ROUTES TO POLYSUBSTITUTED AND CONDENSED PYRIDINES AND DIAZINES – UTILIZATION OF 1,3-BIELECTROPHILES AND TRANSITION METAL-BASED CATALYSIS IN RING SYNTHESIS/MODIFICATION.

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MSc Dmytro Ostrovskyi, geboren am 07.06.1986 in Vyshneve, Ukraine

aus Rostock

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Gutachter:

1. Gutachter:

Prof. Dr. Peter Langer, Institut für Chemie, Universität Rostock

2. Gutachter:

Prof. Dr.Till Opatz, Institut für Chemie, Johannes Gutenberg Universität Mainz

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Dmytro Ostrovskyi

Rostock, July 2011

Abstract

The present work aimed to study the potential of well-known synthetic strategies for the synthesis of imidazo[4,5-b]pyridine-derived (or 1-desazapurine-derived), purine-derived and benzimidazole-derived moieties and their modifications, which could result in appearance of a number of biological activities. This includes [3+3] cyclocondensations, inverse electron-demand Diels-Alder reaction, intramolecular palladium-catalyzed arylation. 6-Nitro-, 6-amino-imidazo[4,5-b]pyridines, imidazo[4,5-b]pyridine-5-carboxylates were prepared from generated *in situ* 1-substituted-1*H*-5-aminoimidazoles and chromone-based precursors. Glycosilated purines and 1-desazapurines were obtained following so-called *salvage* nucleoside synthetic pathway. A number of fused imidazole-containing heterocycles were synthesized with usage of palladium-catalyzed C-C bond formation. In addition, unprecedented method of synthesis of 4-trifluoromethylpyridines was developed, including scope limitation and theoretical mechanistic studies with DFT methods.

Kurzbeschreibung

Die vorliegende Arbeit untersucht das Potential bekannter Synthesestrategien zum Aufbau von Derivaten des Imidazo[4,5-b]pyridins (1-Desazapurin), Purins und Benzimidazols, welche eine hohe biologische Aktivität aufweisen können. Dies beinhaltet [3+3] Zyklokondensationen, Inverse Diels-Alder Reaktionen sowie intramolekulare Palladium katalysierte Arylierungen. 6-Nitro-, 6-Amino-imidazo[4,5-b]pyridin und die Imidazo[4,5-b]pyridin-carboxylate wurden *in situ* aus den entsprechenden 1-substituierten-1*H*-5-aminoimidazolen und den Chromon basierten Vorstufen hergestellt. Glykolysierte Purine und 1-Desazapurine wurden mit Hilfe des sogenannten *Salvage* Nukleosid Synthesewegs hergestellt. Viele Heterozyklen, die eine Imidazoleinheit enthalten, konnten mittels Palladium katalysierten Kupplungsreaktionen synthetisiert werden. Außerdem wurde eine neue Methode für die Synthese von 4-Trifluoromethylpyridinen entwickelt, einschließlich der Eingrenzung der Anwendbarkeit und theoretischen mechanistischen Untersuchungen mittels DFT.

Contents

1. Background

Being intensively developed and deeply incepted into human life during last two centuries, modern heterocyclic chemistry constitutes one of the most fundamental and applicable unit among other natural sciences. Its extreme importance in drug design and besides, in development of new materials, such as dyes, fluorescent markers, organic magnets, etc., is forcing the progress in this field and dispersing already narrow borders between chemistry of heterocyclic compounds and related disciplines. Due to permanently growing needs of chemical industry, new synthetic methodologies, directed towards heterocyclic ring synthesis or its modification are continuing to emerge, staying the actual task during the last several decades.

In the large family of heterocyclic moieties, nitrogen-containing 6-membered heterocycles (azines) are of particular interest. Pyridine **1**, pyrimidine **2** and their fused derivatives, such as purine **3** and its deaza-analogues **4** are found in many nature-occurring bioactive compounds and commercially available drugs.

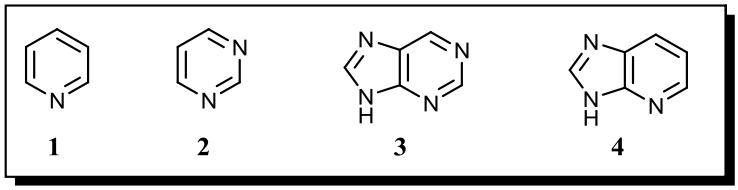


Figure 1. *Important representatives of azines.*

Pyridine itself was discovered in 1849 by the Scottish chemist Thomas Anderson as one of the constituents of bone oil. Lately, it was isolated through fractional distillation of the oil. Being an important reagent and solvent in organic synthesis, it is produced in an amount of more than 20,000 ton per year. Due to increasing demand of pyridine, its production from a coal tar was replaced by gas-phase synthesis from crotonaldehyde, formaldehyde, steam, air and ammonia over silica-alumina catalyst in recent years.

Pyridine core is found in incalculable number of natural products. Nicotinic acid **5** which is known as niacin or vitamin PP is an important bioregulator. Being precursor to NAD+/NADH and NADP+/NADPH, it plays an important role in metabolic processes in living organisms. Nicotine **6** or 3-[(2*S*)-1-methylpyrrolidin-2-yl]pyridine, is a wide-spread alkaloid, that constitutes approximately 0,5-3,0% of the dry weight of tobacco and formed by the incorporation of a pyrrolidine moiety derived

from L-ornitine onto the molecular framework of nicotinic acid. Like nicotine and some similar alkaloids, for example, ricinine **7**, originate from nicotinic acid as well.

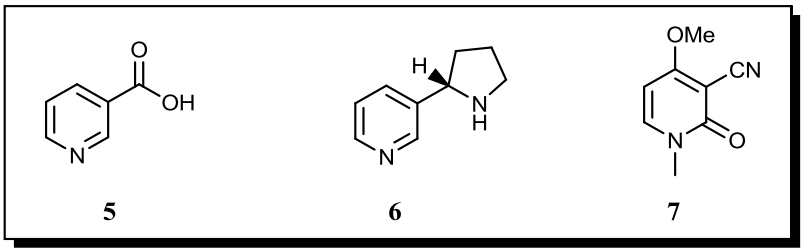


Figure 2. *Naturally occurring pyridine derivatives.*

A number of pyridine-derived compounds found their application in different areas. Paraquat **8**, a derivative of methyl pyridinium salt, is one of the most widely used herbicides in the world. Polyvinyl pyridine, or simply PVP **9** is widely-used polymer, containing corresponding heterocyclic core. Sulfasalazine **10** is an example of pyridine-based commercially available drug, which is known for more than 70 years and prescribed for rheumatoid arthritis.

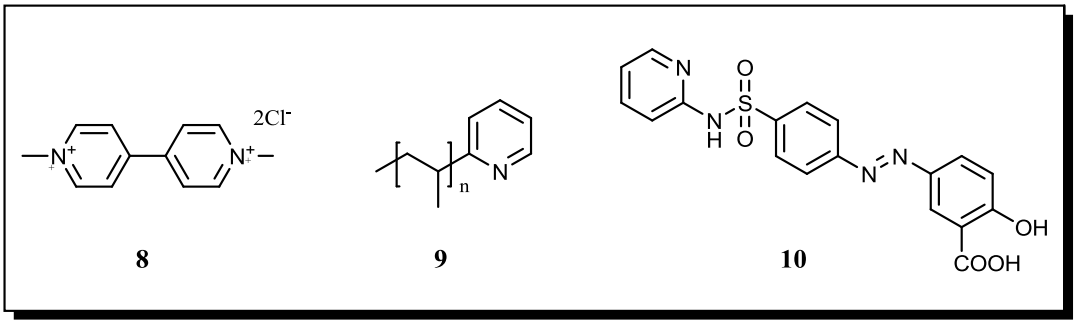


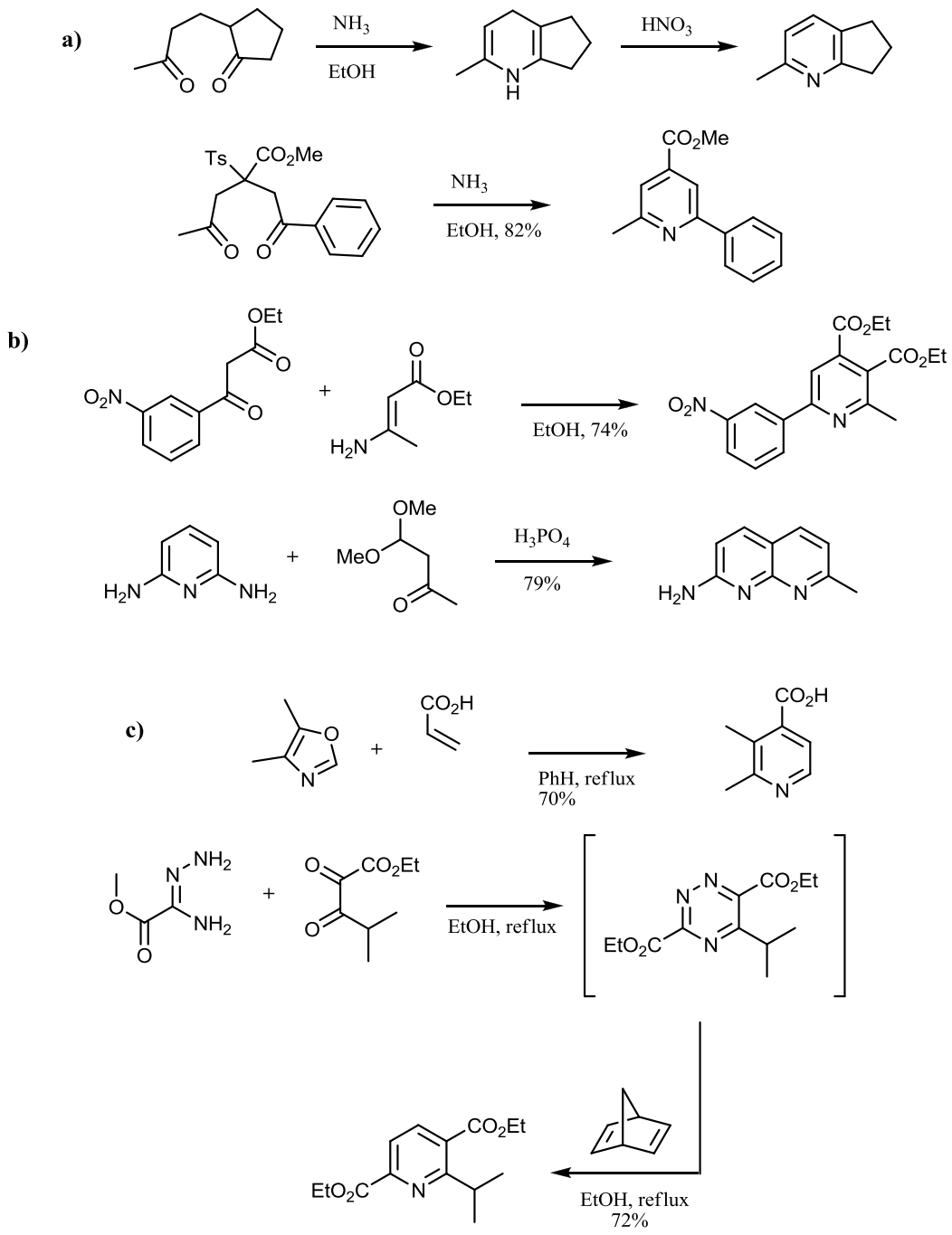
Figure 3. *Pyridines in chemical industry.*

A number of routes, aiming pyridine ring construction, is growing literally day by day, however most of described protocols could be classified as members of one of the three major synthetic concepts, which are illustrated on scheme below[1)]:

a) condensation of 1,5-dicarbonyl compounds or their derivatives with ammonia or its salts, followed by aromatization of the formed dihydropyridines (one of the oldest methods of pyridine construction, still finds its applications);

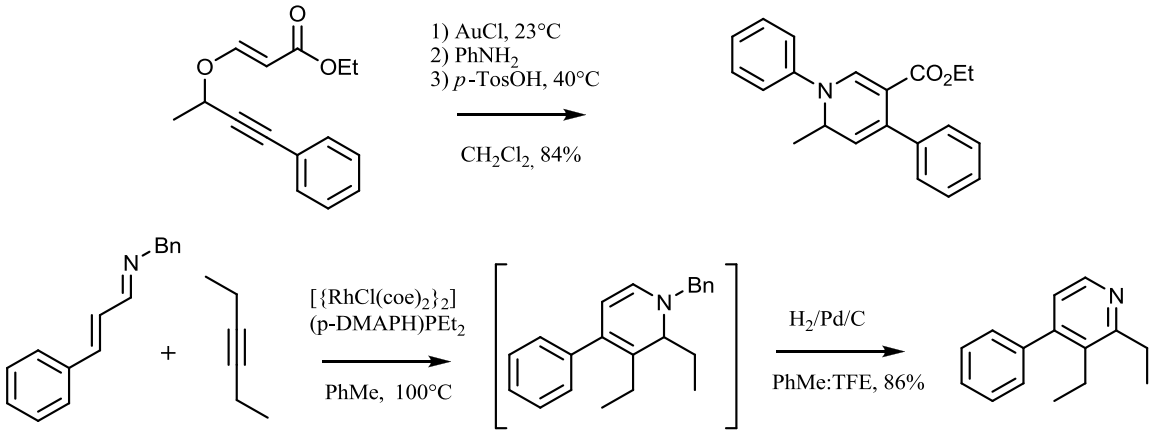
b) cyclocondensation of 1,3-dicarbonyl compounds with the enamine fragment, including 3-amino-enones, or –nitriles, activated anilines and aminoheterocycles (this approach is one of the most versatile, allows to synthesize various unsymmetrically substituted pyridines with simple handling);

c) various 6π cycloadditions, including inverse electron-demand, reactions with subsequent extrusion of small molecules, [2+2+2] approach, involving two alkyne equivalents and nitrile (the basic method, which doesn't rely on condensation chemistry is becoming increasingly important).



Scheme 1. *Examples of general methods of pyridine synthesis.*

Together with the permanent growth of a number of transition-metal catalyzed organic transformations, new approaches to the pyridine synthesis continuously appear. Ring-closing metathesis[2], gold-catalyzed cyclizations[3] and coupling reactions[4] involving palladium vastly enriched synthetic strategies directed towards pyridine ring formation. Some notable examples of the use of transition-metal catalysts are outlined below:



Scheme 2. *Examples of utilization of transition metals in pyridine synthesis.*

Pyrimidine and its derivatives are considered as the most important naturally occurring diazines, mainly due to its presence in nucleic acid in a form of uracil **11**, thymine **12** and cytosine **13**.

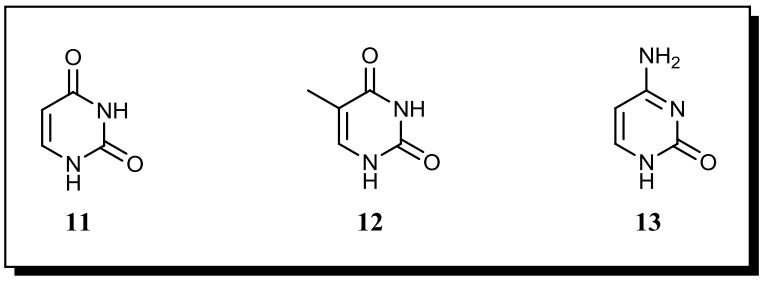


Figure 4. *Naturally occurring pyrimidines.*

As many pyrimidine-derived species show remarkable biological activity, it is no surprise that this heterocyclic core is found in many preparations, such as 5-fluorouracil **14**, which is an effective pyrimidine antimetabolite and used for colorectal cancer and pancreatic cancer treatment or Imatinib Mesylate (known under commercial name Gleevec) **15**, which is used for treatment of chronic myelogenous leukemia.

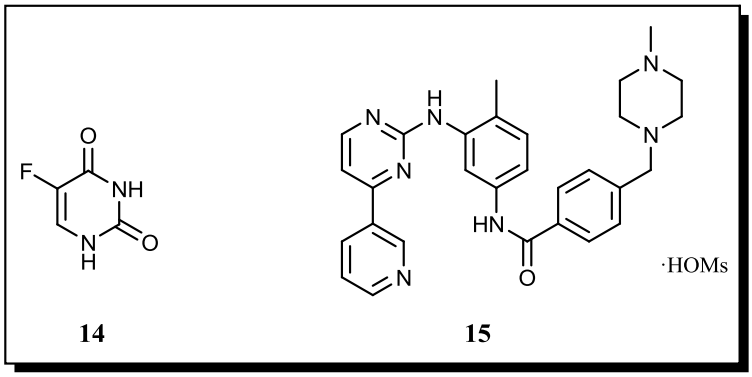


Figure 5. *Drugs, based on pyrimidine core.*

Purines (and their desaza-analogues) are typical representatives of condensed azines, formed by incorpororation of imidazole ring onto pyrimidine species, and are of particular interest for several reasons. Together with certain pyrimidine bases, they are constituents of DNA and RNA, consequently being extremely important in life processes. Their numerous applications in medicine resulted in rapid broadening of chemistry of purines and related systems. A wide range of purine-derived compounds are well-known antiviral, antifungal and antitumor agents, among them 6-mercaptopurine **16**, acyclovir **17**, azathioprine **18**.

