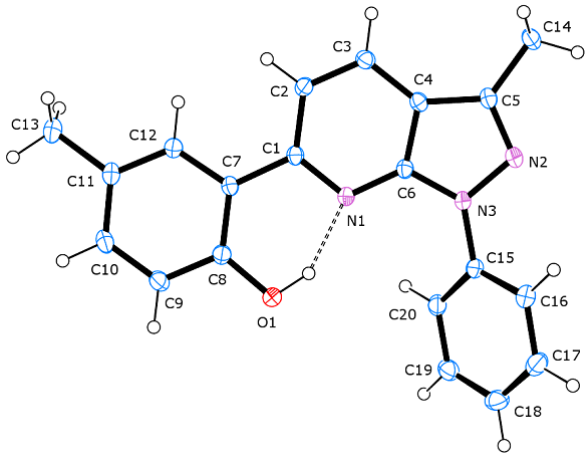
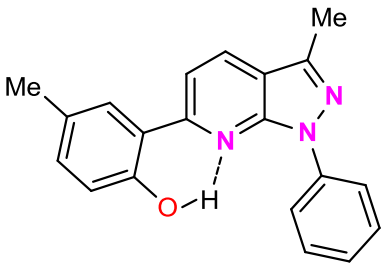
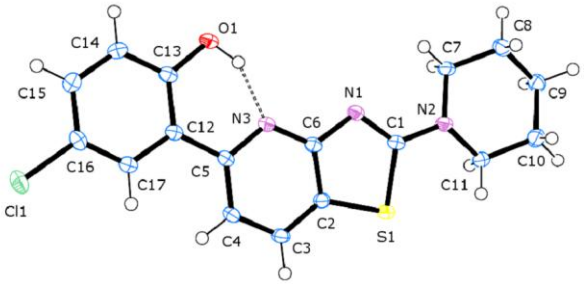
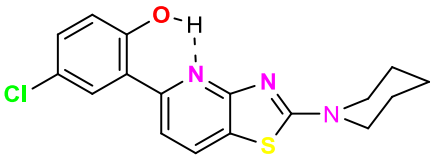


Figure 2.6.2. *Visible correlations in NOESY spectra for compound* ***2.6.4b.***

Furthermore, structures of **2.6.3a**,**b**,**c**, **2.6.5a** and **2.6.7d** (Table 2.6.2) were identified also by X-ray single crystal analysis (Table 2.6.4). It should be noticed that all five structures exactly correspond to expected regioisomers. This is an additional confirmation for regioselectivity of the reaction. In all frameworks we observed a planar core of fused pyridine system. Moreover, the *α*-hydroxyphenyl group was almost at the same plane with fused pyridine core. This can be explained by a hydrogen bond between OH and *N*-atom of pyridine ring. The torsion angle between pyridine core and *o*-hydroxyphenyl moiety is 2.64°-14.39°. The length of hydrogen bonds in all structures is in the range of 1.639-1.781 Å.

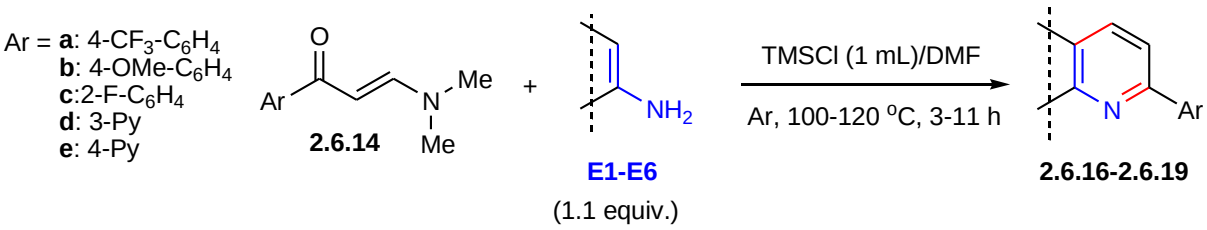
Table 2.6.4. *X-ray crystal structures of compounds* ***2.6.3a-c***, ***2.6.5a***, ***2.6.7d***.

Compound	Crystal	Structure
2.6.3a		
2.6.3b		

2.6.3c		
2.6.5a		
2.6.7d		

2.6.7. Further investigations

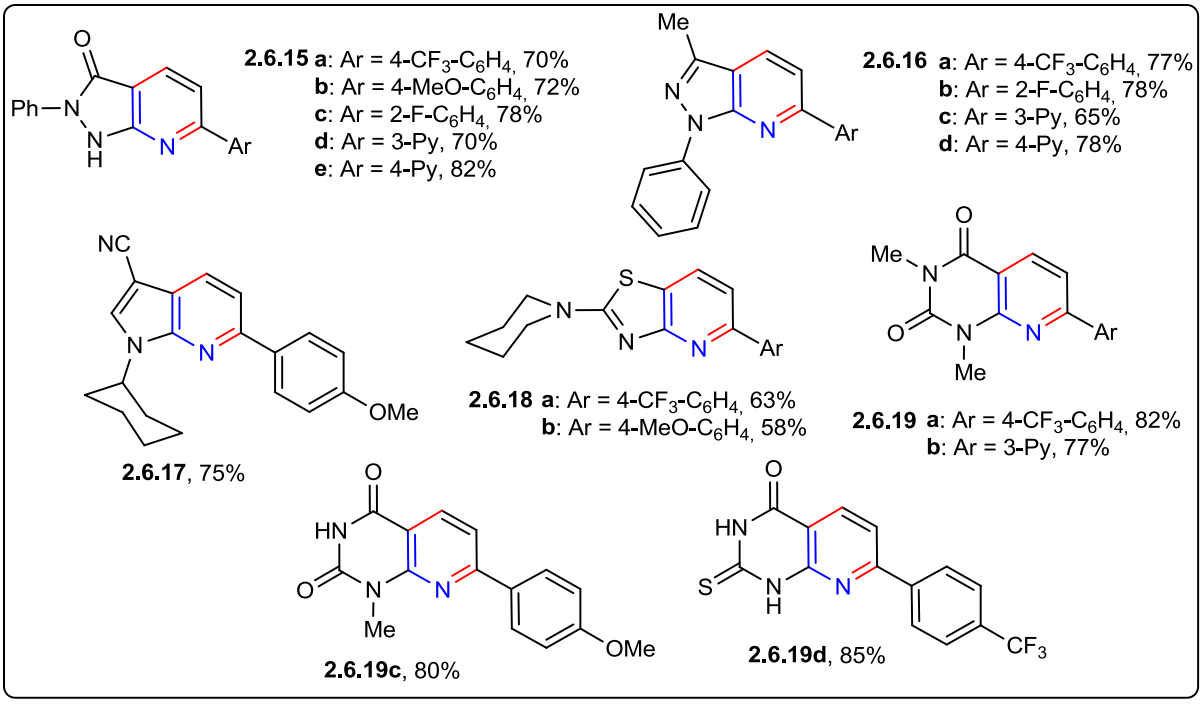
Encouraged by the results regarding enaminones **2.6.1** as starting materials for synthesis of fused pyridine, next the reactivity of similar enaminones without a hydroxyl group was exanimated. The study of regioselectivity of this reaction was relevant since the absence of hydroxyl group could influence on cyclization reaction mechanism (actually it can not go through *in situ* chromone ring formation). Furthermore, using this approach the synthesis of new derivatives of *α*-aryl-substituted fused pyridines would be possible. For this purpose the reaction of (*E*)-3-(dimethylamino)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one **2.6.14** and **E1a** was tasted. Fortunately, the cyclocondensation product **2.6.15a** was isolated in 70% yield (Scheme 2.6.8). According to initial study the structure of obtained product was in good correspondence with previously isolated products.



Scheme 2.6.8. *Preparation of α-aryl-substituted fused pyridine from* ***2.6.14****.*

Being inspired by this finding a list of enaminones **2.6.14** were reacted with electron-excessive aminoheterocycles **E1-E6** as a result 16 examples of different *α*-aryl-substituted fused pyridines were successfully prepared in good yields (Table 2.6.5).

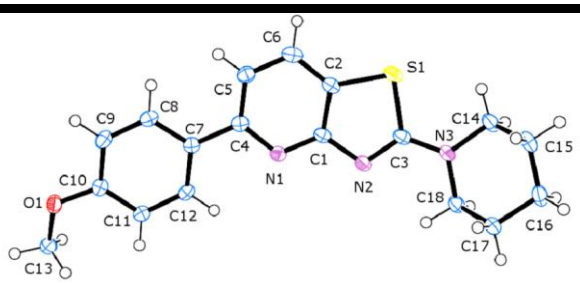
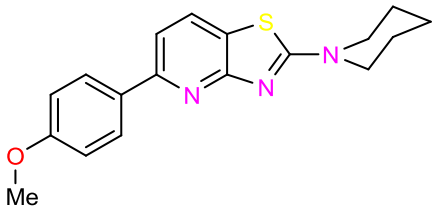
Table 2.6.5. *List of prepared fused pyridines* ***2.6.15-2.6.19****.*



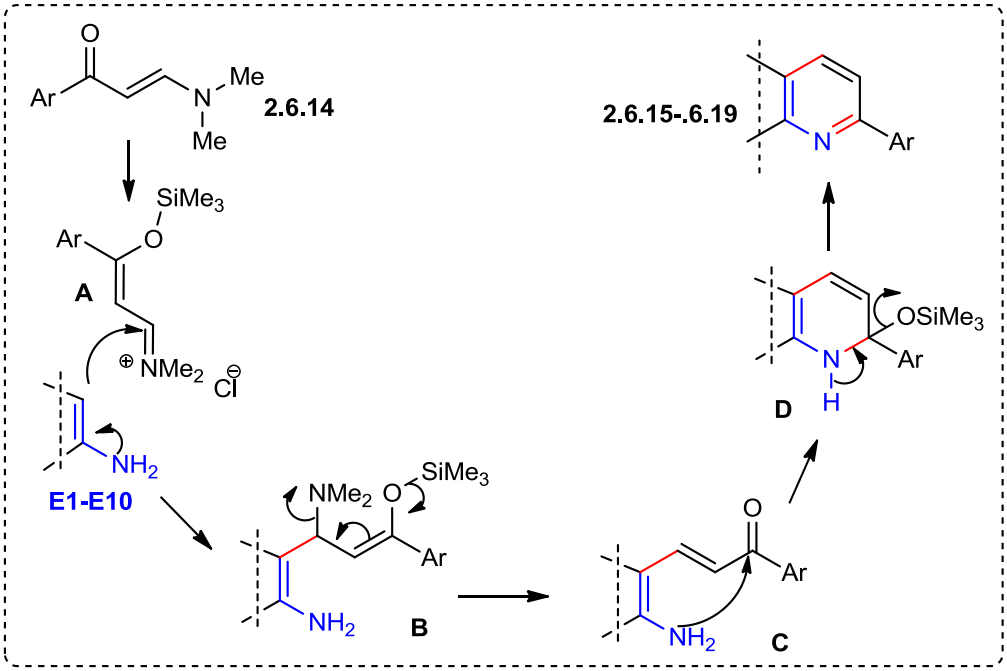
It is important mentioning that when pyridine-substituted enaminones **2.6.14d,e** were used, corresponding fused pyridines were successfully formed. That is, among others preparation of *α*-heteroaryl-substituted fused pyridines by proposed methodology is equally effective. All structures of obtained products were established by 1D NMR. For example with *p*-OMe enaminones **2.6.14b** the singlet of O*Me* appears at 3.81-3.88 ppm in ^{1}H NMR and 55.2-55.4 ppm in ^{13}C NMR (DMSO-d_6). In case of **2.6.14a** CF_3 group was detected in ^{19}F NMR spectra as singlet at -60.9-61.4 ppm (DMSO-d_6). Furthermore, in ^{13}C NMR the characteristic quartet for $\underline{C}F_3$ at 117.2-124.1 ppm with ($^{1}J_{C\text{-}F}$ ~ 280 Hz) and a quartet for $\underline{C}CF_3$ at 128.7-140.2 ppm ($^{2}J_{C\text{-}F}$ ~ 30 Hz) were present (DMSO-d_6). Another specific peak was for 2-F-aryl-substituted

product (Table 2.6.5, compounds **2.6.15c**, **2.6.16b**) in ^{19}F NMR spectra a singlet in -115.9-116.6 ppm emerged (DMSO-d_6). Besides, a doublet located at 113.2-113.5 ppm in ^{13}C NMR that belongs to the carbon atom bounded with fluorine atoms with a coupling constant of $^{1}J_{C\text{-}F}$ ~ 240 Hz was typical for such compounds (DMSO-d_6). The structure of **2.6.18b** was independently confirmed by X-ray crystal structure analysis once more indicating proposed regioselectivity (Table 2.6.6).

Table 2.6.6. *X-ray crystal structures of compound **2.6.18b.***

Compound	Crystal	Structure
2.6.18b		

Here again we could see a planar structure of thiazolo[4,5-*b*]pyridine core like was in earlier examples, in addition interestingly the aryl group is in the same plane with thiazolo[4,5-*b*]pyridine.



Scheme 2.6.9. *Putative mechanism of the the annulation reactions starting from **2.6.14**.*

Considering the possible reaction mechanism, we suppose that the reaction starts with formation of iminium salt of corresponding enamine (intermediate **A**) by the reaction of enones with TMSCl. Further nucleophilic attack of electron-excessive aminoheterocycles to iminium fragment gives rise to second intermediate **B**. Following elimination of Me_2NSiMe_3 and intramolecular attack of amino group to the carbonyl atom forms intermediate **D** which *via* elimination of Me_3SiOH delivers desired product (Scheme 2.6.8). It should be mentioned that other regioisomer of initial *N*-nucleophilic attack of electron-excessive aminoheterocycle was not detected.

2.6.8. Conclusion

In summary the reaction of non-activated 2,3-unsubstituted chromones **2.6.2** and enaminones **2.6.1**, **2.6.14** with different electron-excessive aminoheterocycles was investigated. A wide range of different α-aryl and heteroaryl fused pyridines were successfully synthesised. The scope and limitations of method was illustrated as well. The proposed methodology is relevant since most of prepared α-aryl and heteroaryl fused pyridines are not available by other methods. Furthermore, the investigation of biological activity of these compounds is in progress.

3. [5+1] Synthesis of 4-quinolones

3.1. General methods for the 4-quinolones synthesis

The next topic of investigation was preparation of 4-quinolines, which are an important class of *N*-containing heterocycles.[112] Functionalized 4-quinolones are attractive compounds playing an increasingly important role in drug discovery. This framework is structural unit found in a vast array of natural products[113] and synthetic materials.[114] Over the years, 4-quinolone derivatives have attracted considerable attention from medicinal chemists due to their diverse biological activity. Starting with a serendipitous discovery about 50 years ago,[115] the story of 4-quinolone antibacterial agents started with introduction of nalidixic acid in 1963 (Figure 3.1.1).[116]

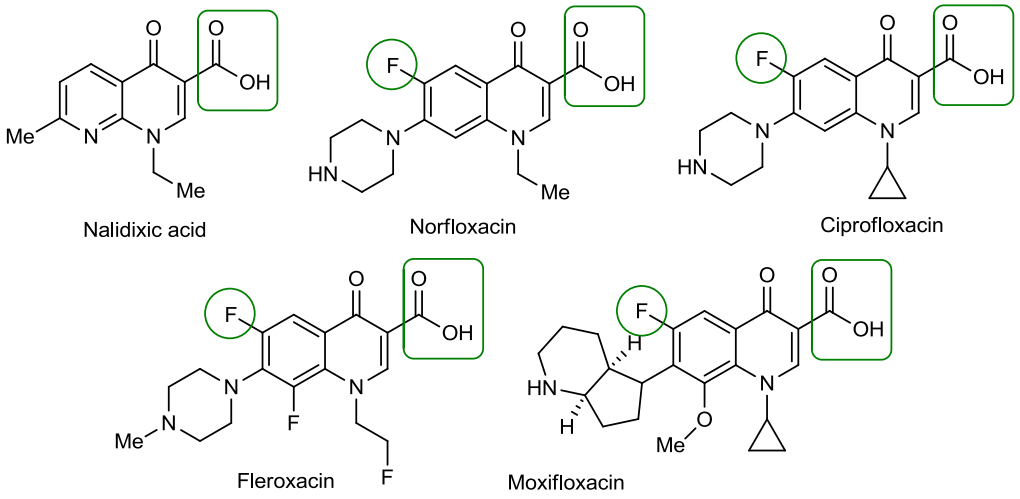
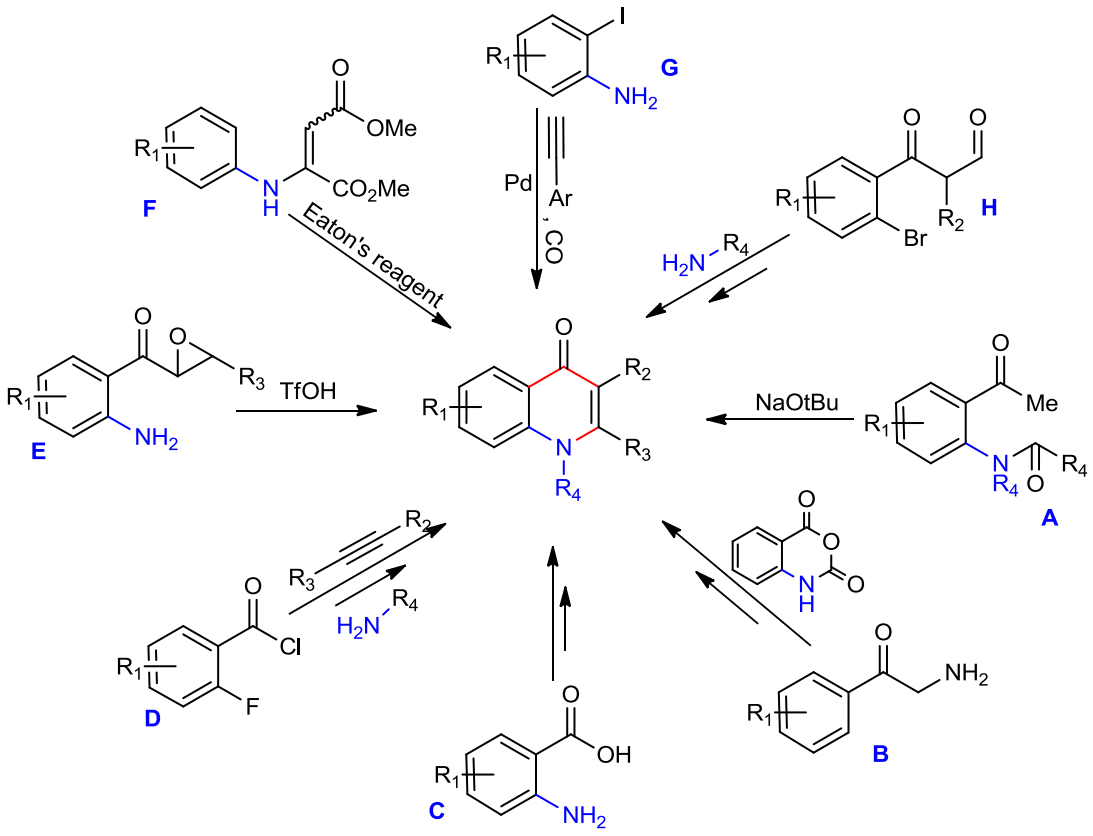


Figure 3.1.1. *Biologicaly relevant 4-quinolone derivatives.*

Although the clinical use of nalidixic acid is limited only to urinary tract infections, the interest was stimulated by its gram-negative activity, uniqueness and relative simplicity of its chemical structure. Next big evaluation in this area was the discovery of Koga *et al*. showing that the 6-fluoroquinolones are not only an order of magnitude more active than the previous agents against gram-negative bacteria, but also have exceptionally broad-spectrum of biological action.[117] Norfloxacin is the first member of modern fluoroquinolones (Figure 3.1.1). Since then a number of other fluoroquinolones were introduced on the market, e.g. ciprofloxacin as an antibiotic against gram-positive bacteria.[118] Fleroxacin has similar properties but in comparison to other fluoroquinolones has excellent bioavailability, high concentrations in plasma and other body fluids and long half-life (10-12 h) in addition to time

heavy side effects.[119] Another example is moxifloxacin which is new antibacterial agent against respiratory diseases (Figure 3.1.1).[120]

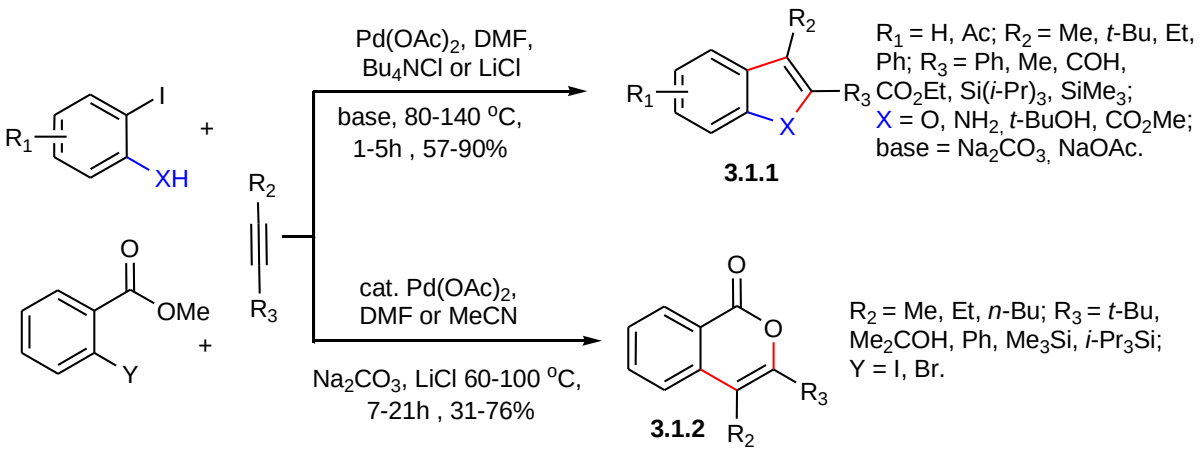
The major demand of these compounds has motivated many chemists to develop different pathways of the synthesis of 4-quinolone core. Numerous synthetic routes to 4-quinolones have been reported involving Camps cyclization (Scheme 3.1.1 **A**),[121] reaction of isatoic anhydrides (Scheme 3.1.1 **B**),[122] cyclization of *N*-substituted phenacyl or acetonyl anthranilates in polyphosphoric acid,[123] cyclization of anthranilic acid derived ynone intermediates (Scheme 3.1.1 **C**),[124] intramolecular coupling of aryl halides with *β*-enaminones (Scheme 3.1.1 **D**),[125] acid-catalyzed cyclization (Scheme 3.1.1 **E**),[126] cycloacylation of aniline derivatives (Scheme 3.1.1 **F**),[127] palladium-catalyzed carbonylative Sonogashira coupling of 2-iodoaniline with arylacetylene (Scheme 3.1.1 **G**),[128] and metal free intramolecular amination (Scheme 3.1.1 **H**).[129]



Scheme 3.1.1. *Some synthetic routes for 4-quinolone ring construction.*

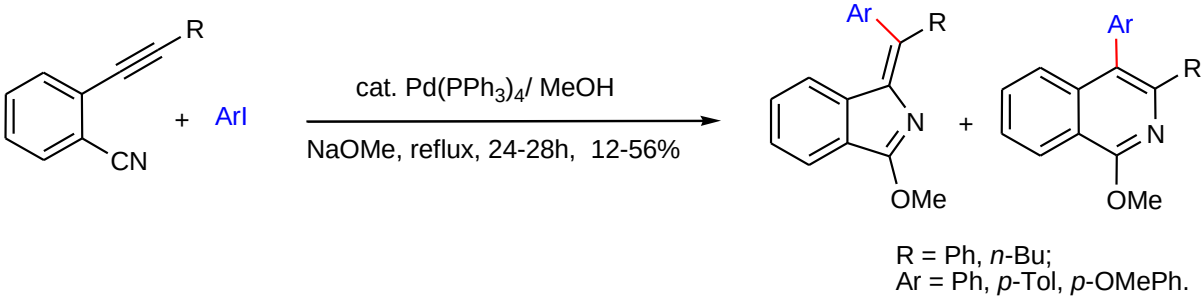
Meanwhile, Pd-mediated reactions nowadays have occupied a privilege position in modern organic and heterocyclic chemistry, since Pd-catalysed carbo- and heterocyclizations open new horizons for assembling of new carbo- and heterocyclic frameworks. For instance Pd-catalyzed annulation of internal alkynes by aryl/vinylic halides bearing an oxygen or nitrogen

nucleophile is a versatile way to generate a wide variety of heterocycles.[130] Thus, in 1995 Larock and co-workers reported the reaction of aryl iodides with internal alkynes using $Pd(OAc)_2$ as a catalyst in the presence of base in DMF leading to *N*-/*O*-heterocycles **3.1.1** in good yields (Scheme 3.1.2).[131] Later from the same group was presented the synthesis of 3,4-disubstituted isocoumarins **3.1.2** in good yields by treating the halogen-containing aromatic esters with internal alkynes in the presence of a Pd-catalyst (Scheme 3.1.2).[132]



Scheme 3.1.2. *Construction of benzofuran, indole and isocoumarine rings.*

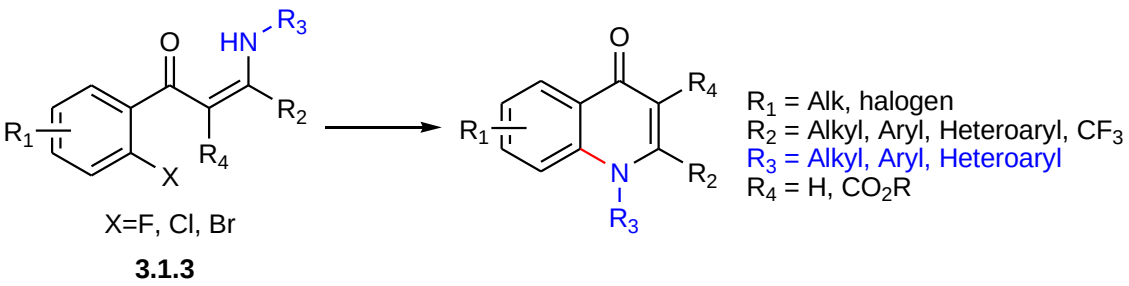
Recently, Wu *et al.* have demonstrated that 2-(2-phenylethynyl)benzonitrile can be cyclised by aryl iodides in the presence of $Pd(PPh_3)_4$ and NaOMe, in MeOH to give 3-diarylmethylideneisoindoles as sole product in moderate yields (Scheme 3.1.3).[133] When 2-(1-hexynyl)benzonitrile was employed, isoindole derivatives were obtained together with isoquinolines.



Scheme 3.1.3. *Synthesis of isoindole and isoquinoline derivatives from o-alkynyl benzonitriles and aryl iodides*

Another interesting structure, that is mostly used in the synthesis of different 4-quinoline derivatives, is *N*-arylenaminone **3.1.3** that was considered as a starting compound in the study

of Cacchi *et al*.. They have presented a CuI mediated construction of 4-quinolone moiety by intramolecular cyclization (Scheme 3.1.4).[134] In other studies this structure was isolated as an intermediate in multistep construction of 4-quinolone structure starting from 4-bromo-2-fluoroacetophenone[135] or *o*-haloaryl acetylenic ketones.[136] The latter was successfully converted to quinolone by catalytic[136] and catalyst-free base mediated cyclization reaction (Scheme 3.1.4).[135,137]



Scheme 3.1.4. *Synthesis of 4-quinolone derivatives starting from N-arylenaminone* ***3.1.3***.

Although all presented methods are interesting and offer variety routes for 4-quinolone synthesis, however the increasing demand of quinolone derivatives, due to their high importance in medical chemistry and drug discovery, motivated us to develop new methods for production of diverse 4-quinolones.

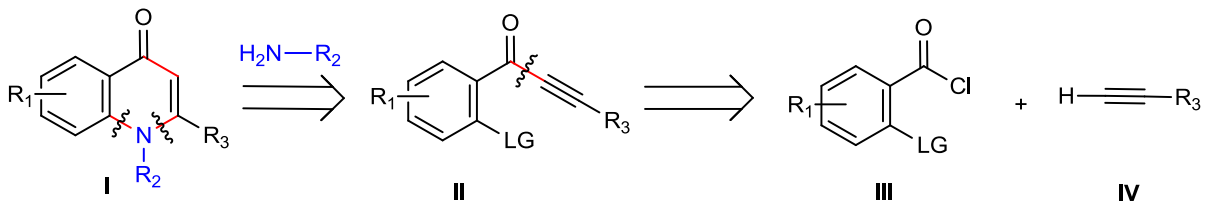
3.2. Efficient [5+1] synthesis of 4-quinolones by domino amination and conjugate addition reactions of 1-(2-fluorophenyl)prop-2-yn-1-ones with amines

3.2.1. Introduction

Although the presented in Scheme 3.1.1, 3.1.4 methods are effective and give relatively high yields of 4-quinolones, most of them are incompatible with sensitive functionalities,[138] includes numerous synthetic steps or need harsh reaction conditions,[121-125,127,139] besides some starting materials are not readily available.[126,139] On this basis we assume that the investigation of new and more general strategies for synthesis of 4-quinolones are essential.

Based on retro-synthetic analysis (Scheme 3.2.1) and previous expertise in the chemistry of Pd-catalyzed cyclizations which were demonstrated above (Scheme 3.1.2, 3.1.3), we have supposed that a possible synthetic pathway towards heteroannulated 4-quinolones **I** can be the

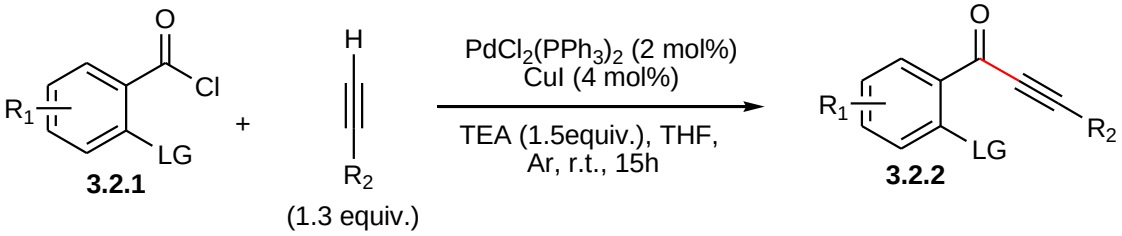
catalyst-free reaction of phenylpropyn-1-ones **II** bearing a good leaving group in *α*-position to the carbonyl function with different amines. It should be noticed that previously by Xu *et al.* was presented a Pd-catalyzed cyclization of *o*-haloaryl acetylenic ketones with amines.[140]



Scheme 3.2.1. *Retrosynthetic analysis of 4-quinolones.*

3.2.2. Synthesis of starting materials

To start our investigation towards synthesis of 4-quinolone derivatives we needed to choose appropriate starting materials. The retrosynthetic analysis shows that initial 1-phenylalk-2-yn-1-ones must bear a good leaving group. It is known from the literature that fluoro or nitro groups in the *ortho*-positions to an EWG substituent can be easily substituted by nucleophiles.[141] Therefore a list of 1-(2-fluorophenyl)alk-2-yn-1-one derivatives **3.2.2** having good leaving groups in appropriate position were synthesis. They are easily available from commercially available fluorinated (or nitrated) benzoyl chlorides **3.2.1** and alkynes by Sonogashira cross-coupling reaction (Scheme 3.2.2).[142]



Scheme 3.2.2. *Synthesis of starting1-(2-fluorophenyl)prop-2yn-1-one **3.2.2** by Sonogashira reaction.*

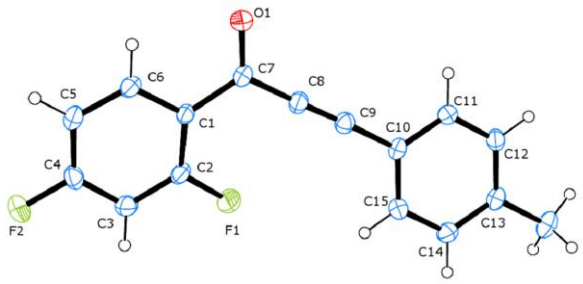
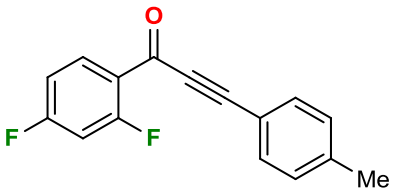
Table 3.2.1. *List of synthesised ynones **3.2.2**.*

3.2.2	LG	R_1	R_2	Yield (%)
a	F	H	Ph	88
b	F	H	4-*t*-BuC_6H_4	78
c	F	5-F	4-*t*-BuC_6H_4	84

d	F	5-F	4-MeC_6H_4	81
e	F	4-F	4-MeC_6H_4	97
f	F	6-F	Ph	70
g	F	6-F	4-MeC_6H_4	73
h	F	6-F	4-*t*-BuC_6H_4	80
i	F	6-F	$(CH_2)_4Me$	70
j	F	3,4,5,6-F	4-*t*-BuC_6H_4	75
k	NO_2	H	Ph	73

In standard conditions for Sonogashira reaction this transformation runs smoothly leading to desired products with good to excellent yields. According to this methodology a number of mono- and multifluorine-substituted starting 1-phenylalk-2-yn-1-ones were synthesised (Table 3.2.1). Moreover, one example of *ortho*-nitro ynone **3.2.2k** was prepared as well, which was used later on (see Chapter 3.2.3) to show the possibility of usage other leaving groups (LG) in this reaction (Table 3.2.1). All compounds were purified by column chromatography (Heptane : Ethyl acetate 30:1). The structure of all starting materials were corroborated by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy, moreover the structure of **3.2.2e** was indepently characterised by X-ray crystal structure analysis (Table 3.2.2).

Table 3.2.2. *X-ray crystal structures of compound **3.2.2e.***

Compound	Crystal	Structure
3.2.2e		

3.2.3. Results and discussions

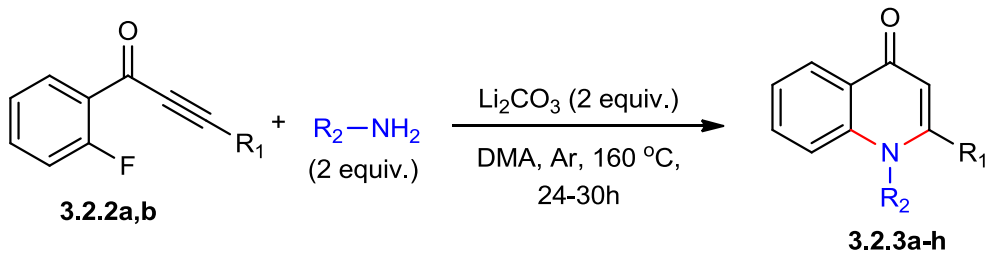
We started our investigation using as model reactants **3.2.2a** and (2-phenylethyl)amine. In order to find optimal conditions for cyclization reaction a number of different reaction conditions were tested (Table 3.2.3). Initially we used 2 equivalents of amine in DMF as a solvent and K_2CO_3 as base. Unfortunately, in these conditions we could isolate the desired

product only in 18% yield. During further investigations turned out, that in this reaction combination of solvent, base and temperature is extremely important. Thus, we found that the yields can be increased by changing the solvent to DMA and increasing the temperature up to 160 ^{o}C (35%). Furthermore, when the base was changed from K_2CO_3 to Li_2CO_3, the yields were dramatically increased (up to 89%, Entry 7), hence these conditions was taken as the optimal. Noteworthy, that when amount of amine was reduced to 1.2 equivalents, the yield was decreased to 71% (see Chapter 3.2.5).

Table 3.2.3. Optimization of the synthesis of 4-quinolone **3.2.3a.**

	Amine	Solvent	Base	Temp (^{o}C)	Time (h)	Yield (%) of **3.2.3a**
1	2 equiv	DMF	K_2CO_3	140	10	18
2	2 equiv	DMF	Li_2CO_3	140	10	25
3	2 equiv	DMA	K_2CO_3	160	12	35
4	2 equiv	DMA	Li_2CO_3	160	12	58
5	2 equiv	DMA	Li_2CO_3	160	18	73
6	2 equiv	DMA	K_2CO_3	160	24	51
7	**2 equiv**	**DMA**	**Li_2CO_3**	**160**	**24**	**89**
8	1.2 equiv	DMA	Li_2CO_3	160	24	75

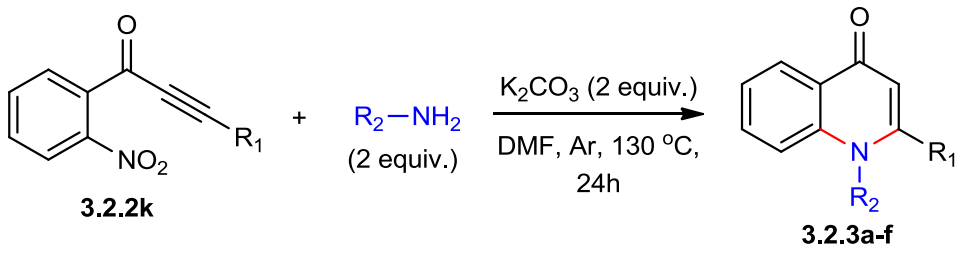
Having an optimized reaction conditions in hand, compounds **3.2.2a** and **3.2.2b** were reacted with the list of amines. Fortunately, a number of corresponding 4-quinolones **3.2.3a-h** were prepared with good to excellent yields (Scheme 3.2.3, Table 3.2.4). Examining the scope of the reaction we observed, that aliphatic amines reacted much better than anilines, probably because of decreased nucleophilicity of anilines.



Scheme 3.2.3. *Synthesis of 4-quinolones **3.2.3a-f** from appropriate 2-fluorophenylpropyn-1-ones **3.2.2a,b** and amines.*

On the next stage of our work the reactivity of nitro-substituted ynone **3.2.2k** was tested and

compared to those for fluorine-substituted starting ynones. Since the nitro group is a good leaving group, we assumed that the reaction can be successful even under milder conditions (Scheme 3.2-4). When the reaction was performed in DMF using K_2CO_3 as a base at 130 ^oC, corresponding products were obtained in good yields. Interestingly any change of the reaction conditions did not increased the yields, moreover the use of other nitro-substituted starting ynones did not change the yields either (Table 3.2.4).

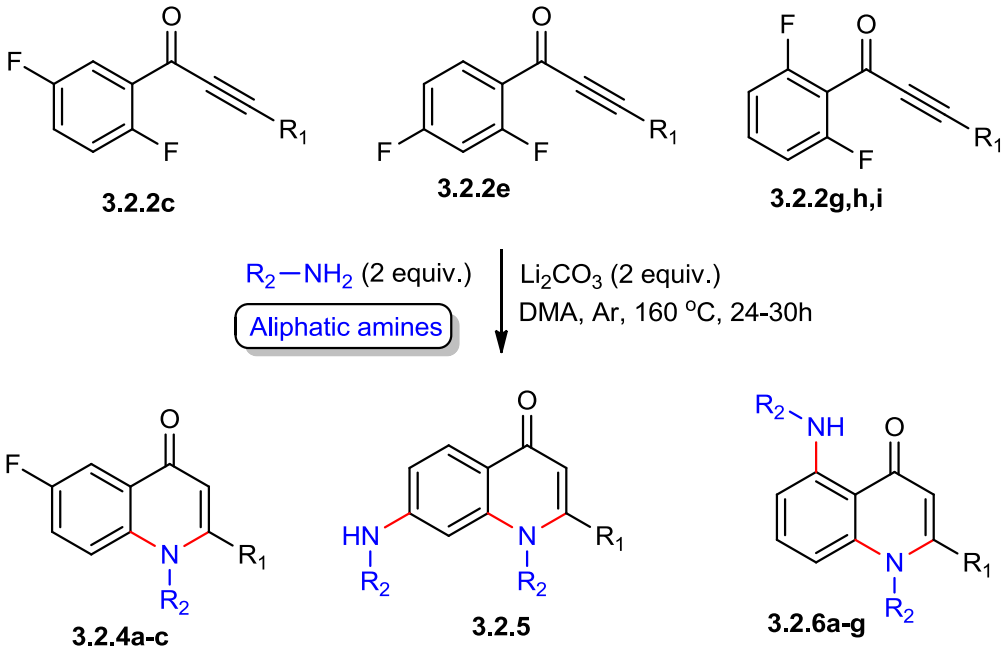


Scheme 3.2.4. *Synthesis of 4-quinolones **3.2.3a-f** from **3.2.2k**.*

Table 3.2.4. *List of 4-quinolones **3.2.3**.*

3.2.3	R_1	R_2	Yields (%) **3.2.2a,b**	Yields (%) **3.2.2k**
a	Ph	$(CH_2)_2Ph$	89	79
b	Ph	$(CH_2)_3Ph$	86	80
c	Ph	CH_2-4-$MeOC_6H_4$	87	77
d	Ph	$(CH_2)_4Me$	84	79
e	Ph	$(CH_2)_5Me$	89	78
f	Ph	3,5-$(MeO)_2C_6H_3$	74	70
g	4-*t*-BuC_6H_4	4-ClC_6H_4	75	-
h	4-*t*-BuC_6H_4	4-BrC_6H_4	73	-

When ynones with two fluorine atoms in the core were examined, we observed an interesting phenomenon (Scheme 3.2.5). Namely, when the second fluorine atom was at *ortho* or *para* position to the carbonyl group (**3.2.2e**, **g**, **h**, **i**), following the cyclzation reaction the second fluorine atom was also substituted by amine, leading to corresponding amino-substituted quinolones **3.2.5**, **3.2.6**. However, in case of second fluorine atom located at *meta*-position to the carbonyl group, further substitution did not took place, that is simple 4-quinolones **3.2.4** were formed with a fluorine atom in the molecule (Table 3.2.5 for the reaction with aliphatic amines).



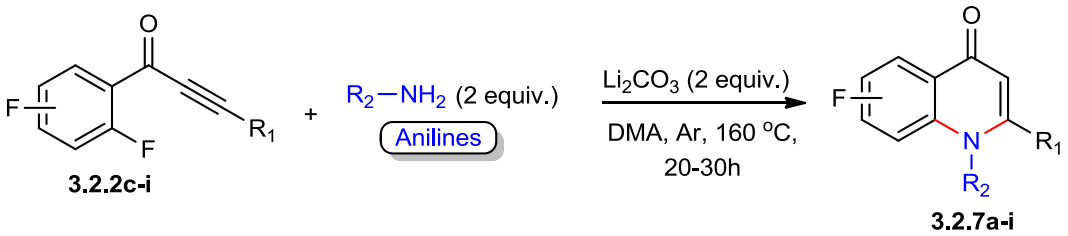
Scheme 3.2-5. *Synthesis of 4-quinolones* ***3.2.4a-c***, ***3.2.5***, ***3.2.6a-g***.

Table 3.2.5. *List of amino-substituted and non-substituted 4-quinlones from aliphatic amines.*

	R_1	R_2	Yileds(%)
3.2.4a	4-Tol	$(CH_2)_5Me$	85
3.2.4b	4-Tol	$(CH_2)_2Ph$	88
3.2.4c	4-Tol	$(CH_2)_3Ph$	83
3.2.5	4-Tol	(*R*)-CH(Ph)Me	33[a]
3.2.6a	4-*t*-BuC_6H_4	$(CH_2)_3Ph$	82
3.2.6b	4-*t*-BuC_6H_4	CH_2-4-MeOC_6H_4	85
3.2.6c	4-*t*-BuC_6H_4	$(CH_2)_2Ph$	93
3.2.6d	4-Tol	$(CH_2)_2$-3,4-$(MeO)_2C_6H_3$	85
3.2.6e	4-Tol	(*R*)-CH(Ph)Me	40[a]
3.2.6f	$(CH_2)_4Me$	$(CH_2)_2Ph$	82
3.2.6g	$(CH_2)_4Me$	$(CH_2)_3Ph$	75

(a) Reaction took 60h.

Interestingly when ynones with two fluorine atoms in the molecule **3.2.2** were reacted with anilines, the only product was simple quinolone with a fluorine atom in the molecule, the further nucleophilic substitution of second fluorine did not took place at all (Scheme 3.2.6, Table 3.2.6).



Scheme 3.2.6. *Synthesis of 4-quinolones **3.2.7a-i** from anilines.*

Table 3.2.6. *List of 4-quinlones **3.2.7** obtained from anilines.*

3.2.7	**3.2.2**	F	R_1	R_2	Yileds (%)
a	**c**	6-F	4-*t*-BuC_6H_4	3,5-$(OMe)_2C_6H_3$	77
b	**c**	6-F	4-*t*-BuC_6H_4	4-MeOC_6H_4	78
c	**e**	7-F	4-Tol	4-*t*-BuC_6H_4	75
d	**e**	7-F	4-Tol	3,5-$Me_2C_6H_3$	79
e	**f**	5-F	Ph	3,5-$Me_2C_6H_3$	77
f	**g**	5-F	4-Tol	3,5-$Me_2C_6H_3$	71
g	**g**	5-F	4-Tol	4-EtC_6H_3	70
h	**h**	5-F	4-*t*-BuC_6H_4	3,5-$(OMe)_2C_6H_3$	73
i	**i**	5-F	$(CH_2)_4$Me	4-MeOC_6H_4	72

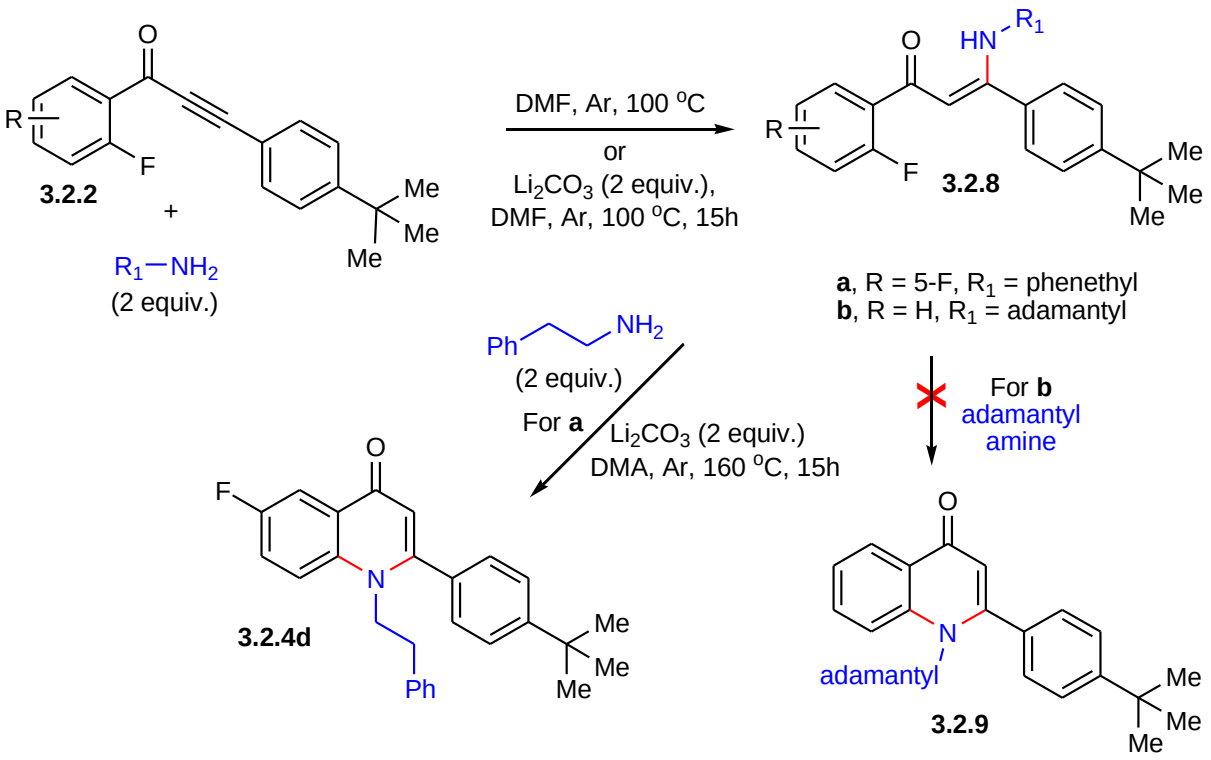
3.2.4. Unsuccessful results

It should be admitted that the reaction of ynones **3.2.2** with electron-deficient heteroaromatic amines, such as benzo[*d*]thiazol-2-amine, pyrimidin-2-amine, or pyridin-2-amine failed, moreover no conversion of starting materials took place. Additionally, the reaction of **3.2.2j** with all types of amines failed, though a number of reaction conditions were tested.

3.2.5. Mechanistic explanation

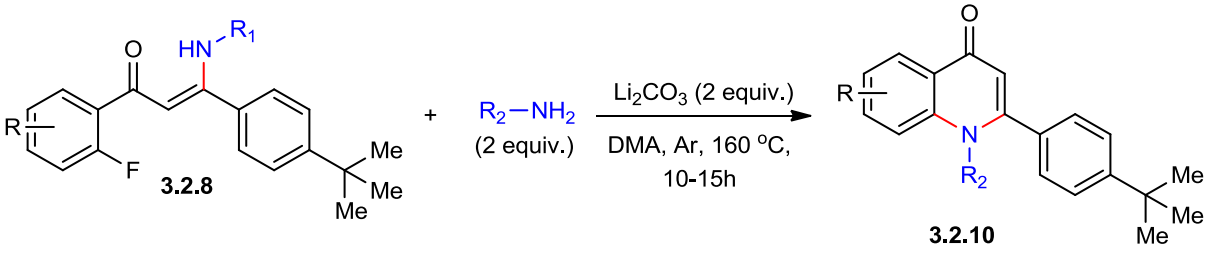
In order to understand the mechanism of the reaction we did some test reactions aiming to isolate some intermediates. For this purpose the reaction of **3.2.2c** with phenethylamine in DMF at 100 ^oC was performed for 10h. Unexpectedly, a spot different from our starting material and product was detected in TLC. Fortunately, we were able to isolated and determine the structure of product, that was a product of Michael type addition of amine to triple bond of alkyne **3.2.8** (Scheme 3.2.7). When the reaction was performed with 2

equivalents of Li_2CO_3, the similar product was obtained. Moreover, we found that it is possible to transfer the intermediate to corresponding quinolone **3.2.4d** in the standard conditions using 1 equivalent of appropriate amine. However, it should be mentioned that in a case of bulky amines the further cyclization was not possible, even under harsh conditions, like treatment with potassium carbonate in *N*-methyl-2-pyrrolidone (NMP) at 190 °C or in diphenyl ether at 220 °C.



Scheme 3.2.7. *Synthesis of the intermediates **3.2.8** and conversion to 4-quinolones.*

Nevertheless, when intermediates **3.2.8** was reacted with 2 equivalents of other amines, corresponding 4-quinolones **3.2.10** were obtained (Scheme 3.2.8, Table 3.2.7), although the yields were lower in comparison to one-pot synthesis of corresponding 4-quinolones.

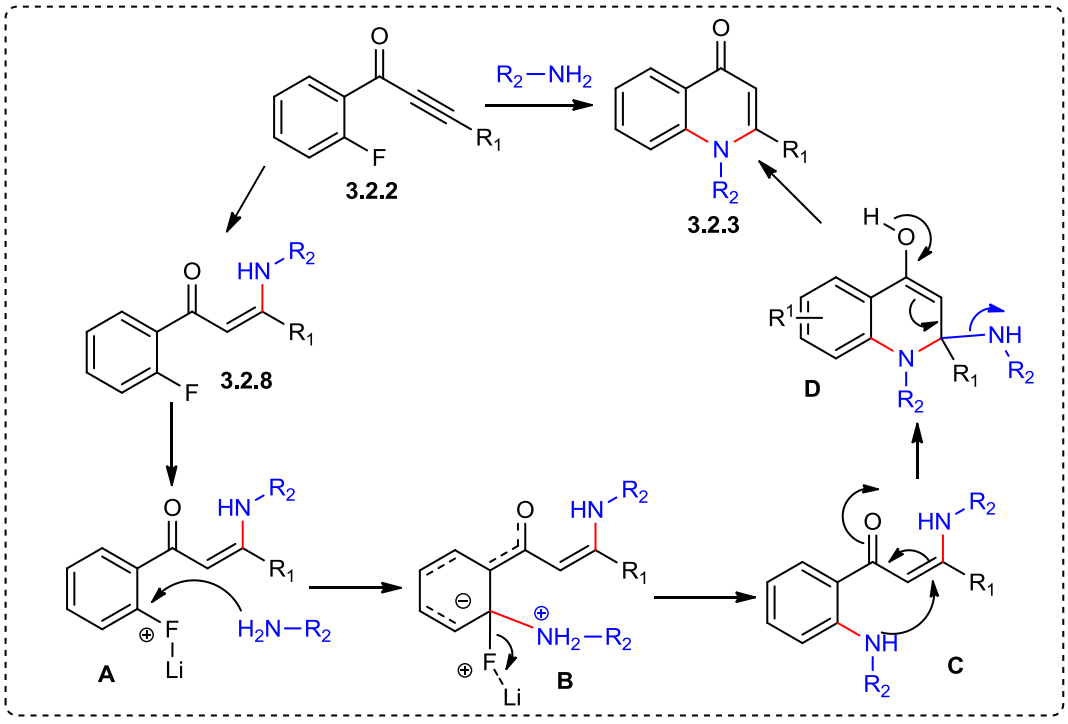


Scheme 3.2.8. *Conversion of intermediates **3.2.8** to the 4-quinolones **3.2.10**.*

Table 3.2.7. *List of 4- quinlones **3.2.10** synthesised from intermediates **3.2.8**.*

3.2.10	R	R_1	R_2	Yileds (%)
a	6-F	$(CH_2)_2Ph$	$3,5\text{-}(OMe)_2C_6H_3$	60
b	6-F	$(CH_2)_2Ph$	$4\text{-}MeOC_6H_4$	64
c	H	adamantyl	$4\text{-}ClC_6H_4$	70
d	H	adamantyl	$4\text{-}BrC_6H_4$	64

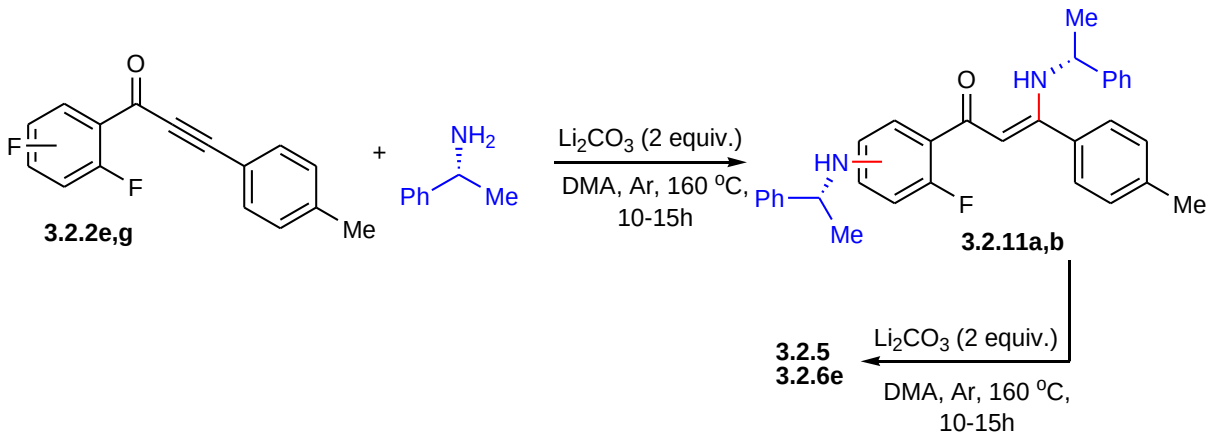
With these positive results in hand we assumed that one-pot synthesis of 4-quinolones starts with formation of intermediates **3.2.8a**,**b** by initial addition of appropriate amine to the alkynes **3.2.2** (Scheme 3.2.9). In the next step Li^+ coordinates to the F forming intermediate **A**. The latter undergoes an aromatic nucleophilic substitution with second molecule of amine *via* intermediate **B**. The elimination of fluorine anion in form of salt LiF delivers the intermediate **C**. Finally an intramolecular Michael addition *via* intermediate **D** leads to corresponding 4-quinolones **3.2.3**. In this step the reaction can go further, since the second fluorine atom may be substituted.



Scheme 3.2.9. *Putative mechanism for 4-quinolone **3.2.3** ring formation.*

Furthermore, in case of ynones, with two fluorine atoms in the molecule **3.2.2**, we could obtain another intermediate. Namely, the reaction of **3.2.2e**,**g** with 1 equivalent of a bulky amine, like (*R*)-(+)-(1-phenethyl)amine (the enantiomorically pure amine was chosen in order

to avoid diasteremeric pairs) leads to compound **3.2.11** (Scheme 3.2.10). These intermediates can also be easily transformed to corresponding quinolones **3.2.5**, **3.2.6e** using standard conditions.



Scheme 3.2.10. *Formation of the intermediates* ***C*** *(Scheme 3.2.9) and its conversion to the 4-quinolones* ***3.2.5***, ***3.2.6e***.

The structures of all intermediates and final products were determinate by ^{1}H, ^{19}F and ^{13}C NMR as well as with mass spectrometry (see Chapter 3.2.6). Moreover, in some cases the structures were also proved by X-Ray crystal structure analysis.

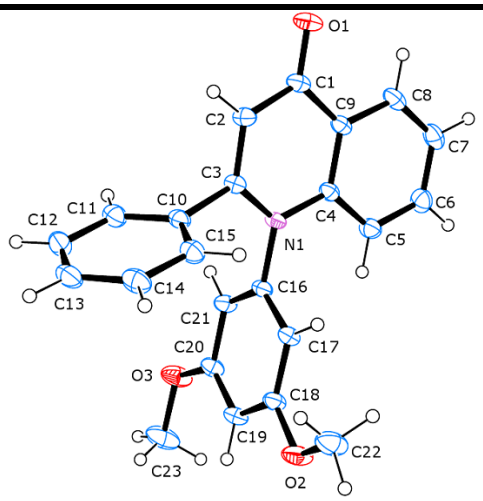
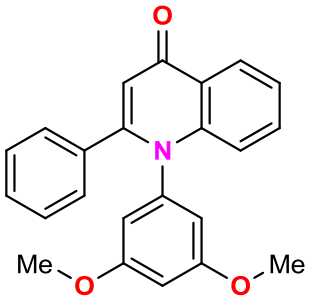
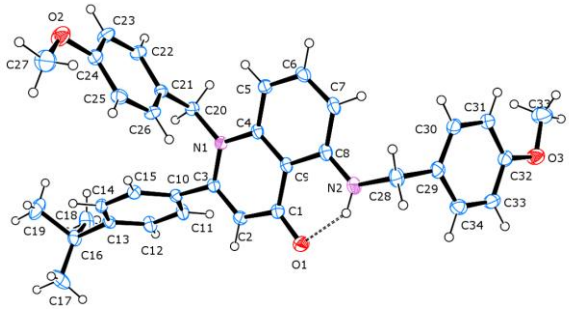
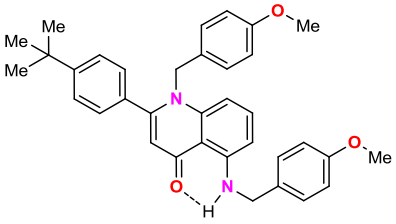
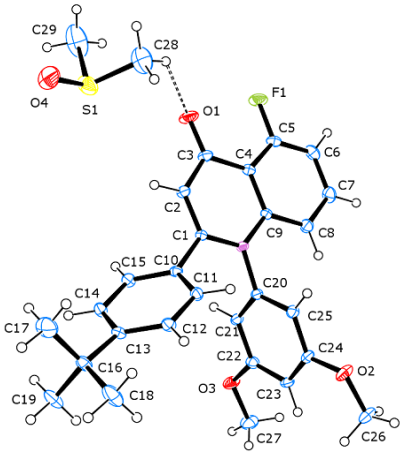
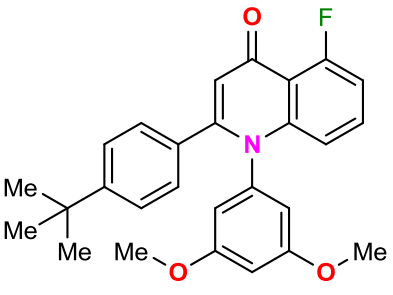
3.2.6. Structure identification

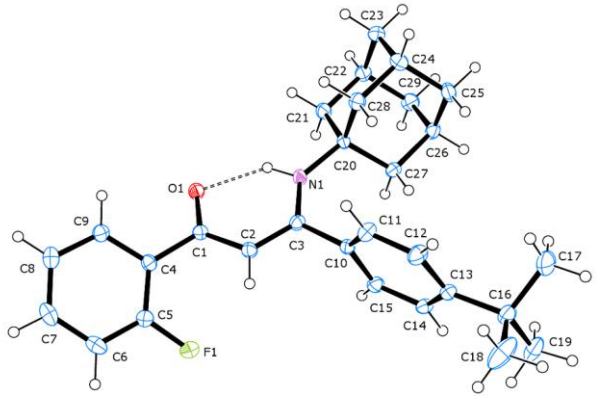
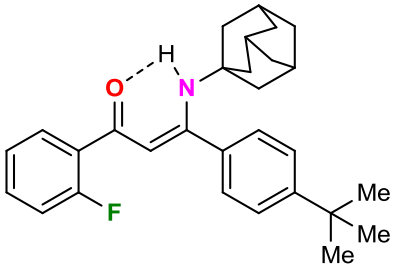
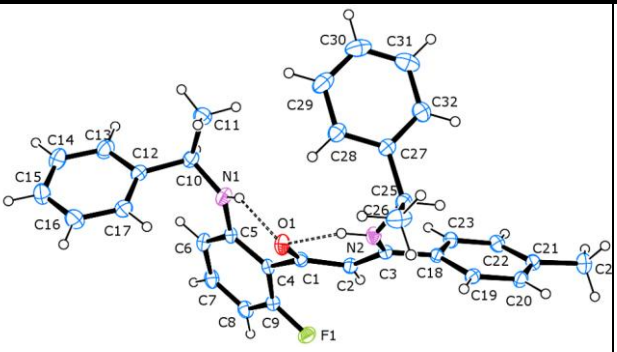
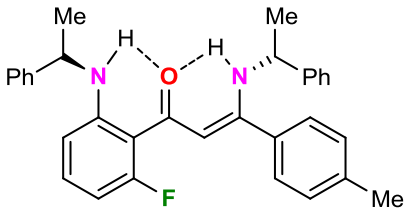
The structures of new synthesised compounds were corroborated by NMR methods, mass and IR spectroscopy. In ^{13}C NMR spectras of starting materials the carbon atoms of triple bond appears in 88.1-89.2 and 93.2-94.2 ppm, additionally the peak of carbon from carbonyl group shows up at 171.1-173.5 ppm ($CDCl_3$). In quinolones the *β*-C*H* was seen in ^{1}H NMR at 6.10-6.49 ppm, besides in ^{13}C NMR peaks of triple bond were gone, instead the *β*-*C* of quinolone ring appears at 111.2-114.7 ppm ($CDCl_3$). In ^{19}F NMR spectra we could see the peaks of fluorine in mono- and 2,6-disubstituted compounds (**3.2.2a**,**b** and **3.2.2f-i** respectively) at -111.0 ppm ($CDCl_3$). For 2,5- and 2,4-difluorine-substituted compounds (**3.2.2c**,**d** and **3.2.2e** respectively) was seen typical doublets at -117.0-117.0 ppm and -106.0-99.7 ppm respectively ($CDCl_3$). Moreover, the typical doublets were also seen in ^{13}C NMR at 160.0-162.0 ppm with a coupling constant 248-258 Hz ($CDCl_3$). Additionally, in case of products, where the second fluorine atom was substituted (**3.2.5, 3.2.6e**), the double peaks of corresponding amines were seen in addition to the broad singlet of N*H* at 10.4-10.76 ppm. In IR spectra peaks of C=O

and NH were detected at 1600-1640 cm^{-1} and 3310-3286 cm^{-1} respectively.

Independently a structure from each type of products was identified by X-ray crystal structure analysis. In the first three structures (Table 3.2.8) were seen the planar structure of quinolone core. In **3.2.6b** a hydrogen bond was seen between NH and carbonyl group. In open chain intermediates **3.2.11** and **3.2.8** O=C-C=C-NH fragment was almost planner due to hydrogen bonds, in addition all substituents were maximum away from each other (Table 3.2.8).

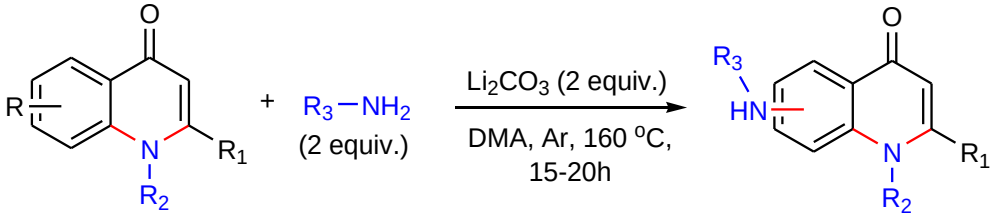
Table 3.2.8. *Crystal structures of **3.2.3f**, **3.2.6b**, **e**, **3.2.7h**, **3.2.8b**.*

Compound	Crystal	Structure
3.2.3f		
3.2.6b		
3.2.7h		

3.2.8b		
3.2.11b		

3.2.7. Further investigations

According to results obtained in the chemistry of ynones with two fluorine atoms, we were interested in preparation of some mixed substituted quinolones. As it was shown before, the second fluorine atom was not possible to substitute using anilines, consequently we tested the reaction of compounds **3.2.7d**,**f**,**g** with aliphatic amines using the standard reaction conditions developed by us. Gratifyingly, we succeed to prepare three examples of quinolones **3.2.12a-c** bearing an amino-substituent at fused benzene ring (Scheme 3.2.11, Table 3.2.9).



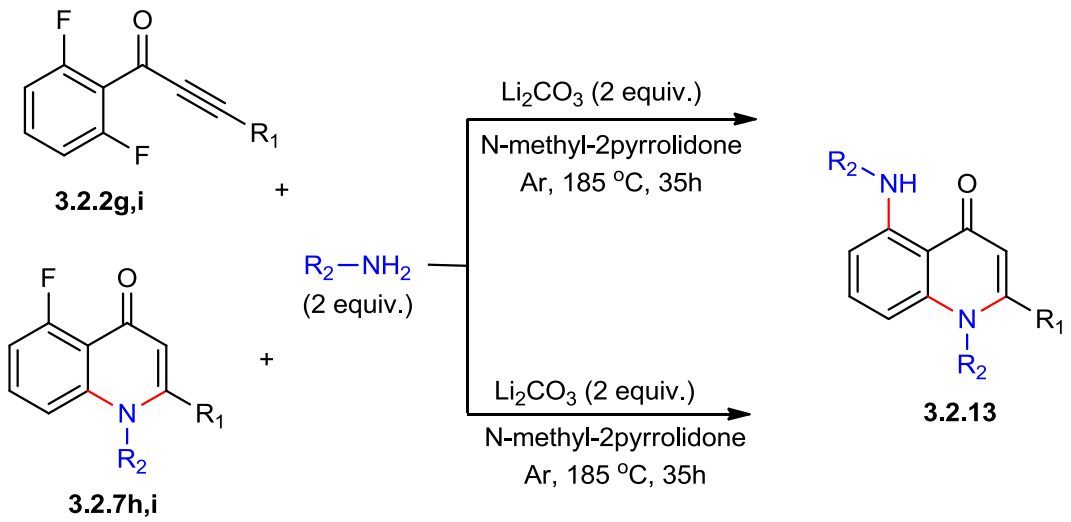
3.2.7d,f,g **3.2.12a-c**

Scheme 3.2.11. *Synthesis of 4-quinolones* ***3.2.12***.

Table 3.2.9. *List of synthesised 4-quinolones* ***3.2.12***.

3.2.12	R	R_1	R_2	R_3	Yields (%)
a	5-F	4-Tol	3,5-$Me_2C_6H_3$	$(CH_2)_2Ph$	97
b	5-F	4-Tol	4-EtC_6H_3	$(CH_2)_2Ph$	84
c	7-F	4-Tol	3,5-$Me_2C_6H_3$	$(CH_2)_5Me$	79

Unexpectedly, during careful examination of the reaction between ynones with two fluorine atoms and electron-rich anilines, we could detect appropriate aminated 4-quinolones, although the yields never overcome 3-5%. In this context the reactions of **3.2.2g**,**i** as well as **3.2.7h**,**i** with anilines were performed under harsher conditions, that is in *N*-methyl-2-pyrrolidone at 185 ^oC for 30h. Luckily, these reactions gave desired aniline disubstituted quinolones **3.2.13** in good yields (Scheme 3.2.12, Table 3.2.10).



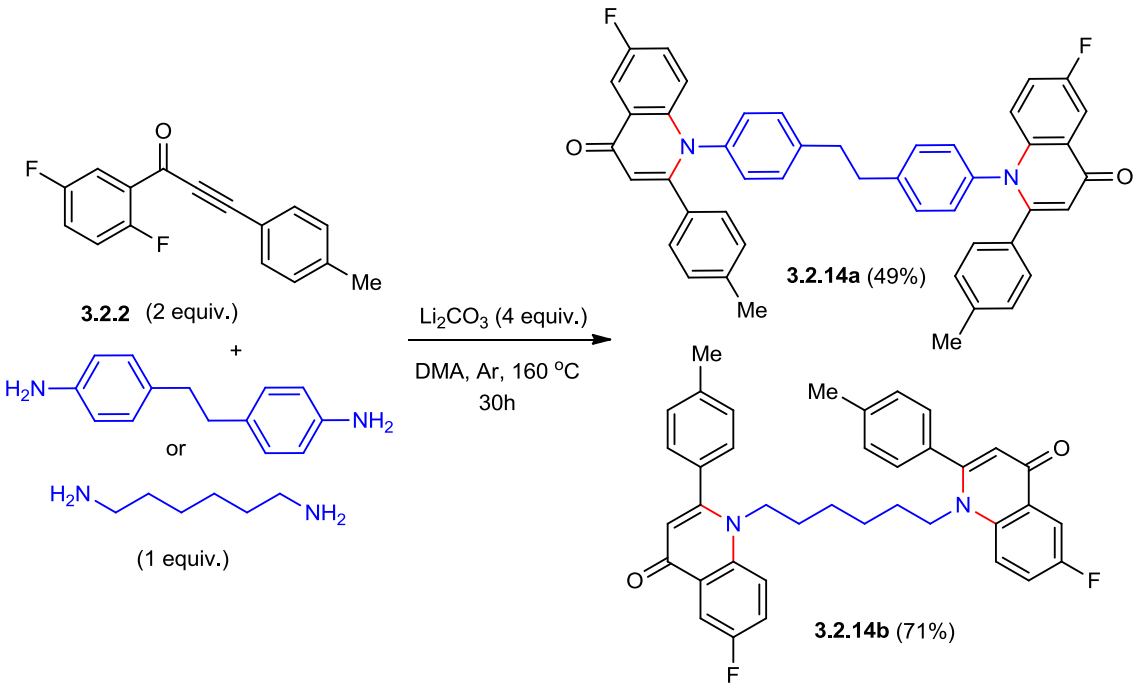
Scheme 3.2.12. *Synthesis of amino-substituted quinolones* ***3.2.13***.

Table 3.2.10. *List of synthesised dianiline-substituted quinolones* ***3.2.13***.

3.2.13	R_1	R_2	Yields (%)
a	4-Tol	4-EtC_6H_4	97
b	$(CH_2)_5Me$	4-$MeOC_6H_4$	84

Furthermore, we were interested in testing of our methodology towards more complex structures. Therefore the reaction of starting ynones **3.2.2** with diamines was carried out under standard reaction condition. The reaction was successful for both aliphatic and aromatic amines (Scheme 3.2.13). These results show that proposed methodology can be useful, for

instance, for construction of quinolin-4-one-containing dendrimers.



Scheme 3.2.13. *Synthesis of N,N'-linked 4-quinolones* ***3.2.14***.

3.2.8. Conclusion

As a conclusion a very easy and practical route for synthesis of different substituted 4-quinolones was developed starting from 1-(2-fluorophenyl)prop-2-yn-1-ones **3.2.2** and aliphatic or aromatic amines. It was possible to isolate some intermediates, which allowed us to explain the mechanism of the reaction in detail. The scope and limitations of the reaction was well studied. Proposed methodology gives a possibility to synthesize more complex 4-quinolone derivatives.

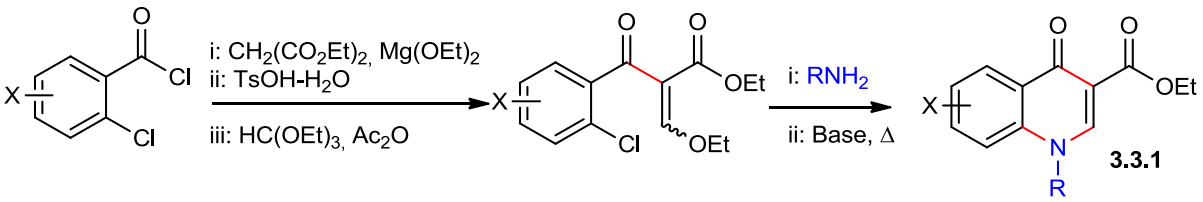
3.3. Amino group induced recyclization/ring formation of (*ortho*-fluoro)-3-bezoylchromones: A new [5+1] domino strategy for syntheszing of 4-quinolones

3.3.1. Introduction

Analysing the structures of pharmaceuticals based on 4-quinolone derivatives (see Figure 3.1.1) one can see that in most of the structures a carboxylic moiety is presented in position 3

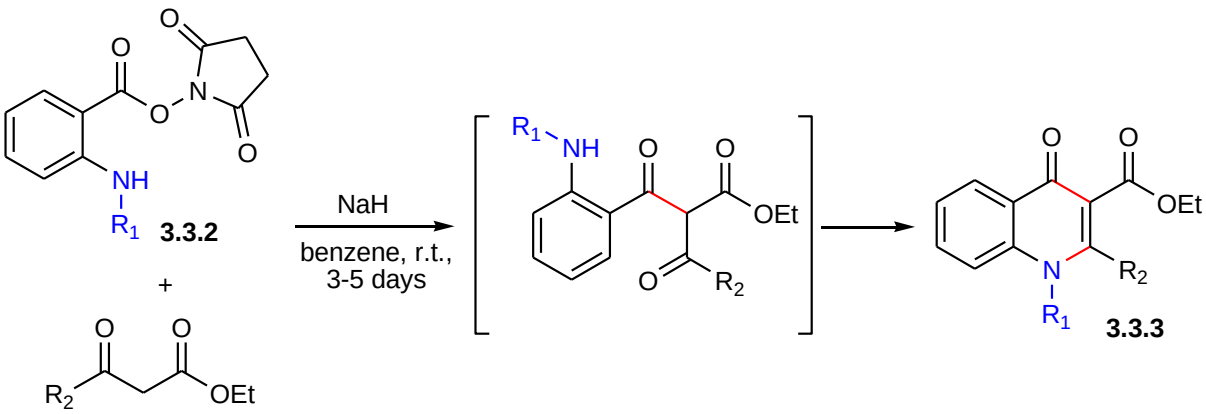
of 4-quinolone core. In course of our study on development of new and efficient methods for synthesis of 4-quinolones with potential bioactivity, on the next stage of our work we examined the possibilities for synthesis of 3-carbonyl-substituted 4-quinolones.