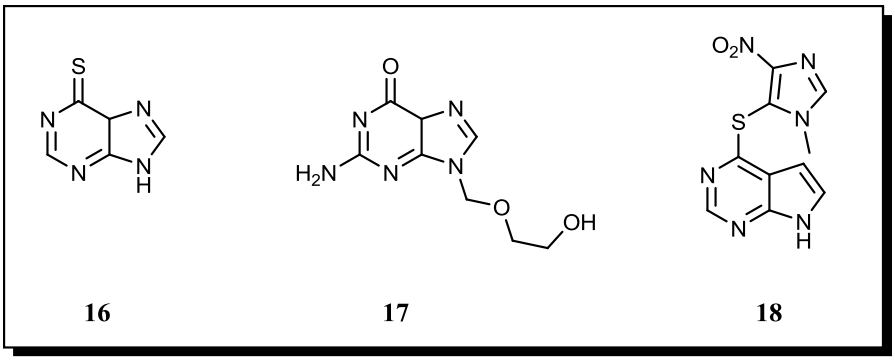


Figure 6. *Drugs, based on purine core.*

In the context of current work, a special attention among other purine desaza-analogues should be paid to 1-desazapurines or imidazo[4,5-b]pyridines, which constitute a small but important class of nitrogen-containing heterocycles and is of considerable relevance in medicinal chemistry. Compounds, that belong to imidazo[4,5-b]-pyridin-2-one class have been shown to be nonsteroidal anti-immflamatory and analgesic agents[5)] and to possess antidepressant[6)], antiphlogistic[7)], cardiotonic[8)] and other activities. In addition, certain members of this class have post-emergence applications on broad-lived plants. As an examples of pharmacologically relevant 1-deazapurines, compounds CCT 129202 **19**

and L-158,809 **20** could be outlined. The first one has been reported as an efficient inhibitor of Aurora-A, the latter is a newly developed cogender of losartan, which is a drug prescribed of hypertension.

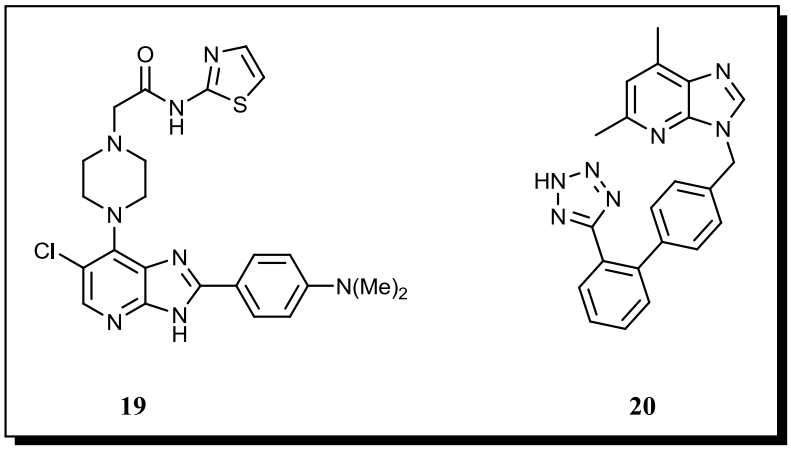


Figure 7. *Pharmacologically relevant imidazo[4,5-b]pyridines.*

Concluding all mentioned above, due to countless applications of pyridine- and purine-containing substances and their analogues in chemical industry, their importance is hard to overestimate. New methods and concepts of organic chemistry are being consistently applied for developing new methodologies to the synthesis of these heterocycles and it is unlikely, that interest in this field will decrease soon. This work is dedicated to the design and synthesis of various pyridines and diazines, and can vastly enrich existing synthetic tools of heterocyclic chemistry.

2. Implementation of chromone-derived bielectophiles in synthesis of functionalized imidazo[4,5-b]pyridines

2.1 Introduction

Ever since chromone **21** chemistry started to develop intensively, utilization of this heterocyclic system as a versatile bielectrophile in numerous cyclyzations has become a matter of common. Various 2- and 3-substituted chromone derivatives including naturally occurring flavones **22** and isoflavones **23** have found their application in synthesis of pyrazoles, isoxazoles, pyrimidines, and other heterocycles.

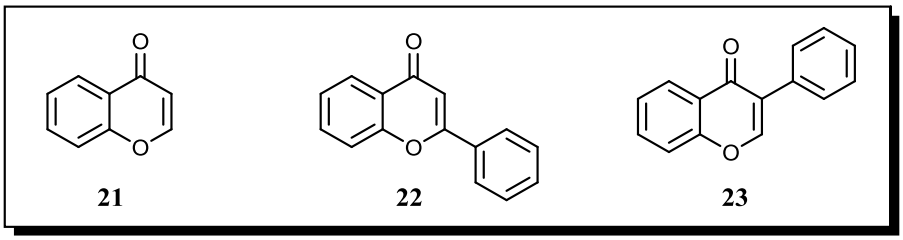
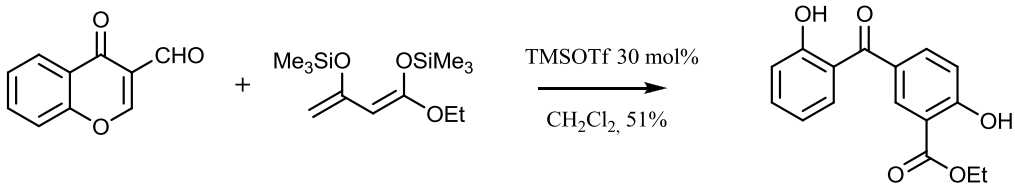


Figure 8. *Chromone scaffolds.*

In this context, synthones, containing electron-withdrawing substituent in position 3 of the heterocyclic core are of particular interest. Introduction of withdrawing species in chromone ring facilitates nucleophilic attack at the carbonyl part of heterocycle and therefore increases its reactivity. On the other hand, groups like carbonyl or nitrile can interact with nucleophiles, resulting in formation of 2-hydroxybenzoyl-derived structures. As an example, the reaction of 3-formylchromone with 1,3-bis(silyl enol ethers)[9], which was developed in Langer's group, leads to the formation of benzophenones via cyclocondesation involving aldehyde function:

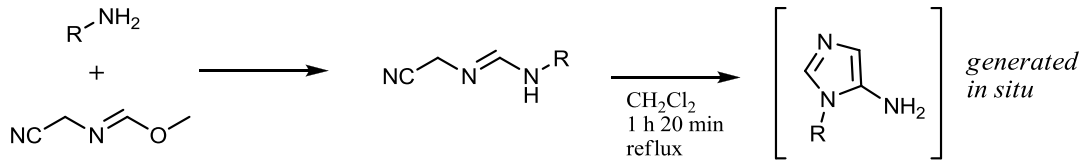


Scheme 3. *3-Formylchromone in benzophenone synthesis.*

Being interested in the development of new methods of imidazo[4,5-b]pyridine ring construction, we considered chromone scaffolds as particularly attractive for starting materials in

cyclocondesation reactions with 1-substituted-5-amino-1*H*-imidazoles. The latter are formally condensed enamines, and therefore could be considered as known and versatile binucleophiles.

1-Substituted-5-amino-1*H*-imidazoles **24**, that were used for our research, were generated *in situ*, following the procedure, previously developed by Iaroshenko et al. in the group of Groth, by reaction of primary amines with methyl N-(cyanomethyl)formimidate[10]:



24

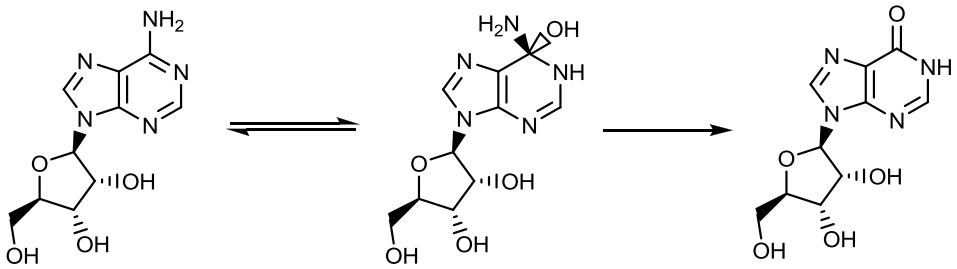
Scheme 4. *Generation of 1-substituted 5-amino-*1*H-imidazoles.*

On basis of the previous work, we anticipated, that bielectrophilic species should be active enough for cyclocondesation reaction to occur at the same conditions, under which 5-aminoimidazoles are generated (due to high sensitivity of the latter). This means to react at 40°C (boiling point of dichloromethane) and preferably without any acid-based catalyst. As it will be shown, 3-substituted chromones that were chosen for preparation of our target molecules perfectly match these requirements.

2.2 Synthesis of 6-nitro and 6-amino-3*H*-imidazo[4,5-b]pyridines using 3-nitro-4*H*-chromen-4-one

2.2.1 Biological justification

The subject of current part of this work is to develop a facile methodology for the preparation of 6-substituted imidazo[4,5-b]pyridines with potent pharmacological importance. Recently, imidazo[4,5-b]pyridine core earned a considerable attention as a useful scaffold in design and synthesis of adenosine deaminase (ADA) inhibitors. ADA is a zinc metalloenzyme, which is involved in purine metabolic process and catalyses deamination of adenosine to inosine via formation of covalent hydrate, therefore playing key role in adenosine methabolism and in a number of physiological processes.



Scheme 5. *Adenosine deamination by ADA.*

Mutations of the gene for adenosine deaminase can result in its low expression, which causes severe combined immunodeficiency disease (SCID)[11]. On the other hand, increasing of ADA level in human tissues was detected in several diseases: bacterial meningitis[12], sarcoidosis[13], rheumatoid arthritis[14], Parkison's disease[15], viral hepatitis[16], hereditary hemolytic anemia[17], and especially different types of cancer, including leukemia, breast cancer and liver cancer[18]. A number of physiologically active substances and commercially available drugs act as ADA inhibitors[19]. These includes lidoflazine (calcium channel blocker, used as coronary vasodilator) **25**, dipyridamole (inhibits thrombus formation via inhibition of the cellular reuptake of adenosine into platelets, red blood cells and endothelial cells leading to increased extracellular concentrations of adenosine) **26**, trazodone (known antidepressant) **27**, phenylbutazone (non-steroidal anti-inflammatory drug, today used only for animals) **28.**

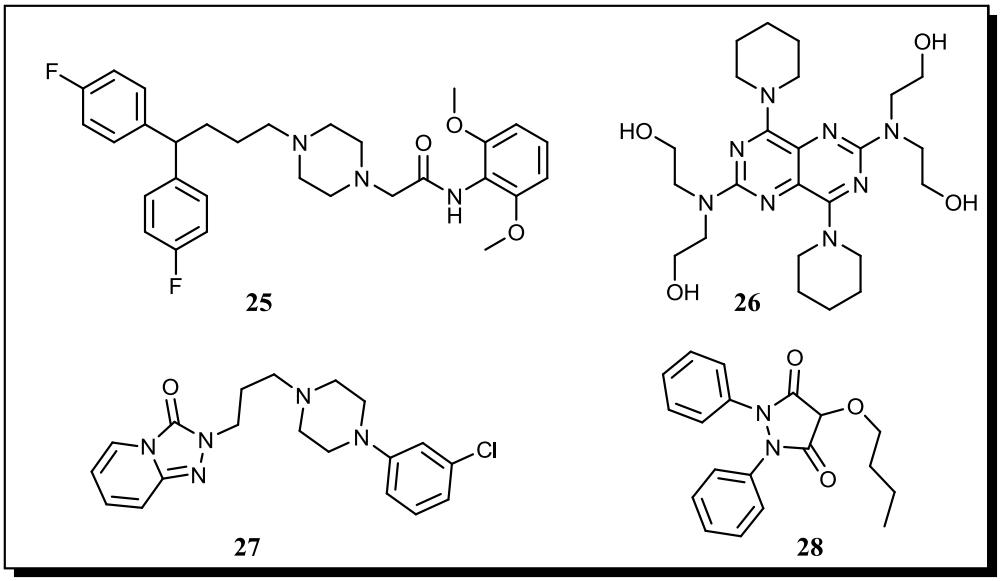


Figure 9. *Drugs, inhibiting ADA.*

It was shown, that some simple molecules, which are able to interact with cysteine residues of any protein moiety, interfere with ADA consequently deactivating it[19]. Among them iodoacetic acid **29**, N-ethylsuccinimide **30**, (4-hydroxyphenyl)(sulfo)mercury **31.** Obviously, these compounds are not suitable for any therapeutic use, however they could be implemented as model structures for further desing of potential ADA inhibitors.

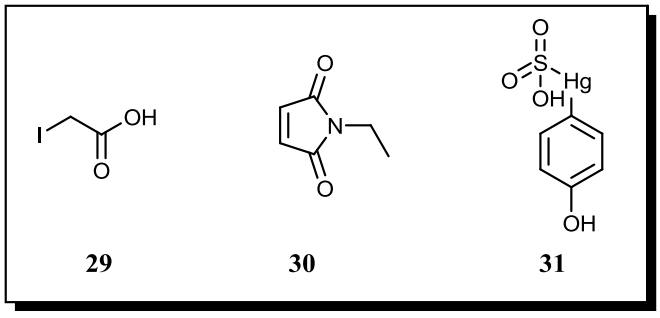


Figure 10. *Simple molecules with ADA inhibiting properties.*

One of classic examples of ADA inhibitors is erythro-9-(2-hydroxy-3-nonyl)adenine or EHNA **32** and substances which originate from EHNA[19]. EHNA has been reported to have a particular mechanism of inhibition. The initial step is a classical competitive inhibition, and then a consecutive rearrangement of the enzyme and of the inhibitor occurs, yielding a tight ADA-inhibitor complex. Chemically, EHNA is formed by adenine coupled in N9 to a chiral hydroxynonyl chain. The *erythro* diastereomer is more active than the *threo* one, and the 2R-3S (+)-enantiomer is the most active.

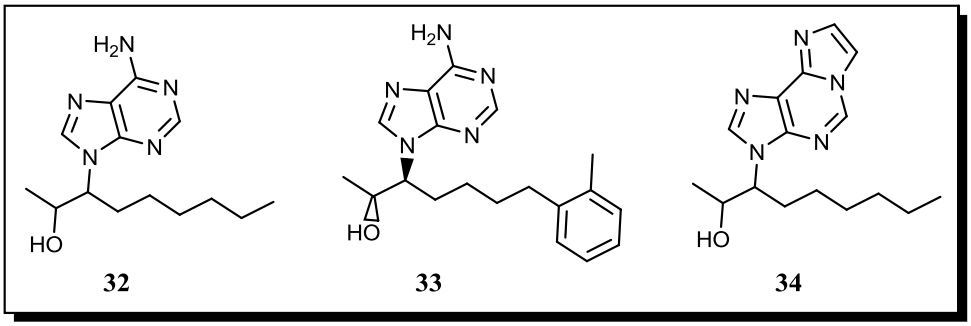


Figure 11. *EHNA and derived ADA inhibitors.*

Different modifications of EHNA were performed, the most notable – introduction of phenyl ring into the side chain of the molecule **33**, that drastically increases inhibition activity and modifying the structure of EHNA into so-called ε-EHNA **34**, fluorescent derivative, showing competitive inhibitory probe and proved to be useful in mechanistic studies of ADA action.

Despite the fact, that most of described inhibitors have found their broad applications in study of ADA inhibition or therapy, the main and, probably, the most efficient strategy remains mimicking the transition state of adenosine deaminase. A bright illustration of this concept is the physiological action of coformycin **35** and pentostatin **36**, which possess extremely-tight (nearly irreversible) binding with ADA. Important, that these molecules contain a tetrahedral carbon (C8) bearing a hydroxyl group, and the potency is greatly dependent on stereochemistry at this position. The 8*R*-diastereomer binds about 10^7 times stronger than the 8*S*. Notably, modifications of the aglicone fragment of **35** led to compounds with reduced inhibitory activity, whereas modifications at the sugar moiety of corresponding molecule, led to derivatives with more reversible and a bit weaker inhibitory activity.

Recently, it has been demonstrated that purine-type nucleosides and nucleotides, which are able to undergo covalent hydration in the aglycone ring system, are potent inhibitors of adenosine deaminase[20]. Commercially available drug Nebularine® **37** represents a potent ADA inhibitor. According to mechanistic studies, it was concluded, that inhibition is based on enzyme-catalyzed stereospecific addition of a water molecule or hydroxide ion to the C(6) position of **37,** to give adduct, which mimics transition state of adenosine deamination.

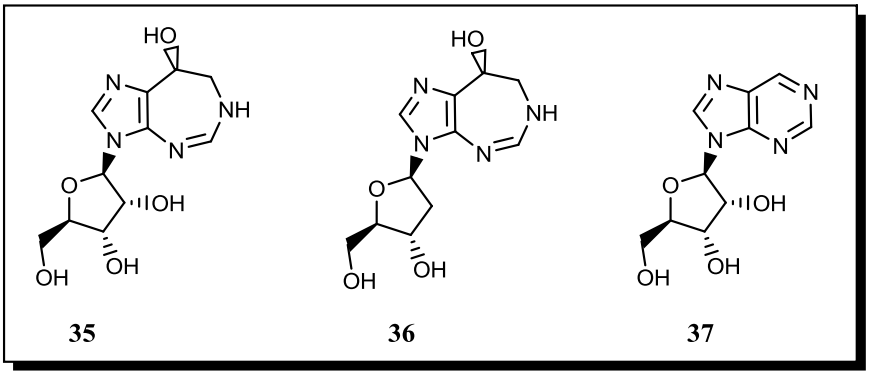
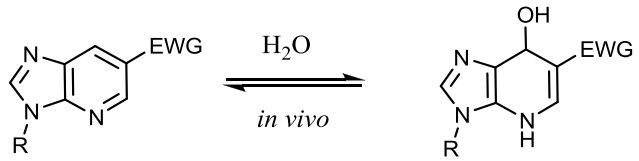


Figure 12. *Simple molecules with ADA inhibiting properties.*

We supposed, that introduction of strong electron-withdrawing substitutuent in the position 1 of 1-desazapurine system will facilitate nucleophilic addition of water and increase stability of hydrated form. This would increase inhibition activity.

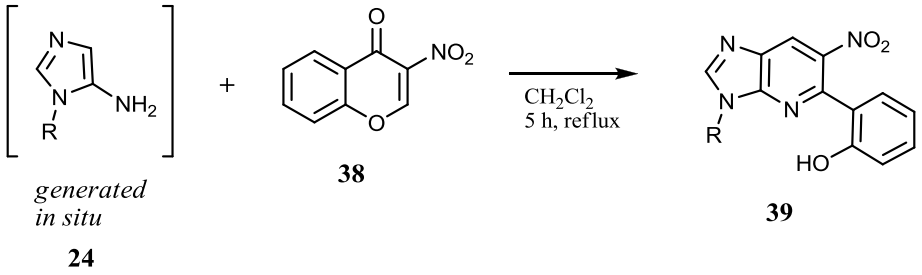


Scheme 6. *Formation of hydrated form of 1-desazapurines with EWG in position 1.*

2.2.2 Synthesis of target compounds

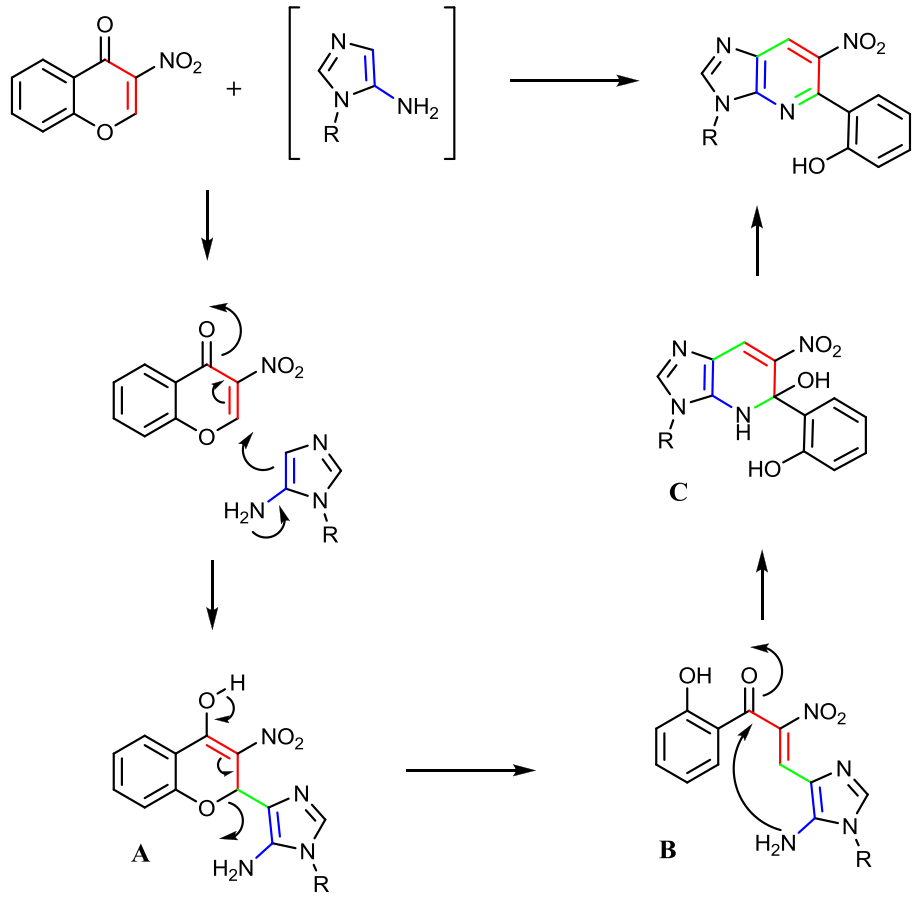
In this concept, we turned our attention to nitro- group, as its remarkable withdrawing properties allow formation of stable hydrates, depending on the pH.[21)] In this sense, 3-nitro-4*H*-chromen-4-one, or simply 3-nitrochromone, **38,** seemed a suitable precursor for the synthesis of corresponding 1-desazapurines. It can be prepared in three steps, starting from 4-hydroxycoumarine, and its properties were scarcely reported in literature, mainly in interactions with ureas and amidines[22)], in which 3-nitrochromone acted as a powerful binucleophile. This encouraged us to test 3-nitrochromone in reactions with corresponding 5-aminoimidazoles.

To our delight, treatment of generated *in situ* aminoimidazoles with equimolar amount of 3-nitro-4*H*-chromen-4-one resulted in the formation of 3-substituted-6-nitro-imidazo[4,5-b]pyridines, showing excellent regioselectivity and product release:



Scheme 7. *Reaction of 5-aminoimidazoles with 3-nitrochromone.*

In most cases, end product could be isolated by simple filtration of the formed precipitate.



Scheme 8. *Proposed mechanism of formation of **39**.*

Proposed mechanism of this transformation involves conjugate addition of the enamine carbon atom of imidazoles **24** to the double bond of γ-pyrone ring to give intermediate **A,** which undergoes ring opening, to give intermediate **B.** Intramolecular attack of the amino function on the carbonyl atom gives intermediate **C,** which converts into imidazo[4,5-b]pyridine moiety with subsequent water elimination.

Notably, the highest yields were observed, when the solutions of 5-aminoimidazoles were preliminary cooled down to 0°C before addition of chromone species, and then stirred at the same temperature for 15 minutes.

Formation of the corresponding regioisomer was confirmed by X-ray structure. The imidazo[4,5-b]pyridine unit is, as expected, has a flat structure; notably, no hydrogen bonding between the hyrdoxy-group and pyridine nitrogen is observed.

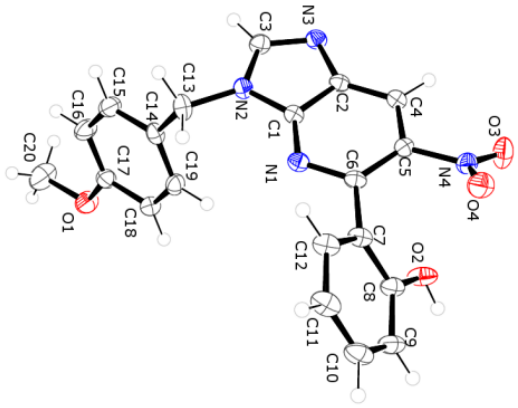
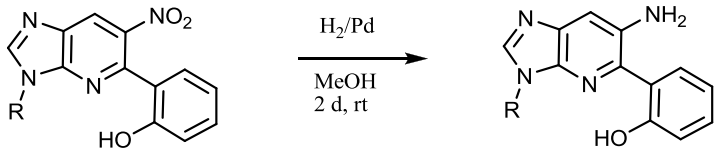


Figure 13. *X-Ray structure of compound **39g**.*

A number of 6-amino-imidazo[4,5-b]pyridines were recognized as pharmacologically relevant. 6-Amino-imidazo[4,5-b]pyridines were previously recognized as VR1-type capsaicin receptor ligands[23], and as inhibitors of src-family tyrosine kinases[24]. Some of these molecules are used to control or prevent cancer. Therefore, we were interested in reduction of nitro-derived compounds by hydrogenation in the presence of palladium on charcoal. The reaction proceeded smoothly, affording 6-amino-imidazo[4,5-b]pyridines with good yields. Interesting, no cleavage of benzyl group (if present) was observed.



39 **40**

Scheme 9. *Reduction of **39**.*

Table 1. *Yields of 6-nitro- and 6-amino-imidazo[4,5-b]pyridines.*

Compound	R	Yields of **39** (%)[a]	Yields of **40** (%)[a]
a	*t*-Bu	96[c]	92[c]
b	All	41[c]	82[c,e]
c	*n*-heptyl	86[b]	84[c]
d	cyclopropyl	69[b]	86[d]
e	cyclopentyl	77[c]	92[c]
f	cyclohexyl	82[c]	85[c]
g	4-methoxybenzyl	85[b]	83[c]
h	3-methoxybenzyl	99[b]	82[d]
i	2,3-(dimethoxy)benzyl	87[c]	78[c]
j	2-chlorobenzyl	76[b]	76[c]
k	4-chlorobenzyl	79[b]	71[c]
l	2-[(4-methoxy)phenyl]ethyl	72[b]	78[c]
m	2-[(3,4-dimethoxy)phenyl]ethyl	91[c]	75[c]
n	2-[(2-methoxy)phenyl]ethyl	73[b]	79[c]
o	2-(phenyl)ethyl	82[c]	80[c]
p	(pyridin-4-yl)methyl	76[b]	79[c]
q	2-(dimethylamino)ethyl	88[c]	81[c]

[a] Yields of isolated products
[b] Isolated by filtration
[c] Isolated by column chromatography
[d] Isolated by filtration through Celite
[e] Allyl substituent was reduced to propyl

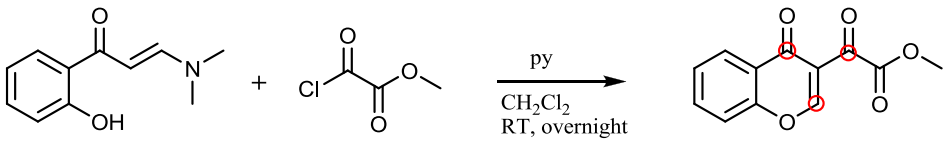
2.2.3 Conclusions

As a conclusion, we have developed a facile method of preparation of 6-nitro- and 6-amino-imidazo[4,5-b]pyridines, starting from 1-substituted-5-amino-1*H*-imidazoles and 3-nitro-4*H*-chromen-4-one. Desired products obtained with excellent regioselectivity, under mild reaction conditions, and with good yields. The biological evaluation of a set of prepared compounds is under investigation.

2.3 3-Methoxalylchromone as a versatile building block for synthesis of carboxymethyl-substituted 1-desazapurines

2.3.1 Research grounds

In comparison to 3-nitrochromone, which has two strongly marked electrophilic centers, chromones, bearing carbonyl group in the position 3, potentially can react with formation of several regioisomers due to presence of the third electrophilic function. Therefore, condensation of 5-amino-1*H*-imidazoles with any compound of this class cannot be easily forecasted, even though a reaction of 3-formylchromone with a number of similar aminoheterocycles is described. Especially, if the carbonyl part of the substituent is activated by a withdrawing group, the addition of the enamine carbon can go either to chromone C-2 atom or to carbonyl group itself. Our task in this project was to develop a practical route to 1-desazapurines, containing ester or carboxylic group in α-position of the pyridine fragment, with usage of 3-methoxalylchromone as a binucleophile and a source of carboxymethyl group. Appropriate building block could be prepared using the procedure, developed in our group[25], according to which, 3-(dimethylamino)-1-(2-hydroxyphenyl)propen-1-one **41** reacts with methyl 2-chloro-2-oxoacetate giving 3-methoxalylchromone **42** in 79% yield.

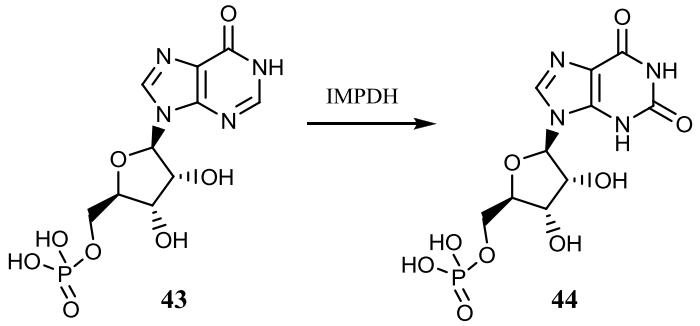


41 **42**

Scheme 10. *Synthesis of 3-methoxalylchromone.*

Obviously, all three electrophilic centers (marked red on the scheme) could react with 1,3-binucleophilic system, like 5-amino-1*H*-imidazoles, forming a number of possible individual products or mixtures. However, previous experience in chemistry of 3-formylchromone was promising in the sense of formation of 1-cabroxymethyl-1-desazapurines.

The main importance of the purine and pseudo-purine scaffolds bearing a carboxyl function in α-position of pyridine fragment in drug design is related to potential inhibition activities of inosine 5'-monophosphate dehydrogenase (IMPDH). IMPDH is an essential purine metabolic enzyme, that catalyzes oxidation of inosine monophosphate **43** to xanthosine monophosphate **44**:



Scheme 11. *Action of IMPDH.*

Recently, IMPDH has become an important target enzyme for drug design[26]. IMPDH inhibitors show a considerable immunosuppressive[27], antiviral[28], antimicrobial[29] and anticancer activity[30]. One of the most known representative IMPDH inhibitors among commercially available medications is mycophenolic acid **45** and its prodrugs, such as Mofetil **46**, which show reversible binding with a target enzyme and are widely used as immunosuppressants and antiviral agents.

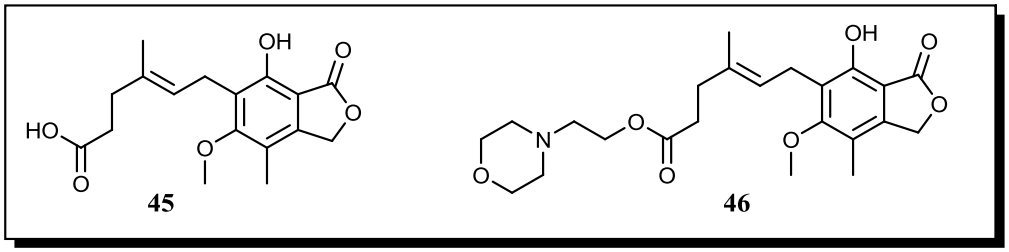


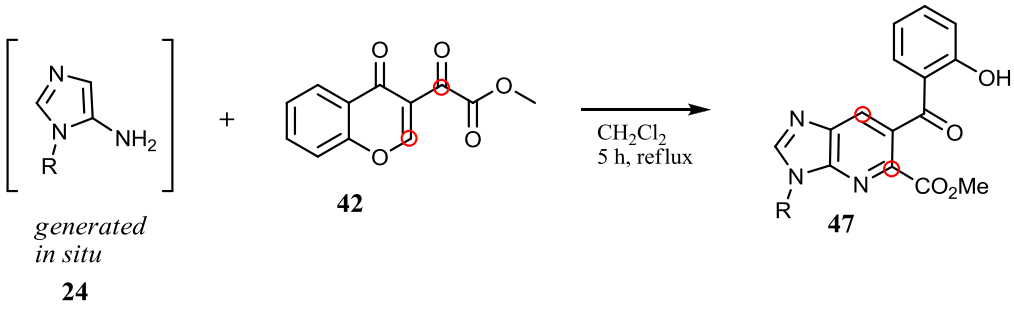
Figure 14. *Most known IMPDH inhibitors.*

We presumed that the reaction of 3-methoxalylchromone and 5-aminoimidazoles will involve C-2 and C-4 atoms of chromone ring, giving a product with carboxylic part at α-position of pyridine fragment. Therefore, our target molecules can be of current interest as promising IMPDH inhibitors.

2.3.2 Chemical evaluation of 3-methoxalylchromone and derived substances

Our studies of the interaction between 3-methoxalylchromone and 1-substituted-5-amino-1*H*-imidazoles started with a test reaction, aiming to form PMB-substituted product. As it was done in the previous part, generated *in situ* imidazole derivative was mixed with equimolar amount of 3-methoxalylchromone at the room temperature and then refluxed during 5 hours, yielding in 23% (in case of 4-methoxybenzylamine was used for 5-aminoimidazole formation) of cyclization product; no other regioisomers were observed. NMR data of the obtained compound indicated a presence of hydroxyl-

group and an imidazo[4,5-b]pyridine ring formation. However regioselectivity of the transformation was not proven, until X-ray crystallographic data had become available. 2D NMR measurements, which were performed, such as NOESY and HMBC seemed to be not informative, however HMBC spectra showed a correlation between a proton of pyridine nucleus and a quarternary carbon 7a of imidazo[4,5-b]pyridine ring. On this basis we made a first assumption, that desirable regioisomer is formed:



Scheme 12. *Cyclocondensation of 5-aminoimidazoles with 3-methoxalylchromone.*

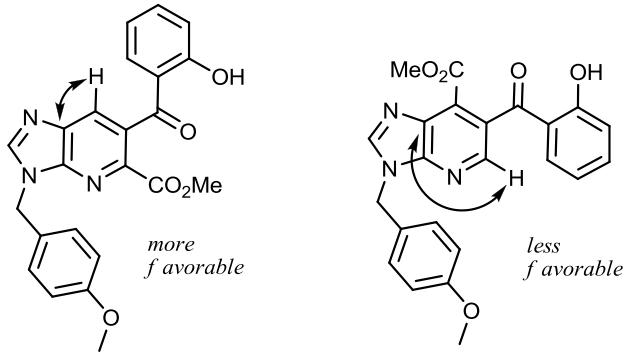


Figure 15. *Correlation of proton from pyridine part with quartenery carbon C-7a, observed in HMBC specrtum. Correlation is more possible to occur in case of H-7 than in case of H-5.*

As it was proven, that the reaction goes on the forecasted pathway, a slight optimization of reaction conditions was performed. Again, as in the case of 3-nitrochromone, the solution of 5-aminoimidazole needed to be cooled down to 0°C, before the bielectrophile should be added. However, in case of 3-methoxalylchromone, more continuous stirring at 0°C after the addition of the reagent is required for higher product outcome (about 30 minutes), which resulted in the yield of 45% (in case of 4-methoxybenzylamine).