As was mentioned before, a bunch of methods are known in the literature for construction of 4-quinolones (Scheme 3.1.1). Among the methods discussed above perhaps the most versatile are methods based on [5+1] cyclizations due to the broad substrate scope allowing the synthesis of target systems with different substituents. In this context except the methodology described by us, worth mentioning the methodology based on the reaction of *N*-arylenaminones and nucleophiles (see Scheme 3.1.4). Furthermore, in the work of Bouzard *et al.* was presented another three step synthesis of 3-CO_2Et-substituted 4-quinolones, starting from 2-chlorobenzoyl chlorides which were first transformed to enol ether fragments that were treated with an amine to prepare corresponding 4-quinolone **3.3.1** (Scheme 3.3.1).[143]



Scheme 3.3.1. *Synthesis of 3-CO_2E-substituted 4-quinolone from ortho-haloaroyl halides.*

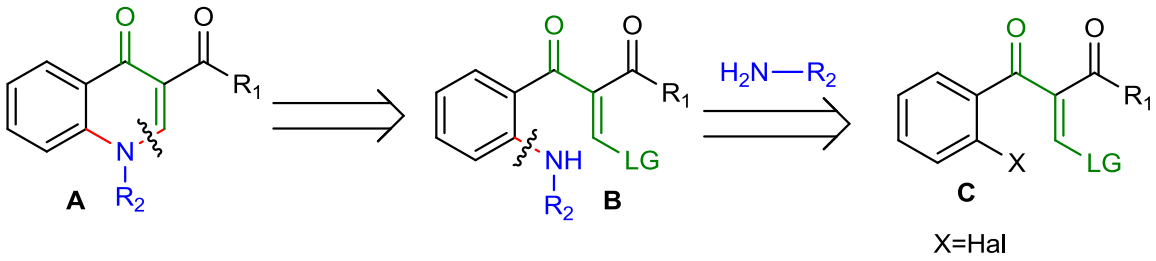
Additionally, a similar pathway was presented by Mitsos *et al*. The reaction of ester of *N*-hydroxysuccinimide and anthranilic acid **3.3.2** with *β*-keto esters gives an intermediate which spontaneously cyclise to corresponding 4-quinolone **3.3.3** (Scheme 3.3.2).[144]



Scheme 3.3.2. *Synthesis of 3-CO_2Et-substituted 4-quinolone starting from* ***3.3.2.***

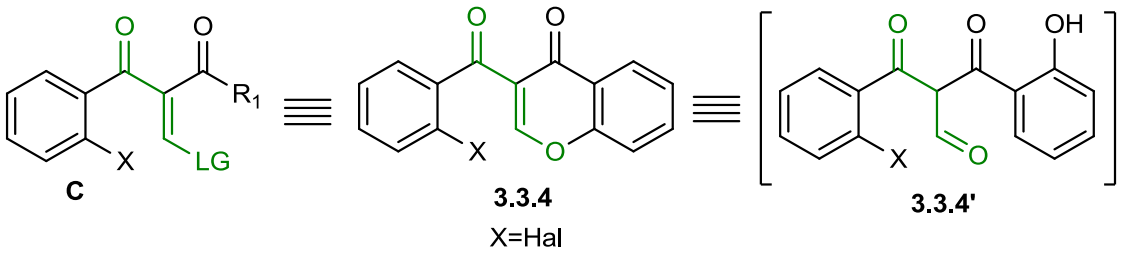
According to the literature data presented above and our previous experience we proposed a new approach for construction of 4-quinolones bearing a carbonyl substituent at position 3

based on the one step domino reaction (Scheme 3.3.3). The retrosynthetic analysis in principle is very much similar to what has been shown in Scheme 3.2.1. The main difference is that in this case instead of hydroamination of alkyne (Scheme 3.2.1 **II**) we have an intramolecular nucleophilic substitution on conjugate push-pull system (Scheme 3.3.3 **B**).



Scheme 3.3.3. *Retrosynthetic analysis of 3-carbonyl-4-quinolones* ***A***.

As it was presented in previous chapters chromones having an EWG (nitro group, carbonyl group etc.) at the position 3 are rather labile toward nucleophiles which can promote some pyrone ring-opening reactions. Moreover, it was proposed to consider such systems as masked diketones that can be used as 1,3-*CCC*-dielectrophiles. Accordingly, summarizing our results on the chemistry of chromones and 4-quinolones, we assumed that 3-benzoyl chromones, bearing a good leaving group in the *ortho*-position of benzoyl moiety, can be considered as useful starting materials for the synthesis of 4-quinolones bearing a carbonyl substituent at position 3 (Scheme 3.3.4).

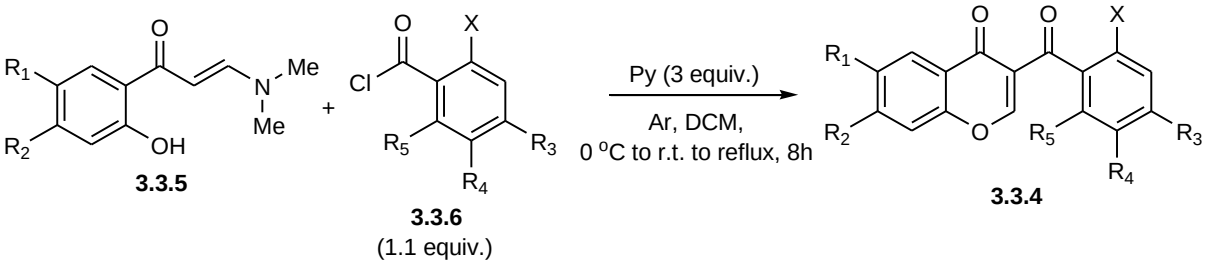


Scheme 3.3.4. *3-Benzoyl chromones as masked dielectrophiles.*

3.3.2. Synthesis of starting materials

In previous chapter we have demonstrated that fluorine atom can be a good leaving group in aromatic nucleophilic substitution reaction. Therefore we synthesized a number of *ortho*-halogen-substituted 3-benzoyl-4*H*-chromen-4-ones **3.3.4** as starting materials for synthesis of 4-quinolones. 3-Benzoyl-4*H*-chromen-4-ones **3.3.4** can be prepared from **3.3.5** and

corresponding halogenated benzoyl chlorides **3.3.6** under reflux in DCM using pyridine as base.[79] According this procedure a list of different 3-benzoyl chromones **3.3.4** were successfully synthesised with good to excellent yields (Scheme 3.3.5, Table 3.3.1).



Scheme 3.3.5. *Synthesys of ortho-halogen-substituted 3-benzoyl-4H-chromen-4-ones **3.3.4**.*

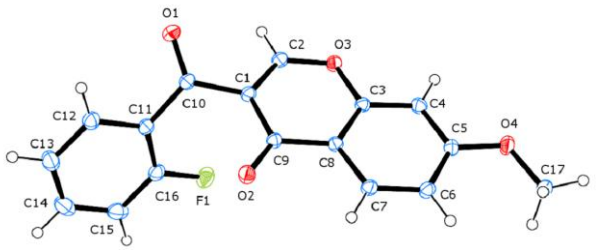
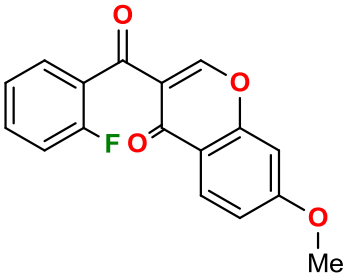
Table 3.3.1. *List of synthesised ortho-halogen benzoyl chromones **3.3.4**.*

3.3.4	X	R_1	R_2	R_3	R_4	R_5	Yileds (%)
a	Br	H	H	H	H	H	81
b	Cl	H	H	H	H	H	80
c	F	H	H	H	H	H	78
d	F	Me	H	H	H	H	80
e	F	H	OMe	H	H	H	88
f	F	Cl	H	H	H	H	71
g	F	Cl	Me	H	H	H	58
h	F	H	H	F	H	H	60
i	F	H	H	H	F	H	95
j	F	Br	H	H	F	H	75
k	F	H	H	H	H	F	66

All compounds were purified by column chromatography. Structures of starting materials were characterised by NMR spectroscopy (^{1}H, ^{13}C, ^{19}F, see Chapter 3.3.5). Furthermore, the structure of **3.3.4e** was also supported by X-ray crystal structure analysis (Table 3.3.2).

Table 3.3.2. *X-ray crystal structures of compound **3.3.4e.***

Compound	Crystal	Structure

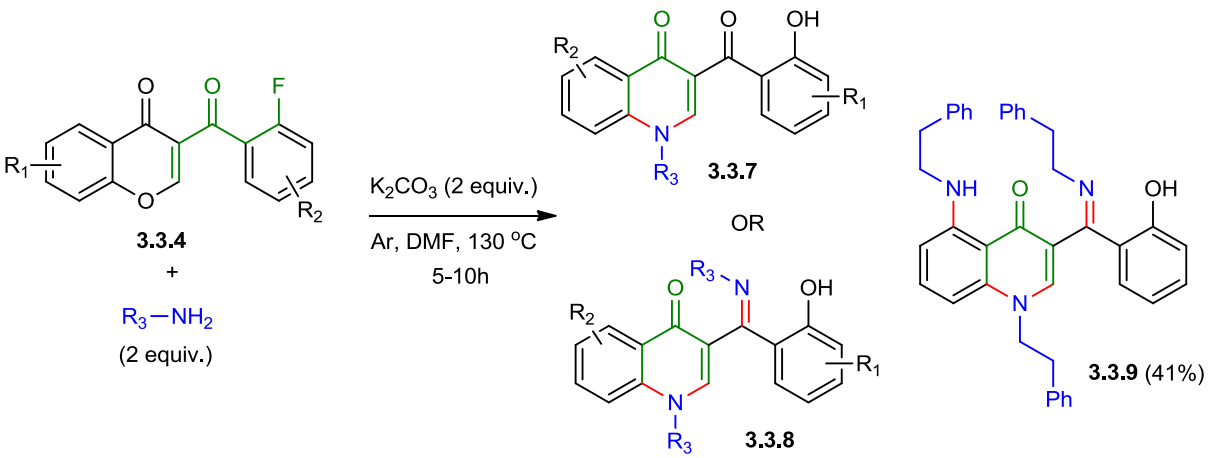
3.3.4e		

3.3.3 Results and discussions

With the list of starting materials in hand we started working on study and optimisation of desired cyclization reaction. For this purpose a test reaction of **3.3.4b** (X = Cl) and phenethylamine was performed in DMF at 100 ^{o}C using K_2CO_3 as a base. Fortunately, starting from initial test reaction desired 4-quinolone ring formation was observed, though the yield was only 22%. The same reaction in similar conditions with chromone **3.3.4a** (X = Br) did not work at all. Since earlier (see Chapter 3.1) with similar transformation we had an excellent results using aromatic nucleophilic substitution of fluorine, next the starting chromone with X = F was tested. Not surprisingly, from primary test reactions the yield was improved to 65%. Interestingly, the use of other bases like Na_2CO_3, Li_2CO_3, Cs_2CO_3, NEt_3 etc. did not increase the yield over 67%. The next tool for optimization of reaction conditions was the manipulation of the temperature. Luckily, performing the reaction in DMF using K_2CO_3 as base at increased up to 130 ^{o}C temperature, we could improve the yield to 82%. Additionally, the change of base and/or solvent (DMA, NMP) did not raise the yield. Having optimal reaction conditions in hand the scope of the reaction was examined with regard to different chromones **3.3.4c-k** and aliphatic amines (Scheme 3.3.6, Table 3.3.3).

Interestingly, we found that in most of the cases the reaction did not stop on quinolone ring formation **3.3.7**, instead of this the formed product reacts with second molecule of amine leading to formation of the appropriate Schiff base **3.3.8**. Notably, the only case when we could avoid the formation of Schiff base was the use of bulky *t*-butylamine **3.3.7a**. In all other cases the formation of simple product **3.3.7** was not detected, even though the reaction was carried out with 1 equivalent of amine. Moreover, in case of chromone **3.3.4h-j** with second fluorine atom located at *meta* or *para* position to carbonyl group, the substitution of second fluorine by appropriate amine in standard reaction conditions was not detected (Table 3.3.3). Nevertheless, in case of chromone **3.3.4k** with second fluorine located in the *ortho*-position of carbonyl group, expectedly substitution of second fluorine with amine accrued (see also previous chapter) leading to single product **3.3.9** detected in 41% yield (Scheme 3.3.6). Thus

a number of aliphatic amines including cyclic amines can be successfully used in the reaction (Table 3.3.3). In addition, the purification of final products was quite easy, in most of the cases a simple recrystallization or washing was enough to get a clean product.



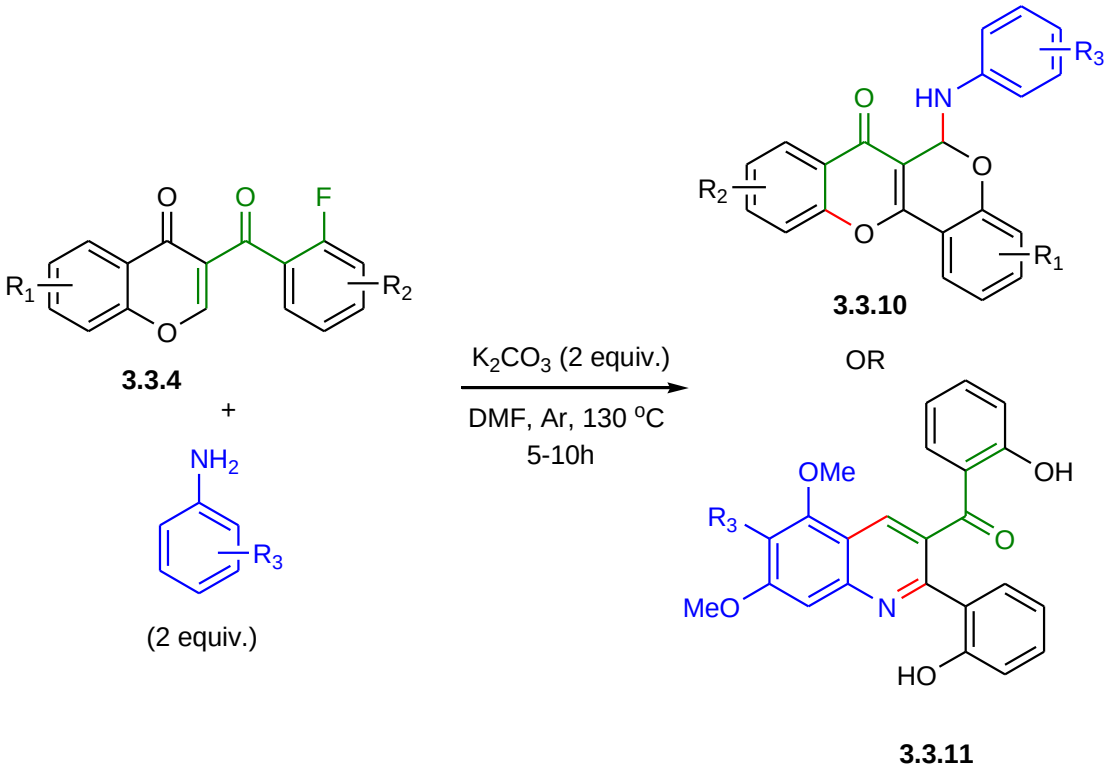
Scheme 3.3.6. *Synthesis of 3-ortho-hydroxybenzoyl-substituted 4-quinolones* ***3.3.7***, ***3.3.8,*** ***3.3.9***.

Table 3.3.3. *List of synthesised 3-ortho-hydroxybenzoyl-substituted 4-quinolones* ***3.3.7***, ***3.3.8***.

	R_1	R_2	R_3	**3.3.7** (%)	**3.3.8** (%)
a	H	H	*t*-Bu	55	-
b	H	H	Cyclohexyl	-	46
c	H	H	Cyclopropyl	-	48
d	H	H	$(CH_2)_2C_6H_5$	-	74
e	H	H	*n*-Hexyl	-	65
f	4-OMe	H	Cyclopentyl	-	55
g	5-Cl	H	$(CH_2)_3C_6H_5$	-	53
h	4-Me-5-Cl	H	*n*-Hexyl	-	70
i	H	6'-F	$(CH_2)_2C_6H_5$	-	78
j	5-Br	6'-F	$(CH_2)_2C_6H_5$	-	40

An interesting result was observed when anilines were used instead of aliphatic amines. Namely in the same reaction conditions depending on substituents of anilines two different products were observed that were condensed chromone derivatives **3.3.10** and small amount of quinoline **3.3.11** (Scheme 3.3.7, Table 3.3.4). Interestingly, so far no single product of quinolone ring formation was observed, although several anilines were examined. Structure of prepared products was determinate by 1D and 2D NMR. The structure of **3.3.11** was also

possible to characterise by X-ray crystal structure analysis (see Chapter 3.3.5).



Scheme 3.3.7. *Synthesis of **3.3.10**, **3.3.11** using anilines.*

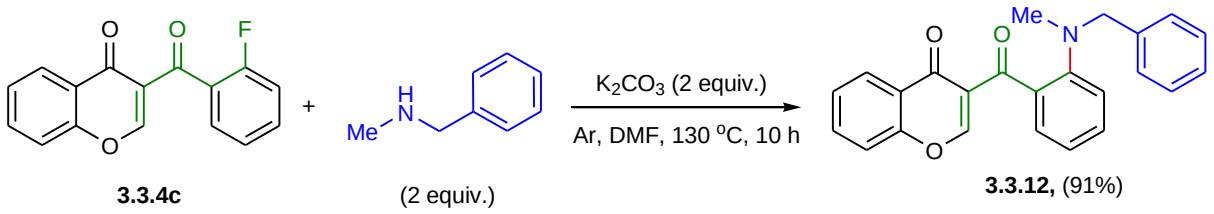
Table 3.3.4. *List of synthesised 4-quinolones **3.3.10** and quinolines **3.3.11**.*

	R_1	R_2	R_3	Yields (**3.3.10**%)	Yields (**3.3.11**%)
a	H	H	4-F	84	-
b	H	H	3-CF_3	74	-
c	5-Cl	H	3-CF_3	50	-
d	4-Me-5-Cl	H	3-CF_3	54	-
e	H	6-F	3,5-Cl_2	71	-
f	H	H	3,4,5-$(OMe)_3$	70	-
g	5-Me	H	OMe	60	10
h	5-Me	H	H	55	8

To date the work on exploration of list of anilines is in progress. Besides, in order to clarify how the electronic effects of substituents in amines can influence on reaction pathway, we are planning to use some heterocyclic amines as well (see also Chapter 3.3.4).

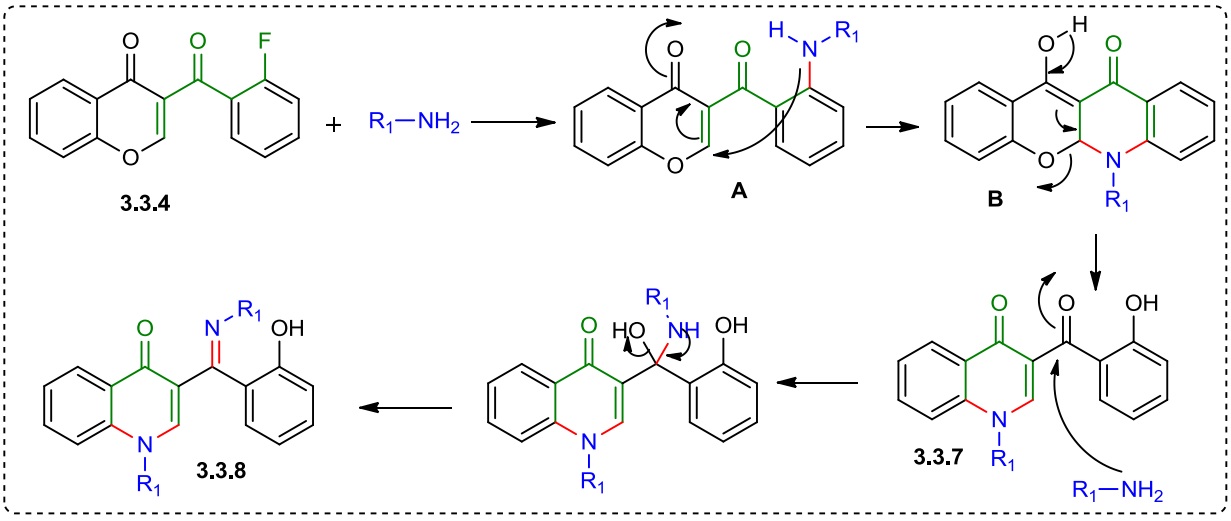
3.3.4. Mechanistic explanation

Before the prediction of anything putative concerning mechanism of the reaction we tried to detect some possible intermediates. For this purpose the reaction of chromone **3.3.4c** with a secondary aliphatic amine was performed using standard reaction conditions. Interestingly, corresponding amino-substituted chromone **3.3.12** was isolated in almost quantitative yield (Scheme 3.3.8). That means that the reaction probably starts with aromatic nucleophilic substitution of fluorine, the usage of secondary amine locks the domino reaction in the first step.



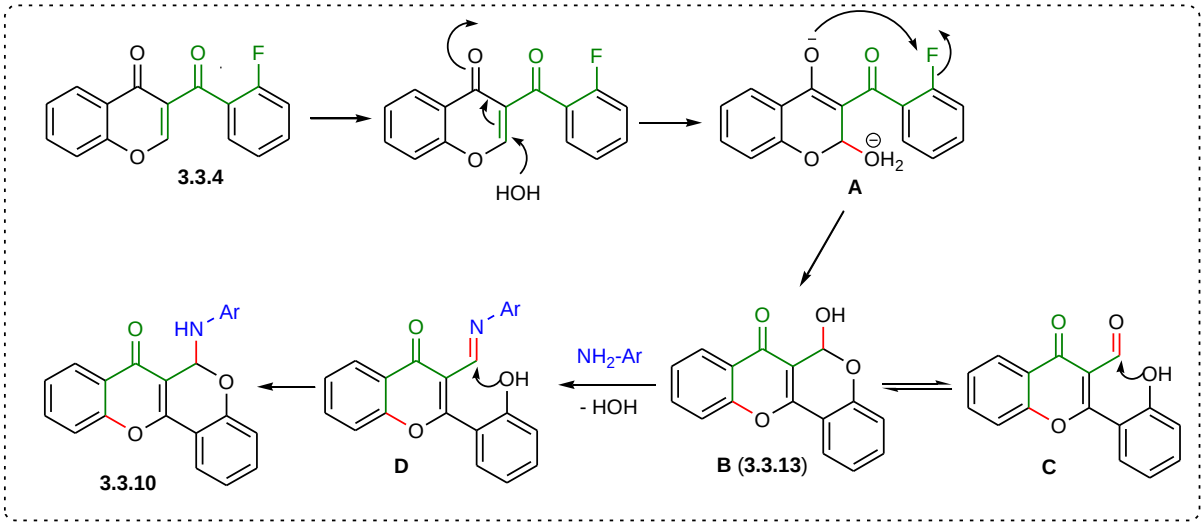
Scheme 3.3.7. *Synthesis of possible intermediate **3.3.12.***

Having these results in hand we assume that the reaction of aliphatic amines with corresponding chromone starts with aromatic nucleophilic substitution of fluorine atom leading to formation of intermediate **A**. The following intramolecular attacks of amino group to 2nd position of chromone moiety forms intermediate **B**. Finally the recyclization of pyrone ring delivers desired 4-quinolones **3.3.7** (Scheme 3.3.9). In most of the cases this is not the final step, the reaction runs further with second molecule of amine leading to the formation of corresponding Schiff bases **3.3.8**.



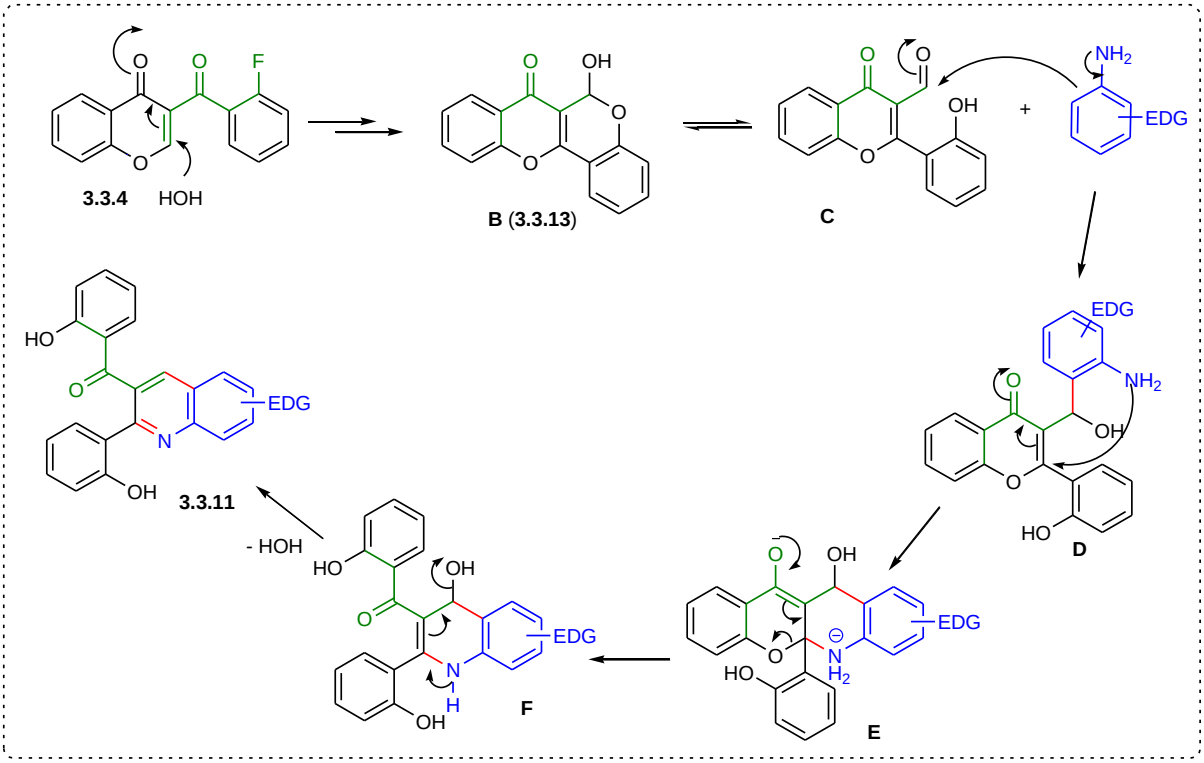
Scheme 3.3.9. *Putative mechanism of 4-quinolone **3.3.7**, **3.3.8** formation.*

The formation of unexpected condensed chromone derivative **3.3.10** can be explained by admitting an unusual behavior of anilines. While the reaction of chromone **3.3.4** with aliphatic amines starts with aromatic nucleophilic substitution of fluorine, in case of anilines the reaction most probably initiates by water that can be presented in the base (K_2CO_3) in trace amounts. We assume that in this case the reaction starts with nucleophilic attack of water onto the position 2 of pyrone fragment, which gives rise to the intermediate **B** *via* intermediate **A**. Fortunately, we could isolate and characterize intermediate **B** (compound **3.3.13**), including by X-ray analysis. Intermediate **B** in basic media can be presented in two tautomeric forms (intermediates **B** and **C**). Hence, in this stage corresponding aniline can attack the carbonyl group of intermediates **C** leading to the formation of Schiff base (intermediates **D**) through release of water that can initiate another cycle. Finally intermediate **D** in basic conditions can be transformed to appropriate hemiaminals **3.3.10**, which most probably are more stable than corresponding hemiacetals (intermediates **B**).



Scheme 3.3.10. *Putative formation of compound **3.3.10**.*

The formation of unusual quinoline derivative **3.3.11** can be explained following the same considerations. Thus, the intermediate **C** (formed by nucleophilic attack of water to pyrone ring of **3.3.4**) can be attacked by enamine-like carbon of electron-excessive aniline forming intermediate **D**. This can be followed by intramolecular nucleophilic attack of amino group to the 2nd position of pyrone ring that will cause a pyrone ring opening *via* intermediate **E**. Finally, the 1,4-dihydroquinoline intermediate (**F**) can form corresponding quinoline derivative **3.3.11** through release of water that can initiate another cycle (Scheme 3.3.11).



Scheme 3.3.11. *Putative mechanism of formation of quinoline derivative* ***3.3.11***.

3.3.5. Structure identification

The structures of new synthesised compounds were corroborated by NMR, mass and IR spectroscopy. In all *ortho*-fluorine-substituted and 2,6-disubstituted 3-benzoyl-4*H*-chromen-4-ones (**3.3.4c-g** and **3.2.2k** respectively) the ^{19}F NMR show the presence of fluorine atom at -111.0 ppm ($CDCl_3$). For 2,4- and 2,5-difluorine-substituted compounds (**3.3.4h** and **3.3.4i** respectively) was seen typical doublets at -106.0 -102.0 ppm and -117.7 -117.0 ppm respectively ($CDCl_3$). Moreover, the typical doublets were also seen in ^{13}C NMR spectra at 160.0 - 162.0 ppm with a coupling constant 248 - 258 Hz ($CDCl_3$). In ^{1}H NMR the typical singlet of quinolone ring in all prepared quinoline derivatives **3.3.7-3.3.9**, **3.3.11** appears at 7.2-7.8 ppm ($CDCl_3$) and 7.7-8.3 ppm (DMSO-d_6). Furthermore, the O*H* gives a broad singlet at 14.5-16.1 ppm ($CDCl_3$) and 16.0 ppm (DMSO-d_6). In ^{13}C NMR corresponding quinolone C*H* occurs at 116.3-118.0 ppm ($CDCl_3$) and 120.2-121.2 ppm (DMSO-d_6). The structures of condensed chromone derivatives **3.3.10** were first studied by 2D NMR spectroscopy. Particularly, in HSQC spectra the proton at 7.02-7.10 ppm (DMSO-d_6) turned to be NH group instead of CH. Accordingly, the chiral C*H* proton next to the NH group gives a doublet at 6.6-6.9 ppm (DMSO-d_6). Furthermore, in HMBC spectra of compound **3.3.10h** the correlation between NH and carbons C-11 and C-12 as well as the correlation between CH and carbons

C-10, C-19, C-24 were seen (Figure 3.3.1). Additionally, in NOESY spectra the correlation between the chiral CH and the *ortho*-CH bonds of aniline moiety is well seen. The typical pick of chiral <u>*C*</u>H in ^{13}C NMR spectra was detected at 76.4-77.8 ppm (DMSO-d_6). In case of quinolines **3.3.11** the proton of pyridine ring gives a singlet at 8.15 ppm ($CDCl_3$), moreover two O<u>*H*</u> groups are seen at 11.8 and 12.7 ppm ($CDCl_3$).

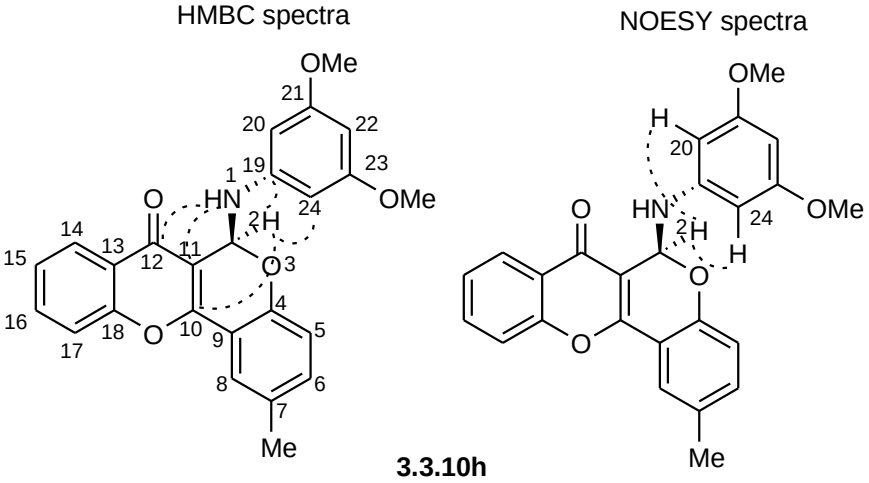
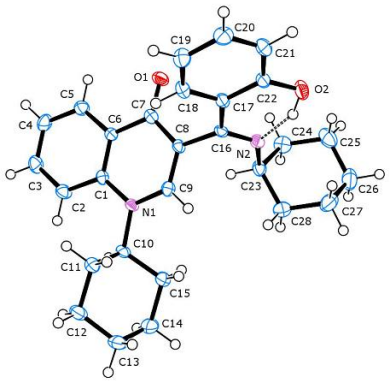
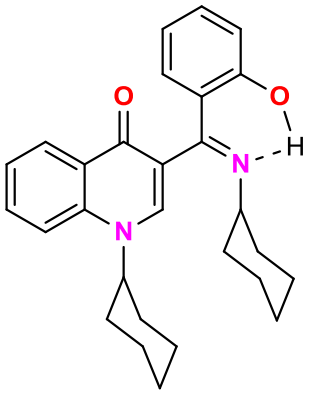
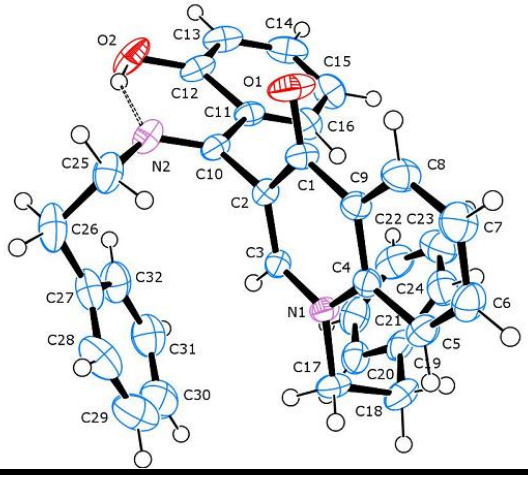
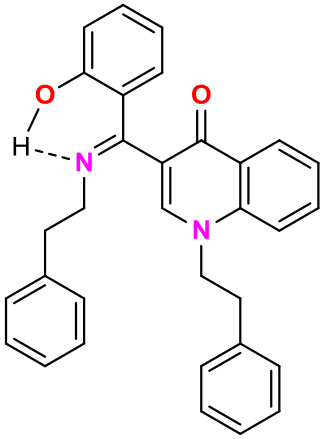
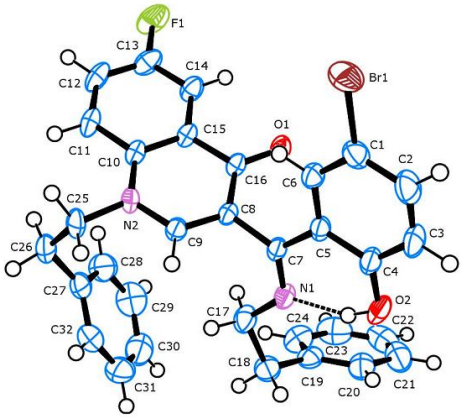
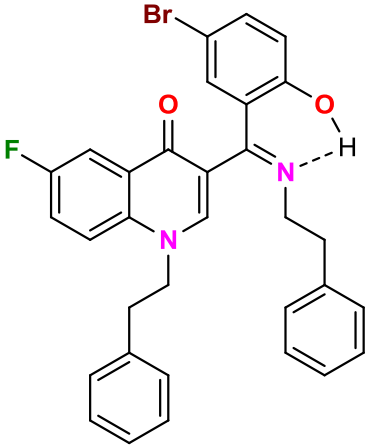
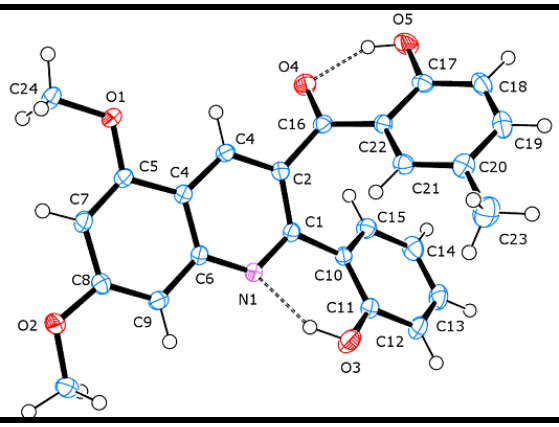
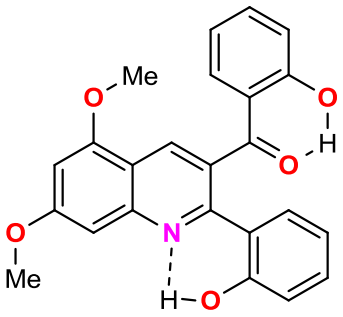
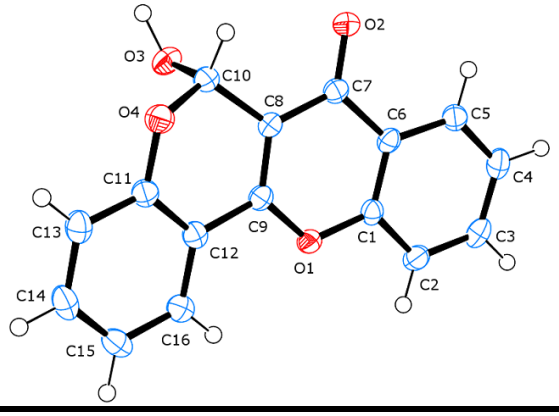
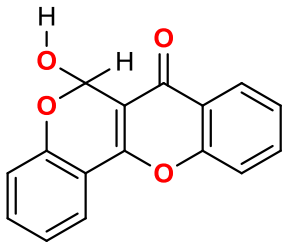


Figure 3.3.1. *2D NMR from **3.3.10h***.

At least a structure from each type of compounds was independently characterized by X-ray crystal structure analysis (Table 3.3.5). In the first three structures was detected the flat framework of quinolone core. Another general property was that in all three structures the fragment of Schiff base was almost perpendicular to the quinolone plane (the torsion angle was 60-90^o). In addition, a hydrogen bond was present in all cases between OH of the benzoyl fragment and nitrogen atom of Schiff base moiety. Besides, the substituents of two nitrogen atoms were maximum away from each other which is probably energetically more favourable for the molecule. Furthermore, in the structure of compound **3.3.8i** was presented the second fluorine atom in *meta*-position to carbonyl group. Similarly, in compound **3.3.11h** the flat core of quinoline system was observed. The *ortho*-hydroxyphenyl and *ortho*-hydroxybenzoyl substituents were out of the quinoline plane (torsion angels were C2-C1-C10-C15 = -33.52^o and C1-C2-C16-C22 = -48.32^o respectively), though two hydrogen bonds between the OH of *ortho*-hydroxyphenyl group and quinoline nitrogen and carbonyl oxygen and OH of *ortho*-hydroxybenzoyl group were detected. Finally, the structure of intermediate **3.3.13** was almost planer, only the C-10 was out from the polycyclic plane (torsion angels are C12-C9-C8-C10 = -7.94^o and C12-C11-O4-C10 = 27.47^o). The identification of all other synthesised compounds was obtained by comparison of the X-ray crystallography and NMR data.

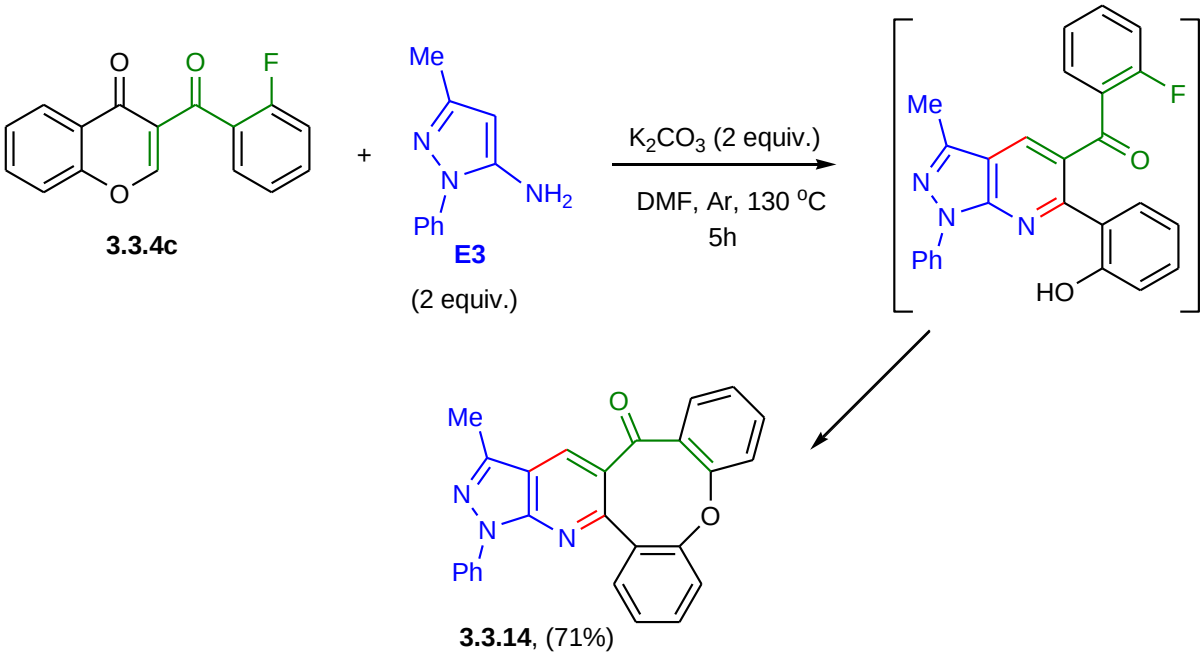
Table 3.3.5. *X-ray crystal structures of* ***3.3.8b,d,i***, ***3.3.11h***, ***3.3.13***.

Compound	Crystal	Structure
3.3.8b		
3.3.8d		
3.3.8i		

3.3.11h		
3.3.13		

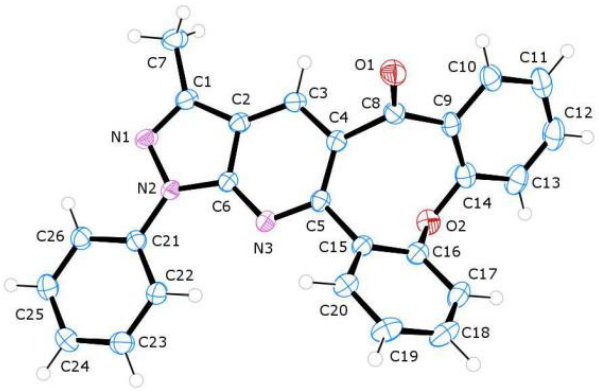
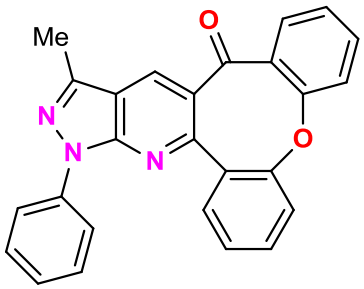
3.2.7. Further investigations

In order to extend the substrate scope of proposed methodology initial chromone **3.3.4c** was reacted with electron-excessive amioheterocycles (see Chapter 2.1, Figure 2.1.2). In this context the test reaction of **3.3.4c** with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **E3** in standard reaction conditions not surprisingly delivered to corresponding pyrazolopyridine fused system **3.3.14** in 71% yield (Scheme 3.3.12). Interestingly, in this case among usual domino pyrone ring opening and pyridine ring closure, we observed an unexpected intramolecular substitution of fluorine by phenol OH that leads to formation of an eight membered ring. We suppose that the formation of pyrazolopyridine system proceeds with similar mechanistic pathway presented in previous chapters. The structure of **3.3.14** was determined by 1D NMR spectroscopy and by X-Ray crystal structure analysis (Table 3.3.6).

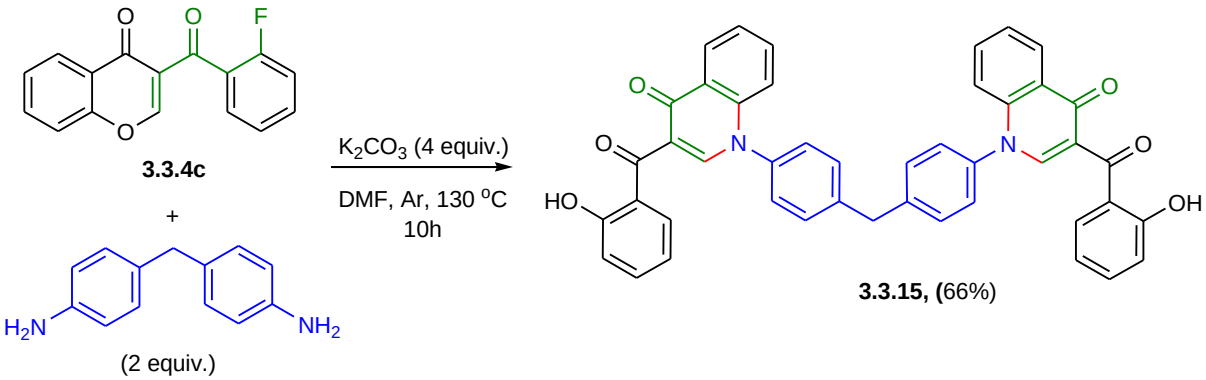


Scheme 3.3.12. *Synthesis of pyrazolo[3,4-b]pyridine **3.3.14** from 5-aminopyrazole **E3**.*

Table 3.3.6. *X-ray crystal structures of **3.3.14**.*

Compound	Crystal	Structure
3.3.14		

Finally, with an eye to extend the work of previous chapter (see Chapter 3.2, Scheme 3.2.13) we tried to perform the synthesis of linked quinolones using diamines. For this purpose the reaction of benzoyl chromone **3.3.4c** with 4-(4-aminobenzyl)benzenamine was examined in standard reaction conditions. Fortunately, we were able to synthesize desired linked 4-quinolone derivative **3.3.15** in moderated yield, thus once more demonstrating the huge synthetic potential of proposed methodology (Scheme 3.3.12).



Scheme 3.3.12. *Synthesis of linked 4-quinolone* ***3.3.15***.

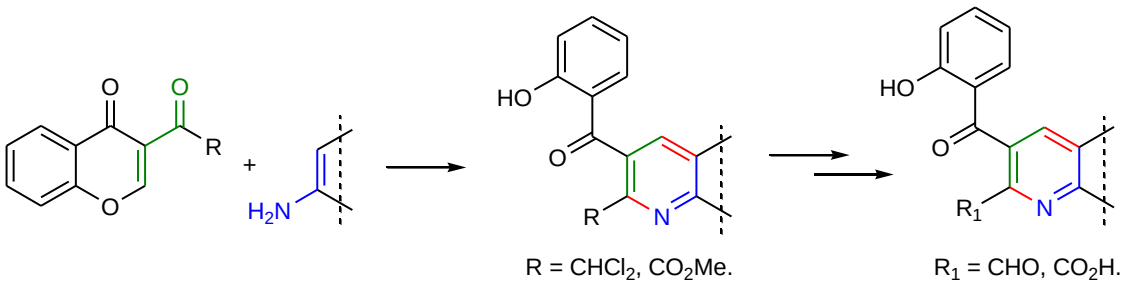
3.3.8. Conclusion

In summary we have demonstrated a new and easy way for synthesis of 4-quinolone derivatives *via* [5+1] domino cycloaddition reaction of *ortho*-fluorine-substituted benzoylchromones **3.3.4** and aliphatic amines. The method proved to be rather sensitive towards the nature of used amines. Particularly, in case of anilines different unexpected products were prepared. Hence, the observed properties made initial chromones an important tool for synthesis of new fused pyridine derivatives. The extension of scope and limitations of the methodology is under extensive study.

4. Summary

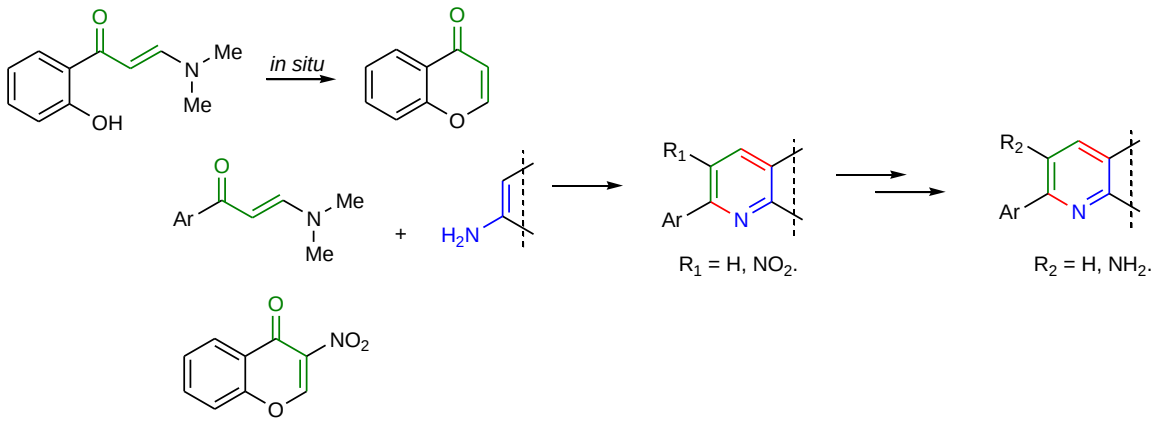
The scope of this thesis is to show the chemical potential of chromones, other masked dielectrophiles and electron-excessive aminoheterocycles as building blocks for the synthesis of new fused pyridine derivatives.

As described in Chapters **2.3** and **2.4** the [3+3] domino reaction of chromones bearing a carbonyl fragment at position 3 with electron-excessive aminoheterocycles in acidic media leads to the formation of fused pyridines bearing a *β*-benzoyl fragment with exceptional regioselectivity. The scope and limitations of the reaction along with some further transformations was studied (Scheme 4.1).



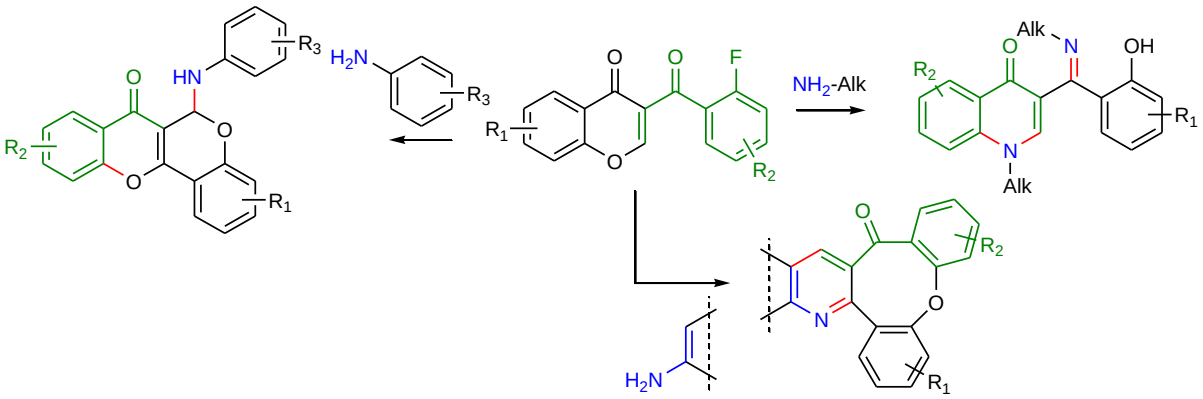
Scheme 4.1.

Further investigations described in Chapters **2.5** and **2.6** show that the [3+3] domino reaction of 2,3-unsubstituted chromones (generated *in situ*), enaminones and chromones bearing an electron withdrawing nitro group at position 3 with electron-excessive aminoheterocycles in acidic media leads to the formation of fused pyridines bearing an *α*-aryl fragment with exceptional regioselectivity. The scope and limitations of the methodology along with some further transformations was studied (Scheme 4.2).



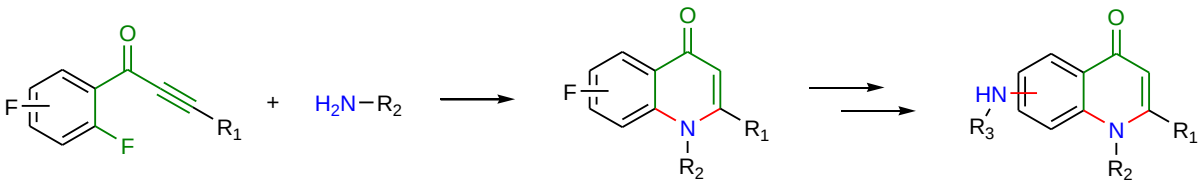
Scheme 4.2.

Subsequently the domino reaction of (*ortho*-fluoro)-3-bezoylchromones with aliphatic amines, anilines and electron-excessive aminoheterocycles was studied (Chapter **3.3**). According to applied nucleophile the reaction provided different final products, namely quinolones and other fused systems. The scope and limitations of the proposed concept was studied (Scheme 4.3).



Scheme 4.3.

Finally inspired by the results of the domino reaction of (*ortho*-fluoro)-3-bezoylchromones with aliphatic amines described in Chapter **3.3**, a new efficient [5+1] synthesis of 4-quinolones by domino amination and conjugate addition reactions of 1-(2-fluorophenyl)prop-2-yn-1-ones with amines was developed (Chapter **3.2**). The scope and limitations of the method along with some further transformations was studied (Scheme 4.4).



Scheme 4.4.

Appendixed

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 = 7.25 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, dt = double of triplet, q = quartet, quint = quintet; 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 $CDCl_3$; δ = 39.7 ppm for DMSO-d_6. 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: q = quartet. The multiplicity of the signals was determined by the DEPT and/or the APT recording technologies.

Mass Spectroscopy (MS): AMD MS40, AMD 402 (AMD Intectra), Varian MAT CH 7, MAT 731.

High Resolution mass spectroscopy (HRMS): 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, $\lambda = 0.71073$ Å).

Melting points: 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.

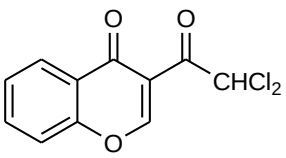
Thin layer chromatography: Merck DC finished aluminum foils silica gel 60 F254 and Macherey finished foils Alugram® Sil G/UV254. Detection under UV light at 254 nm and/or 366 nm without dipping reagent, as well as with vanillin-sulfuric acid reagent (1 mL vanillin in 100 mL stock solution of 85% methanol,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

Chemicals and work technique: All solvents for using were distilled by standard methods. All of the chemicals are standard, commercially available from Merck®, Aldrich®, Arcos® and others.

A.2. General procedures and spectroscopic data

*A.2.1. General procedure for the synthesis of 3-(Dichloroacetyl)chromone **2.3.2**:*

To a dry dichloromethane solution (100 mL) of 3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one **2.3.1** (20 g, 105 mmol), 27 mL of dry pyridine (345 mmol) was added. The solution was set on stirring on ice bath, and corresponding dichlor acetylchloride (11.1 mL, 115.5 mmol) was added dropwise. The reaction mixture was stirred at r.t. for 8 h. Afterwords the solvent was removed in vacuo. The formed solid was well washed with water to give a black crude material, which was then purified by flash column chromatography. Chromone **2.3.2** was obtained as light yellow crystals (19.3 g, 75%), mp 173-174 ^{o}C.



^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.57 (s, 1H, $CHCl_2$), 7.58-7.64 (m, 1H, CH_{Ar}), 7.78 (dd, 1H, ^{3}J = 8.4 Hz, ^{4}J = 0.6 Hz, CH_{Ar}), 7.88-7.94 (m, 1H, CH_{Ar}), 8.15-8.19 (m, 1H, CH_{Ar}), 9.16 (s, 1H, CHO).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 70.5 ($CHCl_2$), 118.2 (CH), 18.7, 123.9 (C), 125.7, 127.0, 135.4 (CH), 155.2 (C), 165.1 (CHO), 173.5, 183.9 (C).

MS (GS, 70eV): *m/z* (%) = 255 (M^+, 1), 257 (1), 221 (34), 173 (100), 121 (35).
HRMS (EI): Calcd for $C_{11}H_6O_3Cl_2$ (M^+) 255.96885. Found 255.968748.
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3005 (w), 1700 (m), 1643 (s), 1611 (s), 1591 (w), 1550 (s), 1463 (s), 1388 (m), 1335 (w), 1309 (s), 1259 (w), 1230 (w), 1204 (w), 1176 (w), 1144 (m), 1033 (w), 1006 (m), 951 (w), 902 (w), 880 (w), 854 (m), 799 (m), 778 (s), 759 (s), 746 (s), 729 (s), 690 (s), 645 (m), 612 (m).

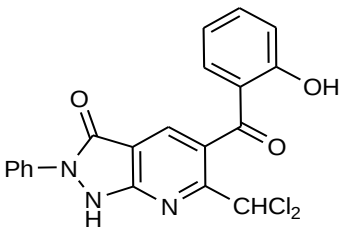
*A.2.2. General procedure for the synthesis of compounds **2.3.3a-c**, **e-p** in acetic acid.*

In a round-bottom flask the mixture of 3-(dichloroacetyl)chromone **2.3.2** (1 equiv.) and appropriate aminoheterocycle **E** (1.1 equiv.) was dissolved in AcOH (10 mL/1.0 mmol of chromone **2.3.2**) and heated under reflux in an inert atmosphere for 2-5 h (controlled by TLC). After completion of the reaction volatiles were evaporated under reduced pressure. The residue was treated with water, filtered, dried in air, and recrystallized from appropriate solvent or subjected to column chromatography (silica gel).

*A.2.3. General procedure for the synthesis of compounds **2.3.3d** in TMSCl/DMF.*

The 3-(dichloroacetyl)chromone **2.3.2** (1 equiv.) and 4-amino-1*H*-imidazole-2(3*H*)-thione **E2b** (1.1 equiv.) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMF (5 mL/1 mmol of chromone **2.3.2**) containing 1 mL of TMSCl. The mixture was heated at 100-120 °C for 7 h (controlled by TLC). After the reaction was completed volatiles were evaporated under reduced pressure. The residue was treated with water, filtered, dried in air, and recrystallized from *i*PrOH:Heptane 2:1.

6-(dichloromethyl)-5-(2-hydroxybenzoyl)-1,2-dihydro-2-phenylpyrazolo[3,4-*b*]pyridin-3-one (2.3.3a).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and 5-amino-1,2-dihydro-2-phenylpyrazol-3-one **E1a** (0.193 g, 1.1 mmol) in 10 mL AcOH. **2.3.3a** was isolated as green solid (0.319 g, 77%), mp = 199-200 °C.
^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.96-7.02 (m, 2H, CH_{Ar}), 7.32 (t, 1H, ^3J = 7.1 Hz, CH_{Ar}), 7.48-7.57 (m, 4H, CH_{Ar}), 7.67 (s, 1H, $CHCl_2$), 7.88 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 8.20 (s, 1H, Py), 10.62 (s, 1H, OH), 12.8 (br. s, 1H, NH).

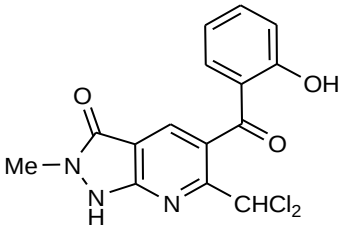
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 68.8 ($CHCl_2$), 109.3 (C), 117.2, 119.5, 120.0 (CH), 123.8, 124.8 (C), 126.0, 129.2, 131.6, 135.1 (CH), 136.3 (C), 137.0 (CH), 155.3, 156.8, 158.1, 158.2 (C), 195.6 (C=O).

MS (GS, 70eV): *m/z* (%) = 413 (M^+, 5), 78 (96), 63 (100), 44 (12).

HRMS (ESI): Calcd for $C_{20}H_{13}Cl_2N_3O_3$ (M+H) 414.0407. Found 414.0409.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3041 (w), 2915 (w), 2352 (w), 2143 (w), 2018 (w), 1962 (w), 1661 (m), 1617 (s), 1597 (s), 1485 (m), 1450 (m), 1404 (w), 1358 (m), 1303 (m), 1242 (s), 1221 (m), 1199 (m), 1156 (m), 1034 (w), 948 (w), 930 (m), 878 (w), 820 (m), 774 (m), 754 (s), 686 (s), 650 (s), 611 (m), 578 (m), 530 (m).

6-(dichloromethyl)-5-(2-hydroxybenzoyl)-1,2-dihydro-2-methylpyrazolo[3,4-*b*]pyridin-3-one (2.3.3b).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and 5-amino-1,2-dihydro-2-methylpyrazol-3-one **E1b** (0.124 g, 1.1 mmol) in 10 mL AcOH. **2.3.3b** was isolated as white solid (0.310 g, 88%), mp = 178-179 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.46 (s, 3H, NMe), 6.94-7.00 (m, 2H, CH_{Ar}), 7.43-7.53 (m, 2H, CH_{Ar}) 7.67 (s, 1H, $CHCl_2$), 8.10 (s, 1H, Py), 10.53 (s, 1H, OH), 12.53 (br. s, 1H, NH).

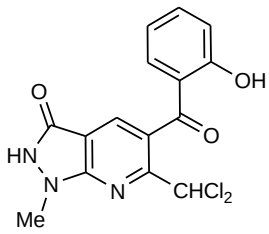
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 30.5 (NMe), 68.9 ($CHCl_2$), 117.1, 119.4 (CH), 123.5, 124.1 (C), 131.4, 134.9, 136.6 (CH), 153.4, 156.9, 157.3, 157.8, 172.0 (C), 195.8 (C=O).

MS (GS, 70eV): *m/z* (%) = 351 (M^+, 64), 316 (M^+-Cl, 100), 281 (89), 268 (M^+-$CHCl_2$, 96), 252 (26), 231 (11), 121 (88).

HRMS (ESI): Calcd for $C_{15}H_{12}Cl_2N_3O_3$ (M+H) 352.0250. Found 352.0249.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3050 (w), 1706 (w), 1622 (m), 1477 (m), 1455 (w), 1361 (m), 1300 (m), 1246 (s), 1205 (s), 1180 (s), 1155 (s), 1033 (m), 917 (s), 867 (w), 849 (w), 818 (s), 767 (s), 754 (s), 707 (s), 693 (s), 680 (s), 649 (m).

6-(dichloromethyl)-5-(2-hydroxybenzoyl)-1,2-dihydro-1-methylpyrazolo[3,4-*b*]pyridin-3-one (2.3.3c).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and 5-amino-1,2-dihydro-2-methylpyrazol-3-one **E1c** (0.124 g, 1.1 mmol) in 10 mL AcOH. **2.3.3c** was isolated as white solid (0.275 g, 78%), mp = 179-181 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.92 (s, 3H, NMe), 6.95-7.01 (m, 2H, CH_{Ar}), 7.43-7.53 (m, 2H, CH_{Ar}), 7.74 (s, 1H, $CHCl_2$), 8.28 (s, 1H, Py), 10.51 (s, 1H, OH), 11.56 (br. s, 1H, NH).

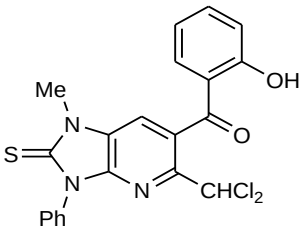
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 33.2 (NMe), 69.3 ($CHCl_2$), 117.2, 119.3 (CH), 122.7, 124.4 (C), 131.4, 134.6, 134.9 (CH), 148.7, 153.6, 154.3, 157.8, 172.0 (C), 196.5 (C=O).

MS (EI, 70eV): *m/z* (%) = 351 (M^+, 29), 316 (M^+-Cl, 100), 281 (74), 268 (M^+-$CHCl_2$, 57), 252 (22), 196 (12), 121 (52).

HRMS (ESI): Calcd for $C_{15}H_{12}Cl_2N_3O_3$ (M+H) 352.0250. Found 352.0247.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3050 (w), 1712 (w), 1599 (m), 1574 (m), 1495 (w), 1479 (w), 1286 (m), 1201 (s), 994 (w), 919 (m), 808 (m), 769 (s), 707 (s), 649 (s).

5-(dichloromethyl)-6-(2-hydroxybenzoyl)-1-methyl-3-phenyl-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (2.3.3d).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and 4-amino-1*H*-imidazole-2(3*H*)-thione **E2b** (0.226 g, 1.1 mmol) in 5mL DMF and 1 mL of TMSCl. **2.3.3d** was isolated as yellow solid (0.382 g, 86%), mp = 233-235 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.76 (s, 3H, Me), 6.94-7.06 (m, 2H, CH_{Ar}), 7.32 (s, 1H, $CHCl_2$), 7.47-7.64 (m, 7H, CH_{Ar}), 8.00 (s, 1 H, Py), 11.03 (s, 1 H, OH).

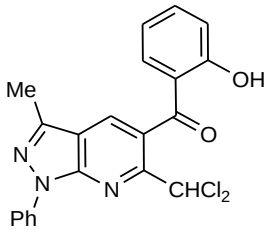
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 31.4 (Me), 69.2 ($CHCl_2$), 116.4, 117.7, 119.4 (CH), 122.2, 126.4, 127.8, 128.4 (C), 129.0, 129.1, 132.6 (CH), 134.2 (C), 136.5 (CH), 145.8, 146.7, 160.1, 173.3 (C), 197.1 (C=O).

MS (EI, 70eV): *m/z* (%) = 443 (M^+, 7), 373 (59), 360 (M^+-$CHCl_2$, 100), 344 (24), 298 (10).

HRMS (ESI): Calcd for $C_{21}H_{16}Cl_2N_3O_2S$ (M+H) 444.0335. Found 444.0334.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1735 (w), 1624 (m), 1598 (m), 1500 (m), 1483 (w), 1422 (s), 1339 (s), 1301 (s), 1202 (s), 1154 (s), 1065 (w), 967 (m), 818 (m), 750 (s), 690 (m), 651 (m).

6-(dichloromethyl)-5-(2-hydroxybenzoyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (2.3.3e).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and 4-amino-1*H*-imidazole-2(3*H*)-thione **E3** (0.190 g, 1.1 mmol) in 10 mL AcOH. **2.3.3e** was isolated as light brown solid (0.284 g, 69%), mp = 205-206 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.61 (s, 3H, Me), 6.96-7.03 (m, 2H, CH_{Ar}), 7.34-7.40 (m, 1H, CH_{Ar}), 7.51-7.64 (m, 5H, CH_{Ar}), 8.36 (dd, 2H, ^{3}J = 8.7 Hz, ^{4}J = 0.9 Hz, CH_{Ar}), 8.53 (s, 1H, Py), 10.81 (s, 1H, OH).

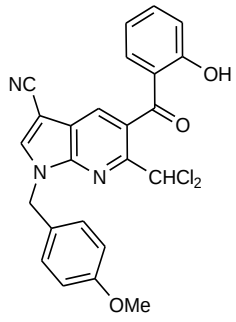
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 12.2 (Me), 69.5 ($CHCl_2$), 116.2 (C), 117.5, 119.4, 119.9 (CH), 123.0 (C), 126.0, 128.3, 129.3, 132.1, 133.5, 135.8 (CH), 138.6, 144.5, 148.8, 153.5, 159.2 (C), 196.8 (C=O).

MS (GC, 70eV): *m/z* (%) = 411 (M^+, 74), 376 (90), 341 (99), 328 (M^+-$CHCl_2$, 100), 312 (41), 291 (32), 256 (21), 179 (12), 121 (25), 77 (43).

HRMS (ESI): Calcd for $C_{21}H_{14}Cl_2N_3O_2$ (M-H) 410.0469. Found 410.048.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1620 (m), 1592 (m), 1559 (w), 1510 (w), 1497 (w), 1482 (w), 1293 (m), 1209 (s), 1154 (m), 947 (w), 930 (m), 806 (m), 752 (s), 665 (s), 630 (s).

1-(4-methoxybenzyl)-5-(2-hydroxybenzoyl)-6-(dichloromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (2.3.3f).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and 1-(4-methoxybenzyl)-5-amino-1*H*-pyrrole-3-carbonitrile **E4a** (0.250 g, 1.1 mmol) in 10 mL AcOH. **2.3.3f** was isolated as white solid (0.383 g, 93%), mp = 238-240 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OMe), 5.54 (s, 2H, CH_2), 6.85-6.93 (m, 3H, CH_{Ar}), 7.12 (d, 1H, ^{3}J = 8.3 Hz, CH_{Ar}), 7.21 (s, 1H, $CHCl_2$), 7.31 (dd, 1H, ^{3}J = 8.2 Hz, ^{4}J = 1.5 Hz, CH_{Ar}), 7.39-7.43 (m, 2H, CH_{Ar}), 7.55-7.61 (m, 1H, CH_{Ar}), 7.88 (s, 1H, pyrrole), 8.08 (s, 1H, Py), 11.79 (s, 1H, OH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 49.1 (CH_2), 55.3 (OMe), 68.6 ($CHCl_2$), 86.1 (CN), 113.9 (C), 114.6, 118.9 (CH), 119.1 (C), 119.4 (CH), 119.5, 125.7, 126.9 (C), 129.6, 130.3, 133.3, 137.7, 137.8 (CH), 146.1, 150.6, 160.0, 163.7 (C), 200.2 (C=O).

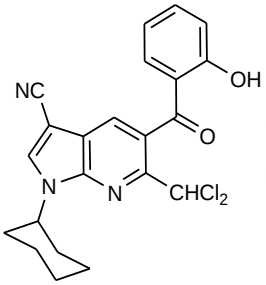
MS (EI, 70eV): *m/z* (%) = 465 (M^+, 22), 430 (14), 395 (25), 382 (M^+-$CHCl_2$, 13), 121 (100), 77 (19).

HRMS (ESI): Calcd for $C_{24}H_{18}Cl_2N_3O_3$ (M+H) 466.072. Found 466.0722.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2223 (s), 1621 (m), 1603 (s), 1550 (w), 1513 (s), 1483 (w), 1350 (m), 1305 (m), 1240 (s), 1154 (s), 1032 (m), 915 (m), 817 (m), 782 (s), 763 (s), 706 (s), 663 (s),

605 (s).

1-(4-methoxybenzyl)-5-(2-hydroxybenzoyl)-6-(dichloromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (2.3.3g).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and 5-amino-1-cyclohexyl-1*H*-pyrrole-3-carbonitrile **E4b** (0.208 g, 1.1 mmol) in 10 mL AcOH. **2.3.3g** was isolated as yellowish solid (0.360 g, 84%), mp 174-176 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.15–2.10 (m, 10H, cyclohexyl), 4.71-4.86 (m, 1H, NCH), 6.95-7.02 (m, 2H, CH_{Ar}), 7.46 (dd, 1H, ^{3}J = 7.8 Hz, ^{4}J = 1.7 Hz, CH_{Ar}), 7.53-7.58 (m, 1H, CH_{Ar}), 7.57 (s, 1H, $CHCl_2$), 8.20 (s, 1H, pyrrole), 8.90 (s, 1H, Py), 10.77 (s, 1H, OH).

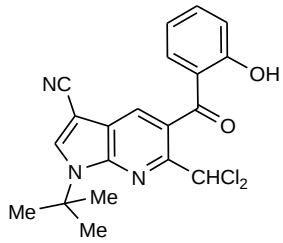
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 24.8, 25.1, 32.0, 39.8 (CH_2), 55.2 (NCH), 69.4 ($CHCl_2$), 84.0 (CN), 114.5 (C), 117.4, 119.1 (CH), 119.4, 123.2 (C), 126.5, 129.9, 132.1, 135.7, 139.3 (CH), 145.2, 149.0, 159.0 (C), 197.2 (C=O).

MS (GC, 70eV): *m/z* (%) = 427 (M^+, 12), 392 (81), 357 (23), 344 (M^+-$CHCl_2$, 67), 309 (13), 275 (41), 262 (100), 246 (43), 207 (27), 121 (16).

HRMS (ESI): Calcd for $C_{22}H_{20}Cl_2N_3O_2$ (M+H) 428.0927. Found 428.0924.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2219 (m), 1621 (s), 1601 (m), 1553 (w), 1521 (w), 1480 (w), 1292 (s), 1189 (s), 1153 (s), 1030 (w), 933 (w), 916 (m), 778 (m), 757 (s), 708 (s), 641 (s).

1-tert-butyl-5-(2-hydroxybenzoyl)-6-(dichloromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (2.3.3h).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and 1-tert-butyl-5-amino-1*H*-pyrrole-3-carbonitrile **E4c** (0.179 g, 1.1 mmol) in 10 mL AcOH. **2.3.3h** was isolated as gray solid (0.317 g, 79%), mp 200-202 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.85 (s, 9H, *t*-Bu), 6.95-7.02 (m, 2H, CH_{Ar}), 7.48 (dd, 1H, ^{3}J = 7.8 Hz, ^{4}J = 1.6 Hz, CH_{Ar}), 7.52-7.58 (m, 1H, CH_{Ar}), 7.60 (s, 1H, $CHCl_2$), 8.17 (s, 1H, pyrrole), 8.80 (s, 1H, Py), 10.75 (s, 1H, OH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 28.5 (*t*-Bu), 59.3 (*Ct*-Bu), 69.5 ($CHCl_2$), 83.1 (CN), 114.7 (C), 117.4, 119.4 (CH), 120.2, 123.2, 125.8 (C), 129.7, 132.0, 135.6, 139.7 (CH), 145.8, 148.3, 158.9 (C), 197.1 (C=O).

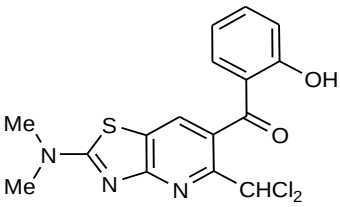
MS (GC, 70eV): *m/z* (%) = 401 (M^+, 10), 366 (36), 318 (40), 310 (28), 275 (32), 274 (32),

262 (100), 246 (32), 218 (11), 121 (10).

HRMS (EI): Calcd for $C_{20}H_{17}Cl_2N_3O_2$ (M^+) 401.0669. Found 401.0670.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2229 (s), 1624 (m), 1601 (m), 1519 (w), 1483 (w), 1418 (m), 1370 (m), 1190 (s), 1083 (w), 1034 (w), 910 (w), 864 (w), 758 (s), 706 (s), 646 (s), 607 (m).

5-(dichloromethyl)-6-(2-hydroxybenzoyl)-*N*,*N*-dimethylthiazolo[4,5-*b*]pyridin-2-amine (2.3.3i).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and N^2,N^2-dimethylthiazole-2,4-diamine **E5a** (0.157 g, 1.1 mmol) in 10 mL AcOH. **2.3.3i** was isolated as gray solid (0.318 g, 73%), mp 244-245 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.25 (s, 6H, NMe_2), 6.93-7.00 (m, 2H, CH_{Ar}), 7.42 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.6 Hz, CH_{Ar}), 7.51 (s, 1H, $CHCl_2$), 7.48-7.54 (m, 1H, CH_{Ar}), 8.29 (s, 1H, Py), 10.64 (s, 1H, OH).

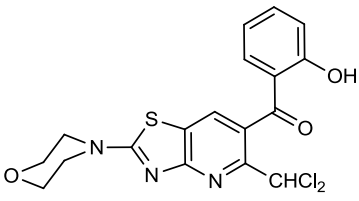
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 39.8 (NMe_2), 69.4 ($CHCl_2$), 117.3, 119.3 (CH), 123.1, 123.8, 125.9 (C), 131.5, 131.6, 135.0 (CH), 151.7, 158.3, 165.4, 172.6 (C), 196.6 (C=O).

MS (EI, 70eV): *m/z* (%) = 381 (M^+, 35), 346 (73), 311 (69), 298 (M^+-$CHCl_2$, 100), 282 (64), 268 (12), 263 (14), 261 (21), 226 (15), 121 (11).

HRMS (ESI): Calcd for $C_{16}H_{14}Cl_2N_3O_2S$ (M+H) 382.0178. Found 382.0181.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1620 (w), 1602 (m), 1556 (s), 1505 (w), 1478 (w), 1403 (m), 1292 (s), 1217 (s), 1158 (m), 931 (m), 793 (s), 744 (s), 702 (s), 664 (m).

5-(dichloromethyl)-6-(2-hydroxybenzoyl)-2-morpholinothiazolo[4,5-*b*]pyridine (2.3.3j).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and 2-morpholinothiazol-4-amine **E5b** (0.204 g, 1.1 mmol) in 10 mL AcOH. **2.3.3j** was isolated as yellow solid (0.297 g, 70%), mp 226-228 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.72-3.76 (m, 8H, morpholine), 6.93-7.00 (m, 2H, CH_{Ar}), 7.43 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.6 Hz, CH_{Ar}), 7.49-7.52 (m, 2H, $CHCl_2$, CH_{Ar}), 8.33 (s, 1H, Py), 10.64 (s, 1H, OH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 48.7, 66.2 (CH_2 morpholine), 68.3 ($CHCl_2$), 118.8, 119.3 (CH), 119.6, 123.1, 125.2 (C), 129.7, 133.1, 137.6 (CH), 152.7, 163.4. 165.5, 172.0 (C), 199.8 (C=O).

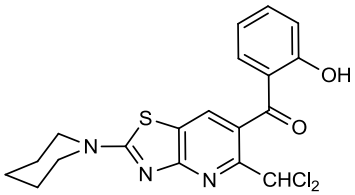
MS (EI, 70eV): *m/z* (%) = 423 (M^+, 33), 390 (25), 389 (21), 388 (70), 387 (20), 354 (11), 353 (48), 352 (21), 342 (15), 341 (47), 340 (M^+-$CHCl_2$, 100), 324 (32), 303 (14), 296 (16), 266

(12), 246 (11), 121 (14).

HRMS (ESI): Calcd for $C_{18}H_{16}Cl_2N_3O_3S$ (M+H) 424.0827. Found 424.0286.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1620 (w), 1599 (w), 1544 (m), 1505 (m), 1485 (m), 1424 (m), 1290 (s), 1214 (s), 1111 (s), 1025 (m), 931 (m), 790 (m), 749 (s).

5-(dichloromethyl)-6-(2-hydroxybenzoyl)-2-pyperidinothiazolo[4,5-*b*]pyridine (2.3.3k).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and 2-(piperidin-1-yl)thiazol-4-amine **E5c** (0.201 g, 1.1 mmol) in 10 mL AcOH. **2.3.3k** was isolated as yellow solid (0.312 g, 74%), mp 263-264 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (m, 6H, piperidine), 3.73 (m, 4H, piperidine), 6.84 (td, 1H, ^{3}J = 8.1 Hz, ^{4}J = 1.0 Hz, CH_{Ar}), 7.01 (s, 1H, $CHCl_2$), 7.06 (dd, 1H, ^{3}J = 8.4 Hz, ^{4}J = 0.7 Hz, CH_{Ar}), 7.32 (dd, 1H, ^{3}J = 8.0 Hz, ^{4}J = 1.1 Hz, CH_{Ar}), 7.49-7.54 (m, 1H, CH_{Ar}), 7.81 (s, 1H, Py), 11.78 (s, 1H, OH).

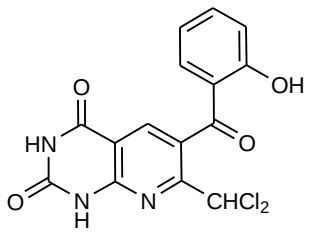
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.0, 25.4, 50.0 (CH_2 piperidine), 68.4 ($CHCl_2$), 118.7, 119.2 (CH), 119.6, 122.4, 125.4 (C), 129.2, 133.1, 137.4 (CH), 152.5, 163.3, 166.1, 171.5 (C), 199.9 (C=O).

MS (EI, 70eV): *m/z* (%) = 421 (M^+, 16), 386 (22), 351 (81), 338 (M^+-$CHCl_2$, 100), 322 (47), 295 (16), 268 (13), 121 (14), 84 (13), 69 (16).

HRMS (ESI): Calcd for $C_{19}H_{18}Cl_2N_3O_2S$ (M+H) 422.0491. Found 422.0494.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2938 (m), 1617 (m), 1594 (w), 1538 (s), 1503 (m), 1482 (w), 1316 (m), 1291 (s), 1248 (m), 1213 (s), 1125 (m), 934 (m), 850 (w), 787 (m), 732 (s), 705 (s), 627 (m), 604 (m).

6-(2-hydroxybenzoyl)-7-(dichloromethyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.3.3l).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and 6-aminopyrimidine-2,4(1*H*,3*H*)-dione **E6a** (0.140 g, 1.1 mmol) in 10 mL AcOH. **2.3.3l** was isolated as white solid (0.253 g, 69%), mp 237-238 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.96-7.01 (m, 2H, CH_{Ar}), 7.45-7.54 (m, 2H, CH_{Ar}), 7.56 (s, 1H, $CHCl_2$), 8.20 (s, 1H, Py), 10.59 (s, 1H, OH), 11.68 (s, 1H, NH), 12.28 (s, 1H, NH).

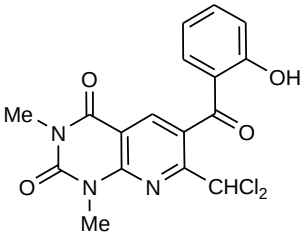
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 68.1 ($CHCl_2$), 110.4 (C), 117.2, 119.5 (CH), 123.8, 126.0 (C), 131.4, 135.3, 139.5 (C), 150.2, 153.6, 158.0, 158.1, 161.2 (C), 194.8 (C=O).

MS (EI, 70eV): *m/z* (%) = 366 (M^+, 2), 330 (69), 295 (62), 282 (M^+-$CHCl_2$, 100), 266 (11), 239 (11), 223 (7), 196 (8), 121 (22), 69 (14), 57 (10), 44 (15).

HRMS (ESI): Calcd for $C_{15}H_8Cl_2N_3O_4$ (M-H) 366.9897. Found 366.9914.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3176 (w), 3051 (w), 1682 (s), 1603 (s), 1574 (s), 1504 (w), 1481 (m), 1403 (m), 1294 (m), 1242 (s), 1155 (m), 921 (m), 754 (s), 650 (s).

6-(2-hydroxybenzoyl)-7-(dichloromethyl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.3.3m).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **E6b** (0.171 g, 1.1 mmol) in 10 mL AcOH. **2.3.3m** was isolated as yellow solid (0.303 g, 77%), mp 196-197 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.28 (s, 3H, Me), 3.66 (s, 3H, Me), 6.96-7.01 (m, 2H, CH_{Ar}), 7.47 (dd, 1H, ^3J = 8.2 Hz, ^4J = 1.6 Hz, CH_{Ar}), 7.51-7.57 (m, 1 H, CH_{Ar}), 7.61 (s, 1H, $CHCl_2$), 8.25 (s, 1H, Py), 10.57 (s, 1H, OH).

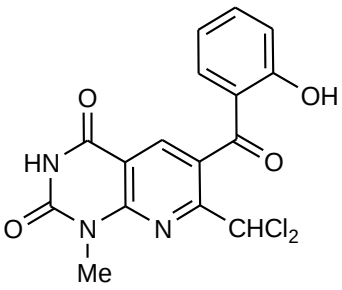
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 28.5, 29.4 (Me), 68.4 ($CHCl_2$), 110.6 (C), 117.2, 119.5 (CH), 123.6, 125.9 (C), 131.4, 135.4, 140.1 (CH), 150.8, 151.4, 157.3, 158.0, 160.0 (C), 194.5 (CH).

MS (EI, 70eV): *m/z* (%) = 393 (M^+, 3), 358 (99), 310 (M^+-$CHCl_2$, 100), 294 (21), 120 (44), 69 (11).

HRMS (EI): Calcd for $C_{17}H_{13}Cl_2N_3O_4$ (M^+) 393.0278. Found 393.0271.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1712 (m), 1666 (m), 1656 (m), 1628 (m), 1601 (s), 1572 (m), 1485 (m), 1357 (m), 1243 (s), 1156 (m), 1089 (w), 959 (w), 917 (m), 783 (s), 751 (s), 667 (m).

6-(2-hydroxybenzoyl)-7-(dichloromethyl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.3.3n).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and 6-amino-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **E6c** (0.155 g, 1.1 mmol) in 10 mL AcOH. **2.3.3n** was isolated as yellow solid (0.270 g, 71%), mp 235-236 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.58 (s, 3H, Me), 6.97-7.01 (m, 2H, CH_{Ar}), 7.46 (dd, 1H, ^3J = 8.1 Hz, ^4J = 1.7 Hz, CH_{Ar}), 7.51-7.57 (m, 1H, CH_{Ar}), 7.62 (s, 1H, $CHCl_2$), 8.32 (s, 1H, Py), 10.57 (s, 1H, OH), 11.94 (s, 1H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 28.5 (Me), 68.4 ($CHCl_2$), 111.5 (C), 117.2, 119.5 (CH),

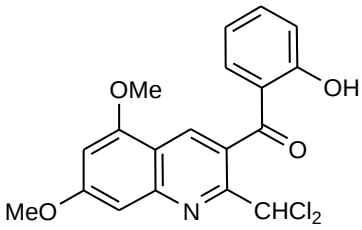
123.6, 125.6 (C), 131.4, 135.3, 139.6 (CH), 150.5, 152.8, 157.4, 157.9, 160.2 (C), 194.6 (C=O).

MS (EI, 70eV): *m/z* (%) = 380 (M^+, 2), 344 (42), 309 (52), 296 (M^+-$CHCl_2$, 100), 280 (12), 121 (21).

HRMS (EI): Calcd for $C_{16}H_{11}Cl_2N_3O_4$ (M^+) 379.0121. Found 379.0115.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3330 (w), 3035 (w), 1732 (m), 1699 (s), 1596 (s), 1567 (m), 1475 (m), 1338 (m), 1279 (m), 1157 (s), 1100 (m), 900 (m), 755 (s), 597 (s).

2-(dichloromethyl)-3-(2-hydroxybenzoyl)-5,7-dimethoxyquinoline (2.3.3o).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and 3,5-dimethoxybenzenamine **E7a** (0.168 g, 1.1 mmol) in 10 mL AcOH. **2.3.3o** was isolated as white solid (0.282 g, 72%), mp 188-189 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.92 (s, 3H, OMe), 3.99 (s, 3H, OMe), 6.80 (s, 1H, CH_{Ar}), 6.96-7.01 (m, 2H, CH_{Ar}), 7.16 (s, 1H, CH_{Ar}), 7.47-7.53 (m, 2H, CH_{Ar}), 7.70 (s, 1H, $CHCl_2$), 8.41 (s, 1H, Py), 10.55 (s, 1H, OH).

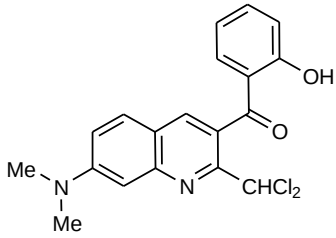
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 56.1, 56.4 (OMe), 69.3 ($CHCl_2$), 93.7, 100.3 (CH), 114.3 (C), 117.2, 119.4 (CH), 123.9, 125.5 (C), 131.5, 134.0, 135.0 (CH), 149.7, 154.1, 156.0, 158.1, 163.9 (C), 196.5 (C=O).

MS (EI, 70eV): *m/z* (%) = 391 (M^+, 47), 356 (M^+-Cl, 100), 339 (10), 321 (49), 292 (21), 271 (42), 236 (22), 206 (12), 121 (23), 65 (13).

HRMS (ESI): Calcd for $C_{19}H_{16}Cl_2NO_4$ (M+H) 392.0451. Found 392.0457.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1620 (s), 1600 (s), 1571 (m), 1480 (w), 1291 (m), 1203 (s), 1043 (w), 1033 (m), 915 (m), 815 (m), 760 (s), 630 (m).

2-(dichloromethyl)-3-(2-hydroxybenzoyl)-*N*,*N*-dimethylquinolin-7-amine (2.3.3p).



Starting from 3-(dichloroacetyl)chromone **2.3.2** (0.257 g, 1 mmol) and N^1,N^1-dimethylbenzene-1,3-diamine **E8** (0.152 g, 1.1 mmol) in 10 mL AcOH. **2.3.3p** was isolated as yellow solid (0.255 g, 60%), mp 186-188 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.14 (s, 6H, NMe_2), 6.94-7.02 (m, 2H, CH_{Ar}), 7.05 (d, 1H, ^4J = 2.4 Hz, CH_{Ar}), 7.37 (dd, 1H, ^3J = 9.2 Hz, ^4J = 2.5 Hz, CH_{Ar}), 7.44-7.54 (m, 2H, CH_{Ar}), 7.71 (s, 1H, $CHCl_2$), 7.89 (d, 1H, ^3J = 9.2 Hz, CH_{Ar}), 8.25 (s, 1H, Py), 10.61 (s, 1H, OH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 39.9 (NMe_2), 69.7 ($CHCl_2$), 104.7, 117.2, 118.0, 118.2 (CH), 119.3, 123.4, 124.0 (C), 129.8, 131.5, 134.7, 139.8 (CH), 149.4, 153.0, 153.7, 158.3 (C), 197.0 (C=O).

MS (EI, 70eV): *m/z* (%) = 374 (M^+, 100), 339 (37), 322 (18), 291 (54), 207 (18), 137 (17).

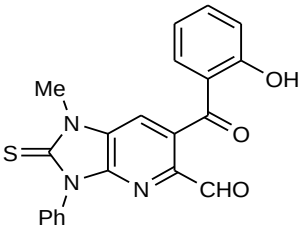
HRMS (EI): Calcd for $C_{19}H_{16}Cl_2N_2O_2$ (M^+) 374.0655. Found 374.0658.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1614 (w), 1576 (m), 1505 (m), 1479 (w), 1330 (m), 1146 (m), 971 (w), 914 (m), 810 (s), 752 (s), 704 (s), 631 (m).

*A.2.4. General procedure for the synthesis of compounds **2.3.5a-f**.*

The fused pyridine derivative **2.3.3** (1 equiv.) and potassium hydroxide (4 equiv.) were dissolved in ethanol (10 mL/1 equiv. of **2.3.3**) and heated under reflux for 2 h (under argon atmosphere). After completion of the reaction (TLC control), the reaction mixture was diluted with 10 M HCl (5 mL). The precipitate was filtered, washed with H_2O, dried in vacuum at 60 °C for 3 h. The residue was purified by recrystallization from appropriate solvent or by using column chromatography (silica gel).

5-(formyl)-6-(2-hydroxybenzoyl)-1-methyl-3-phenyl-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (2.3.5a).



Starting from **2.3.3d** (0.150 g, 0.33 mmol) and potassium hydroxide (0.074 g, 1.32 mmol) in 10 mL ethanol. **2.3.5a** was isolated as white solid (0.09 g, 70%), mp 183-184 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.55 (s, 3H, Me), 6.93 (t, 1H, ^3J = 9.2 Hz, CH_{Ar}), 7.00-7.07 (m, 2H, CH_{Ar}), 7.61 (d, 1H, ^3J = 9.2 Hz, CH_{Ar}), 7.61-7.69 (m, 5H, CH_{Ar}), 8.22 (s, 1H, Py), 10.08 (s, 1H, OH), 11.03 (s, 1H, COH).

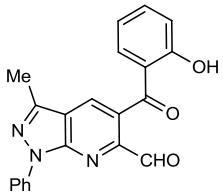
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 31.4 (Me), 116.9, 118.7, 119.3 (CH), 123.2, 126.4, 129.0 (C), 129.4, 130.0, 131.1, 132.6 (CH), 134.2 (C), 137.5 (CH), 145.8, 146.7, 161.1, 173.3 (C), 192.2 (CHO), 197.1 (C=O).

MS (EI, 70eV): *m/z* (%) = 389 (M^+, 5), 312 (39), 297 (100), 268 (10).

HRMS (ESI): Calcd for $C_{21}H_{16}N_3O_3S$ (M+H) 390.0688. Found 390.0689.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2725 (m), 1633 (w), 1512 (m), 1500 (m), 1488 (w), 1453 (m), 1388 (m), 1332 (m), 1153 (m), 969 (w), 909 (s), 815 (m), 744 (s), 701 (s), 608 (s).

6-formyl-5-(2-hydroxybenzoyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (2.3.5b).



Starting from **2.3.3f** (0.150 g, 0.32 mmol) and potassium hydroxide (0.071 g, 1.28 mmol) in 10 mL ethanol. **2.3.5b** was isolated as yellowish solid (0.095 g, 72%), mp 155-157 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.63 (s, 3H, Me), 7.02-7.11 (m, 2H, CH_{Ar}), 7.40-7.48 (m, 1H, CH_{Ar}), 7.61-7.68 (m, 4H, CH_{Ar}), 8.51 (dd, 2H, ^{3}J = 8.4 Hz, ^{4}J = 1.0 Hz, CH_{Ar}), 8.43 (s, 1H, Py), 10.09 (s, 1H, OH), 10.84 (s, 1H, COH).

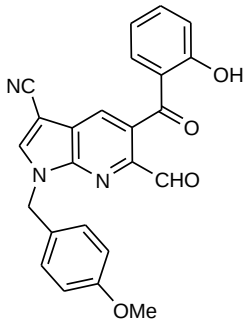
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 12.2 (Me), 117.2, 118.5, 119.9 (CH), 120.1, 123.6, 126.4 (C), 128.9, 130.2, 132.4, 133.9 (CH), 136.1 (C), 138.8 (CH), 145.5, 149.0, 153.5, 159.3 (C), 191.8 (CHO), 196.8 (C=O).

MS (EI, 70eV): *m/z* (%) = 357 (M^{+}, 34), 342 (80), 325 (79), 296 (100), 312 (41), 219 (42), 191 (21).

HRMS (ESI): Calcd for $C_{21}H_{16}N_3O_3$ (M+H) 358.1161. Found 358.1162.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2733 (m), 1632 (w), 1577 (m), 1532 (m), 1497 (w), 1462 (m), 1332 (m), 1294 (m), 1211 (s), 1111 (s), 953 (m), 931 (m), 808 (m), 750 (s), 665 (s), 630 (s), 601 (m).

1-(4-methoxybenzyl)-5-(2-hydroxybenzoyl)-6-(formyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (2.3.5c).



Starting from **2.3.3f** (0.150 g, 0.36 mmol) and potassium hydroxide (0.081 g, 1.44 mmol) in 10 mL ethanol. **2.3.5c** was isolated as white solid (0.104 g, 81%), mp 169-171 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.82 (s, 3H, OMe), 5.51 (s, 2H, CH_2), 6.92-6.98 (m, 3H, CH_{Ar}), 7.23 (d, 1H, ^{3}J = 8.0 Hz, CH_{Ar}), 7.39 (dd, 1H, ^{3}J = 8.0 Hz, ^{4}J = 1.4 Hz, CH_{Ar}), 7.42-7.48 (m, 2H, CH_{Ar}), 7.57-7.63 (m, 1H, CH_{Ar}), 7.93 (s, 1H, pirrole), 8.18 (s, 1H, Py), 10.09 (s, 1H, OH), 11.79 (s, 1H, COH).

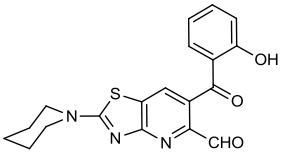
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 49.1 (CH_2), 55.3 (OMe), 86.5 (CN), 114.6 (C), 114.9, 119.2 (CH), 119.9 (C), 120.4, 120.6 (CH), 125.8, 127.0 (C), 129.9, 130.6, 133.7 (CH), 138.1 (C), 138.4 (CH), 146.2, 150.6, 160.6, 164.0 (C), 192.0 (CHO), 200.2 (C=O).

MS (EI, 70eV): *m/z* (%) = 411 (M^{+}, 32), 380 (24), 354 (31), 325 (13), 248 (100).

HRMS (ESI): Calcd for $C_{24}H_{18}N_3O_4$ (M+H) 412.1256. Found 412.1253.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2782 (s), 1623 (m), 1600 (m), 1551 (w), 1510 (m), 1483 (w), 1355 (m), 1303 (m), 1240 (s), 1155 (m), 1030 (m), 910 (s), 816 (m), 705 (s), 665 (m), 605 (s).

5-formyl-6-(2-hydroxybenzoyl)-2-pyperidinothiazolo[4,5-*b*]pyridine (2.3.5d).



Starting from **2.3.3k** (0.150 g, 0.35 mmol) and potassium hydroxide (0.078 g, 1.40 mmol) in 10 mL ethanol. **2.3.5d** was isolated as white solid (0.083 g, 65%), mp 143-145 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.73 (m, 6H, piperidine), 3.75 (m, 4H, piperidine), 6.79 (td, 1H, ^{3}J = 8.0 Hz, ^{4}J = 0.9 Hz, CH_{Ar}), 7.11 (dd, 1H, ^{3}J = 8.3 Hz, ^{4}J = 0.8 Hz, CH_{Ar}), 7.42 (dd, 1H, ^{3}J = 8.0 Hz, ^{4}J = 1.6 Hz, CH_{Ar}), 7.51–7.57 (m, 1H, CH_{Ar}), 7.91 (s, 1H, Py), 10.11 (s, 1H, OH), 11.70 (s, 1H, COH).

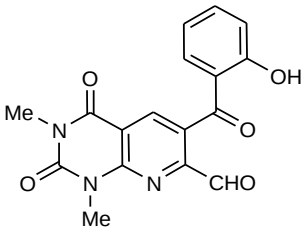
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 24.0, 25.4, 50.0 (CH_2 piperidine), 119.7, 120.2 (CH), 120.8, 122.9, 126.4 (C), 129.9, 134.1, 138.4 (CH), 152.6, 163.3, 166.9, 171.5 (C), 191.6 (CHO), 199.9 (C=O).

MS (EI, 70eV): *m/z* (%) = 367 (M^+, 16), 338 (32), 321 (71), 244 (100), 216 (46).

HRMS (ESI): Calcd for $C_{19}H_{18}N_3O_3S$ (M+H) 368.1223. Found 368.1229.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2845 (m), 1622 (m), 1582 (w), 1510 (m), 1482 (w), 1333 (m), 1290 (m), 1213 (s), 1113 (m), 931 (m), 852 (w), 787 (s), 729 (s), 707 (s), 623 (m), 605 (m).

6-(2-hydroxybenzoyl)-7-(formyl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.3.5e).



Starting from **2.3.3m** (0.150 g, 0.38 mmol) and potassium hydroxide (0.085 g, 1.52 mmol) in 10 mL ethanol. **2.3.5e** was isolated as yellow solid (0.103 g, 80%), mp 221-223 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.30 (s, 3H, Me), 3.70 (s, 3H, Me), 7.01-7.07 (m, 2H, CH_{Ar}), 7.51 (dd, 1H, ^{3}J = 8.1 Hz, ^{4}J = 1.5 Hz, CH_{Ar}), 7.54-7.59 (m, 1H, CH_{Ar}), 8.33 (s, 1H, Py), 10.02 (s, 1H, OH), 10.59 (s, 1H, COH).

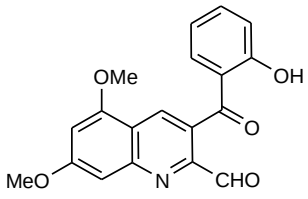
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 28.5, 29.4 (Me), 110.6 (C), 117.4, 119.8 (CH), 124.2, 126.2 (C), 131.6, 135.9, 141.2 (CH), 151.1, 152.1, 157.9, 158.1, 160.0 (C), 192.7 (CHO), 194.5 (C=O).

MS (EI, 70eV): *m/z* (%) = 339 (M^+, 9), 324 (69), 309 (100), 292 (23), 263 (14).

HRMS (EI): Calcd for $C_{17}H_{13}N_3O_5$ (M^+) 339.0986. Found 339.0988.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2779 (m), 1738 (m), 1656 (m), 1630 (m), 1607 (m), 1569 (m), 1485 (m), 1359 (s), 1225 (s), 1162 (s), 1100 (w), 963 (w), 916 (m), 789 (s), 756 (s), 661 (m).

2-formyl-3-(2-hydroxybenzoyl)-5,7-dimethoxyquinoline (2.3.5f).



Starting from **2.3.3o** (0.150 g, 0.38 mmol) and potassium hydroxide (0.085 g, 1.52 mmol) in 10 mL ethanol. **2.3.5f** was isolated as white solid (0.099 g, 77%), mp 223-225 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.98 (s, 3H, OMe), 4.00 (s, 3H, OMe), 6.87 (s, 1H, CH_{Ar}), 7.01-7.06 (m, 2H, CH_{Ar}), 7.25 (s, 1H, CH_{Ar}), 7.51-7.58 (m, 2H, CH_{Ar}), 8.36 (s, 1H, Py), 10.13 (s, 1H, OH), 10.55 (s, 1H, COH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 56.1, 56.4 (OMe), 94.7, 100.9 (CH), 114.7 (C), 117.6, 119.7 (CH), 124.2, 125.9 (C), 132.1, 134.0, 135.6 (CH), 150.1, 154.1, 156.0, 158.2, 163.9 (C), 191.6 (CHO), 196.5 (C=O).

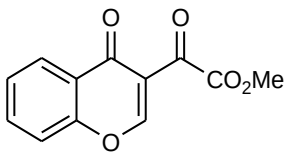
MS (EI, 70eV): *m/z* (%) = 337 (M^+, 27), 306 (40), 370 (100), 253 (36), 224 (12), 196 (11).

HRMS (EI): Calcd for $C_{19}H_{15}NO_5$ (M^+) 337.1229. Found 337.1227.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2755 (m), 1623 (s), 1601 (m), 1589 (m), 1462 (m), 1301 (s), 1209 (m), 1055 (w), 1003 (m), 921 (s), 817 (s), 760 (s), 608 (m).

*A.2.4. General procedure for the synthesis of 3-methoxalylchromone **2.4.1**:*

To a dry dichloromethane solution (100 mL) of 3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one **2.3.1** (20 g, 105 mmol) was added 27 mL dry pyridine (345 mmol). The solution was set on stirring on ice bath, subsequently corresponding methyloxalylchloride (10.6 mL, 115.5 mmol) was added dropwise. Afterwards the reaction mixture was stirred at r.t. for 8 h. Next the reaction mixture was stripped of solvents and liquid residues. The residue was washed with water. 3-Methoxalylchromone **2.4.1** was obtained as light pink crystals (19.1 g, 79%), mp 133-135 ^{o}C.



^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.88 (s, 3H, OMe), 7.61 (t, 1H, ^{3}J = 7.3 Hz, CH_{Ar}), 7.78-7.81 (m, 1H, CH_{Ar}), 7.90-7.95 (m, 1H, CH_{Ar}), 8.11 (dd, 1H, ^{3}J = 7.9 Hz, ^{4}J = 1.5 Hz, CH_{Ar}), 9.12 (s, 1H, Pyranone).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 52.7 (OMe), 118.5 (C), 118.9 (CH), 123.9 (C), 125.2, 127.0, 135.6 (CH), 155.6, 164.0 (C), 164.6 (CH), 174.1, 184.6 (C).

MS (GC, 70 eV): *m/z* (%) = 232 (M^+, 3), 204 (21), 189 (16), 173 (100), 121 (40).

HRMS (ESI): Calcd for $C_{12}H_9O_5$ (M+H) 233.0459. Found 233.0461.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1728 (m), 1693 (m), 1645 (s), 1465 (m), 1395 (m), 1328 (s), 1231 (m), 1171 (m), 1107 (m), 1016 (s), 854 (m), 800 (m), 763 (s), 705 (s).

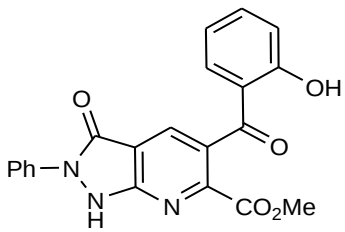
*A.2.5. General procedure for the synthesis of compounds **2.4.2a-b**, **h-q** in acetic acid.*

In a round-bottom flask the mixture of 3-methoxalylchromone **2.4.1** (1 equiv.) and appropriate aminoheterocycle **E** (1.1 equiv.) was dissolved in AcOH (10 mL/1.0 mmol of chromone **2.4.1**) and heated under reflux in an inert atmosphere for 2-5 h (controlled by TLC). After completion of the reaction volatiles were evaporated under reduced pressure. The residue was treated with water, filtered, dried in air, and recrystallized from appropriate solvent or subjected to column chromatography (silica gel).

*A.2.6. General procedure for the synthesis of compounds **2.4.2c-g** in TMSCl/DMF.*

The 3-methoxalylchromone **2.4.1** (1 equiv.) and 4-amino-1*H*-imidazole-2(3*H*)-thione **E2** (1.1 equiv.) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMF (5 mL/1 mmol of chromone **2.4.1**) containing 1 mL of TMSCl. The mixture was heated at 100-120 °C for 5-7 h (controlled by TLC). After the reaction was completed volatiles were evaporated under reduced pressure. The residue was treated with water, filtered, dried in air, and recrystallized from appropriate solvent or subjected to column chromatography (silica gel).

Methyl 5-(2-hydroxybenzoyl)-2,3-dihydro-3-oxo-2-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylate (2.4.2a).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 5-amino-1,2-dihydro-2-phenylpyrazol-3-one **E1a** (0.193 g, 1.1 mmol) in 10 mL AcOH. **2.4.2a** was isolated as green solid (0.222 g, 57%), mp 222-224 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.76 (s, 3H, OMe), 6.93-7.02 (m, 2H, CH_{Ar}), 7.33 (t, 1H, ^{3}J = 7.6 Hz, CH_{Ar}), 7.46-7.58 (m, 4H, CH_{Ar}), 7.88 (d, 2H, ^{3}J = 8.1 Hz, CH_{Ar}), 8.34 (s, 1H, Py), 10.77 (s, 1H, OH), 12.5 (br. S, 1H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 52.8 (OMe), 110.0 (C), 117.2, 119.4, 120.1 (CH), 122.6 (C), 126.0, 128.0, 129.2, 131.5, 135.2, 135.8 (CH), 136.4, 152.0, 155.2, 157.0, 158.5, 165.6 (C), 195.2 (C=O).

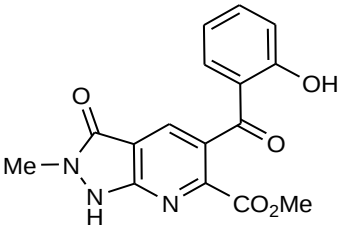
MS (EI, 70 eV): *m/z* (%) = 389 (M^+, 14), 357 (28), 344 (11), 330 (M^+-CO_2Me, 100).

HRMS (ESI): Calcd for $C_{21}H_{16}O_5N_3$ (M+H) 390.1084. Found 390.1083.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3033 (w), 1720 (w), 1643 (s), 1482 (w), 1438 (w), 1356 (m), 1296 (m), 1253 (m), 1201 (m), 1182 (m), 1147 (m), 1120 (m), 1088 (m), 1033 (w), 928 (w), 870 (w),

828 (w), 752 (s), 684 (s), 662 (m).

Methyl 5-(2-hydroxybenzoyl)-2,3-dihydro-2-methyl-3-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylate (2.4.2b).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 5-amino-1,2-dihydro-2-methylpyrazol-3-one **E1b** (0.124 g, 1.1 mmol) in 10 mL AcOH. **2.4.2b** was isolated as white solid (0.262 g, 80%), mp 245-247 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.49 (s, 3H, NMe), 3.73 (s, 3H, OMe), 6.91-7.01 (m, 2H, CH_{Ar}), 7.41 (t, 1H, ^{3}J = 7.8 Hz, CH_{Ar}), 7.50 (d, 1H, ^{3}J = 7.5 Hz, CH_{Ar}), 8.22 (s, 1H, Py), 10.71 (s, 1H, OH), 12.37 (s, 1H, NH).

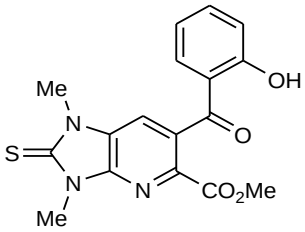
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 30.7 (Me), 52.7 (OMe), 108.4 (C), 117.2, 119.3 (CH), 122.8, 126.5 (C), 131.4, 135.0, 135.3 (CH), 151.7, 153.4, 156.6, 158.3, 165.9 (C), 195.3 (C=O).

MS (EI, 70 eV): *m/z* (%) = 327 (M^{+}, 9), 295 (10), 268 (100), 239 (12), 196 (10), 121 (18).

HRMS (ESI): Calcd for $C_{16}H_{14}O_5N_3$ (M+H) 328.0928. Found 328.0927.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3106 (w), 1715 (m), 1682 (s), 1614 (s), 1567 (w), 1480 (w), 1439 (m), 1360 (w), 1310 (m), 1241 (s), 1148 (s), 1115 (w), 1031 (w), 973 (w), 918 (m), 850 (w), 803 (w), 786 (m), 767 (s), 731 (s), 723 (s), 651 (s), 632 (m), 614 (s).

Methyl 6-(2-hydroxybenzoyl)-2,3-dihydro-1,3-dimethyl-2-thioxo-1*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (2.4.2c).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 4-amino-1,3-dimethyl-1*H*-imidazole-2(3*H*)-thione **E2a** (0.157 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.4.2c** was isolated as white solid (0.254 g, 71%), mp 273-275 ^{o}C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.35 (s, 6H, 2xNMe), 3.73 (s, 3H, OMe), 6.88-7.01 (m, 2H, CH_{Ar}), 7.32-7.50 (m, 2H, CH_{Ar}), 8.07 (s, 1H, Py), 11.20 (s, 1H, OH).

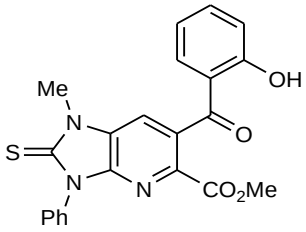
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 29.9, 30.7 (Me), 52.5 (OMe), 115.5, 117.5, 119.3 (CH), 121.3, 127.9 (C), 132.2 (CH), 136.2 (CH), 138.1, 144.7, 160.3, 164.9, 173.3 (C), 198.0 (C=O).

MS (GC, 70 eV): *m/z* (%) = 357 (M^{+}, 9), 325 (100), 297 (22), 281 (15), 264 (24).

HRMS (ESI): Calcd for $C_{17}H_{16}O_4N_3S$ (M+H) 358.0856. Found 358.0857.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1715 (m), 1631 (m), 1480 (w), 1439 (m), 1404 (w), 1360 (w), 1310 (m), 1196 (m), 1115 (w), 1031 (w), 973 (w), 918 (m), 850 (w), 803 (w), 786 (m), 731 (s), 723 (s), 651 (s), 632 (m), 614 (s).

Methyl 6-(2-hydroxybenzoyl)-2,3-dihydro-1-methyl-3-phenyl-2-thioxo-1*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (2.4.2d).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 4-amino-1-methyl-3-phenyl-1*H*-imidazole-2(3*H*)-thione **E2b** (0.226 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.4.2d** was isolated as white solid (0.306 g, 73%), mp 291-292 ^{o}C.

^{1}H NMR (250 MHz, DMSO-d_6,80 ^{o}C): δ = 3.57 (s, 3H, NMe), 3.81 (s, 3H, OMe), 6.88 (t, 1H, ^{3}J = 7.2 Hz, CH_{Ar}), 7.02 (d, 1H, ^{3}J = 8.0 Hz, CH_{Ar}), 7.34 (d, 1H, ^{3}J = 7.1 Hz, CH_{Ar}), 7.54-7.63 (m, 6H, CH_{Ar}), 8.04 (s, 1H, Py), 11.10 (s, 1H, OH).

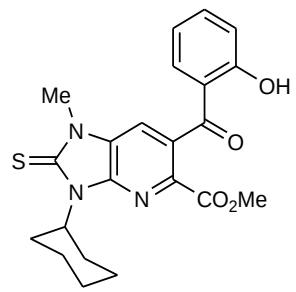
^{13}C NMR (125.7 MHz, DMSO-d_6, 303K): δ = 31.3 (Me), 52.4 (OMe), 115.7, 117.4, 119.1 (CH), 121.1, 128.0 (C), 128.5, 129.0, 129.1, 132.0 (CH), 133.3, 134.2 (C), 136.0 (CH), 138.3, 145.1, 160.1, 164.7, 173.5 (C), 197.6 (C=O).

MS (EI, 70 eV): *m/z* (%) = 419 (M^{+}, 10), 387 (55), 360 (M^{+}-CO_2Me, 100), 342 (15), 121 (14), 93 (10), 77 (33), 65 (18), 51 (11).

HRMS (EI): Calcd for $C_{22}H_{17}N_3O_4S$ (M^{+}) 419.09343. Found 419.09360.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3053 (w), 1710 (m), 1668 (w), 1621 (m), 1607 (s), 1469 (m), 1447 (s), 1419 (s), 1387 (s), 1340 (s), 1267 (s), 1192 (m), 1148 (m), 1125 (s), 1109 (m), 1030 (m), 954 (m), 924 (w), 904 (w), 879 (m), 816 (w), 798 (m), 760 (s), 704 (s), 689 (s), 672 (m), 631 (m), 570 (m).

Methyl 6-(2-hydroxybenzoyl)-3-cyclohexyl-2,3-dihydro-1-methyl-2-thioxo-1*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (2.4.2e).

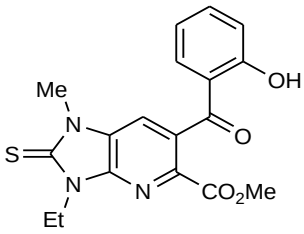


Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 4-amino-3-cyclohexyl-1-methyl-1*H*-imidazole-2(3*H*)-thione **E2c** (0.205 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.4.2e** was isolated as pink solid (0.272 g, 64%), mp 291-292 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.16-1.95 (m, 10H, cyclohexyl), 3.37 (m, 1H, CHN), 3.70 (s, 3H, NMe), 3.75 (s, 3H, OMe), 6.89-6.94 (m, 1H, CH_{Ar}), 7.03 (d, 1H, ^{3}J = 7.7 Hz, CH_{Ar}), 7.46-7.56 (m, 2H, CH_{Ar}), 8.08 (s, 1H, Py), 11.01 (s, 1H, OH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 24.2, 24.7 (CH_2 cyclohexyl), 30.7 (CHN), 31.8 (CH_2 cyclohexyl), 48.6 (Me), 53.0 (OMe), 112.4 (C), 117.6, 119.3 (CH), 120.2, 121.3 (C), 128.6, 131.7 (CH), 134.2 (C), 136.2 (CH), 137.9, 138.1, 145.8, 160.0, 163.9 (C), 195.7 (C=O).
MS (GC, 70 eV): *m/z* (%) = 425 (M^+, 33), 382 (100), 366 (M^+-CO_2Me, 62), 310 (9), 284 (17).
HRMS (EI): Calcd for $C_{22}H_{23}N_3O_4S$ (M^+) 425.14038. Found 425.14045.
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929 (w), 2853 (w), 2139 (w), 1947 (w), 1737 (m), 1614 (s), 1574 (s), 1438 (m), 1340 (m), 1297 (m), 1275 (w), 1241 (s), 1150 (m), 1069 (w), 1031 (w), 976 (w), 887 (m), 822 (m), 758 (s), 712 (s), 679 (m), 559 (m).

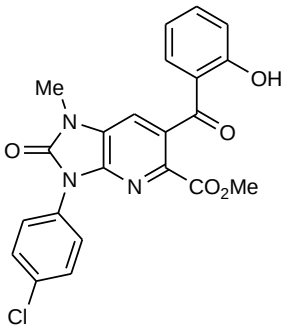
Methyl 6-(2-hydroxybenzoyl)-3-ethyl-2,3-dihydro-1-methyl-2-thioxo-1*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (2.4.2f).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 4-amino-3-ethyl-1-methyl-1*H*-imidazole-2(3*H*)-thione **E2d** (0.173 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.4.2f** was isolated as yellow solid (0.260 g, 70%), mp 212-213 ^{o}C.

^{1}H NMR (500 MHz, DMSO-d_6, 70 ^{o}C): δ = 1.34 (t, 3H, ^3J = 7.2 Hz, Me), 3.48 (q, 2H, ^3J = 7.2 Hz, CH_2), 3.69 (s, 6H, OMe, NMe), 6.90 (t, 1H, ^3J = 8.0 Hz, CH_{Ar}), 7.04 (d, 1H, ^3J = 8.0 Hz, CH_{Ar}), 7.40-7.42 (m, 1H, CH_{Ar}), 7.52-7.55 (m, 1H, CH_{Ar}), 7.94 (s, 1H, Py), 11.0 (s, 1H, OH).
^{13}C NMR (125.8 MHz, DMSO-d_6, 70 ^{o}C): δ = 13.8, 31.9 (Me), 46.0 (CH_2), 52.1 (OMe), 116.3, 117.4, 118.9 (CH), 120.9 (C), 131.5 (CH), 135.9 (C), 137.0 (CH), 137.7, 138.2, 141.6, 145.8, 160.0, 163.6 (C), 196.1 (C=O).
MS (GC, 70 eV): *m/z* (%) = 371 (M^+, 11), 356 (23), 324 (18), 312 (100).
HRMS (ESI): Calcd for $C_{18}H_{18}N_3O_4S$ (M+H) 372.1013. Found 372.1015.
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2561 (w), 1719 (m), 1625 (s), 1575 (s), 1438 (m), 1369 (m), 1348 (m), 1299 (s), 1261 (s), 1243 (s), 1216 (s), 1184 (s), 1126 (s), 1107 (m), 1032 (w), 910 (m), 887 (m), 821 (m), 800 (m), 759 (s), 731 (s), 685 (s).

Methyl 6-(2-hydroxybenzoyl)-3-(4-chlorophenyl)-2,3-dihydro-1-methyl-2-oxo-1*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (2.4.2g).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 4-amino-3-(4-chlorophenyl)-1-methyl-1*H*-imidazol-2(3*H*)-one **E2e** (0.246 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.4.2g** was isolated as white solid (0.302 g, 69%), mp 275-277 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.46 (s, 3H, NMe), 3.60 (s, 3H, OMe), 6.87 (td, 1H, ^{3}J = 8.0 Hz, ^{4}J = 0.9 Hz, CH_{Ar}), 7.03 (dd, 1H, ^{3}J = 8.0 Hz, ^{4}J = 0.9 Hz, CH_{Ar}), 7.30 (dd, 1H, ^{3}J = 8.0 Hz, ^{4}J = 1.6 Hz, CH_{Ar}), 7.55 (td, 1H, ^{3}J = 8.0 Hz, ^{4}J = 1.6 Hz, CH_{Ar}), 7.66-7.76 (m, 4H, C_6H_4), 7.88 (s, 1H, Py), 11.30 (s, 1H, OH).

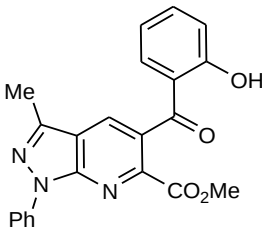
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 27.5 (Me), 52.3 (OMe), 113.5, 117.6, 119.3 (CH), 121.1, 127.1 (C), 128.2, 129.1 (CH), 131.8 (C), 132.1 (CH), 132.3, 133.0, 135.7 (C), 136.2 (CH), 142.6, 152.8, 160.4, 164.9 (C), 198.6 (C=O).

MS (EI, 70 eV): *m/z* (%) = 437 (M^+, 3), 405 (24), 378 (M^+-CO_2Me, 100), 348 (11).

HRMS (EI): Calcd for $C_{22}H_{16}ClN_3O_5$ (M^+) 437.07730. Found 437.07733.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1735 (s), 1713 (s), 1628 (s), 1499 (m), 1482 (s), 1450 (m), 1399 (m), 1301 (m), 1245 (s), 1217 (s), 1190 (m), 1118 (m), 1086 (m), 1058 (w), 1015 (m), 961 (w), 929 (s), 910 (m), 874 (w), 799 (w), 742 (s), 733 (s), 708 (m), 674 (m), 624 (w), 587 (s), 566 (m).

Methyl 5-(2-hydroxybenzoyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylate (2.4.2h).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and and 4-amino-1*H*-imidazole-2(3*H*)-thione **E3** (0.190 g, 1.1 mmol) in 10 mL AcOH. **2.4.2h** was isolated as light yellow solid (0.283 g, 73%), mp 179-180 ^{o}C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.65 (s, 3H, Me), 3.72 (s, 3H, OMe), 6.93 (t, 1H, ^{3}J = 7.8 Hz, CH_{Ar}), 7.01 (d, 1H, ^{3}J = 8.0 Hz, CH_{Ar}), 7.37 (t, 1H, ^{3}J = 7.4 Hz, CH_{Ar}), 7.48 (dd, 1H, ^{3}J = 8.2 Hz, ^{4}J = 1.6 Hz, CH_{Ar}), 7.52-7.60 (m, 3H, CH_{Ar}), 8.23 (d, 2H, ^{3}J = 7.7 Hz, CH_{Ar}), 8.65 (s, 1H, Py), 10.94 (s, 1H, OH).

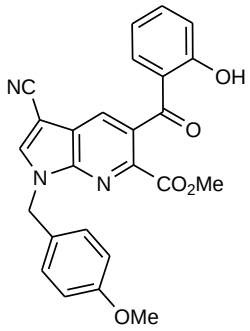
^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 12.2 (Me), 52.8 (OMe), 116.9 (C), 117.4, 119.3, 120.4 (CH), 122.1, 126.2 (C), 129.3, 129.6, 131.9, 132.2, 135.7 (CH), 138.5, 144.3, 147.0, 148.8, 159.4, 165.5 (C), 196.8 (C=O).

MS (GC, 70 eV): *m/z* (%) = 387 (M^+, 5), 328 (M^+-CO_2Me, 100).

HRMS (ESI): Calcd for $C_{22}H_{18}N_3O_4$ (M+H) 388.1292. Found 388.1297.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3049 (w), 2925 (w), 1710 (m), 1625 (w), 1610 (w), 1595 (m), 1486 (m), 1441 (m), 1330 (w), 1292 (m), 1266 (s), 1240 (s), 1166 (s), 1119 (m), 1102 (m), 1034 (w), 1011 (w), 837 (w), 819 (w), 780 (m), 752 (s), 709 (m), 691 (s), 667 (s), 637 (s), 569 (m).

Methyl 1-(4-methoxybenzyl)-5-(2-hydroxybenzoyl)-3-cyano-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate (2.4.2i).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 1-(4-methoxybenzyl)-5-amino-1*H*-pyrrole-3-carbonitrile **E4a** (0.250 g, 1.1 mmol) in 10 mL AcOH. **2.4.2i** was isolated as brown solid (0.344 g, 78%), mp 186-187 ^{o}C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.72 (s, 6H, 2xOMe), 5.54 (s, 2H, CH_2), 6.91-7.02 (m, 4H, CH_{Ar}), 7.34-7.55 (m, 4H, CH_{Ar}), 8.39 (s, 1H, Py), 8.88 (s, 1H, pirrole), 11.06 (s, 1H, OH).

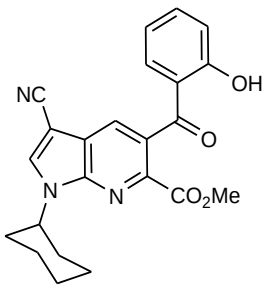
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 47.9 (CH_2), 52.7, 55.1 (OMe), 84.3 (CN), 114.1 (CH), 114.2 (C), 117.4, 119.3 (CH), 120.4, 121.8, 128.2 (C), 128.5, 129.4 (CH), 131.2 (C), 132.1, 135.8, 141.6 (CH), 142.1, 145.1, 159.1, 159.8, 165.4 (C), 197.7 (C=O).

MS (EI, 70 eV): *m/z* (%) = 441 (M^+, 27), 121 (100), 91 (13), 77 (20).

HRMS (ESI): Calcd for $C_{25}H_{20}O_5N_3$ (M+H) 442.1244. Found 442.1242.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3056 (w), 2236 (w), 1645 (m), 1627 (m), 1600 (m), 1515 (m), 1481 (w), 1458 (m), 1409 (m), 1360 (s), 1309 (m), 1291 (s), 1217 (m), 1209 (m), 1155 (w), 1114 (w), 1084 (w), 1038 (w), 993 (w), 905 (m), 887 (w), 857 (w), 763 (s), 751 (s),741 (s), 675 (w), 575 (w), 560 (m).

Methyl 5-(2-hydroxybenzoyl)-3-cyano-1-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate (2.4.2j).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 5-amino-1-cyclohexyl-1*H*-pyrrole-3-carbonitrile **E4b** (0.208 g, 1.1 mmol) in 10 mL AcOH. **2.4.2j** was isolated as brown solid (0.303 g, 75%), mp 185–187 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.25-2.05 (m, 10H, cyclohexyl), 3.71 (s, 3H, MeO), 4.79-4.81 (m, 1H, CHN), 6.90 (td, 1H, ^{3}J = 8.0 Hz, ^{4}J = 0.9 Hz, CH_{Ar}), 6.99 (d, 1H, ^{3}J = 8.3 Hz, CH_{Ar}), 7.37 (dd, 1H, ^{3}J = 7.7 Hz, ^{4}J = 1.7 Hz, CH_{Ar}), 7.50-7.53 (m, 1H, CH_{Ar}), 8.36 (s, 1H, Py), 8.99 (s, 1H, pirrole), 11.05 (s, 1H, OH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 24.7, 25.1, 32.4 (CH_2 cyclohexyl), 52.8 (OMe), 54.3

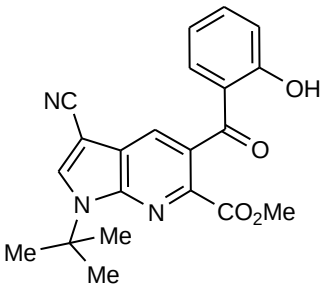
(CHN), 84.1 (CN), 114.5 (C), 117.4, 119.3 (CH), 120.4, 121.7 (C), 128.5 (CH), 131.0 (C), 132.0, 135.8, 139.5 (CH), 141.9, 144.7, 160.0, 165.5 (C), 197.6 (C=O).

MS (GC, 70 eV): *m/z* (%) = 403 (M^+, 6), 371 (5), 344 (M^+-CO_2Me, 100), 289 (23), 262 (38).

HRMS (ESI): Calcd for $C_{23}H_{22}O_4N_3$ (M+H) 404.1605. Found 404.1607.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2933 (w), 2855 (w), 2226 (m), 1719 (m), 1636 (m), 1483 (w), 1448 (m), 1374 (m), 1300 (m), 1263 (s), 1202 (s), 1147 (s), 1083 (m), 748 (s), 671 (m), 630 (m).

Methyl 1-tert-butyl-5-(2-hydroxybenzoyl)-3-cyano-1*H*-pyrrolo[2,3-*b*]pyridine-6-carboxylate (2.4.2k).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 1-tert-butyl-5-amino-1*H*-pyrrole-3-carbonitrile **E4c** (0.179 g, 1.1 mmol) in 10 mL AcOH. **2.4.2k** was isolated as yellow solid (0.336 g, 89%), mp 145-147 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88 (s, 9H, *t*-Bu), 3.78 (s, 3H, OMe), 6.79 (td, 1H, ^3J = 8.0 Hz, ^4J = 0.9 Hz, CH_{Ar}), 7.06 (d, 1H, ^3J = 8.0 Hz, CH_{Ar}), 7.16 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.5 Hz, CH_{Ar}), 7.45–7.51 (m, 1H, CH_{Ar}), 8.10 (s, 1H, Py), 8.12 (s, 1H, pirrole), 11.82 (s, 1H, OH).

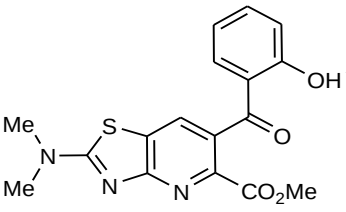
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 28.6 (*t*-Bu), 52.7 (OMe), 59.4 (*Ct*-Bu), 83.0 (CN), 114.6 (C), 117.4, 119.3 (CH), 121.7, 121.8 (C), 127.9 (CH), 130.7 (C), 132.1, 135.8, 140.2 (CH), 140.5, 145.3, 159.8, 165.4 (C), 197.8 (C=O).

MS (GC, 70 eV): *m/z* (%) = 377 (M^+, 4), 318 (49), 289 (35), 262 (100).

HRMS (ESI): Calcd for $C_{21}H_{20}O_4N_3$ (M+H) 378.1448. Found 378.1448.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2985 (w), 2224 (m), 1709 (m), 1628 (m), 1606 (m), 1519 (w), 1484 (w), 1417 (m), 1377 (m), 1301 (m), 1264 (s), 1198 (s), 1163 (m), 1102 (m), 1031 (w), 947 (m), 877 (m), 821 (m), 764 (m), 729 (s), 673 (m), 622 (m).

Methyl 6-(2-hydroxybenzoyl)-2-(dimethylamino)thiazolo[4,5-*b*]pyridine-5-carboxylate (2.4.2l).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and N^2,N^2-dimethylthiazole-2,4-diamine **E5a** (0.157 g, 1.1 mmol) in 10 mL AcOH. **2.4.2l** was isolated as yellow solid (0.243 g, 68%), mp 190-192 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.23 (s, 6H, NMe_2), 3.67 (s, 3H, OMe), 6.90 (td, 1H, ^3J = 8.0 Hz, ^4J = 1.0 Hz, CH_{Ar}), 7.00 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.0

Hz, CH_{Ar}), 7.36 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.7 Hz, CH_{Ar}), 7.48–7.54 (m, 1H, CH_{Ar}), 8.40 (s, 1H, Py), 11.00 (s, 1H, OH).

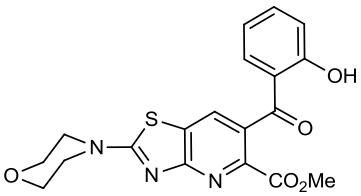
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 40.0 (NMe_2), 52.3 (OMe), 117.4, 119.3 (CH), 122.1, 127.5, 127.6 (C), 130.1, 131.7, 135.5 (CH), 144.8, 159.4, 164.5, 165.9, 171.9 (C), 197.3 (C=O).

MS (GC, 70 eV): *m/z* (%) = 357 (M^+, 1), 298 (M^+-CO_2Me, 100).

HRMS (ESI): Calcd for $C_{17}H_{16}N_3O_4S$ (M+H) 358.0856. Found 358.0856.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1712 (m), 1625 (w), 1562 (m), 1504 (w), 1483 (w), 1386 (w), 1352 (m), 1286 (s), 1228 (s), 1151 (m), 943 (m), 927 (w), 832 (w), 811 (m), 771 (s), 760 (s), 725 (m), 705 (w), 678 (m), 632 (w), 619 (m).

Methyl 6-(2-hydroxybenzoyl)-2-morpholinothiazolo[4,5-*b*]pyridine-5-carboxylate (2.4.2m).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 2-morpholinothiazol-4-amine **E5b** (0.204 g, 1.1 mmol) in 10 mL AcOH. **2.4.2m** was isolated as brown solid (0.283 g, 71%), mp 244-246 ^{o}C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.67 (s, 3H, OMe), 3.70–3.77 (m, 8H, morpholine), 6.90 (td, 1H, ^3J = 8.1 Hz, ^4J = 1.0 Hz, CH_{Ar}), 7.00 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.0 Hz, CH_{Ar}), 7.36 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.6 Hz, CH_{Ar}), 7.50-7.53 (m, 1H, CH_{Ar}), 8.44 (s, 1H, Py), 10.97 (s, 1H, OH).

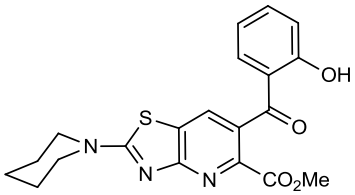
^{13}C NMR (125.8 MHz, DMSO-d_6): δ = 23.4, 24.9, 49.2 (CH_2 morpholine), 52.3 (OMe), 117.4, 119.3 (CH), 122.0, 127.2, 128.2 (C), 130.4, 131.7, 135.5 (CH), 144.7, 159.4, 164.1, 165.8, 172.1 (C), 197.2 (C=O).

MS (EI, 70 eV): *m/z* (%) = 399 (M^+, 3), 367 (10), 340 (M^+-CO_2Me, 100), 282 (13), 69 (12).

HRMS (ESI): Calcd for $C_{19}H_{18}N_3O_5S$ (M+H) 400.0962. Found 400.0964.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922 (w), 1716 (m), 1623 (w), 1558 (s), 1507 (w), 1437 (m), 1389 (m), 1280 (s), 1257 (s), 1146 (m), 1063 (s), 1024 (m), 957 (w), 862 (w), 829 (w), 757 (s), 743 (s), 717 (m), 677 (m), 624 (m).

Methyl 6-(2-hydroxybenzoyl)-2-(piperidin-1-yl)thiazolo[4,5-*b*]pyridine-5-carboxylate (2.4.2n).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 2-(piperidin-1-yl)thiazol-4-amine **E5c** (0.201 g, 1.1 mmol) in 10 mL AcOH. **2.4.2n** was isolated as orange solid (0.306 g, 77%), mp 166-168^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.66 (s, 6H, piperidine), 3.66 (s, 7H, piperidine, OMe), 6.88-6.93 (m, 1H, CH_{Ar}), 7.00 (dd, 1H, ^{3}J = 8.2 Hz, ^{4}J = 0.8 Hz, CH_{Ar}), 7.35 (dd, 1H, ^{3}J = 7.8 Hz, ^{4}J = 1.6 Hz, CH_{Ar}), 7.48–7.54 (m, 1H, CH_{Ar}), 8.38 (s, 1H, Py), 11.00 (s, 1H, OH).

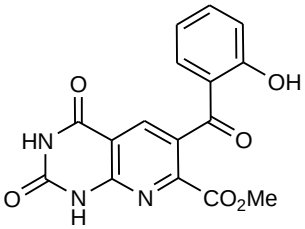
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 23.4, 24.9, 49.2 (CH_2 piperidine), 52.3 (OMe), 117.4, 119.2 (CH), 122.0, 127.3, 127.7 (C), 130.0, 131.7, 135.5 (CH), 144.7, 159.5, 164.6, 165.9, 171.3 (C), 197.3 (C=O).

MS (EI, 70 eV): *m/z* (%) = 397 (M^+, 14), 365 (48), 338 (M^+-CO_2Me, 100), 308 (24), 282 (38), 269 (18), 121 (11), 69 (10), 41 (15).

HRMS (ESI): Calcd for $C_{20}H_{20}O_4N_3S$ (M+H) 398.1169. Found 398.1177.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2938 (w), 2852 (w), 1711 (m), 1672 (m), 1547 (s), 1505 (m), 1439 (m), 1428 (m), 1392 (m), 1324 (s), 1283 (s), 1215 (s), 1124 (s), 1008 (w), 941 (m), 883 (m), 855 (m), 756 (s), 719 (s), 677 (m), 632 (s).

Methyl 6-(2-hydroxybenzoyl)-1,2,3,4-tetrahydro-2,4-dioxopyrido[2,3-*d*]pyrimidine-7-carboxylate (2.4.2o).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 6-aminopyrimidine-2,4(1*H*,3*H*)-dione **E6a** (0.140 g, 1.1 mmol) in 10 mL AcOH. **2.4.2o** was isolated as white solid (0.218 g, 64%), mp 262-264 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.73 (s, 3H, OMe), 6.92-7.00 (m, 2H, CH_{Ar}), 7.43 (dd, 1H, ^{3}J = 7.9 Hz, ^{4}J = 1.6 Hz, CH_{Ar}), 7.48-7.54 (m, 1H, CH_{Ar}), 8.32 (s, 1H, Py), 10.68 (s, 1H, OH), 11.73 (s, 1H, NH), 12.22 (s, 1H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 52.9 (OMe), 111.0 (C), 117.2, 119.5 (CH), 122.7, 129.1 (C), 131.3, 135.3, 138.4 (CH), 150.3, 152.3, 153.1, 158.3, 161.5, 165.2 (C), 194.3 (C=O).

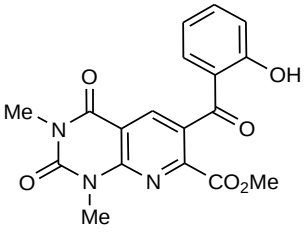
MS (EI, 70 eV): *m/z* (%) = 341 (M^+, 7), 282 (M^+-CO_2Me, 100), 238 (41), 210 (22), 121 (19), 65 (10).

HRMS (ESI): Calcd for $C_{16}H_{12}N_3O_6$ (M+H) 342.0721. Found 342.0726.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3197 (w), 3095 (w), 1748 (w), 1731 (m), 1692 (m), 1636 (m), 1574 (m), 1505 (w), 1484 (w), 1399 (w), 1360 (w), 1328 (m), 1270 (s), 1243 (m), 1147 (m), 1116 (w),

1053 (w), 1015 (w), 920 (w), 829 (m), 818 (m), 793 (w), 759 (s), 722 (m), 688 (m), 657 (m), 627 (w).

Methyl 6-(2-hydroxybenzoyl)-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-7-carboxylate (2.4.2p).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **E6b** (0.171 g, 1.1 mmol) in 10 mL AcOH. **2.4.2p** was isolated as white solid (0.203 g, 55%), mp 203-204 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.31 (s, 3H, NMe), 3.59 (s, 3H, NMe), 3.74 (s, 3H, OMe), 6.93-7.00 (m, 2H, CH_{Ar}), 7.45 (dd, 1H, ^{3}J = 7.4 Hz, ^{4}J = 1.6 Hz, CH_{Ar}), 7.49-7.55 (m, 1H, CH_{Ar}), 8.44 (s, 1H, Py), 10.66 (s, 1H, OH).

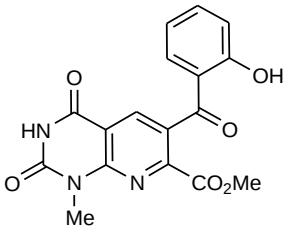
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 28.3, 29.5 (Me), 52.9 (OMe), 111.3 (C), 117.2, 119.4 (CH), 122.7, 129.3 (C), 131.2, 135.3, 138.7 (CH), 150.8, 151.1, 151.5, 158.2, 160.0, 165.1 (C), 193.9 (C=O).

MS (EI, 70 eV): *m/z* (%) = 369 (M^{+}, 1), 337 (71), 309 (51), 280 (21), 225 (10), 197 (100), 140 (9), 81 (10).

HRMS (ESI): Calcd for $C_{18}H_{16}O_6N_3$ (M+H) 370.1034. Found 370.1034.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1714 (m), 1660 (s), 1633 (s), 1603 (s), 1464 (m), 1409 (w), 1352 (m), 1290 (s), 1264 (s), 1239 (s), 1214 (s), 1151 (m), 1081 (w), 1052 (w), 959 (w), 906 (m), 868 (m), 812 (w), 788 (s), 751 (s), 713 (m), 689 (m), 663 (m).

Methyl 6-(2-hydroxybenzoyl)-1,2,3,4-tetrahydro-1-methyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-7-carboxylate (2.4.2q).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 6-amino-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **E6c** (0.155 g, 1.1 mmol) in 10 mL AcOH. **2.4.2q** was isolated as yellow solid (0.213 g, 60%), mp 243-245 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.51 (s, 3H, NMe), 3.74 (s, 3H, OMe), 6.93-7.00 (m, 2H, CH_{Ar}), 7.43-7.54 (m, 2H, CH_{Ar}), 8.38 (s, 1H, Py), 10.66 (s, 1H, OH), 12.00 (s, 1H, NH).

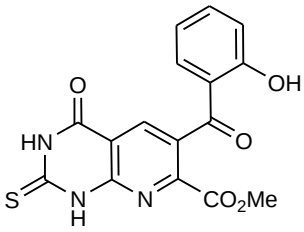
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 28.6 (Me), 52.9 (OMe), 112.1 (C), 117.2, 119.4 (CH), 122.7, 128.9 (C), 131.2, 135.3, 138.4 (CH), 150.5, 151.6, 152.6, 158.2, 160.4, 165.2 (C), 194.0 (C=O).

MS (EI, 70 eV): *m/z* (%) = 355 (M^+, 2), 296 (100), 253 (29), 197 (33), 121 (12).

HRMS (ESI): Calcd for $C_{17}H_{12}N_3O_6$ (M-H) 354.0732. Found 354.0737.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3051 (w), 1724 (m), 1690 (s), 1630 (s), 1598 (s), 1449 (m), 1338 (m), 1297 (m), 1241 (s), 1207 (s), 1144 (m), 1122 (m), 1024 (s), 896 (m), 854 (m), 828 (m), 785 (s), 751 (s), 711 (s), 672 (s).

Methyl 6-(2-hydroxybenzoyl)-1,2,3,4-tetrahydro-4-oxo-2-thioxopyrido[2,3-*d*]pyrimidine-7-carboxylate (2.4.2r).



Starting from 3-methoxalylchromone **2.4.1** (0.232 g, 1 mmol) and 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one **E6d** (0.157 g, 1.1 mmol) in 10 mL AcOH. **2.4.2r** was isolated as yellow solid (0.157 g, 44%), mp 260-262 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.73 (s, 3H, OMe), 6.93-7.00 (m, 2H, CH_{Ar}), 7.44-7.55 (m, 2H, CH_{Ar}), 8.33 (s, 1H, Py), 10.69 (s, 1H, OH), 12.83 (s, 1H, OH), 13.54 (s, 1H, SH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 52.9 (OMe), 113.0 (C), 117.2, 119.4 (CH), 122.5, 130.4 (C), 131.3, 135.4, 138.1 (CH), 151.9, 152.3, 158.3, 158.9, 164.9, 176.6 (C), 193.9 (C=O).

MS (EI, 70 eV): *m/z* (%) = 357 (M^+, 15), 325 (13), 298 (M^+-CO_2Me, 100), 281 (15), 239 (58), 210 (9), 121 (16), 78 (12), 63 (13).

HRMS (ESI): Calcd for $C_{16}H_{12}O_5N_3S$ (M+H) 358.0492. Found 358.0493.

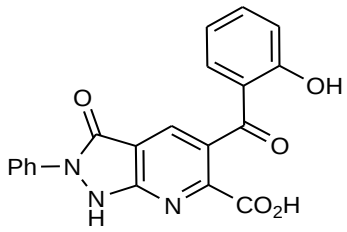
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3090 (w), 1728 (m), 1682 (m), 1594 (s), 1551 (s), 1450 (m), 1340 (m), 1317 (m), 1275 (s), 1227 (s), 1135 (s), 1052 (m), 921 (m), 799 (m), 783 (m), 760 (s), 733 (m), 694 (m), 652 (m), 640 (m).

*A.2.7. General procedure for the synthesis of compounds **2.4.6a-d**.*

The fused pyridine derivative **2.4.2** (1 equiv.) and potassium hydroxide (4 equiv.) were dissolved in methanol (10 mL/1 equiv. of **2.3.3**) and heated under reflux for 2 h (under argon atmosphere). After completion of the reaction (TLC control), the reaction mixture was diluted with conc. HCl till slightly acidic pH (pH = 4-5). The precipitate was filtered, washed once with methanol and three times with distilled water, and dried in air.

5-(2-hydroxybenzoyl)-2,3-dihydro-3-oxo-2-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-6-

carboxylic acid (2.4.6a).



Starting from **2.4.2a** (0.150 g, 0.38 mmol) and potassium hydroxide (0.085 g, 1.52 mmol) in 10 mL methanol. **2.4.6a** was isolated as white solid (0.114 g, 80%), mp 165-166 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.93-7.04 (m, 2H, CH_{Ar}), 7.34 (t, 1H, ^{3}J = 7.4 Hz, CH_{Ar}), 7.46-7.60 (m, 4H, CH_{Ar}), 7.91 (d, 2H, ^{3}J = 7.6 Hz, CH_{Ar}), 8.33 (s, 1H, Py), 10.99 (s, 1H, OH), 12.57 (s, 1H, NH), 13.85 (s, 1H, OH).

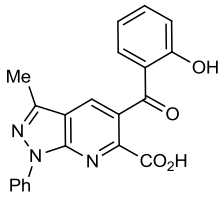
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 110.0 (C), 117.4, 119.3, 120.0 (CH), 122.2 (C), 125.9 (CH), 128.1 (C), 129.2, 131.9, 135.1, 135.5 (CH), 136.5, 153.3, 157.3, 166.5 (C), 196.4 (C=O).

MS (EI, 70 eV): *m/z* (%) = 375 (M^{+}, 14), 330 (100), 253 (37).

HRMS (ESI): Calcd for $C_{20}H_{14}O_5N_3$ (M+H) 376.0928. Found 376.0924.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3401 (w), 3046 (w), 1722 (m), 1653 (s), 1625 (m), 1596 (s), 1575 (m), 1490 (s), 1446 (m), 1348 (m), 1304 (m), 1245 (s), 1156 (s), 951 (w), 925 (m), 824 (m), 762 (s), 691 (s), 655 (s), 635 (s).

5-(2-hydroxybenzoyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylic acid (2.4.6b).



Starting from **2.4.2h** (0.150 g, 0.38 mmol) and potassium hydroxide (0.085 g, 1.52 mmol) in 10 mL methanol. **2.4.6b** was isolated as white solid (0.116 g, 82%), mp 128-130 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.65 (s, 3H, Me), 6.89-7.02 (m, 2H, CH_{Ar}), 7.35-7.63 (m, 5H, CH_{Ar}), 8.36 (d, 2H, ^{3}J = 7.7 Hz, CH_{Ar}), 8.61 (s, 1H, Py), 11.19 (s, 1H, OH), 13.71 (s, 1H, OH).

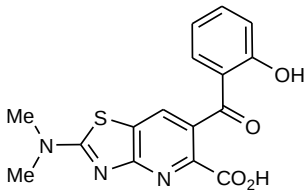
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 12.2 (Me), 116.8 (C), 117.5, 119.3, 120.3 (CH), 121.7 (C), 126.1, 129.3 (CH), 129.7 (C), 131.5, 132.3, 135.9 (CH), 138.6, 144.1, 137.9, 148.8, 160.1, 166.5 (C), 198.0 (C=O).

MS (EI, 70 eV): *m/z* (%) = 373 (M^{+}, 11), 328 (100), 251 (23), 236 (19).

HRMS (ESI): Calcd for $C_{21}H_{16}O_4N_3$ (M+H) 374.1136. Found 374.1135.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1706 (w), 1629 (s), 1595 (m), 1506 (w), 1444 (m), 1294 (s), 1152 (s), 1142 (m), 1117 (m), 1103 (m), 945 (s), 909 (m), 787 (m), 760 (s), 746 (s), 687 (s), 668 (s), 640 (s).

6-(2-hydroxybenzoyl)-2-(dimethylamino)thiazolo[4,5-*b*]pyridine-5-carboxylic acid (2.4.6c).



Starting from **2.4.2l** (0.150 g, 0.42 mmol) and potassium hydroxide (0.094 g, 1.68 mmol) in 10 mL methanol. **2.4.6c** was isolated as white solid (0.114 g, 79%), mp 132-134 ^{o}C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.25 (s, 6H, NMe_2), 6.89 (t, 1H, ^{3}J = 7.7 Hz, CH_{Ar}), 6.99 (d, 1H, ^{3}J = 8.1 Hz, CH_{Ar}), 7.31 (t, 1H, ^{3}J = 7.8 Hz, ^{4}J = 1.3 Hz, CH_{Ar}), 7.48-7.55 (m, 1H, CH_{Ar}), 8.36 (s, 1H, Py), 11.28 (s, 1H, OH), 14.01 (s, 1H, OH).

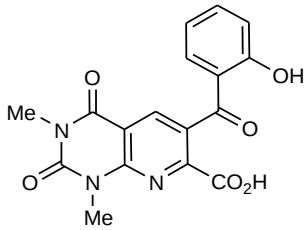
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 39.7 (NMe_2), 117.5, 119.3 (CH), 121.5, 127.7, 127.9 (C), 129.6, 132.1, 135.8 (CH), 145.0, 160.3, 164.2, 166.7, 171.7 (C), 198.7 (C=O).

MS (EI, 70 eV): *m/z* (%) = 343 (M^+, 9), 298 (100), 254 (23).

HRMS (ESI): Calcd for $C_{16}H_{14}O_4N_3S$ (M+H) 344.0689. Found 344.0690.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924 (w), 1706 (m), 1620 (m), 1597 (s), 1565 (s), 1519 (w), 1486 (w), 1449 (w), 1403 (s), 1339 (s), 1286 (s), 1239 (s), 1215 (s), 1151 (m), 1106 (m), 945 (m), 914 (w), 896 (m), 829 (w), 798 (w), 781 (w), 758 (s), 720 (s), 681 (m), 627 (m).

6-(2-hydroxybenzoyl)-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidine-7-carboxylic acid (2.4.6d).



Starting from **2.4.2p** (0.150 g, 0.41 mmol) and potassium hydroxide (0.092 g, 1.64 mmol) in 10 mL methanol. **2.4.6d** was isolated as white solid (0.118 g, 81%), mp 254-256 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.31 (s, 3H, NMe), 3.62 (s, 3H, NMe), 6.91-7.00 (m, 2H, CH_{Ar}), 7.41-7.55 (m, 2H, CH_{Ar}), 8.41 (s, 1H, Py), 10.84 (s, 1H, OH), 13.94 (s, 1H, OH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 28.3, 29.5 (NMe), 111.0 (C), 117.3, 119.3 (CH), 122.2, 129.6 (C), 131.5, 135.6, 138.1 (CH), 150.8, 150.9, 152.3, 160.0, 161.1, 166.0 (C), 195.1 (C=O).

MS (EI, 70 eV): *m/z* (%) = 355 (M^+, 7), 310 (100), 280 (15).

HRMS (ESI): Calcd for $C_{17}H_{14}O_6N_3$ (M+H) 356.0877. Found 356.087.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3052 (w), 1706 (m), 1650 (s), 1625 (s), 1598 (s), 1471 (m), 1449 (m), 1358 (m), 1288 (m), 1262 (w), 1213 (s), 1152 (s), 1052 (m), 954 (w), 908 (m), 812 (w), 790 (m), 763 (m), 751 (s), 704 (m), 663 (s).

A.2.8. General procedure for the synthesis of 4-Hydroxy-3-nitrocoumarin.

To the suspension of 4-hydroxycoumarin (40.0 g, 250 mmol) and sodium nitrite (0.8 g, 12 mmol) in acetic acid (120 mL) under stirring at room temperature was added 65% nitric acid (35 mL) in small portions. The reaction mixture was heated at 50-60 °C under intensive stirring for 15 min. The resulting solid was filtered and washed with water to give yellow crystals (44.6 g, 87%), mp 174-175 °C (lit.[98a] mp 177 °C).

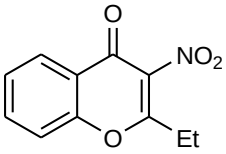
A.2.9. General procedure for the synthesis of 2'-Hydroxy-2-nitroacetophenone.

4-Hydroxy-3-nitrocoumarin (12.6 g, 60 mmol) was dissolved in 5% water solution of potassium hydroxide (450 mL). The resulting reddish solution was heated at 55 °C for 1.5 h. After cooling to the reaction mixture an acetic acid was added dropwise under intensive stirring (till pH = 5). The precipitate was rapidly filtered and washed with water to afford a colorless solid (8.8 g, 81%), mp 106 °C (lit.[98a] mp 106-107 °C).

*A.2.10. General procedure for the synthesis of 3-Nitrochromone derivatives **2.5.1**.*

To a solution of 2′-hydroxy-2-nitroacetophenone (1 equiv.) in appropriate orthoester (8 equiv.) a concentrated sulfuric acid (0.5 equiv.) was added dropwise. Afterwards the reaction mixture was refluxed for 6 h and distilled to dryness.The formed solid was washed with water and recrystallized from methanol to give corresponding chromone **2.5.1a-e**.

2-Ethyl-3-Nitrochromone (2.5.1c)



Starting from 2′-hydroxy-2-nitroacetophenone (5 g, 27.6 mmol), trimethyl orthopropionate (31 mL, 221 mmol) and sulfuric acid (1.35 g, 13.8 mmol). **2.5.1c** was isolated as colorless solid, mp 178–179 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.40 (t, 3H, ^{3}J = 7.5 Hz, Me), 2.82 (q, 2H, ^{3}J = 7.5 Hz, CH_2), 7.42-7.52 (m, 2H, CH_{Ar}), 7.71-7.76 (m, 1H, CH_{Ar}), 8.19 (dd, 1H, ^{3}J = 8.0 Hz, ^{4}J = 1.5 Hz, CH_{Ar}).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 11.0 (Me), 25.1 (CH_2), 118.1 (CH), 122.5, 123.3 (C), 126.3 (CH), 134.9 (C), 138.3, 155.2 (CH), 167.2, 168.2 (C).

MS (EI, 70 eV): *m/z* (%) = 219 (M^+, 100), 202 (46), 120 (37), 115 (52).

HRMS (EI): Calcd for $C_{11}H_9NO_4$ (M^+) 219.0522. Found 219.0523.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2993 (w), 1732 (w), 1654 (s), 1615 (m), 1568 (w), 1519 (s), 1456 (s),

1372 (s), 1326 (m), 1209 (w), 1140 (m), 1042 (m), 969 (w), 902 (m), 787 (s), 768 (s), 596 (m).

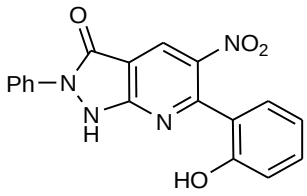
*A.2.11. General procedure for the synthesis of compounds **2.5.3a-c**, **e-l** in acetic acid.*

In a round-bottom flask the mixture of 3-nitrochromone **2.5.1a** (1 equiv.) and appropriate aminoheterocycle **E** (1.1 equiv.) was dissolved in AcOH (10 mL/1.0 mmol of chromone **2.5.1a**) and heated under reflux in an inert atmosphere for 1-15 h (controlled by TLC). After completion of the reaction volatiles were evaporated under reduced pressure. The residue was treated with water, filtered, dried in air, and recrystallized from appropriate solvent or subjected to column chromatography (silica gel).

*A.2.12. General procedure for the synthesis of compounds **2.5.3d, m-p** in TMSCl/DMF.*

The 3-nitrochromone **2.5.1a** (1 equiv.) and 4-amino-1*H*-imidazole-2(3*H*)-thione **E2b**, **E7**-**E9** (1.1 equiv.) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMF (5 mL/1 mmol of chromone **2.3.2**) containing 1 mL of TMSCl. The mixture was heated at 100-140 °C for 2-12 h (controlled by TLC). After the reaction was completed volatiles were evaporated under reduced pressure. The residue was treated with water, filtered, dried in air, and recrystallized from appropriate solvent or subjected to column chromatography (silica gel).

6-(2-Hydroxyphenyl)-5-nitro-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (2.5.3a).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and 5-amino-1,2-dihydro-2-phenylpyrazol-3-one **E1a** (0.193 g, 1.1 mmol) in 10 mL AcOH. **2.5.3a** was isolated as dark green solid (0.340 g, 98%), mp 248-250 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.88 (d, 1H, ^{3}J = 8.0 Hz, CH_{Ar}), 6.99 (t, 1H, ^{3}J = 7.4 Hz, CH_{Ar}), 7.28-7.37 (m, 2H, CH_{Ar}), 7.51-7.56 (m, 3H, CH_{Ar}), 7.92 (d, 2H, ^{3}J = 8.0 Hz, CH_{Ar}), 8.75 (s, 1H, Py), 10.14 (s, 1H, OH), 12.0-13.5 (br s, 1H, NH).

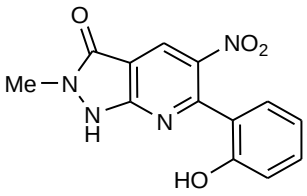
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 107.9 (C), 115.3, 119.4, 119.9 (CH), 124.0 (C), 125.8, 129.2, 130.2, 131.2, 131.4 (CH), 136.8, 140.3, 153.8, 154.7, 157.3 (C).