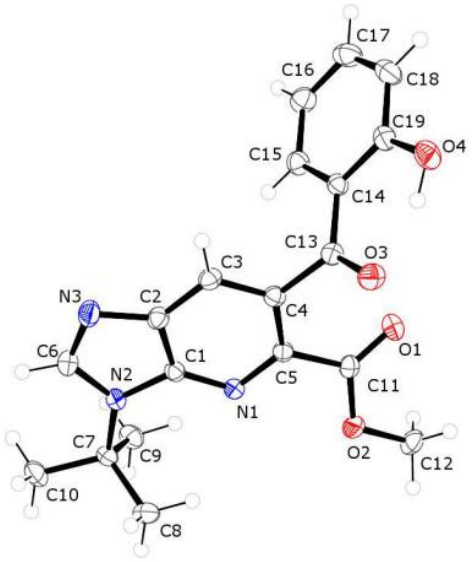
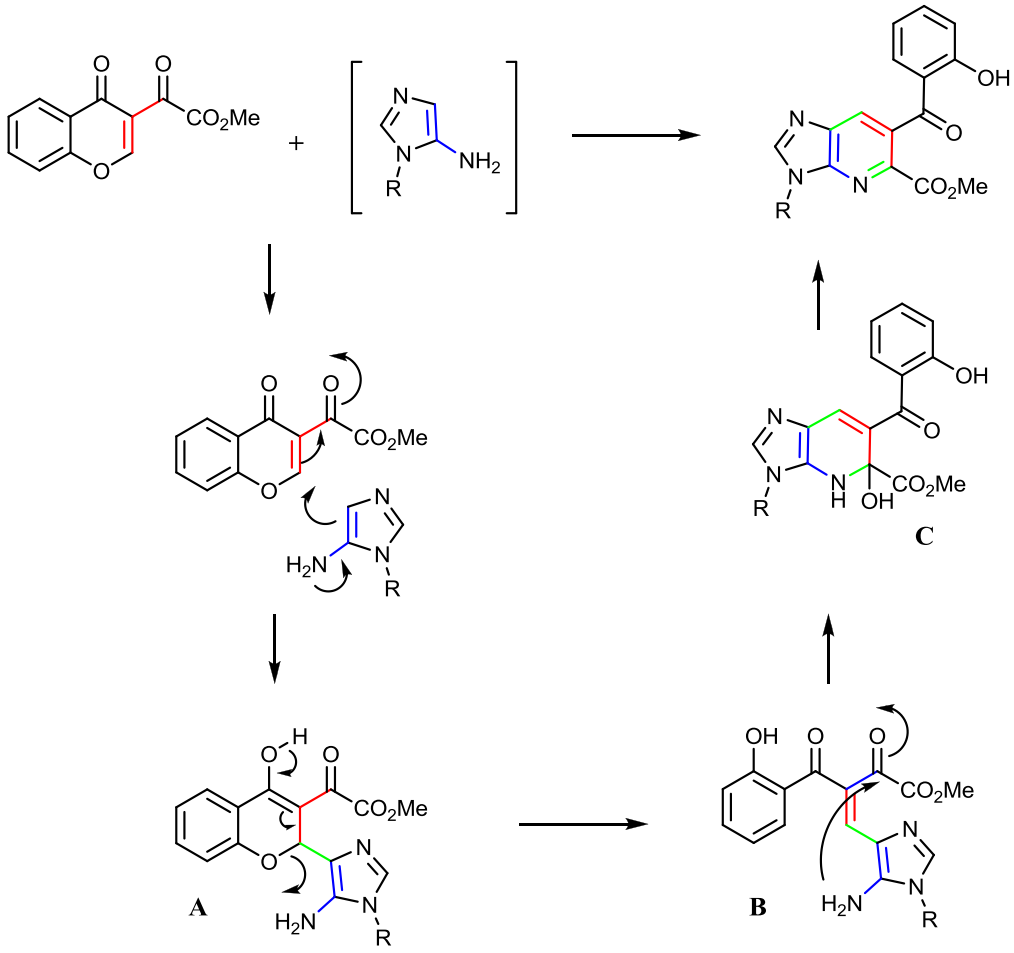


Figure 16. *X-Ray structure of compound **47a**.*

An interesting feature of the obtained product is a possibility to undergo Dakine oxidation, potentially resulting in the introduction of carboxylic acid residue in the position 6 of heterocycle. This, in correspondence with the previous chapter, can lead to the formation of the fragment with potential ADA inhibition properties.

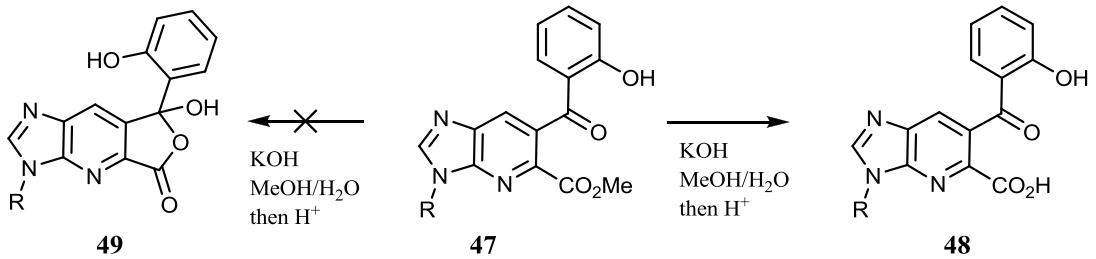
After products identification and process optimization were done, a range of aliphatic amines were tested in current one-pot procedure. The table outlined below (Table 2) indicates a poor variety of yields in all cases.

The formation of products can be explained by conjugate addition of the enamine carbon atom of 6 to the double bond of to give intermediate A. Subsequent pyrone ring opening delivers an intermediate of type B. Intramolecular attack of the amino group on the carbonyl group affords intermediate C, which undergoes elimination of water to give pyridines.



Scheme 13. *Proposed mechanism of formation of **47**.*

All isolated compounds were treated with a water/methanol solution of potassium hydroxide to give, after acidification with concentrated hydrochloric acid, the corresponding carboxylic acids. Theoretically, there are two possible transformation pathways in case of treatment with base - hydrolysis resulting in formation of carboxylic acid **48** or alternatively, lactone **49** formation, involving neighboring carbonyl function, which in fact was not observed:



Scheme 14. *Possible pathways of hydrolysis of **47**.*

Formation of the carboxylic acid derivative was presumed as more probable and it was confirmed by X-Ray crystallographic analysis. Carboxylic acid, which originates from allylamine, was crystallized from DMF and exists in the form of hydrogen bonded dimer:

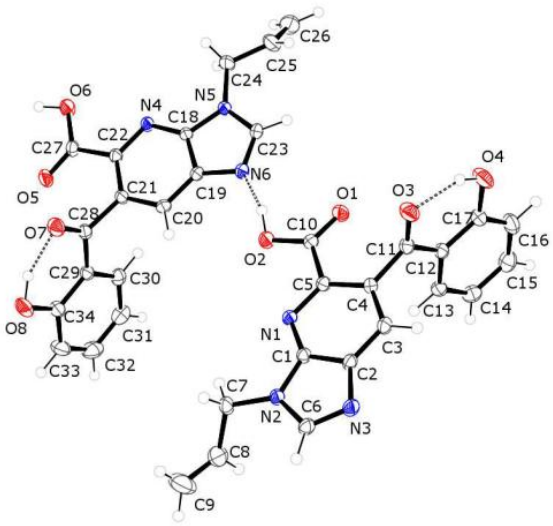


Figure 17. *X-Ray structure of compound **48b**.*

Table 2. *Yields of carboxy-substitited imidazo[4,5-b]pyridines.*

Compound	R	Yields of methyl esters **47** (%)[a]	Yields of carboxylic acids **48** (%)[a]
a	*t*-Bu	48	69
b	All	44	75
c	cyclopropyl	47	86
d	cyclopentyl	46	82
e	cyclohexyl	51	87
f	4-methoxybenzyl	50	88
g	4-chlorobenzyl	44	74
h	2-[(4-methoxy)phenyl]ethyl	45	73
i	2-[(2-methoxy)phenyl]ethyl	50	81
j	2-(phenyl)ethyl	54	90

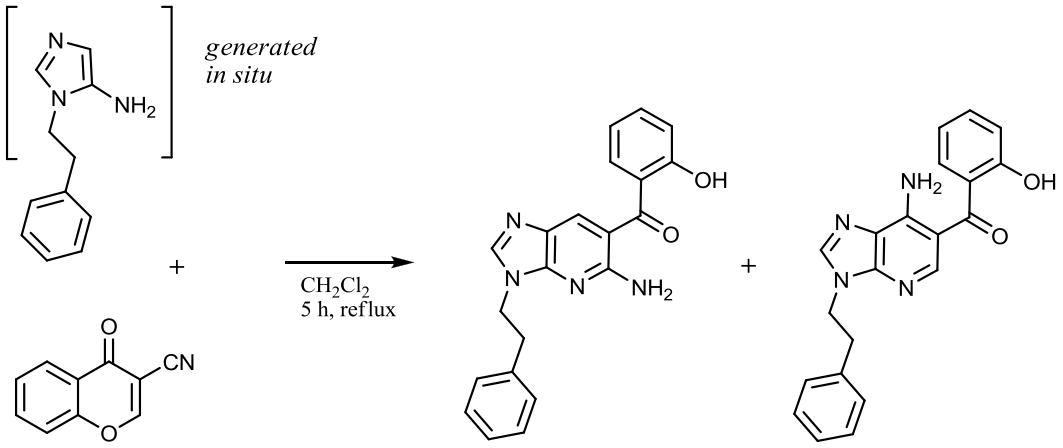
[a)] Yields of isolated products

2.3.3 Conclusions

In a conclusion of this chapter, we have developed a straightforward route to by far unknown carboxymethyl-substituted 1-desazapurines. Bearing a strong-withdrawing group these compound are potential inhibitors of IMPDH and ADA, and can show a broad variety of biological activities. All target substances are obtained in moderate yields via classical approach involving [3+3] cyclocondesation of enamine fragment-containing heterocycle (imidazole in our case) and bielectrophile (3-methoxalylchromone).

2.3 Unsuccessful trial

3-Cyanochromone was tested in the [3+3] cyclocondensation reaction with 1-phenethyl-5-aminoimidazole. In comparison with 3-nitro- or 3-methoxalylchromone, reaction pathway in this case is not easy to predict, as nucleophilic attack can equiprobably occur on carbonyl group of heterocycle or on cyanogroup. In our transformation, we were able to identify, that carbonyl group stays unreactive towards 1-phenethyl-5-amino-1*H*-imidazole, however, the reaction didn't proceed regioselectively, and two isomers, bearing amino-function in position 4 and 6 of imidazo[4,5-b]pyridine ring respectively, can be isolated in unseperable mixture of 1:1.

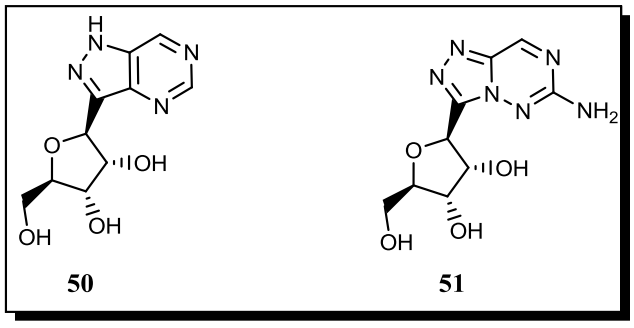


Scheme 15. *Interaction of 1-phenethyl-5-aminoimidazole with 3-cyanochromone.*

3. Design and synthesis of novel purine and 1-desazapurine glycosides as potential inhibitors of adenosine deaminase

3.1 Introduction

Our previous studies, dedicated to the synthesis of ADA inhibitors, are aimed at the development of some new synthetic methodologies that could be implemented in the search for new substances with valuable inhibiting properties. In this chapter, we switched our efforts to a more specific goal, namely the synthesis of adenosine isosteres with specific structural peculiarities, which would increase the inhibition activity. As it was indicated before, the key step of inosine formation via ADA-catalyzed deamination is the nucleophilic addition of water to position 6 of the adenine fragment[19), 31)]. In the case of enzyme inhibition it is important to favor the stability of the hydrated adduct and, on the other hand, to observe the structural similarity, required by enzyme binding pocket. A number of ribosides, designed according to all major sterical requirements often show mediocre inhibition activity - a considerable stabilization by the enzyme is necessary for hydrated form to exist in an amount higher than traces. To favour the formation and stability of hydrated form chemists developed some ribose glycosides, containing more electron deficient aglycone fragment, e.g. deaminoformycin **50**, showing 18 times stronger binding, than Nebularine[32)]:



50 **51**

Figure 18. *Ribose-derived ADA inhibitors.*

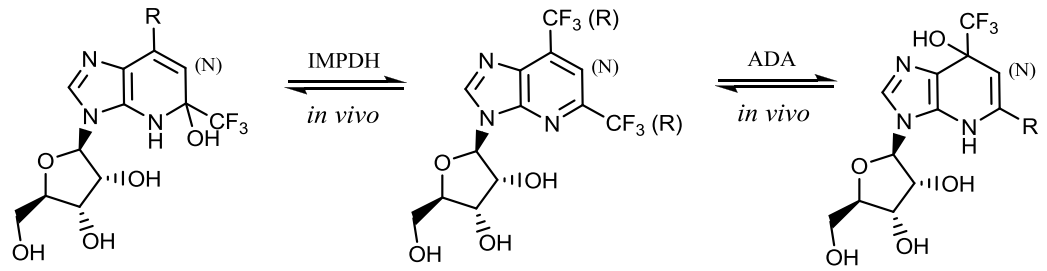
An excellent work of Lindell et al.,[33)] which was based on calculations of the enthalpy of covalent hydration of a number of different nucleosides, indicated that triazolotriazine riboside **51** shows good results in the covalent addition of water and in the binding affinity. These studies proved that a stronger electron-withdrawing character of the aglycone facilitates the hydration process by increasing

the absolute value of enthalpy. This principle we applied in our work which is dedicated to the synthesis of new potential ADA inhibitors, originating from the purine and 1-desazapurine core structure.

To inhibit an enzyme by mimicking its transition state, it is obligatory to match the requirements of the targeted binding pocket. In this sense, purine and 1-desazapurine systems, bearing a trifluoromethyl group at position 6, seem to be beneficial. Numerous studies indicated an isosterical similarity of the trifluoromethyl group with the amino group.[34] Therefore, a change of the substitution pattern from an amino to a trifluoromethyl group should not significantly influence the substrate recognition. The sterical similarity of the trifluoromethyl and the amino group, in combination with the highly withdrawing character of the CF_3 residue, makes 6-trifluoromethyl-substituted purines and 1-desazapurines interesting substrates for studies of ADA inhibition.

On the other hand, purines and their isosteres, bearing a perfluoroalkyl substituent at positions 2 and/or 6, should be also considered as potential inosine monophosphate dehydrogenase (IMPDH) inhibitors, due to the possibility of covalent binding of the Cys 331 moiety of the active side of the enzyme with the sufficiently strong electrophilic carbon atoms C-6 and C-2 to form stable Meisenheimer-type adducts[35]. It was shown that, for example, the 6-chloro-substituted purine base is dehalogenated by IMPDH and a covalent bond is formed at position C-6 with Cys 331.

Motivated by potential pharmacological importance of fluorinated purine and 1-desazapurine glycosides, we focused our efforts on the synthesis of the target compounds.