MS (EI, 70 eV): *m/z* (%) = 348 (M^{+}, 47), 318 (48), 303 (100), 289 (9), 274 (19), 183 (22), 156 (12), 77 (42).

HRMS (ESI): Calcd for $C_{18}H_{13}N_4O_4$ (M+H) 349.0931. Found 349.0926.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3055 (w), 1652 (w), 1605 (m), 1583 (m), 1527 (m), 1483 (w), 1407 (m), 1339 (s), 1275 (m), 1240 (m), 1179 (m), 1157 (m), 1098 (w), 982 (w), 950 (w), 918 (w), 885 (w), 843 (w), 791 (s), 746 (s), 702 (s), 679 (s), 639 (s), 611 (s).

6-(2-Hydroxyphenyl)-2-methyl-5-nitro-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (2.5.3b).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and 5-amino-1,2-dihydro-2-methylpyrazol-3-one **E1b** (0.124 g, 1.1 mmol) in 10 mL AcOH. **2.5.3b** was isolated as red solid (0.248 g, 87%), mp 295-297 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.48 (s, 3H, Me), 6.85 (d, 1H, ^3J = 8.1 Hz, CH_{Ar}), 6.95 (td, 1H, ^3J = 7.4 Hz, ^4J = 0.7 Hz, CH_{Ar}), 7.30 (m, 1H, CH_{Ar}), 7.48 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.6 Hz, CH_{Ar}), 8.65 (s, 1H, Py), 10.01 (s, 1H, OH), 12.5-13.0 (br s, 1H, NH).

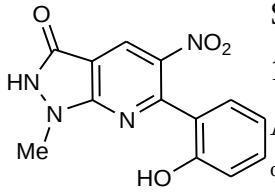
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 30.6 (Me), 105.7 (C), 115.1, 119.3 (CH), 125.1 (C), 130.1, 130.9 (CH), 140.8, 153.0, 154.4, 154.5, 157.1 (C).

MS (EI, 70 eV): *m/z* (%) = 286 (M^+, 32), 256 (79), 241 (37), 183 (23), 169 (23), 156 (16), 131 (26), 119 (25), 105 (18), 77 (29), 69 (100).

HRMS (ESI): Calcd for $C_{13}H_{11}N_4O_4$ (M+H) 287.07748. Found 287.07720.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929 (w), 1645 (m), 1621 (m), 1582 (m), 1532 (m), 1504 (m), 1447 (m), 1318 (m), 1240 (m), 1116 (w), 1092 (w), 1033 (w), 999 (w), 961 (w), 939 (w), 861 (m), 793 (s), 755 (s), 701 (s), 634 (s).

6-(2-Hydroxyphenyl)-1-methyl-5-nitro-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (2.5.3c).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and 5-amino-1,2-dihydro-2-methylpyrazol-3-one **E1c** (0.124 g, 1.1 mmol) in 10 mL AcOH. **2.5.3c** was isolated as yellow solid (0.226 mg, 79%), mp 272-274 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.86 (s, 3H, Me), 6.83 (d, 1H, ^3J = 8.1 Hz, CH_{Ar}), 6.97 (td, 1H, ^3J = 7.5 Hz, ^4J = 0.8 Hz, CH_{Ar}), 7.29 (m, 1H, CH_{Ar}), 7.53 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.5 Hz, CH_{Ar}), 8.77 (s, 1H, Py), 9.91 (s, 1H, OH), 11.63 (s, 1H, NH).

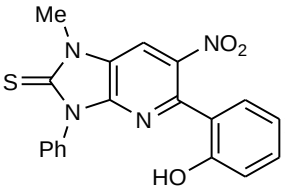
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 33.2 (Me), 102.0 (C), 115.0, 119.3 (CH), 125.7 (C), 127.9, 130.2, 130.5 (CH), 140.5, 148.9, 151.2, 154.0, 154.5 (C).

MS (EI, 70 eV): *m/z* (%) = 286 (M^+, 52), 241 (100).

HRMS (ESI): Calcd for $C_{13}H_{11}N_4O_4$ (M+H) 287.06789. Found 287.03788.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2256 (w), 1583 (m), 1488 (w), 1453 (w), 1404 (w), 1369 (w), 1349 (m), 1288 (w), 1230 (m), 1160 (m), 1116 (w), 1015 (w), 933 (w), 920 (w), 844 (w), 820 (w), 796 (m), 751 (s), 672 (m), 656 (m), 617 (m).

5-(2-Hydroxyphenyl)-1-methyl-6-nitro-3-phenyl-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (2.5.3d).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and 4-amino-1-methyl-3-phenyl-1*H*-imidazole-2(3*H*)-thione **E2b** (0.226 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.5.3d** was isolated as orange solid (0.359 g, 95%), mp 164-166 ^{o}C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.86 (s, 3H, Me), 6.79-6.92 (m, 2H, CH_{Ar}), 7.19-7.30 (m, 2H, CH_{Ar}), 7.51-7.59 (m, 5H, CH_{Ar}), 7.93 (s, 1H, Py), 8.58 (s, 1H, OH).

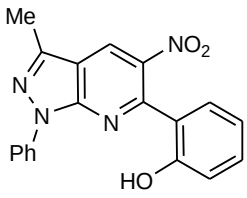
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 31.6 (Me), 112.8, 117.9, 119.7 (CH), 120.5, 124.7 (C), 127.7, 129.3, 129.7 (CH), 129.9, 131.9, 133.3, 142.1, 145.5, 145.8, 155.1, 174.5 (C).

MS (EI, 70 eV): *m/z* (%) = 378 (M^+, 100), 348 (60), 332 (90), 316 (12), 77 (14), 57 (10).

HRMS (ESI): Calcd for $C_{19}H_{15}N_4O_3S$ (M+H) 379.0859. Found 379.0860.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1602 (w), 1534 (m), 1500 (m), 1466 (s), 1424 (s), 1376 (m), 1323 (s), 1286 (s), 1245 (m), 1198 (s), 1158 (m), 1114 (m), 1079 (m), 904 (s), 806 (s), 782 (w), 766 (s), 753 (s), 726 (s), 711 (s), 686 (s), 647 (s), 603 (m).

2-(3-Methyl-5-nitro-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)phenol (2.5.3e).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and 4-amino-1*H*-imidazole-2(3*H*)-thione **E3** (0.190 g, 1.1 mmol) in 10 mL AcOH. **2.5.3e** was isolated as yellow solid (0.336 g, 97%), mp 204-206 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.69 (s, 3H, Me), 6.87 (d, 1H, ^{3}J = 7.6 Hz, CH_{Ar}), 7.01 (t, 1H, ^{3}J = 7.2 Hz, CH_{Ar}), 7.30-7.37 (m, 2H, CH_{Ar}), 7.55 (t, 2H, ^{3}J = 7.6 Hz, CH_{Ar}), 7.65 (m, 1H, CH_{Ar}), 8.22 (d, 2H, ^{3}J = 7.6 Hz, CH_{Ar}), 9.09 (s, 1H, Py), 10.05 (s, 1H, OH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.3 (Me), 114.5 (C), 115.1, 119.6, 120.5 (CH), 125.2 (C), 126.3, 128.3, 129.3, 130.5, 130.9 (CH), 138.4, 142.3, 145.2, 149.3, 150.9, 154.7 (C).

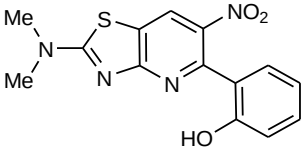
MS (EI, 70 eV): *m/z* (%) = 346 (M^+, 100), 316 (10), 300 (63), 283 (30), 221 (10), 77 (18).

HRMS (ESI): Calcd for $C_{19}H_{15}N_4O_3$ (M+H) 347.1136. Found 347.1141.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3393 (m), 1592 (m), 1575 (m), 1495 (s), 1452 (m), 1421 (m), 1383 (w), 1308 (s), 1286 (m), 1193 (m), 1118 (m), 982 (w), 916 (m), 845 (m), 807 (w), 780 (m), 752 (s),

691 (s), 682 (m), 672 (m), 639 (m), 632 (m).

2-[2-(Dimethylamino)-6-nitrothiazolo[4,5-*b*]pyridin-5-yl]phenol (2.5.3f).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and N^2,N^2-dimethylthiazole-2,4-diamine **E5a** (0.157 g, 1.1 mmol) in 10 mL AcOH. **2.5.2f** was isolated as brown solid (0.205 g, 65%), mp 266-268 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.25 (s, 6H, NMe_2), 6.82 (d, 1H, ^3J = 8.0 Hz, CH_{Ar}), 6.94 (t, 1H, ^3J = 7.4 Hz, CH_{Ar}), 7.25 (t, 1H, ^3J = 7.4 Hz, CH_{Ar}), 7.48 (d, 1H, ^3J = 7.0 Hz, CH_{Ar}), 8.86 (s, 1H, Py), 9.81 (s, 1H, OH).

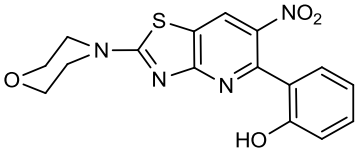
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 39.7 (NMe_2), 114.9, 119.2 (CH), 123.2, 125.7 (C), 126.3, 130.1, 130.2 (CH), 139.8, 149.0, 154.4, 166.0, 173.1 (C).

MS (GC, 70 eV): *m/z* (%) = 316 (M^+, 39), 270 (100), 254 (17), 227 (17), 207 (49).

HRMS (ESI): Calcd for $C_{14}H_{13}N_4O_3S$ (M+H) 317.0703. Found 317.0707.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2921 (w), 2852 (w), 1601 (w), 1549 (s), 1497 (w), 1450 (w), 1408 (m), 1307 (s), 1279 (s), 1181 (m), 1098 (s), 1079 (m), 972 (w), 901 (s), 861 (m), 827 (m), 781 (m), 765 (s), 745 (s), 667 (s), 619 (m).

2-(2-Morpholino-6-nitrothiazolo[4,5-*b*]pyridin-5-yl)phenol (2.5.3g).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and 2-morpholinothiazol-4-amine **E5b** (0.204 g, 1.1 mmol) in 10 mL AcOH. **2.5.3g** was isolated as yellow solid (0.322 g, 90%), mp 229-231 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.72-3.76 (m, 8H, morpholine), 6.82 (dd, 1H, ^3J = 8.1 Hz, ^4J = 0.8 Hz, CH_{Ar}), 6.94 (td, 1H, ^3J = 7.5 Hz, ^4J = 1.0 Hz, CH_{Ar}), 7.26 (m, 1H, CH_{Ar}), 7.49 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.7 Hz, CH_{Ar}), 8.89 (s, 1H, Py), 9.84 (s, 1H, OH).

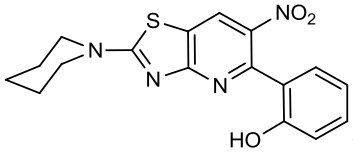
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 48.1, 65.4 (CH_2 morpholine), 114.9, 119.2 (C), 122.7, 125.5 (C), 126.6, 130.2, 130.3 (CH), 140.2, 149.0, 154.4, 165.6, 173.2 (C).

MS (GC, 70 eV): *m/z* (%) = 358 (M^+, 34), 312 (100), 69 (13).

HRMS (ESI): Calcd for $C_{16}H_{15}N_4O_4S$ (M+H) 359.0809. Found 359.0805.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3408 (w), 1599 (w), 1540 (s), 1492 (m), 1448 (w), 1409 (m), 1345 (m), 1329 (s), 1311 (s), 1283 (s), 1238 (m), 1182 (w), 1112 (s), 1083 (w), 1028 (m), 896 (s), 864 (w), 840 (w), 759 (s), 711 (w), 674 (w), 631 (m), 609 (m).

2-[6-Nitro-2-(piperidin-1-yl)thiazolo[4,5-*b*]pyridin-5-yl]phenol (2.5.3h).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and 2-(piperidin-1-yl)thiazol-4-amine **E5c** (0.201 g, 1.1 mmol) in 10 mL AcOH. **2.5.3h** was isolated as yellow solid (0.253 g, 71%), mp 109-110°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74 (s, 6H, piperidine), 3.72 (s, 4H, piperidine), 6.86 (m, 1H), 7.02 (dd, 1H, ^3J = 8.2 Hz, ^4J = 1.0 Hz, CH_{Ar}), 7.22-7.31 (m, 3H, CH_{Ar}), 8.34 (s, 1H, Py), 9.95 (br s, 1H, OH).

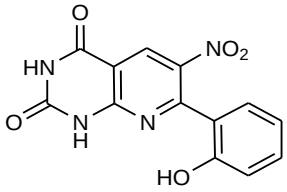
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.9, 25.4, 50.1 (CH_2 piperidine), 118.1, 119.8 (CH), 119.9, 123.0 (C), 126.5, 129.4, 131.6 (CH), 138.8, 149.8, 156.1, 164.8, 172.6 (C).

MS (EI, 70 eV): *m/z* (%) = 356 (M^+, 54), 310 (100).

HRMS (EI): Calcd for $C_{17}H_{16}N_4O_3S$ (M^+) 356.09376. Found 356.09383.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2937 (w), 1595 (w), 1537 (s), 1447 (m), 1416 (w), 1306 (s), 1251 (m), 1118 (m), 1009 (m), 904 (w), 886 (m), 851 (m), 832 (w), 782 (m), 750 (s), 709 (m), 680 (w), 629 (w).

7-(2-Hydroxyphenyl)-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.5.3i).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and 6-aminopyrimidine-2,4(1*H*,3*H*)-dione **E6a** (0.140 g, 1.1 mmol) in 10 mL AcOH. **2.5.3i** was isolated as yellow solid (0.252 g, 84%), mp 217-219 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.86 (d, 1H, ^3J = 8.1 Hz, CH_{Ar}), 6.98 (t, 1H, ^3J = 7.5 Hz, CH_{Ar}), 7.34 (m, 1H, CH_{Ar}), 7.50 (dd, 1H, ^3J = 7.5 Hz, ^4J = 1.0 Hz, CH_{Ar}), 8.64 (s, 1H, Py), 10.19 (s, 1H, OH), 11.75 (s, 1H, NH), 12.24 (s, 1H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 108.4 (C), 115.2, 119.3 (CH), 123.8 (C), 130.4, 131.6, 132.8 (CH), 141.9, 150.3, 153.5, 154.8, 155.5, 161.2 (C).

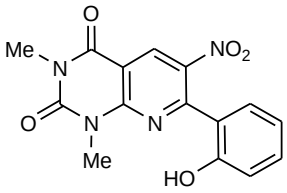
MS (EI, 70 eV): *m/z* (%) = 300 (M^+, 96), 270 (100), 255 (40), 231 (13), 211 (35), 182 (11), 168 (21), 156 (17), 128 (10).

HRMS (ESI): Calcd for $C_{13}H_9N_4O_5$ (M+H) 301.05675. Found 301.05635.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3306 (w), 3012 (w), 2824 (w), 1668 (m), 1599 (m), 1537 (m), 1494 (w), 1348 (s), 1300 (m), 1203 (m), 1145 (w), 1114 (w), 1096 (w), 1017 (w), 978 (w), 884 (w), 841 (w), 808 (w), 794 (w), 751 (s), 656 (m), 590 (m), 559 (m).

7-(2-Hydroxyphenyl)-1,3-dimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

(2.5.3j).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **E6b** (0.171 g, 1.1 mmol) in 10 mL AcOH. **2.5.3j** was isolated as yellow solid (0.318 g, 97%), mp 280-282 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.33 (s, 3H, Me), 3.61 (s, 3H, Me), 6.87 (d, 1H, ^{3}J = 7.9 Hz, CH_{Ar}), 7.01 (t, 1H, ^{3}J = 7.3 Hz, CH_{Ar}), 7.36 (td, 1H, ^{3}J = 8.0 Hz, ^{4}J = 1.6 Hz, CH_{Ar}), 7.64 (dd, 1H, ^{3}J = 7.6 Hz, ^{4}J = 1.5 Hz, CH_{Ar}), 8.73 (s, 1H, Py), 10.29 (s, 1H, OH).

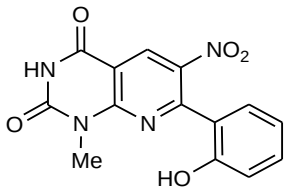
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 28.3, 29.7 (Me), 108.5 (C), 115.2, 119.6 (CH), 123.8 (C), 130.6, 131.9, 133.2 (CH), 141.8, 150.9, 151.3, 154.4, 155.0, 159.7 (C).

MS (GC, 70 eV): *m/z* (%) = 328 (M^{+}, 1), 281 (100), 253 (28), 196 (12), 169 (41).

HRMS (ESI): Calcd for $C_{15}H_{13}N_4O_5$ (M+H) 329.0880. Found 329.0883.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3256 (w), 1706 (m), 1650 (s), 1594 (s), 1537 (m), 1446 (m), 1419 (m), 1353 (s), 1289 (m), 1197 (m), 1096 (m), 1067 (w), 1038 (w), 1010 (w), 949 (w), 844 (w), 795 (m), 779 (m), 765 (s), 700 (s), 593 (m).

7-(2-Hydroxyphenyl)-1-methyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.5.3k).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and 6-amino-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **E6c** (0.155 g, 1.1 mmol) in 10 mL AcOH. **2.5.3k** was isolated as yellow solid (0.229 g, 73%), mp 230-232 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.53 (s, 3H, Me), 6.86 (d, 1H, ^{3}J = 8.0 Hz, CH_{Ar}), 7.00 (td, 1H, ^{3}J = 7.4 Hz, ^{4}J = 0.7 Hz, CH_{Ar}), 7.30-7.37 (m, 1H, CH_{Ar}), 7.63 (dd, 1H, ^{3}J = 7.6 Hz, ^{4}J = 1.6 Hz, CH_{Ar}), 8.67 (s, 1H, Py), 10.28 (s, 1H, OH), 12.01 (s, 1H, NH).

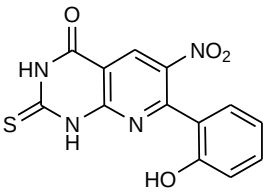
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 28.8 (Me), 109.3 (C), 115.3, 119.6 (CH), 123.9 (C), 130.6, 131.9, 132.9 (CH), 141.6, 150.6, 152.7, 154.4, 155.0, 160.1 (C).

MS (GC, 70 eV): *m/z* (%) = 314 (M^{+}, 100), 281 (11), 267 (55), 225 (57), 207 (27), 195 (15), 168 (63), 140 (17), 115 (13), 92 (13).

HRMS (ESI): Calcd for $C_{14}H_{11}N_4O_5$ (M+H) 315.0724. Found 315.0725.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3288 (w), 3153 (w), 2820 (w), 1707 (w), 1674 (m), 1602 (m), 1498 (w), 1446 (m), 1426 (w), 1372 (m), 1343 (s), 1196 (m), 1155 (m), 1038 (w), 976 (m), 863 (m), 842 (m), 815 (m), 765 (s), 749 (s), 737 (s), 659 (m).

7-(2-Hydroxyphenyl)-2-mercapto-6-nitropyrido[2,3-*d*]pyrimidin-4-ol (2.5.3l).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one **E6d** (0.157 g, 1.1 mmol) in 10 mL AcOH. **2.5.3l** was isolated as yellow solid (0.250 g, 79%), mp 307-309 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.86 (d, 1H, ^{3}J = 8.2 Hz, CH_{Ar}), 6.99 (td, 1H, ^{3}J = 7.5 Hz, ^{4}J = 0.8 Hz, CH_{Ar}), 7.32-7.38 (m, 1H, CH_{Ar}), 7.52 (dd, 1H, ^{3}J = 7.6 Hz, ^{4}J = 1.7 Hz, CH_{Ar}), 8.64 (s, 1H, Py), 10.25 (s, 1H, OH), 12.86 (s, 1H, SH), 13.53 (s, 1H, OH).

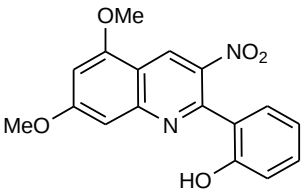
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 110.5 (C), 115.2, 119.4 (CH), 123.5 (C), 130.5, 131.5, 132.7 (CH), 142.5, 152.3, 154.8, 155.7, 158.7, 176.7 (C).

MS (GC, 70 eV): *m/z* (%) = 316 (M^{+}, 100), 286 (11), 270 (48), 253 (19).

HRMS (ESI): Calcd for $C_{13}H_9N_4O_4S$ (M+H) 317.0339. Found 317.0336.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3188 (w), 1683 (m), 1605 (m), 1584 (m), 1520 (m), 1485 (w), 1417 (w), 1352 (s), 1262 (m), 1194 (w), 1159 (m), 1131 (s), 948 (m), 805 (s), 744 (s), 692 (s), 659 (s), 629 (s).

2-(5,7-Dimethoxy-3-nitroquinolin-2-yl)phenol (2.5.3m).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and 3,5-dimethoxybenzenamine **E7a** (0.168 g, 1.1 mmol) in 10 mL AcOH. **2.5.3m** was isolated as yellow solid (0.202 g, 62%), mp 208-209 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.97 (s, 3H, OMe), 4.00 (s, 3H, OMe), 6.55 (br. s, 1H, CH_{Ar}), 6.86-6.94 (m, 2H, CH_{Ar}), 7.08 (dd, 1H, ^{3}J = 8.3 Hz, ^{4}J = 1.0 Hz, CH_{Ar}), 7.27 (dd, 1H, ^{3}J = 8.0 Hz, ^{4}J = 1.4 Hz, CH_{Ar}), 7.31-7.35 (m, 1H, CH_{Ar}), 8.88 (s, 1H, Py), 11.70 (s, 1H, OH).

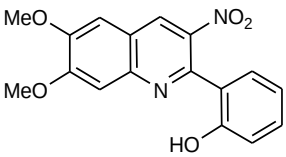
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 56.0, 56.1 (OMe), 98.8, 99.9 (CH), 113.5, 118.3 (C), 118.5, 119.6, 129.1, 129.7, 132.3 (CH), 140.8, 148.5, 151.5, 156.8, 157.5, 165.0 (C).

MS (GC, 70 eV): *m/z* (%) = 326 (M^{+}, 73), 318 (48), 280 (100), 265 (27), 222 (20), 194 (12).

HRMS (ESI): Calcd for $C_{17}H_{15}N_2O_5$ (M+H) 327.0975. Found 327.0976.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1609 (m), 1582 (m), 1500 (m), 1452 (s), 1382 (m), 1346 (m), 1237 (s), 1204 (m), 1160 (s), 1135 (s), 1039 (m), 970 (w), 939 (m), 831 (s), 797 (s), 774 (m), 751 (s), 742 (s), 722 (m), 703 (m), 667 (m), 641 (s).

2-(6,7-Dimethoxy-3-nitroquinolin-2-yl)phenol (2.5.3n).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and 3,4-dimethoxybenzenamine **E7c** (0.168 g, 1.1 mmol) in 10 mL AcOH. **2.5.3n** was isolated as reddish solid (0.271 g, 83%), mp 202-204 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.94 (s, 3H, OMe), 4.01 (s, 3H, OMe), 6.79 (s, 1H, CH_{Ar}), 6.85 (d, 1H, ^3J = 7.9 Hz, CH_{Ar}), 6.98 (t, 1H, ^3J = 7.5 Hz, CH_{Ar}), 7.09 (s, 1H, CH_{Ar}), 7.27-7.33 (m, 1H, CH_{Ar}), 7.59 (dd, 1H, ^3J = 7.5 Hz, ^4J = 1.3 Hz, CH_{Ar}), 8.82 (s, 1H, Py), 9.95 (s, 1H, OH).

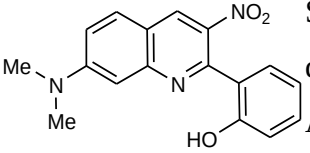
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 56.0, 56.5 (OMe), 99.7, 100.1 (CH), 112.8 (C), 114.9, 119.3 (CH), 125.3 (C), 127.1, 130.3, 130.6 (CH), 141.9, 150.4, 150.8, 154.6, 156.5, 164.3 (C).

MS (GC, 70 eV): *m/z* (%) = 326 (M^+, 73), 280 (100), 265 (27), 236 (13), 222 (21), 194 (11).

HRMS (ESI): Calcd for $C_{17}H_{15}N_2O_5$ (M+H) 327.09755. Found 327.09798.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1591 (m), 1525 (m), 1499 (w), 1453 (m), 1382 (m), 1346 (s), 1237 (m), 1204 (m), 1160 (s), 1134 (s), 1039 (m), 939 (m), 831 (s), 797 (m), 751 (s), 742 (s), 703 (m), 667 (m), 641 (s).

2-(7-(Dimethylamino)-3-nitroquinolin-2-yl)phenol (2.5.3o).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and N^1,N^1-dimethylbenzene-1,3-diamine **E8** (0.152 g, 1.1 mmol) in 10 mL AcOH. **2.5.3o** was isolated as dark red solid (0.281 g, 91%), mp 236-238 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.18 (s, 6H, NMe_2), 6.98-7.03 (m, 2H, CH_{Ar}), 7.19 (s, 1H, CH_{Ar}), 7.38 (m, 1H, CH_{Ar}), 7.52 (m, 1H, CH_{Ar}), 7.59 (dd, 1H, ^3J = 7.5 Hz, ^4J = 1.2 Hz, CH_{Ar}), 8.11 (d, 1H, ^3J = 9.5 Hz, CH_{Ar}), 9.13 (s, 1H, Py), 10.0-10.8 (br s, 1H, OH).

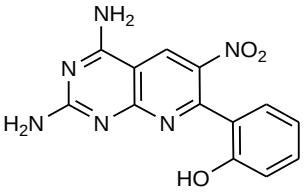
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 48.6 (NMe_2), 100.3, 115.3 (CH), 118.2 (C), 118.8 (CH), 119.2 (C), 121.8, 130.3, 131.0, 131.7, 135.5 (CH), 138.9, 146.1, 149.2, 154.4, 155.0 (C).

MS (GC, 70 eV): *m/z* (%) = 309 (M^+, 45), 263 (100), 247 (35), 219 (15).

HRMS (EI): Calcd for $C_{17}H_{15}N_3O_3$ (M^+) 309.11079. Found 309.11112.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3202 (w), 2914 (w), 1644 (w), 1603 (w), 1573 (m), 1515 (m), 1443 (w), 1421 (w), 1331 (m), 1268 (m), 1216 (w), 1158 (m), 1101 (w), 1066 (w), 1017 (m), 956 (w), 900 (m), 823 (m), 771 (m), 755 (s), 713 (m), 623 (m), 611 (m).

2-(2,4-Diamino-6-nitropyrido[2,3-*d*]pyrimidin-7-yl)phenol (2.5.3p).



Starting from 3-nitrochromone **2.5.1a** (0.191 g, 1 mmol) and pyrimidine-2,4,6-triamine **E9** (0.138 g, 1.1 mmol) in 10 mL AcOH. **2.5.3p** was isolated as yellow solid (0.193 g, 65%), mp 285-287 ^{o}C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 6.91-7.03 (m, 2H, CH_{Ar}), 7.33-7.39 (m, 1H, CH_{Ar}), 7.53-7.57 (m, 1H, CH_{Ar}), 8.08 (s, 1H, NH), 8.84 (s, 1H, NH), 9.31 (s, 1H, NH), 9.49 (s, 1H, Py), 9.62 (s, 1H, NH), 10.41 (s, 1H, OH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 103.6 (C), 115.3, 119.4 (CH), 123.4 (C), 130.3, 131.8, 132.0 (CH), 142.6, 151.0, 155.0, 156.0, 156.7, 162.7 (C).

MS (EI, 70 eV): *m/z* (%) = 298 (M^+, 100), 282 (15), 266 (33), 220 (28).

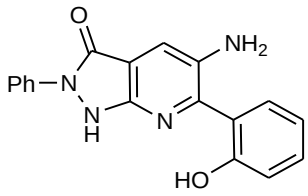
HRMS (ESI): Calcd for $C_{13}H_{11}N_6O_3$ (M+H) 299.08871. Found 299.08841.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3119 (w), 1681 (w), 1645 (m), 1606 (m), 1515 (m), 1464 (w), 1450 (w), 1425 (m), 1402 (m), 1358 (m), 1300 (m), 1200 (m), 1158 (m), 989 (w), 977 (w), 921 (w), 870 (w), 795 (m), 755 (m), 650 (m).

*A.2.12. General procedure for the synthesis of compounds **2.5.5a-n**.*

To a Schlenk flask equipped with a magnetic stir bar and filled with corresponding fused pyridine derivative **2.5.3** (1 equiv.) was added 10% Pd/C (0.1 equiv.). The flask was fitted with a rubber septum and then held under vacuum for 3 min, after that, it was filled with MeOH (25 ml for 0.5 g of fused pyridine derivative) and hydrogen. Holding under vacuum was repeated one more time, and after sequential filling with hydrogen, the reaction mixture was stirred for 2 days under H_2 atmosphere. After the reaction was stopped, the mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness or (if necessary) was purified by column chromatography typically using Heptane/Ethyl acetate mixtures or recrystallized from appropriate solvent to provide the desired product.

5-Amino-6-(2-hydroxyphenyl)-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (2.5.5a).



Starting from 3-nitrochromone **2.5.3a** (0.150 g, 0.43 mmol). **2.5.5a** was isolated as green solid (0.108 g, 78%), mp 195-196 ^{o}C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 4.52-5.51 (br. s, 2H, NH_2), 6.93-7.02 (m, 2H, CH_{Ar}), 7.23-7.54 (m, 6H, CH_{Ar}), 7.95 (br. s, 2H, CH_{Ar}), 10.0-11.0 (br s, 1H, OH), 15.01 (br s, 1H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 110.3 (C), 116.4, 117.0, 119.0, 119.3, 124.7 (CH),

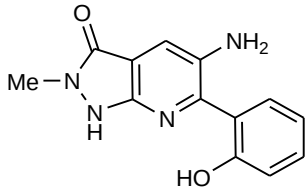
125.6 (C), 128.9, 130.0, 131.1 (CH), 137.9, 138.6, 150.0, 151.5, 154.7, 159.4 (C).

MS (EI, 70 eV): *m/z* (%) = 318 (M^+, 100), 302 (28).

HRMS (ESI): calcd for $C_{18}H_{15}N_4O_2$ (M+H) 319.1132. Found 319.1130.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3301 (w), 1645 (m), 1593 (m), 1487 (m), 1422 (s), 1343 (w), 1292 (m), 1274 (m), 1211 (m), 1150 (m), 1116 (w), 845 (w), 815 (w), 788 (w), 753 (s), 705 (m), 684 (s), 664 (s), 603 (s).

5-Amino-6-(2-hydroxyphenyl)-2-methyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (2.5.5b).



Starting from 3-nitrochromone**2.5.3b** (0.150 g, 0.52 mmol). **2.5.5b** was isolated as red solid (0.128 g, 96%), mp 281-283 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.34 (s, 3H, Me), 4.51-5.33 (br s, 2H, NH_2), 6.91-7.00 (m, 2H, CH_{Ar}), 7.26-7.35 (m, 2H, CH_{Ar}), 7.46 (s, 1H, Py), 9.71-10.71 (br. s, 1H, OH), 12.6 (br s, 1H, NH).

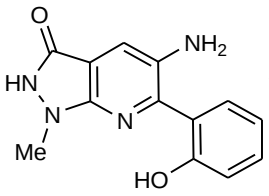
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 30.4 (Me), 109.9 (C), 116.4, 117.0, 119.3 (CH), 125.6 (C), 129.8, 131.1 (CH), 138.0, 148.8, 151.1, 154.6, 159.8 (C).

MS (EI, 70 eV): *m/z* (%) = 256 (M^+, 100), 73 (21), 44 (29).

HRMS (ESI): Calcd for $C_{13}H_{13}N_4O_2$ (M+H) 257.10330. Found 257.10293.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3363 (w), 1569 (m), 1478 (m), 1449 (m), 1426 (m), 1325 (w), 1295 (w), 1259 (m), 1234 (m), 1184 (m), 1161 (m), 1098 (w), 1055 (w), 1035 (w), 1018 (w), 959 (w), 904 (w), 851 (w), 834 (w), 759 (s), 685 (s).

5-Amino-6-(2-hydroxyphenyl)-1-methyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (2.5.5c).



Starting from 3-nitrochromone **2.5.3c** (0.150 g, 0.52 mmol). **2.5.5c** was isolated as red solid (0.122 g, 92%), mp 255-257 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.66 (s, 3H, Me), 4.05-6.01 (br. s, 2H, NH_2), 6.92-6.98 (m, 2H, CH_{Ar}), 7.26-7.32 (m, 2H, CH_{Ar}), 7.40 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.6 Hz, CH_{Ar}), 7.44 (s, 1H, Py), 9.0–12.0 (br s, 1H, OH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 33.3 (Me), 104.4 (C), 114.1, 116.6 (CH), 126.5 (C), 129.7, 131.4, 135.6 (CH), 147.2, 148.2, 152.0, 154.8 (C).

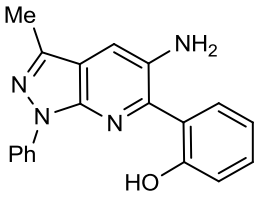
MS (EI, 70 eV): *m/z* (%) = 256 (M^+, 32), 240 (27), 201 (26), 183 (23), 152 (11), 77 (21).

HRMS (ESI): Calcd for $C_{13}H_{13}N_4O_2$ (M+H) 257.10330. Found 257.10349.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2931 (w), 2672 (w), 1605 (m), 1582 (m), 1550 (m), 1504 (w), 1475 (w),

1455 (w), 1425 (w), 1379 (w), 1299 (w), 1247 (m), 1229 (m), 1153 (m), 1112 (w), 1068 (w), 1014 (w), 885 (w), 809 (m), 759 (s), 699 (m), 682 (m), 647 (s), 614 (m).

2-(5-Amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)phenol (2.5.5d).



Starting from 3-nitrochromone **2.5.3e** (0.150 g, 0.43 mmol). **2.5.5d** was isolated as brown solid (0.118 g, 87%), mp 160-162 ^{o}C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.55 (s, 3H, Me), 4.02-6.04 (br s, 2H, NH_2), 6.94-7.03 (m, 2H, CH_{Ar}), 7.19 (tt, 1H, ^{3}J = 7.4 Hz, ^{4}J = 1.0 Hz, CH_{Ar}), 7.30-.35 (m, 1H, CH_{Ar}), 7.41 (dd, 1H, ^{3}J = 7.6 Hz, ^{4}J = 1.6 Hz, CH_{Ar}), 7.44-7.49 (m, 2H, CH_{Ar}), 7.52 (s, 1H, Py), 8.28-8.31 (m, 2H, CH_{Ar}), 9.5-10.5 (br s, 1H, OH).

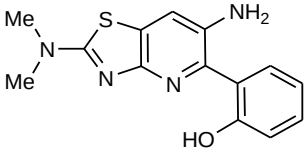
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.3 (Me), 112.8, 116.5 (CH), 116.5 (C), 118.7, 119.9, 124.2 (CH), 126.5 (C), 129.0, 129.8, 131.5 (CH), 138.0, 139.8, 140.8, 145.1, 147.2, 155.0 (C) 162.3 (CH).

MS (EI, 70 eV): *m/z* (%) = 316 (M^+, 100), 300 (10).

HRMS (ESI): Calcd for $C_{19}H_{17}N_4O$ (M+H) 317.13969. Found 317.13947.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3354 (w), 1667 (w), 1597 (m), 1505 (m), 1395 (s), 1288 (m), 1236 (m), 1201 (m), 1141 (m), 1075 (m), 996 (m), 900 (w), 803 (w), 746 (s), 665 (m).

2-[6-Amino-2-(dimethylamino)thiazolo[4,5-*b*]pyridin-5-yl]phenol (2.5.5e).



Starting from 3-nitrochromone **2.5.3f** (0.150 g, 0.47 mmol). **2.5.5e** was isolated as yellow solid (0.064 g, 48%), mp 158-160 ^{o}C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.14 (s, 6H, NMe_2), 4.85 (s, 2H, NH_2), 6.88-6.95 (m, 2H, CH_{Ar}), 7.20-7.26 (m, 1H, CH_{Ar}), 7.54 (dd, 1H, ^{3}J = 7.8 Hz, ^{4}J = 1.6 Hz, CH_{Ar}), 7.61 (s, 1H, Py), 10.75 (br s, 1H, OH).

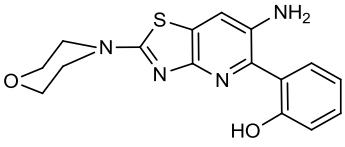
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 39.4 (NMe_2), 116.6, 117.5, 119.0 (CH), 124.5, 125.2 (C), 129.0, 130.5 (CH), 136.1, 140.4, 155.0, 156.3, 167.0 (C).

MS (EI, 70 eV): *m/z* (%) = 286 (M^+, 90), 270 (25).

HRMS (EI): Calcd for $C_{14}H_{14}N_4OS$ (M^+) 286.08046. Found 286.08045.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3324 (w), 2923 (w), 1583 (s), 1537 (s), 1487 (w), 1435 (m), 1403 (s), 1351 (m), 1274 (m), 1233 (m), 1204 (m), 1121 (m), 1073 (m), 1039 (w), 975 (w), 920 (w), 859 (m), 826 (m), 755 (s), 729 (s), 615 (m).

2-(6-Amino-2-morpholinothiazolo[4,5-*b*]pyridin-5-yl)phenol (2.5.5f).



Starting from 3-nitrochromone **2.5.3g** (0.150 g, 0.418 mmol). **2.5.5f** was isolated as brown solid (0.091 g, 66%), mp 148-150 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.72-3.75 (m, 8H, morpholine), 4.87-4.91 (br s, 2H, NH_2), 6.82 (d, 1H, ^3J = 8.6 Hz, CH_{Ar}), 6.94 (t, 1H, ^3J = 7.2 Hz, CH_{Ar}), 7.21-7.25 (m, 1H, CH_{Ar}), 7.50 (dd, 1H, ^3J = 7.7 Hz, ^4J = 1.6 Hz, CH_{Ar}), 8.89 (s, 1H, Py), 9.83 (s, 1H, OH).

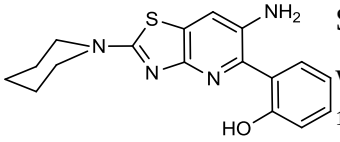
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 47.8, 65.5 (CH_2 morpholine), 116.5, 117.2, 119.1 (CH), 124.0, 125.3, 129.1, 130.7 (C), 136.9 (CH), 140.8, 154.9, 155.5, 167.4 (C).

MS (EI, 70 eV): *m/z* (%) = 328 (M^+, 100), 312 (14), 91 (17).

HRMS (ESI): Calcd for $C_{16}H_{17}N_4O_2S$ (M+H) 329.10667. Found 329.10649.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961 (w), 2850 (w), 1525 (s), 1486 (w), 1422 (s), 1339 (m), 1234 (s), 1211 (m), 1182 (m), 1111 (s), 1073 (m), 1025 (m), 937 (w), 896 (m), 860 (m), 755 (s), 679 (m), 646 (s), 597 (m).

2-[6-Amino-2-(piperidin-1-yl)thiazolo[4,5-*b*]pyridin-5-yl]phenol (2.5.5g).



Starting from 3-nitrochromone **2.5.3h** (0.150 g, 0.42 mmol). **2.5.5g** was isolated as yellow solid (0.096 g, 70%), mp 126-128 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.63 (s, 6H, piperidine), 3.55 (s, 4H, piperidine), 4.86 (br s, 2H, NH_2), 6.88-6.95 (m, 2H, CH_{Ar}), 7.22 (t, 1H, ^3J = 7.05 Hz, CH_{Ar}), 7.52 (d, 1H, ^3J = 8.05 Hz, CH_{Ar}), 7.59 (s, 1H, Py), 10.3-11.0 (br s, 1H, OH).

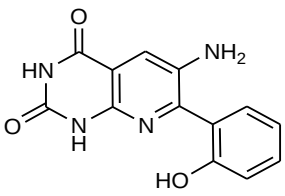
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 23.6, 24.8, 48.8 (CH_2 piperidine), 116.6, 117.4, 119.0 (CH), 124.2, 125.3, 129.1, 130.6 (C), 136.4 (CH), 140.4, 155.0, 156.0, 166.8 (C).

MS (EI, 70 eV): *m/z* (%) = 326 (M^+, 100), 310 (41), 257 (13).

HRMS (ESI): Calcd for $C_{17}H_{19}N_4OS$ (M+H) 327.12013. Found 327.12830.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2935 (w), 2852 (w), 1558 (m), 1531 (s), 1418 (s), 1307 (s), 1246 (s), 1195 (m), 1155 (m), 1120 (m), 1074 (m), 1010 (m), 885 (m), 851 (m), 749 (s), 679 (m), 629 (m), 586 (s).

6-Amino-7-(2-hydroxyphenyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.5.5h).



Starting from 3-nitrochromone **2.5.3i** (0.150 g, 0.50 mmol). **2.5.5h** was isolated as brown solid (0.131 g, 97%), mp 309-311 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.2-5.8 (br s, 2H, NH_2), 6.91 (t, 1H, ^3J = 7.4 Hz, CH_{Ar}), 6.99 (d, 1H, ^3J = 7.8 Hz, CH_{Ar}), 7.25-7.31 (m, 1H, CH_{Ar}), 7.35 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.5 Hz, CH_{Ar}), 7.68 (s, 1H, Py), 10.0-12.0 (br s,

3H, OH, NH).

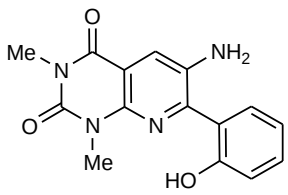
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 109.0 (C), 116.4, 119.0, 120.7 (CH), 124.6 (C), 130.2, 130.9 (CH), 139.0, 143.4, 149.1, 150.2, 154.9, 162.6 (C).

MS (EI, 70 eV): *m/z* (%) = 270 (M^+, 96), 224 (16), 160 (17), 128 (100), 97 (31).

HRMS (ESI): Calcd for $C_{13}H_{11}N_4O_3$ (M+H) 271.08257. Found 271.08298.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3246 (w), 3043 (w), 1682 (m), 1608 (m), 1487 (w), 1416 (m), 1385 (m), 1299 (w), 1275 (w), 1239 (w), 1215 (w), 1101 (w), 1043 (w), 888 (w), 851 (m), 813 (w), 749 (m), 677 (w), 624 (m), 574 (s).

6-Amino-7-(2-hydroxyphenyl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.5.5i).



Starting from 3-nitrochromone **2.5.3j** (0.150 g, 0.46 mmol). **2.5.5i** was isolated as green solid (0.090 g, 66%), mp 299-301 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.30 (s, 3H, Me), 3.50 (s, 3H, Me), 4.5-5.7 (br s, 2H, NH_2), 6.91-7.02 (m, 2H, CH_{Ar}), 7.28-7.41 (m, 2H, CH_{Ar}), 7.80 (s, 1H, Py), 9.4-11.0 (br s, 1H, OH).

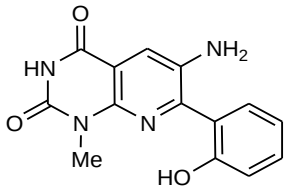
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 28.0, 28.9 (Me), 109.4 (C), 116.3, 119.3, 121.5 (CH), 125.2 (C), 130.2, 131.4 (CH), 139.1, 141.8, 148.3, 150.6, 154.7, 161.0 (C).

MS (EI, 70 eV): *m/z* (%) = 298 (M^+, 100), 281 (18), 207 (19).

HRMS (ESI): Calcd for $C_{15}H_{15}N_4O_3$ (M+H) 299.1139. Found 299.1138.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3427 (w), 3349 (w), 3271 (w), 1694 (m), 1634 (s), 1604 (s), 1470 (m), 1447 (s), 1356 (s), 1300 (s), 1105 (m), 1066 (m), 1018 (m), 981 (m), 911 (m), 834 (w), 804 (w), 781 (m), 738 (s), 692 (m), 675 (m), 638 (m).

6-Amino-7-(2-hydroxyphenyl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.5.5j).



Starting from 3-nitrochromone **2.5.3k** (0.150 g, 0.48 mmol). **2.5.5j** was isolated as brown solid (0.120 g, 88%), mp 290-292 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.44 (s, 3H, Me), 4.5-5.7 (br s, 2H, NH_2), 6.92-7.01 (m, 2H, CH_{Ar}), 7.28-7.38 (m, 1H, CH_{Ar}), 7.40 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.5 Hz, CH_{Ar}), 7.76 (s, 1H, Py), 10.0–12.0 (br s, 2H, OH, NH).

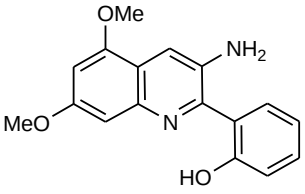
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 28.0 (Me), 110.2 (C), 116.4, 119.3, 121.4 (CH), 125.2 (C), 130.2, 131.2 (CH), 138.9, 143.1, 148.1, 150.4, 154.7, 161.5 (C).

MS (EI, 70 eV): *m/z* (%) = 284 (M^+, 100), 240 (14), 78 (15).

HRMS (ESI): Calcd for $C_{14}H_{13}N_4O_3$ (M+H) 285.09822. Found 285.09838.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3341 (w), 3152 (w), 3041 (w), 2844 (w), 1681 (s), 1610 (m), 1586 (m), 1468 (m), 1451 (m), 1411 (s), 1379 (m), 1286 (m), 1229 (m), 1149 (w), 1103 (w), 1077 (w), 998 (w), 943 (m), 813 (m), 788 (m), 765 (w), 734 (s), 723 (s), 687 (m), 665 (w), 636 (m).

2-(3-Amino-5,7-dimethoxyquinolin-2-yl)phenol (2.5.5k).



Starting from 3-nitrochromone **2.5.3m** (0.150 g, 0.46 mmol). **2.5.5k** was isolated as brown solid (0.109 g, 80%), mp 166-168 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.84 (s, 3H, OMe), 3.94 (s, 3H, OMe), 5.04 (br. s, 2H, NH_2), 6.56 (s, 1H, CH_{Ar}), 6.84 (s, 1H, CH_{Ar}), 6.91-7.02 (m, 2H, CH_{Ar}), 7.27-7.32 (m, 1H, CH_{Ar}), 7.57 (d, 1H, ^3J = 7.5 Hz, CH_{Ar}), 7.70 (s, 1H, Py), 10.5-11.5 (br. s, 1H, OH).

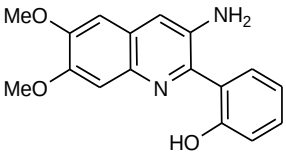
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.2, 55.8 (OMe), 98.0, 98.9, 112.2 (CH), 116.3 (C), 116.4, 119.0 (CH), 124.8 (C), 129.8, 130.5 (CH), 138.5, 142.1, 149.1, 154.0, 155.5, 157.5 (C).

MS (GC, 70 eV): *m/z* (%) = 296 (M^+, 92), 280 (35).

HRMS (ESI): Calcd for $C_{17}H_{17}N_2O_3$ (M+H) 297.12337. Found 297.12324.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1582 (m), 1446 (m), 1422 (w), 1396 (m), 1347 (w), 1331 (w), 1273 (m), 1204 (s), 1156 (s), 1104 (m), 975 (w), 950 (w), 935 (w), 911 (m), 827 (m), 753 (s), 700 (s), 642 (m), 626 (s).

2-(3-Amino-6,7-dimethoxyquinolin-2-yl)phenol (2.5.5l).



Starting from 3-nitrochromone **2.5.3n** (0.150 g, 0.46 mmol). **2.5.5l** was isolated as brown solid (0.127 g, 93%), mp 177-179 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.84 (s, 3H, OMe), 3.94 (s, 3H, OMe), 5.16 (br s, 2H, NH_2), 6.56 (s, 1H, CH_{Ar}), 6.85 (s, 1H, CH_{Ar}), 6.89-7.01 (m, 2H, CH_{Ar}), 7.26-7.28 (m, 1H, CH_{Ar}), 7.56 (d, 1H, ^3J = 7.6 Hz, CH_{Ar}), 7.69 (s, 1H, Py), 10.93 (s, 1H, OH).

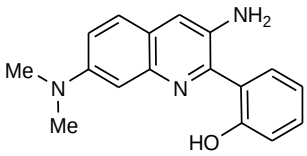
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.2, 55.8 (OMe), 97.9, 98.9, 112.2 (CH), 116.4 (C), 116.5, 118.8 (CH), 125.0 (C), 129.8, 130.6 (CH), 138.6, 142.2, 149.3, 154.0, 155.8, 157.5 (C).

MS (GC, 70 eV): *m/z* (%) = 296 (M^+, 76), 295 (100), 280 (27).

HRMS (ESI): Calcd for $C_{17}H_{16}N_2O_3$ (M^+) 296.11554. Found 296.115439.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1582 (m), 1504 (w), 1445 (m), 1396 (w), 1348 (w), 1330 (w), 1272 (m), 1204 (s), 1155 (m), 1126 (m), 1104 (m), 1046 (m), 935 (w), 911 (m), 826 (m), 751 (s), 700 (m), 642 (m), 626 (m).

2-(3-Amino-7-(dimethylamino)quinolin-2-yl)phenol (2.5.5m).



Starting from 3-nitrochromone **2.5.3o** (0.150 g, 0.49 mmol). **2.5.5m** was isolated as brown solid (0.127 g, 94%), mp 240-242 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.98 (s, 6H, NMe_2), 4.91 (br s, 2H, NH_2), 6.91-6.99 (m, 3H, CH_{Ar}), 7.18-7.31 (m, 2H, CH_{Ar}), 7.41 (s, 1H, CH_{Ar}), 7.55 (d, 1H, ^3J = 8.5 Hz, CH_{Ar}), 7.68 (dd, 1H, ^3J = 7.5 Hz, ^4J = 1.4 Hz, CH_{Ar}), 11.0-11.8 (br s, 1H, OH).

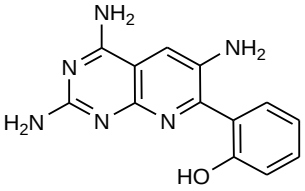
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 40.4 (NMe_2), 106.3, 116.6, 117.3, 117.8, 118.9 (CH), 121.2, 124.6 (C), 125.8, 130.0, 130.2 (CH), 137.5, 142.3, 148.7, 148.8, 155.9 (C).

MS (GC, 70 eV): *m/z* (%) = 279 (M^+, 94), 278 (100), 262 (37).

HRMS (ESI): Calcd for $C_{17}H_{18}N_3O$ (M+H) 280.14444. Found 280.14436.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3392 (w), 3324 (w), 2919 (w), 1623 (m), 1602 (w), 1573 (w), 1553 (w), 1505 (m), 1428 (m), 1280 (m), 1244 (m), 1223 (m), 1184 (m), 1148 (m), 1008 (m), 971 (w), 936 (w), 918 (w), 884 (w), 823 (m), 793 (m), 757 (s), 725 (m), 693 (s).

2-(2,4,7-Triaminopyrido[3,2-*d*]pyrimidin-6-yl)phenol (2.5.5n).



Starting from 3-nitrochromone **2.5.3p** (0.150 g, 0.5 mmol). **2.5.5n** was isolated as green solid (0.133 g, 93%), mp 169-171 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.04 (br s, 2H, NH_2), 6.91-6.96 (m, 1H, CH_{Ar}), 7.07 (d, 1H, ^3J = 8.0 Hz, CH_{Ar}), 7.21-7.34 (m, 2H, CH_{Ar}), 7.94 (s, 1H, Py), 8.84 (s, 1H, NH_2), 9.10 (s, 1H, NH_2), 10.33 (br. s, 1H, OH), 12.50 (br. s, 2H, NH_2).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 104.5 (C), 116.3, 119.3 (CH), 124.2 (C), 130.5, 130.9 (CH), 140.5, 141.2, 151.4, 154.7, 155.1, 162.3, 162.9 (C).

MS (GC, 70 eV): *m/z* (%) = 268 (M^+, 100), 252 (22), 207 (15), 84 (17).

HRMS (ESI): Calcd for $C_{13}H_{13}N_6O$ (M+H) 269.11454. Found 269.11528.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3306 (w), 1514 (w), 1434 (m), 1409 (m), 1384 (m), 1352 (m), 1293 (m), 1241 (m), 1154 (w), 1100 (w), 1007 (w), 831 (w), 753 (m), 701 (m).

*A.2.13. General procedure for the synthesis of compounds **2.6.2a-h**.*

In a pressure tube under the flow of argon to the DMF (10 mL/2 mmol of **2.6.1**) solution of corresponding **2.6.1** (1 equiv.) was added TMSCl (1 mL/2 mmol of **2.6.1**). The reaction

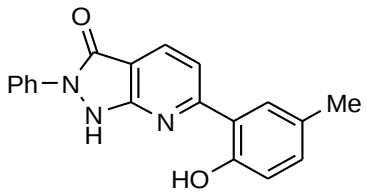
mixture was heated at 100 °C for 3h (TLC control). After the formation of chromone was completed the solution was evaporated under reduced pressure, the residue was treated with water, filtered and dried on the air and recrystallized from appropriate solvent.

All prepared chromones were previously synthesised and could be find in the literature.[192]

*A.2.14. General procedure for the synthesis of compounds **2.6.3-2.6.12**.*

Corresponding chromone **2.6.2a-e** or enaminone **2.6.1a-e** (1 equiv.) and appropriate amine **E** (1.1 equiv.) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMF (5 mL/1 mmol of chromone **2.6.2**) containing 1 mL of TMSCl. The mixture was heated at 100-120 °C for 1-5 h (controlled by TLC). After the reaction was completed volatiles were evaporated under reduced pressure. The residue was treated with water, filtered, dried in air, and recrystallized from appropriate solvent or subjected to column chromatography (silica gel). (**Notice:** Calculations for each compound are presented starting from chromone **2.6.2**)

1,2-dihydro-6-(2-hydroxy-5-methylphenyl)-2-phenylpyrazolo[3,4-*b*]pyridin-3-one (2.6.3a).



Starting from chromone **2.6.2b** (0.160 g, 1 mmol) and 5-amino-1,2-dihydro-2-phenylpyrazol-3-one **E1a** (0.193 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.3a** was isolated as brown solid (0.190 g, 60%), mp 238-240 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.30 (s, 3H, Me), 6.94 (d, 1H, ^3J = 8.3 Hz, CH_{Ar}), 7.18 (dd, 1H, ^3J = 8.3 Hz, ^4J = 1.7 Hz, CH_{Ar}), 7.25-7.30 (m, 1H, CH_{Ar}), 7.49-7.55 (m, 2H, CH_{Ar}), 7.85-7.97 (m, 4H, CH_{Ar}), 8.32 (d, 1H, ^3J = 8.3 Hz, CH_{Ar}), 9.02 (br. s, 1H, OH), 11.04 (br. s, 1H, NH).

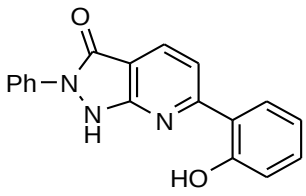
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 34.0 (Me), 108.5 (C), 114.7, 117.7, 119.3 (CH), 119.7 (C), 125.2 (CH), 127.9 (C), 128.7, 129.1, 132.9, 134.4 (CH), 137.2, 154.9, 156.2, 158.1, 160.0 (C).

MS (EI, 70 eV): *m/z* (%) = 317 (M^+, 100), 288 (19), 77 (14).

HRMS (EI): Calcd for $C_{19}H_{15}N_3O_2$ (M^+) 317.11588. Found 317.115490.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2967 (w), 2766 (w), 2456 (w), 1665 (w), 1593 (m), 1486 (m), 1447 (m), 1392 (w), 1295 (m), 1231 (m), 1124 (m), 1076 (w), 1026 (w), 884 (w), 809 (m), 746 (s), 684 (s), 603 (m).

1,2-dihydro-6-(2-hydroxyphenyl)-2-phenylpyrazolo[3,4-*b*]pyridin-3-one (2.6.3b)



Starting from chromone **2.6.2a** (0.146 g, 1 mmol) and 5-amino-1,2-dihydro-2-phenylpyrazol-3-one **E1a** (0.193 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.3b** was isolated as orange solid (0.233 g, 77%), mp 180-182 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.95-7.02 (m, 2H, CH_{Ar}), 7.25-7.30 (m, 1H, CH_{Ar}), 7.35-7.41 (m, 1H, CH_{Ar}), 7.50-7.55 (m, 2H, CH_{Ar}), 7.93 (d, 3H, ^{3}J = 7.6 Hz, CH_{Ar}), 8.05 (d, 1H, ^{3}J = 7.7 Hz, CH_{Ar}), 8.33 (d, 1H, ^{3}J = 8.3 Hz, CH_{Ar}), 11.80 (br. s, 1H, OH), 12.67 (br. s, 1H, NH).

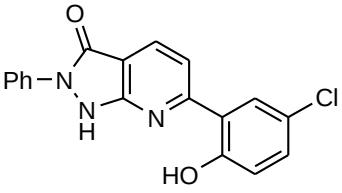
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 108.6, 114.8 (C), 117.8, 119.3, 119.4 (CH), 120.0 (C), 125.2, 128.7, 129.1, 132.3, 134.8 (CH), 137.1, 155.0, 158.0, 158.4, 160.0 (C).

MS (EI, 70eV): *m/z* (%) = 302 (M^+, 100), 274 (22), 77 (43).

HRMS (EI): Calcd for $C_{18}H_{13}N_3O_2$ (M^+) 303.10023. Found 303.100464.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3024 (w), 1661 (m), 1600 (m), 1484 (m), 1445 (m), 1414 (m), 1295 (w), 1273 (m), 1239 (m), 1187 (w), 1154 (w), 1033 (w), 935 (w), 903 (w), 815 (m), 752 (s), 689 (m), 603 (m).

6-(5-chloro-2-hydroxyphenyl)-1,2-dihydro-2-phenylpyrazolo[3,4-*b*]pyridin-3-one (2.6.3c).



Starting from chromone **2.6.2d** (0.181 g, 1 mmol) and 5-amino-1,2-dihydro-2-phenylpyrazol-3-one **E1a** (0.193 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.3c** was isolated as brown solid (0.310 g, 92%), mp 301-303 ^{o}C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.07 (d, 1H, ^{3}J = 8.7 Hz, CH_{Ar}), 7.27 (t, 1H, ^{3}J = 7.5 Hz, CH_{Ar}), 7.39 (dd, 1H, ^{3}J = 8.7 Hz, ^{3}J = 2.7 Hz, CH_{Ar}), 7.49-7.55 (m, 2H, CH_{Ar}), 7.92-8.06 (m, 4H, CH_{Ar}), 8.31 (d, 1H, ^{3}J = 8.3 Hz, CH_{Ar}), 11.92 (br. s, 1H, OH), 12.39 (br. s, 1H, NH).

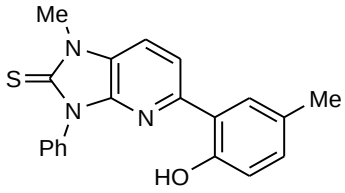
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 109.0, 115.9 (C), 119.4, 119.5 (CH), 122.5, 123.0 (C), 125.3, 128.3, 129.1, 131.4, 134.7 (CH), 155.3, 155.4, 156.8, 158.0, 178.9 (C).

MS (EI, 70eV): *m/z* (%) = 337 (M^+, 100), 308 (13).

HRMS (ESI): Calcd for $C_{18}H_{13}N_3O_2Cl$ (M+H) 338.79255. Found 338.79257.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3391 (w), 2991 (w), 2771 (w), 2450 (w), 1661 (m), 1591 (m), 1486 (m), 1447 (m), 1389 (m), 1336 (w), 1292 (m), 1245 (m), 1207 (w), 1175 (m), 1126 (w), 1099 (w), 1075 (w), 1023 (w), 944 (w), 868 (w), 828 (m), 810 (m), 757 (s), 719 (s), 686 (m).

5-(2-hydroxy-5-methylphenyl)-1-methyl-3-phenyl-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (2.6.4a).



Starting from chromone **2.6.2b** (0.160 g, 1 mmol) and 4-amino-1-methyl-3-phenyl-1*H*-imidazole-2(3*H*)-thione **E2b** (0.225 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.4a** was isolated as brown solid (0.312 g, 90%), mp 224-225 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.25 (s, 3H, Me), 3.80 (s, 3H, NMe), 6.70 (d, 1H, , ^{3}J = 8.2 Hz, CH_{Ar}), 7.01 (dd, 1H, ^{3}J = 8.2 Hz, ^{4}J = 1.5 Hz, CH_{Ar}), 7.48-7.66 (m, 5H, CH_{Ar}), 7.70 (s, 1H, CH_{Ar}), 7.99-8.05 (m, 2H, CH_{Ar}), 11.76 (s, 1H, OH).

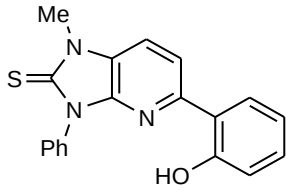
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.2, 31.2 (Me), 115.6, 117.4, 118.7 (CH), 119.4, 124.8 (C), 127.3 (CH), 127.6 (C), 128.1, 129.0, 129.2, 131.2 (CH), 134.2, 142.7, 150.0, 154.9, 170.6 (C).

MS (GC, 70eV): *m/z* (%) = 347 (M^{+}, 100), 332 (15).

HRMS (ESI): Calcd for $C_{20}H_{18}N_3OS$ (M+H) 348.2558. Found 348.2559.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2912 (w), 1496 (w), 1464 (m), 1434 (m), 1381 (m), 1329 (m), 1282 (s), 1249 (s), 1215 (m), 1183 (m), 1135 (m), 1189 (m), 1024 (w), 911 (w), 815 (s), 793 (s), 773 (m), 758 (s), 733 (m), 686 (s), 648 (m).

5-(2-hydroxyphenyl)-1-methyl-3-phenyl-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (2.6.4b).



Starting from chromone **2.6.2a** (0.146 g, 1 mmol) and 4-amino-1-methyl-3-phenyl-1*H*-imidazole-2(3*H*)-thione **E2b** (0.225 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.4b** was isolated as white solid (0.300 g, 90%), mp 220-222 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.82 (s, 3H, Me), 6.81-6.91 (m, 2H, CH_{Ar}), 7.19-7.25 (m, 1H, CH_{Ar}), 7.54-7.67 (m, 5H, CH_{Ar}), 7.91 (dd, 1H, ^{3}J = 8.1 Hz, ^{4}J = 1.4 Hz, CH_{Ar}), 8.03-8.10 (m, 2H, CH_{Ar}), 11.90 (s, 1H, OH).

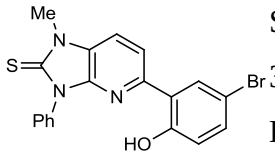
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 31.2 (Me), 116.0, 117.5, 118.7, 119.2 (CH), 120.2, 125.0 (C), 127.5, 128.2, 129.0, 129.3, 130.5 (CH), 134.2, 142.9, 149.9, 157.0, 170.7 (C).

MS (GC, 70eV): *m/z* (%) = 333 (M^{+}, 100), 318 (19).

HRMS (EI): Calcd for $C_{19}H_{15}N_3OS$ (M^{+}) 333.08521. Found 333.092105.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3051 (w), 1615 (w), 1593 (w), 1499 (w), 1466 (m), 1427 (m), 1332 (s), 1296 (m), 1281 (m), 1248 (m), 1227 (m), 1203 (m), 1164 (m), 1041 (m), 1090 (m), 1022 (w), 963 (w), 932 (w), 812 (s), 753 (s), 734 (m), 706 (s), 689 (s), 636 (s).

5-(5-bromo-2-hydroxyphenyl)-1-methyl-3-phenyl-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (2.6.4c).



Starting from chromone **2.6.2c** (0.225 g, 1 mmol) and 4-amino-1-methyl-3-phenyl-1*H*-imidazole-2(3*H*)-thione **E2b** (0.225 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.4c** was isolated as brown solid (0.313 g, 76%), mp 248-250 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.58 (s, 3H, Me), 6.57 (d, 1H, ^{3}J = 8.9 Hz, CH_{Ar}), 7.11 (dd, 1H, ^{3}J = 8.7 Hz, ^{4}J = 2.2 Hz, CH_{Ar}), 7.29-7.42 (m, 5H, CH_{Ar}), 7.79-7.80 (m, 2H, CH_{Ar}), 7.83 (s, 1H, CH_{Ar}), 11.64 (s, 1H, OH).

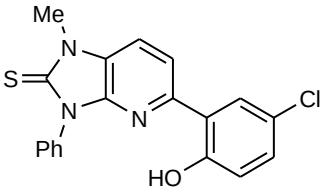
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 31.2 (Me), 110.5 (C), 116.9, 118.5, 119.7 (CH), 123.0, 125.5 (C), 128.2, 129.0, 129.2, 129.9, 132.8 (CH), 134.2, 141.2, 143.2, 148.1, 156.0, 171.0 (C).

MS (GC, 70eV): *m/z* (%) = 412 (M^{+}, 100), 166 (12).

HRMS (ESI): Calcd for $C_{19}H_{15}N_3OSBr$ (M+H) 413.11258. Found 413.11261.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2913 (w), 1499 (w), 1463 (m), 1431 (w), 1384 (m), 1329 (m), 1280 (s), 1247 (m), 1200 (m), 1148 (m), 1090 (w), 969 (w), 934 (w), 864 (w), 819 (s), 714 (w), 687 (s), 640 (m), 582 (w).

5-(5-chloro-2-hydroxyphenyl)-1-methyl-3-phenyl-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (2.6.4d).



Starting from chromone **2.6.2d** (0.181 g, 1 mmol) and 4-amino-1-methyl-3-phenyl-1*H*-imidazole-2(3*H*)-thione **E2b** (0.225 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.4d** was isolated as yellow solid (0.224 g, 61%), mp 252-254 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.83 (s, 3H, Me), 6.87 (d, 1H, ^{3}J = 8.7 Hz, CH_{Ar}), 7.23 (s, 1H, CH_{Ar}), 7.62 (s, 5H, CH_{Ar}), 7.92 (s, 1H, CH_{Ar}), 8.05-8.18 (m, 2H, CH_{Ar}), 11.90 (br. s, 1H, OH).

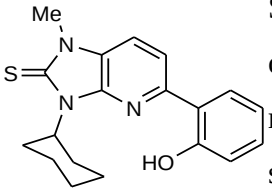
^{13}C NMR Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 367 (M^{+}, 100), 352 (11).

HRMS (ESI): Calcd for $C_{19}H_{15}N_3OSCl$ (M+H) 368.06189. Found 368.06207.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2915 (w), 1618 (w), 1498 (m), 1462 (s), 1434 (m), 1383 (m), 1330 (s), 1297 (s), 1279 (s), 1247 (m), 1189 (m), 1150 (m), 1086 (m), 1026 (w), 971 (w), 935 (w), 904 (w), 865 (w), 819 (s), 754 (m), 722 (m), 687 (s), 658 (m), 584 (m).

3-cyclohexyl-5-(2-hydroxyphenyl)-1-methyl-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (2.6.4e).



Starting from chromone **2.6.2a** (0.146 g, 1 mmol) and 4-amino-3-cyclohexyl-1-methyl-1*H*-imidazole-2(3*H*)-thione **E2c** (0.232 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.4e** was isolated as yellow solid (0.231 g, 68%), mp 250-251 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.16-1.49 (m, 3H, cyclohexyl), 1.75-1.93 (m, 5H, cyclohexyl), 2.35-2.43 (m, 2H, cyclohexyl), 3.75 (s, 3H, Me), 5.07-5.15 (m, 1H, NCH), 6.93-7.00 (m, 2H, CH_{Ar}), 7.26-7.33 (m, 1H, CH_{Ar}), 7.96-8.08 (m, 3H, CH_{Ar}), 12.02 (s, 1H, OH).

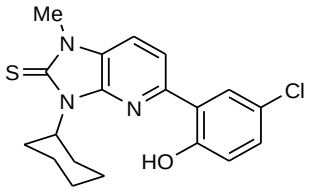
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 25.0, 25.5, 29.0, 31.4 (CH_2 cyclohexyl), 56.1 (NCH), 115.9, 117.4, 118.3, 119.5 (CH), 121.3, 124.8 (C), 128.1, 130.4 (CH), 142.2, 149.0, 156.8, 169.8 (C).

MS (GC, 70eV): *m/z* (%) = 339 (M^+, 48), 257 (100).

HRMS (EI): Calcd for $C_{19}H_{21}ON_3S$ (M^+) 339.13998. Found 339.139863.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2918 (w), 2858 (w), 1614 (w), 1504 (w), 1465 (m), 1428 (m), 1382 (m), 1325 (m), 1282 (m), 1238 (m), 1167 (m), 1139 (m), 1044 (m), 894 (w), 808 (s), 738 (s), 685 (m), 657 (m), 620 (m).

5-(5-chloro-2-hydroxyphenyl)-3-cyclohexyl-1-methyl-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (2.6.4f).



Starting from chromone **2.6.2d** (0.181 g, 1 mmol) and 4-amino-3-cyclohexyl-1-methyl-1*H*-imidazole-2(3*H*)-thione **E2c** (0.232 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.4f** was isolated as yellow solid (0.220 g, 59%), mp 185-187 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.16-1.48 (m, 3H, cyclohexyl), 1.61-1.99 (m, 5H, cyclohexyl), 2.36-2.44 (m, 2H, cyclohexyl), 3.75 (s, 3H, Me), 5.05-5.13 (m, 1H, NCH), 7.02 (d, 1H, ^{3}J = 8.5 Hz, CH_{Ar}), 7.30 (dd, 1H, ^{3}J = 8.8 Hz, ^{4}J = 2.5 Hz, CH_{Ar}), 7.95-8.02 (m, 2H, CH_{Ar}), 8.14 (d, 1H, ^{3}J = 8.8 Hz, CH_{Ar}), 11.91 (s, 1H, OH).

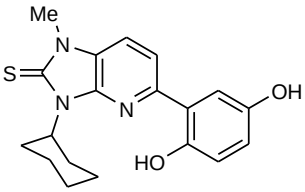
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 25.0, 25.5, 29.0 (CH_2 cyclohexyl), 31.4 (Me), 56.2 (NCH), 116.7, 118.0, 119.1 (CH), 123.1, 123.4, 125.2 (C), 127.6, 129.7 (CH), 142.5, 147.2, 155.4, 170.0 (C).

MS (GC, 70eV): *m/z* (%) = 373 (M^+, 42), 291 (100).

HRMS (ESI): Calcd for $C_{19}H_{21}ON_3SCl$ (M+H) 374.10884. Found 374.10876.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2934 (w), 2854 (w), 1615 (w), 1468 (m), 1434 (m), 1383 (m), 1338 (m), 1323 (m), 1295 (m), 1279 (s), 1244 (m), 1213 (w), 1170 (m), 1141 (m), 1092 (w), 933 (w), 864 (w), 825 (m), 806 (s), 718 (m), 655 (m), 625 (w), 582 (m).

3-cyclohexyl-5-(2,5-dihydroxyphenyl)-1-methyl-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (2.6.4g).



Starting from chromone **2.6.2f** (0.176 g, 1 mmol) and 4-amino-3-cyclohexyl-1-methyl-1*H*-imidazole-2(3*H*)-thione **E2c** (0.232 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.4g** was isolated as yellow solid (0.228 g, 68%), mp 307-309 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.21-1.53 (m, 3H, cyclohexyl), 1.62-2.11 (m, 5H, cyclohexyl), 2.29-2.40 (m, 2H, cyclohexyl), 3.73 (s, 3H, Me), 5.06-5.14 (m, 1H, NCH), 6.36-6.41 (m, 2H, CH_{Ar}), 7.82 (d, 1H, ^{3}J = 8.7 Hz, CH_{Ar}), 7.88-7.95 (m, 2H, CH_{Ar}), 9.77 (s, 1H, OH), 12.44 (s, 1H, OH).

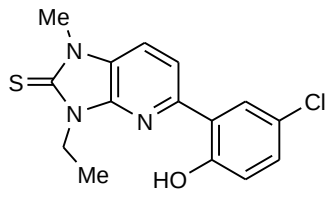
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 25.0, 25.6, 29.0 (CH_2 cyclohexyl), 31.4 (Me), 56.0 (NCH), 103.4, 107.8 (CH), 112.2 (C), 114.2, 118.7 (CH), 123.9 (C), 128.8 (CH), 141.6, 150.0, 158.7, 160.0, 169.2 (C).

MS (EI, 70eV): *m/z* (%) = 355 (M^+, 74), 273 (100), 168 (10).

HRMS (EI): Calcd for $C_{19}H_{21}O_2N_3S$ (M^+) 355.13490. Found 355.134366.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3305 (w), 3139 (w), 2929 (m), 2862 (w), 1610 (m), 1465 (s), 1437 (s), 1385 (m), 1323 (s), 1298 (s), 1250 (s), 1221 (m), 1169 (s), 1140 (s), 1122 (m), 1046 (m), 976 (m), 946 (m), 840 (w), 791 (s), 721 (m), 652 (m), 611 (m).

5-(5-chloro-2-hydroxyphenyl)-3-ethyl-1-methyl-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (2.6.4h).



Starting from chromone **2.6.2d** (0.181 g, 1 mmol) and 4-amino-3-ethyl-1-methyl-1*H*-imidazole-2(3*H*)-thione **E2d** (0.173 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.4h** was isolated as green solid (0.185 g, 58%), mp 204-206 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.33 (t, 3H, ^{3}J = 7.1 Hz, Me), 3.73 (s, 3H, NMe), 4.34 (q, 2H, ^{3}J = 7.1 Hz, CH_2), 6.96 (d, 1H, ^{3}J = 8.5 Hz, CH_{Ar}), 7.26 (dd, 1H, ^{3}J = 8.7 Hz, ^{4}J = 2.7 Hz, CH_{Ar}), 7.89-7.93 (m, 2H, CH_{Ar}), 8.05 (d, 1H, ^{3}J = 8.5 Hz, CH_{Ar}), 11.64 (br. s, 1H, OH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.7 (Me), 30.9 (NMe), 38.1 (CH_2), 117.2, 117.7,

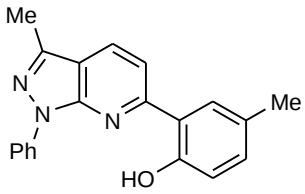
118.9 (CH), 123.0, 123.7, 125.0 (C), 127.7, 129.8 (CH), 142.5, 147.8, 155.2, 169.9 (C).

MS (GC, 70eV): *m/z* (%) = 319 (M^+, 100), 291 (50).

HRMS (ESI): Calcd for $C_{15}H_{15}N_3OSCl$ (M+H) 320.06189, Found 320.06194.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2938 (w), 1469 (m), 1436, 1383 (s), 1341 (m), 1316 (m), 1278 (s), 1244 (m), 1187 (m), 1148 (w), 1122 (s), 1089 (m), 1028 (w), 957 (w), 867 (w), 858 (w), 846 (w), 829 (m), 802 (s), 774 (w), 753 (w), 718 (m), 673 (w), 652 (m).

4-methyl-2-(3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)phenol (2.6.5a).



Starting from chromone **2.6.2b** (0.160 g, 1 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **E3** (0.190 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.5a** was isolated as yellow solid (0.306 g, 97%), mp 139-140 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.30 (s, 3H, Me), 2.60 (s, 3H, Me), 6.88 (d, 1H, ^3J = 8.8 Hz, CH_{Ar}), 7.14 (dd, 1H, ^3J = 8.3 Hz, ^3J = 1.9 Hz, CH_{Ar}), 7.38 (t, 1H, ^3J = 7.8 Hz, CH_{Ar}), 7.59 (t, 2H, ^3J = 7.8 Hz, CH_{Ar}), 7.86 (s, 1H, CH_{Ar}), 7.97-8.04 (m, 3H, CH_{Ar}), 8.42 (d, 1H, ^3J = 8.8 Hz, CH_{Ar}), 12.43 (s, 1H, OH).

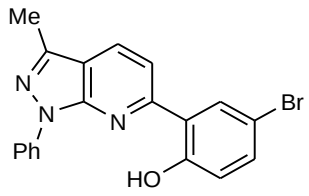
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.1, 20.2 (Me), 114.8 (CH), 115.1 (C), 117.5 (CH), 120.2 (C), 121.2, 126.2 (CH), 127.8 (C), 128.7, 129.4, 131.8, 132.3 (CH), 138.5, 143.2, 147.7, 155.9, 156.3 (C).

MS (GC, 70eV): *m/z* (%) = 315 (M^+, 100), 286 (20).

HRMS (EI): Calcd for $C_{20}H_{17}N_3O$ (M^+) 315.13661. Found 315.136368.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3380 (m), 2984 (m), 2770 (m), 2447 (w), 1580 (m), 1468 (s), 1439 (m), 1403 (m), 1307 (w), 1284 (m), 1245 (m), 1193 (m), 1163 (m), 1130 (m), 1081 (m), 1022 (m), 961 (w), 888 (w), 813 (s), 765 (m), 748 (s), 729 (s), 686 (s), 666 (s), 636 (s).