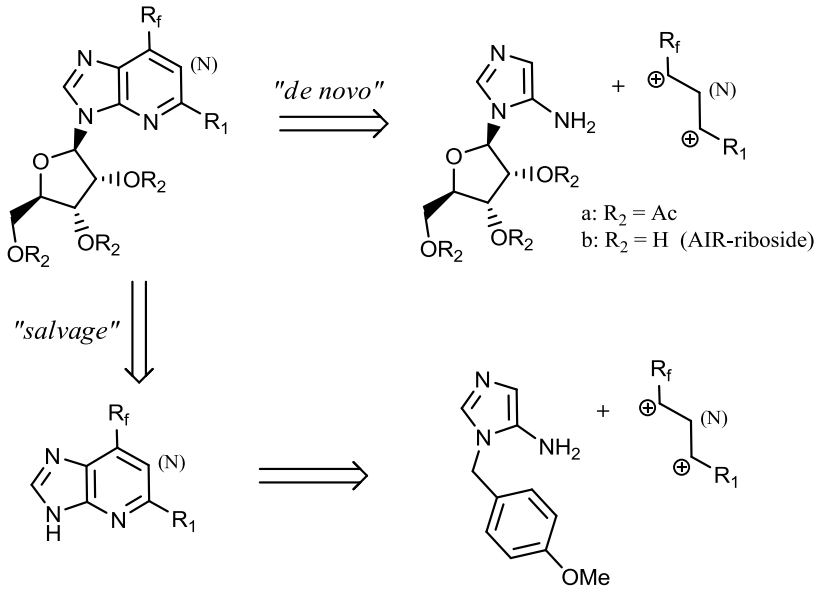


Scheme 16. *Possible interaction of target substrates with ADA and IMPDH.*

3.2 Synthetic pathways towards target glycosides

The first necessary step in our research was to perform retrosynthetic analysis. Two natural synthetic pathways for the purine nucleosides biosynthesis are known – so-called *de novo* and *salvage*[36]. The first one is built on the regioselective electrophilic annulation of the pyridine and

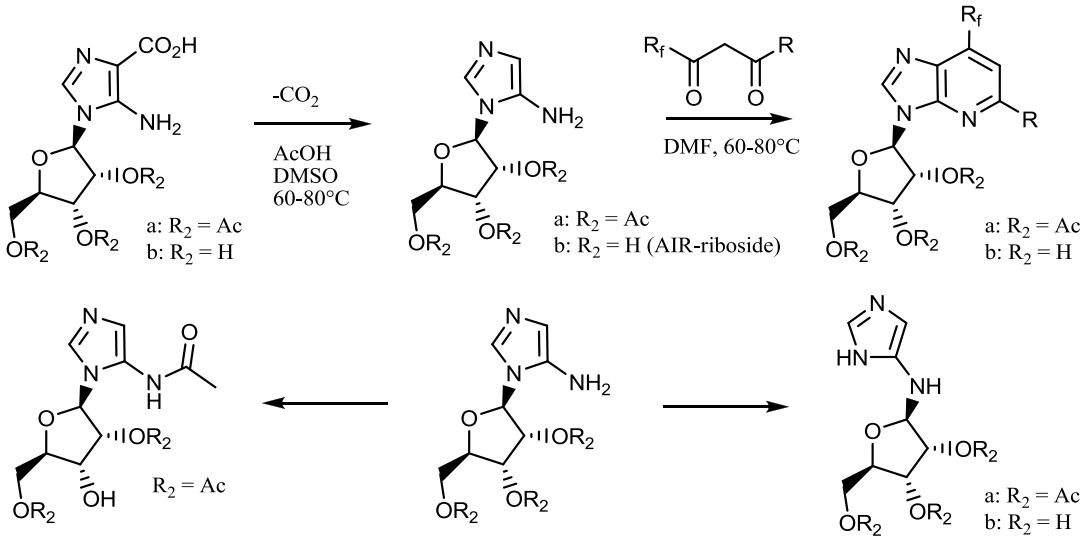
pyrimidine ring on the enamine moiety of the so-called AIR-riboside (see Scheme 17) using diverse fluorine-containing 1,3-CCC- and 1,3-CNC-dielectrophiles. The second strategy relies on the initial assembly of the CF_3-containing purine/1-desazapurine framework starting with 5-aminoimidazole which bears a *p*-methoxybenzyl (PMB) protecting group at position 9. Subsequent deprotection and glycosylation will furnish the desired scaffolds:



Scheme 17. *"Salvage" and "de novo" pathways of 1-desazapurine glycosides synthesis.*

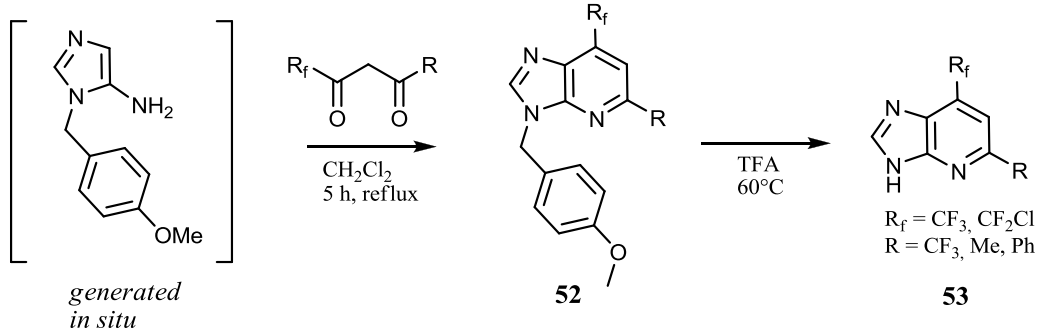
It was assumed, that *de novo* pathway could be more practical as the construction of aglycone fragment is performed using ribosyl-derived imidazole, synthone which contains both sugar and heterocyclic species. However, preliminary studies of Leonard et al.[37] and Iaroshenko et al. exposed this approach. First of all, preparation and handling of AIR-riboside is problematic and all tested procedures didn't release the product in sufficient amount. Synthetic route, that follows *de novo* pathway started from corresponding carboxylic acid, which undergoes decarboxylation, while heated in DMSO in presence of acetic acid, giving AIR-riboside or its acetylated analogue. A number of different protocols were tested in the next step, aiming imidazo[4,5-b]pyridine ring formation; unfortunately all tested reaction conditions did not provide satisfactory product outcome (this includes usage of acetic acid, methanol, acetonitrile and water as solvents and *p*-toluenesulfonic acid as catalyst). The best result was obtained with heating in dry DMF, however, even in this case, products were isolated in maximum of 13% yield.

These poor results could be explained by Dimroth-like rearrangement of AIR-riboside, resulting in the formation of 1-unsubstituted imidazole species or migration of acetyl group from the ribose residue to exocyclic nitrogen (proposed by Leonard et al.).[37)]



Scheme 18. *"De novo" synthetic pathway and possible explanations of its failure.*

Based on these data, we turned our attention to the *salvage* pathway. As a source of generated *in situ* PMB-substituted 5-amino-1*H*-imidazole we used already described reaction of methyl N-(cyanomethyl)-formimidate with *p*-methoxybenzylamine. Subsequent cyclocondesation with fluorinated 1,3-diketones afforded 1-desazapurines **52** in good yields (Table 3).



Scheme 19. *Two-step synthesys of N-unsubstituted 1-desazapurines.*

Table 3. *Yields of fluorinated imidazo[4,5-b]pyridines.*

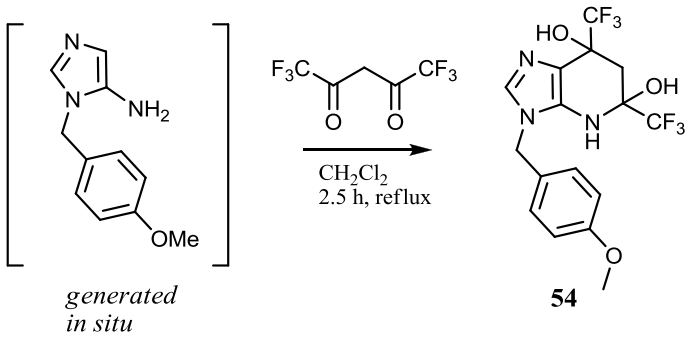
Compound	R_f	R	Yields of **52**, (%)[a)]	Yields of **53**, (%)[a)]
a	CF_3	Me	68	60
b	CF_3	Ph	81	84
c	CF_3	CF_3	58	49

d	CF_2Cl	Me	73	65

[a)] Yields of isolated products

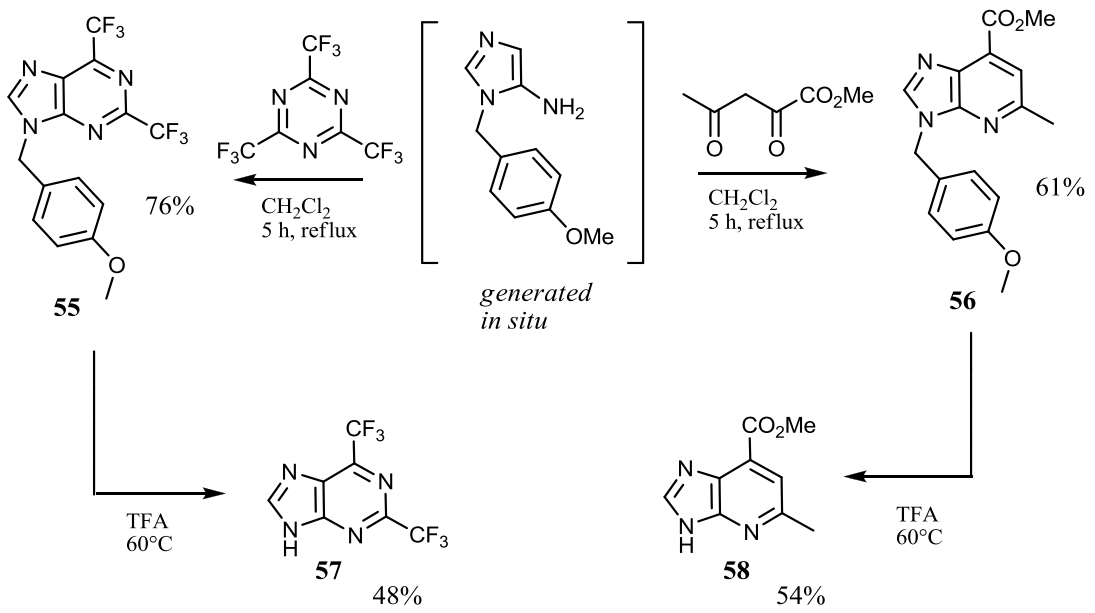
Subsequent cleavage of PMB group by heating in trifluoroacetic acid with followed recrystallisation from isopropanol provided N-unsubstituted 1-desazapurines in good yields, according to the known procedure[10)]; however, electron-withdrawing properties of substituents in heterocyclic fragment have remarkable influence on reaction time. In case of **52a** and **52d**, transformation was completed within one day, but in case of **52c**, about a week is required for complete conversion of starting material.

Notably, in case of **52c** we were able to isolate hydrated intermediate **54**, which was not previously described. Hydrate **54** was precipitating from reaction mixture as white crystals after 2.5 hours of heating in boiling DCM. Structure of **54** was confirmed using 2D NMR methods. Unfortunately, the latter were not enough to identify the stereoselectivity of formation of **54**. All our attempts to get a suitable sample for X-ray analysis failed, because of aromatization, as two molecules of water eliminate during a prolonged stay of corresponding hydrate in any solution. Despite this fact, hydrate **54** is relatively stable and can be stored at room temperature for months. It could be transformed in the corresponding imidazo[4,5-b]pyridine by prolonged heating in DCM or by addition of acetic acid to the reaction mixture.



Scheme 20. *Preparation of hydrated intermediate **54**.*

We were also interested in the synthesis of 2,6-bis-trifluoromethylated purine and carboxymethyl-substituted 1-desazapurine, as these compounds fit the requirements of our concept as well.

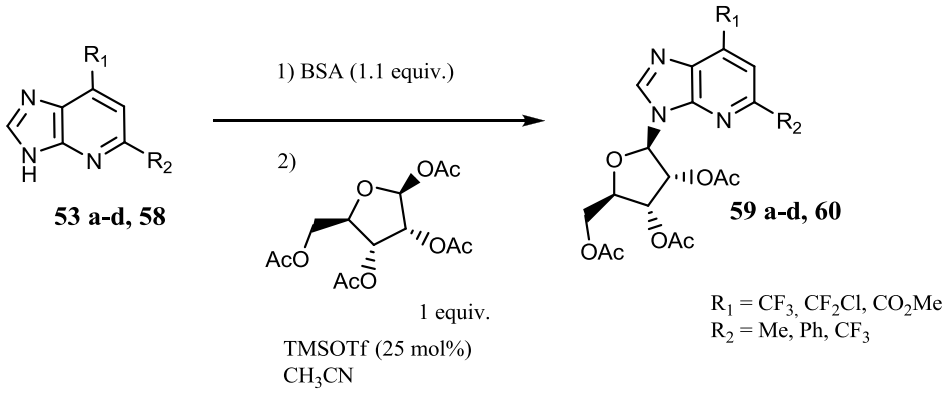


Scheme 21. *Synthesis of carboxymethyl-substituted 1-desazapurine and 2,6-bis-trifluoromethyl-substituted purine.*

Preparation of compounds **56** and **58** was performed following the same protocol, as for **52** and **53;** compound **55** was prepared following so-called inverse electron-demand Diels-Alder reaction of corresponding aminoheterocycle and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine[38]. Deprotection of the purine scaffold by heating in TFA lasts about 10 days, which fits the consistent pattern, observed in the case of 1-desazapurines (purine **57** is the most electron-deficient among all prepared compounds). It should be also noted, that yield of **57** suffers from partial decomposition starting material in TFA.

The key step of *salvage* pathway for our target compounds is a glycosilation reaction of deprotected heterocycle with acetylated β-D-ribose. Such transformation requires acid catalysis, because carbocation at the epimeric position of the sugar should be generated. Addition of sugar to heterocycle via based-catalysed deprotonation of the latter is less common; therefore we studied a number of Lewis-acid-involved glycosilations and came to a conclusion, that so-called silyl Hilbert-Jones method[39] must be beneficial in our case. This typical procedure is based on a preliminary activation of heterocyclic moiety with N,O-bis(trimethylsilyl)acetamide (BSA), resulting in generation of N-silylated intermediate, which reacts with tetraacetylribose in presence of weak Lewis acid, such as TMSOTf. We decided to test 5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine **53a** in this transformation. 1.1 equiv. of BSA was added to a suspension of **53a** in dry acetonitrile and after boiling for 20 min, a clear solution was formed - this indicates the successful initial silylation. Afterwards, a solution of 1 equiv. of acetylated sugar in CH_3CN and catalytic amount of TMSOTf (25 mol%) was added and after boiling

during two hours, we observed almost complete conversion of imidazo[4,5-b]pyridine into its glycosilated derivative in 61% yield. Prolongation of the reaction time, unfortunately, didn't afford higher yields, as decomposition processes take place simultaneously.



Scheme 22. *Glycosilation reactions of imidazo[4,5-b]pyridines with β-D-ribose .*

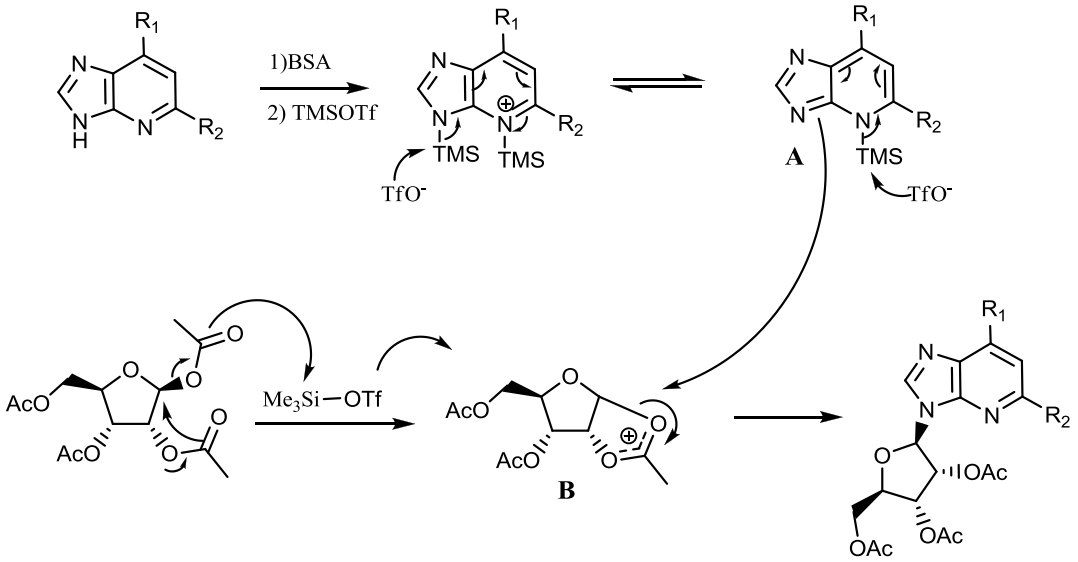
This result encouraged us to test all obtained heterocycles **53** and **58** in the reaction with tetraacetylribose. In all cases, desired products were isolated in moderate to good yields (Table 4).

Table 5. *Yields of acetylated β-D-ribosides.*

Compound	R_f	R	Yields of end products, (%)[a)]
59a	CF_3	Me	61
59b	CF_3	Ph	67
59c	CF_3	CF_3	45
59d	CF_2Cl	Me	77
60	CO_2Me	Me	41

[a)] Yields of isolated products

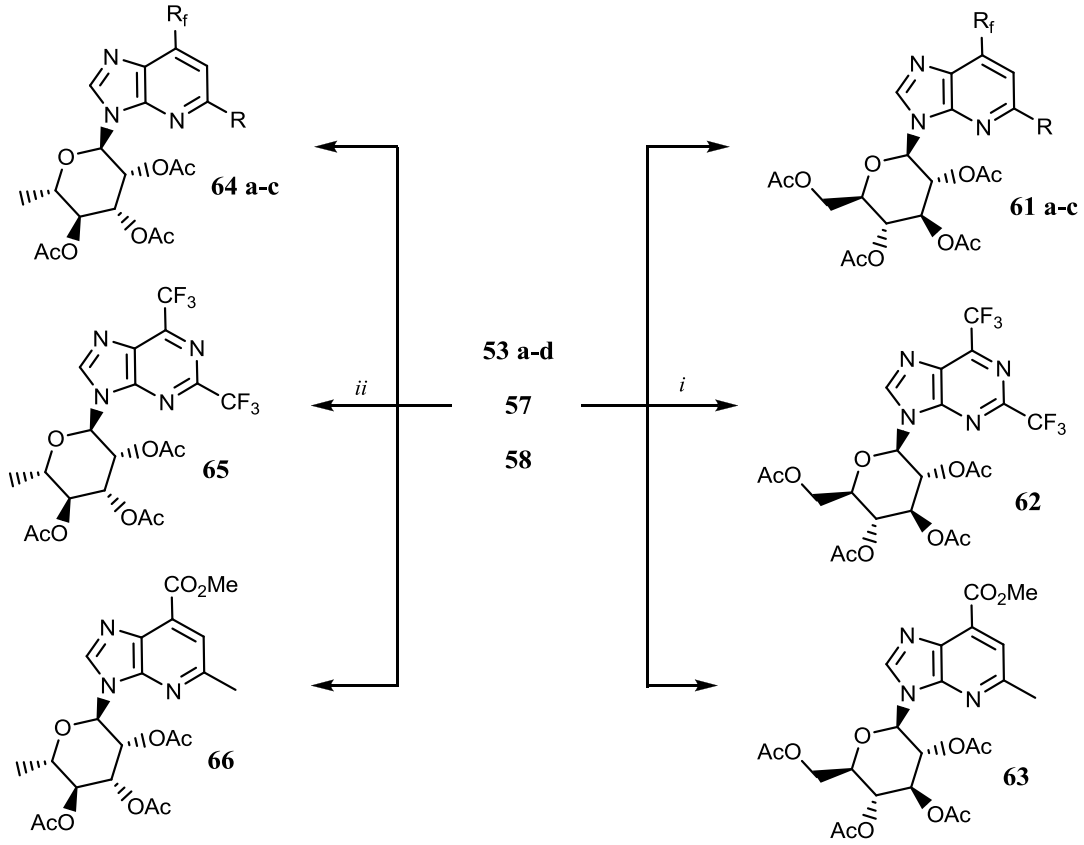
We proposed the mechanism of acetylated riboside formation, which is generally similar to the known mechanistic pathway for naturally occurring purines[40)]. Preliminary silylated heterocycle is being rearranged in the intermediate **A** by the action of TMSOTf, which afterwards attacks on the cyclic cation **B**, which is formed via nucleophilic attack of neighboring acetyl group on deacetylated anomeric position of sugar. This results in formation of the desired nucleoside.



Scheme 23. *Proposed mechanism of 1-desazapurine nucleoside synthesis.*

As it is seen from the reaction pathway, generated ribosyl-cation theoretically can react with heterocyclic species with formation of or 1- or 3-ribosyl-heterocycle. To unequivocally define, which product was delivered, X-ray analysis is required. Unfortunately, all isolated products have oil-like consistence, therefore it was impossible to obtain a suitable sample for measurements. Unfortunately, 2D NMR correlations such as NOESY and HMBC, didn't provide us any hint, that desired 3-ribosyl-imidazo[4,5-b]pyridines were formed, as HMBC correlations were proven to be useless, and no correlations between C-2 or C-3 atoms of sugars and quartenary carbons of aglycone was observed.

According to the previously elaborated strategy, we introduced β-D-glucosyl and α-L-rhamnosyl residues onto our heterocycles **53**, **57**, **58.** Implementing the same procedure as for β-D-ribose, we however observed lower yields in case of hexoses. This could be explained by the fact, that carbocation stabilization by the neighboring acetyl group in case of pyranose is generally much weaker, than the same for furanose. Another important feature is the yields of β-D-glucosyl-derived species was lower the observed yields for α-L-rhamnosyl derivatives (Table 5). It seems logical from the thermodynamical viewpoint, as β-D-glucose is the most stable monosaccharide known; therefore, cation formation is less energetically favorable than for any other pyranose, including α-L-rhamnose. It is noteworthly, that in case of 5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine **53c**, the product of reaction with β-D-glucose is the only isolated glycoside, showing tendency to decomposition during storage at the room temperature.



i: 1. BSA (1.1 eq.); 2. penta-O-acetyl-β–D-glucopyranose, TMSOTf (25 mol. %);
ii: 1. BSA (1.1 eq.); 2. tetra-O-acetyl-α–L-rhamnopyranose, TMSOTf (25 mol. %).

Scheme 24. *Glycosilation reactions of imidazo[4,5-b]pyridines and 2,6-bis(trifluoromethyl)-9H-purine with β-D-glycose and α-L-rhamnose* .

Again, we used only 2D NMR measurements to confirm the regioselectivity of the reaction; unfortunately NOESY and HMBC experiments were useless, as in the case of ribosides.

Table 6. *Yields of acetylated β-D-glycosides and α-L-rhamnosides.*

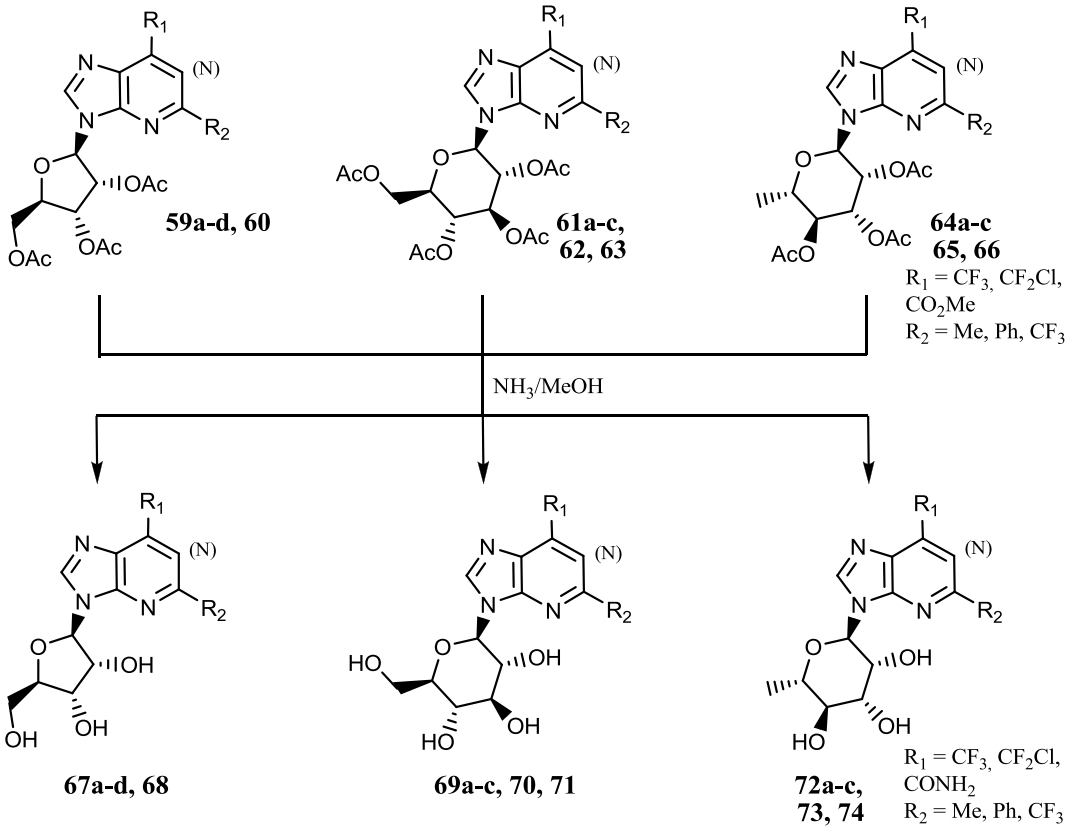
Compound	R_f	R	Yields of end products, (%)[a)]
61a	CF_3	Me	50
61b	CF_3	Ph	52
61c	CF_3	CF_3	43
62[b)]	-	-	38
63[c)]	-	-	54
64a	CF_3	Me	55
64b	CF_3	Ph	53

64c	CF_3	CF_3	49
65[b)]	-	-	48
66[c)]	-	-	54

[a)] Yields of isolated products
[b)] 2,6-bis(Trifluoromethyl)-9*H*-purine **57** was used
[c)] Methyl 5-methyl-3*H*-imidazo[4,5-b]pyridine-7-carboxylate **58** was used

As soon as all acetylated glycosides were synthesized, our last aim was to cleave acetyl groups from the sugar residue. Two possibilities were considered: treatment of our substrates with catalytic amount of MeONa in methanol or with 7M solution of ammonia in methanol. As a test substrate, we have chosen compound **61c**, as the most sensitive to harsh acidic or basic conditions. In the first case, after 3-4 hours, no starting material was observed, however partial decomposition took place (TLC indicated three spots, visible under 254 nm wavelength). The yield of target compound after purification was 62%. The second procedure required more continuous stirring (up to 24 hours), but deacetylation proceeded smoothly and without any signs of decomposition. The only byproduct formed was acetamide, which could be easily separated by column chromatography or even by sublimation under vacuum. The yield of deprotected glycoside in the second case was 96% after acetamide sublimation. Thus we have chosen the second pathway for our purposes.

All previously obtained compounds were successfully deacetylated with excellent yields (Table 7). Interesting, purification process depends on the product consistence. Solid glycosides could be isolated pure by the sublimation of acetamide from the mixture, however oily substances, even after several repetitions of the sublimation, still contained considerable traces of the byproduct; therefore, column chromatography was obligatory in these cases.



Scheme 25. *Deprotection of acetylated glycosides.*

It is important to mention, that ester group of imidazo[4,5-b]pyrinie (if present), was transformed into the primary amide substituent, which is, in fact, a desireable transformation. Introduction of the amide residue could only increase the binding affinity to the target enzyme. In case of compound **72b** X-ray analysis was accomplished. The crystal structure of **72b** inevitably proved, that the glycosilation reaction took place at the position 9 of 1-desazapurine nucleus. Moreover, 2D NMR measurements were performed to tie up C-H and O-H protons of sugar part with the signals of ^{1}H NMR.

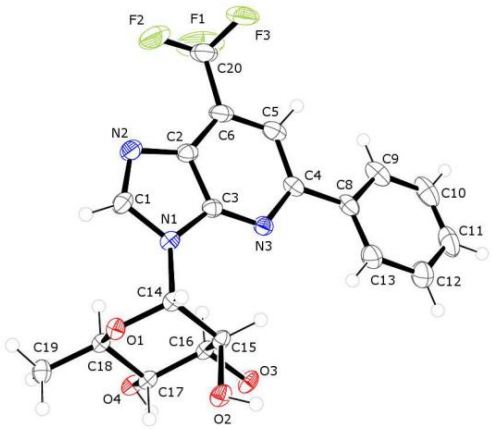


Figure 19. *X-Ray structure of compound **72b**.*

Table 7. *Yields of deacetylated β-D-ribosides, β-D-glycosides and α-L-rhamnosides.*

Compound	R_1	R_2	Monosaccharide	Yields of end products, (%)[a)]
67a	CF_3	Me	β-D-ribose	99
67b	CF_3	Ph	β-D-ribose	96
67c	CF_3	CF_3	β-D-ribose	94
67d	CF_2Cl	Me	β-D-ribose	95
68	$CONH_2$	Me	β-D-ribose	99
69a	CF_3	Me	β-D-glycose	95
69b	CF_3	Ph	β-D-glycose	98
69c	CF_3	CF_3	β-D-glycose	97
70[b)]	CF_3	CF_3	β-D-glycose	95
71	$CONH_2$	Me	β-D-glycose	97
72a	CF_3	Me	α-L-rhamnose	94
72b	CF_3	Ph	α-L-rhamnose	99
72c	CF_3	CF_3	α-L-rhamnose	97
73[b)]	CF_3	CF_3	α-L-rhamnose	96
74	$CONH_2$	Me	α-L-rhamnose	98

[a)] Yields of isolated products

[b)] 2,6-bis(Trifluoromethyl)-9*H*-purine **57** was used

3.3 Conclusions

In a conclusion of this chapter, we have synthesized a number of potential ADA inhibitors, ribosides based on purine or 1-desazapurine core. Bearing an electron-withdrawing substituent at the position 6 of aglycone fragment, they potentially can form more thermodynamically stable hydrated form in comparison with adenosine and bind with the enzymatic pocket irreversibly. As an extension of these studies a number of glycosides and rhamnosides were prepared following the same *salvage* protocol as for ribose-derived compounds. A number of tests, aiming biological evaluation of prepared substrates are currently in progress.

4. Synthesis of polycyclic N-heterocycles based on Pd-catalyzed intramolecular arylation of 1-desazapurines and related substrates

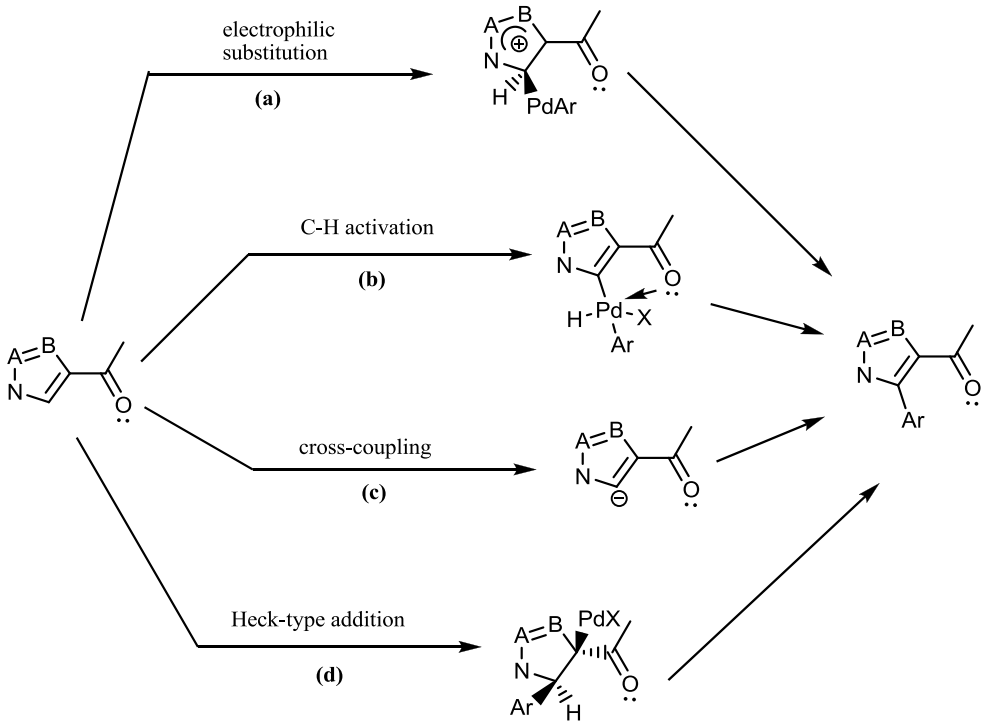
4.1 Introduction

Discovery of transition metal-catalyzed C-C bond formation is without a doubt one of the most important achievement of organic chemistry in the 20-th century. Through the numerous implementations as a pivotal step in the synthesis of pharmacologically relevant substrates, this protocol has earned a reputation of extremely reliable and versatile method. Incalculable variations, including regio and even stereoselective transformations, were developed during the years of research. A bright recognition of this extraordinary achievement was indicated by Nobel Prize Award 2010, which was given to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki, whose input in the development of Pd-catalyzed C-C bond formation is hard to overestimate.

Generally speaking, the C-C bond formation can be efficiently catalyzed by a number of transition metals, such as Pd,[41] Pt,[42] Rh,[43] Ru,[44] Ir[45] as well as Cu,[46] Co,[47] and Ni[48]. These days, despite its exhaustive studies, Pd-catalyzed reactions are considered as the most efficient and economical at the same time, as they have opened new ways to aromatic of aliphatic rings construction and modification. Nowadays, functionalization of heterocycles by direct C-C bond formation is an important strategy for the derivatisation of heterocyclic and carbocyclic compounds. Direct arylation[49], alkylation[50], acylation[51], sulfonation[52], and halogenation[53], of aromatic molecules were performed most of all by the application of Pd catalysts.

In this part of the work we attempted to synthesize tetracyclic and pentacyclic molecules, originating from purines, 1-desazapurines and benzimidazoles via intramolecular Pd-catalyzed arylation of the latter. Interesting, in comparison to the name reactions, involving Pd catalysts, such Heck, Suzuki, Sonogashira, etc., arylation of heterocycles by aryl halogenides remains unclear from the mechanistic viewpoint. In the review of Seregin and Gevorgyan[54], four possible mechanistic pathways were proposed (Scheme 26): electrophilic aromatic substitution **(a)**, C-H activation **(b)**, cross coupling **(c)** and Heck-type addition **(d)**. Studies, summarized in corresponding review, pointed out pathway **(a)** as the most probable for electron-rich heterocycles. Regarding our substrates, it is possible to assume, that

pathway **(b)** could be dominant - Pd insertion is facilitated by higher C-H acidity of more electron poor purines and 1-desazapurines.