4-bromo-2-(3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)phenol (2.6.5b)



Starting from chromone **2.6.2c** (0.225 g, 1 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **E3** (0.190 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.5b** was isolated as yellow solid (0.349 g, 92%), mp 180-181 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.62 (s, 3H, Me), 6.94 (d, 1H, ^3J = 8.8 Hz, CH_{Ar}), 7.38 (t, 1H, ^3J = 7.7 Hz, CH_{Ar}), 7.47 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.2 Hz, CH_{Ar}), 7.86 (t, 2H, ^3J = 7.7 Hz, CH_{Ar}), 8.00-8.09 (m, 3H, CH_{Ar}), 8.18 (s, 1H, CH_{Ar}), 8.44 (d, 1H, ^3J = 8.8 Hz, CH_{Ar}), 12.44 (s, 1H, OH).

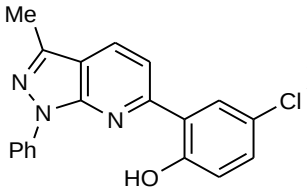
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.1 (Me), 110.5 (C), 115.5, 115.6, 119.7, 121.1 (CH), 123.4 (C), 126.2, 129.3, 131.1, 131.9, 133.8 (CH), 138.5, 143.2, 147.9, 154.5, 156.9 (C).

MS (GC, 70eV): *m/z* (%) = 381 (99), 379 (M^+, 100).

HRMS (ESI): Calcd for $C_{19}H_{15}N_3OBr$ (M+H) 380.0393. Found 380.03927.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3061 (m), 1593 (s), 1578 (m), 1510 (m), 1474 (m), 1430 (m), 1398 (m), 1362 (m), 1286 (s), 1240 (m), 1206 (s), 1192 (m), 1171 (m), 1092 (m), 1013 (w), 954 (w), 852 (w), 814 (s), 779 (m), 747 (s), 701 (m), 687 (s), 665 (s), 633 (s), 596 (m).

4-chloro-2-(3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)phenol (2.6.5c).



Starting from chromone **2.6.2d** (0.181 g, 1 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **E3** (0.190 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.5c** was isolated as yellow solid (0.252 g, 75%), mp 186-188 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.31 (s, 3H, Me), 6.93-7.60 (m, 5H, CH_{Ar}), 8.08 (s, 4H, CH_{Ar}), 8.33-8.64 (m, 1H, CH_{Ar}), 12.42 (s, 1H, OH).

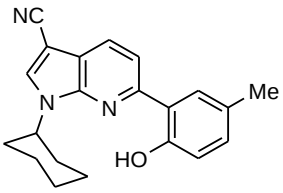
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.1 (Me), 112.2, 115.6, 119.3, 121.1 (CH), 123.0 (C), 123.9 (CH), 125.3 (C), 126.2, 128.3 (CH), 129.4 (C), 131.0, 132.0, 134.1 (CH), 138.5, 143.2, 156.5, 157.3 (C).

MS (GC, 70eV): *m/z* (%) = 335 (M^+, 100).

HRMS (EI): Calcd for $C_{19}H_{14}N_3OCl$ (M^+) 335.08199. Found 335.081761.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3063 (m), 1641 (w), 1596 (m), 1579 (m), 1513 (m), 1480 (m), 1466 (m), 1434 (m), 1398 (m), 1364 (m), 1331 (w), 1286 (s), 1241 (m), 1207 (m), 1194 (m), 1133 (w), 1104 (m), 1081 (m), 1024 (w), 901 (w), 834 (w), 812 (s), 779 (m), 746 (s), 713 (m), 687 (s), 653 (m), 633 (m).

1-cyclohexyl-6-(2-hydroxy-5-methylphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (2.6.6a).



Starting from chromone **2.6.2b** (0.160 g, 1 mmol) and 5-amino-1-cyclohexyl-1*H*-pyrrole-3-carbonitrile **E4b** (0.208 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.6a** was isolated as yellow solid (0.258 g, 78%), mp 168-170 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.24-1.54 (m, 4H, cyclhexyl), 1.72-2.08 (m, 6H, cyclhexyl), 2.30 (s, 3H, Me), 4.53-4.61 (m, 1H, NCH), 6.86 (d, 1H, ^3J = 8.4 Hz, CH_{Ar}), 7.11 (d, 1H, ^3J = 7.9 Hz, CH_{Ar}), 7.81 (s, 1H, CH_{Ar}), 8.05 (d, 1H, ^3J = 8.4 Hz, CH_{Ar}), 8.25 (d, 1H, ^3J

= 8.7 Hz, CH_{Ar}), 8.61 (s, 1H, CH_{Ar}), 12.37 (s, 1H, OH).

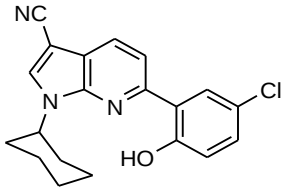
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.2, 24.8, 25.2 (CH_2 cyclohexyl), 32.1 (Me), 55.0 (NCH), 83.1 (CN), 115.2 (C), 115.6, 117.4 (CH), 118.2, 120.3, 127.8 (C), 128.2, 129.5 (CH), 131.6, 135.6, 143.2, 152.1, 155.4 (C).

MS (GC, 70eV): *m/z* (%) = 331 (M^+, 77), 246 (100), 220 (13).

HRMS (EI): Calcd for $C_{21}H_{21}ON_3$ (M^+) 331.16791. Found 331.167627.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3114 (w), 2922 (m), 2857 (m), 2219 (s), 1604 (w), 1579 (m), 1521 (m), 1490 (m), 1443 (s), 1403 (m), 1361 (m), 1282 (s), 1245 (m), 1222 (s), 1209 (s), 1184 (s), 1152 (m), 1028 (m), 862 (w), 819 (s), 791 (s), 764 (m), 732 (m), 673 (m), 648 (s), 615 (m).

6-(5-chloro-2-hydroxyphenyl)-1-cyclohexyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (2.6.6b).



Starting from chromone **2.6.2d** (0.181 g, 1 mmol) and 5-amino-1-cyclohexyl-1*H*-pyrrole-3-carbonitrile **E4b** (0.208 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.6b** was isolated as yellow solid (0.218 g, 62%), mp 208-210 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23-1.86 (m, 6H, cyclohexyl), 1.97-2.02 (m, 2H, cyclohexyl), 2.16-2.23 (m, 2H, cyclohexyl), 4.52-4.63 (m, 1H, NCH), 6.98 (d, 1H, ^3J = 8.9 Hz, CH_{Ar}), 7.25 (dd, 1H, ^3J = 8.5 Hz, ^3J = 2.5 Hz, CH_{Ar}), 7.79-7.83 (m, 3H, CH_{Ar}), 8.19 (d, 1H, ^3J = 8.5 Hz, CH_{Ar}), 13.34 (s, 1H, OH).

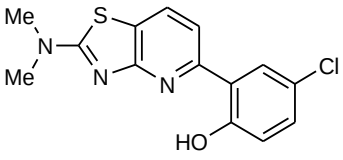
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 25.2, 25.5, 29.7 (CH_2 cyclohexyl), 33.1 (Me), 55.6 (NCH), 85.3 (CN), 114.3 (CH), 114.6, 119.3, 120.6, 124.2 (C), 126.5, 130.3, 131.1, 132.8 (CH), 143.8, 143.0, 152.0, 157.4 (C).

MS (GC, 70eV): *m/z* (%) = 351 (M^+, 100).

HRMS (EI): Calcd for $C_{20}H_{18}ON_3Cl$ (M^+) 351.11329. Found 351.113058.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3113 (w), 922 (w), 2219 (w), 1639 (w), 1580 (w), 1539 (w), 1474 (m), 1446 (m), 1399 (m), 1357 (w), 1278 (m), 1215 (m), 1185 (m), 1027 (w), 891 (w), 817 (s), 795 (m), 727 (m), 680 (m), 648 (s), 615 (m).

4-chloro-2-(2-(dimethylamino)thiazolo[4,5-*b*]pyridin-5-yl)phenol (2.6.7a).



Starting from chromone **2.6.2d** (0.181 g, 1 mmol) and N^2,N^2-dimethylthiazole-2,4-diamine **E5a** (0.157 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.7a** was isolated as brown solid (0.186 g, 61%), mp 255-256 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.23 (s, 6H, NMe_2), 6.94 (d, 1H, ^3J = 8.1 Hz, CH_{Ar}), 7.30 (d, 1H, ^3J = 7.0 Hz, CH_{Ar}), 7.89 (d, 1H, ^3J = 7.6 Hz, CH_{Ar}), 8.06 (s, 1H, CH_{Ar}), 8.36 (d, 1H, ^3J = 7.6 Hz, CH_{Ar}), 14.21 (s, 1H, OH).

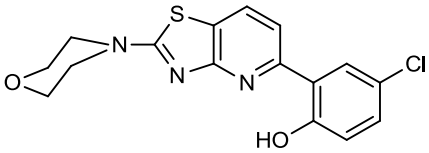
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 26.1 (NMe_2), 112.1, 119.6 (CH), 120.9, 122.5, 124.0 (C), 126.4, 130.3, 131.6 (CH), 134.0, 152.1, 157.6, 161.2 (C).

MS (GC, 70eV): *m/z* (%) = 305 (M^+, 100), 290 (12), 276 (12).

HRMS (ESI): Calcd for $C_{14}H_{13}ON_3SCl$ (M+H) 306.04624. Found 306.04684.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1598 (w), 1579 (w), 1538 (m), 1488 (w), 1404 (w), 1348 (m), 1278 (m), 1218 (m), 1173 (m), 1140 (m), 1100 (w), 1083 (m), 961 (w), 914 (m), 877 (m), 817 (s), 747 (m), 731 (m), 709 (m), 660 (s).

4-chloro-2-(2-morpholinothiazolo[4,5-*b*]pyridin-5-yl)phenol (2.6.7b).



Starting from chromone **2.6.2d** (0.181 g, 1 mmol) and 2-morpholinothiazol-4-amine **E5b** (0.204 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.7b** was isolated as red-brown solid (0.209 g, 60%), mp 257-259 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (s, 8H, morpholine), 6.96 (s, 1H, CH_{Ar}), 7.30 (s, 1H, CH_{Ar}), 7.95-8.07 (m, 2H, CH_{Ar}), 8.40 (s, 1H, CH_{Ar}), 14.05 (s, 1H, O*H*).

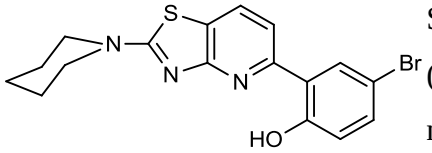
^{13}C NMR (62.9 MHz, DMSO-d_6): δ =47.9, 65.4 (CH_2 morpholine), 112.8, 119.6 (CH), 120.9, 122.6, 123.4 (C), 126.5, 130.3, 131.9 (CH), 152.3, 157.5, 160.8, 171.2 (C).

MS (EI, 70eV): *m/z* (%) = 347 (M^+, 62), 269 (100), 206 (12).

HRMS (EI): Calcd for $C_{16}H_{14}O_2N_3SCl$ (M^+) 347.04898. Found 347.048741.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1575 (w), 1529 (s), 1478 (m), 1426 (m), 1371 (m), 1330 (m), 1280 (s), 1230 (s), 1217 (m), 1189 (m), 1115 (s), 1030 (m), 965 (w), 896 (m), 872 (m), 825 (s), 730 (m), 621 (m).

4-bromo-2-(2-(piperidin-1-yl)thiazolo[4,5-*b*]pyridin-5-yl)phenol (2.6.7c).



Starting from chromone **2.6.2c** (0.225 g, 1 mmol) and 2-(piperidin-1-yl)thiazol-4-amine **E5c** (0.201 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.7c** was isolated as red-brown solid (0.242 g, 62%), mp 194-196 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.66 (s, 6H, piperidine), 3.67 (s, 4H, piperidine), 6.87-6.90 (m, 1H, C*H*$_{Ar}$), 7.42 (s, 1H, C*H*$_{Ar}$), 7.89 (s, 1H, C*H*$_{Ar}$), 8.16 (s, 1H, C*H*$_{Ar}$), 8.33-8.35 (s, 1H, C*H*$_{Ar}$), 14.15 (s, 1H, OH).

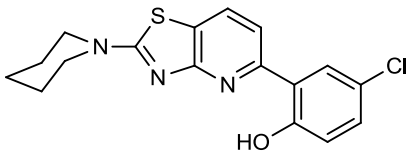
^{13}C NMR due to bed solubility was not possible to measure

MS (EI, 70eV): *m/z* (%) = 389 (M^+, 100).

HRMS (ESI): Calcd for $C_{17}H_{17}N_3OSBr$ (M+H) 390.02702. Found 390.02783.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925 (w), 1573 (m), 1523 (s), 1485 (m), 1423 (m), 1365 (m), 1328 (m), 1281 (s), 1272 (s), 1249 (s), 1213 (s), 1123 (m), 1086 (m), 1009 (m), 909 (m), 872 (m), 823 (s), 811 (s), 747 (m), 696 (w), 655 (m), 622 (m).

4-chloro-2-(2-(piperidin-1-yl)thiazolo[4,5-*b*]pyridin-5-yl)phenol (2.6.7d).



Starting from chromone **2.6.2d** (0.181 g, 1 mmol) and 2-(piperidin-1-yl)thiazol-4-amine **E5c** (0.201 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.7d** was isolated as red-brown solid (0.190 g, 55%), mp 194-196 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (s, 6H, piperidine), 3.66 (s, 4H, piperidine), 6.97 (d, 1H, ^3J = 8.5 Hz, CH_{Ar}), 7.18 (dd, 1H, ^3J = 8.7 Hz, ^4J = 1.8 Hz, CH_{Ar}), 7.42 (d, 1H, ^3J = 8.2 Hz, CH_{Ar}), 7.69 (d, 1H, ^3J = 2.2 Hz, CH_{Ar}), 7.91 (d, 1H, ^3J = 8.2 Hz, CH_{Ar}), 13.77 (s, 1H, OH).

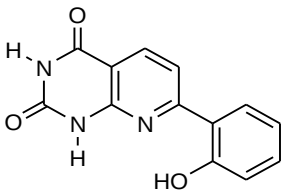
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.0, 25.3, 49.6 (CH_2 piperidine), 111.3 (CH), 119.9 (C), 120.4 (CH), 123.3, 123.4 (C), 125.9, 130.3, 130.5 (CH), 153.0, 158.0, 161.4, 170.6 (C).

MS (GC, 70eV): *m/z* (%) = 345 (M^+, 100), 316 (21), 289 (16), 227 (15), 207 (11), 172 (11), 155 (16).

HRMS (ESI): Calcd for $C_{17}H_{17}ON_3SCl$ (M+H) 346.07754. Found 346.07691.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925 (w), 1573 (w), 1519 (m), 1487 (m), 1423 (m), 1360 (m), 1326 (m), 1269 (s), 1214 (s), 1122 (m), 1009 (w), 957 (w), 901 (m), 857 (m), 824 (s), 811 (s), 747 (m), 730 (m), 698 (w), 666 (s), 623 (m).

7-(2-hydroxyphenyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.6.8a)



Starting from chromone **2.6.2a** (0.146 g, 1 mmol) and 6-aminopyrimidine-2,4(1*H*,3*H*)-dione **E6a** (0.140 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.8a** was isolated as white solid (0.200 g, 89%), mp more then 375 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.92-7.00 (m, 2H, CH_{Ar}), 7.35-7.41 (m, 1H, CH_{Ar}), 7.96 (d, 1H, ^3J = 8.4 Hz, CH_{Ar}), 8.04 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.4 Hz, CH_{Ar}), 8.33 (d, 1H, ^3J = 8.4 Hz, CH_{Ar}), 11.51 (s, 1H, OH), 12.03 (s, 1H, NH), 12.52 (s, 1H, NH).

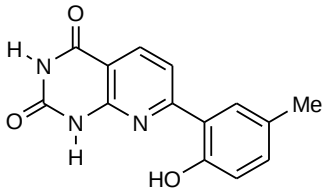
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 107.9 (C), 114.9, 118.2 (CH), 118.7, 119.2 (C), 128.4, 132.7, 137.5 (CH), 150.4, 150.7, 158.9, 160.8, 161.8 (C).

MS (EI, 70eV): *m/z* (%) = 255 (M^+, 12), 184 (20).

HRMS (EI): Calcd for $C_{13}H_9N_3O_3$ (M^+) 256.07167. Found 256.07177.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3152 (w), 2984 (w), 2765 (m), 2456 (w), 1710 (m), 1667 (m), 1592 (m), 1475 (m), 1414 (m), 1277 (m), 1220 (m), 1151 (m), 1007 (w), 942 (w), 859 (m), 803 (m), 749 (s), 680 (m), 643 (m).

7-(2-hydroxy-5-methylphenyl)pyrido[2,3-*d*]pyrimidine-2,4-diol (2.6.8b).



Starting from chromone **2.6.2b** (0.160 g, 1 mmol) and 6-aminopyrimidine-2,4(1*H*,3*H*)-dione **E6a** (0.140 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.8b** was isolated as green solid (0.237 g, 88%), mp more then 375 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.28 (s, 3H, Me), 6.86 (d, 1H, ^3J = 8.2 Hz, CH_{Ar}), 7.17 (dd, 1H, ^3J = 8.4 Hz, ^4J = 1.7 Hz, CH_{Ar}), 7.83 (s, 1H, CH_{Ar}), 7.93 (d, 1H, ^3J = 8.4 Hz, CH_{Ar}), 8.30 (d, 1H, ^3J = 8.4 Hz, C*H*$_{Ar}$), 8.93 (s, 1H, O*H*), 11.45 (s, 1H, OH), 12.00 (s, 1H, OH).

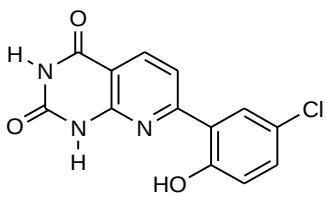
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 34.9 (Me), 107.7 (C), 114.8, 118.1 (CH), 118.2, 127.8 (C), 128.2, 133.5, 137.4 (CH), 150.4, 150.7, 156.8, 160.9, 161.8 (C).

MS (GC, 70eV): *m/z* (%) = 269 (M^+, 100), 198 (16).

HRMS (EI): Calcd for $C_{14}H_{11}O_3N_3$ (M^+) 269.07949. Found 269.079464.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3426 (w), 2981 (w), 2764 (m), 2457 (w), 1709 (m), 1661 (s), 1591 (s), 1472 (m), 1409 (s), 1365 (m), 1266 (m), 1241 (m), 1203 (m), 1115 (w), 1054 (w), 1025 (m), 950 (w), 878 (w), 800 (s), 767 (s), 706 (m), 678 (m), 651 (m), 588 (m).

7-(5-chloro-2-hydroxyphenyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.6.8c).



Starting from chromone **2.6.2d** (0.181 g, 1 mmol) and 6-aminopyrimidine-2,4(1*H*,3*H*)-dione **E6a** (0.140 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.8c** was isolated as orange solid (0.246 g, 85%), mp more then 375 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.99 (d, 1H, ^3J = 8.8 Hz, CH_{Ar}), 7.38 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.5 Hz, CH_{Ar}), 8.00-8.07 (m, 2H, CH_{Ar}), 8.31 (d, 1H, ^3J = 8.4 Hz, CH_{Ar}), 11.52 (s, 1H, OH), 11.99 (s, 1H, NH), 12.40 (s, 1H, NH).

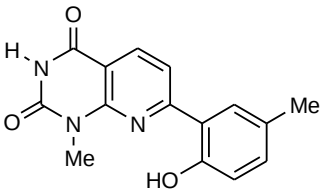
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 108.5 (C), 115.7, 120.0 (CH), 120.6, 123.0 (C), 127.8, 132.1, 137.6 (CH), 150.3, 150.8, 157.4, 159.1, 161.8 (C).

MS (EI, 70eV): *m/z* (%) = 289 (M^+, 100), 218 (27).

HRMS (ESI): Calcd for $C_{13}H_9O_3N_3Cl$ (M+H) 290.0327. Found 290.0331.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3167 (w), 3043 (w), 1716 (m), 1659 (m), 1586 (m), 1467 (m), 1403 (m), 1344 (m), 1265 (m), 1241 (m), 1171 (m), 1100 (w), 1045 (w), 946 (w), 829 (m), 799 (s), 773 (m), 730 (m), 693 (s), 646 (m).

7-(2-hydroxy-5-methylphenyl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.6.8d).



Starting from chromone **2.6.2b** (0.160 g, 1 mmol) and 6-amino-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **E6c** (0.155 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.8d** was isolated as white solid (0.255 g, 90%), mp 332-333 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.29 (s, 3H, Me), 3.54 (s, 3H, NMe), 6.91 (d, 1H, ^3J = 8.6 Hz, CH_{Ar}), 7.16 (dd, 1H, ^3J = 8.2 Hz, ^4J = 2.0 Hz, CH_{Ar}), 7.81 (s, 1H, CH_{Ar}), 7.98 (d, 1H, ^3J = 8.2 Hz, CH_{Ar}), 8.35 (d, 1H, ^3J = 8.2 Hz, CH_{Ar}), 11.46 (br. s, 2H, OH).

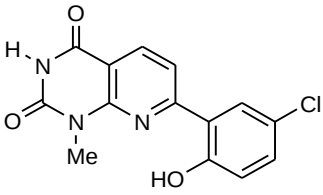
^{13}C NMR due to bed solubility was not possible to measure

MS (EI, 70eV): *m/z* (%) = 283 (M^+, 100), 254 (33), 185 (20).

HRMS (EI): Calcd for $C_{15}H_{13}N_3O_3$ (M^+) 283.09514. Found 283.094282.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3182 (w), 2764 (m), 2457 (w), 1714 (m), 1682 (s), 1595 (s), 1470 (m), 1404 (m), 1365 (m), 1277 (m), 1225 (m), 1159 (w), 1131 (w), 1078 (w), 1027 (w), 831 (m), 804 (m), 774 (m), 734 (m), 690 (m), 669 (m), 611 (w).

7-(5-chloro-2-hydroxyphenyl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.6.8e)



Starting from chromone **2.6.2d** (0.181 g, 1 mmol) and 6-amino-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **E6c** (0.155 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.8e** was isolated as yellow solid (0.197 g, 65%), mp 148-150 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.54 (s, 3H, Me), 7.04 (d, 1H, ^3J = 7.8 Hz, CH_{Ar}), 7.40 (d, 1H, ^3J = 8.0 Hz, CH_{Ar}), 8.07-8.11 (m, 2H, CH_{Ar}), 8.39 (d, 1H, ^3J = 7.3 Hz, CH_{Ar}), 11.76 (s, 2H, OH, NH).

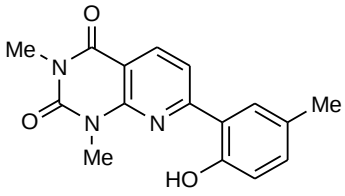
^{13}C NMR due to bed solubility was not possible to measure

MS (EI, 70eV): *m/z* (%) = 303 (M^+, 100), 274 (23), 205 (27), 168 (20), 99 (11), 78 (36).

HRMS (EI): Calcd for $C_{14}H_{10}O_3N_3Cl$ (M^+) 303.04052. Found 303.040878.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1709 (m), 1594 (s), 1484 (m), 1406 (s), 1365 (m), 1285 (s), 1239 (w), 1162 (w), 1102 (w), 1074 (w), 1025 (w), 979 (w), 838 (m), 806 (m), 734 (w), 719 (s), 697 (m), 686 (m), 651 (w).

7-(2-hydroxy-5-methylphenyl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.6.8f).



Starting from chromone **2.6.2b** (0.160 g, 1 mmol) and 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **E6b** (0.170 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.8f** was isolated as white solid (0.193 g, 65%), mp 304-306°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3H, Me), 3.50 (s, 3H, NMe), 3.75 (s, 3H, NMe), 6.95 (d, 1H, ^3J = 8.4 Hz, CH_{Ar}), 7.22 (dd, 2H, ^3J = 8.4 Hz, ^4J = 1.4 Hz, CH_{Ar}), 7.65 (s, 1H, CH_{Ar}), 8.53 (d, 1H, ^3J = 8.4 Hz, CH_{Ar}), 12.94 (br. s, 1H, OH).

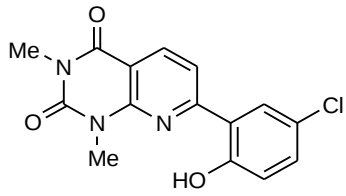
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.7, 28.6, 29.8 (Me), 105.8 (C), 108.3, 114.2 (CH), 118.6 (C), 127.5 (CH), 128.8 (C), 134.5, 138.7 (CH), 143.1, 149.4, 151.3, 155.0, 162.1 (C).

MS (GC, 70eV): *m/z* (%) = 297 (M^+, 100), 268 (25), 185 (14).

HRMS (EI): Calcd for $C_{16}H_{15}N_3O_3N_3$ (M^+) 297.11079. Found 297.110626.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1712 (w), 1652 (s), 1599 (s), 1478 (m), 1424 (s), 1358 (s), 1280 (s), 1233 (m), 1221 (s), 1130 (m), 1103 (m), 1063 (w), 1018 (m), 831 (m), 798 (s), 776 (m), 747 (s), 734 (m), 712 (s), 665 (m), 646 (m).

7-(5-chloro-2-hydroxyphenyl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.6.8g).



Starting from chromone **2.6.2d** (0.181 g, 1 mmol) and 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **E6b** (0.170 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.8g** was isolated as yellow solid (0.308 g, 97%), mp 252-253°C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.32 (s, 3H, NMe), 3.62 (s, 3H, NCH_3), 7.11 (d, 1H, ^3J = 8.7 Hz, CH_{Ar}), 6.39 (dd, 1H, ^3J = 9.0 Hz, ^4J = 3.0 Hz, CH_{Ar}), 8.05 (d, 1H, ^3J = 2.7 Hz, CH_{Ar}), 8.12 (d, 1H, ^3J = 8.3 Hz, CH_{Ar}), 8.43 (d, 1H, ^3J = 8.3 Hz, CH_{Ar}), 11.70 (s, 1H, OH).

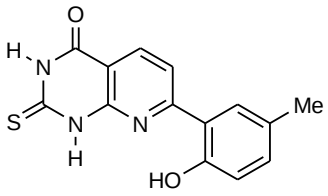
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 28.1, 29.2 (Me), 108.8 (C), 117.9, 119.2 (CH), 123.1, 123.4 (C), 128.8, 131.5, 137.7 (CH), 149.8, 151.0, 156.3, 158.0, 160.4 (C).

MS (GC, 70eV): *m/z* (%) = 317 (M^+, 100), 288 (21), 205 (19).

HRMS (EI): Calcd for $C_{15}H_{12}N_3O_3Cl$ (M^+) 317.05617. Found 317.05629.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3362 (w), 2962 (w), 2767 (m), 2452 (w), 1708 (m), 1658 (s), 1598 (s), 1468 (s), 1424 (s), 1354 (m), 1284 (m), 1096 (m), 1052 (w), 1022 (m), 847 (m), 804 (s), 747 (m), 711 (m), 691 (m), 651 (m).

7-(2-hydroxy-5-methylphenyl)-2-mercaptopyrido[2,3-*d*]pyrimidin-4-ol (2.6.8h).



Starting from chromone **2.6.2b** (0.160 g, 1 mmol) and 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one **E6d** (0.157 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.8h** was isolated as green solid (0.254 g, 89%), mp 371-374 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.29 (s, 3H, Me), 6.87 (d, 1H, ^3J = 8.4 Hz, CH_{Ar}), 7.20 (dd, 1H, ^3J = 8.4 Hz, ^4J = 1.7 Hz, CH_{Ar}), 7.87 (s, 1H, CH_{Ar}), 8.04 (d, 1H, ^3J = 8.7 Hz, CH_{Ar}), 8.33 (d, 1H, ^3J = 8.7 Hz, CH_{Ar}), 12.08 (s, 1H, OH), 12.65 (s, 1H, OH), 13.47 (s, 1H, SH).

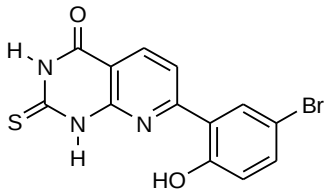
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 34.1 (Me), 109.8 (C), 116.3 (CH), 118.0 (C), 118.3 (CH), 127.9 (C), 128.3, 133.8, 137.2 (CH), 149.8, 156.9, 159.2, 161.2, 175.9 (C).

MS (EI, 70eV): *m/z* (%) = 285 (M^+, 100), 168 (26), 99 (14).

HRMS (EI): Calcd for $C_{14}H_{11}O_2N_3S$ (M^+) 285.05665. Found 285.056686.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3134 (w), 2768 (w), 1683 (m), 1609 (s), 1545 (s), 1481 (s), 1417 (m), 1282 (m), 1239 (s), 1200 (s), 1161 (s), 1133 (s), 812 (s), 777 (s), 692 (m), 660 (m), 610 (w), 578 (s), 543 (s).

7-(5-bromo-2-hydroxyphenyl)-4-mercaptopyrido[2,3-*d*]pyrimidin-2-ol (2.6.8i).



Starting from chromone **2.6.2c** (0.225 g, 1 mmol) and 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one **E6d** (0.157 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.8i** was isolated as brown solid (0.277g, 79%), mp more then 375 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.00 (d, 1H, ^3J = 8.8 Hz, CH_{Ar}), 7.52 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.5 Hz, CH_{Ar}), 8.14 (d, 1H, ^3J = 8.6 Hz, CH_{Ar}), 8.23 (s, 1H, CH_{Ar}), 8.34 (d, 1H, ^3J = 8.6 Hz, CH_{Ar}), 12.20 (s, 1H, OH), 12.67 (s, 1H, OH), 13.44 (s, 1H, SH).

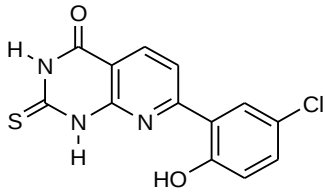
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 110.4, 110.5 (C), 117.5, 120.5 (CH), 121.2 (C), 130.9, 135.1, 137.3 (CH), 150.0, 157.8, 159.2, 159.4, 175.9 (C).

MS (EI, 70eV): *m/z* (%) = 348 (M^+, 100), 207 (16).

HRMS (EI): Calcd for $C_{13}H_8O_2N_3SBr$ (M^+) 348.95151. Found 348.950828.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3184 (w), 2932 (w), 2758 (m), 2456 (w), 1665 (s), 1621 (m), 1586 (s), 1470 (s), 1413 (m), 1356 (s), 1272 (s), 1236 (s), 1205 (s), 1175 (s), 1087 (w), 1026 (w), 838 (m), 814 (m), 787 (s), 723 (m), 664 (m).

7-(5-chloro-2-hydroxyphenyl)-2-mercaptopyrido[2,3-*d*]pyrimidin-4-ol (2.6.8j).



Starting from chromone **2.6.2d** (0.181 g, 1 mmol) and 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one **E6d** (0.157 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.8j** was isolated as yellow solid (0.241 g, 79%), mp more then 375 ^{o}C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.01 (d, 1H, ^{3}J = 8.4 Hz, CH_{Ar}), 7.41 (td, 1H, ^{3}J = 8.8 Hz, ^{4}J = 2.5 Hz, CH_{Ar}), 8.11-8.15 (m, 2H, CH_{Ar}), 8.35 (d, 1H, ^{3}J = 8.4 Hz, CH_{Ar}), 12.24 (s, 1H, OH), 12.69 (s, 1H, OH), 13.47 (s, 1H, SH).

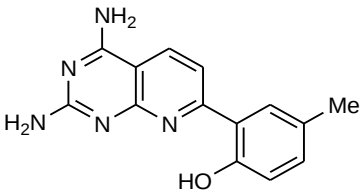
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 110.5 (C), 117.1, 120.2 (CH), 120.3, 123.1 (C), 127.8, 132.4, 137.4 (CH), 149.9, 157.6, 159.2, 159.5, 176.0 (C).

MS (GC, 70eV): *m/z* (%) = 305 (M^+, 100), 277 (12), 218 (12), 168 (28), 99 (16).

HRMS (EI): Calcd for $C_{13}H_8O_2N_3SCl$ (M^+) 305.00203. Found 305.001007.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3186 (w), 1665 (m), 1606 (m), 1587 (s), 1558 (m), 1470 (m), 1414 (m), 1356 (m), 1271 (m), 1236 (m), 1192 (m), 1136 (m), 1098 (w), 1051 (w), 941 (w), 838 (m), 815 (m), 785 (s), 735 (m), 699 (w), 667 (m), 575 (m), 540 (m).

2-(2,4-diaminopyrido[2,3-*d*]pyrimidin-7-yl)-4-methylphenol (2.6.9a).



Starting from chromone **2.6.2b** (0.160 g, 1 mmol) and pyrimidine-2,4,6-triamine **E9** (0.138 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.9a** was isolated as yellow solid (0.160 g, 60%), mp 152-154^{o}C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.28 (s, 3H, Me), 6.90 (d, 1H, ^{3}J = 8.2 Hz, CH_{Ar}), 7.19 (d, 1H, ^{3}J = 8.0 Hz, CH_{Ar}), 7.88 (br. s, 2H, NH_2), 8.17 (d, 1H, ^{3}J = 8.5 Hz, CH_{Ar}), 8.50 (br. s, 1H, NH_2), 8.87 (d, 1H, ^{3}J = 8.5 Hz, CH_{Ar}), 9.04 (br. s, 1H, NH_2), 11.94 (br. s, 1H, NH_2), 13.20 (s, 1H, OH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 30.6 (Me), 103.1 (C), 117.5, 117.8 (CH), 118.9, 128.0 (C), 128.9, 133.8, 135.5 (CH), 148.7, 156.0, 156.6, 161.6, 162.7 (C).

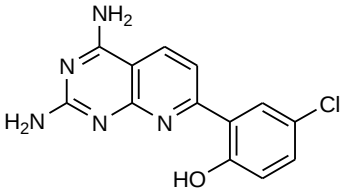
MS (GC, 70eV): *m/z* (%) = 267 (M^+, 100).

HRMS (EI): Calcd for $C_{14}H_{13}ON_5$ (M^+) 267.11146. Found 267.111500.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3412 (w), 3131 (w), 1645 (m), 1608 (m), 1524 (w), 1480 (m), 1460 (m),

1370 (m), 1344 (m), 1291 (m), 1242 (m), 1214 (m), 1184 (m), 1147 (m), 1043 (m), 1004 (m), 874 (w), 835 (m), 800 (s), 770 (m), 742 (s), 701 (s), 674 (s), 646 (s).

2-(2,4-diaminopyrido[2,3-d]pyrimidin-7-yl)-4-chlorophenol (2.6.9b).



Starting from chromone **2.6.2d** (0.181 g, 1 mmol) and pyrimidine-2,4,6-triamine **E9** (0.138 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.9b** was isolated as yellow solid (0.201 g, 70%), mp more than 375 ^{o}C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.08 (d, 1H, ^{3}J = 8.9 Hz, CH_{Ar}), 7.40 (td, 1H, ^{3}J = 8.9 Hz, ^{4}J = 2.5 Hz, CH_{Ar}), 7.81 (br. s, 1H, NH_2), 8.08 (d, 1H, ^{3}J = 2.5 Hz, CH_{Ar}), 8.23 (d, 1H, ^{3}J = 8.9 Hz, CH_{Ar}), 8.52 (br. s, 1H, NH_2), 8.88 (d, 1H, ^{3}J = 8.5 Hz, CH_{Ar}), 9.07 (br. s, 1H, NH_2), 9.41 (br. s, 1H, NH_2), 12.04 (s, 1H, OH).

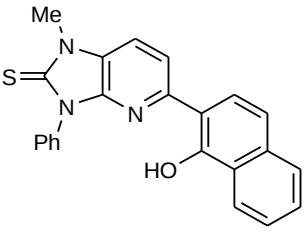
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 103.4 (C), 118.5, 119.7 (CH), 121.6, 123.1 (C), 128.4, 132.1, 135.6 (CH), 148.9, 156.1, 157.0, 159.7, 162.7 (C).

MS (GC, 70eV): *m/z* (%) = 287 (M^+, 100), 122 (16), 105 (36), 77 (16).

HRMS (ESI): Calcd for $C_{13}H_{11}N_5OCl$ (M+H) 288.06466. Found 288.06522.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3307 (w), 3140 (w), 2586 (w), 1682 (w), 1645 (s), 1605 (s), 1525 (w), 1453 (s), 1400 (w), 1285 (m), 1235 (m), 1192 (m), 1145 (w), 1041 (w), 981 (w), 802 (s), 738 (m), 695 (m).

5-(1-hydroxynaphthalen-2-yl)-1-methyl-3-phenyl-1H-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (2.6.10)



Starting from chromone **2.6.2e** (0.196 g, 1 mmol) and 4-amino-1-methyl-3-phenyl-1*H*-imidazole-2(3*H*)-thione **E2b** (0.225 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.10** was isolated as green solid (0.276 g, 72%), mp 305-306 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.85 (s, 3H, Me), 7.42-7.54 (m, 3H, CH_{Ar}), 7.64-7.73 (m, 5H, CH_{Ar}), 7.82 (s, 1H, CH_{Ar}), 8.09-8.24 (m, 4H, CH_{Ar}), 13.61 (br. s, 1H, OH).

^{13}C NMR due to bed solubility was not possible to measure

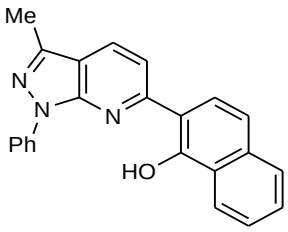
MS (GC, 70eV): *m/z* (%) = 383 (M^+, 100), 207 (13).

HRMS (EI): Calcd for $C_{23}H_{17}N_3OS$ (M^+) 383.10868. Found 383.107368.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3049 (w), 1614 (w), 1569 (w), 1499 (w), 1462 (s), 1438 (m), 1402 (m), 1337 (s), 1295 (s), 1223 (m), 1203 (m), 1139 (m), 1063 (w), 1027 (w), 977 (w), 853 (w), 795

(s), 769 (m), 723 (m), 704 (m), 622 (m).

2-(3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)naphthalen-1-ol (2.6.11).



Starting from chromone **2.6.2e** (0.196 g, 1 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **E3** (0.190 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.11** was isolated as white solid (0.295 g, 84%), mp 186-187 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.65 (s, 3H, Me), 7.46-7.71 (m, 6H, CH_{Ar}), 7.88-7.97 (m, 3H, CH_{Ar}), 8.20-8.25 (m, 2H, CH_{Ar}), 8.33 (d, 1H, ^{3}J = 8.0 Hz, CH_{Ar}), 8.57 (d, 1H, ^{3}J = 8.5 Hz, CH_{Ar}), 14.88 (s, 1H, OH).

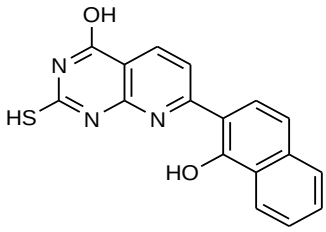
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 34.0 (Me), 112.0, 113.8, 115.2 (C), 118.6, 121.9, 123.0, 124.3, 125.3, 125.6, 126.8 (CH), 127.3 (C), 128.1, 129.6 (CH), 132.9, 134.9, 138.2, 143.5, 146.8, 156.2, 156.7 (C).

MS (GC, 70eV): *m/z* (%) = 351 (M^{+}, 100).

HRMS (ESI): Calcd for $C_{23}H_{18}N_3O$ (M+H) 352.1444. Found 352.14452.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3400 (w), 2980 (m), 2763 (s), 2456 (w), 1582 (s), 1508 (m), 1480 (m), 1431 (m), 1389 (s), 1349 (m), 1304 (m), 1231 (m), 1176 (m), 1119 (w), 1057 (m), 1023 (m), 850 (m), 804 (m), 790 (s), 772 (s), 753 (s), 722 (m), 691 (s), 648 (s), 608 (m), 570 (m).

7-(1-hydroxynaphthalen-2-yl)-4-mercaptopyrido[2,3-*d*]pyrimidin-2-ol (2.6.12)



Starting from chromone **2.6.2e** (0.196 g, 1 mmol) and 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one **E6d** (0.157 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.12** was isolated as white solid (0.270 g, 84%), mp 278-280 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.41 (d, 1H, ^{3}J = 8.8 Hz, CH_{Ar}), 7.51-7.62 (m, 2H, CH_{Ar}), 7.83 (d, 1H, ^{3}J = 7.5 Hz, CH_{Ar}), 8.03-8.06 (m, 2H, CH_{Ar}), 8.30-8.35 (m, 2H, CH_{Ar}), 12.65 (s, 1H, OH), 13.56 (s, 1H, OH), 13.99 (s, 1H, SH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 109.4, 110.8 (C), 115.8, 118.6, 123.3, 123.8 (CH), 125.4 (C), 125.8, 127.3, 128.6 (CH), 135.4 (C), 137.3 (CH), 149.5, 157.2, 159.1, 161.2, 175.9 (C).

MS (GC, 70eV): *m/z* (%) = 321 (M^{+}, 100), 234 (12), 78 (12).

HRMS (EI): Calcd for $C_{17}H_{11}O_2N_3S$ (M^{+}) 321.05665. Found 321.056049.

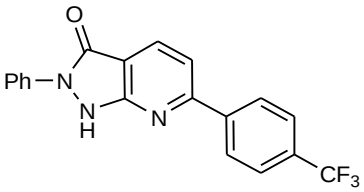
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3284 (w), 1702 (w), 1672 (m), 1611 (m), 1581 (m), 1512 (m), 1472 (m), 1396 (s), 1344 (m), 1273 (m), 1242 (m), 1178 (s), 1148 (m), 1126 (s), 1108 (m), 949 (w), 868

(s), 808 (m), 786 (s), 764 (s), 723 (m), 650 (m).

*A.2.15. General procedure for the synthesis of compounds **2.6.15-2.6.19**.*

Corresponding enaminone **2.6.14a-e** (1 equiv.) and appropriate amine **E** (1.1 equiv.) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMF (5 mL/1 mmol of chromone **2.6.14**) containing 1 mL of TMSCl. The mixture was heated at 100-120 °C for 1-6 h (controlled by TLC). After the reaction was completed volatiles were evaporated under reduced pressure. The residue was treated with water, filtered, dried in air, and recrystallized from appropriate solvent or subjected to column chromatography (silica gel).

6-(3-(trifluoromethyl)phenyl)-1,2-dihydro-2-phenylpyrazolo[3,4-*b*]pyridin-3-one (2.6.15a).



Starting from chromone **2.6.14a** (0.243 g, 1 mmol) and 5-amino-1,2-dihydro-2-phenylpyrazol-3-one **E1a** (0.193 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.15a** was isolated as yellow solid (0.249g, 70%), mp 161-162 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.26-7.31 (m, 1H, CH_{Ar}), 7.45-7.55 (m, 2H, CH_{Ar}), 7.90-7.95 (m, 5H, CH_{Ar}), 8.34-8.40 (m, 3H, CH_{Ar}), 11.80 (br.s, 1H, NH).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -61.2 (CF_3).

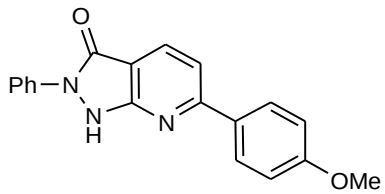
^{13}C NMR Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 355 (M^+, 100), 286 (37).

HRMS (EI): Calcd for $C_{20}H_{14}N_3F_3$ (M^+) 355.09221. Found 355.09222.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3382 (w), 3013 (m), 2773 (m), 2448 (w), 1651 (m), 1620 (m), 1594 (m), 1501 (m), 1441 (m), 1403 (m), 1325 (m), 1301 (m), 1158 (m), 1120 (s), 1067 (s), 1017 (s), 935 (w), 857 (m), 825 (s), 792 (s), 746 (s), 711 (s), 682 (s).

1,2-dihydro-6-(4-methoxyphenyl)-2-phenylpyrazolo[3,4-*b*]pyridin-3-one (2.6.15b).



Starting from chromone **2.6.14b** (0.205 g, 1 mmol) and 5-amino-1,2-dihydro-2-phenylpyrazol-3-one **E1a** (0.193 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.15b** was isolated as orange solid (0.228 g, 72%), mp 173-174 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.88 (s, 3H, OMe), 7.11 (d, 2H, ^{3}J = 8.9 Hz, CH_{Ar}),

7.24-7.29 (m, 1H, CH_{Ar}), 7.49-7.55 (m, 2H, CH_{Ar}), 7.75 (d, 1H, ^3J = 8.3 Hz, CH_{Ar}), 7.93-7.96 (m, 2H, CH_{Ar}), 8.16 (d, 2H, ^3J = 8.9 Hz, CH_{Ar}), 8.23 (d, 1H, ^3J = 8.1 Hz, CH_{Ar}), 10.31 (br s, 1H, NH).

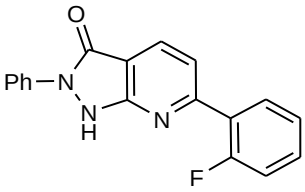
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.4 (OMe), 108.5 (CH), 113.9, 114.4, 118.8, 119.3, 125.0, 128.9 (CH), 129.0 (C), 129.9 (CH), 134.2 (C), 135.7 (CH), 137.4, 157.4, 158.7, 159.6, 161.1 (C).

MS (EI, 70eV): *m/z* (%) = 317 (M^+, 100), 288 (20).

HRMS (EI): Calcd for $C_{19}H_{15}N_3O_2$ (M^+) 317.11588. Found 317.115965.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2936 (w), 2761 (m), 2456 (m), 1594 (m), 1576 (m), 1479 (m), 1356 (m), 1319 (m), 1299 (m), 1257 (s), 1221 (m), 1182 (m), 1064 (m), 1025 (m), 809 (m), 783 (m), 769 (m), 754 (m), 721 (w), 693 (m), 670 (w).

6-(2-fluorophenyl)-1,2-dihydro-2-phenylpyrazolo[3,4-*b*]pyridin-3-one (2.6.15c).



Starting from chromone **2.6.14c** (0.193 g, 1 mmol) and 5-amino-1,2-dihydro-2-phenylpyrazol-3-one **E1a** (0.193 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.15c** was isolated as brown solid (0.241 g, 78%), mp 241-243 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.25-7.30 (m, 1H, CH_{Ar}), 7.36-7.42 (m, 2H, CH_{Ar}), 7.49-7.60 (m, 4H, CH_{Ar}), 7.92-8.00 (m, 3H, CH_{Ar}), 8.32 (d, 1H, ^3J = 8.3 Hz, CH_{Ar}), 11.65 (br s, 1H, NH).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -115.9 (CF).

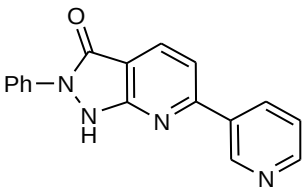
^{13}C NMR: Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 315 (M^+, 100), 276 (41), 207 (15), 77 (17).

HRMS (ESI): Calcd for $C_{18}H_{13}FN_3O$ (M+H) 316.10372. Found 316.10335.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1643 (m), 1593 (m), 1497 (m), 1441 (m), 1415 (m), 1335 (w), 1302 (m), 1280 (m), 1203 (m), 1128 (w), 1085 (w), 1026 (w), 937 (w), 893 (w), 789 (w), 760 (s), 740 (s), 712 (w), 661 (s).

1,2-dihydro-2-phenyl-6-(pyridin-3-yl)pyrazolo[3,4-*b*]pyridin-3-one (2.6.15d).



Starting from chromone **2.6.14d** (0.176 g, 1 mmol) and 5-amino-1,2-dihydro-2-phenylpyrazol-3-one **E1a** (0.193 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.15d** was isolated as yellow solid (0.202 g, 70%), mp 268-270 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.25-7.31 (m, 1H, CH_{Ar}), 7.50-7.55 (m, 2H, CH_{Ar}), 7.91-

7.94 (m, 2H, CH_{Ar}), 8.01-8.10 (m, 2H, CH_{Ar}), 8.42 (d, 1H, ^3J = 8.1 Hz, CH_{Ar}), 8.96 (d, 1H, ^3J = 5.2 Hz, CH_{Ar}), 9.09 (d, 1H, ^3J = 8.7 Hz, CH_{Ar}), 9.53 (s, 1H, CH_{Ar}), 11.90 (br s, 1H, NH).

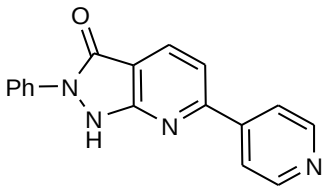
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 110.6 (C), 115.4, 119.6, 125.4, 126.6, 129.1, 135.1 (CH), 135.7, 136.9 (CH), 141.2, 142.5, 144.4 (CH), 154.9, 157.1, 158.0 (C).

MS (EI, 70eV): *m/z* (%) = 288 (M^+, 100), 259 (50), 77 (28).

HRMS (EI): Calcd for $C_{17}H_{12}N_4O$ (M^+) 288.10056. Found 288.100698.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3052 (w), 2442 (m), 2062 (w), 1651 (s), 1607 (m), 1538 (m), 1495 (m), 1445 (m), 1422 (m), 1345 (m), 1304 (s), 1280 (m), 1034 (w), 1016 (w), 941 (w), 814 (m), 789 (m), 770 (s), 724 (m), 680 (s), 623 (m), 602 (m).

1,2-dihydro-2-phenyl-6-(pyridin-4-yl)pyrazolo[3,4-*b*]pyridin-3-one (2.6.15e).



Starting from chromone **2.6.14e** (0.176 g, 1 mmol) and 5-amino-1,2-dihydro-2-phenylpyrazol-3-one **E1a** (0.193 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.15e** was isolated as yellow solid (0.236 g, 82%), mp 272-274 °C.

^{1}H NMR (300 MHz, CF_3COOD/DMSO-d_6): δ = 7.20-7.25 (m, 3H, CH_{Ar}), 7.38-7.41 (m, 2H, CH_{Ar}), 7.69 (d, 1H, ^3J = 8.2 Hz, CH_{Ar}), 8.37-8.42 (m, 3H, CH_{Ar}), 8.60-8.62 (m, 2H, CH_{Ar}), 11.94 (s, 1H, NH).

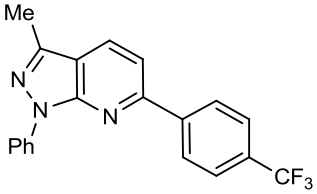
^{13}C NMR (75.5MHz, CF_3COOD/DMSO-d_6): δ = 110.8, 115.2, 117.6, (C), 119.5 (CH), 122.1 (C), 125.7, 127.5, 131.5, 131.9 (CH), 135.0 (C) 139.3, 143.7 (CH), 154.9, 156.5, 158.6 (C).

MS (EI, 70eV): *m/z* (%) = 288 (M^+, 100), 259 (39).

HRMS (ESI): Calcd for $C_{17}H_{13}N_4O$ (M+H) 289.10839. Found 289.10874.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3059 (w), 2397 (m), 2068 (w), 1652 (m), 1630 (m), 1591 (m), 1496 (m), 1417 (m), 1343 (w), 1300 (m), 1279 (m), 1128 (w), 1083 (w), 1001 (w), 942 (w), 814 (m), 786 (m), 767 (s), 718 (m), 689 (m), 634 (m), 601 (m).

6-(3-(trifluoromethyl)phenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (2.6.16a).



Starting from chromone **2.6.14a** (0.243 g, 1 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **E3** (0.190 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.16a** was isolated as yellow solid (0.247g, 70%), mp 151-152 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.62 (s, 3H, Me), 7.29-7.34 (m, 1H, CH_{Ar}), 7.54-7.59 (m, 2H, CH_{Ar}), 7.89 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 7.97 (d, 1H, ^3J = 8.5 Hz, CH_{Ar}), 8.32-8.44 (m, 5H, CH_{Ar}).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -61.0 (CF_3).

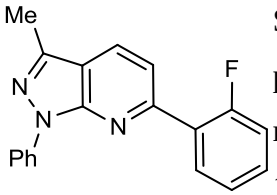
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.3 (Me), 115.1 (CH), 116.3 (C), 119.9 (CH), 124.2 (q, ^1J = 272 Hz, CF_3), 125.3 (CH), 125.7, 125.8 (q, ^3J = 4 Hz, *C*HCCF_3), 128.0, 129.2 (CH), 129.6 (q, ^2J = 32 Hz, *C*CF_3), 131.9 (CH), 139.2, 142.2, 143.0, 150.2, 150.9, 154.2, 165.5 (C).

MS (GC, 70eV): *m/z* (%) = 353 (M^+, 100), 338 (17).

HRMS (ESI): Calcd for $C_{20}H_{15}N_3F_3$ (M+H) 354.12126. Found 354.12094.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1592 (m), 1504 (s), 1394 (m), 1315 (s), 1283 (m), 1164 (s), 1124 (s), 1081 (m), 1068 (s), 1013 (m), 956 (w), 908 (w), 856 (w), 838 (w), 815 (s), 749 (s), 690 (s), 665 (s), 593 (m).

6-(2-fluorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (2.6.16b).



Starting from chromone **2.6.14c** (0.193 g, 1 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **E3** (0.190 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.16b** was isolated as yellow solid (0.236 g, 78%), mp 110-111 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.62 (s, 3H, Me), 7.26-7.31 (m, 1H, CH_{Ar}), 7.35-7.42 (m, 2H, CH_{Ar}), 7.51-7.58 (m, 3H, CH_{Ar}), 7.70 (dd, 1H, ^3J = 8.4 Hz, ^4J = 2.2 Hz, CH_{Ar}), 8.01 (dt, 1H, ^3J = 8.4 Hz, ^3J = 2.0 Hz, CH_{Ar}), 8.30-8.33 (m, 2H, CH_{Ar}), 8.41 (d, 1H, ^3J = 7.8 Hz, CH_{Ar}).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -116.6 (CF).

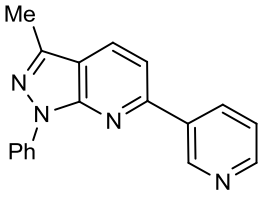
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.2 (Me), 113.2 (d, ^1J = 240 Hz, CF), 115.6 (C), 116.4 (d, ^2J = 22.7 Hz, CH), 118.0 (d, ^3J = 8.0 Hz, CH), 119.8 (CH), 125.0 (d, ^4J = 3.5 Hz, CH), 125.3 (CH), 126.9 (d, ^3J = 11.4 Hz, C) , 129.1, 131.0, 131.3 (CH), 142.9, 150.1, 152.4 (d, ^4J = 2.8 Hz, C), 160.0 (d, ^1J = 249.1 Hz, CF).

MS (GC, 70eV): *m/z* (%) = 303 (M^+, 100), 288 (21).

HRMS (EI): Calcd for $C_{19}H_{14}N_3F$ (M^+) 303.11663. Found 303.116564.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1596 (m), 1504 (m), 1461 (m), 1392 (s), 1309 (m), 1286 (m), 1205 (m), 1161 (m), 1107 (m), 1088 (m), 1030 (m), 957 (w), 901 (w), 820 (m), 797 (m), 742 (s), 682 (s), 658 (s), 631 (m).

3-methyl-1-phenyl-6-(pyridin-3-yl)-1*H*-pyrazolo[3,4-*b*]pyridine (2.6.16c).



Starting from chromone **2.6.14d** (0.176 g, 1 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **E3** (0.190 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.15c** was isolated as yellow solid (0.186 g, 65%), mp 196-198 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.63 (s, 3H, Me), 7.30-7.35 (m, 1H, CH_{Ar}), 7.54-7.59 (m, 2H, CH_{Ar}), 8.07-8.13 (m, 2H, CH_{Ar}), 8.28-8.31 (m, 2H, CH_{Ar}), 8.52 (d, 1H, ^{3}J = 8.3 Hz, CH_{Ar}), 8.94 (dd, 1H, ^{3}J = 5.4 Hz, ^{4}J = 1.0 Hz, CH_{Ar}), 9.16 (dt, 1H, ^{3}J = 8.3 Hz, ^{4}J = 1.8 Hz, CH_{Ar}), 9.59 (s, 1H, CH_{Ar}).

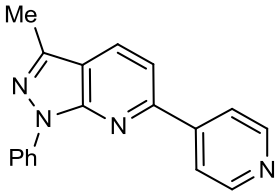
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 12.2 (Me), 115.1 (CH), 116.8, 120.0, 125.5, 126.7, 129.2, 132.2 (CH), 136.4, 138.9 (C), 141.5, 142.2, 143.1 (CH), 143.8, 149.9, 150.6 (C).

MS (GC, 70eV): *m/z* (%) = 286 (M^{+}, 100), 271 (16).

HRMS (ESI): Calcd for $C_{18}H_{15}N_4$ (M+H) 287.12912. Found 287.12936.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3343 (w), 2451 (m), 2072 (w), 1591 (m), 1556 (m), 1486 (m), 1395 (m), 1360 (m), 1283 (w), 1199 (m), 1161 (m), 1113 (w), 1085 (w), 1013 (w), 910 (w), 833 (w), 803 (m), 775 (m), 754 (s), 708 (m), 681 (m), 669 (s), 630 (s).

3-methyl-1-phenyl-6-(pyridin-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridine (2.6.16d).



Starting from chromone **2.6.14e** (0.176 g, 1 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **E3** (0.190 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.16d** was isolated as yellow solid (0.223 g, 78%), mp 123-125 ^{o}C.

^{1}H NMR (300 MHz, CF_3COOD/DMSO-d_6): δ = 1.42 (s, 3H, CH_3), 6.10-6.22 (m, 3H, CH_{Ar}), 6.49-6.51 (m, 2H, CH_{Ar}), 6.75 (d, 1H, ^{3}J = 8.1 Hz, CH_{Ar}), 7.18 (d, 1H, ^{3}J = 8.1 Hz, CH_{Ar}), 7.36-7.38 (m, 2H, CH_{Ar}), 7.59 (m, 1H, CH_{Ar}).

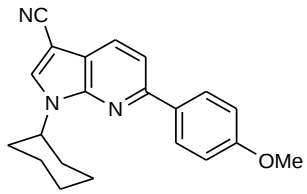
^{3}C NMR (62.9 MHz, CF_3COOD/DMSO-d_6): δ = 13.3 (Me), 118.1 (C), 119.2, 125.5, 127.0, 130.7, 131.3, 135.8 (CH), 137.0 (C), 143.5 (CH), 146.4, 151.2, 155.2, 157.2 (C).

MS (GC, 70eV): *m/z* (%) = 286 (M^{+}, 100), 271 (18).

HRMS (ESI): Calcd for $C_{18}H_{15}N_4$ (M+H) 287.2256. Found 287.2255.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2317 (w), 2064 (w), 1630 (m), 1588 (m), 1498 (m), 1445 (m), 1324 (w), 1247 (m), 1164 (m), 1097 (m), 1082 (m), 997 (m), 833 (m), 803 (s), 763 (s), 692 (m), 661 (m), 594 (m).

1-cyclohexyl-6-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (2.6.17).



Starting from chromone **2.6.14b** (0.205 g, 1 mmol) and 5-amino-1-cyclohexyl-1*H*-pyrrole-3-carbonitrile **E4b** (0.208 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.17** was isolated as yellow solid (0.248 g, 75%), mp 150-152 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.20-1.57 (m, 3H, cyclohexyl), 1.72-1.93 (m, 5H, cyclohexyl), 2.01-2.04 (m, 2H, cyclohexyl), 3.83 (s, 3H, OMe), 4.76-4.84 (m, 1H, NCH), 7.07 (d, 2H, ^{3}J = 8.9 Hz, CH_{Ar}), 7.84 (d, 1H, ^{3}J = 8.5 Hz, CH_{Ar}), 8.10-8.14 (m, 3H, CH_{Ar}), 8.58 (s, 1H, CH_{Ar}).

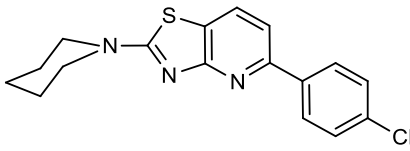
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 24.9, 25.2, 32.4 (cyclohexyl), 54.0 (NCH), 55.2 (OMe), 82.5 (CN), 114.2, 114.6 (CH), 115.6, 117.8 (C), 128.0, 128.4 (CH), 131.0 (C), 135.3 (CH), 145.6, 151.5, 160.1 (C).

MS (GC, 70eV): *m/z* (%) = 331 (M^{+}, 46), 249 (100), 234 (11), 206 (13).

HRMS (EI): Calcd for $C_{21}H_{21}ON_3$ (M^{+}) 331.4112. Found 331.41121.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922 (m), 2851 (m), 2221 (m), 1698 (w), 1600 (m), 1581 (m), 1513 (m), 1467 (m), 1427 (m), 1396 (m), 1304 (w), 1279 (m), 1251 (s), 1222 (m), 1179 (s), 1106 (m), 1027 (m), 891 (w), 838 (m), 798 (s), 779 (s), 641 (m), 611 (s).

5-(3-(trifluoromethyl)phenyl)-2-(piperidin-1-yl)thiazolo[4,5-*b*]pyridine (2.6.18a).



Starting from chromone **2.6.14a** (0.243 g, 1 mmol) and 2-(piperidin-1-yl)thiazol-4-amine **E5c** (0.190 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.18a** was isolated as yellow solid (0.229 g, 63%), mp 187-188 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.66 (s, 6H, piperidine), 3.65 (s, 4H, piperidine), 7.71 (d, 1H, ^{3}J = 8.2 Hz, CH_{Ar}), 7.83 (d, 2H, ^{3}J = 8.2 Hz, CH_{Ar}), 8.26-8.33 (m, 3H, CH_{Ar}).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -60.9 (CF_3).

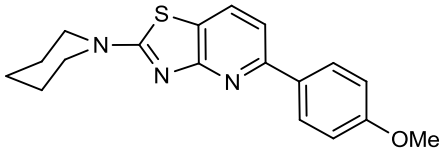
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 23.6, 24.9, 48.9 (CH_2 piperidine), 109.0 (C), 110.3, 113.3 (CH), 120.3 (q, ^{1}J = 230 Hz, CF_3), 124.6, 125.5 (C), 127.1 (CH), 128.7 (q, ^{2}J = 31 Hz, *C*CF_3), 130.4 (CH), 142.8, 151.4, 164.4, 169.7 (C).

MS (GC, 70eV): *m/z* (%) = 363 (M^{+}, 100), 334 (55), 230 (18), 307 (47), 295 (24).

HRMS (EI): Calcd for $C_{18}H_{16}N_3SF_3$ (M^{+}) 363.4115. Found 363.4116.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2944 (w), 1614 (w), 1582 (w), 1559 (w), 1531 (m), 1444 (w), 1396 (w), 1322 (m), 1263 (m), 1217 (w), 1153 (m), 1105 (s), 1063 (m), 1008 (m), 909 (w), 882 (w), 837 (m), 812 (s), 769 (m), 738 (m), 703 (w).

5-(4-methoxyphenyl)-2-(piperidin-1-yl)thiazolo[4,5-*b*]pyridine (2.6.18b).



Starting from chromone **2.6.14b** (0.205 g, 1 mmol) and 2-(piperidin-1-yl)thiazol-4-amine **E5c** (0.190 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.18a** was isolated as brown solid (0.189 g, 58%), mp 173-175 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.66 (s, 6H, piperidine), 3.64 (s, 4H, piperidine), 3.81 (s, 3H, OMe), 7.01-7.04 (m, 2H, CH_{Ar}), 7.54 (d, 1H, ^{3}J = 8.1 Hz, CH_{Ar}), 8.02-8.05 (m, 2H, CH_{Ar}), 8.16 (d, 1H, ^{3}J = 8.1 Hz, CH_{Ar}).

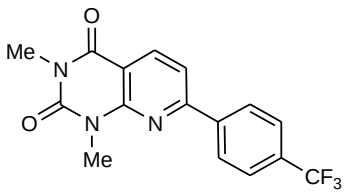
^{13}C NMR (62.9 MHz, DMSO-d_6):δ = 23.6, 24.9, 48.9 (CH_2 piperidine), 55.2 (OMe), 112.0, 114.0 (CH), 122.3 (C), 127.7, 130.1 (CH), 131.4, 145.6, 153.0, 159.9, 164.1, 169.5 (C).

MS (GC, 70eV): *m/z* (%) = 325 (M^+, 100), 296 (28), 289 (16), 282 (15), 269 (31), 242 (19).

HRMS (EI): Calcd for $C_{18}H_{19}ON_3S$ (M^+) 325.12433, Found 325.124003.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2934 (w), 1597 (m), 1537 (m), 1507 (m), 1446 (m), 1393 (m), 1359 (m), 1337 (m), 1284 (m), 1245 (s), 1208 (m), 1176 (m), 1028 (m), 1005 (m), 881 (m), 803 (s), 767 (m), 729 (m), 613 (m).

7-(3-(trifluoromethyl)phenyl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.6.19a).



Starting from chromone **2.6.14a** (0.243 g, 1 mmol) and 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **E6b** (0.170 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.19a** was isolated as yellow solid (0.275 g, 82%), mp 173-175 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.32 (s, 3H, Me), 3.66 (s, 3H, Me), 7.85 (d, 2H, ^{3}J = 8.3 Hz, CH_{Ar}), 7.93 (d, 1H, ^{3}J = 8.3 Hz, CH_{Ar}), 8.36 (d, 2H, ^{3}J = 8.0 Hz, CH_{Ar}), 8.43 (d, 1H, ^{3}J = 8.5 Hz, CH_{Ar}).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -61.4 (CF_3).

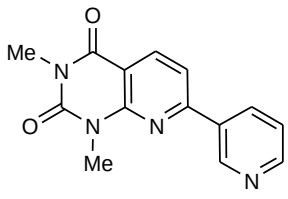
^{13}C NMR Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 335 (M^+, 100), 307 (43), 223 (53).

HRMS (ESI): Calcd for $C_{16}H_{13}N_3O_2F_3$ (M+H) 336.09544. Found 336.09613.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3362 (m), 2964 (m), 2766 (m), 2457 (w), 1709 (m), 1657 (s), 1595 (s), 1574 (m), 1470 (m), 1424 (m), 1314 (s), 1289 (m), 1170 (m), 1154 (m), 1112 (s), 1072 (s), 1001 (m), 889 (w), 835 (m), 791 (s), 744 (m), 705 (w), 664 (w), 589 (w).

1,3-dimethyl-7-(pyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.6.19b).



Starting from chromone **2.6.14d** (0.176 g, 1 mmol) and 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **E6b** (0.170 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.19b** was isolated as yellow solid (0.220 g, 77%), mp 216-217 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.32 (s, 3H, Me), 3.68 (s, 3H, Me), 7.95-7.99 (m, 1H, CH_{Ar}), 8.11 (d, 1H, ^{3}J = 8.1 Hz, CH_{Ar}), 8.51 (d, 1H, ^{3}J = 8.1 Hz, CH_{Ar}), 8.91 (dd, 1H, ^{3}J = 5.3 Hz, ^{4}J = 1.4 Hz, CH_{Ar}), 9.03 (d, 1H, ^{3}J = 8.3 Hz, ^{4}J = 1.8 Hz, CH_{Ar}), 9.56 (d, 1H, ^{3}J = 1.8 Hz, CH_{Ar}).

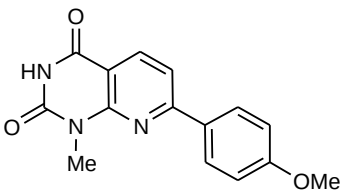
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 28.1, 29.2 (Me), 110.3 (C), 115.8, 125.8 (CH), 134.2 (C), 138.6, 139.3, 144.6, 146.9 (CH), 150.6, 151.0, 155.6, 160.5 (C).

MS (EI, 70eV): *m/z* (%) = 268 (M^{+}, 100).

HRMS (EI): Calcd for $C_{14}H_{12}N_4O_2$ (M^{+}) 268.1022. Found 268.10233.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3043 (w), 2351 (w), 2109 (w), 1996 (w), 1705 (m), 1651 (s), 1594 (s), 1553 (m), 1478 (m), 1423 (s), 1373 (m), 1346 (s), 1291 (s), 1226 (m), 1101 (m), 1062 (m), 937 (w), 869 (w), 829 (m), 791 (s), 748 (s), 685 (s), 622 (s).

7-(4-methoxyphenyl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.6.19c).



Starting from chromone **2.6.14b** (0.205 g, 1 mmol) and 6-amino-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **E6c** (0.155 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.19c** was isolated as yellow solid (0.189 g, 80%), mp 236-238 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.58 (s, 3H, Me), 3.86 (s, 3H, OMe), 7.09 (d, 2H, ^{3}J = 9.0 Hz, CH_{Ar}), 7.80 (d, 1H, ^{3}J = 8.0 Hz, CH_{Ar}), 8.18 (d, 2H, ^{3}J = 9.0 Hz, CH_{Ar}), 8.29 (d, 1H, ^{3}J = 8.0 Hz, CH_{Ar}), 11.64 (s, 1H, NH).

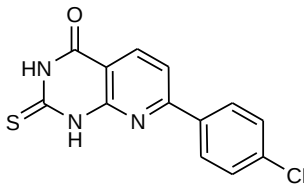
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 28.0 (Me), 55.3 (OMe), 108.8 (C), 113.9, 114.3, 128.9 (CH), 129.4 (C), 137.4 (CH), 150.8, 151.7, 159.5, 161.1, 161.4 (C).

MS (EI, 70eV): *m/z* (%) = 283 (M^{+}, 100), 254 (34), 185 (26), 170 (13).

HRMS (EI): Calcd for $C_{15}H_{13}O_3N_3$ (M^{+}) 283.2865, Found 283.2866.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3167 (w), 3036 (w), 2835 (w), 1692 (s), 1585 (s), 1521 (m), 1454 (m), 1404 (s), 1338 (m), 1299 (m), 1251 (s), 1205 (m), 1177 (m), 1080 (m), 1020 (m), 974 (w), 860 (m), 833 (m), 790 (s), 749 (m), 694 (m), 636 (s).

6-(3-(trifluoromethyl)phenyl)-4-mercaptopyrido[3,2-*d*]pyrimidin-2-ol (2.6.19d).



Starting from chromone **2.6.14a** (0.243 g, 1 mmol) and 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one **E6d** (0.157 g, 1.1 mmol) in 5 mL DMF and 1 mL of TMSCl. **2.6.19d** was isolated as green solid (0.274 g, 85%), mp 172-174 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.92-7.98 (m, 2H, CH_{Ar}), 8.03 (d, 1H, ^{3}J = 8.0 Hz, CH_{Ar}), 8.37-8.41 (m, 3H, CH_{Ar}), 12.64 (s, 1H, OH), 13.22 (s, 1H, SH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 111.5 (C), 117.4 (CH), 124.1 (q, ^{1}J = 272 Hz, CF_3), 125.8, 125.9, 128.1 (CH), 130.5 (q, ^{2}J = 32 Hz, *C*CF_3), 137.7 (CH), 140.5, 151.5, 159.0, 159.4, 162.3, 176.1 (C).

MS (GC, 70eV): *m/z* (%) = 323 (M^+, 100), 280 (18), 265 (13), 236 (12).

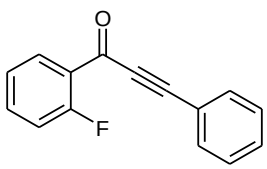
HRMS (ESI): Calcd for $C_{14}H_9ON_3SF_3$ (M+H) 324.04129. Found 324.04038.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2938 (w), 2762 (s), 2457 (w), 1682 (m), 1611 (s), 1574 (m), 1476 (m), 1412 (m), 1322 (s), 1276 (m), 1238 (m), 1159 (s), 1110 (s), 1070 (s), 1027 (m), 887 (w), 831 (s), 791 (s), 762 (m), 654 (w).

*A.2.16. General procedure for the synthesis of compounds **3.2.2**.*

To a Schlenk flask equipped with a magnetic stir bar $PdCl_2(PPh_3)_2$ (0.02 equiv.) and CuI (0.04 equiv.) were added. The flask was fitted with a rubber septum and then held under vacuum and back filled with argon. Afterwards THF (40 mL/10 mmol of **3.2.1**), fluorinated benzoyl chloride (1 equiv.) and triethylamine (1.5 equiv.) were added successively. Afterwards the holding under vacuum and back filling with argon was repeated three times. At the end corresponding acetylene was added (1.3 equiv.) and the reaction was stirred at room temperature for 15 h. After the reaction was completed (TLC control) to the reaction mixture was added distilled water and extracted with DCM. The organic layers were collected, dried with Na_2SO_4 and evaporated to crude mass. The residue was purified by column chromatography over silica gel (Heptane : Ethyl acetate - 30:1).

1-(2-fluorophenyl)-3-phenylprop-2-yn-1-one (3.2.2a).



Starting from 2-fluorobenzoyl chloride **3.2.1a** (1.585 g, 10 mmol), 1-ethynylbenzene (1.326 g, 13 mmol) and TEA (1.515 g, 15 mmol) in 40 mL THF. **3.2.2a** was isolated as yellow oil (1.97 g, 88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.97-7.03 (m, 1H, CH_{Ar}), 7.08-7.14 (m, 1H, CH_{Ar}), 7.20-7.32 (m, 3H, CH_{Ar}), 7.37-7.50 (m, 3H, CH_{Ar}), 7.95 (dt, 1H, ^{3}J = 7.6 Hz, ^{4}J =

1.7 Hz, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.3 (CF).

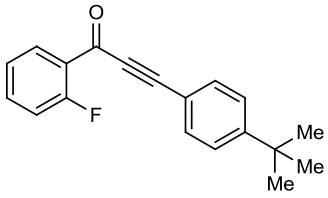
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 88.1 (C), 92.5 (t, ^4J = 3.1 Hz, C), 116.7 (d, ^2J = 22.2 Hz, CH_{Ar}), 119.5 (C), 123.8 (d, ^4J = 4.0 Hz, CH), 125.1 (d, ^3J = 7.5 Hz, C), 128.3, 130.6, 131.4, 132.7 (CH), 135.3 (d, ^3J = 8.8 Hz, CH), 161.6 (d, ^1J = 260.0 Hz, CF), 173.5 (C).

MS (GC, 70eV): *m/z* (%) = 224 (M^+, 58), 196 (100), 129 (72).

HRMS (EI): Calcd for $C_{15}H_9FO$ (M^+) 224.06319. Found 224.063269.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3063 (w), 2195 (s), 1627 (s), 1606 (s), 1482 (s), 1453 (s), 1306 (s), 1228 (m), 1203 (s), 1154 (m), 1101 (m), 1026 (m), 1010 (s), 994 (s), 839 (m), 778 (m), 747 (s), 686 (s), 617 (s).

3-(4-tert-butylphenyl)-1-(2-fluorophenyl)prop-2-yn-1-one (3.2.2b).



Starting from 2-fluorobenzoyl chloride **3.2.1a** (1.585 g, 10 mmol), 1-tert-butyl-4-ethynylbenzene (2.054 g, 13 mmol) and TEA (1.515 g, 15 mmol) in 40 mL THF. **3.2.2b** was isolated as yellow oil (1.62 g, 78%).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 9H, *t*-Bu), 7.14-7.21 (m, 1H, CH_{Ar}), 7.24-7.29 (m, 1H, CH_{Ar}), 7.43 (dt, 2H, ^3J = 8.6 Hz, ^4J = 1.9 Hz, CH_{Ar}), 7.53-7.58 (m, 1H, CH_{Ar}), 7.60 (dt, 2H, ^3J = 8.6 Hz, ^4J = 1.9 Hz, CH_{Ar}), 8.10 (dt, 1H, ^3J = 7.6 Hz, ^4J = 1.9 Hz, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.0 (CF).

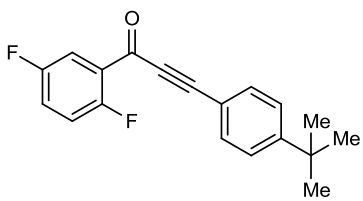
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 31.0 (*t*-Bu), 35.1 (C), 88.4 (C), 93.8 (d, ^4J = 3.2 Hz, C), 117.0 (C), 117.1 (d, ^2J = 21.9 Hz, CH_{Ar}), 124.1 (d, ^4J = 3.8 Hz, CH), 125.7, 131.8, 133.1 (CH), 135.4 (d, ^3J = 8.7 Hz, CH), 154.7 (C), 162.1 (d, ^1J = 262.0 Hz, CF), 174.3 (C).

MS (GC, 70eV): *m/z* (%) = 280 (M^+, 30), 265 (100), 123 (17).

HRMS (EI): Calcd for $C_{19}H_{17}FO$ (M^+) 280.12579. Found 280.126387.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2162 (w), 2193 (s), 1629 (s), 1606 (s), 1504 (w), 1481 (m), 1453 (s), 1364 (w), 1305 (s), 1267 (m), 1207 (s), 1187 (m), 1154 (m), 1100 (m), 1006 (s), 834 (s), 776 (m), 749 (s), 679 (m), 637 (s), 564 (s).

3-(4-tert-butylphenyl)-1-(2,5-difluorophenyl)prop-2-yn-1-one (3.2.2c).



Starting from 2,5-difluorobenzoyl chloride **3.2.1b** (1.765 g, 10 mmol), 1-tert-butyl-4-ethynylbenzene (2.054 g, 13 mmol) and TEA (1.515 g, 15 mmol) in 40 mL THF. **3.2.2c** was isolated as yellow oil (2.503 g, 84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 9H, *t*-Bu), 7.01-7.08 (m, 1H, CH_{Ar}), 7.11-7.19 (m, 1H, CH_{Ar}), 7.33 (d, 2H, ^{3}J = 8.7 Hz, CH_{Ar}), 7.50 (d, 2H, ^{3}J = 8.7 Hz, CH_{Ar}), 7.62-7.68 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -117.3 (d, *J* = 18.2 Hz, CF), -117.0 (d, *J* = 18.2 Hz, CF).

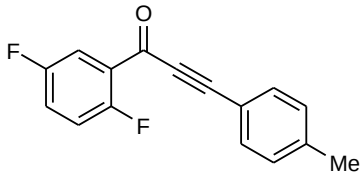
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 30.9 (Me), 35.1, 88.1 (C), 94.6 (d, ^{4}J = 3.4 Hz, C), 116.7 (C), 117.4 (dd, ^{2}J = 24.9 Hz, ^{4}J = 1.2 Hz, CH), 118.5 (dd, ^{2}J = 24.9 Hz, ^{3}J = 8.6 Hz, CH), 121.5 (dd, ^{2}J = 24.3 Hz, ^{3}J = 9.8 Hz, CH), 125.7 (CH), 126.5 (dd, ^{3}J = 10.0 Hz, ^{4}J = 6.6 Hz, C), 133.2 (CH), 155.0 (C), 158.0 (d, ^{1}J = 256.6 Hz, CF), 158.2 (d, ^{1}J = 253.6 Hz, CF), 172.7 (C).

MS (GC, 70eV): *m/z* (%) = 298 (M^+, 26), 283 (100), 141 (19).

HRMS (EI): Calcd for $C_{19}H_{16}F_2O$ (M^+) 298.11637. Found 298.116143.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 2186 (s), 1634 (m), 1589 (m), 1487 (s), 1419 (s), 1364 (s), 1312 (m), 1291 (m), 1252 (s), 1190 (m), 1154 (s), 1101 (m), 1037 (m), 1010 (m), 914 (m), 884 (w), 823 (s), 778 (m), 753 (s), 702 (m), 654 (m), 564 (s).

1-(2,5-difluorophenyl)-3-p-tolylprop-2-yn-1-one (3.2.2d).



Starting from 2,5-difluorobenzoyl chloride **3.2.1b** (1.765 g, 10 mmol), 1-ethynyl-4-methylbenzene (2.054 g, 13 mmol) and TEA (1.508 g, 15 mmol) in 40 mL THF. **3.2.2d** was isolated as yellow oil (2.150 g, 84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3H, Me), 7.11-7.29 (m, 4H, CH_{Ar}), 7.54-7.57 (m, 2H, CH_{Ar}), 7.72-7.78 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -117.3 (d, *J* = 18.3 Hz, CF), -117.1 (d, *J* = 18.3 Hz, CF).

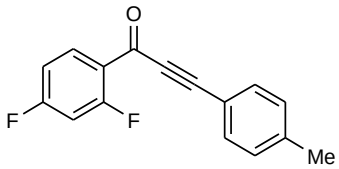
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.8 (Me), 88.2 (C), 94.7 (d, ^{4}J = 3.5 Hz, C), 116.7 (C), 117.4 (dd, ^{2}J = 24.2 Hz, ^{4}J = 1.7 Hz, CH), 118.5 (dd, ^{2}J = 25.0 Hz, ^{3}J = 8.4 Hz, CH), 122.1 (dd, ^{2}J = 23,9 Hz, ^{3}J = 9.5 Hz, CH), 126.5-126.7 (C), 129.5, 133.4 (CH), 142.0 (C), 158.1 (d, ^{1}J = 256.6 Hz, CF), 158.2 (d, ^{1}J = 253.6 Hz, CF), 172.8 (C).

MS (GC, 70eV): *m/z* (%) = 256 (M^+, 67), 228 (48), 207 (13), 143 (100), 63 (22).

HRMS (ESI): Calcd for $C_{16}H_{11}F_2O$ (M+H) 257.07725. Found 257.07736.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922 (w), 2187 (s), 1615 (m), 1582 (m), 1483 (m), 1420 (s), 1316 (m), 1925 (m), 1246 (s), 1191 (m), 1150 (s), 1108 (m), 1039 (m), 911 (m), 895 (m), 812 (s), 768 (m), 737 (s), 658 (m).

1-(2,4-difluorophenyl)-3-p-tolylprop-2-yn-1-one (3.2.2e).



Starting from 2,4-difluorobenzoyl chlorideloride **3.2.1c** (1.765 g, 10 mmol), 1-ethynyl-4-methylbenzene (2.054 g, 13 mmol) and TEA (1.508 g, 15 mmol) in 40 mL THF. **3.2.2e** was isolated as yellow oil (2.483 g, 97%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3H, Me), 7.11-7.29 (m, 4H, CH_{Ar}), 7.54-7.57 (m, 2H, CH_{Ar}), 7.72-7.78 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -106.0 (d, *J* = 13.1 Hz, CF), -99.7 (d, *J* = 13.1 Hz, CF).

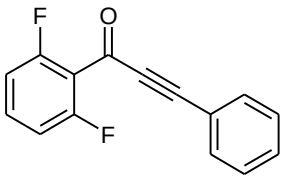
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.7 (Me), 88.2 (C), 94.0 (d, ^{4}J = 3.5 Hz, C), 105.2 (t, ^{2}J = 22.6 Hz, CH), 111.86 (dd, ^{2}J = 22.0 Hz, ^{4}J = 3.9 Hz, CH), 116.8 (C), 122.5 (dd, ^{3}J = 7.6 Hz, ^{4}J = 3.6 Hz, C), 129.5, 133.2 (CH), 133.7 (dd, ^{3}J = 11.2 Hz, ^{4}J = 1.8 Hz, CH), 141.8 (C), 163.0 (dd, ^{1}J = 264.7 Hz, ^{4}J = 12.6 Hz, CF), 166.2 (d, ^{1}J = 258.2 Hz, ^{4}J = 11.7 Hz, CF), 172.7 (C).

MS (GC, 70eV): *m/z* (%) = 256 (M^+, 93), 228 (95), 207 (16), 143 (100), 113 (23), 63 (28).

HRMS (ESI): Calcd for $C_{16}H_{11}F_2O$ (M+H) 257.07725. Found 257.07696.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2198 (s), 1629 (m), 1601 (s), 1495 (m), 1426 (m), 1307 (s), 1267 (s), 1231 (m), 1198 (m), 1179 (m), 1104 (s), 1028 (m), 967 (m), 852 (s), 811 (s), 746 (s), 666 (m), 594 (s).

1-(2,6-difluorophenyl)-3-phenylprop-2-yn-1-one (3.2.2f).



Starting from 2,6-difluorobenzoyl chlorideloride **3.2.1d** (1.765 g, 10 mmol), 1-ethynylbenzene (1.326 g, 13 mmol) and TEA (1.508 g, 15 mmol) in 40 mL THF. **3.2.2f** was isolated as yellow oil (1.694 g, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.79-6.84 (m, 2H, CH_{Ar}), 7.18-7.33 (m, 4H, CH_{Ar}), 7.41-7.44 (m, 2H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.0 (CF).

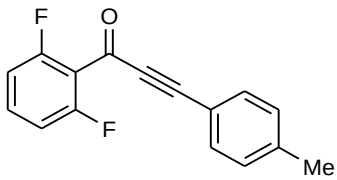
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 89.2 (C), 93.4 (C), 112.3 (dd, ^{2}J = 22.4 Hz, ^{4}J = 3.4 Hz, 2xCH), 116.0, 117.6 (C), 128.7 (CH), 131.1 (C), 133.3 (CH), 133.7 (t, ^{3}J = 11.3 Hz, CH), 161.0 (d, ^{1}J = 259.8 Hz, ^{4}J = 5.9 Hz, CF), 171.3 (C).

MS (GC, 70eV): *m/z* (%) = 242 (M^+, 44), 214 (100), 129 (59).

HRMS (EI): Calcd for $C_{15}H_8F_2O$ (M^+) 242.05377. Found 242.053779.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3060 (w), 2193 (s), 1641 (s), 1619 (s), 1489 (w), 1464 (s), 1302 (m), 1288 (m), 1236 (m), 1202 (m), 1068 (w), 1031 (m), 1002 (s), 990 (s), 818 (w), 793 (s), 754 (s), 685 (s), 591 (w), 571 (s), 535 (m).

1-(2,6-difluorophenyl)-3-*p*-tolylprop-2-yn-1-one (3.2.2g).



Starting from 2,6-difluorobenzoyl chlorideloride **3.2.1d** (1.765 g, 10 mmol), 1-ethynyl-4-methylbenzene (2.054 g, 13 mmol) and TEA (1.508 g, 15 mmol) in 40 mL THF. **3.2.2g** was isolated as yellow oil (1.868 g, 73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (s, 3H, Me), 6.75-6.80 (m, 2H, CH_{Ar}), 6.97-7.05 (m, 2H, CH_{Ar}), 7.20-7.32 (m, 3H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.0 (CF).

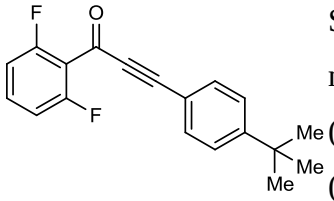
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.8 (Me), 89.2 (C), 94.2 (d, ^{4}J = 2.9 Hz, C), 112.1-112.5 (m, 2xCH), 116.7 (C), 117.7 (t, J = 15.0 Hz, C), 129.4 (CH), 132.0 (d, ^{2}J = 42.2 Hz, C), 133.4 (CH), 133.6 (d, ^{3}J = 10.7 Hz, CH), 142.0 (C), 160.8 (dd, ^{1}J = 258.4 Hz, ^{4}J = 5.9 Hz, CF), 171.3 (C).

MS (GC, 70eV): *m/z* (%) = 256 (M^+, 81), 228 (88), 143 (100).

HRMS (ESI): Calcd for $C_{16}H_{11}F_2O$ (M+H) 257.07725. Found 257.07721.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3032 (w), 2189 (s), 1643 (s), 1619 (s), 1508 (m), 1302(s), 1236 (s), 1202 (m), 1177 (m), 1067 (w), 1027 (m), 994 (s), 815 (s), 793 (s), 755 (w), 725 (m), 687 (w), 572 (m).

3-(4-tert-butylphenyl)-1-(2,6-difluorophenyl)prop-2-yn-1-one (3.2.2h).



Starting from 2,6-difluorobenzoyl chlorideloride **3.2.1d** (1.765 g, 10 mmol), 1-tert-butyl-4-ethynylbenzene (2.054 g, 13 mmol) and TEA (1.508 g, 15 mmol) in 40 mL THF. **3.2.2h** was isolated as yellow oil (2.384 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 9H, *t*-Bu), 6.95-7.01 (m, 2H, CH_{Ar}), 7.39-7.48 (m, 3H, CH_{Ar}), 7.54-7.58 (m, 2H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.0 (CF).

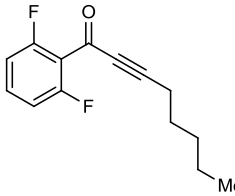
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 31.0 (*t*-Bu), 35.1, 89.2, 94.2 (C), 112.1-112.5 (m, 2xCH), 116.7 (C), 125.7, 133.2 (CH), 133.5 (d, J = 12.6 Hz, CH), 155.0 (C), 160.9 (d, ^{1}J = 258.5 Hz, ^{4}J = 5.7 Hz, CF), 171.4 (C).

MS (GC, 70eV): *m/z* (%) = 298 (M^+, 30), 283 (100), 227(12), 141 (23).

HRMS (EI): Calcd for $C_{19}H_{16}FO$ (M^+) 298.11637. Found 298.116627.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 2191 (s), 1644 (s), 1619 (s), 1504 (w), 1465 (s), 1364 (w), 1302 (s), 1237 (s), 1205 (m), 1109 (w), 1067 (w), 1026 (s), 994 (s), 835 (s), 793 (s), 688 (m), 564 (s).

1-(2,6-difluorophenyl)oct-2-yn-1-one (3.2.2i).



Starting from 2,6-difluorobenzoyl chlorideloride **3.2.1d** (1.765 g, 10 mmol), hept-1-yne (1.248 g, 13 mmol) and TEA (1.508 g, 15 mmol) in 40 mL THF. **3.2.2i** was isolated as yellow oil (1.652 g, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, 3H, ^3J = 7.2 Hz, CH_3CH$_2$), 1.28-1.45 (m, 4H, 2xCH_2), 1.56-1.66 (m, 2H, CH_2), 2.42 (t, 2H, ^3J = 7.1 Hz, CCH_2), 6.94 (t, 2H, ^3J = 8.4 Hz, CH_{Ar}), 7.37-7.44 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.4 (CF).

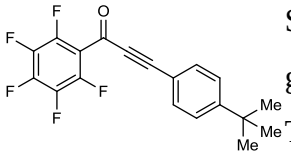
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.9 (CH_3), 20.9, 27.5, 28.1, 47.1 (CH_2), 89.2, 94.2, 116.7 (C), 117.7 (t, ^3J = 15.0 Hz, C), 132.0 (d, ^4J = 3.1 Hz, C), 133.4 (CH), 142.0 (C), 161.0 (d, ^1J = 258.9 Hz, ^4J = 5.7 Hz, CF), 171.3 (C).

MS (GC, 70eV): *m/z* (%) = 236 (M^+, 1), 180 (17), 151 (21), 141 (100), 113 (17).

HRMS (EI): Calcd for $C_{14}H_{14}F_2O$ (M^+) 236.10127. Found 236.10129.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2932 (w), 2862 (s), 2206 (m), 1650 (s), 1619 (s), 1466 (s), 1280 (m), 1252 (s), 1233 (s), 1121 (w), 1009 (s), 915 (w), 870 (w), 794 (s), 758 (w), 690 (w), 570 (m).

3-(4-tert-butylphenyl)-1-(perfluorophenyl)prop-2-yn-1-one (3.2.2j).



Starting from 2,3,4,5,6-pentafluorobenzoyl chlorideloride **3.2.1e** (2.305 g, 10 mmol), 1-tert-butyl-4-ethynylbenzene (2.054 g, 13 mmol) and TEA (1.508 g, 15 mmol) in 40 mL THF. **3.2.2j** was isolated as yellow solid (2.640 g, 75%), mp 127-129 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 9H, *t*-Bu), 7.33-7.52 (m, 4H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -162.1 (CF), -153.3 (t, ^3J = 19.5 Hz, CF), -136.3 (CF), -136.2 (CF).

^{13}C NMR (62.9 MHz, $CDCl_3$):δ = 31.1 (t-Bu), 34.9 (d, ^4J = 2.8 Hz, C), 73.5, 81.5 (C), 118.7 (d, ^3J = 19.7 Hz, CF), 125.5 (d, ^4J = 5.0 Hz, CH), 131.9 (d, ^3J = 35.8 Hz, CH), 152.9 (d, ^3J = 36.6 Hz, C).

MS (GC, 70eV): *m/z* (%) = 352 (M^+, 100).

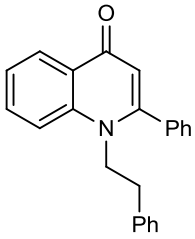
HRMS (EI): Calcd for $C_{19}H_{13}F_5O$ (M^+) 352.08866. Found 352.08870.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961 (w), 1524 (m), 1498 (s), 1392 (w), 1363 (m), 1267 (w), 1116 (m), 1060 (m), 1017 (w), 987 (s), 964 (s), 835 (s), 771 (w), 736 (w), 651 (w), 561 (s).

*A.2.17. General procedure for the synthesis of compounds **3.2.3-3.2.7**.*

The 1-(2-fluorophenyl)prop-2-yn-1-one derivative **3.2.2a-i** (1 equiv.), corresponding amine (2 equiv.) and Li_2CO_3 (2 equiv.) were placed in a pressure tube or in the Schlenk flask under the flow of dry argon and dissolved in dry DMA (7 mL/1 mmol of **3.2.2**). The mixture was heated at 160 °C for 24-30 h (controlled by TLC). After the reaction was completed volatiles were evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (Heptane : Ethyl acetate - 3:1). Preparation of compounds **3.2.10a-d** were performed according this procedure.

2-phenyl-1-(3-phenylpropyl)quinolin-4(1*H*)-one (3.2.3a).



Starting from 1-(2-fluorophenyl)-3-phenylprop-2-yn-1-one **3.2.3a** (0.224 g, 1 mmol), 2-phenylethanamine (0.242 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.3a** was isolated as yellow solid (0.289 g, 89%), mp 145-146 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.92 (t, 2H, ^3J = 7.6 Hz, $(CH_2)_2$), 4.28 (t, 2H, ^3J = 7.6 Hz, $(CH_2)_2$), 6.25 (s, 1H, CH_{Ar}), 6.72-6.76 (m, 2H, CH_{Ar}), 7.15-7.20 (m, 5H, CH_{Ar}), 7.41-7.51 (m, 4H, CH_{Ar}), 7.66-7.79 (m, 2H, CH_{Ar}), 8.55 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.2 Hz, CH_{Ar}).

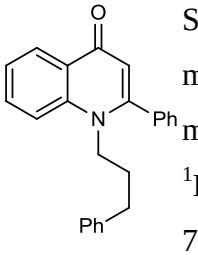
^{13}C NMR (62.9 MHz, $CDCl_3$):δ = 34.8, 49.4 (CH_2), 112.8, 116.2, 123.8, 127.0, 128.3, 128.5, 128.7, 128.8, 129.4, 132.5 (CH), 135.7, 136.8, 140.4, 154.9, 177.1 (C).

MS (GC, 70eV): *m/z* (%) = 325 (M^+, 31), 234 (100), 132 (18).

HRMS (EI): Calcd for $C_{23}H_{19}NO$ (M^+) 325.14612. Found 325.14617.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1616 (m), 1589 (s), 1553 (s), 1483 (m), 1416 (m), 1368 (w), 1311 (m), 1268 (m), 1174 (m), 1143 (m), 1074 (w), 1003 (w), 862 (w), 776 (m), 755 (s), 704 (s), 669 (m), 557 (m).

2-phenyl-1-(3-phenylpropyl)quinolin-4(1*H*)-one (3.2.3b).



Starting from 1-(2-fluorophenyl)-3-phenylprop-2-yn-1-one **3.2.3a** (0.224 g, 1 mmol), 3-phenylpropan-1-amine (0.270 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.3b** was isolated as yellow viscous oil (0.292 g, 86%).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.93-2.03 (m, 2H, $(CH_2)_3$), 2.46 (t, 2H, ^3J = 7.6 Hz, $(CH_2)_3$), 3.96-4.01 (m, 2H, $(CH_2)_3$), 6.23 (s, 1H, CH_{Ar}), 6.97-7.00 (m, 2H, CH_{Ar}), 7.14-7.48 (m, 10H, CH_{Ar}), 7.56-7.62 (m, 1H, CH_{Ar}), 8.49 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.5 Hz, CH_{Ar}).

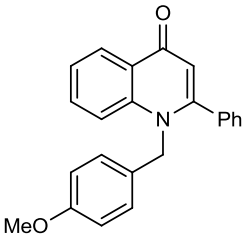
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 29.8, 32.6, 47.5 (CH_2), 112.8, 116.1, 123.7, 126.3, 127.0, 128.1, 128.2, 128.5, 128.8, 129.5, 132.3 (CH), 135.8, 139.8, 140.5, 154.6, 177.0 (C).

MS (GC, 70eV): *m/z* (%) = 339 (M^+, 35), 375 (41), 361 (100), 243 (42), 91 (41).

HRMS (ESI): Calcd for $C_{24}H_{21}NO$ (M^+) 339.16177. Found 339.16188.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2937 (w), 1625 (s), 1594 (s), 1484 (m), 1463 (m), 1417 (s), 1299 (m), 1265 (m), 1212 (w), 1172 (m), 1078 (w), 1029 (w), 912 (w), 835 (s), 778 (m), 759 (s), 697 (s), 672 (s), 623 (m), 547 (m).

1-(4-methoxybenzyl)-2-phenylquinolin-4(1*H*)-one (3.2.3c).



Starting from 1-(2-fluorophenyl)-3-phenylprop-2-yn-1-one **3.2.3a** (0.224 g, 1 mmol), (4-methoxyphenyl)methanamine (0.274 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.3c** was isolated as yellow solid (0.292 g, 86%), mp 209-210 ^oC.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3H, OMe), 5.20 (s, 2H, CH_2), 6.33 (s, 1H, CH_{Ar}), 6.78-6.81 (m, 2H, CH_{Ar}), 6.87-6.90 (m, 2H, CH_{Ar}), 7.30-7.42 (m, 7H, CH_{Ar}), 7.48-7.54 (m, 1H, CH_{Ar}), 8.50 (dd, 1H, ^3J = 8.7 Hz, ^4J = 1.5 Hz, CH_{Ar}).

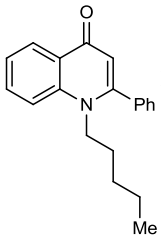
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 51.7 (OMe), 55.2 (CH_2), 113.0, 114.4, 117.4, 123.7, 126.6, 126.7 (CH), 127.2 (C), 128.1, 128.6, 129.6, 132.3 (CH), 135.6, 141.1, 155.1, 159.0, 177.5 (C).

MS (GC, 70eV): *m/z* (%) = 341 (M^+, 7), 121 (100).

HRMS (EI): Calcd for $C_{23}H_{19}NO_2$ (M^+) 341.14103. Found 341.14099.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1623 (m), 1598 (s), 1514 (s), 1487 (s), 1429 (m), 1361 (w), 1313 (m), 1251 (s), 1176 (s), 1143 (m), 1034 (m), 960 (m), 833 (s), 806 (m), 760 (s), 703 (s).

1-pentyl-2-phenylquinolin-4(1*H*)-one (3.2.3d).



Starting from 1-(2-fluorophenyl)-3-phenylprop-2-yn-1-one **3.2.3a** (0.224 g, 1 mmol), pentyl amine (0.170 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.3d** was isolated as yellow oil (0.244 g, 84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.73 (t, 3H, ^3J = 7.0 Hz, *Me*$(CH_2)_3CH_2$), 1.03-1.13 (m, 4H, $Me(CH_2)_3CH_2$), 1.57-1.67 (m, 2H, $Me(CH_2)_3CH_2$), 3.95 (t, 2H, ^3J = 8.0 Hz, $Me(CH_2)_3CH_2$), 6.19 (s, 1H, CH_{Ar}), 7.31-7.36 (m, 3H, CH_{Ar}), 7.43-7.51 (m, 4H, CH_{Ar}), 7.61-7.67 (m, 1H, CH_{Ar}), 8.46 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.6 Hz, CH_{Ar}).

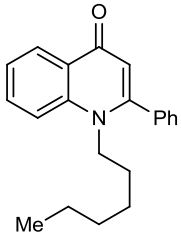
^{13}C NMR (75.5 MHz, $CDCl_3$):δ = 12.9 (Me), 20.9, 27.5, 28.1, 47.1 (CH_2), 111.7, 115.3, 122.5, 125.9 (CH), 126.3 (C), 127.2, 127.7 (CH), 128.1 (C), 128.4, 131.2 (CH), 135.0, 139.6, 153.5, 176.3 (C).

MS (GC, 70eV): *m/z* (%) = 291 (M^+, 50), 234 (100), 132 (17).

HRMS (EI): Calcd for $C_{20}H_{21}NO$ (M^+) 291.16177. Found 291.16171.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927 (m), 2863 (m), 1618 (s), 1595 (s), 1480 (s), 1422 (m), 1308 (m), 1267 (m), 1177 (m), 1080 (m), 963 (w), 835 (s), 756 (s), 703 (s), 668 (m).

1-hexyl-2-phenylquinolin-4(1*H*)-one (3.2.3e).



Starting from 1-(2-fluorophenyl)-3-phenylprop-2-yn-1-one **3.2.3a** (0.224 g, 1 mmol), hexyl amine (0.198 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.3e** was isolated as yellow oil (0.271 g, 89%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79 (t, 3H, ^3J = 7.2 Hz, *Me*$(CH_2)_4CH_2$), 1.06-1.20 (m, 6H, Me(C*H*$_2$)$_4$ CH_2), 1.60-1.68 (m, 2H, Me(C*H*$_2$)$_4$$CH_2$), 4.00 (t, 2H, ^3J = 8.0 Hz, Me$(CH_2)_4$C*H*$_2$), 6.27 (s, 1H, CH_{Ar}), 7.36-7.42 (m, 3H, CH_{Ar}), 7.46-7.54 (m, 4H, CH_{Ar}), 7.66-7.71 (m, 1H, CH_{Ar}), 8.51 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.6 Hz, CH_{Ar}).

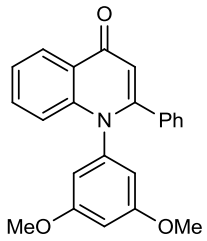
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.8 (CH_3), 22.2, 26.0, 28.6, 30.9, 48.2 (CH_2), 112.7, 116.2, 123.6, 127.0 (CH), 127.2 (C), 128.3, 128.7, 129.4, 132.2 (CH), 136.0, 140.5, 154.7, 177.0 (C).

MS (GC, 70eV): *m/z* (%) = 305 (M^+, 56), 234 (100), 132 (17).

HRMS (EI): Calcd for $C_{21}H_{23}NO$ (M^+) 305.17742. Found 305.17731.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3044 (w), 2927 (m), 1617 (m), 1594 (s), 1570 (m), 1479 (s), 1421 (m), 1306 (m), 1266 (m), 1177 (m), 1138 (m), 1035 (w), 923 (w), 835 (s), 758 (s), 703 (s), 668 (m), 550 (m).

1-(3,5-dimethoxyphenyl)-2-phenylquinolin-4(1*H*)-one (3.2.3f).



Starting from 1-(2-fluorophenyl)-3-phenylprop-2-yn-1-one **3.2.3a** (0.224 g, 1 mmol), 3,5-dimethoxybenzenamine (0.306 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.3f** was isolated as yellow solid (0.264 g, 74%), mp 216-218 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.66 (s, 6H, 2xOMe), 6.10 (s, 1H, CH_{Ar}), 6.47 (t, 1H, ^4J = 2.1 Hz, CH_{Ar}), 6.64 (d, 2H, ^4J = 2.4 Hz, CH_{Ar}), 6.99 (d, 1H, ^3J = 8.6 Hz, CH_{Ar}), 7.25-7.29 (m, 3H, CH_{Ar}), 7.38-7.43 (m, 3H, CH_{Ar}), 7.58-7.64 (m, 1H, CH_{Ar}), 8.25 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.4 Hz, CH_{Ar}).

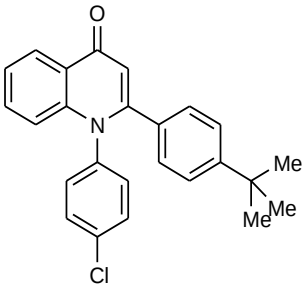
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 55.5 (OMe), 100.8, 108.6, 111.2, 118.3, 123.6, 125.1 (CH), 125.4 (C), 127.6, 128.6, 129.0, 132.2 (CH), 133.0, 135.5, 140.3, 142.1, 153.8, 160.7, 176.0 (C).

MS (GC, 70eV): *m/z* (%) = 357 (M^+, 100), 329 (42).

HRMS (EI): Calcd for $C_{23}H_{19}NO_3$ (M^+) 357.13594. Found 357.136003.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3035 (w), 2197 (w), 1628 (m), 1590 (s), 1462 (s), 1417 (s), 1359 (m), 1314 (m), 1264 (m), 1205 (s), 1150 (s), 1053 (s), 927 (m), 891 (w), 830 (m9, 773 (m), 754 (s), 712 (s), 639 (w).

2-(4-tert-butylphenyl)-1-(4-chlorophenyl)quinolin-4(1*H*)-one (5g).



Starting from 3-(4-tert-butylphenyl)-1-(2-fluorophenyl)prop-2-yn-1-one **3.2.3b** (0.280 g, 1 mmol), 4-chlorobenzenamine (0.254 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.3g** was isolated as yellow oil (0.291 g, 75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 9H, *t*-Bu), 6.42 (s, 1H, CH_{Ar}), 6.87 (d, 1H, ^3J = 8.6 Hz, CH_{Ar}), 7.04-7.11 (m, 4H, CH_{Ar}), 7.20-7.22 (m, 2H, CH_{Ar}), 7.32-7.50 (m, 4H, CH_{Ar}), 8.50 (dd, 1H, ^3J = 8.1 Hz, ^4J = 1.3 Hz, CH_{Ar}).

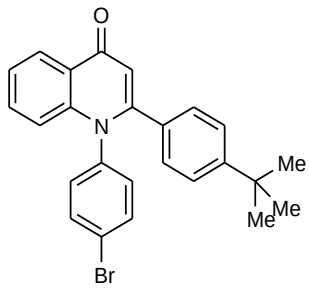
^{13}C NMR (62.9 MHz, $CDCl_3$):δ = 31.1 (*t*-Bu), 34.6 (C), 112.8, 117.7, 123.9, 125.0, 126.4, 128.9, 129.8, 131.3, 131.9 (CH), 132.4, 134.8, 137.8, 142.5, 152.1, 153.9, 178.1 (C).

MS (GC, 70eV): *m/z* (%) = 387 (M^+, 100), 372 (46), 344 (20).

HRMS (EI): Calcd for $C_{25}H_{22}ClNO$ (M^+) 387.13844. Found 387.138553.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 1631 (s), 1603 (s), 1557 (w), 1505 (m), 1489 (s), 1408 (m), 1318 (m), 1269 (m), 1137 (w), 1081 (m), 1023 (m), 970 (w), 833 (s), 742 (s), 666 (m), 638 (m), 548 (m).

2-(4-tert-butylphenyl)-1-(4-bromophenyl)quinolin-4(1*H*)-one (3.2.3h).



Starting from 3-(4-tert-butylphenyl)-1-(2-fluorophenyl)prop-2-yn-1-one **3.2.3b** (0.280 g, 1 mmol), 4-bromobenzenamine (0.344 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.3h** was isolated as brown solid (0.315 g, 73%), mp 245-246 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 9H, *t*-Bu), 6.49 (s, 1H, CH_{Ar}), 6.88 (d, 1H, ^3J = 8.9 Hz, CH_{Ar}), 7.02-7.07 (m, 4H, CH_{Ar}), 7.20-7.23 (m, 2H, CH_{Ar}), 7.35-7.51 (m, 4H, CH_{Ar}), 8.50 (dd, 1H, ^3J = 7.9 Hz, ^4J = 1.2 Hz, CH_{Ar}).

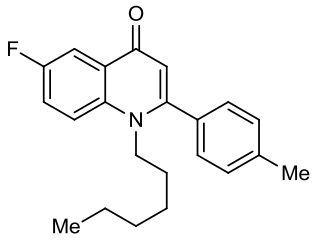
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 31.1 (*t*-Bu), 34.6 (C), 112.7, 117.7 (CH), 122.9 (C), 124.1, 125.0, 126.4, 128.9, 131.6, 132.1, 132.8 (CH), 138.3, 152.2, 154.2, 172.7, 177.6, 186.6 (C).

MS (GC, 70eV): *m/z* (%) = 433 (M^+, 100), 431 (99), 416 (36), 388 (17), 309 (11), 207 (15).

HRMS (EI): Calcd for $C_{25}H_{22}BrNO$ (M^+) 431.08793. Found 431.087506.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 1630 (s), 1602 (s), 1505 (w), 1486 (s), 1469 (m), 1408 (m), 1363 (w), 1318 (m), 1269 (m), 1137 (w), 1068 (w), 1020 (m), 670 (w), 876 (w), 832 (s), 744 (s), 730 (m), 637 (m).

6-fluoro-1-hexyl-2-p-tolylquinolin-4(1*H*)-one (3.2.4a).



Starting from 1-(2,5-difluorophenyl)-3-p-tolylprop-2-yn-1-one **3.2.3d** (0.256 g, 1 mmol), pentyl amine (0.170 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.4a** was isolated as white solid (0.286 g, 85%), mp 181-182 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.77 (t, 3H, ^3J = 7.3 Hz, *Me*$(CH_2)_4CH_2$), 1.07-1.18 (m, 6H, Me(C*H*$_2)_4CH_2$), 1.59-1.64 (m, 2H, Me(C*H*$_2)_4CH_2$), 2.42 (s, 3H, Me), 3.99 (t, 2H, ^3J = 8.2 Hz, Me$(CH_2)_4$C*H*$_2$), 6.16 (s, 1H, CH_{Ar}), 7.22-7.29 (m, 4H, CH_{Ar}), 7.74-7.41 (m, 1H, CH_{Ar}), 7.49-7.53 (m, 1H, CH_{Ar}), 8.10 (dd, 1H, ^3J = 9.0 Hz, ^4J = 3.0 Hz,CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -118.8 (CF).

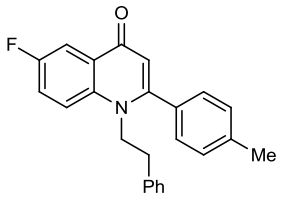
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.8, 21.3 (Me), 22.3, 26.9, 28.6, 29.6, 48.4 (CH_2), 111.4 (d, ^2J = 22.5 Hz, CH), 112.2 (CH), 118.6 (d, ^3J = 8.1 Hz, CH), 120.5 (d, ^2J = 27 Hz, CH), 128.1 (CH), 128.8 (d, ^3J = 7.0 Hz, C), 129.4 (CH), 132.9, 137.1, 139.6, 154.8 (C), 158.9 (d, ^1J = 244.3 Hz, CF), 176.3 (C).

MS (GC, 70eV): *m/z* (%) = 337 (M^+, 52), 266 (100), 150 (18).

HRMS (EI): Calcd for $C_{22}H_{24}FNO$ (M^+) 337.18419. Found 337.18421.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3470 (m), 2928 (m), 1597 (s), 1564 (s), 1510 (m), 1471 (s), 1397 (m), 1299 (m), 1255 (w), 1205 (w), 1160 (m), 1115 (w), 1007 (w), 936 (m), 892 (m), 846 (s), 821 (s), 710 (m), 617 (m).

6-fluoro-1-phenethyl-2-p-tolylquinolin-4(1*H*)-one (3.2.4b).



Starting from 1-(2,5-difluorophenyl)-3-p-tolylprop-2-yn-1-one **3.2.3d** (0.256 g, 1 mmol), 2-phenylethanamine (0.242 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.4b** was isolated as yellow oil (0.314 g, 88%).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3H, Me), 2.90 (t, 2H, ^3J = 7.5 Hz, $(CH_2)_2$), 4.28 (t, 2H, ^3J = 7.5 Hz, $(CH_2)_2$), 6.16 (s, 1H, CH_{Ar}), 6.73-6.76 (m, 2H, CH_{Ar}), 7.03-7.06 (m, 2H,

CH_{Ar}), 7.15-7.22 (m, 5H, CH_{Ar}), 7.43-7.49 (m, 1H, CH_{Ar}), 7.62-7.67 (m, 1H, CH_{Ar}), 8.18 (dd, 1H, ^3J = 8.9 Hz, ^4J = 3.1 Hz, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -117.8 (CF).

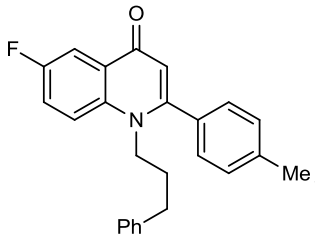
^{13}C NMR (62.9 MHz, $CDCl_3$):δ = 21.4 (Me), 34.5, 49.5 (CH_2), 111.8 (d, ^2J = 21.4 Hz, CH), 112.3 (CH), 118.5 (d, ^3J = 7.6 Hz, CH), 120.8 (d, ^2J = 25.5 Hz, CH), 127.0, 128.1, 128.5, 128.8 (CH), 129.0 (d, ^2J = 40 Hz, C), 132.7, 136.7, 137.0, 139.6, 155.0 (C), 159.0 (d, ^1J = 247.9 Hz, CF), 176.3 (C).

MS (GC, 70eV): *m/z* (%) = 357 (M^+, 1), 234 (100).

HRMS (EI): Calcd for $C_{24}H_{20}FNO$ (M^+) 357.15289. Found 357.15290.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1633 (m), 1613 (s), 1510 (m), 1479 (s), 1396 (m), 1350 (w), 1295 (m), 1203 (w), 1155 (m), 1063 (w), 1002 (w), 930 (m), 898 (m), 832 (s), 806 (m), 779 (m), 746 (m), 729 (m), 698 (m).

6-fluoro-1-(3-phenylpropyl)-2-p-tolylquinolin-4(1*H*)-one (3.2.4c).



Starting from 1-(2,5-difluorophenyl)-3-p-tolylprop-2-yn-1-one **3.2.3d** (0.256 g, 1 mmol), 3-phenylpropan-1-amine (0.270 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.4c** was isolated as white solid (0.308 g, 83%), mp 163-165 ^{o}C.

H NMR (300 MHz, $CDCl_3$): δ = 1.84-1.92 (m, 2H, $(CH_2)_3$), 2.35-2.41 (m, 5H, Me, $(CH_2)_3$), 3.88-3.94 (m, 2H, $(CH_2)_3$), 6.08 (s, 1H, CH_{Ar}), 6.89-6.92 (m, 2H, CH_{Ar}), 7.07-7.21 (m, 8H, CH_{Ar}), 7.56-7.62 (m, 1H, CH_{Ar}), 8.02 (dd, 1H, ^3J = 9.0 Hz, ^4J = 2.6 Hz, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -118.1 (CF).

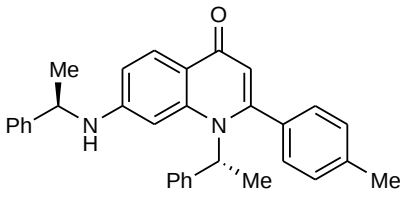
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.4 (Me), 29.9, 31.5, 46.6 (CH_2), 110.4 (d, ^2J = 23.1 Hz, CH), 111.2 (CH), 117.4 (d, ^4J = 7.2 Hz, CH), 119.1 (d, ^2J = 25.4 Hz, CH), 125.3, 127.0, 127.2, 127.5 (CH), 127.8 (d, ^2J = 27.5 Hz, C), 128.4 (CH), 131.7, 136.0 (C), 138.7 (d, ^3J = 13.1 Hz, CH), 153.7 (C), 157.9 (d, ^1J = 247.8 Hz, CF), 175.3 (C).

MS (GC, 70eV): *m/z* (%) = 371 (M^+, 77), 266 (100), 253 (19), 150 (20), 91 (27).

HRMS (EI): Calcd for $C_{25}H_{22}FNO$ (M^+) 371.16854. Found 371.16856.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2919 (w), 1634 (s), 1604 (s), 1576 (m), 1510 (m), 1470 (s), 1394 (m), 1295 (m), 1244 (w), 1201 (m), 1145 (s), 1055 (w), 975 (w), 930 (m), 888 (s), 833 (s), 822 (s), 746 (s), 700 (s), 561 (m).

7-((R)-1-phenylethylamino)-1-((R)-1-phenylethyl)-2-p-tolylquinolin-4(1*H*)-one (3.2.5).



Starting from 1-(2,4-difluorophenyl)-3-p-tolylprop-2-yn-1-one **3.2.3e** (0.256 g, 1 mmol), (*R*)-1-phenylethanamine (0.274 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.5** was isolated as yellow solid (0.151 g, 33%), mp 163-165 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.43 (t, 6H, ^3J = 6.3 Hz, CH*Me*), 2.27 (s, 3H, Me), 4.38-4.55 (m, 2H, C*H*Me), 5.63 (d, 1H, ^4J = 1.7 Hz, CH_{Ar}), 5.99 (dd, 1H, ^3J = 14.2 Hz, ^4J = 2.2 Hz, CH_{Ar}), 6.26 (dd, 1H, ^3J = 8.7 Hz, ^4J = 2.2 Hz, CH_{Ar}), 7.04-7.24 (m, 14H, CH_{Ar}), 7.64 (t, 1H, ^3J = 8.7 Hz, CH_{Ar}), 11.58 (d, 1H, ^3J = 9.5 Hz, NH).

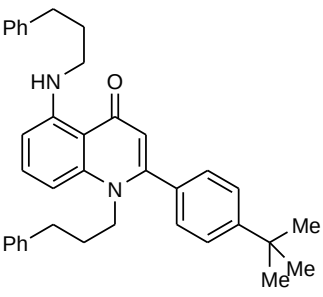
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.3, 24.5, 24.9 (Me), 53.2, 54.0 (CH), 98.0 (d, *J* = 10.0 Hz, CH), 99.4 (d, *J* = 30.3 Hz, CH), 109.3 (C), 117.3 (d, *J* = 11.3 Hz, CH), 125.7, 126.7, 127.2, 127.7, 128.5, 128.7, 128.8 (CH), 131.6 (d, *J* = 5.1 Hz, CH), 131.7 (d, *J* = 11.4 Hz, CH), 133.2, 139.2, 144.0, 144.5 (C), 150.9 (d, *J* = 10.7 Hz, C), 160.4, 162.4 (d, *J* = 249.3 Hz, C), 184.8 (C).

MS (GC, 70eV): *m/z* (%) = 458 (M^+, 19), 353 (100).

HRMS (EI): Calcd for $C_{32}H_{30}N_2O$ (M^+) 458.59341. Found 458.59344.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3312 (w), 2969 (w), 1621 (w), 1575 (s), 1556 (s), 1488 (m), 1447 (m), 1318 (s), 1238 (s), 1205 (m), 1106 (s), 975 (w), 908 (w), 823 (m), 783 (m), 759 (m), 696 (s).

5-(3-phenylpropylamino)-2-(4-tert-butylphenyl)-1-(3-phenylpropyl)quinolin-4(1*H*)-one (3.2.6a).



Starting from 3-(4-tert-butylphenyl)-1-(2,6-difluorophenyl)prop-2-yn-1-one **3.2.3h** (0.298 g, 1 mmol), 3-phenylpropan-1-amine (0.270 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.6a** was isolated as yellow solid (0.433 g, 82%), mp 215-216 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 9H, *t*-Bu), 1.97-2.12 (m, 4H, CH_2), 2.45 (t, 2H, ^3J = 7.5 Hz, CH_2), 2.81 (t, 2H, ^3J = 7.5 Hz, CH_2), 3.22 (t, 2H, ^3J = 6.4 Hz, CH_2), 3.91 (t, 2H, ^3J = 8.0 Hz, CH_2), 6.07 (s, 1H, CH_{Ar}), 6.29-6.36 (m, 2H, CH_{Ar}), 7.00-7.02 (m, 2H, CH_{Ar}), 7.16-7.31 (m, 11H, CH_{Ar}), 7.44-7.47 (m, 2H, CH_{Ar}), 10.47 (s, 1H, NH).

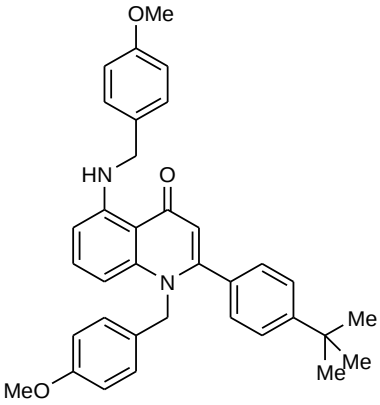
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 29.3, 30.2 (CH_2), 31.2 (*t*-Bu), 32.6, 33.3 (CH_2), 34.7 (C), 42.0, 48.0 (CH_2), 100.2, 101.9, 112.5 (CH), 113.2 (C), 125.5, 125.7, 126.1, 127.9, 128.1, 128.3, 128.4, 128.5 (CH), 132.9 (C), 133.3 (CH), 140.2, 141.7, 143.2, 152.1, 152.3, 153.0, 180.8 (C).

MS (GC, 70eV): *m/z* (%) = 528 (M^+, 33), 437 (42), 423 (100), 305 (17), 91 (50).

HRMS (ESI): Calcd for $C_{37}H_{41}N_2O$ (M+H) 529.32134. Found 529.32191.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2951 (w), 1617 (s), 1520 (m), 1450 (s), 1386 (w), 1264 (s), 1167 (s), 1121 (w), 1015 (w), 909 (w), 840 (m), 740 (s), 697 (s), 563 (m).

1-(4-methoxybenzyl)-5-(4-methoxybenzylamino)-2-(4-tert-butylphenyl)quinolin-4(1*H*)-one (3.2.6b).



Starting from 3-(4-tert-butylphenyl)-1-(2,6-difluorophenyl)prop-2-yn-1-one **3.2.3h** (0.298 g, 1 mmol), (4-methoxyphenyl)methanamine (0.274 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.6b** was isolated as yellow solid (0.452 g, 85%), mp 192-193 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 9H, *t*-Bu), 3.76 (s, 3H, OMe), 3.78 (s, 3H, OMe), 4.40 (s, 2H, CH_2), 5.12 (s, 2H, CH_2), 6.23-6.38 (m, 3H, CH_{Ar}), 6.79-6.93 (m, 6H, CH_{Ar}), 7.15-7.25 (m, 3H, CH_{Ar}), 7.30-7.37 (m, 4H, CH_{Ar}), 10.76 (s, 1H, NH).

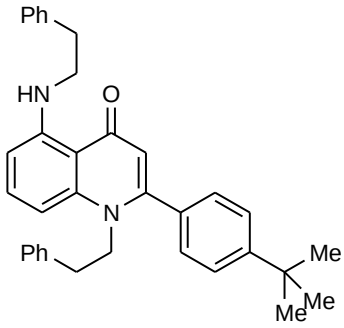
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 31.2 (*t*-Bu), 34.8 (C), 46.6, 52.4 (CH_2), 55.2, 55.3 (OMe), 102.4, 103.1 (CH), 112.6 (C), 113.2, 114.0, 114.2 (CH), 125.5, 126.8, 127.9, 128.3 (CH), 128.6, 130.9, 132.6 (C), 133.4 (CH), 143.6, 151.5, 152.7, 154.0, 158.6, 158.8, 180.8 (C).

MS (GC, 70eV): *m/z* (%) = 532 (M^+, 8), 411 (47), 121 (100).

HRMS (EI): Calcd for $C_{35}H_{36}N_2O_3$ (M^+) 532.27204. Found 532.272902.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955 (w), 1614 (s), 1504 (s), 1447 (s), 1360 (w), 1244 (s), 1170 (s), 1110 (m), 1030 (m), 925 (w), 814 (m), 740 (m), 676 (m), 561 (m).

2-(4-tert-butylphenyl)-1-phenethyl-5-(phenethylamino)quinolin-4(1*H*)-one (3.2.6c).



Starting from 3-(4-tert-butylphenyl)-1-(2,6-difluorophenyl)prop-2-yn-1-one **3.2.3h** (0.298 g, 1 mmol), 2-phenylethanamine (0.242 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.6c** was isolated as yellow solid (0.465 g, 93%), mp 185-187 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.35 (s, 9H, *t*-Bu), 2.49-2.51 (m, 2H, CH_2), 2.80-2.85 (m, 2H, CH_2), 2.94 (t, 2H, ^3J = 7.0 Hz, CH_2), 3.37-3.46 (m, 2H, CH_2), 4.07 (t, 2H, ^3J = 8.1 Hz, CH_2), 6.47 (d, 1H, ^3J = 8.5 Hz, CH_{Ar}), 6.71-6.74 (m, 2H, CH_{Ar}), 6.90 (d, 1H, ^3J = 8.5 Hz, CH_{Ar}), 7.14-7.36 (m, 11H, CH_{Ar}), 7.47-7.54 (m, 4H, CH_{Ar}), 10.4 (t, 1H, ^3J = 5.1 Hz, NH).

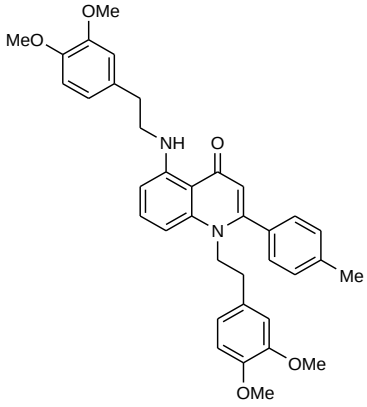
^{13}C NMR due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 500 (M^+, 3), 409 (100), 289 (14), 105 (35).

HRMS (ESI): Calcd for $C_{35}H_{37}N_2O$ (M+H) 501.29004. Found 501.29016.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 1635 (m), 1614 (m), 1585 (m), 1464 (m), 1401 (m), 1328 (w), 1257 (w), 1197 (m), 1153 (s), 1122 (m), 1057 (m), 837 (s), 794 (w), 752 (m), 711 (m), 664 (m), 583 (m).

1-(3,4-dimethoxyphenethyl)-5-(3,4-dimethoxyphenethylamino)-2-p-tolylquinolin-4(1*H*)-one (3.2.6d).



Starting from 1-(2,6-difluorophenyl)-3-p-tolylprop-2-yn-1-one **3.2.3h** (0.256 g, 1 mmol), 2-(3,4-dimethoxyphenyl)ethanamine (0.362 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.6d** was isolated as yellow solid (0.491 g, 85%), mp 85-87 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3H, Me), 2.81 (t, 2H, ^3J = 7.4 Hz, CH_2), 2.95-2.99 (m, 2H, CH_2), 3.40-3.46 (m, 2H, CH_2), 3.65 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.11 (t, 2H, ^3J = 7.4 Hz, CH_2), 5.95 (s, 1H, CH_{Ar}), 6.10 (d, 1H, ^4J = 2.0 Hz, CH_{Ar}), 6.32 (dd, 1H, ^3J = 8.2 Hz, ^4J = 1.7 Hz, CH_{Ar}), 6.38 (d, 1H, ^3J = 8.3 Hz, CH_{Ar}), 6.61-6.67 (m, 2H, CH_{Ar}), 6.79-6.87 (m, 3H, CH_{Ar}), 6.98 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.19 (d, 2H, ^3J = 7.4 Hz, CH_{Ar}), 7.42 (t, 1H, ^3J = 8.3 Hz, CH_{Ar}), 10.51 (s, 1H, NH).

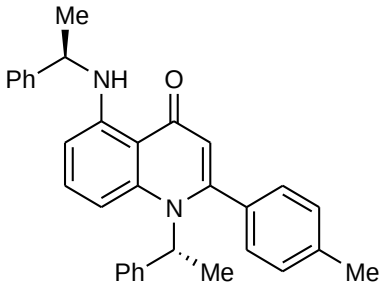
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.1 (Me), 33.6, 34.9, 44.9, 49.7 (CH_2), 55.4, 55.6, 55.7, 55.8 (OMe), 110.3, 101.9, 111.1, 111.2, 111.4, 112.0 (CH), 112.5 (C), 113.0, 120.5, 128.2, 128.9 (CH), 129.4, 132.2, 132.9 (C), 133.3 (CH), 138.8, 143.0, 147.4, 147.7, 148.7, 148.8, 151.9, 152.9, 180.7 (C).

MS (GC, 70eV): *m/z* (%) = 578 (M^+, 3), 427 (100), 165 (85).

HRMS (ESI): Calcd for $C_{36}H_{39}N_2O_5$ (M+H) 579.28535. Found 579.2862.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2932 (w), 1616 (m), 1590 (m), 1505 (s), 1447 (m), 1257 (m), 1234 (s), 1138 (s), 1025 (s), 910 (w), 827 (m), 806 (m), 763 (m), 726 (m), 637 (m).

5-((*R*)-1-phenylethylamino)-1-((*R*)-1-phenylethyl)-2-p-tolylquinolin-4(1*H*)-one (3.2.6e).



Starting from 1-(2,6-difluorophenyl)-3-p-tolylprop-2-yn-1-one **3.2.3h** (0.256 g, 1 mmol), (*R*)-1-phenylethanamine (0.274 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.6e** was isolated as yellow solid (0.183 g, 40%), mp 123-125 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.54 (d, 3H, ^3J = 6.7 Hz, CH*Me*), 1.78 (d, 3H, ^3J = 6.7 Hz, CH*Me*), 2.30 (s, 3H, Me), 4.43 (q, 1H, ^3J = 6.7 Hz, C*H*Me), 5.68 (q, 1H, ^3J = 6.7 Hz, C*H*Me), 5.94 (d, 1H, ^3J = 8.5 Hz, CH_{Ar}), 6.07 (d, 1H, ^3J = 8.5 Hz, CH_{Ar}), 6.11 (s, 1H, CH_{Ar}), 6.80 (t, 1H, ^3J = 8.5 Hz, CH_{Ar}), 7.07-7.34 (m, 14H, CH_{Ar}), 10.81 (s, 1H, NH).

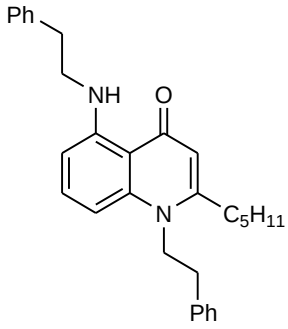
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.3, 21.3, 25.0 (Me), 53.1, 58.9 (CH), 103.5, 105.3, 113.5, 125.1, 126.0, 126.7, 127.0, 127.5, 128.5, 128.7, 129.5, 132.0 (CH), 133.6, 139.5, 140.5, 141.8, 145.2, 150.9, 154.2, 181.0 (C).

MS (GC, 70eV): *m/z* (%) = 458 (M^+, 19), 443 (22), 353 (100), 207 (28), 105 (19).

HRMS (EI): Calcd for $C_{32}H_{30}N_2O$ (M^+) 458.23527. Found 458.235207.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2966 (w), 1616 (s), 1519 (m), 1505 (s), 1445 (s), 1377 (m), 1339 (w), 1267 (m), 1216 (m), 1159 (s), 1019 (w), 827 (m), 744 (m), 697 (s).

2-pentyl-1-phenethyl-5-(phenethylamino)quinolin-4(1*H*)-one (3.2.6f).



Starting from 1-(2,6-difluorophenyl)oct-2-yn-1-one **3.2.3i** (0.236 g, 1 mmol), 2-phenylethanamine (0.242 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.6f** was isolated as yellow oli (0.359 g, 82%).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.78-0.83 (m, 3H, $CH_2(CH_2)_3$*Me*), 1.17-1.26 (m, 4H, $CH_2(CH_2)_3$Me), 1.46-1.51 (m, 2H, $CH_2(CH_2)_3$Me), 2.29 (t, 2H, ^3J = 6.5 Hz, $CH_2(CH_2)_3$Me), 2.92-2.97 (m, 4H, CH_2CH_2), 3.36 (t, 2H, ^3J = 7.3 Hz, CH_2CH_2), 4.13 (t, 2H, ^3J = 7.3 Hz, CH_2CH_2), 5.92 (s, 1H, CH_{Ar}), 6.28 (d, 1H, ^3J = 8.7 Hz, CH_{Ar}), 6.53 (d, 1H, ^3J = 8.7 Hz, CH_{Ar}), 7.04-7.34 (m, 11H, CH_{Ar}), 10.44 (s, 1H, NH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.8 (Me), 22.3, 28.2, 31.3, 33.3, 34.4, 35.4, 44.8, 47.5 (CH_2), 99.8, 101.7, 111.4 (CH), 112.2 (C), 126.2, 127.0, 128.4, 128.6, 128.7, 128.9, 133.2 (CH), 137.5, 139.6, 143.4, 151.9, 152.6, 181.2 (C).

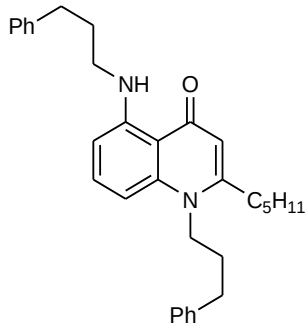
MS (GC, 70eV): *m/z* (%) = 438 (M^+, 4), 347 (100), 105 (42).

HRMS (ESI): Calcd for $C_{30}H_{35}N_2O$ (M+H) 439.27439. Found 439.27482.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2943 (w), 2865 (w), 1626 (s), 1596 (s), 1554 (m), 1516 (m), 1453 (w), 1365 (w), 1264 (s), 1208 (w), 1172 (m), 1080 (w), 1029 (w), 854 (w), 828 (m), 750 (m), 738

(m), 696 (s), 628 (m).

5-(3-phenylpropylamino)-2-pentyl-1-(3-phenylpropyl)quinolin-4(1*H*)-one (3.2.6g).



Starting from 1-(2,6-difluorophenyl)oct-2-yn-1-one **3.2.3i** (0.236 g, 1 mmol), 3-phenylpropan-1-amine (0.270 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.6g** was isolated as yellow oli (0.350 g, 75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88-0.93 (m, 3H, $CH_2(CH_2)_3$*Me*), 1.26-1.29 (m, 4H, $CH_2(CH_2)_3$Me), 1.49-1.59 (m, 2H, $CH_2(CH_2)_3$Me), 2.00-2.09 (m, 4H, $CH_2(CH_2)_3$Me, $(CH_2)_3$), 2.38-2.43 (m, 2H, $(CH_2)_3$), 2.74-2.83 (m, 4H, $(CH_2)_3$), 3.19 (t, 2H, ^3J = 6.6 Hz, $(CH_2)_3$), 3.95 (m, 2H, $(CH_2)_3$), 6.03 (s, 1H, CH_{Ar}), 6.25 (d, 1H, ^3J = 8.2 Hz, CH_{Ar}), 6.33 (d, 1H, ^3J = 8.6 Hz, CH_{Ar}), 7.16-7.37 (m, 11H, CH_{Ar}), 10.47 (s, 1H, NH).

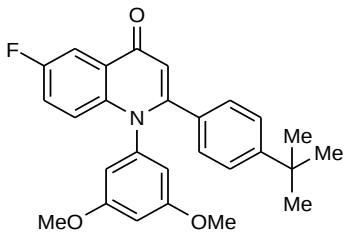
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.8 (Me), 22.3, 28.5, 29.4, 30.3, 31.3, 32.7, 33.2, 33.3, 42.0, 45.6 (CH_2), 99.5, 101.5, 111.3 (CH), 112.1 (C), 125.7, 126.5, 128.2, 128.3, 128.5, 128.6, 133.0 (CH), 140.1, 141.7, 143.6, 152.0, 152.5, 181.2 (C).

MS (GC, 70eV): *m/z* (%) = 466 (M^+, 35), 375 (41), 361 (100), 243 (42), 91 (41).

HRMS (ESI): Calcd for $C_{32}H_{39}N_2O$ (M+H) 467.30569. Found 467.30601.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927 (w), 2857 (w), 1616 (s), 1594 (s), 1557 (m), 1518 (s), 1451 (s), 1370 (w), 1267 (s), 1170 (s), 1029 (w), 910 (w), 837 (w), 739 (s), 697 (s), 620 (m).

2-(4-tert-butylphenyl)-6-fluoro-1-(3,5-dimethoxyphenyl)quinolin-4(1*H*)-one (3.2.7a).



Starting from 3-(4-tert-butylphenyl)-1-(2,6-difluorophenyl)prop-2-yn-1-one **3.2.3c** (0.298 g, 1 mmol), 3,5-dimethoxybenzenamine (0.306 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.7a** was isolated as yellow solid (0.332 g, 77%), mp 121-122 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 9H, *t*-Bu), 3.67 (s, 6H, 2xOMe), 6.29 (q, 2H, ^4J = 2.3 Hz, CH_{Ar}), 6.38-6.40 (m, 2H, CH_{Ar}), 7.04-7.24 (m, 6H, CH_{Ar}), 8.10 (dd, 1H, ^3J = 8.9 Hz, ^4J = 3.0 Hz, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -117.8 (CF).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 31.1 (*t*-Bu), 34.6 (C), 55.6 (2xOMe), 101.1, 108.3 (CH), 110.3 (d, ^2J = 22.4 Hz, CH_{Ar}), 111.8 (CH_{Ar}), 120.1-120.6 (m, CH_{Ar}), 124.8 (CH_{Ar}), 127.4 (d, ^4J = 7.0 Hz, C), 128.6 (CH_{Ar}), 132.5, 138.8, 140.5, 152.0, 154.0, 159.2 (d, ^1J = 245.7 Hz,

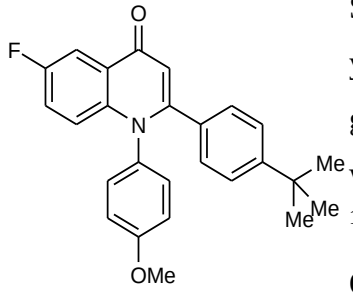
CF), 177.0 (C).

MS (GC, 70eV): *m/z* (%) = 431 (M^+, 100), 416 (42).

HRMS (ESI): Calcd for $C_{27}H_{27}FNO_3$ (M+H) 432.19695. Found 432.19788.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961 (w), 1611 (s), 1579 (s), 1506 (w), 1456 (s), 1427 (m), 1386 (m), 1290 (m), 1252 (m), 1193 (m), 1152 (s), 1057 (m), 1012 (w), 930 (m), 834 (s), 700 (m), 603 (m).

2-(4-tert-butylphenyl)-6-fluoro-1-(4-methoxyphenyl)quinolin-4(1*H*)-one (3.2.7b).



Starting from 3-(4-tert-butylphenyl)-1-(2,6-difluorophenyl)prop-2-yn-1-one **3.2.3c** (0.298 g, 1 mmol), 4-methoxybenzenamine (0.246 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.7b** was isolated as white solid (0.313 g, 78%), mp 185-186 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 9H, *t*-Bu), 3.78 (s, 3H, OMe), 6.42 (s, 1H, CH_{Ar}), 6.83-6.86 (m, 2H, CH_{Ar}), 6.90-6.95 (m, 2H, CH_{Ar}), 7.01-7.08 (m, 4H, CH_{Ar}), 7.14-7.21 (m, 2H, CH_{Ar}), 8.10 (dd, 1H, ^3J = 8.9 Hz, ^4J = 2.9 Hz, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -117.8 (CF).

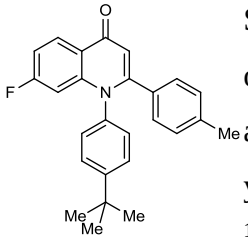
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 31.1 (*t*-Bu), 34.6 (C), 55.5 (OMe), 110.6 (d, ^3J = 19.8 Hz, CH), 114.7, 120.1 (CH), 120.5 (d, ^4J = 7.4 Hz, CH), 124.8, 128.9, 130.8 (CH), 131.7, 132.5, 139.5, 151.8, 154.7, 159.2 (d, ^1J = 245.3 Hz, CF), 159.5, 176.9 (C).

MS (GC, 70eV): *m/z* (%) = 401 (M^+, 100), 386 (29), 358 (13).

HRMS (EI): Calcd for $C_{26}H_{24}FNO_2$ (M^+) 401.17856. Found 401.179009.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958 (w), 1609 (s), 1580 (m), 1505 (s), 1480 (s), 1391 (m), 1361 (m), 1294 (m), 1243 (s), 1173 (s), 1135 (m), 1084 (w), 1032 (m), 927 (m), 884 (m), 860 (w), 832 (s), 795 (s), 713 (w), 631 (m), 540 (s).

1-(4-tert-butylphenyl)-7-fluoro-2-p-tolylquinolin-4(1*H*)-one (3.2.7c).



Starting from 3-(4-tert-butylphenyl)-1-(2,6-difluorophenyl)prop-2-yn-1-one **3.2.3e** (0.256 g, 1 mmol), 4-tert-butylbenzenamine (0.298 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.7c** was isolated as yellow solid (0.289 g, 75%), mp 218-220 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 9H, *t*-Bu), 2.24 (s, 3H, Me), 6.43 (s, 1H, CH_{Ar}), 6.59 (dd, 1H, ^3J = 11.2 Hz, ^4J = 2.2 Hz, CH_{Ar}), 6.94-7.10 (m, 7H, CH_{Ar}), 7.32-7.37 (m, 2H, CH_{Ar}), 8.46-8.52 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -105.5 (CF).

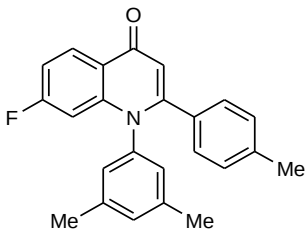
^{13}C NMR (62.9 MHz, $CDCl_3$):δ = 21.1 (Me), 31.2 (*t*-Bu), 34.8 (C), 104.2 (d, ^2J = 27.6 Hz, CH), 112.5 (d, ^2J = 22.3 Hz, CH), 112.7 (CH), 122.7 (C), 126.6, 128.5, 129.0, 129.1, 129.2 (CH), 132.5, 136.1, 138.7 (C), 144.2 (d, ^3J = 11.5 Hz, C), 152.5, 154.9 (C), 164.7 (d, ^1J = 249.5 Hz, CF), 177.1 (C).

MS (GC, 70eV): *m/z* (%) = 385 (M^+, 100), 370 (59).

HRMS (ESI): calcd for $C_{26}H_{25}FNO$ (M+H) 386.19147, found 386.1918.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963 (w), 1639 (s), 1601 (s), 1510 (s), 1449 (s), 1392 (s), 1306 (s), 1263 (m), 1175 (m), 1124 (w), 1083 (w), 1027 (w), 986 (w), 841 (s), 814 (s), 754 (w), 660 (w), 634 (w), 571 (m).

7-fluoro-1-(3,5-dimethylphenyl)-2-p-tolylquinolin-4(1*H*)-one (3.2.7d).



Starting from 3-(4-tert-butylphenyl)-1-(2,6-difluorophenyl)prop-2-yn-1-one **3.2.3e** (0.256 g, 1 mmol), 3,5-dimethylbenzenamine (0.242 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.7d** was isolated as yellow solid (0.282 g, 79%), mp 271-273 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 6H, 2xMe), 2.25 (s, 3H, Me), 6.37 (s, 1H, CH_{Ar}), 6.57 (dd, 1H, ^3J = 11.3 Hz, ^4J = 2.4 Hz, CH_{Ar}), 6.73 (s, 2H, CH_{Ar}), 6.94-7.08 (m, 6H, CH_{Ar}), 8.44-8.50 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -105.7 (CF).

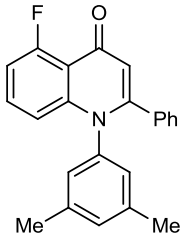
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.0, 21.2 (Me), 104.2 (d, ^2J = 27.1 Hz, CH), 112.4 (d, ^2J = 23.2 Hz, CH), 112.6 (CH), 122.7 (C), 127.2, 128.5, 128.9 (CH), 129.1 (d, ^3J = 10.6 Hz, CH), 130.7 (CH), 132.6 (C), 138.6 (d, ^4J = 2.6 Hz, C), 139.5 (C), 144.1 (d, ^3J = 11.3 Hz, C), 154.7 (C), 164.7 (d, ^1J = 250.8 Hz, CF), 177.2 (C).

MS (GC, 70eV): *m/z* (%) = 357 (M^+, 100), 329 (91), 150 (13).

HRMS (ESI): Calcd for $C_{24}H_{21}FNO$ (M+H) 358.16017. Found 358.16006.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2917 (w), 1633 (s), 1601 (s), 1511 (w), 1441 (s), 1386 (s), 1313 (m), 1261 (m), 1166 (m), 1125 (m), 1080 (w), 1021 (w), 951 (w), 848 (s), 819 (s), 763 (m), 709 (m), 640 (w), 596 (w).

5-fluoro-1-(3,5-dimethylphenyl)-2-phenylquinolin-4(1*H*)-one (3.2.7e).



Starting from 1-(2,6-difluorophenyl)-3-phenylprop-2-yn-1-one **3.2.3f** (0.242 g, 1 mmol), 3,5-dimethylbenzenamine (0.242 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.7e** was isolated as yellow solid (0.264 g, 77%), mp 132-133 ^oC.

^1H NMR (300 MHz, $CDCl_3$) δ = 2.21 (s, 6H, 2xMe), 6.36 (s, 1H, CH_{Ar}), 6.69-6.72 (m, 3H, CH_{Ar}), 6.91-6.98 (m, 2H, CH_{Ar}), 7.12-7.20 (m, 5H, CH_{Ar}), 7.30-7.37 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -112.1 (CF).

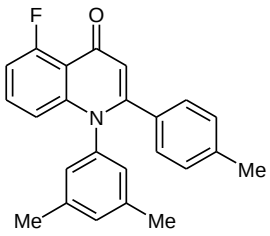
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21.0 (Me), 110.1 (d, ^2J = 17.4 Hz, CH), 114.1 (CH), 114.2 (d, ^4J = 4.6 Hz, CH), 116.2 (d, ^3J = 8.6 Hz, C), 127.3, 127.7, 128.6, 129.0, 130.5 (CH), 131.7 (d, ^3J = 10.3 Hz, C), 135.2, 138.9, 139.5 (C), 144.8 (d, ^4J = 3.8 Hz, C), 153.4 (C), 161.7 (d, ^1J = 259.4 Hz, CF), 176.8 (C).

MS (GC, 70eV): *m/z* (%) = 343 (M^+, 97), 315 (100), 299 (14).

HRMS (EI): Calcd for $C_{23}H_{18}FNO$ (M^+) 343.13669. Found 343.137067.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3047 (w), 1614 (s), 1471 (s), 1403 (s), 1307 (m), 1198 (w), 1120 (w), 1056 (m), 932 (w), 846 (M), 799 (m), 753 (s), 728 (m), 702 (s), 648 (m), 536 (m).

5-fluoro-1-(3,5-dimethylphenyl)-2-p-tolylquinolin-4(1*H*)-one (3.2.7f).



Starting from 1-(2,6-difluorophenyl)-3-p-tolylprop-2-yn-1-one **3.2.3g** (0.256 g, 1 mmol), 3,5-dimethylbenzenamine (0.242 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.7f** was isolated as yellow solid (0.253 g, 71%), mp 133-134 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.22 (s, 6H, 2xMe), 2.24 (s, 3H, Me), 6.32 (s, 1H, CH_{Ar}), 6.67-6.72 (m, 3H, CH_{Ar}), 6.89-7.03 (m, 6H, CH_{Ar}), 7.27-7.35 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -112.3 (CF).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.0, 21.1 (Me), 109.9 (d, ^2J = 21.5 Hz, CH), 114.2 (CH), 116.1 (d, ^3J = 7.2 Hz, CH), 127.3, 128.4, 128.9, 130.5 (CH), 131.5 (d, ^3J = 10.8 Hz, CH), 132.4, 138.5, 139.1, 139.4 (C), 144.8 (d, ^4J = 3.8 Hz, C), 153.5 (C), 161.8 (d, ^1J = 259.6 Hz, CF), 176.8 (C).

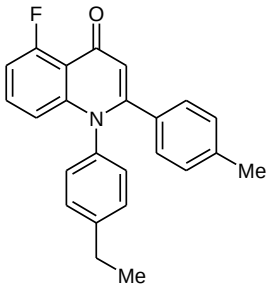
MS (GC, 70eV): *m/z* (%) = 357 (M^+, 79), 329 (100).

HRMS (ESI): Calcd for $C_{24}H_{21}FNO$ (M+H) 358.16017. Found 358.16034.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2917 (w), 1633 (s), 1614 (s), 1510 (w), 1471 (s), 1398 (s), 1305 (m), 1195 (w), 1116 (w), 1089 (w), 1056 (m), 933 (w), 830 (s), 795 (m), 752 (s), 726 (m), 666 (w),

602 (w).

1-(4-ethylphenyl)-5-fluoro-2-p-tolylquinolin-4(1*H*)-one (3.2.7g).



Starting from1-(2,6-difluorophenyl)-3-p-tolylprop-2-yn-1-one **3.2.3g** (0.256 g, 1 mmol), 4-ethylbenzenamine (0.242 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.7g** was isolated as yellow solid (0.250 g, 70%), mp 250-251 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, 3H, ^3J = 7.7 Hz, CH_2Me), 2.24 (s, 3H, Me), 2.62 (q, 2H, ^3J = 7.7 Hz, CH_2Me), 6.33 (s, 1H, CH_{Ar}), 6.66 (d, 1H, ^3J = 8.8 Hz, CH_{Ar}), 6.90-7.02 (m, 7H, CH_{Ar}), 7.14-7.17 (m, 2H, CH_{Ar}), 7.27-7.35 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.5 (CF).

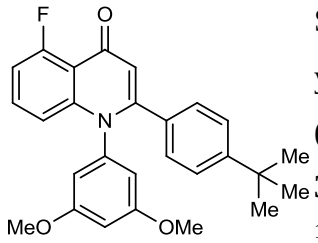
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.1 (CH_2Me), 21.1 (Me), 28.4 (CH_2Me), 110.0 (d, ^2J = 21.4 Hz, CH), 114.1 0 (d, ^4J = 4.4 Hz, CH), 114.3, 128.5, 129.0, 129.6 (CH), 131.6 (d, ^3J = 11.8 Hz, CH), 132.4, 136.9, 138.5 (C), 145.0 (d, ^4J = 3.8 Hz, C), 145.3, 153.6 (C), 161.8 (d, ^1J = 262.1 Hz, CF), 176.9 (C).

MS (GC, 70eV): *m/z* (%) = 357 (M^+, 94), 329 (100), 314 (18).

HRMS (ESI): Calcd for $C_{24}H_{21}FNO$ (M+H) 358.16017. Found 358.16061.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3057 (w), 2970 (w), 1633 (s), 1614 (s), 1511 (s), 1475 (s), 1407 (s), 1306 (m), 1253 (m), 1190 (w), 1122 (w), 1104 (w), 1037 (m), 920 (w), 857 (m), 831 (s), 789 (m), 747 (s), 650 (m), 598 (w).

2-(4-tert-butylphenyl)-5-fluoro-1-(3,5-dimethoxyphenyl)quinolin-4(1*H*)-one (3.2.7h).



Starting from 3-(4-tert-butylphenyl)-1-(2,6-difluorophenyl)prop-2-yn-1-one **3.2.3h** (0.298 g, 1 mmol), 3,5-dimethoxybenzenamine (0.306 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.7h** was isolated as yellow solid (0.315 g, 73%), mp 263-265 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (s, 9H, *t*-Bu), 3.65 (s, 6H, 2xOMe), 6.01 (s, 1H, CH_{Ar}), 6.47-6.48 (m, 1H, CH_{Ar}), 6.62-6.63 (m, 2H, CH_{Ar}), 6.78 (d, 1H, ^3J = 9.1 Hz, CH_{Ar}), 7.06-7.12 (m, 1H, CH_{Ar}), 7.28 (br. s, 4H, CH_{Ar}), 7.50-7.57 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -113.4.

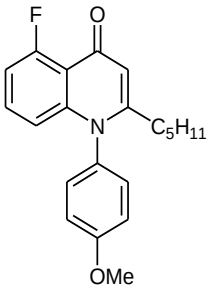
^{13}C NMR (62.9 MHz, $CDCl_3$):δ = 28.9 (*t*-Bu), 32.3 (C), 52.9, 53.6 (OMe), 99.0, 106.5 (CH), 107.7 (d, *J* = 21.4 Hz, CH), 111.1, 112.4 (CH), 113.4 (C), 122.4, 126-9, 130.3 (CH), 138.6 (C), 142.3 (d, *J* = 4.4 Hz, C), 149.1, 151.0, 157.0, 158.0, 160.5, 173.0 (C).

MS (GC, 70eV): *m/z* (%) = 431 (M^+, 100), 416 (20), 388 (19).

HRMS (ESI): calcd for $C_{27}H_{27}FNO_3$ (M+H) 432.19695, found 432.19743.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3003 (w), 1621 (s), 1558 (m), 1517 (m), 1504 (m), 1447 (s), 1365 (m), 1291 (m), 1257 (m), 1171 (m), 1122 (w), 1023 (w), 1000 (w), 842 (s), 742 (s), 660 (m), 565 (s).

5-fluoro-1-(4-methoxyphenyl)-2-pentylquinolin-4(1*H*)-one (3.2.7i).



Starting from 1-(2,6-difluorophenyl)oct-2-yn-1-one **3.2.3i** (0.236 g, 1 mmol), 4-methoxybenzenamine (0.146 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.7i** was isolated as yellow oil (0.244 g, 72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, 3H, ^3J = 6.7 Hz, CH_2Me), 1.15-1.20 (m, 4H, CH_2), 1.47-1.53 (m, 2H, CH_2), 2.24 (t, 2H, ^3J = 7.2 Hz, CCH_2), 3.91 (s, 3H, OMe), 6.33 (s, 1H, CH_{Ar}), 6.46 (d, 1H, ^3J = 8.5 Hz,CH_{Ar}), 6.87-6.93 (m, 1H, CH_{Ar}), 7.07-7.18 (m, 4H, CH_{Ar}), 7.23-7.31 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -112.2 (CF).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.8 (CH_2*Me*), 22.3, 27.9, 31.2, 33.5 (CH_2), 55.7 (OMe), 109.9 (d, ^2J = 23 Hz,CH), 111.7 (CH), 113.8 (d, ^4J = 5 Hz,CH), 115.5, 130.1 (CH), 131.2-131.5 (m, CH), 145.5, 154.9, 159.7, 162.0 (d, ^1J = 258.6 Hz,CH), 162.9, 176.9 (C).