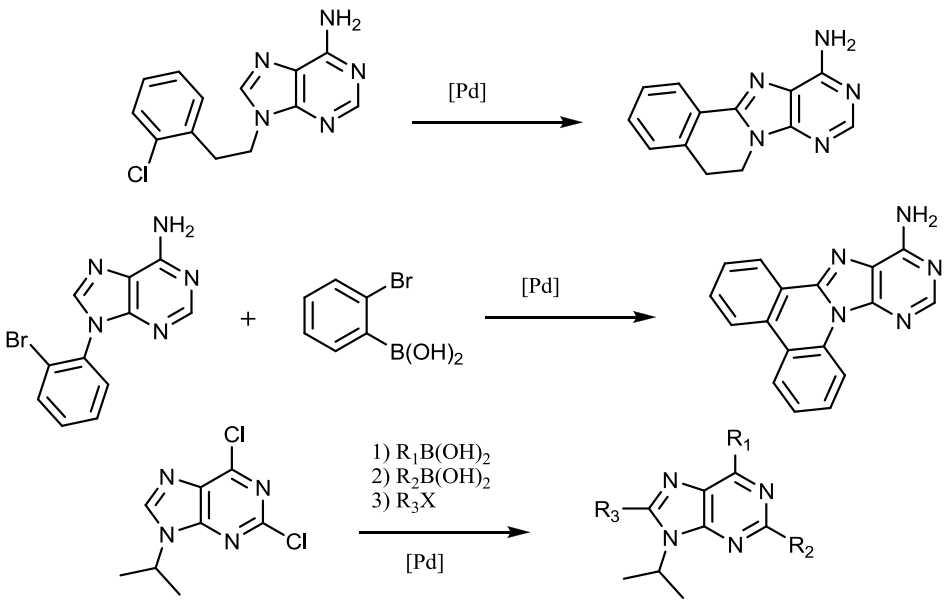


Scheme 26. *Possible mechanistic pathways of direct arylation.*

Arylation of purines and purine-like scaffolds earned a considerable attention in recent years; introduction of aryl or hetaryl substituent onto biologically relevant molecules, originating from purines, can lead to unprecedented changes in *in vivo* actions. An extensive work by Hocek et al., which goaled modification of adenine core by direct intramolecular arylation of adenine[55] at position 2 and various modifications via Suzuki protocol[56] is a bright illustration of this fact (Scheme 27).

The same working group performed Pd-catalyzed modification of 7-desazaadenine with (cytosin-5-yl)ethynyl, following the Sonogashira reaction protocol and used isolated inremediates as nucleotide building blocks in construction of DNA helix, promoted by DNA polymerase[57]. Obtained macromolecules are of considerable interest as DNA methyltransferases and DNA glycosidases inhibitors.

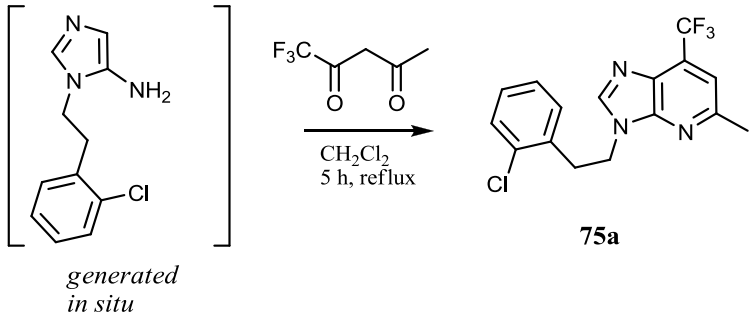
Recently, many reports, indicating arylated purine-based scaffolds showing extraordinary range of biologicall activities[58] have appeared. All mentioned data strongly emphasizes the importance of our studies directed towards intramolecular arylation of purine-like molecules.



Scheme 27. *Modifications of purines by Pd-catalyzed arylation reactions.*

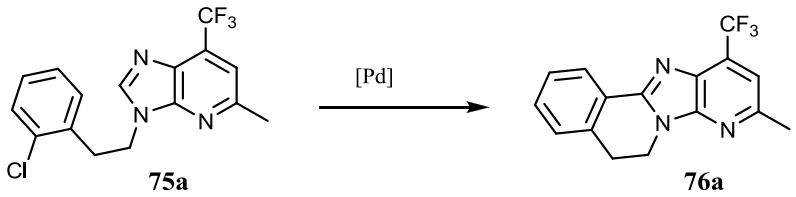
4.2 Intramolecular arylation using aryl chlorides

In the beginning of our research we decided to investigate the scope of intramolecular arylation of trifluoromethyl-containing imidazo[4,5-b]pyridines. As a model substrate we have chosen 3-(2-chlorophenethyl)-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine **75a** to test in the corresponding reaction with usage of various catalytic systems. The latter substance could be easily prepared using our standard procedure, involving generated *in situ* 1-substituted 5-amino-1*H*-imidazoles, and was isolated in 80% yield:



Scheme 28. *Synthesis of scaffold **75a**.*

As a source of Pd, we used $Pd(OAc)_2$, as the most common for such type of transformations. Our initial trial includes implementation of DMF as a solvent and potassium carbonate as a base, which is obligatory to use for hydrochloric acid neutralization. The mixture of **75a**, 5 mol% of $Pd(OAc)_2$ and 2,5 equiv. of K_2CO_3 was heated in DMF up to 140°C under inert atmosphere. After 15 hours, no further product formation was observed and compound **76a** was isolated in a traceable amount of 8% overall yield. Absence of characteristical peak of H-2 proton of **75a** in NMR spectrum convinced us, that the target substance is formed.



75a **76a**

Scheme 29. *Pd-catalyseddirect intramolecular arylation of 3-(2-chlorophenethyl)-5-methyl-7-(trifluoromethyl)-3H-imidazo[4,5-b]pyridine.*

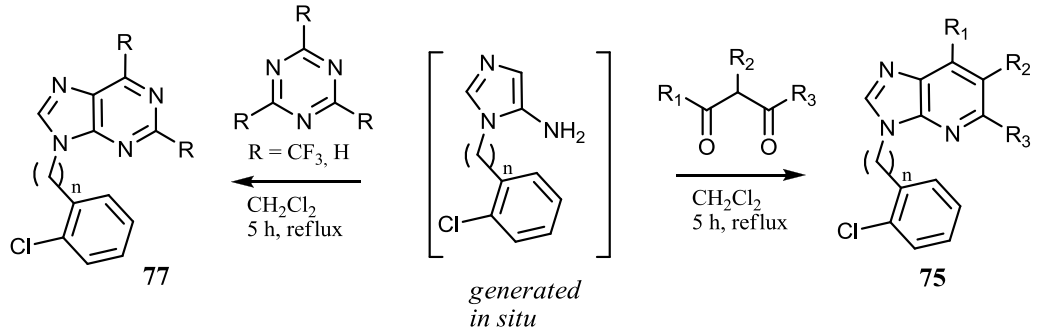
This result forwarded us to modify the catalytic system - an addition of chelating ligand was obviously necessary. $P(t\text{-}Bu)_3$, $P(Ph)_3$ and $P(Cy)_3$ were used in an 10 mol % amount. Tricyclohexylphosphine in a form of tetrafluroborate salt, which is easier in handling and storage[59], in combination with $Pd(OAc)_2$ and potassium carbonate showed superior result, yielding the end product in 93% quantity. Potassium phosphate, which was tested as a base, didn't show higher tendency to facilitate product formation (Table 8).

Table 8. *Optmization of arylation reaction conditions for **75a**.*

Entry	Reaction conditions	Yields of end product, (%)[a]
1	$Pd(OAc)_2$ (5 mol %), K_2CO_3 (2,5 equiv.), DMF, 140°C, 15 h	8
2	$Pd(OAc)_2$ (5 mol %), K_3PO_4 (2,5 equiv.), DMF, 140°C, 20 h	5
3	$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), K_2CO_3 (2,5 equiv.), DMF, 140°C, 9 h	56
4	$Pd(OAc)_2$ (5 mol %), $P(Cy)_3 \cdot HBF_4$ (10 mol %), K_2CO_3 (2,5 equiv.), DMF, 140°C, 7 h	93
5	$Pd(OAc)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (10 mol %), K_2CO_3 (2,5 equiv.), DMF, 140°C, 7 h	83

[a] Yields of isolated products

Identification of the optimal conditions pushed us to examine a whole range of 1-desazapurines and purines in formation of 6- and 5-memberd rings via intramolecular arylation. 1-Desazapurines were synthesized in the same manner as compound **75a**, staring from 2-chlorobenzylamine (if 5-memberd ring formation was planned) or 2-chlorophenethylamine (to obtain 6-membered ring). As 1,3-dicarbonyl compounds, aside from fluorinated substrates, acetylpyruvate and nitromalonic dialdehyde were tested as well. Purines were prepared following inverse electron-demamd Diels-Alder protocol. 1,3,5-triazine and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine were used as dienes (Scheme 30).



Scheme 30. *Prereration of precursors for following intramolecular arylation.*

Most of the scaffolds **75** and **77** were isolated in good or excellent yields, although reaction of 5-aminoimidazoles with 1,3,5-triazine resulted in the formation of 9-substituted purines in moderate yields even after prolonged heating in DCM (up to 7 hours).

Table 9. *Yields of imidazo[4,5-b]pyridines **75**.*

Compound	n	R_1	R_2	R_3	Yields of end products, (%)[a)]
75a	2	CF_3	H	Me	80
75b	1	CF_3	H	Me	68
75c	2	CF_3	H	Ph	82
75d	1	CF_3	H	Ph	72
75e	2	CF_3	H	2-Thenoyl	87
75f	1	CF_3	H	2-Thenoyl	63
75g	2	CF_3	H	2-Furyl	71
75h	1	CF_3	H	2-Furyl	59
75i	2	CF_3	H	CF_3	55
75j	1	CF_3	H	CF_3	57

75k	2	CO_2Me	H	Me	61
75l	1	CO_2Me	H	Me	55
75m	2	CF_2Cl	H	Me	84
75n	1	CF_2Cl	H	Me	77
75o	2	H	NO_2	H	44
75p	1	H	NO_2	H	43

[a)] Yields of isolated products

Table 10. *Yields of purines 77.*

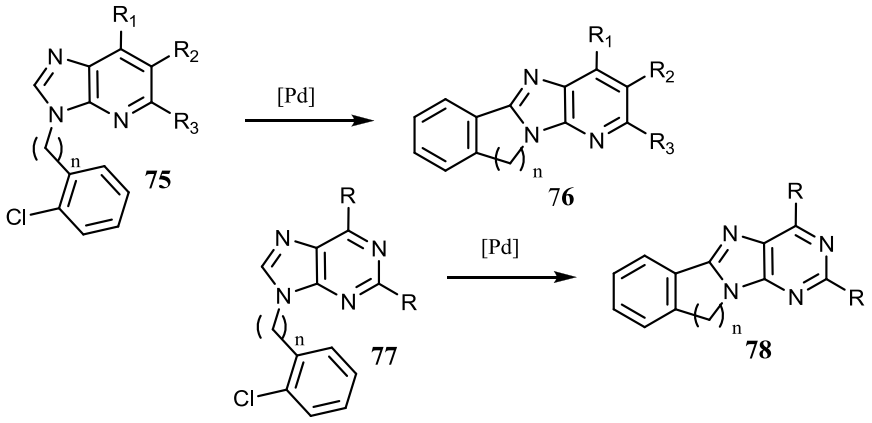
Compound	n	R	Yields of end product, (%)[a)]
77a	2	CF_3	68
77b	1	CF_3	69
77c	2	H	36
77d	1	H	39

[a)] Yields of isolated products

All obtained products were examined in the follow-up intermolecular arylation reaction to test the ability of catalytic system 4 (Table 8) to promote the expected transformation of a number of differently substituted 1-desazapurines and purines. The expected condensed heterocycles were formed in excellent yields in most cases; however some scaffolds showed no reaction activity or tendency to decomposition. Initially, compounds **75k** and **75l**, bearing carboxymethyl-group didn't form cyclized products, inseparable mixture of side-products was isolated after column chromatography in both cases instead. To force arylation process, we had to modify reaction conditions to increase the reactivity of the starting material and to prevent decomposition at the same time. Firstly, we decided to implement a milder base, such as potassium acetate, to check, if the decomposition processes are slowed down. After heating of the reaction mixture at 140°C during 5 hours, we observed no decomposition products, as in case of potassium carbonate, however cyclized product appeared only in traceable amount. Therefore, we implemented biphenyl-derived XPhoS ligand instead of $P(Cy)_3$ in an amount of 10 mol%, and six-membered ring formation proceeded while the heating temperature was decreased to 120°C. Product of arylation of **75k**, was isolated in 39% yield; unfortunately, in case of **75l**, no product was formed under all tested conditions.

Studies, described above, allowed us to overcome most of the appeared difficulties (Table 11, 12). Five-membered cycles were not formed in case of **75p**, **77d** and **78d**. Notably, **75m** and **75n**,

proved to be absolutely unreactive; obviously, CF_2Cl- group has a detrimental effect on the reaction, which was not previously observed.



Scheme 31. *Intramolecular arylation of compounds **75**, **77**.*

Table 9. *Yields of arylated substrates **76**.*

Compound	n	R_1	R_2	R_3	Yields of end products, (%)[a]
76a	2	CF_3	H	Me	93[b]
76b	1	CF_3	H	Me	67[b]
76c	2	CF_3	H	Ph	95[b]
76d	1	CF_3	H	Ph	76[b]
76e	2	CF_3	H	2-Thenoyl	88[b]
76f	1	CF_3	H	2-Thenoyl	69[b]
76g	2	CF_3	H	2-Furyl	79[b]
76h	1	CF_3	H	2-Furyl	52[b]
76i	2	CF_3	H	CF_3	94[b]
76j	1	CF_3	H	CF_3	64[c]
76k	2	CO_2Me	H	Me	39[d]
76l	1	CO_2Me	H	Me	0[b-d]
76m	2	CF_2Cl	H	Me	0[b-d]
76n	1	CF_2Cl	H	Me	0[b-d]
76o	2	H	NO_2	H	69[b]
76p	1	H	NO_2	H	0[b-d]

[a] Yields of isolated products
[b] Conditions: $Pd(OAc)_2$ (5 mol %), $P(Cy)_3 \cdot HBF_4$ (10 mol %), K_2CO_3 (2,5 equiv.), DMF, 140°C, 7 h.
[c] Conditions: $Pd(OAc)_2$ (5 mol %), XPhoS (10 mol %), K_2CO_3 (2,5 equiv.), DMF, 120°C, 6 h.
[d] Conditions: $Pd(OAc)_2$ (5 mol %), XPhoS (10 mol %), KOAc (2 equiv.), DMF, 120°C, 6 h.

Table 10. *Yields of fused purines **78**.*

Compound	n	R	Yields of end product, (%)[a)]
78a	2	CF_3	90[c]
78b	1	CF_3	47[c]
78c	2	H	96[b]
78d	1	H	0[b,c]

[a)] Yields of isolated products
[b)] Conditions: $Pd(OAc)_2$ (5 mol %), $P(Cy)_3 \cdot HBF_4$ (10 mol %), K_2CO_3 (2,5 equiv.), DMF, 140°C, 7 h.
[c)] Conditions: $Pd(OAc)_2$ (5 mol %), XPhoS (10 mol %), K_2CO_3 (2,5 equiv.), DMF, 120°C, 6 h.

It is also worth mentioning, that generally, in case of n = 1, the yields of isolated products were considerably lower for 1-desazapurines and purines as well. Fluorinated purines **77a**, **77b** and cyclized products, originating from them showed much higher tendency to decomposition than corresponding 1-desazapurines, and products **78a-b**, were isolated in slight lower yields in comparison to analogically substituted **76i-j**.

Formation of products **76**, **78** was confirmed by NMR spectras and by X-ray analysis independently (compound **78b**). As it is seen from the layout, fused purine **78b** is in plain.

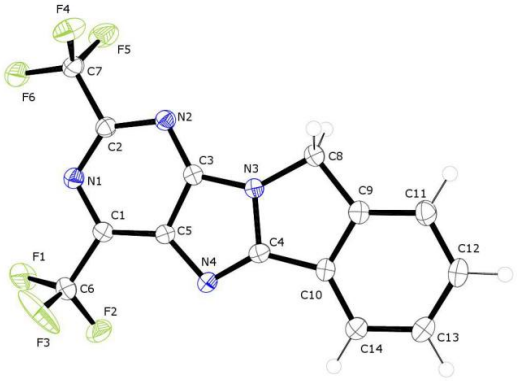


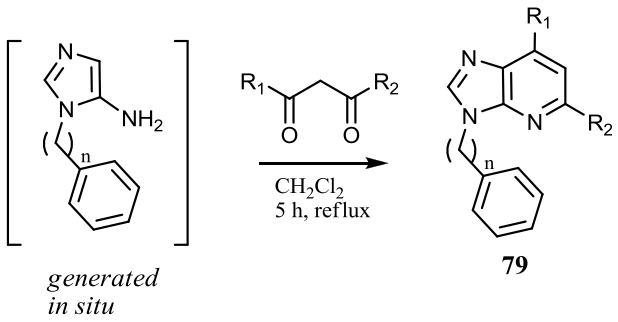
Figure 20. *X-Ray structure of compound **78b**.*

4.3 Oxidative-type arylation of 1-desazapurines

After our successful studies of direct intermolecular arylation, we turned our attention to more economical oxidative-type arylation reactions. In this case Ar-H particle serves a coupling partner instead of aryl halogenide, thus C-C bond is formed by oxidation of both interacting carbons. Oxidative-type C-C bond formation via Pd-catalyzed reactions is a comparatively novel variation of a known

synthetic methodology, however it has already found numerous applications in the synthesis and modification of heterocycles, such as indoles[60], 1,2,3-triazines[61] and many others. Standard protocol of oxidative arylation normally involves transition metal-base catalyst, so-called sacrificial oxidant, mainly responsible for carbon oxidation, and co-oxidant, which is usually necessary for complete transformation of starting material. Simply air or pure oxygen could serve as the co-oxidant.