MS (GC, 70eV): *m/z* (%) = 339 (M^+, 22), 296 (17), 283 (100), 268 (13), 121 (29).

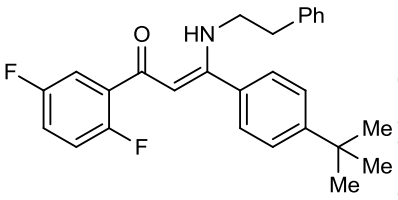
HRMS (EI): Calcd for $C_{22}H_{22}FNO_2$ (M^+) 339.16291. Found 339.162750.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923 (m), 1613 (s), 1507 (s), 1469 (s), 1408 (s), 1296 (m), 1235 (s), 1170 (m), 1107 (m), 1038 (s), 826 (m), 798 (m), 551 (m).

*A.2.18. General procedure for the synthesis of compounds **3.2.8**.*

Corresponding 1-(2-fluorophenyl)prop-2-yn-1-one derivative **3.2.2b,c** (1 equiv.) and Li_2CO_3 (2 equiv.) were placed in a pressure tube or in the Schlenk flask under the flow of dry argon and dissolved in dry DMA (7 mL/1 mmol of **3.2.2**). The mixture was heated at 100 °C for 15 h (controlled by TLC). After the reaction was completed volatiles were evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (Heptane : Ethyl acetate - 5:1).

(*Z*)-3-(4-tert-butylphenyl)-1-(2,5-difluorophenyl)-3-(phenethylamino)prop-2-en-1-one (3.2.8a).



Starting from 3-(4-tert-butylphenyl)-1-(2,5-difluorophenyl)prop-2-yn-1-one **3.2.3c** (0.298 g, 1 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.8a** was isolated as yellow oil (0.310 g, 74%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 9H, *t*-Bu), 2.85 (t, 2H, ^3J = 6.9 Hz, CH_2), 3.48 (m, 2H, CH_2), 5.66 (d, 1H, ^4J = 2.0 Hz, CHC), 6.95-7.01 (m, 2H, CH_{Ar}), 7.07-7.09 (m, 2H, CH_{Ar}), 7.16-7.25 (m, 5H, CH_{Ar}), 7.37-7.40 (m, 2H, CH_{Ar}), 7.49-7.54 (m, 1H, CH_{Ar}), 11.47 (s, 1H, NH).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -118.8 (d, ^3J = 18.6 Hz, CF), -118.1 (d, ^3J = 18.6 Hz, CF).

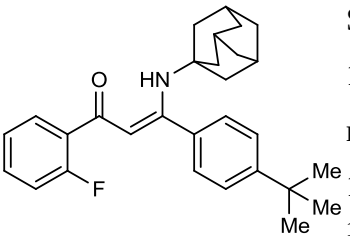
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 31.2 (Me), 34.7 (C), 37.3, 46.5 (CH_2), 97.5 (d, ^3J = 9.9 Hz, CH), 116.4 (dd, ^2J = 24.8 Hz, ^4J = 3.5 Hz, CH), 117.3 (dd, ^2J = 27.4 Hz, ^3J = 8.2 Hz, CH), 117.9 (dd, ^2J = 24.5 Hz, ^3J = 8.7 Hz, CH), 125.4, 126.6, 127.4, 128.5, 128.8 (CH), 130.3 (dd, ^3J = 16.0 Hz, ^4J = 6.5 Hz, C), 132.0, 138.1, 152.9, 156.2 (d, ^1J = 244.6 Hz, CF), 158.6 (d, ^1J = 240.0 Hz, CF), 167.6 (C), 182.8 (d, ^4J = 3.0 Hz, C).

MS (GC, 70eV): *m/z* (%) = 419 (M^+, 19), 328 (100), 272 (10), 141 (51).

HRMS (EI): Calcd for $C_{27}H_{27}F_2ON$ (M^+) 419.20552. Found 419.205681.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2948 (w), 1568 (m), 1538 (m), 1484 (m), 1456 (m), 1412 (m), 1364 (w), 1327 (m), 1288 (m), 1267 (m), 1246 (m), 1161 (m), 1143 (m), 1099 (m), 1065 (w), 1019 (w), 990 (w), 908 (w), 844 (m), 814 (s), 794 (m), 776 (m), 743 (s), 697 (s), 632 (m).

(*Z*)-3-(4-tert-butylphenyl)-1-(2-fluorophenyl)-3-(adeamantylamino)prop-2-en-1-one (3.2.8b).



Starting from 3-(4-tert-butylphenyl)-1-(2-fluorophenyl)prop-2-yn-1-one **3.2.3b** (0.280 g, 1 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.8b** was isolated as yellow solid (0.349 g, 81%), mp 116-118 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (s, 9H, *t*-Bu), 1.40-1.53 (m, 6H, Adamantyl), 1.73-1.74 (m, 6H, Adamantyl), 1.20 (br. s, 3H, Adamantyl), 6.92-6.99 (m, 1H, CH_{Ar}), 7.09 (dt, 1H, ^3J = 7.6 Hz, ^4J = 1.1 Hz, CH_{Ar}), 7.20-7.32 (m, 6H, CH_{Ar}), 7.76 (dt, 1H, ^3J = 7.7 Hz, ^4J = 1.9 Hz, CH_{Ar}), 11.68 (s, 1H, NH).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -112.3 (CF).

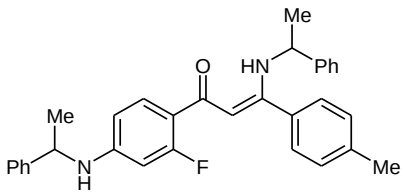
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 29.5 (CH), 31.3 (*t*-Bu), 34.7 (C), 35.9, 44.4 (CH_2), 55.2 (CH), 99.5 (C), 116.0 (d, ^2J = 24.6 Hz, CH), 123.9 (d, ^4J = 3.5 Hz, CH), 124.5, 127.8 (CH), 129.1 (d, ^3J = 13.7 Hz, C), 130.4 (d, ^4J = 3.0 Hz, CH), 131.4 (d, ^3J = 8.8 Hz, CH), 134.8,

152.2 (C), 160.3 (d, ^{1}J = 252.1 Hz, C), 167.3 (C), 183.8 (d, ^{4}J = 3.1 Hz, C).
MS (GC, 70eV): *m/z* (%) = 431 (M^{+}, 100), 374 (41), 336 (24), 308 (67), 252 (17), 123 (52).
HRMS (ESI): Calcd for $C_{29}H_{34}FNO$ (M+H) 432.26244. Found 432.27007.
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2904 (m), 1610 (m), 1583 (s), 1493 (m), 1477 (m), 1448 (m), 1398 (w), 1338 (s), 1299 (s), 1208 (m), 1150 (m), 1098 (m), 1086 (m), 1028 (m), 880 (w), 839 (m), 760 (s), 676 (w), 628 (w), 582 (m).

*A.2.19. General procedure for the synthesis of compounds **3.2.11a,b**.*

Corresponding 1-(2-fluorophenyl)prop-2-yn-1-one derivative **3.2.2e,g** (1 equiv.), appropriate amine (1 equiv.) and Li_2CO_3 (2 equiv.) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMA (7 mL/1 mmol of **3.2.2**). The mixture was heated at 160 °C for 10 h (controlled by TLC). After the reaction was completed volatiles were evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (Heptane : Ethyl acetate - 5:1).

(*Z*)-3-(1-phenylethylamino)-1-(2-(1-phenylethylamino)-4-fluorophenyl)-3-p-tolylprop-2-en-1-one (3.2.11a).



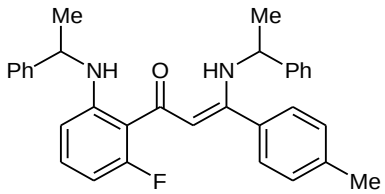
Starting from 1-(2,4-difluorophenyl)-3-p-tolylprop-2-yn-1-one **3.2.3e** (0.256 g, 1 mmol), (*R*)-(+)-(1-phenethyl)amine (0.121 g, 1 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.11a** was isolated as yellow solid (0.306 g, 64%), mp 174-176 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (d, 3H, ^{3}J = 6.8 Hz, CH*Me*), 1.54 (d, 3H, ^{3}J = 6.8 Hz, CH*Me*), 2.28 (s, 3H, Me), 4.39-4.54 (m, 2H, 2xC*H*Me), 5.54 (s, 1H, CH_{Ar}), 5.95-6.08 (m, 2H, CH_{Ar}), 7.06 (s, 4H, CH_{Ar}), 7.09-7.32 (m, 10H, CH_{Ar}), 7.47-7.52 (m, 1H, CH_{Ar}), 9.22 (s, 1H, NH), 11.19 (d, 1H, *J* = 10.2 Hz, NH).
^{19}F NMR (282 MHz, $CDCl_3$): δ = -107.0 (CF).
^{13}C NMR (62.9 MHz, $CDCl_3$):δ = 21.3, 24.6, 25.1 (Me), 53.0, 54.0 (CH), 95.1 (CH), 99.0 (d, ^{2}J = 25.0 Hz, CH), 101.5 (d, ^{2}J = 25.0 Hz, CH), 117.5 (C), 125.7, 125.8, 126.8, 126.9, 127.6, 128.6, 128.7, 128.9 (CH), 130.8 (d, *J* = 200.0 Hz, CH), 131.7 (d, *J* = 11.4 Hz, CH), 133.4, 139.2 (C), 144.7 (d, ^{3}J = 18.7 Hz, C), 151.4 (d, ^{3}J = 11.4 Hz, C), 165.0 (C), 165.5 (d, ^{1}J = 251.6 Hz, CF), 191.4 (C).
MS (GC, 70eV): *m/z* (%) = 478 (M^{+}, 3), 373 (84), 355 (18), 240 (100), 105 (74).

HRMS (ESI): Calcd for $C_{32}H_{32}N_2O$ (M+H) 479.24932. Found 479.24955.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3262 (w), 2968 (w), 1621 (w), 1594 (m), 1556 (s), 1507 (s), 1451 (s), 1371 (w), 1338 (m), 1303 (m), 1279 (m), 1191 (s), 1138 (m), 1105 (s), 1017 (m), 908 (w), 827 (m), 775 (s), 697 (s), 592 (m).

(*Z*)-3-(1-phenylethylamino)-1-(2-(1-phenylethylamino)-6-fluorophenyl)-3-p-tolylprop-2-en-1-one (3.2.11b).



Starting from 1-(2,6-difluorophenyl)-3-p-tolylprop-2-yn-1-one **3.2.3g** (0.256 g, 1 mmol), (*R*)-(+)-(1-phenethyl)amine (0.121 g, 1 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL DMA. **3.2.11b** was isolated as yellow solid (0.330 g, 69%), mp 154-156 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.52 (d, 6H, ^3J = 6.8 Hz, 2xCH*Me*), 2.30 (s, 3H, Me), 4.44-4.46 (m, 1H, C*H*Me), 4.54-4.64 (m, 1H, C*H*Me), 5.57 (d, 1H, ^3J = 4.6 Hz, NH), 6.07 (d, 1H, ^3J = 8.8 Hz, CH_{Ar}), 6.12-6.19 (m, 1H, CH_{Ar}), 6.81-6.88 (m, 1H, CH_{Ar}), 7.07-7.42 (m, 14H, CH_{Ar}), 7.86-7.91 (m, 1H, CH_{Ar}), 11.49 (d, 1H, *J* = 10.2 Hz, NH).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -108.9 (CF).

^{13}C NMR (62.9 MHz, $CDCl_3$): Due to bed solubility was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 478 (M^+, 2), 373 (87), 355 (31), 240 (100), 105 (100).

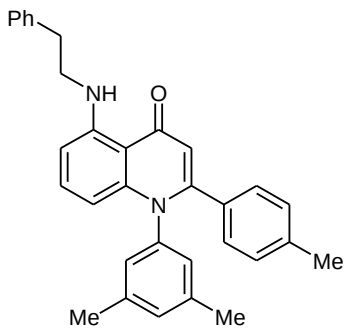
HRMS (ESI): Calcd for $C_{32}H_{32}FN_2O_5$ (M+H) 479.24932. Found 479.25022.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3342 (w), 2976 (w), 1613 (m), 1557 (s), 1489 (s), 1449 (s), 1412 (m), 1333 (s), 1267 (m), 1241 (m), 1205 (m), 1140 (m), 1085 (m), 1016 (m), 871 (w), 819 (m), 800 (s), 752 (s), 697 (s), 670 (m), 576 (m).

*A.2.20. General procedure for the synthesis of compounds **3.2.12**.*

Corresponding quinolone **3.2.3d,f,g** (1 equiv.), appropriate amine (2 equiv.) and Li_2CO_3 (2 equiv.) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMA (7 mL/1 mmol of **3.2.3**). The mixture was heated at 160 °C for 26 h (controlled by TLC). After the reaction was completed volatiles were evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (Heptane : Ethyl acetate - 2:1).

1-(3,5-dimethylphenyl)-5-(phenethylamino)-2-p-tolylquinolin-4(1*H*)-one (3.2.12a).



Starting from **3.2.7f** (0.150 g, 0.42 mmol), phenethylamine (0.101 g, 0.84 mmol) and Li_2CO_3 (0.062 g, 0.84 mmol) in 4 mL DMA. **3.2.12a** was isolated as yellow solid (0.187 g, 97%), mp 154 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 6H, 2xMe), 2.24 (s, 3H, Me), 3.05 (t, 2H, ^3J = 7.5 Hz, CH_2), 3.47 (t, 2H, ^3J = 7.5 Hz, CH_2), 5.88 (d, 1H, ^3J = 8.1 Hz, CH_{Ar}), 6.20 (s, 1H, CH_{Ar}), 6.33 (d, 1H, ^3J = 8.1 Hz, CH_{Ar}), 6.70 (s, 2H, CH_{Ar}), 6.88-7.03 (m, 5H, CH_{Ar}), 7.12-7.23 (m, 2 H, CH_{Ar}), 7.32-7.33 (m, 4H, CH_{Ar}), 10.38 (s, 1H, NH).

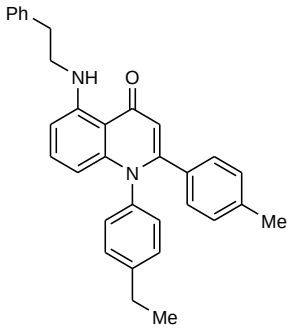
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.0, 21.2 (Me), 35.4, 44.9 (CH_2), 101.8, 103.0 (CH), 111.7 (C), 112.8, 126.3, 17.6, 128.3, 128.5, 128.8, 129.0, 130.0, 132.8, 132.9 (CH), 138.1, 139.0, 139.7, 145.5, 151.2, 152.5, 181.5 (C).

MS (GC, 70eV): *m/z* (%) = 458 (M^+, 3), 367 (100).

HRMS (ESI): Calcd for $C_{32}H_{31}N_2O$ (M+H) 459.24309. Found 459.24347.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3207 (w), 2831 (w), 1619 (s), 1586 (m), 1519 (m), 1505 (s), 1441 (s), 1382 (m), 1348 (m), 1307 (m), 1251 (s), 1182 (m), 1125 (s), 1024 (w), 839 (s), 746 (s), 697 (s), 658 (m), 586 (m).

1-(4-ethylphenyl)-5-(phenethylamino)-2-p-tolylquinolin-4(1*H*)-one (3.2.12b).



Starting from **3.2.7f** (0.150 g, 0.42 mmol), phenethylamine (0.101 g, 0.84 mmol) and Li_2CO_3 (0.062 g, 0.84 mmol) in 4 mL DMA. **3.2.12b** was isolated as yellow oil (0.162 g, 84%).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, 3H, ^3J = 7.6 Hz, *Me*CH_2), 2.24 (s, 3H, Me), 2.61 (q, 2H, ^3J = 7.6 Hz, MeC*H*$_2$), 3.05 (t, 2H, ^3J = 7.3 Hz, C*H*$_2$CH$_2$), 3.47 (t, 2H, ^3J = 7.3 Hz, C*H*$_2$CH$_2$), 5.87 (d, 1H, ^3J = 8.4 Hz, CH_{Ar}), 6.23 (s, 1H, CH_{Ar}), 6.34 (d, 1H, ^3J = 8.0 Hz, CH_{Ar}), 6.92-7.00 (m, 6H, CH_{Ar}), 7.11-7.23 (m, 4H, CH_{Ar}), 7.30-7.33 (m, 4H, CH_{Ar}), 10.39 (s, 1H, NH).

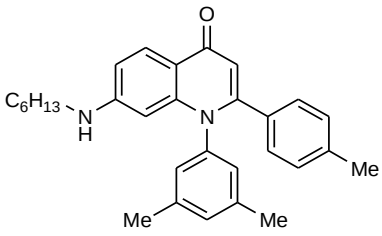
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.2 (*Me*CH_2), 21.2 (Me), 28.4, 35.4, 44.9 (CH_2), 102.0, 103.0, 111.7 (CH), 112.8 (C), 126.3, 128.4, 128.5, 128.7, 128.8, 129.1, 129.7 (CH), 132.9, 137.5, 138.2, 139.7, 144.7, 145.6, 151.2, 152.7, 181.4 (C).

MS (GC, 70eV): *m/z* (%) = 458 (M^+, 3), 367 (100).

HRMS (ESI): Calcd for $C_{32}H_{31}N_2O$ (M+H) 459.24309. Found 459.24349.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3214 (w), 2962 (w), 2865 (w), 1619 (m), 1504 (s), 1344 (w), 1267 (s), 1183 (m), 1021 (m), 851 (m), 816 (m), 740 (m), 698 (s), 565 (m).

5,7-(hexylamino)-1-(3,5-dimethylphenyl)-2-p-tolylquinolin-4(1*H*)-one (3.2.12c).



Starting from **3.2.7d** (0.150 g, 0.42 mmol), hexyl amine (0.084 g, 0.84 mmol) and Li_2CO_3 (0.062 g, 0.84 mmol) in 4 mL DMA. **3.2.12c** was isolated as yellow oil (0.146 g, 79%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84-0.91 (m, 3H, *Me*$(CH_2)_4CH_2$), 1.13-1.30 (m, 6H, Me$(CH_2)_4CH_2$), 1.43-1.50 (m, 2H, Me$(CH_2)_4CH_2$), 2.23 (s, 6H, 2xMe), 2.24 (s, 3H, Me), 2.91-3.00 (m, 2H, Me$(CH_2)_4CH_2$), 4.06 (br. s, 1H, NH), 5.80 (d, 1H, ^4J = 2.0 Hz, CH_{Ar}), 6.27 (s, 1H, CH_{Ar}), 6.62 (dd, 1H, ^3J = 8.7 Hz, ^4J = 2.0 Hz, CH_{Ar}), 6.74 (s, 2H, CH_{Ar}), 6.90-7.04 (m, 5H, CH_{Ar}), 8.25 (d, 1H, ^3J = 8.2 Hz, CH_{Ar}).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.9, 20.9, 21.1 (Me), 22.5, 26.6, 28.9, 31.5, 43.2 (CH_2), 96.9, 111.7 (CH), 117.4 (C), 127.4, 127.5, 128.2, 129.0, 130.0 (CH), 133.3, 138.0, 138.9, 139.3, 144.9, 151.2, 153.1 (C).

MS (GC, 70eV): *m/z* (%) = 438 (M^+, 54), 367 (100).

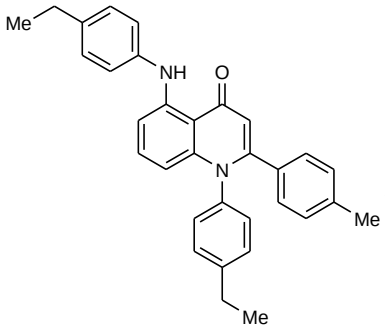
HRMS (ESI): Calcd for $C_{30}H_{35}N_2O$ (M+H) 439.27439. Found 439.27378.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3307 (w), 2922 (w), 1596 (s), 1556 (s), 1512 (m), 1441 (s), 1396 (m), 1296 (m), 1220 (m), 1148 (m), 1017 (m), 848 (m), 815 (m), 706 (m), 636 (m).

*A.2.21. General procedure for the synthesis of compounds **3.2.13**.*

Corresponding 1-(2-fluorophenyl)prop-2-yn-1-one derivative **3.2.2g,i** (1 equiv.), appropriate amine (2 equiv.) and Li_2CO_3 (2 equiv.) were placed in a pressure tube under the flow of dry argon and dissolved in dry NMP (7 mL/1 mmol of **3.2.2**). The mixture was heated at 185 °C for 35 h (controlled by TLC). After the reaction was completed volatiles were evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (Heptane : Ethyl acetate - 1:1).

5-(4-ethylphenylamino)-1-(4-ethylphenyl)-2-p-tolylquinolin-4(1*H*)-one (3.2.13a).



Starting from 1-(2,6-difluorophenyl)-3-p-tolylprop-2-yn-1-one **3.2.3h** (0.256 g, 1 mmol), 4-ethylphenyl amine (0.240 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL *N*-methyl-2-pyrrollidine. **3.2.13a** was isolated as yellow solid (0.362 g, 79%), mp 174-175 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.11-1.20 (m, 6H, 2x*Me*CH_2), 2.17 (s, 3H, Me), 2.51-2.61 (m, 4H, 2xMe*C*H_2), 5.91 (dd, 1H, ^3J = 8.4 Hz, ^4J = 0.8 Hz, CH_{Ar}), 6.22 (s, 1H, CH_{Ar}), 6.84-6.95 (m, 7H, CH_{Ar}), 7.00-7.12 (m, 5H, CH_{Ar}), 7.18-7.21 (m, 2H, CH_{Ar}), 11.99 (s, 1H, NH).

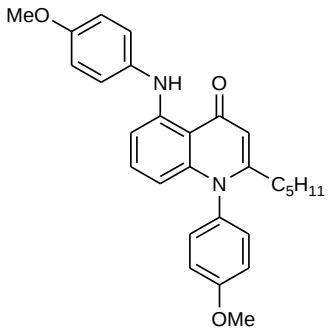
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.2, 15.7 (2x*Me*CH_2), 21.2 (Me), 28.3, 28.4 (2xMe*C*H_2), 104.5, 104.9 (CH), 112.7 (C), 128.5, 128.6, 128.8, 129.0, 129.7, 132.5 (CH), 132.7, 137.4, 138.4, 138.7, 139.5, 144.9, 145.6, 148.9, 153.2, 181.4 (C).

MS (GC, 70eV): *m/z* (%) = 458 (M^+, 100), 443 (38).

HRMS (ESI): Calcd for $C_{32}H_{31}N_2O$ (M+H) 459.24309. Found 459.24294.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960 (w), 1623 (m), 1591 (s), 1564 (m), 1504 (m), 1441 (s), 1376 (w), 1342 (w), 1274 (s), 1176 (m), 1112 (w), 1038 (w), 1018 (w), 844 (s), 819 (s), 751 (m), 721 (m), 636 (m).

5-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-2-pentylquinolin-4(1*H*)-one (3.2.13b).



Starting from 1-(2,6-difluorophenyl)oct-2-yn-1-one **3.2.3i** (0.236 g, 1 mmol), 4-methoxyphenyl amine (0.244 g, 2 mmol) and Li_2CO_3 (0.148 g, 2 mmol) in 7 mL *N*-methyl-2-pyrrollidine. **3.2.13b** was isolated as yellow oil (0.338 g, 80%).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.75 (t, 3H, ^3J = 7.0 Hz, *Me*CH_2), 1.09-1.18 (m, 4H, CH_2), 1.40-1.45 (m, 2H, CH_2), 2.15 (t, 2H, ^3J = 7.7 Hz, CCH_2), 3.73 (s, 3H, OMe), 3.83 (s, 3H, OMe), 5.67 (dd, 1H, ^3J = 8.4 Hz, ^4J = 0.8 Hz, CH_{Ar}), 6.13 (s, 1H, CH_{Ar}), 6.60 (dd, 1H, ^3J = 8.3 Hz, ^4J = 0.8 Hz, CH_{Ar}), 6.81-6.85 (m, 2H, CH_{Ar}), 6.92-7.01 (m, 3H, CH_{Ar}), 7.05-7.09 (m, 2H, CH_{Ar}), 7.15-7.16 (m, 2H, CH_{Ar}), 11.80 (s, 1H, NH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.8 (*Me*CH_2), 22.3, 27.9, 31.2, 33.55 (CH_2), 55.5, 55.6 (2xOMe), 103.7, 104.3, 110.2 (CH), 111.7 (C), 114.5, 115.3, 125.7, 130.2, 131.9, 132.2 (CH), 134.0 (C), 146.1, 150.0, 154.0, 156.3, 159.9, 181.7 (C).

MS (GC, 70eV): *m/z* (%) = 442 (M^+, 100), 427 (90).

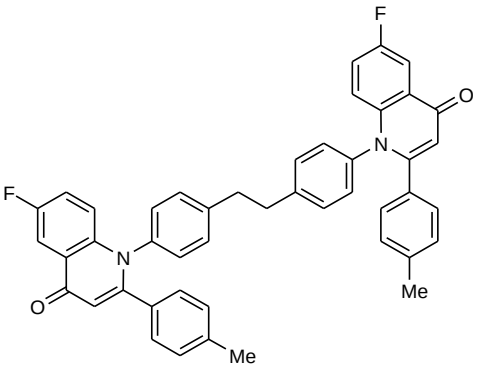
HRMS (ESI): Calcd for $C_{28}H_{31}N_2O_3$ (M+H) 443.22564. Found 443.23317.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928 (w), 1624 (s), 1601 (s), 1452 (s), 1263 (s), 1207 (s), 1123 (m), 1109 (s), 883 (m), 867 (s), 787 (m), 704 (w), 661 (s).

*A.2.22. General procedure for the synthesis of compounds **3.2.14**.*

Corresponding 1-(2-fluorophenyl)prop-2-yn-1-one derivative **3.2.2d** (2 equiv.), appropriate amine (1 equiv.) and Li_2CO_3 (4 equiv.) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMA (7 mL/1 mmol of **3.2.2**). The mixture was heated at 160 °C for 24-30 h (controlled by TLC). After the reaction was completed volatiles were evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (Heptane : Ethyl acetate - 3:1).

1,1'-(ethane-1,2diylbis(4,1-phenylene))bis(6-fluoro-2-(p-tolyl)quinolin-4(1*H*)-one) (3.2.14a).



Starting from 1-(2,5-difluorophenyl)-3-p-tolylprop-2-yn-1-one **3.2.3d** (0.512 g, 2 mmol), 4-(4-aminophenethyl)benzenamine (0.212 g, 1 mmol) and Li_2CO_3 (0.296 g, 4 mmol) in 7 mL DMA. **3.2.14a** was isolated as yellow oil (0.335 g, 49%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.20 (br. s, 6H, 2xMe), 2.85 (br. s, 4H, 2xCH_2), 6.38 (s, 2H, CH_{Ar}), 6.82 (dd, 2H, ^3J = 9.4 Hz, ^3J= 4.4 Hz, CH_{Ar}), 6.90-7.06 (m, 16H, CH_{Ar}), 7.12-7.19 (m, 2H, CH_{Ar}), 8.11 (dd, 2H, ^3J = 8.8 Hz, ^3J = 3.0 Hz, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -117.6 (CF).

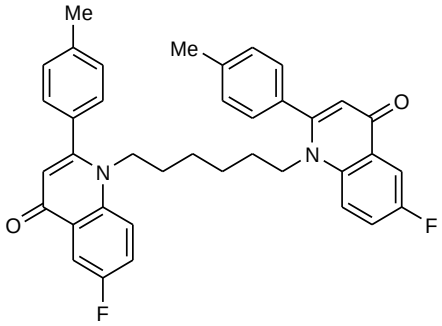
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.2 (Me), 37.3 (CH_2), 110.8 (d, ^2J = 22.3 Hz, CH), 112.0 (CH), 120.1 (d, ^3J = 8.8 Hz, CH), 128.4 (d, ^3J = 8.8 Hz, CH), 127.5 (d, ^3J = 6.7 Hz, C), 128.6, 129.1, 129.6, 129.9 (CH), 132.7, 137.2, 138.6, 139.2, 141.9, 154.2 (C), 159.2 (d, ^1J = 251.6 Hz, CF), 176.9 (d, ^4J = 2.5 Hz, C).

MS (EI, 70eV): *m/z* (%) = 684 (M^+, 100), 342 (44), 314 (10), 226 (43).

HRMS (EI): Calcd for $C_{46}H_{34}F_2N_2O_2$ (M^+) 684.25829. Found 684.258764.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3033 (w), 2920 (w), 1603 (s), 1510 (s), 1469 (s), 1384 (m), 1306 (s), 1253 (w), 1180 (m), 1099 (w), 1021 (w), 927 (s), 854 (m), 817 (s), 725 (s), 632 (m), 596 (m), 553 (s).

1,1'-(hexane-1,6diyl)bis(6-fluoro-2-(p-tolyl)quinolin-4(1*H*)-one) (3.2.14b).



Starting from 1-(2,5-difluorophenyl)-3-p-tolylprop-2-yn-1-one **3.2.3d** (0.512 g, 2 mmol), hexane-1,6-diamine (0.116 g, 1 mmol) and Li_2CO_3 (0.296 g, 4 mmol) in 7 mL DMA. **3.2.14b** was isolated as white solid (0.417 g, 71%), mp more than 350 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 0.80 (br. s, 4H, 2xCH_2), 1.41 (br. s, 4H, 2xCH_2), 2.36 (s, 6H, Me), 3.96 (br. s, 4H, 2xCH_2), 5.89 (s, 2H, CH_{Ar}), 7.28 (m, 8H, CH_{Ar}), 7.62-7.68 (m, 2H, CH_{Ar}), 7.84-7.90 (m, 4H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -117.6 (CF).

^{13}C NMR Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 588 (M^+, 44), 266 (33), 207 (21), 150 (19).

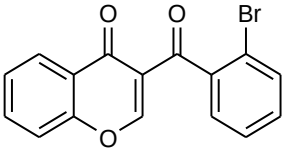
HRMS (ESI): Calcd for $C_{38}H_{35}F_2N_2O_2$ (M+H) 589.26611. Found 589.26599.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1613 (w), 1479 (s), 1417 (s), 1293 (w), 1154 (w), 1087 (w), 931 (w), 859 (m), 828 (w), 740 (w).

*A.2.23. General procedure for the synthesis of 3-(2-halobenzoil)chromones **3.3.4**:*

To a dry dichloromethane solution (10 mL/1 mmol **3.3.5**) of corresponding enaminone **3.3.5** (1 equiv.) was added dry pyridine (3 equiv.). The solution was set on stirring on ice bath. Afterwards corresponding halogenated benzoyl chloride **3.3.6** (1.1 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 8 h. After the reaction was completed volatiles were evaporated under reduced pressure. The residue was treated with water, filtered, dried in air, and purified by flash column chromatography.

3-(2-bromobenzoil)-4*H*-chromen-4-one (3.3.4a).



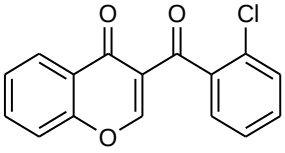
Starting from (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one **3.3.5a** (1.911 g, 10 mmol), 2-bromobenzoyl chloride (2.387g, 11 mmol) and pyridine (6.33 g, 30 mmol) in 100 mL DCM. **3.3.4a** was isolated as white solid (2.67 g, 81%), mp 132-133 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.11-7.15 (m, 1H, CH_{Ar}), 7.26-7.30 (m, 1H, CH_{Ar}), 7.48-7.58 (m, 3H, CH_{Ar}), 7.72-7.86 (m, 2H, CH_{Ar}), 8.25-8.32 (m, 1H, CH_{Ar}), 8.45 (s, 1H, CH_{Ar}).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 118.7, 124.2, 124.5, 125.3 (CH), 126.1, 128.5 (C),

128.6, 129.4 (CH), 129.5 (C), 133.6, 134.8, 136.9 (CH), 155.8, 158.8, 174.3, 191.6 (C).

3-(2-chlorobenzoil)-4*H*-chromen-4-one (3.3.4b).

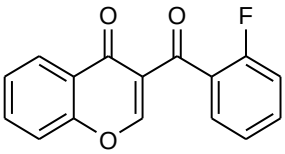


Starting from (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one **3.3.5a** (1.911 g, 10 mmol), 2-bromobenzoyl chloride (1.925 g, 11 mmol) and pyridine (6.33 g, 30 mmol) in 100 mL DCM. **3.3.4b** was isolated as white solid (2.28 g, 80%), mp 130-131 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08-7.10 (m, 1H, CH_{Ar}), 7.20-7.28 (m, 1H, CH_{Ar}), 7.50-7.55 (m, 3H, CH_{Ar}), 7.80-7.90 (m, 2H, CH_{Ar}), 8.30-8.35 (m, 1H, CH_{Ar}), 8.41 (s, 1H, CH_{Ar}).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 118.9, 124.4, 124.6, 125.1 (CH), 126.0, 128.8 (C), 128.9, 129.3 (CH), 129.5 (C), 133.8, 135.0, 136.9 (CH), 155.9, 159.0, 174.5, 192.0 (C).

3-(2-fluorobenzoil)-4*H*-chromen-4-one (3.3.4c).



Starting from (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one **3.3.5a** (1.911 g, 10 mmol), 2-fluorobenzoyl chloride (1.744 g, 11 mmol) and pyridine (6.33 g, 30 mmol) in 100 mL DCM. **3.3.4c** was isolated as white solid (2.09 g, 78%), mp 141-143 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.04-7.10 (m, 1H, CH_{Ar}), 7.25 (dt, 1H, ^{3}J = 7.6 Hz, ^{4}J = 1.1 Hz, CH_{Ar}), 7.41-7.54 (m, 3H, CH_{Ar}), 7.68-7.76 (m, 2H, CH_{Ar}), 8.20 (dt, 1H, ^{3}J = 7.8 Hz, ^{4}J = 1.7 Hz, CH_{Ar}), 8.43 (s, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.4.

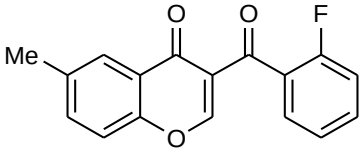
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 115.7, 116.0, 118.3 (CH), 124.4 (d, J = 3.1 Hz, CH), 125.0, 125.8 (C), 126.2, 126.4 (CH), 127.4 (d, ^{3}J = 12.6 Hz, C), 130.5 (d, J = 2.4 Hz, CH), 134.3 (CH), 156.0, 159.5 (CH), 162.1 (d, ^{1}J = 253.5 Hz, CF), 174.5, 188.7 (C).

MS (GC, 70eV): *m/z* (%) = 268 (M^+, 1), 249 (100)

HRMS (EI): Calcd for $C_{16}H_9FO_3$ (M^+) 268.05302. Found 268.05297.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922 (w), 1664 (m), 1642 (s), 1608 (s), 1563 (s), 1460 (s), 1388 (m), 1340 (m), 1300 (s), 1239 (m), 1207 (m), 1136 (m), 1099 (m), 973 (m), 864 (s), 757 (s), 706 (m), 629 (m).

6-methyl-3-(2-fluorobenzoil)-4*H*-chromen-4-one (3.3.4d).



Starting from (*E*)-3-(dimethylamino)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one **3.3.5b** (2.05 g, 10 mmol), 2-fluorobenzoyl chloride (1.744 g, 11 mmol) and pyridine (6.33 g,

30 mmol) in 100 mL DCM. **3.3.4d** was isolated as white solid (2.256 g, 80%), mp 97-99 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3H, Me), 6.86-6.93 (m, 1H, CH_{Ar}), 7.06-7.11 (m, 1H, CH_{Ar}), 7.22 (s, 1H, CH_{Ar}), 7.31-7.39 (m, 2H, CH_{Ar}), 7.56 (dt, 1H, ^{3}J = 7 Hz, ^{4}J = 2 Hz, CH_{Ar}), 7.81-7.82 (m, 1H, CH_{Ar}), 8.24 (s, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.4 (CF).

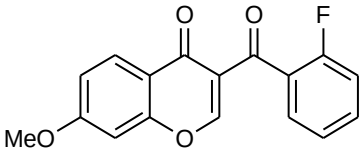
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.9 (Me), 100.6 (CH), 115.8 (d, ^{2}J = 22.1 Hz, CH), 118.6 (CH), 124.4 (d, J = 3.4 Hz, CH), 124.6, 125.3, 125.6 (C), 125.8 (CH), 127.4 (d, ^{3}J = 12.7 Hz, C), 130.4 (d, J = 1.9 Hz, CH), 134.3 (d, ^{3}J = 8.8 Hz, CH), 135.6 (CH), 136.4, 154.3 (C), 159.4 (CH), 161.2 (d, ^{1}J = 254.7 Hz, CF), 174.6, 188.9 (C).

MS (GC, 70eV): *m/z* (%) = 282 (M^+, 70), 263 (42), 253 (100), 235 (39), 187 (25), 135 (28), 95 (38).

HRMS (EI): Calcd for $C_{17}H_{11}FO_3$ (M^+) 282.06867. Found 282.06832.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1660 (m), 1612 (s), 1555 (m), 1478 (s), 1452 (m), 1372 (w), 1311 (S), 1216 (m), 1154 (w), 1127 (w), 1103 (m), 978 (w), 941 (w), 908 (m), 863 (m), 820 (m), 802 (m), 781 (s), 766 (s), 637 (s).

7-methoxy-3-(2-fluorobenzoil)-4*H*-chromen-4-one (3.3.4e).



Starting from (*E*)-3-(dimethylamino)-1-(2-hydroxy-4-methoxyphenyl)prop-2-en-1-one **3.3.5c** (2.211 g, 10 mmol), 2-fluorobenzoyl chloride (1.744 g, 11 mmol) and pyridine (6.33 g, 30 mmol) in 100 mL DCM. **3.3.4e** was isolated as light brown solid (2.041 g, 88%), mp 154-155 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3H, OMe), 6.89 (d, 1H, ^{4}J = 2.4 Hz, CH_{Ar}), 6.97-7.09 (m, 2H, CH_{Ar}), 7.22-7.27 (m, 1H, CH_{Ar}), 7.48-7.56 (m, 1H, CH_{Ar}), 7.72 (dt, 1H, ^{3}J = 7.6 Hz, ^{4}J = 1.7 Hz,CH_{Ar}), 8.10 (d, 1H, ^{3}J = 8.9 Hz, CH_{Ar}), 8.35 (s, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.4 (CF).

^{13}C NMR (75.5 MHz, $CDCl_3$):δ = 54.9 (OMe), 100.6 (CH), 115.4 (d, ^{2}J = 22.3 Hz, CH), 115.9 (CH), 118.4 (C), 124.2 (d, J = 3.2 Hz, CH), 125.7 (C), 127.4 (d, ^{3}J = 13.5 Hz, C), 127.6 (CH), 130.3 (d, J = 3.1 Hz, CH), 134.2 (d, ^{3}J = 9.7 Hz, CH), 158.1 (CH), 160.2 (d, ^{1}J = 254.1 Hz, CF), 172.9, 187.9 (C).

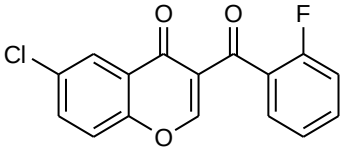
MS (GC, 70eV): *m/z* (%) = 298 (M^+, 61), 279 (35), 269 (100), 251 (28), 151 (25).

HRMS (EI): Calcd for $C_{17}H_{11}FO_4$ (M^+) 298.06359. Found 298.06287.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2852 (w), 1683 (m), 1569 (m), 1613 (s), 1454 (m), 1390 (w), 1356 (w), 1313 (m), 1278 (s), 1203 (m), 1163 (m), 1135 (m), 1089 (m), 1024 (m), 867 (m), 844 (m),

777 (s), 749 (s), 649 (m), 572 (m).

6-chloro-3-(2-fluorobenzoil)-4*H*-chromen-4-one (3.3.4f).



Starting from (*E*)-1-(5-chloro-2-hydroxyphenyl)-3-(dimethylamino)prop-2-en-1-one **3.3.5d** (2.255 g, 10 mmol), 2-fluorobenzoyl chloride (1.744 g, 11 mmol) and pyridine (6.33 g, 30 mmol) in 100 mL DCM. **3.3.4f** was isolated as yellow solid (2.148 g, 71%), mp 97-99 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07 (ddd, 1H, ^{3}J = 10.7 Hz, ^{4}J = 8.3 Hz, ^{5}J = 0.9 Hz, CH_{Ar}), 7.24-7.30 (m, 1H, CH_{Ar}), 7.48 (d, 1H, ^{3}J = 8.9 Hz, CH_{Ar}), 7.50-7.58 (m, 1H, CH_{Ar}), 7.65 (dd, 1H, ^{3}J = 8.9 Hz, ^{4}J = 2.6 Hz, CH_{Ar}), 7.72-7.77 (m, 1H, CH_{Ar}), 8.16 (d, 1H, ^{4}J = 2.6 Hz, CH_{Ar}), 8.41 (s, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.2 (CF).

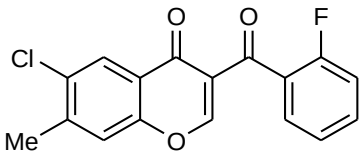
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 115.9 (d, ^{2}J = 21.8 Hz, CH), 120.0 (CH), 124.5 (d, J = 3.4 Hz, CH), 125.8 (CH), 128.9 (C), 127.1 (d, ^{3}J = 10.9 Hz, C), 130.5 (CH), 132.3 (C), 134.5, 134.6 (CH), 154.3 (C), 159.4 (CH), 161.2 (d, ^{1}J = 253.7 Hz, CF), 173.4, 188.1 (C).

MS (GC, 70eV): *m/z* (%) = 302 (M^{+}, 69), 273 (100), 255 (35), 207 (32), 155 (31), 123 (69), 95 (51).

HRMS (EI): Calcd for $C_{16}H_8ClO_2$ (M^{+}) 303.98664. Found 303.98572.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3056 (w), 1644 (s), 1608 (s), 1560 (m) 1482 (w), 1463 (s), 1436 (m), 1335 (m), 1315 (s), 1260 (m), 1211 (m), 1140 (m), 1101 (m), 1037 (w), 985 (m), 951 (m), 887 (m), 863 (m), 835 (m), 820 (s), 783 (s), 761 (s), 735 (m), 674 (m), 631 (s).

3-(2-fluorobenzoil)-6-chloro-7-methyl-4*H*-chromen-4-one (3.3.4g).



Starting from (*E*)-1-(5-chloro-2-hydroxy-4-methylphenyl)-3-(dimethylamino)prop-2-en-1-one **3.3.5e** (2.391 g, 10 mmol), 2-fluorobenzoyl chloride (1.744 g, 11 mmol) and pyridine (6.33 g, 30 mmol) in 100 mL DCM. **3.3.4g** was isolated as yellow solid (1.836 g, 58%), mp 143-144 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.51 (s, 3H, Me), 7.03-7.10 (m, 1H, CH_{Ar}), 7.24-7.29 (m, 1H, CH_{Ar}), 7.40 (s, 1H, CH_{Ar}), 7.50-7.58 (m, 1H, CH_{Ar}), 7.74 (dt, 1H, ^{3}J = 7.5 Hz, ^{4}J = 1.8 Hz, CH_{Ar}), 8.15 (s, 1H, CH_{Ar}), 8.38 (s, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -117.3 (CF).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.9 (Me), 100.6 (CH), 115.9 (d, ^{2}J = 22.6 Hz, CH), 120.1

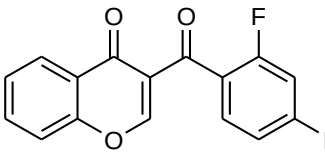
(CH), 124.0 (C), 124.4 (d, J = 2.8 Hz, CH), 125.7 (C), 126.1 (CH), 127.2 (d, ^{3}J = 12.2 Hz, C), 130.5 (d, J = 2.0 Hz, CH), 132.9 (C), 134.5 (d, ^{3}J = 7.9 Hz, CH), 143.9, 154.3 (C), 161.2 (d, ^{1}J = 253.6 Hz, CF), 173.3, 188.4 (C).

MS (GC, 70eV): *m/z* (%) = 316 (M^+, 65), 287 (100), 269 (34), 221 (21), 169 (25), 123 (36), 95 (39).

HRMS (EI): Calcd for $C_{17}H_{10}O_3FCl$ (M^+) 316.02970. Found 316.02908.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3040 (w), 1651 (s), 1620 (s), 1547 (m), 1486 (w), 1452 (s), 1412 (m), 1334 (m), 1308 (s), 1259 (m), 1226 (m), 1183 (m), 1145 (m), 1126 (m), 1104 (m), 1039 (w), 1003 (m), 966 (m), 934 (w), 910 (m), 871 (s), 797 (m), 768 (s), 750 (s), 704 (w), 667 (m), 638 (s).

3-(2,4-fluorobenzoil)-4*H*-chromen-4-one (3.3.4h).



Starting from (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one **3.3.5a** (1.911 g, 10 mmol), 2,4-difluorobenzoyl chloride (1.942 g, 11 mmol) and pyridine (6.33 g, 30 mmol) in 100 mL DCM. **3.3.4h** was isolated as brown solid (1.716 g, 60%), mp 138-140 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.78-7.03 (m, 3H, CH_{Ar}), 7.43-7.55 (m, 1H, CH_{Ar}), 7.70-7.82 (m, 1H, CH_{Ar}), 8.03-8.10 (m, 1H, CH_{Ar}), 8.20-8.23 (m, 1H, CH_{Ar}), 8.44 (s, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -106.0 (d, ^{3}J = 13.1 Hz, CF), -102.0 (d, ^{3}J = 13.1 Hz, CF).

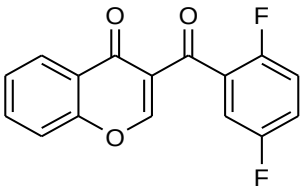
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 104.3 (t, ^{2}J = 25.9 Hz, CH), 112.0 (dd, ^{2}J = 21.7 Hz, J = 3.8 Hz, CH), 118.3 (CH), 124.0 (dd, ^{3}J = 12.6 Hz, J = 3.8 Hz, C), 124.8, 125.7 (C), 126.2, 126.3 (CH), 132.3 (dd, ^{3}J = 10.6 Hz, J = 3.8 Hz, CH), 138.4 (CH), 156.0 (C), 159.5 (CH), 161.9 (dd, ^{1}J = 237.8 Hz, ^{3}J = 12.6 Hz, CF), 165.9 (dd, ^{1}J = 237.8 Hz, ^{3}J = 12.6 Hz, CF), 174.4 (d, J = 2.2 Hz, C=O), 187.3 (C=O).

MS (GC, 70eV): *m/z* (%) = 286 (M^+, 85), 267 (48), 257 (100), 239 (57), 173 (30), 141 (45).

HRMS (EI): Calcd for $C_{16}H_8F_2O_3$ (M^+) 286.04360. Found 286.04384.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3080 (w), 1640 (s), 1609 (s), 1487 (w), 1464 (s), 1426 (m), 1384 (m), 1348 (m), 1294 (m), 1213 (m), 1138 (m), 1096 (s), 1028 (w), 977 (m), 855 (s), 802 (w), 757 (s), 662 (m), 302 (m).

3-(2,5-fluorobenzoil)-4*H*-chromen-4-one (3.3.4i).



Starting from (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one **3.3.5a** (1.911 g, 10 mmol), 2,5-difluorobenzoyl chloride (1.942 g, 11 mmol) and pyridine (6.33 g, 30 mmol) in 100 mL DCM. **3.3.4i** was isolated as yellow solid (2.717 g, 95%), mp 138-140 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00-7.08 (m, 1H, CH_{Ar}), 7.17-7.23 (m, 1H, CH_{Ar}), 7.38-7.54 (m, 2H, CH_{Ar}), 7.70-7.75 (m, 2H, CH_{Ar}), 8.20 (dd, 1H, ^{3}J = 8.0 Hz, ^{4}J = 1.6 Hz, CH_{Ar}), 8.45 (s, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -117.9 (d, *J* = 17.7 Hz, CF), -117.2 (d, *J* = 17.7 Hz, CF).

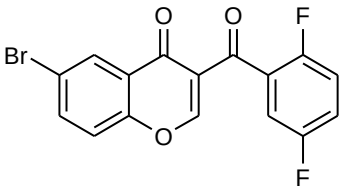
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 116.6 (dd, ^{2}J = 25.5 Hz, *J* = 3.3 Hz, CH), 117.2 (dd, ^{2}J = 25.5 Hz, *J* = 8.2 Hz, CH), 118.3 (CH), 120.7 (dd, ^{2}J = 25.5 Hz, *J* = 9.4 Hz, CH), 124.9, 125.3 (C), 126.3 (d, *J* = 5.3 Hz, CH), 128.4 (dd, *J* = 16.7 Hz, *J* = 7.3 Hz, CH), 134.5 (CH), 156.0 (C), 157.1 (d, ^{1}J = 247.2 Hz, CF), 158.6 (d, *J* = 242.2 Hz, CF), 159.8 (CH), 174.4, 187.6 (C).

MS (GC, 70eV): *m/z* (%) = 286 (M^+, 80), 267 (57), 257 (100), 239 (66), 173 (35), 141 (22), 121 (39).

HRMS (EI): Calcd for $C_{16}H_8F_2O_3$ (M^+) 286.04360. Found 286.043440.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3068 (w), 1636 (s), 1614 (m), 1566 (m), 1483 (m), 1461 (s), 1422 (m), 1392 (m), 1344 (m), 1316 (m), 1287 (w), 1260 (m), 1230 (m), 1186 (s), 1131 (m), 1000 (w), 961 (w), 929 (w), 891 (m), 833 (s), 773 (s), 750 (s), 700 (m), 637 (m), 591 (w), 540 (m).

3-(2,5-fluorobenzoil)-6-bromo-4*H*-chromen-4-one (3.3.4j).



Starting from (*E*)-1-(5-bromo-2-hydroxyphenyl)-3-(dimethylamino)prop-2-en-1-one **3.3.5f** (2.700 g, 10 mmol), 2,5-difluorobenzoyl chloride (1.942 g, 11 mmol) and pyridine (6.33 g, 30 mmol) in 100 mL DCM. **3.3.4j** was isolated as white solid (2.737 g, 675%), mp 153-155 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00-7.08 (m, 1H, CH_{Ar}), 7.17-7.27 (m, 1H, CH_{Ar}), 7.38-7.44 (m, 2H, CH_{Ar}), 7.80 (dd, 1H, ^{3}J = 8.0 Hz, ^{4}J = 2.5 Hz, CH_{Ar}), 8.31 (d, 1H, ^{4}J = 3 Hz, CH_{Ar}), 8.42 (s, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -117.7 (d, *J* = 18 Hz, CF), -117.0 (d, *J* = 18 Hz, CF).

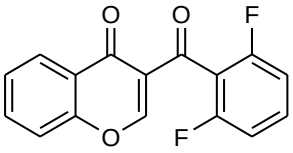
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 116.6 (dd, ^{2}J = 25.6 Hz, *J* = 3.3 Hz, CH), 117.2 (dd, ^{2}J = 25.6 Hz, *J* = 8.7 Hz, CH), 119.9 (C), 120.2 (CH), 121.0 (dd, ^{2}J = 25.6 Hz, *J* = 8.6 Hz, CH), 125.4, 126.1 (C), 128.0 (dd, ^{3}J = 14.3 Hz, *J* = 7.2 Hz, C), 129.0 (CH), 137.5 (CH), 154.8 (C), 157.2 (d, ^{1}J = 248.4 Hz, CF), 158.6 (d, ^{1}J = 280.1 Hz, CF), 159.7 (CH), 173.1 (d, *J* = 2.3 Hz, C=O), 187.0 (C=O).

MS (GC, 70eV): *m/z* (%) = 366 (M^+, 91), 365 (35), 347 (69), 346 (12), 337 (100), 336 (48), 335 (95), 319 (68), 317 (64), 251 (36), 199 (32), 141 (50), 113 (62).

HRMS (EI): Calcd for $C_{16}H_7F_2O_3Br$ (M^+) 363.95411. Found 363.954477.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3067 (w), 1645 (s), 1606 (m), 1557 (m), 1488 (m), 1459 (s), 1423 (m), 1372 (w), 1329 (m), 1307 (m), 1278 (m), 1251 (m), 1192 (m), 1177 (s), 1126 (m), 1093 (m), 1062 (w), 1005 (w), 932 (w), 893 (m), 878 (m), 824 (s), 804 (s), 769 (m), 750 (s), 676 (s), 640 (m), 603 (m), 539 (m).

3-(2,6-fluorobenzoil)-4*H*-chromen-4-one (3.3.4k).



Starting from (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one **3.3.5a** (1.911 g, 10 mmol), 2,6-difluorobenzoyl chloride (1.942 g, 11 mmol) and pyridine (6.33 g, 30 mmol) in 100 mL DCM. **3.3.4k** was isolated as white solid (1.888 g, 66%), mp 114-116 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.92-6.99 (m, 2H, CH_{Ar}), 7.37-7.48 (m, 2H, CH_{Ar}), 7.51-7.54 (m, 1H, CH_{Ar}), 7.69-7.75 (m, 1H, CH_{Ar}), 8.19 (dd, 1H, ^3J = 7.9 Hz, ^4J = 1.5 Hz, CH_{Ar}), 8.64 (s, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -113.1 (CF).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 111.7 (dd, ^2J = 22.8 Hz, J = 2.6 Hz, CH), 118.3 (CH), 123.8, 125.1, 126.4 (CH), 132.4 (t, ^3J = 10.4 Hz, CH), 134.5 (CH), 155.9 (C), 160.1 (dd, ^1J = 252.6 Hz, J = 6.5 Hz, CF), 161.6 (CH), 174.2, 185.1 (C).

MS (GC, 70eV): *m/z* (%) = 286 (M^+, 75), 267 (44), 257 (27), 239 (100), 173 (30), 141 (28), 121 (28).

HRMS (EI): Calcd for $C_{16}H_8F_2O_3$ (M^+) 286.04361. Found 286.043442.

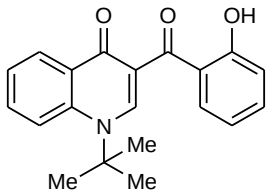
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3074 (w), 1674 (m), 1656 (s), 1611 (m), 1552 (m), 1459 (s), 1384 (m), 1307 (m), 1286 (m), 1265 (m), 1232 (m), 1206 (m), 1144 (m), 994 (s), 964 (s), 865 (m), 789 (s), 760 (s), 717 (s), 680 (m), 591 (m).

*A.2.24. General procedure for the synthesis of compounds **3.3.7-3.3.13**:*

Corresponding *ortho*-F-benzoyl chromone derivative **3.3.4** (1 equiv.), appropriate amine or aminoheterocycle (2 equiv.) and K_2CO_3 (2 equiv.) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMF (7 mL/1 mmol of **3.3.4**). The mixture was heated at 130 °C for 24-30 h (controlled by TLC). After the reaction was completed volatiles were evaporated under reduced pressure. The residue was purified by column chromatography over

silica gel (Heptane : Ethyl acetate - 3:1) or by recrystalisation from appropriate solvant.

1-tert-butyl-3-(2-hydroxy benzoyl)quinolin-4(1*H*)-one (3.3.7a).



Starting from 3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4a** (0.268 g, 1 mmol), tert-buthyl amine (0.146 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.7a** was isolated as colourless solid (0.177 g, 55%), mp 230-231 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.15 (s, 9H, *t*-Bu), 6.34 (d, 1H, ^3J = 10.6 Hz, CH_{Ar}), 7.01 (d, 1H, ^3J = 8.3 Hz, CH_{Ar}), 7.16 (t, 1H, ^3J = 8.0 Hz, CH_{Ar}), 7.51 (t, 1H, ^3J = 7.0 Hz, CH_{Ar}), 7.77-7.87 (m, 2H, CH_{Ar}), 7.97 (t, 1H, ^3J = 8.1 Hz, CH_{Ar}), 8.06 (d, 1H, ^3J = 7.7 Hz, CH_{Ar}), 8.08 (d, 1H, ^3J = 7.7 Hz, CH_{Ar}), 16.09 (br. s, 1H, OH).

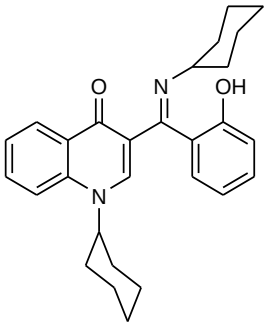
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 30.1 (*t*-Bu), 49.6 (*Ct*-Bu), 80.1 (CH), 111.8, 115.8 (C), 118.4, 118.6, 120.9, 123.6, 123.9, 125.0, 125.2, 133.3, 134.1 (CH), 154.4, 154.6, 155.1, 173.4 (C).

MS (GC, 70eV): *m/z* (%) = 321 (M^+, 30), 264 (64), 249 (100).

HRMS (EI): Calcd for $C_{20}H_{19}NO_3$ (M^+) 321.13594. Found 321.136189.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3303 (w), 2965 (w), 1638 (s), 1604 (m), 1561 (m), 1514 (w), 1465 (s), 1419 (s), 1360 (w), 1327 (w), 1311 (w), 1258 (m), 1205 (m), 1142 (m), 1099 (m), 1023 (w), 949 (w), 900 (w), 869 (m), 840 (m), 755 (s), 709 (s), 673 (m), 614 (m), 555 (m).

1-cyclohexyl-3-((*E*)-(cyclohexylimino)(2-hydroxyphenyl)methyl)quinolin-4(1*H*)-one (3.3.8b).



Starting from 3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4a** (0.268 g, 1 mmol), cyclohexyl amine (0.198 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.8b** was isolated as yellow solid (0.197 g, 46%), mp 230-231 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.20-1.80 (m, 20H, cyclohexyl), 3.30 (br. s, 1H, cyclohexyl), 4.73 (br. s, 1H, cyclohexyl), 6.64 (t, 1H, ^3J = 8.1 Hz, CH_{Ar}), 6.86 (d, 1H,^3J = 8.1 Hz, CH_{Ar}), 6.86 (d, 1H, ^3J = 8.1 Hz, CH_{Ar}), 7.25 (t, 1H, ^3J = 7.1 Hz, CH_{Ar}), 7.47 (t, 1H, ^3J = 7.1 Hz, CH_{Ar}), 7.83 (t, 1H, ^3J = 8.1 Hz, CH_{Ar}), 8.06 (d, 1H, ^3J = 9.1 Hz, CH_{Ar}), 8.22-8.29 (m, 2H, CH_{Ar}), 16.09 (s, 1H, OH).

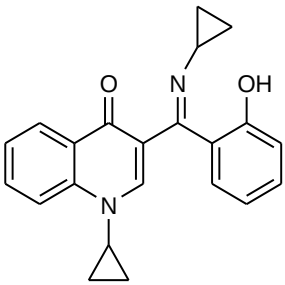
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 23.4, 24.6, 25.1, 25.2, 31.4, 31.6, 32.9, 33.4 (cyclohxyl CH_2), 57.7, 58.8 (cyclohexyl CH), 113.9 (C), 116.4, 117.1, 117.5 (CH), 119.8 (C), 123.8, 126.2 (CH), 128.2, 128.9 (C), 130.5, 131.9, 132.6, 138.9 (CH), 139.9, 163.1, 167.7, 172.9 (C).

MS (GC, 70eV): *m/z* (%) = 428 (M^+, 90), 411 (26), 345 (27), 332 (100), 250 (35). 220 (18), 171 (14).

HRMS (EI): Calcd for $C_{28}H_{32}N_2O_2$ (M^+) 428.24638. Found 428.24655.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3307 (w), 2922 (m), 2848 (w), 1626 (m), 1582 (m), 1554 (m), 1486 (m), 1445 (w), 1361 (m), 1309 (w), 1257 (w), 1216 (m), 1190 (w), 1150 (w), 1099 (w), 1002 (w), 913 (w), 889 (m), 859 (w), 838 (w), 750 (s), 709 (m), 635 (w), 575 (w), 534 (w).

1-cyclopropyl-3-((*E*)-(cyclopropylimino)(2-hydroxyphenyl)methyl)quinolin-4(1*H*)-one (3.3.8c).



Starting from 3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4a** (0.268 g, 1 mmol), cyclopropyl amine (0.114 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.8c** was isolated as yellowviscous oil (0.165 g, 48%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.84-1.06 (m, 4H, cyclopropyl, CH_2), 1.24-1.31 (m, 4H, cyclopropyl, CH_2), 2.84-2.94 (m, 1H, cyclopropyl CH), 3.44-3.51 (m, 1H, cyclopropyl CH), 6.64 (t, 1H, ^3J = 7.2 Hz, CH_{Ar}), 6.89 (d, 1H, ^3J = 7.7 Hz, CH_{Ar}), 7.04-7.07 (m, 1H, CH_{Ar}), 7.14-7.20 (m, 1H, CH_{Ar}), 7.71-7.78 (m, 2H, CH_{Ar}), 7.99 (d, 1H, ^3J = 8.6 Hz, CH_{Ar}), 8.47 (d, 1H, ^3J = 8.3 Hz, CH_{Ar}), 14.51 (s, 1H, OH).

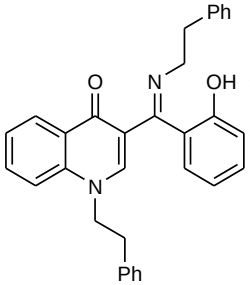
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 7.8, 10.0 (cyclopropyl CH_2), 33.9, 34.0 (C), 114.3 (C), 116.8, 117.4, 117.1 (CH), 120.1 (C), 124.1, 125.8 (CH), 125.9 (C), 130.3, 131.3, 132.3 (CH), 141.3 (C), 142.8 (CH), 161.0, 167.6, 173.4 (C).

MS (GC, 70eV): *m/z* (%) = 344 (M^+, 4), 238 (100), 221 (18), 147 (76), 121 (43).

HRMS (ESI): Calcd for $C_{22}H_{21}N_2O_2$ (M+H) 345.15975. Found 345.16062.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922 (w), 1620 (m), 1586 (s), 1480 (s), 1401 (w), 1339 (m), 1247 (m), 1166 (m), 1113 (w), 1035 (w), 943 (w), 866 (w), 752 (s), 704 (m), 644 (m).

3-((*E*)-(2-hydroxyphenyl)(phenethylimino)methyl)-1-phenethylquinolin-4(1*H*)-one (3.3.8d).



Starting from 3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4a** (0.268 g, 1 mmol), phenethyl amine (0.242 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.8d** was isolated as yellow solid (0.349 g, 74%), mp 172-174 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.85-2.90 (m, 2H, CH_2), 3.10-3.14 (m, 2H, CH_2), 3.34-3.52 (m, 2H, CH_2), 4.55-4.63 (m, 2H, CH_2), 6.62 (t,

1H, ^{3}J = 7.5 Hz, CH_{Ar}), 6.76-6.83 (m, 2H, CH_{Ar}), 7.07-7.30 (m, 11H, CH_{Ar}), 7.50 (t, 1H, ^{3}J = 7.6 Hz, CH_{Ar}), 7.64 (s, 1H, CH_{Ar}), 7.84-8.00 (m, 2H, CH_{Ar}), 8.25 (d, 1H, ^{3}J = 7.6 Hz, CH_{Ar}), 15.4 (s, 1H, OH).

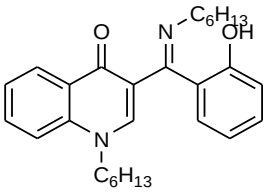
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 34.0, 36.1, 52.3, 53.4 (CH_2), 113.1 (C), 117.1, 117.2, 117.3 (CH), 119.4 (C), 124.1, 126.0, 126.2, 126.6, 128.3, 128.4, 128.7, 128.9, 130.6, 132.0, 132.6 (CH), 137.2, 139.2, 139.7 (C), 143.5 (CH), 162.3, 169.6, 172.9.

MS (GC, 70eV): *m/z* (%) = 472 (M^+, 100), 455 (20), 381 (18), 367 (35), 354 (98), 262 (26), 105 (97).

HRMS (ESI): Calcd for $C_{32}H_{29}N_2O_2$ (M+H) 473.22336. Found 473.22235.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3027 (w), 1712 (w), 1660 (w), 1623 (m), 1605 (m), 1598 (m), 1553 1486 (m), 1451 (m), 1375 (m), 1338 (m), 1307 (m), 1229 (m), 1183 (m), 1149 (m), 1082 (m), 1000 (m), 926 (m), 855 (m), 742 (s), 694 (s), 627 (m), 559 (m).

1-hexyl-3-((*E*)-(hexylimino)(2-hydroxyphenyl)methyl)quinolin-4(1*H*)-one (3.3.8e).



Starting from 3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4a** (0.268 g, 1 mmol), hexyl amine (0.202 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.8e** was isolated as yellow viscous oil (0.281 g, 65%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.53-0.60 (m, 6H, hexyl), 0.94-1.12 (m, 12H, hexyl), 1.37-1.63 (m, 4H, hexyl), 3.19 (br.s, 2H, CH_2 hexyl), 3.88 (t, 2H, ^{3}J = 7.1 Hz, CH_2), 6.30-6.35 (m, 1H, CH_{Ar}), 6.70 (d, 1H, ^{3}J = 8.3 Hz, CH_{Ar}), 6.83 (dd, 1H, ^{3}J = 8.0 Hz, ^{4}J = 1.7 Hz, CH_{Ar}), 6.92-6.97 (m, 1H, CH_{Ar}), 7.16-7.26 (m, 3H, CH_{Ar}), 7.44-7.50 (m, 1H, CH_{Ar}), 8.23 (dd, 1H, ^{3}J = 8.1 Hz, ^{4}J = 1.5 Hz, CH_{Ar}), 15.6 (s, 1H, OH).

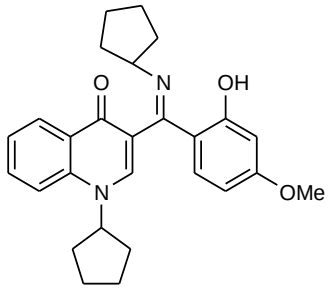
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.8, 14.0 (Me), 22.4, 22.5, 26.4, 27.1, 28.8, 30.5, 31.2, 31.5, 51.2, 53.7 (CH_2), 114.8 (C), 115.6, 116.8, 118.5 (CH), 119.6 (C), 124.4 (CH), 127.1 (C), 127.7, 130.4, 132.3, 132.6 (CH), 139.3 (C), 142.6 (CH), 164.6, 168.2, 174.0 (C).

MS (GC, 70eV): *m/z* (%) = 432 (M^+, 74), 375 (100), 334 (72), 248 (28).

HRMS (EI): Calcd for $C_{28}H_{36}N_2O_2$ (M^+) 432.27713. Found 432.27756.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3038 (w), 2924 (s), 2854 (m), 1621 (s), 1603 (s), 1577 (s), 1552 (s), 1489 (s), 1451 (m), 1413 (m), 1389 (m), 1345 (m), 1311 (m), 1269 (m), 1232 (s), 1176 (m), 1152 (m), 1055 (w), 966 (w), 864 (w), 824 w), 786 (w), 753 (s), 706 (m), 660 (w), 625 (w), 529 (w).

1-cyclopentyl-3-((*Z*)-(cyclopentylimino)(2-hydroxy-4-methoxyphenyl)methyl)quinolin-4(1*H*)-one (3.3.8f).



Starting from 7-methoxy-3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4e** (0.298 g, 1 mmol), cyclopentyl amine (0.170 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.8f** was isolated as yellow solid (0.237 g, 55%), mp 220-222 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.56-2.03 (m, 14H, cyclopentyl), 2.27-2.36 (m, 2H, cyclopentyl), 3.76 (s, 3h, OMe), 3.83-3.90 (m, 1H, NCH), 4.97-5.04 (m, 1H, NCH), 6.09 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.4 Hz, CH_{Ar}), 6.35 (d, 1H, ^4J = 2.6 Hz, CH_{Ar}), 6.88 (d, 1H, ^3J = 9.0 Hz, CH_{Ar}), 7.43-7.49 (m, 1H, CH_{Ar}), 7.59 (s, 1H, CH_{Ar}), 7.68-7.79 (m, 2H, CH_{Ar}), 8.52-8.56 (m, 1H, CH_{Ar}), 12.71 (br. s, 1H, OH).

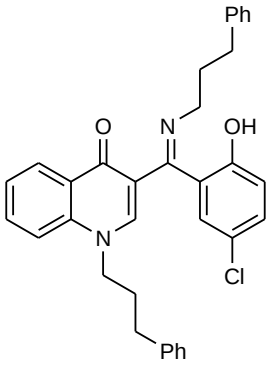
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 23.8, 24.2, 24.3, 32.2, 32.3, 32.4, 34.2, 35.1 (cyclopentyl CH_2), 55.2 (OMe), 60.2, 61.0 (cyclopentyl CH), 102.3, 105.5 (CH), 112.6, 114.6 (C), 115.6, 124.4 (CH), 127.3 (C), 127.9, 131.8, 132.6, 138.1 (CH), 140.4, 164.2, 166.4, 171.6, 173.8 (C).

MS (GC, 70eV): *m/z* (%) = 430 (M^+, 67), 413 (35), 399 (23), 361 (21), 348 (100), 293 (35). 251 (23), 168 (35).

HRMS (EI): Calcd for $C_{27}H_{30}N_2O_3$ (M^+) 430.22509. Found 430.22451.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2952 (w), 2859 (w), 1581 (s), 1552 (m), 1514 (w), 1485 (m), 1444 (m), 1412 (w), 1345 (m), 1281 (w), 1208 (s), 1169 (m), 1119 (m), 1100 (m), 1035 (m), 957 (m), 856 (w), 831 (m), 796 (m), 752 (s), 708 (m), 645 (w).

3-((*E*)-(3-phenylpropylimino)(5-chloro-2-hydroxyphenyl)methyl)-1-(3-phenylpropyl)quinolin-4(1*H*)-one (3.3.8g).



Starting from 6-chloro-3-(2-fluorobenzoil)-4*H*-chromen-4-on **3.3.4f** (0.302 g, 1 mmol), 3-phenylpropan-1-amine (0.270 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.8g** was isolated as orange solid (0.283 g, 53%), mp 87-89 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.00-2.32 (m, 4H, 2xCH_2), 2.71-2.77 (m, 4H, 2xCH_2), 3.30-3.41 (m, 1H, CH_2), 3.58-3.71 (m, 1H, CH_2), 4.07-4.22 (m, 2H, CH_2), 6.94 (d, 1H, ^3J = 8.9 Hz, CH_{Ar}), 7.07-7.40 (m, 14H, CH_{Ar}), 7.45-7.51 (m, 1H, CH_{Ar}), 7.67-7.77 (m, 1H, CH_{Ar}), 8.51 (dd, 1H, ^3J = 8.1 Hz, ^4J = 1.6 Hz, CH_{Ar}), 16.0 (br. s, 1H, OH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 30.0, 31.7, 32.5, 33.3, 50.5, 52.7 (CH_2), 114.2 (C), 115.6, 120.0 (CH), 120.3, 121.4 (C), 124.6, 125.7, 126.6 (CH), 127.0 (C), 127.7, 128.2, 128.4, 128.7,

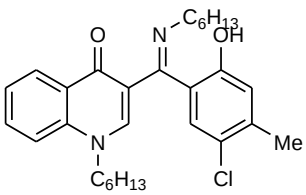
129.4, 132.2, 132.8 (CH), 139.3, 139.4, 141.3 (C), 142.2 (CH), 163.0, 167.9, 173.8 (C).

MS (GC, 70eV): *m/z* (%) = 534 (M^+, 13), 443 (100), 430 (14), 91 (47).

HRMS (ESI): Calcd for $C_{34}H_{32}N_2O_2Cl$ (M+H) 535.21468. Found 535.21473.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3025 (w), 2924 (w), 1623 (s), 1600 (s), 1576 (s), 1552 (m), 1487 (s), 1415 (w), 1379 (m), 1328 (w), 1287 (m), 1226 (m), 1173 (m), 1087 (w), 1029 (w), 983 (w), 883 (w), 822 (m), 745 (s), 697 (s), 647 (m), 529 (w).

3-((*E*)-(5-chloro-2-hydroxy-4-methylphenyl)(hexylimino)methyl)-1-hexylquinolin-4(1*H*)-one (3.3.8h).



Starting from 3-(2-fluorobenzoil)-6-chloro-7-methyl-4*H*-chromen-4-one **3.3.4g** (0.316 g, 1 mmol), hexyl amine (0.202 g, 2 mmol)and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.8h** was isolated as yellow solid (0.336 g, 70%), mp 128-130 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 0.79-0.87 (m, 6H, hexyl CH_3), 1.20-1.37 (m, 12H, hexyl CH_2), 1.61-1.72 (m, 2H, hexyl CH_2), 1.87 (br.s, 2H, hexyl CH_2), 2.24 (s, 3H, Me), 3.22-3.33 (m, 1H, hexyl CH_2), 3.51-3.62 (m, 1H, hexyl CH_2), 4.16 (t, 2H, ^3J = 7.0 Hz, hexyl CH_2), 6.78 (s, 1H, CH_{Ar}), 7.02 (s, 1H, CH_{Ar}), 7.41-7.52 (m, 2H, CH_{Ar}), 7.70-7.77 (m, 1H, CH_{Ar}), 8.46 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.5 Hz, CH_{Ar}), 15.8 (br. s, 1H, OH).

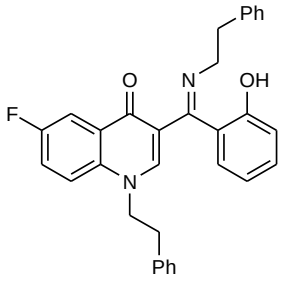
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.8, 13.9 (Me), 20.2, 22.3, 22.4, 26.3, 27.0, 28.8, 30.3, 31.2, 31.5 (CH_2), 114.0 (C), 115.7 (CH), 118.4 (C), 120.8, 121.7, 124.5 (CH), 127.1 (C), 127.6, 129.7, 132.7 (CH), 139.3, 140.8 (C), 142.6 (CH), 163.7, 167.3, 173.9 (C).

MS (GC, 70eV): *m/z* (%) = 480 (M^+, 69), 463 (23), 423 (100), 382 (63), 179 (16).

HRMS (ESI): Calcd for $C_{29}H_{37}N_2O_2Cl$ (M+H) 481.26163. Found 481.26226.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3041 (w), 2926 (m), 2855 (w), 1623 (m), 1599 (s), 1577 (s), 1552 (m), 1490 (s), 1461 (m), 1384 (m), 1271 (w), 1231 (s), 1168 (s), 1135 (w), 1055 (w), 1008 (w), 965 (w), 883 (w), 858 (m), 795 (w), 763 (s), 732 (w), 708 (m), 690 (m), 626 (w), 576 (w).

3-((*E*)-(5-bromo-2-hydroxyphenyl)(phenethylimino)methyl)-1-phenethylquinolin-4(1*H*)-one (3.3.8i).



Starting from 3-(2,5-fluorobenzoil)-4*H*-chromen-4-one **3.3.4i** (0.286 g, 1 mmol), phenethyl amine (0.242 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.8i** was isolated as brown viscous oil (0.382 g, 78%).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.99 (t, 2H, ^3J = 6.9 Hz, CH_2), 3.10 (t,

2H, ^{3}J = 6.9 Hz, CH_2), 3.56 (br. s, 1H, CH_2), 3.66-3.76 (m, 1H, CH_2), 4.26 (t, 2H, ^{3}J = 6.4 Hz, CH_2), 6.53-6.59 (m, 2H, CH_{Ar}), 6.70-6.73 (m, 1H, CH_{Ar}), 6.93-6.97 (m, 3H, CH_{Ar}), 7.12-7.27 (m, 9H, CH_{Ar}), 7.47-7.59 (m, 2H, CH_{Ar}), 8.15 (dd, 1H, ^{3}J = 8.7 Hz, ^{4}J = 2.7 Hz, CH_{Ar}), 15.32 (br. s, 1H, OH).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -116.3 (CF).

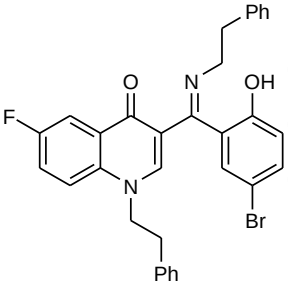
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 34.8, 36.7, 53.2, 55.1 (CH_2), 108.7 (C), 112.6 (d, ^{2}J = 23.4 Hz, CH), 114.0 (C), 117.4 (CH), 117.8 (d, ^{3}J = 8 Hz, CH), 118.0 (CH), 119.5 (C), 121.3 (d, ^{2}J = 25.6 Hz, CH), 126.1, 127.5, 128.4 (d, ^{3}J = 11.3 Hz, CH), 129.1 (d, J = 3.0 Hz, CH), 130.3, 132.2 (CH), 135.6, 136.1, 139.9 (C), 142.3 (CH), 159.4 (d, ^{1}J = 247.7 Hz, CF), 163.3, 168.1, 173.2 (C).

MS (GC, 70eV): *m/z* (%) = 490 (M^+, 33), 385 (13), 372 (32), 315 (19), 283 (18), 105 (28), 73 (100).

HRMS (EI): Calcd for $C_{32}H_{27}N_2O_2F$ (M^+) 491.21293. Found 491.21309.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3388 (w), 3025 (w), 2927 (w), 1602 (m), 1560 (m), 1490 (s), 1453 (m), 1380 (m), 1335 (m), 1281 (m), 1224 (m), 1175 (m), 1151 (m), 1083 (w), 1030 (w), 895 (m), 815 (m), 748 (s), 697 (s).

3-((*E*)-(5-bromo-2-hydroxyphenyl)(phenethylimino)methyl)-6-fluoro-1-phenethylquinolin-4(1*H*)-one (3.3.8j).



Starting from 3-(2,5-fluorobenzoil)-6-bromo-4*H*-chromen-4-one **3.3.4g** (0.363 g, 1 mmol), phenethyl amine (0.242 g, 2 mmol)and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.8j** was isolated as yellow solid (0.224 g, 40%), mp 200-202 ^{o}C.

^{1}HNMR (300 MHz, DMSO-d_6): δ = 2.93-3.11 (m, 4H, 2xCH_2), 3.26-3.37 (m, 1H, CH_2), 3.66-3.76 (m, 1H, CH_2), 4.25 (t, 2H, ^{3}J = 6.8 Hz, CH_2), 6.49 (s, 1H, CH_{Ar}), 6.81 (d, 1H, ^{3}J = 8.8 Hz, CH_{Ar}), 6.96-6.97 (m, 2H, CH_{Ar}), 6.98-6.99 (m, 1H, CH_{Ar}), 7.11-7.28 (m, 9H, CH_{Ar}), 7.48-7.58 (m, 2H, CH_{Ar}), 8.11 (dd, 1H, ^{3}J = 8.6 Hz, ^{4}J = 2.6 Hz, CH_{Ar}), 15.57 (br. s, 1H, OH).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -115.4.

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 34.9, 36.8, 53.2, 55.0 (CH_2), 108.7 (C), 112.5 (d, ^{2}J = 23.3 Hz, CH), 113.2 (C), 117.9 (d, ^{3}J = 8.1 Hz, CH), 120.2 (CH), 120.9 (C), 121.5 (d, ^{2}J = 26.3 Hz, CH), 126.3, 127.5, 128.4, 128.5, 129.1, 132.3, 135.0 (CH), 135.7, 136.1, 139.5 (C), 142.0 (CH), 159.5 (d, J = 26 Hz, CF), 162.6, 167.5, 173.1 (C).

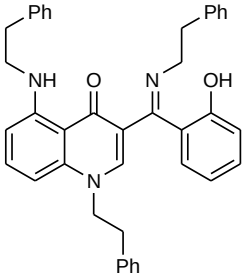
MS (GC, 70eV): *m/z* (%) = 570 (M^+, 30), 569 (14), 568 (32), 450 (31), 360 (32), 310 (35),

105 (100).

HRMS (EI): Calcd for $C_{32}H_{26}N_2O_2FBr^{81}$ (M^+) 570.11357. Found 570.11322.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2919 (w), 1619 (m), 1581 (m), 1556 (m), 1489 (m), 1380 (m), 1332 (m), 1281 (m), 1226 (m), 1169 (m), 1081 (w), 1056 (w), 999 (w), 925 (w), 895 (w), 818 (m), 786 (w), 748 (m), 698), 565 (m).

(*E*)-3-((2-hydroxyphenyl)(phenethylimino)methyl)-1-phenethyl-5-(phenetylamino)quinolin-4(1*H*)-one (3.3.9).



Starting from 3-(2,6-fluorobenzoil)-4*H*-chromen-4-one **3.3.4k** (0.286 g, 1 mmol), phenethyl amine (0.242 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.9** was isolated as yellow viscous oil (0.242 g, 41%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.96-3.13 (m, 6H, 3xCH_2), 3.37-3.46 (m, 4H, 2xCH_2), 4.09 (br. s, 2H, CH_2), 4.55-4.63 (m, 2H, CH_2), 6.28 (s, 1H, CH_{Ar}), 6.42 (d, 1H, ^3J = 7.5 Hz, CH_{Ar}), 6.53-6.59 (m, 2H, CH_{Ar}), 6.78-6.81 (m, 1H, CH_{Ar}), 6.90-7.00 (m, 3H, CH_{Ar}), 7.12-7.31 (s, 14H, CH_{Ar}), 7.46 (t, 1H, ^3J = 8.4 Hz, CH_{Ar}), 10.32 (t, 1H, ^3J = 4.6 Hz, NH), 15.57 (br. s, 1H, OH).

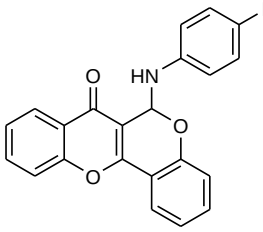
^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 34.1, 35.3, 37.0, 44.9, 53.0, 55.5 (CH_2), 99.5, 103.0 (CH), 111.9, 114.7 (C), 117.2, 118.0 (CH), 119.6 (C), 126.1, 126.3, 127.2, 128.3, 128.4, 128.6, 128.7, 129.0, 129.2, 130.5, 132.1, 133.9, 136.6 (CH), 139.4, 139.9 (C), 140.9 (CH), 141.7, 152.3, 163.5, 168.7, 177.8 (C).

MS (GC, 70eV): *m/z* (%) = 591 (M^+, 16), 500 (15), 396 (18), 105 (15), 43 (100).

HRMS (ESI): Calcd for $C_{40}H_{37}N_3O_2$ (M+H) 592.29585. Found 592.29622.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3207 (w), 3026 (w), 2922 (w), 2851 (w), 1631 (m), 1596 (m), 1570 (m), 1513 (m), 1469 (m), 1452 (m), 1303 (m), 1268 (m), 1186 (m), 1152 (m), 1080 (w), 908 (w), 850 (w), 796 (w), 746 (s), 697 (s).

6-((4-fluoro phenyl)amino)chromeno[4,3-*b*]chromen-7(6*H*)-one (3.3.10a).



Starting from 3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4a** (0.268 g, 1 mmol), p-fluoro aniline (0.222 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.10a** was isolated as yellow solid (0.302 g, 84%), mp 274-276 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.71 (d, 1H, ^3J = 8.0 Hz, C*H*NH), 6.86-6.91 (m, 2H, CH_{Ar}), 6.99-7.07 (m, 4H, CHN*H*, CH_{Ar}), 7.23 (t, 1H, ^3J = 8.0 Hz, CH_{Ar}), 7.48-7.58 (m, 2H, CH_{Ar}), 7.83-7.93 (m, 2H, CH_{Ar}), 8.03-8.12 (m, 2H, CH_{Ar}).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -126.5 (CF).

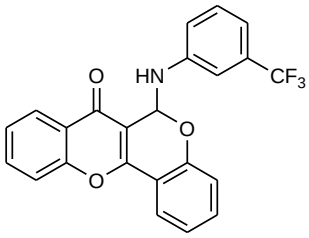
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 77.8 (CH), 110.3 (C), 114.4 (d, ^{3}J = 8.0 Hz, CH), 115.3 (CH), 115.5 (C), 115.6 (CH), 118.4 (d, ^{3}J = 8.0 Hz, CH), 121.7 (CH), 123.7 (C), 123.8, 125.0, 125.6, 133.8, 134.5 (CH), 140.1 (d, ^{2}J = 50.8 Hz, C), 141.9, 154.5, 155.0, 155.2 (C), 155.6 (d, ^{1}J = 232.8 Hz, CF), 173.5 (C=O).

MS (GC, 70eV): *m/z* (%) = 359 (M^+, 1), 249 (100).

HRMS (ESI): Calcd for $C_{22}H_{15}FNO_3$ (M+H) 360.10305. Found 360.1038.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3312 (m), 2958 (w), 1636 (s), 1603 (m), 1563 (w), 1530 (m), 1506 (s), 1464 (s), 1426 (s), 1347 (w), 1306 (m), 1253 (w), 1207 (m), 1149 (m), 1130 (m), 1088 (m), 1027 (w), 921 (s), 867 (m), 825 (s), 760 (s), 700 (m), 658 (m), 603 (m), 554 (m).

6-((3-trifluoromethyl)phenyl)amino)chromeno[4,3-*b*]chromen-7(6*H*)-one (3.3.10b).



Starting from 3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4a** (0.268 g, 1 mmol), m-trifluoromrthyl aniline (0.322 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.10b** was isolated as yellow solid (0.303 g, 74%), mp 277-279 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.83 (d, 1H, ^{3}J = 7.7 Hz, NHC*H*), 7.04-7.07 (m, 2H, N*H*CH, CH_{Ar}), 7.14-7.27 (m, 3H, CH_{Ar}), 7.40-7.45 (m, 1H, CH_{Ar}), 7.49-7.58 (m, 3H, CH_{Ar}), 7.84-7.91 (m, 2H, CH_{Ar}), 8.05-8.13 (m, 2H, CH_{Ar}),

^{19}F NMR (282 MHz, $CDCl_3$): δ = -61.3 (CF_3).

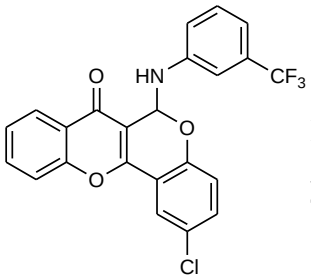
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 76.9 (CH), 109.4 (q, *J* = 4 Hz, CH), 110.0 (C), 114.5 (q, *J* = 4 Hz, CH), 115.4 (C), 117.0, 118.3, 118.5, 122.1 (CH), 123.6 (C), 123.9 (CH), 124.3 (q, ^{1}J = 272 Hz, CF_3), 125.0, 125.7 (CH), 129.9 (q, ^{2}J = 31 Hz, CCF_3), 130.2, 133.9, 134.6 (CH), 145.9, 154.3, 155.1, 155.2, 173.5 (C).

MS (GC, 70eV): *m/z* (%) = 409 (M^+, 1), 249 (100).

HRMS (ESI): Calcd for $C_{23}H_{14}NNaO_3F_3$ (M+Na) 432.0818. Found 432.08149.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3297 (w), 1634 (m), 1601 (m), 1563 (m), 1539 (m), 1489 (m), 1466 (m), 1425 (s), 1342 (s), 1312 (m), 1263 (m), 1214 (m), 1166 (m), 1136 (m), 1089 (s), 1068 (s), 1025 (m), 996 (w), 927 (m), 868 (m), 856 (m), 760 (s), 695 (s), 564 (m).

2-chlorio-6-((3-trifluoromethyl)phenyl)amino)chromeno[4,3-*b*]chromen-7(6*H*)-one (3.3.10c).



Starting from 6-chloro-3-(2-fluorobenzoil)-4*H*-chromen-4-on **3.3.4f** (0.302 g, 1 mmol), m-trifluoromrthyl aniline (0.322 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.9c** was isolated as yellow solid (0.222 g, 50%), mp 272-274 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 6.87 (d, 1H, ^3J = 7.7 Hz, NHC*H*), 7.05-7.13 (m, 3H, N*H*CH, CH_{Ar}), 7.17-7.20 (m, 1H, CH_{Ar}), 7.39-7.47 (m, 1H, CH_{Ar}), 7.50-7.59 (m, 3H, CH_{Ar}), 7.90-7.95 (m, 2H, OH, CH_{Ar}), 8.09-8.12 (m, 2H, CH_{Ar}).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -61.3 (CF_3).

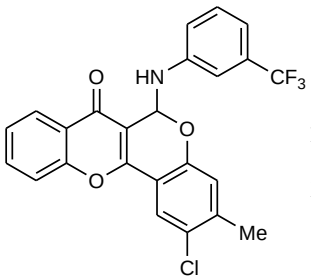
^{13}C NMR Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 443 (M^+, 36), 441 (100), 145 (20).

HRMS (ESI): Calcd for $C_{23}H_{13}ClF_3NNaO_3$ (M+Na) 466.04283. Found 466.04275.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3292 (w), 1620 (m), 1562 (m), 1465 (m), 1409 (s), 1376 (m), 1339 (w), 1291 (m), 1248 (m), 1211 (m), 1168 (m), 1138 (m), 1090 (s), 1046 (m), 927 (m), 861 (m), 821 (s), 782 (m), 761 (s), 693 (s), 659 (m), 612 (m), 598 (m).

2-chloro-3-methyl-6-((3-trifluoromethyl)phenyl)amino)chromeno[4,3-*b*]chromen-7(6*H*)-one (3.3.10d).



Starting from 3-(2-fluorobenzoil)-6-chloro-7-methyl-4*H*-chromen-4-one **3.3.4g** (0.316 g, 1 mmol), m-trifluoromrthyl aniline (0.322 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.10d** was isolated as white solid (0.247 g, 54%), mp 297-299 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.33 (s, 3H, Me), 6.83 (d, 1H, ^3J = 7.9 Hz, NHC*H*), 7.05-7.21 (m, 4H, N*H*CH, CH_{Ar}), 7.39-7.58 (m, 3H, CH_{Ar}), 7.90-7.93 (m, 2H, CH_{Ar}), 8.04 (s, 1H, CH_{Ar}), 8.10 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -61.2 (CF_3).

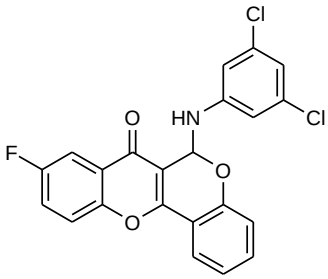
^{13}C NMR Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 457 (M^+, 1), 297 (100), 161 (26).

HRMS (ESI): Calcd for $C_{24}H_{15}NClF_3NaO_3$ (M+Na) 480.05848. Found 480.05841.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3307 (w), 1614 (m), 1573 (w), 1540 (m), 1477 (m), 1427 (m), 1337 (s), 1294 (w), 1270 (w), 1246 (w). 1165 (m), 1111 (s), 1068 (s), 1005 (w), 974 (w), 921 (m), 893 (s), 876 (m), 856 (m), 838 (m), 783 (m), 764 (s), 695 (m), 675 (m), 554 (m).

6-((3,5-dichlorophenyl)amino)-9-fluorochromeno[4,3-*b*]chromen-7(6*H*)-one (3.3.10e).



Starting from 3-(2,5-fluorobenzoil)-4*H*-chromen-4-one **3.3.4i** (0.286 g, 1 mmol), 3,5-dichloro aniline (0.324 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.10e** was isolated as white solid (0.304 g, 71%), mp 285-286 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 6.83 (d, 1H, ^3J = 7.6 Hz, NHC*H*), 6.90 (br. s, 3H, CH_{Ar}), 7.10 (d, 1H, ^3J = 8.1 Hz, N*H*CH), 7.25 (t, 1H, ^3J = 7.2 Hz, CH_{Ar}), 7.51-7.60 (m, 2H, CH_{Ar}), 7.78-7.83 (m, 2H, CH_{Ar}), 7.96-8.00 (m, 1H, CH_{Ar}), 8.06 (m, 1H, CH_{Ar}).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -114.9 (CF).

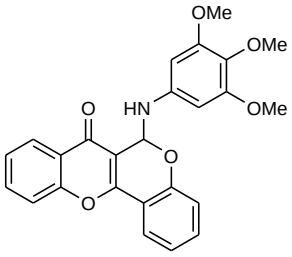
^{13}C NMR Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 427 (M^+, 1), 297 (100).

HRMS (ESI): Calcd for $C_{22}H_{12}NCl_2FO_3$ (M+H) 428.01783. Found 428.01788.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3290 (m), 1626 (m), 1580 (s), 1556 (s), 1479 (m), 1446 (m), 1409 (m), 1356 (m), 1272 (w), 1253 (m), 1209 (m), 1129 (m), 1105 (m), 1088 (m), 1014 (w), 989 (w), 961 (m), 923 (m), 872 (m), 824 (m), 773 (m), 763 (s), 746 (m), 668 (m), 611 (m).

6-((3,4,5-trimethoxyphenyl)amino)chromeno[4,3-*b*]chromen-7(6*H*)-one (3.3.10f).



Starting from 3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4c** (0.268 g, 1 mmol), 3,4,5-trimethoxy aniline (0.366 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.10f** was isolated as yellow solid (0.302 g, 60%), mp 265-267 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.57 (s, 3H, OMe), 3.74 (s, 6H, 2xOMe), 6.18 (s, 2H, CH_{Ar}), 6.74 (d, 1H, ^3J = 7.4 Hz, NHC*H*), 6.95 (d, 1H, ^3J = 7.4 Hz, CH_{Ar}), 7.08 (d, 1H, ^3J = 8.2 Hz, N*H*CH), 7.22 (t, 1H, ^3J = 7.4 Hz, CH_{Ar}), 7.50-7.57 (m, 2H, CH_{Ar}), 7.84-7.92 (m, 2H, CH_{Ar}), 8.03-8.12 (m, 2H, CH_{Ar}).

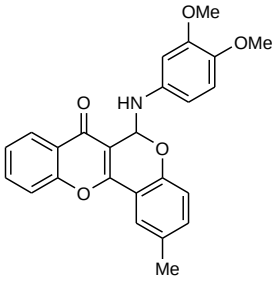
^{13}C NMR Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 431 (M^+, 3), 249 (100).

HRMS (ESI): Calcd for $C_{25}H_{22}NO_6$ (M+H) 432.14416. Found 432.14418.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3322 (m), 2938 (w), 1638 (s), 1600 (s), 1563 (m), 1530 (m), 1509 (m), 1456 (s), 1422 (s), 1348 (w), 1310 (w), 1236 (s), 1196 (s), 1121 (s), 1101 (s), 1010 (m), 912 (m), 883 (m), 850 (m), 804 (m), 757 (s), 705 (m), 651 (m).

6-((3,4-dimethoxyphenyl)amino)-2-methylchromeno[4,3-*b*]chromen-7(6*H*)-one (3.3.10g).



Starting from 6-methyl-3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4d** (0.282 g, 1 mmol), 3,4-dimethoxy aniline (0.306 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.10g** was isolated as yellowsolid (0.249 g, 60%), mp 258-260 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.38 (s, 3H, Me), 3.67 (s, 3H, OMe), 3.69 (s, 3H, OMe), 6.44-6.46 (m, 2H, CH_{Ar}), 6.64 (d, 1H, ^3J = 7.8 Hz, NHC*H*), 6.74 (d, 1H, ^3J = 7.8 Hz, CH_{Ar}), 6.81 (d, 1H, ^3J = 7.8 Hz, CH_{Ar}), 6.94 (d, 1H, ^3J = 7.8 Hz, N*H*CH), 7.29-7.33 (m, 1H, CH_{Ar}), 7.51-7.56 (m, 1H, CH_{Ar}), 7.83-7.7.91 (m, 3H, CH_{Ar}), 8.09 (d, 1H, ^3J = 7.4 Hz, CH_{Ar}).

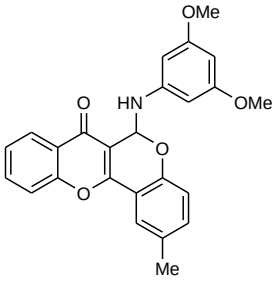
^{13}C NMR Due to bed solubility it was not possible to measure.

MS (GC, 70eV): *m/z* (%) = 415 (M^+, 3), 263 (100).

HRMS (ESI): Calcd for $C_{25}H_{22}NO_5$ (M+H) 416.14925. Found 416.14892.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3312 (m), 1635 (s), 101 (m), 1515 (m), 1463 (s), 1429 (s), 1355 (w), 1318 (m), 1296 (w), 1257 (m), 1227 (s), 1202 (s), 1168 (m), 1134 (s), 1106 (s), 1028 (m), 928 (m), 910 (m), 859 (m), 828 (s), 786 (m), 757 (s), 702 (m), 670 (m).

6-((3,5-dimethoxyphenyl)amino)-2-methylchromeno[4,3-*b*]chromen-7(6*H*)-one (3.3.10c).



Starting from 6-methyl-3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4d** (0.282 g, 1 mmol), 3,5-dimethoxy aniline (0.306 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.10h** was isolated as yellowsolid (0.228 g, 55%), mp 268-270 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.38 (s, 3H, Me), 3.68 (s, 6H, 2xOMe), 5.92 (t, 1H, ^4J = 2 Hz, CH_{Ar}), 6.04 (d, 2H, ^4J = 2 Hz, CH_{Ar}), 6.67 (d, 1H, ^3J = 7.7 Hz, NHC*H*), 6.96 (d, 1H, ^3J = 8.3 Hz, CH_{Ar}), 7.02 (d, 1H, ^3J = 7.7 Hz, N*H*CH), 7.30-7.34 (m, 1H, CH_{Ar}), 7.51-7.57 (m, 1H, CH_{Ar}), 7.83-7.7.93 (m, 3H, CH_{Ar}), 8.10 (d, 1H, ^3J = 8.1 Hz, CH_{Ar}).

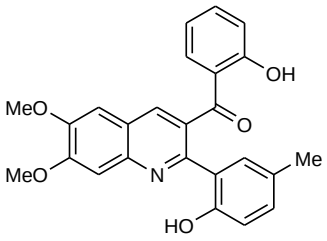
^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.2 (Me), 54.8 (OMe), 77.1, 90.8, 92.2 (CH), 110.3, 115.3 (C), 118.2, 118.4, 123.5 (CH), 123.7 (C), 125.0, 125.6 (CH), 130.9 (C), 134.5 (CH), 147.2, 152.4, 155.2, 161.1, 173.5 (C).

MS (GC, 70eV): *m/z* (%) = 415 (M^+, 3), 263 (100).

HRMS (ESI): Calcd for $C_{25}H_{22}NO_5$ (M+H) 416.14925. Found 416.14974.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3317 (m), 1634 (m), 1596 (s), 1564 (s), 1540 (m), 1465 (s), 1429 (s), 1343 (w), 1296 (w), 1224 (w), 1195 (s), 1175 (m), 1144 (s), 1109 (s), 1059 (m), 1001 (m), 928 (m), 910 (m), 860 (s), 812 (s), 786 (m), 758 (s), 705 (m), 677 (s), 621 (m), 560 (m).

6-((3,4-dimethoxyphenyl)amino)-2-methylchromeno[4,3-*b*]chromen-7(6*H*)-one (3.3.11g).



Starting from 6-methyl-3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4d** (0.282 g, 1 mmol), 3,4-dimethoxy aniline (0.306 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.12g** was isolated as yellow solid (0.042 g, 10%), mp 173-174 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.08 (s, 3H, Me), 4.04 (s, 3H, OMe), 4.10 (s, 3H, OMe), 6.62-6.69 (m, 1H, CH_{Ar}), 6.92 (d, 1H, ^3J = 8.4 Hz, NHC*H*), 7.00-7.05 (m, 2H, CH_{Ar}), 7.11 (s, 1H, CH_{Ar}), 7.14-7.24 (m, 3H, CH_{Ar}), 7.42 (s, 1H, CH_{Ar}), 8.15 (s, 1H, Py), 11.84 (s, 1H, OH), 12.72 (br. s, 1H, OH).

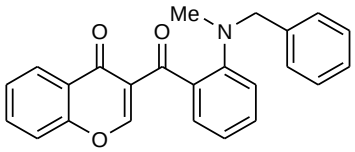
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.2 (Me), 56.3, 56.5 (OMe), 105.3, 106.5, 117.9, 118.2, 119.0 (CH), 119.1, 120.1, 121.1, 128.4, 129.4 (C), 130.1, 131.2, 132.4, 136.9, 138.1 (CH), 142.9, 150.9, 153.7, 154.6, 158.2, 161.3, 201.8 (C).

MS (GC, 70eV): *m/z* (%) = 415 (M^+, 3), 263 (100).

HRMS (ESI): Calcd for $C_{25}H_{22}NO_5$ (M+H) 416.14925. Found 416.14892.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3305 (s), 1619 (w), 1580 (w), 1499 (m), 1474 (m), 1372 (w), 1282 (w), 1243 (m), 1195 (m), 1155 (m), 1009 (m), 953 (w), 910 (w), 886 (w), 851 (m), 827 (m), 777 (m), 757 (m), 711 (m), 689 (m), 656 (m).

3-(2-(benzyl(metyl)amino)benzyl)-4*H*-chromen-4-one (3.3.13).



Starting from 3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4c** (0.268 g, 1 mmol), *N*-methyl-1-phenylmethanamine (0.242 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.8g** was isolated as white solid (0.336 g, 91%), mp 149-150 ^oC.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3H, Me), 3.90 (q, 2H, ^3J = 9.7 Hz, CH_2), 6.48 (s, 1H, Chromone), 7.04-7.11 (m, 2H, CH_{Ar}), 7.15-7.33 (m, 5H, CH_{Ar}), 7.38-7.49 (m, 2H, CH_{Ar}), 7.53-7.56 (m, 1H, CH_{Ar}), 7.65-7.72 (m, 1H, CH_{Ar}), 7.89 (dd, 1H, ^3J = 8.2 Hz, ^4J = 1.8 Hz, CH_{Ar}).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 35.5 (Me), 56.6 (CH_2), 88.4, 109.2, 114.8 (C), 116.36, 117.9, 120.8, 123.6 (CH), 124.4 (C), 125.1, 126.0, 127.0, 128.2, 128.6, 133.6, 133.9 (CH), 155.5, 156.5, 157.7, 175.1 (C).

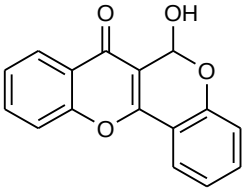
MS (GC, 70eV): *m/z* (%) = 369 (M^+, 1), 249 (100), 120 (27).

HRMS (ESI): Calcd for $C_{24}H_{20}NO_3$ (M+H) 370.14377. Found 370.14384.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2997 (w), 1640 (m), 1601 (m), 1563 (m), 1485 (w), 1463 (m), 1416 (s),

1350 (m), 1330 ‘(m), 1258 (m), 1209 (m), 1164 (m), 1148 (m), 1107 (w), 1047 (s), 994 (w), 964 (m), 906 (m), 882 (m), 840 (m)m 790 (w), 758 (s), 744 (s), 698 (s), 663 (m), 638 (m).

6-Hydroxychromeno[4,3-*b*]chromen-7(6*H*)-one (3.3.14).



3.3.14 was isolated as white solid, mp 240-241 ^{o}C.

^{1}H NMR (300 MHz, DMSO): δ = 6.55 (s, 1H, C*H*OH), 7.16-7.27 (m, 2H, CH_{Ar}), 7.50-7.61 (m, 2H, CH_{Ar}), 7.64 (br. s, 1H, CHO*H*), 7.79-7.90 (m, 2H, CH_{Ar}), 8.01-8.04 (m, 1H, CH_{Ar}), 8.09-8.12 (m, 1H, CH_{Ar}).

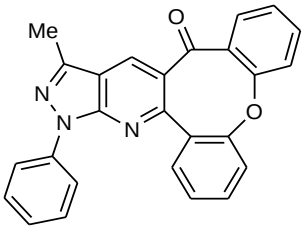
^{13}C NMR (62.9 MHz, DMSO): δ = 87.3 (CHOH), 111.5, 114.6 (C), 117.9, 118.5, 122.0, 123.6 (CH), 123.7 (C), 125.0, 125.6, 133.8, 134.5 (CH), 154.1, 154.6, 155.1, 173.8 (C).

MS (GC, 70eV): *m/z* (%) = 266 (M^{+}, 100).

HRMS (EI): calcd for $C_{16}H_{10}O_4$ (M^{+}) 266.05791, found 266.05793.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3024 (w), 1641 (m), 1600 (m), 1557 (m), 1477 (w), 1416 (s), 1351 (m), 1331 (m), 1258 (m), 1210 (m), 1164 (m), 1100 (w), 1051 (s), 994 (w), 906 (m), 882 (m), 840 (m)m 790 (w), 758 (s), 698 (s), 650 (m).

13-methyl-11-phenyldibenzo[2,3:7,8]oxocino[4,5-*b*]pyrazolo[4,3-*e*]pyridine-15(11*H*)-one (3.3.15).



Starting from 3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4a** (0.268 g, 1 mmol), 4-amino-1*H*-imidazole-2(3*H*)-thione **E3** (0.346 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) in 7 mL DMF. **3.3.13** was isolated as yellowsolid (0.286 g, 71%), mp 250-251 ^{o}C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.40 (s, 3H, Me), 6.07-7.10 (m, 1H, CH_{Ar}), 7.17-7.45 (m, 7H, CH_{Ar}), 7.51-7.57 (m, 1H, CH_{Ar}), 7.66 (dd, 1H, ^{3}J = 7.4 Hz, ^{3}J = 1.7 Hz, CH_{Ar}), 7.98-8.01 (m, 2H, CH_{Ar}), 8.28-8.31 (m, 2H, CH_{Ar}).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.5 (Me), 115.7 (C), 120.6, 121.7, 122.4, 125.0, 125.6, 126.1, 129.0, 130.1, 130.6, 130.8, 130.9, 131.6 (CH), 132.8, 133.7 (C), 135.2 (CH), 139.4, 143.3, 150.7, 151.1, 127.5, 161.1, 194.9 (C).

MS (GC, 70eV): *m/z* (%) = 403 (M^{+}, 100).

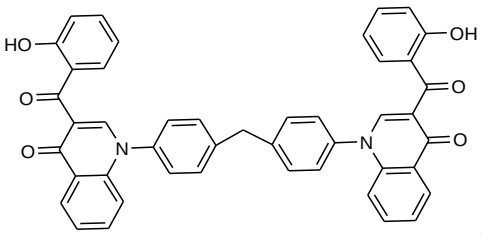
HRMS (ESI): Calcd for $C_{26}H_{18}N_3O_2$ (M+H) 404.13935, found 404.1389.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3064 (s), 1645 (w), 1594 (s), 1495 (m), 1446 (m), 1382 (m), 1340 (w), 1308 (m), 1280 (s), 1210 (m), 1120 (m), 1102 (m), 1080 (m), 998 (w), 908 (w), 781 (m), 754 (s), 711 (m), 689 (s), 661 (m), 626 (m), 607 (m).

*A.2.25. General procedure for the synthesis of compound **3.3.14**:*

Corresponding *ortho*-F-benzoyl chromone derivative **3.3.4** (2 equiv.), appropriate amine (1 equiv.) and K_2CO_3 (4 equiv.) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMF (7 mL/1 mmol of **3.3.4**). The mixture was heated at 120 °C for 30 h (controlled by TLC). After the reaction was completed volatiles were evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (Heptane : Ethyl acetate - 1:1).

1,1'-(methylenbis(4,1-phenylene))bis(3-(2-hydroxybenzoyl)quinolin-4(1*H*)-one (3.3.16).



Starting from 3-(2-fluorobenzoil)-4*H*-chromen-4-one **3.3.4a** (0.536 g, 2 mmol), 4,4'-methylendiamine (0.198 g, 1 mmol) and K_2CO_3 (0.552 g, 4 mmol) in 7 mL DMF. **3.3.14** was isolated as yellowsolid (0.458 g, 66%), mp more than 375 ^{o}C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.72 (s, 2H, CH_2), 6.71 (d, 2H, ^{3}J = 8.0 Hz, CH_{Ar}), 6.82 (d, 2H, ^{3}J = 8.3 Hz, CH_{Ar}), 7.00-7.06 (m, 8H, CH_{Ar}), 7.19-7.24 (m, 2H, CH_{Ar}), 7.47-7.57 (m, 6H, CH_{Ar}), 7.84-7.92 (m, 4H, OH, CH_{Ar}), 8.03-8.12 (m, 4H, CH_{Ar}).

^{13}C NMR Due to bed solubility it was not possible to measure.

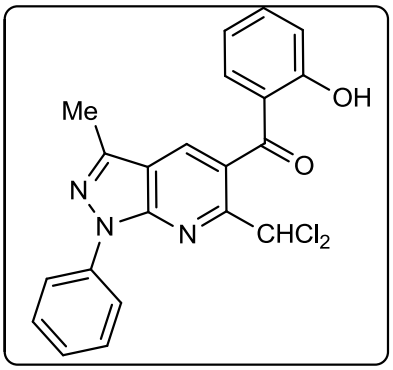
MS (GC, 70eV): *m/z* (%) = 694 (M^+, 100).

HRMS (ESI): Calcd for $C_{45}H_{31}N_2O_6$ (M+H) 695.21766. Found 695.21771.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3305 (m), 1626 (s), 1559 (s), 1517 (m), 1466 (m), 1427 (s), 1297 (m), 1249 (m), 1212 (m), 1137 (m), 1095 (m), 915 (m), 849 (m), 812 (m), 754 (s), 701 (m), 663 (m), 599 (m), 558 (m).

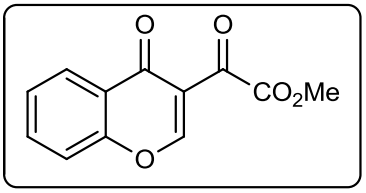
A3. Crystallographic data

Crystal data and structure refinement for ***2.3.3e***



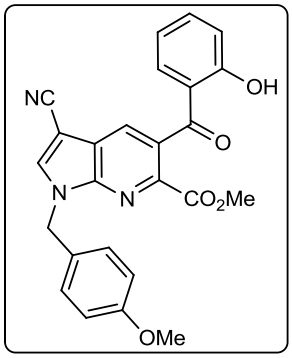
Identification code	sm305	
Empirical formula	$C_{21}H_{15}Cl_2N_3O_2$	
Formula weight	412.26	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 12.5227 (3) Å	α = 90°
	b = 14.4854 (3) Å	β = 111.858 (1)°
	c = 11.1599 (2) Å	γ = 90°
Volume	1878.83 (3) Å^3	
Z	4	
Calculated density	1.457 mg/m^3	
Absorption coefficient	0.37 mm^{-1}	
F(000)	848	
Crystal size	0.31 x 0.16 x 0.12 mm	
Θ range for data collection	4.8 to 59.7°	
Limiting indices:	-16≤h≤17, -20≤k≤19, -15≤l≤15	
Reflections collected / unique	20936/ 5421 [R(Int) = 0.0305]	
Completeness to Θ	27.58°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5421 / 0 / 258	
Goodness-of-fit on F^2	1.079	
Final R indices [I>2σ(I)]	R1 = 0.0578, wR2 = 0.1057	
R indices (all data)	R1 = 0.0394, wR2 = 0.0985	
Largest diff. peak and hole	0.372 and -0.390 e. Å^{-3}	

*Crystal data and structure refinement for **2.4.1***



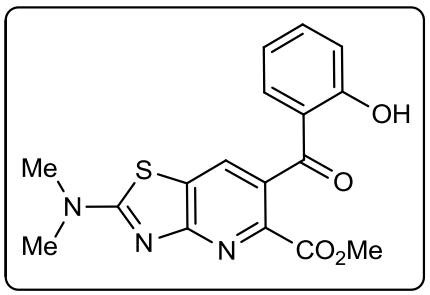
Identification code	g104	
Empirical formula	$C_{12}H_8O_5$	
Formula weight	232.18	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/n$	
Unit cell dimensions	a = 10.4760 (8) Å	α = 90°
	b = 6.7599 (5) Å	β = 93.438 (1)°
	c = 14.5944 (10) Å	γ = 90°
Volume	1031.67 (13) Å^3	
Z	4	
Calculated density	1.495 mg/m^3	
Absorption coefficient	0.12 mm^{-1}	
F(000)	480	
Crystal size	1.00 x 0.22 x 0.04 mm	
Θ range for data collection	4.9 to 53.6°	
Limiting indices:	-14≤h≤13, -6≤k≤9, -20≤l≤20	
Reflections collected / unique	20936 / 5421 [R(Int) = 0.0355]	
Completeness to Θ	27.59°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2982 / 0 / 155	
Goodness-of-fit on F^2	1.011	
Final R indices [I>2σ(I)]	R1 = 0.0946, wR2 = 0.1368	
R indices (all data)	R1 = 0.0494, wR2 = 0.1225	
Largest diff. peak and hole	0.321and -0.206 e. Å^{-3}	

Crystal data and structure refinement for ***2.4.2i***



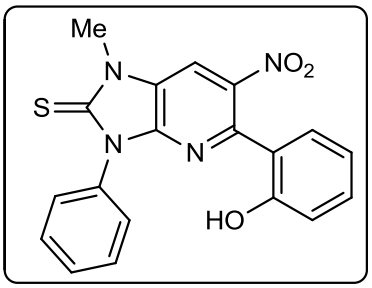
Identification code	sm305	
Empirical formula	$C_{21}H_{15}Cl_2N_3O_2$	
Formula weight	412.26	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 12.5227 (3) Å	α = 90°
	b = 14.4854 (3) Å	β = 111.858 (1)°
	c = 11.1599 (2) Å	γ = 90°
Volume	1878.83 (7) $Å^3$	
Z	4	
Calculated density	1.457 mg/m^3	
Absorption coefficient	0.37 mm^{-1}	
F(000)	480	
Crystal size	0.37 x 0.16 x 0.12 mm	
Θ range for data collection	4.8 to 59.7°	
Limiting indices:	-16≤h≤17, -20≤k≤19, -15≤l≤15	
Reflections collected / unique	20936/ 5421 [R(Int) = 0.0305]	
Completeness to Θ	27.58°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5421 / 0 / 258	
Goodness-of-fit on F^2	1.079	
Final R indices [I>2σ(I)]	R1 = 0.0578, wR2 = 0.1057	
R indices (all data)	R1 = 0.0394, wR2 = 0.0985	
Largest diff. peak and hole	0.372 and -0.390 e. $Å^{-3}$	

Crystal data and structure refinement for ***2.4.2l***



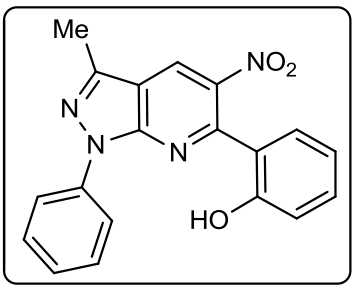
Identification code	sm285	
Empirical formula	$C_{17}H_{15}N_3O_4S$	
Formula weight	357.38	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 15.5148 (4) Å	α = 90°
	b = 8.3533 (2) Å	β = 98.6393 (1)°
	c = 12.6393 (3) Å	γ = 90°
Volume	1619.37 (7) Å^3	
Z	4	
Calculated density	1.466 mg/m^3	
Absorption coefficient	0.23 mm^{-1}	
F(000)	744	
Crystal size	0.44 x 0.42 x 0.08 mm	
Θ range for data collection	5.6 to 60.0°	
Limiting indices:	-13≤h≤21, -8≤k≤11, -17≤l≤15	
Reflections collected / unique	17166 / 4697 [R(Int) = 0.0223]	
Completeness to Θ	27.34°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4697 / 0 / 233	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2σ(I)]	R1 = 0.0480, wR2 = 0.1068	
R indices (all data)	R1 = 0.0377, wR2 = 0.1017	
Largest diff. peak and hole	0.358 and -0.345 e. Å^{-3}	

Crystal data and structure refinement for ***2.5.3d***



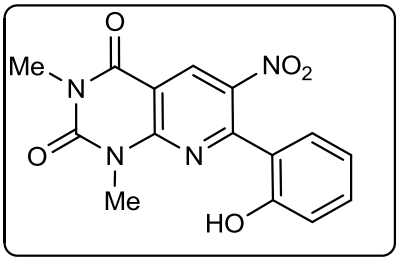
Identification code	sm282	
Empirical formula	$C_{19}H_{14}N_4O_3S.CHCl_3$	
Formula weight	497.77	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 14.2696 (9) Å	α = 90°
	b = 5.9365 (4) Å	β = 95.353 (2)°
	c = 25.2475 (16) Å	γ = 90°
Volume	2129.4 (2) $Å^3$	
Z	4	
Calculated density	1.533 mg/m^3	
Absorption coefficient	0.56 mm^{-1}	
F(000)	744	
Crystal size	0.40 x 0.10 x 0.06 mm	
Θ range for data collection	5.7 to 49.7°	
Limiting indices:	-13≤h≤21, -8≤k≤11, -17≤l≤15	
Reflections collected / unique	15941 / 4195 [R(Int) = 0.0493]	
Completeness to Θ	23.22°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4195 / 0 / 286	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2σ(I)]	R1 = 0.1073, wR2 = 0.1161	
R indices (all data)	R1 = 0.0498, wR2 = 0.1013	
Largest diff. peak and hole	1.196 and -0.678 e. $Å^{-3}$	

*Crystal data and structure refinement for **2.5.3e***



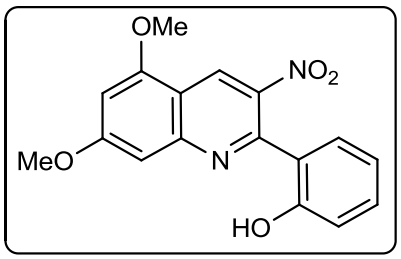
Identification code	ag045	
Empirical formula	$C_{19}H_{14}N_4O_3$	
Formula weight	346.34	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/n$	
Unit cell dimensions	a = 11.1798 (3) Å	α = 90°
	b = 8.3934 (5) Å	β = 99.528 (2)°
	c = 17.7153 (5) Å	γ = 90°
Volume	1639.41 (9) Å^3	
Z	4	
Calculated density	1.403 mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	720	
Crystal size	0.42 x 0.23 x 0.15 mm	
Θ range for data collection	4.7 to 61.4°	
Limiting indices:	-15≤h≤12, -11≤k≤11, -24≤l≤24	
Reflections collected / unique	18031 / 4769 [R(Int) = 0.0332]	
Completeness to Θ	27.67°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4769 / 0 / 240	
Goodness-of-fit on F^2	1.083	
Final R indices [I>2σ(I)]	R1 = 0.0606, wR2 = 0.1182	
R indices (all data)	R1 = 0.0429, wR2 = 0.1105	
Largest diff. peak and hole	0.316 and -0.259 e. Å^{-3}	

Crystal data and structure refinement for ***2.5.3j***



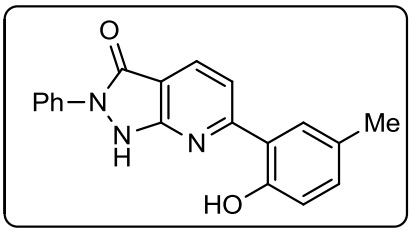
Identification code	ag050	
Empirical formula	$C_{15}H_{12}N_4O_5$	
Formula weight	328.29	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/n$	
Unit cell dimensions	a = 8.2923 (3) Å	α = 90°
	b = 16.8902 (5) Å	β = 90.925 (2)°
	c = 17.7153 (5) Å	γ = 90°
Volume	1517.44 (8) $Å^3$	
Z	4	
Calculated density	1.437 mg/m^3	
Absorption coefficient	0.11 mm^{-1}	
F(000)	680	
Crystal size	0.33 x 0.28 x 0.09 mm	
Θ range for data collection	4.8 to 60.9°	
Limiting indices:	$-11\leq h\leq 11$, $-14\leq k\leq 15$, $-23\leq l\leq 23$	
Reflections collected / unique	16871 / 4437 [R(Int) = 0.0294]	
Completeness to Θ	27.77°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4437 / 0 / 223	
Goodness-of-fit on F^2	1.063	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0631, wR2 = 0.1231	
R indices (all data)	R1 = 0.0420, wR2 = 0.1143	
Largest diff. peak and hole	0.329 and -0.266 e. $Å^{-3}$	

Crystal data and structure refinement for ***2.5.3m***



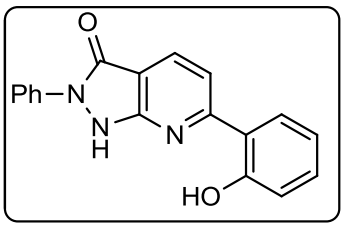
Identification code	sm319	
Empirical formula	$C_{17}H_{14}N_2O_5$	
Formula weight	326.30	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic *Pca*2_1	
Unit cell dimensions	*a* = 15.2372 (17) Å	α = 90°
	b = 13.6592 (15) Å	β = 90°
	c = 14.0634 (14) Å	γ = 90°
Volume	2927.0 (5) Å^3	
Z	8	
Calculated density	1.481 mg/m^3	
Absorption coefficient	0.11 mm^{-1}	
F(000)	1360	
Crystal size	0.51 x 0.25 x 0.14 mm	
Θ range for data collection	4.9 to 59.7°	
Limiting indices:	-19≤h≤20, -18≤k≤18, -19≤l≤19	
Reflections collected / unique	26058 / 7741 [R(Int) = 0.0258]	
Completeness to Θ	27.51°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7741 / 1 / 445	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2σ(I)]	R1 = 0.0442, wR2 = 0.0952	
R indices (all data)	R1 = 0.0357, wR2 = 0.0911	
Largest diff. peak and hole	0.287 and -0.241 e. Å^{-3}	

Crystal data and structure refinement for ***2.6.3a***



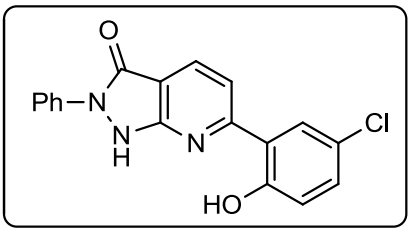
Identification code	ag132	
Empirical formula	$C_{19}H_{15}N_3O_2$	
Formula weight	317.34	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 13.5332 (7) Å	α = 90°
	b = 11.4883 (6) Å	β = 111.013 (2)°
	c = 10.2680 (5) Å	γ = 90°
Volume	1490.24 (13) $Å^3$	
Z	4	
Calculated density	1.414 mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	664	
Crystal size	0.30 x 0.28 x 0.08 mm	
Θ range for data collection	5.5 to 50.3°	
Limiting indices:	$-19\leq h\leq 19$, $-16\leq k\leq 12$, $-14\leq l\leq 14$	
Reflections collected / unique	17580 / 4342 [R(Int) = 0.0571]	
Completeness to Θ	27.6°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4342 / 0 / 226	
Goodness-of-fit on F^2	1.022	
Final R indices [I>2σ(I)]	R1 = 0.0947, wR2 = 0.1206	
R indices (all data)	R1 = 0.0494, wR2 = 0.1064	
Largest diff. peak and hole	0.220 and -0.282 e. $Å^{-3}$	

Crystal data and structure refinement for ***2.6.3b***



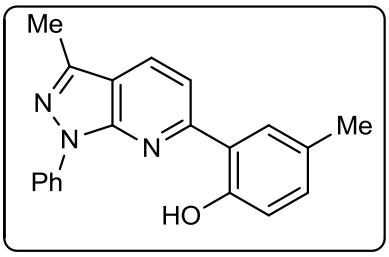
Identification code	ag145	
Empirical formula	$C_{18}H_{13}N_3O_2$	
Formula weight	303.31	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic $P2_12_12_1$	
Unit cell dimensions	a = 6.1634 (6) Å	α = 90°
	b = 11.2748 (10) Å	β = 90°
	c = 19.9532 (5) Å	γ = 90°
Volume	1386.6 (2) Å^3	
Z	4	
Calculated density	1.453 mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	632	
Crystal size	0.55 x 0.13 x 0.06 mm	
Θ range for data collection	5.5 to 43.1°	
Limiting indices:	-7≤h≤8, -14≤k≤14, -25≤l≤25	
Reflections collected / unique	13573 / 3171 [R(Int) = 0.0593]	
Completeness to Θ	24.77°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3171 / 0 / 216	
Goodness-of-fit on F^2	0.990	
Final R indices [I>2σ(I)]	R1 = 0.0759, wR2 = 0.0939	
R indices (all data)	R1 = 0.0446, wR2 = 0.0.848	
Largest diff. peak and hole	0.175 and -0.226 e. Å^{-3}	

Crystal data and structure refinement for ***2.6.3c***



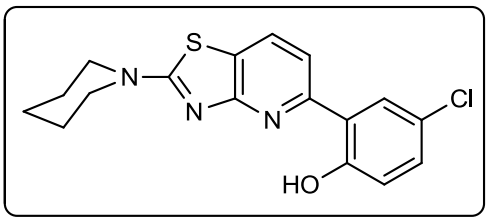
Identification code	ag124	
Empirical formula	$C_{18}H_{12}ClN_3O_2$	
Formula weight	337.76	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 13.5897 (4) Å	α = 90°
	b = 11.4742 (3) Å	β = 110.969 (2)°
	c = 10.2062 (3) Å	γ = 90°
Volume	1486.07 (7) Å^3	
Z	4	
Calculated density	1.510 mg/m^3	
Absorption coefficient	0.27 mm^{-1}	
F(000)	696	
Crystal size	0.33 x 0.26 x 0.14 mm	
Θ range for data collection	5.6 to 64.7°	
Limiting indices:	-18≤h≤18, -15≤k≤15, -13≤l≤13	
Reflections collected / unique	17175 / 3944 [R(Int) = 0.0238]	
Completeness to Θ	26.22°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3944 / 0 / 225	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2σ(I)]	R1 = 0.0454, wR2 = 0.0971	
R indices (all data)	R1 = 0.0347, wR2 = 0.0.971	
Largest diff. peak and hole	0.325 and -0.239 e. Å^{-3}	

Crystal data and structure refinement for ***2.6.5a***



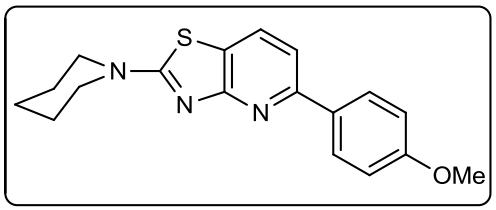
Identification code	ag140	
Empirical formula	$C_{20}H_{17}N_3O$	
Formula weight	315.37	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 12.7467 (5) Å	α = 90°
	b = 16.7588 (6) Å	β = 105.053 (2)°
	c = 7.5184 (3) Å	γ = 90°
Volume	1550.96 (10) Å^3	
Z	4	
Calculated density	1.351 mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	664	
Crystal size	0.70 x 0.21 x 0.07 mm	
Θ range for data collection	4.9 to 61.0°	
Limiting indices:	-17≤h≤17, -22≤k≤22, -10≤l≤7	
Reflections collected / unique	17175 / 3944 [R(Int) = 0.0238]	
Completeness to Θ	26.05°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4114 / 0 / 223	
Goodness-of-fit on F^2	1.097	
Final R indices [I>2σ(I)]	R1 = 0.0612, wR2 = 0.1272	
R indices (all data)	R1 = 0.0443, wR2 = 0.1195	
Largest diff. peak and hole	0.329 and -0.235 e. Å^{-3}	

Crystal data and structure refinement for ***2.6.7d***



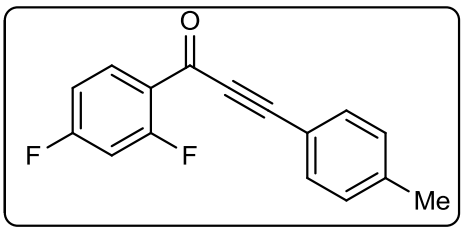
Identification code	ag148	
Empirical formula	$C_{17}H_{16}ClN_3OS$	
Formula weight	345.84	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/n$	
Unit cell dimensions	a = 7.0888 (4) Å	α = 90°
	b = 24.9100 (13) Å	β = 101.728 (3)°
	c = 8.8454 (4) Å	γ = 90°
Volume	1529.33 (14) Å^3	
Z	4	
Calculated density	1.502 mg/m^3	
Absorption coefficient	0.39 mm^{-1}	
F(000)	720	
Crystal size	0.39 x 0.27 x 0.07 mm	
Θ range for data collection	6.1 to 56.7°	
Limiting indices:	$-9\leq h\leq 9$, $-35\leq k\leq 35$, $-12\leq l\leq 11$	
Reflections collected / unique	170935 / 4447 [R(Int) = 0.0463]	
Completeness to Θ	27.51°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4447 / 0 / 212	
Goodness-of-fit on F^2	1.047	
Final R indices [I>2σ(I)]	R1 = 0.0673, wR2 = 0.0933	
R indices (all data)	R1 = 0.0403, wR2 = 0.0855	
Largest diff. peak and hole	0.402 and -0.279 e. Å^{-3}	

Crystal data and structure refinement for ***2.6.18b***



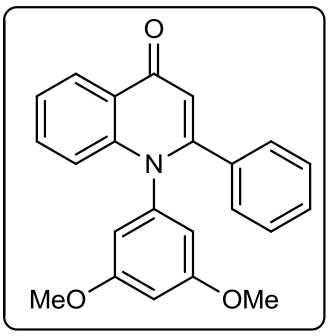
Identification code	ag188	
Empirical formula	$C_{18}H_{19}N_3OS$	
Formula weight	325.42	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic $P2_12_12_1$	
Unit cell dimensions	a = 6.3395 (2) Å	α = 90°
	b = 7.8493 (3) Å	β = 90°
	c = 31.3577 (10) Å	γ = 90°
Volume	1560.38 (10) Å^3	
Z	4	
Calculated density	1.385 mg/m^3	
Absorption coefficient	0.22 mm^{-1}	
F(000)	688	
Crystal size	0.42 x 0.39 x 0.03 mm	
Θ range for data collection	5.2 to 60.9°	
Limiting indices:	-8≤h≤7, -11≤k≤6, -43≤l≤44	
Reflections collected / unique	14344 / 4521 [R(Int) = 0.0322]	
Completeness to Θ	27.1°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4521 / 0 / 209	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2σ(I)]	R1 = 0.0498, wR2 = 0.0824	
R indices (all data)	R1 = 0.0365, wR2 = 0.0772	
Largest diff. peak and hole	0.264 and -0.255 e. Å^{-3}	

*Crystal data and structure refinement for **3.2.2e***



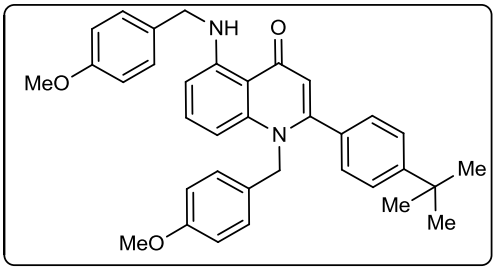
Identification code	sm537	
Empirical formula	$C_{16}H_{10}F_2O$	
Formula weight	256.24	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic $P2_12_12_1$	
Unit cell dimensions	a = 3.8619 (2) Å	α = 90°
	b = 11.3140 (4) Å	β = 90°
	c = 28.0022 (8) Å	γ = 90°
Volume	1223.52 (8) Å^3	
Z	4	
Calculated density	1.391 mg/m^3	
Absorption coefficient	0.11 mm^{-1}	
F(000)	528	
Crystal size	0.45 x 0.13 x 0.09 mm	
Θ range for data collection	4.6 to 47.0°	
Limiting indices:	-5≤h≤5, -15≤k≤15, -38≤l≤35	
Reflections collected / unique	13135 / 3253 [R(Int) = 0.0446]	
Completeness to Θ	26.17°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3253 / 0 / 173	
Goodness-of-fit on F^2	1.007	
Final R indices [I>2σ(I)]	R1 = 0.0888, wR2 = 0.1198	
R indices (all data)	R1 = 0.0463, wR2 = 0.1077	
Largest diff. peak and hole	0.474 and -0.220 e. Å^{-3}	

Crystal data and structure refinement for ***3.2.3f***



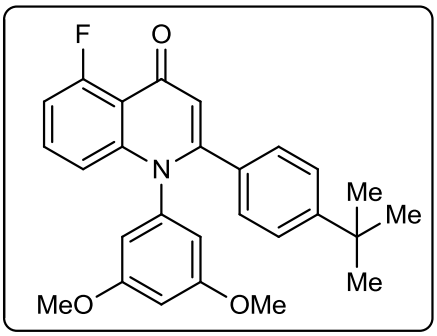
Identification code	sm500	
Empirical formula	$C_{23}H_{19}NO_3$	
Formula weight	357.39	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic *Pbca*	
Unit cell dimensions	*a* = 7.7611 (3) Å	α = 90°
	b = 15.9902 (7) Å	β = 90°
	c = 29.7957 (12) Å	γ = 90°
Volume	3697.7 (3) $Å^3$	
Z	8	
Calculated density	1.284 mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	1504	
Crystal size	0.91 x 0.18 x 0.10 mm	
Θ range for data collection	5.9 to 59.5°	
Limiting indices:	$-10\leq h\leq 9$, $-21\leq k\leq 21$, $-41\leq l\leq 41$	
Reflections collected / unique	20523 / 5250 [R(Int) = 0.0269]	
Completeness to Θ	27.45°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5250 / 0 / 246	
Goodness-of-fit on F^2	1.034	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0738, wR2 = 0.1228	
R indices (all data)	R1 = 0.0512, wR2 = 0.1111	
Largest diff. peak and hole	0.247 and -0.245 e. $Å^{-3}$	

Crystal data and structure refinement for ***3.2.6b***



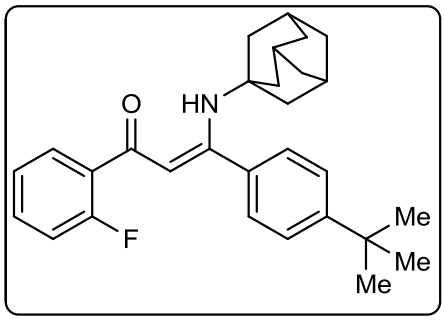
Identification code	sm515r	
Empirical formula	$C_{35}H_{36}N_2O_3$	
Formula weight	532.66	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/n$	
Unit cell dimensions	a = 11.3533 (3) Å	α = 90°
	b = 14.1741 (5) Å	β = 103.552 (1)°
	c = 17.9575 (5) Å	γ = 90°
Volume	2809.31 (15) $Å^3$	
Z	4	
Calculated density	1.259 mg/m^3	
Absorption coefficient	0.08 mm^{-1}	
F(000)	1136	
Crystal size	0.60 x 0.15 x 0.14 mm	
Θ range for data collection	4.7 to 56.4°	
Limiting indices:	-15≤h≤11, -18≤k≤18, -24≤l≤24	
Reflections collected / unique	27727 / 7368 [R(Int) = 0.0297]	
Completeness to Θ	26.26°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7368 / 0 / 383	
Goodness-of-fit on F^2	1.075	
Final R indices [I>2σ(I)]	R1 = 0.0793, wR2 = 0.1199	
R indices (all data)	R1 = 0.0455, wR2 = 0.1091	
Largest diff. peak and hole	0.270 and -0.213 e. $Å^{-3}$	

Crystal data and structure refinement for ***3.2.7h***



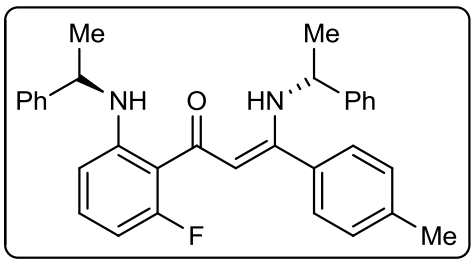
Identification code	sm515r	
Empirical formula	$C_{29}H_{32}FNO_4S$	
Formula weight	509.62	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic *P*1	
Unit cell dimensions	*a* = 9.6165 (5) Å	α = 77.745 (3)°
	b = 11.5053 (6) Å	β = 85.414 (3)°
	c = 12.1257 (6) Å	γ = 85.328 (3)°
Volume	1303.96 (12) $Å^3$	
Z	2	
Calculated density	1.298 mg/m^3	
Absorption coefficient	0.17 mm^{-1}	
F(000)	540	
Crystal size	0.24 x 0.16 x 0.12 mm	
Θ range for data collection	5.3 to 58.5°	
Limiting indices:	-13≤h≤13, -16≤k≤16, -17≤l≤17	
Reflections collected / unique	27764 / 13605 [R(Int) = 0.0307]	
Completeness to Θ	27.87°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	13605 / 9 / 676	
Goodness-of-fit on F^2	1.020	
Final R indices [I>2σ(I)]	R1 = 0.0763, wR2 = 0.1118	
R indices (all data)	R1 = 0.0499, wR2 = 0.1022	
Largest diff. peak and hole	0.279 and -0.360 e. $Å^{-3}$	

*Crystal data and structure refinement for **3.2.8b***



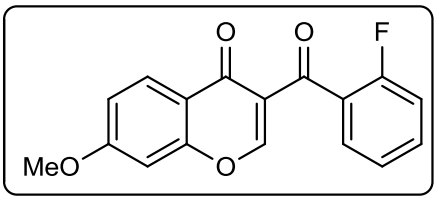
Identification code	sm504	
Empirical formula	$C_{29}H_{34}FNO$	
Formula weight	431.57	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic P_1	
Unit cell dimensions	a = 6.6652 (8) Å	α = 80.328 (8)°
	b = 12.7975 (17) Å	β = 87.550 (8)°
	c = 14.5555 (19) Å	γ = 76.956 (8)°
Volume	1192.5 (3) $Å^3$	
Z	2	
Calculated density	1.202 mg/m^3	
Absorption coefficient	0.08 mm^{-1}	
F(000)	464	
Crystal size	0.61 x 0.13 x 0.09 mm	
Θ range for data collection	4.7 to 58.6°	
Limiting indices:	-8≤h≤8, -16≤k≤16, -18≤l≤19	
Reflections collected / unique	22164 / 5750 [R(Int) = 0.0350]	
Completeness to Θ	25.65°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5750 / 0 / 296	
Goodness-of-fit on F^2	1.058	
Final R indices [I>2σ(I)]	R1 = 0.0777, wR2 = 0.1168	
R indices (all data)	R1 = 0.0460, wR2 = 0.1066	
Largest diff. peak and hole	0.181 and -0.235 e. $Å^{-3}$	

Crystal data and structure refinement for ***3.2.11b***



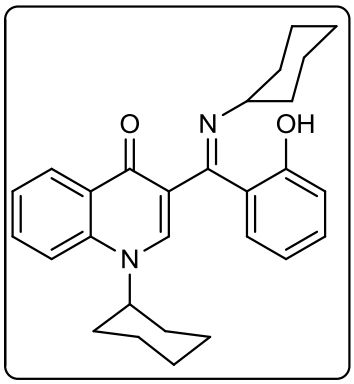
Identification code	sm550_1	
Empirical formula	$C_{32}H_{31}FN_2O$	
Formula weight	478.59	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic $P2_12_12_1$	
Unit cell dimensions	a = 7.9842 (2) Å	α = 90°
	b = 14.5796 (3) Å	β = 90°
	c = 22.5905 (5) Å	γ = 90°
Volume	2629.68 (10) Å^3	
Z	4	
Calculated density	1.209 mg/m^3	
Absorption coefficient	0.08 mm^{-1}	
F(000)	1016	
Crystal size	0.69 x 0.22 x 0.18 mm	
Θ range for data collection	4.6 to 56.8°	
Limiting indices:	-11≤h≤11, -21≤k≤19, -19≤l≤32	
Reflections collected / unique	31551 / 8396 [R(Int) = 0.0727]	
Completeness to Θ	28.29°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8396 / 0 / 336	
Goodness-of-fit on F^2	1.048	
Final R indices [I>2σ(I)]	R1 = 0.0625, wR2 = 0.1012	
R indices (all data)	R1 = 0.0434, wR2 = 0.0957	
Largest diff. peak and hole	0.201 and -0.191 e. Å^{-3}	

*Crystal data and structure refinement for **3.3.4e***



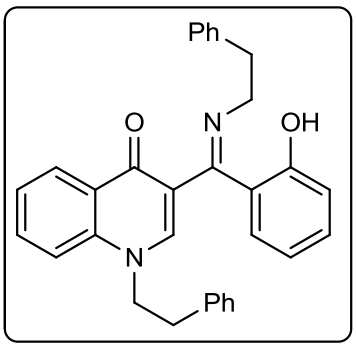
Identification code	sm458	
Empirical formula	$C_{17}H_{11}FO_4$	
Formula weight	298.26	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/n$	
Unit cell dimensions	a = 7.7191 (2) Å	α = 90°
	b = 13.9145 (3) Å	β = 99.863 (1)°
	c = 12.5580 (3) Å	γ = 90°
Volume	1328.89 (5) $Å^3$	
Z	4	
Calculated density	1.491 mg/m^3	
Absorption coefficient	0.12 mm^{-1}	
F(000)	616	
Crystal size	0.32 x 0.31 x 0.24 mm	
Θ range for data collection	6.1 to 62.0°	
Limiting indices:	-10≤h≤8, -15≤k≤19, -16≤l≤17	
Reflections collected / unique	15570 / 3878 [R(Int) = 0.0174]	
Completeness to Θ	27.32°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3878 / 0 / 200	
Goodness-of-fit on F^2	1.044	
Final R indices [I>2σ(I)]	R1 = 0.0437, wR2 = 0.1081	
R indices (all data)	R1 = 0.0379, wR2 = 0.1048	
Largest diff. peak and hole	0.415 and -0.200 e. $Å^{-3}$	

*Crystal data and structure refinement for **3.3.8b***



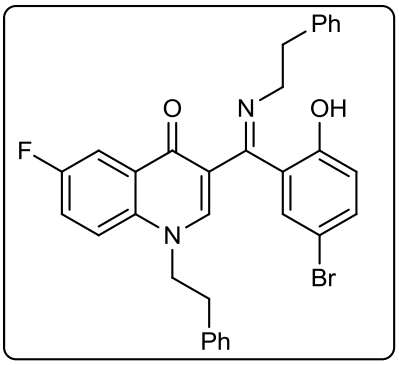
Identification code	sm406	
Empirical formula	$C_{28}H_{32}N_2O_4$	
Formula weight	428.56	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, *C*2/*c*	
Unit cell dimensions	*a* = 23.8305 (13) Å	α = 90°
	b = 9.8495 (5) Å	β = 102.587 (3)°
	c = 19.7081 (11) Å	γ = 90°
Volume	4514.7 (4) $Å^3$	
Z	8	
Calculated density	1.261 mg/m^3	
Absorption coefficient	0.08 mm^{-1}	
F(000)	1840	
Crystal size	0.63 x 0.05 x 0.04 mm	
Θ range for data collection	4.9 to 43.3°	
Limiting indices:	-30≤h≤30, -12≤k≤12, -25≤l≤25	
Reflections collected / unique	24312 / 4929 [R(Int) = 0.1167]	
Completeness to Θ	24.05°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4929 / 0 / 293	
Goodness-of-fit on F^2	0.980	
Final R indices [I>2σ(I)]	R1 = 0.1595, wR2 = 0.1295	
R indices (all data)	R1 = 0.0600, wR2 = 0.0979	
Largest diff. peak and hole	0.221 and -0.230 e. $Å^{-3}$	

Crystal data and structure refinement for ***3.3.8d***



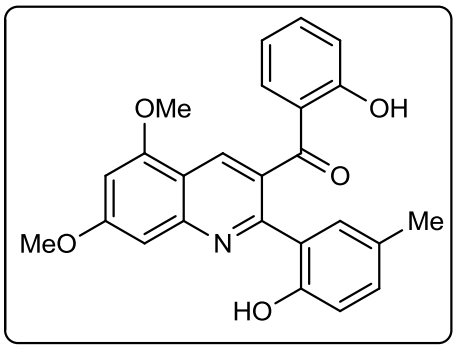
Identification code	sm395	
Empirical formula	$C_{32}H_{28}N_2O_4$	
Formula weight	472.56	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, *C*2/*c*	
Unit cell dimensions	*a* = 31.6167 (10) Å	α = 90°
	b = 10.4048 (3) Å	β = 114.191 (2)°
	c = 16.4565 (5) Å	γ = 90°
Volume	4938.2 (3) $Å^3$	
Z	8	
Calculated density	1.271 mg/m^3	
Absorption coefficient	0.08 mm^{-1}	
F(000)	2000	
Crystal size	0.52 x 0.33 x 0.17 mm	
Θ range for data collection	5.0 to 50.0°	
Limiting indices:	-44≤h≤45, -14≤k≤14, -23≤l≤23	
Reflections collected / unique	36127 / 7608 [R(Int) = 0.0487]	
Completeness to Θ	28.75°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7608 / 15 / 367	
Goodness-of-fit on F^2	1.008	
Final R indices [I>2σ(I)]	R1 = 0.0835, wR2 = 0.1282	
R indices (all data)	R1 = 0.0481, wR2 = 0.1076	
Largest diff. peak and hole	0.265 and -0.215 e. $Å^{-3}$	

Crystal data and structure refinement for ***3.3.8i***



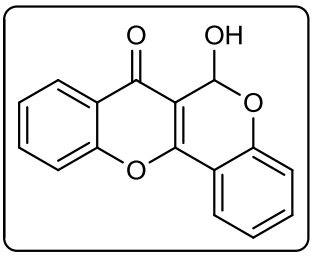
Identification code	sm805	
Empirical formula	$C_{32}H_{26}FN_2O_2$	
Formula weight	569.46	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/n$	
Unit cell dimensions	a = 12.1385 (4) Å	α = 90°
	b = 10.7741 (3) Å	β = 94.598 (2)°
	c = 20.8967 (5) Å	γ = 90°
Volume	2724.10 (14) Å^3	
Z	4	
Calculated density	1.389 mg/m^3	
Absorption coefficient	1.55 mm^{-1}	
F(000)	1168	
Crystal size	0.52 x 0.43 x 0.25 mm	
Θ range for data collection	2.5 to 30.0°	
Limiting indices:	-17≤h≤17, -15≤k≤15, -30≤l≤30	
Reflections collected / unique	76363 / 8727 [R(Int) = 0.0501]	
Completeness to Θ	29.0°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8727 / 17 / 372	
Goodness-of-fit on F^2	1.029	
Final R indices [I>2σ(I)]	R1 = 0.0571, wR2 = 0.0879	
R indices (all data)	R1 = 0.0358, wR2 = 0.0798	
Largest diff. peak and hole	0.484 and -0.559 e. Å^{-3}	

Crystal data and structure refinement for ***3.3.11h***



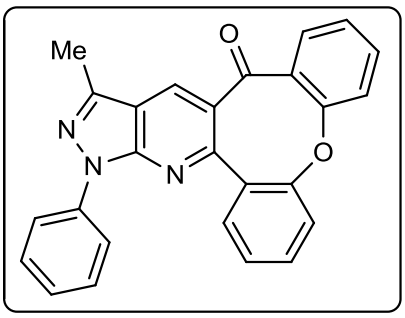
Identification code	sm447	
Empirical formula	$C_{25}H_{21}NO_5$	
Formula weight	415.43	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/n$	
Unit cell dimensions	a = 7.6454 (3) Å	α = 90.303 (2)°
	b = 10.9083 (5) Å	β = 99.563 (2)°
	c = 12.5017 (5) Å	γ = 104.055 (3)°
Volume	996.22 (7) Å^3	
Z	2	
Calculated density	1.385 mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	436	
Crystal size	0.25 x 0.10 x 0.08 mm	
Θ range for data collection	5.0 to 60.8°	
Limiting indices:	-10≤h≤10, -15≤k≤15, -17≤l≤17	
Reflections collected / unique	21491 / 5759 [R(Int) = 0.0331]	
Completeness to Θ	27.21°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5759 / 0 / 291	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2σ(I)]	R1 = 0.0824, wR2 = 0.1242	
R indices (all data)	R1 = 0.0478, wR2 = 0.1136	
Largest diff. peak and hole	0.325 and -0.228 e. Å^{-3}	

*Crystal data and structure refinement for **3.3.13***



Identification code	sm407	
Empirical formula	$C_{16}H_{10}O_4$	
Formula weight	266.24	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic, *Pbcn*	
Unit cell dimensions	*a* = 10.7720 (6) Å	α = 90°
	b = 12.0538 (7) Å	β = 90°
	c = 18.4416 (10) Å	γ = 90°
Volume	2394.5 (2) $Å^3$	
Z	8	
Calculated density	1.477 mg/m^3	
Absorption coefficient	0.11 mm^{-1}	
F(000)	1104	
Crystal size	0.38 x 0.13 x 0.06 mm	
Θ range for data collection	5.5 to 60.4°	
Limiting indices:	-14≤h≤12, -16≤k≤16, -25≤l≤25	
Reflections collected / unique	20244 / 3178 [R(Int) = 0.0365]	
Completeness to Θ	26.09°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3178 / 0 / 185	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2σ(I)]	R1 = 0.0595, wR2 = 0.1107	
R indices (all data)	R1 = 0.0446, wR2 = 0.1033	
Largest diff. peak and hole	0.288 and -0.201 e. $Å^{-3}$	

*Crystal data and structure refinement for **3.3.14***



Identification code	sm497	
Empirical formula	$C_{26}H_{17}N_3O_2$	
Formula weight	403.42	
Temperature	173 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 8.5696 (2) Å	α = 90°
	b = 19.5048 (5) Å	β = 106.200 (2)°
	c = 11.9606 (3) Å	γ = 90°
Volume	1919.86 (8) Å^3	
Z	4	
Calculated density	1.396 mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	840	
Crystal size	0.22 x 0.17 x 0.14 mm	
Θ range for data collection	2.7 to 26.0°	
Limiting indices:	-12≤h≤11, -25≤k≤28, -16≤l≤17	
Reflections collected / unique	30523 / 6102 [R(Int) = 0.0659]	
Completeness to Θ	28.19°	
Absorption correction	multi scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6102 / 0 / 281	
Goodness-of-fit on F^2	1.033	
Final R indices [I>2σ(I)]	R1 = 0.1384, wR2 = 0.1281	
R indices (all data)	R1 = 0.0571, wR2 = 0.0983	
Largest diff. peak and hole	0.245 and -0.271 e. Å^{-3}	

A.4. List of Abbreviation.

Ac	Acyl
ADA	Adenosine deaminase
Alk	Alkyl
Ar	Aryl
Ar	Argon (under the arrow)
AIDS	Acquired immunodeficiency syndrom
CN	Nitril
Bu	Butyl
t-Bu	*tert*-Butyl
br.	Broad (NMR)
d	Doublet (NMR)
dd	Double doublet (NMR)
ddd	Double double doublet (NMR)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMFDMA	*N*,*N*-dimethylformamide dimethyl acetal
DNA	Deoxyribonucleic acid
dt	Double triplet (NMR)
EDG	Electron donating group
EI	Electronic ionization (HRMS)
ESI	Electrospray ionization (HRMS)
Et	Ethyl
equiv.	Equivalent
EWG	Electron withdrawing group
GMP	Guanosine-5´-monophosphate
GC-MS	Gass chromatography-mass spectrometry
h	hour
HIV	Human immunodeficiency virus
HMBC	Heteronuclear multiple bond correlation spectroscopy
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry

HSQC	Heteronuclear single quantum correlation spectroscopy
IMP	Inosine-5´-monophosphate
IMPDH	Inosine-5´-monophosphate dehydrogenase
IR	Infrared spectrometry
m	Multiplet (NMR)
m	Medium (IR)
Me	Methyl
NAD	Nicotinamide adenine dinucleotide
NADP	Nicotinamide adenine dinucleotide phosphate
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance spectroscopy
NOESY	Nuclear overhauser effect spectroscopy
Nu	Nucleophile
Ph	Phenyl
ppm	Parts per million
i-Pr	Isopropyl
Py	Pyridine
q	Quartet (NMR)
R_f	Retardation factor
R_F	Polifluoroalkyl group
RM	Reaction mixture
RNA	Ribonucleic acid
r.t.	Room temperature
SCID	Severe combined immunodeficiency
SEM	2-(trimethylsilyl)ethoxy)-methyl
t	triplet
td	Triple doublet (NMR)
TFA	Trifluoroacetic acid
THP	Tetrahydropyranyl ether
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride
TMSOTf	Trimethylsilyl trifluoromethansulfonate
Tol	Toluene
tt	Triple triplet

ttt	Triple triple triplet
w	Week (IR)
XMP	Xantosine-5´-monophosphate

A.5. List of References

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Declaration

Hereby I declare that this tesis 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.

Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe, keine außer den von mir angegebenen Hilfsmitteln and Quellen dazu verwendet habe und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

Satenik Mkrctyan

June 2014, Rostock

Curriculum Vital

Personal data

	Satenik Mkrtchyan
Nationality	Armenian
Date and place of Birth	14.02.1986, Gyumri, Armenia
Gender	Female
Marital status	Married
Email	satenikmk@yahoo.co.uk

Education

Present	PhD at University of Rostock (2010-2014)
Master degree	Yerevan State University; specialization. Organic chemistry (2007-2009). Average mark is 4.9 (according to the German education standard 1.3)
Bachelor	Yerevan State University; specialization. Organic chemistry (2003-2007). Average mark is 5.0 (according to the German education standard 1.0)
Full secondary	School№ 10 after A. Petrosyan (1993-2003).
Language skills	Armenian (excellent), Russian (excellent), English (good), German (average), French (average).

List of publication

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Poster contributions to academic conferences

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   14th JCF-Frühjahrssymposium, Rostock, March, 18th-21th, 2012.

2. Satenik Mkrtchyan, Viktor O. Iaroshenko, Alexander Villinger. "*Efficient [5+1]-Synthesis of 4-Quinolones by domino amination/conjugation addition reaction of 1-(2-fluorophenyl)prop-2-yn-1-ones"*
   15th JCF-Frühjahrssymposium, Berlin, March, 6th-9th, 2013.