Synthons which were planned to test in oxidative-type reactions were prepared by the same procedure as all imidazo[4,5-b]pyridines, starting from aliphatic amine, methyl N-(cyanomethyl)formimidate and 1,3-diketone:



Scheme 32. *Synthesis of compounds **79**.*

We were interested to implement the corresponding synthetic method for the formation of 6- as well as 7-membered cycles, because azepine-like structures is a common motif in pharmaceutical industry and routes to such type of structures are often relatively complicated - even direct intramolecular Pd-catalyzed cyclization often doesn't give a proper outcome. Therefore, aside from phenethylamine, we used 3-phenylpropylamine for generation of 5-amino-1*H*-imidazoles, which give us imidazo[4,5-b]pyridine ring with propyl substituent at the position 3 of heterocycle. All products **79** were isolated in good yields (Table 11).

Table 11. *Yields of imidazo[4,5-b]pyridines **79**.*

Compound	n	R_1	R_2	Yields of end product, (%)[a]
79a	2	CF_3	Me	72
79b	2	CF_3	Ph	68
79c	3	CF_3	Me	69
79d	3	CF_3	Ph	53

[a] Yields of isolated products

To gain the best conditions for oxidative arylation, a number of optimizations of reaction conditions were necessary. In the beginning of this research we have chosen $Pd(OAc)_2$ as the most suitable catalyst for this procedure. First of all, in all known cases oxidative-type arylations require Pd (II), which is being reduced to Pd (0) and then oxidized to Pd (II) during catalytic cycle. Moreover, palladium (II) acetate is most widely used and most stable Pd-based catalyst, which is important for harsh oxidative reaction conditions. Copper (II) acetate was chosen to be used as sacrificial oxidant, as the most common for this transformation. Various solvents, bases and amounts of catalysts were tested (Table 12). 5-Methyl-3-phenethyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine **79a** was chosen as a model compound.

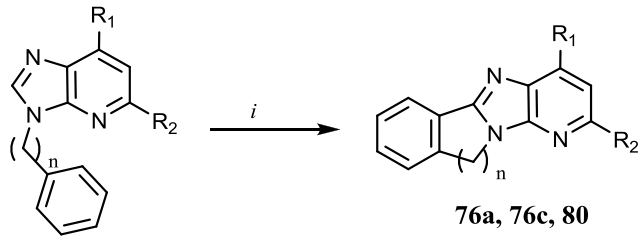
Table 12. *Optmization of oxidative arylation reaction conditions for **79a**.*

Entry	Reaction conditions	Yields of end product, (%)[a)]
1	$Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2 \cdot H_2O$ (2,5 equiv.), K_2CO_3 (2 equiv.), DMF/air, 150°C, 10 h	0
2	$Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2 \cdot H_2O$ (2,5 equiv.), AcOH/air, 110°C, 20 h	18
3	$Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (2,5 equiv.), K_2CO_3 (2 equiv.), DMF/air, 150°C, 10 h	0
4	$Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (2,5 equiv.), K_2CO_3 (2 equiv.), DMA/air, 150°C, 10 h	0
5	$Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (2,5 equiv.), K_2CO_3 (2 equiv.), DMSO/air, 160°C, 10 h	0
6	$Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (2,5 equiv.), K_2CO_3 (2 equiv.), PhMe:AcOH = 4:1/air, 120°C, 20 h	24
7	$Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (2,5 equiv.), K_2CO_3 (2 equiv.), PhMe:PivOH = 4:1/air, 130°C, 20 h	34
9	$Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (2,5 equiv.), K_2CO_3 (2 equiv.), AcOH /air, 110°C, 20 h	42
10	$Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (2,5 equiv.), AcOH /air, 110°C, 8h	61
11	$Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (2,5 equiv.), K_2CO_3 (2 equiv.), PivOH /air, 130°C, 8 h	61
12	$Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (2,5 equiv.), AcOH /O_2, 110°C, 8h	61

[a)] Yields of isolated products

As it is seen from the table, cyclized product was obtained with the best yield in acidic media, while the amount of catalyst had to be increased up to 10 mol %. Usage of pure oxygen as co-oxidant or pivalic acid as a solvent didn't affect the product outcome or reaction time. Notably as well, generation of potassium salt of pivalic acid via addition of K_2CO_3 to the reaction mixtire didn't increase the overall yield, despite the known fact, that potassium pivaloate can play a crucial role in reaction pathway as chelating agent for palladium[62]. As we have found, a crucial role played the quality of the $Cu(OAc)_2$. The use of the hydrated form of the salt decreases drastically the overall yields.

With these optimal conditions in hand we have tested all substrates **79** in oxidative cyclization reactions. Desired structures were isolated in good yields. A slightly better product outcome was observed for methyl-substituted derivatives, probably because phenyl ring can interact in some side-reactions. For the compounds with formed 7-membered ring, the reaction time is considerably bigger, than for the ones with 6-membered, although the overall yields are not vastly different.



79 **76a, 76c, 80**

i: $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (2,5 equiv.), AcOH /air, 110°C.

Scheme 33. *Intramolecular oxidative arylation of **79**.*

Table 13. *Yields of fused imidazo[4,5-b]pyridines via oxidative arylation.*

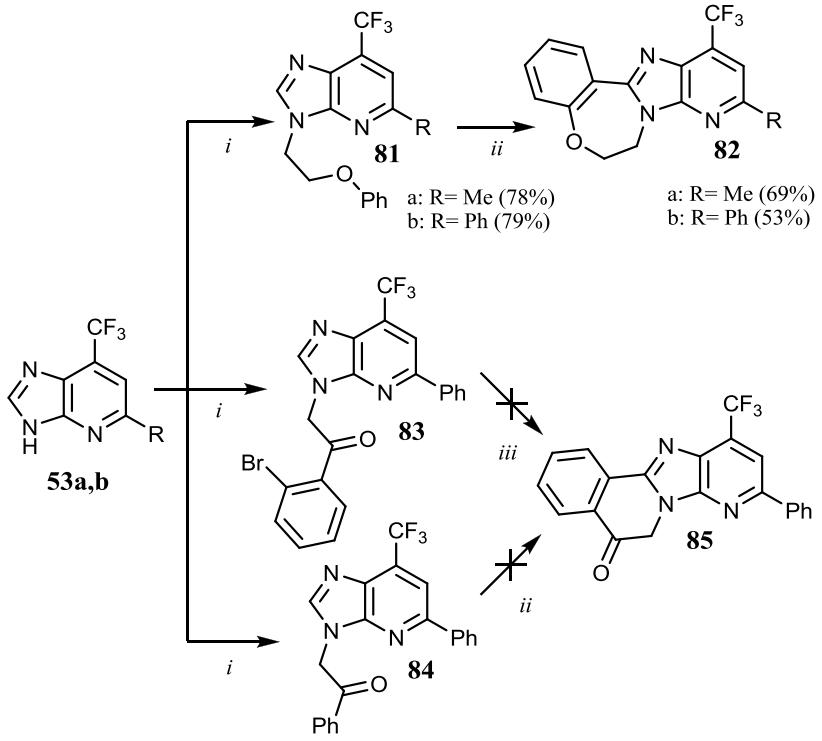
Compound	n	R_1	R_2	Reaction time, h	Yields of end product, (%)[a)]
76a	2	CF_3	Me	8	61
76c	2	CF_3	Ph	8	52
80a	3	CF_3	Me	14	57
80b	3	CF_3	Ph	13	48

[a)] Yields of isolated products

4.4 Synthesis of oxygen-containing fused 1-desazapurines

Motivated by our success, we decided to change the type of the linkers between coupling partners to the oxygen-containing ones. For this purpose we synthesized imidazo[4,5-b]pyridines **53a**

and **53b**, which was afterwards alkylated with (2-bromoethoxy)benzene and 2-bromo-1-phenylethanones under basic conditions (Scheme 34). Sodium hydride as a base showed a bit better result than potassium carbonate in formation of **81a**, thus NaH was used later on. Obtained alkylated products were tested in further modifications involving intramolecular arylation. Unfortunately, only substrates **81** could be successfully converted into corresponding fused oxazepines **82**, while compounds with the carbonyl group appeared to be absolutely unreactive under both direct and oxidative protocols and showed tendency to slow decomposition.



i: 1 equiv. of alkylating agent, 1.1 equiv. NaH, DMF, 2h;
ii: $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (2,5 equiv.), AcOH/air, 110°C, 8 h;
iii: $Pd(OAc)_2$ (5 mol %), XPhoS (10 mol %), KOAc (2 equiv.), DMF, 120°C.

Scheme 34. *Usage of Pd-based catalysis for the synthesis of oxygen-containing fused 1-desazapurines.*

Notably, similar to substrates **76** and **80,** methyl-substituted product was isolated in a higher yield than the one bearing phenyl ring. The better yields for oxazepines in comparison with azepines can be explained by additional stabilization of Pd-introduced intermediate through a coordination with oxygen atom.

Crystal structure of compound **82a** proved the formation of seven-membered ring. As it is senn from the Figure 21, 1-desazapurine part of the molecule is in plain, although oxazepine fragment is not rigid.

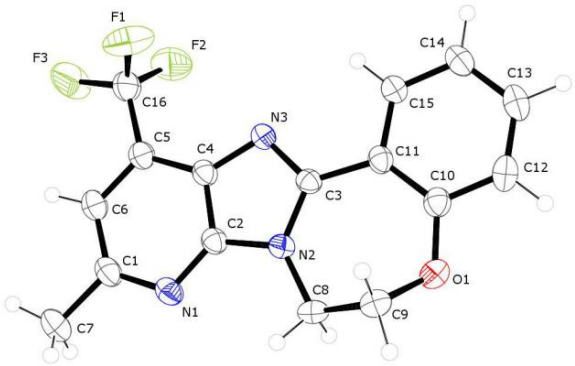
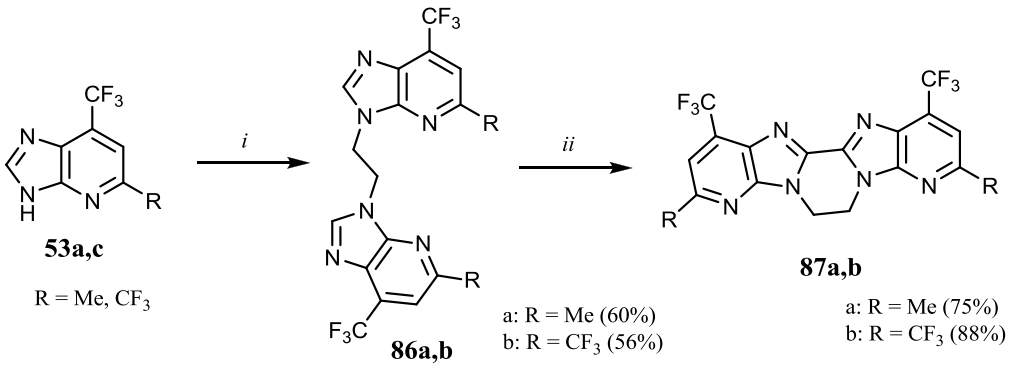


Figure 21. *X-Ray structure of compound **82a**.*

4.5 "Dimerization" of 1-desazapurines and benzimidazoles via oxidative arylation and synthesis of 5,6-dihydrobenzimidazo[2,1-*a*]isoquinolines

Our next step was to synthesize the intermediates, bearing imidazo[4,5-b]pyridine ring on the both sides of the linker, therefore both would become coupling partners in the oxidative arylation. For the preparation of these synthons we have chosen compounds **53a** and **53c** as the introduction of much more withdrawing CF_3 group instead of methyl substituent could drastically distinguish C-H acidity of H-2 proton and affect the reaction process.

The initial alkylation of imidazo[4,5-b]pyridines with 1,2-dibromoethane promoted by potassium carbonate resulted in a poor yield of target dimer because many side-reactions took place. However sodium hydride showed sufficient results and substances **86a**, **86b** were isolated in moderate yields (Scheme 35). Scaffolds **86** were then used in the oxidative arylation process under previously developed conditions. As we expected, introduction of the second trifluoromethyl group had an extraordinary influence on the reaction. 5,7-bis(Trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine **53c**, due to its electron poverty, was completely unreactive, as copper (II) acetate appeared to be a weak oxidant. Although, if AgOAc is used, reaction proceeds very fast and with excellent yield. Compound, derived from **53a**, was formed smoothly and with excellent yield as well.



i: 1 equiv. of alkylating agent, 1,1 equiv. NaH, DMF, 2h;
ii: $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2,5 equiv.), AcOH/air, 110°C, 8h (a); or $Pd(OAc)_2$ (10 mol%), AgOAc (2,5 equiv.), AcOH/air, 110°C, 8h (b).

Scheme 35. *Formation of fused 1-desazapurine dimers by oxidative cyclization.*

Formation of **87a** was independently confirmed by X-Ray analysis (Figure 22). Pentacyclic core of **87a** is slightly out of the plain due to ethylene fragment.

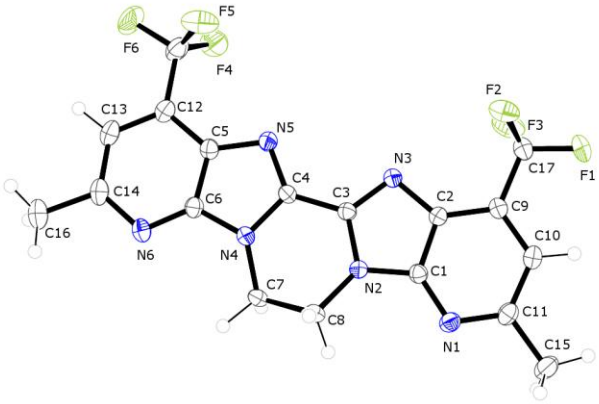
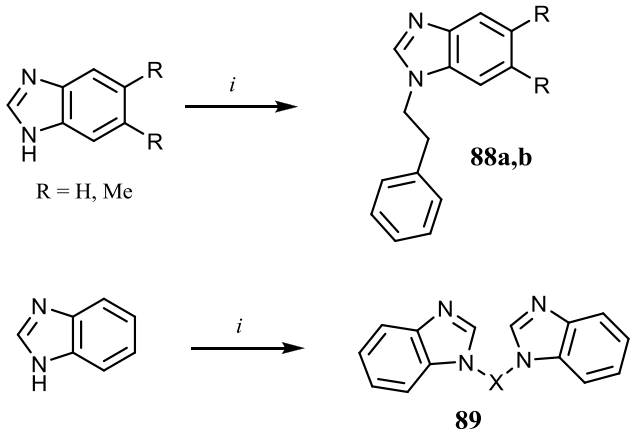


Figure 22. *X-Ray structure of compound **87a**.*

After comprehensive studies of arylation of purines and 1-desazapurines at the position 2 of the heterocyclic nucleus were finished, we focused our efforts on the same transformation, involving simple benimidazoles. Pd insertion in C-H bond of position 2 of benzimidazole ring is, reciprocally to imidazo[4,5-b]pyridines, is not stabilized by any coordinating species, but H-2 proton of benzimidazoles is much less acidic. Thus, we kept in mind, that our initial conditions for oxidative C-H functionalization could be not suitable for this type of molecules.

We started our investigation with alkylation of benzimidazole and 5,6-dimethylbenzimidazole with phenethylbromide. Alkylated products were tested in oxidative cyclization, following the procedure, developed for imidazo[4,5-b]pyridines. Cyclized products formation was observed by TLC

during reaction time, nevertheless, the amount of isolated fused benzimidazoles wasn't above 10% yield after 20 hours heating in acetic acid; optimization of reaction conditions was necessary. To line up the suitable catalyst, oxidant and solvent, we decided to synthesize scaffolds, bearing two benzimidazole fragments on both sides of the linker (similarly to compounds **87**). We supposed, that higher C-H acidity of benzimidazole in comparison to benzene will facilitate corresponding cyclization, as it was observed for imidazo[4,5-b]pyridines. For this purpose a set of compounds **89** were prepared.



Scheme 36. *Synthesis of alkylated benzimidazoles.*

Table 14. *Yields of alkalated benzimidazoles **88, 89**.*

Compound	R	X	Yields of end product, (%)[a)]
88a	H	-	69
88b	Me	-	64
89a	-	$(-CH_2-)_2$	60
89b	-	$(-CH_2-)_3$	76
89c	-	$(-CH_2-)_4$	69
89d	-	$(-CH_2-)_5$	67
89e	-	$-(CH_2)_2O(CH_2)_2-$	76
89f	-	1,2-phenylenedi(methylene)-	83

[a)] Yields of isolated products

The first test reaction of substrate **89a** using our initial conditions didn't result in any product formation. We anticipated, that pivalic acid instead of AcOH can be more efficient, as it is possible to

heat the reaction mixture to more, than 120°C. Moreover, with the addition of K_2CO_3, potassium pivaloate is formed and as it was mentioned above, this salt can efficiently coordinate palladium and stabilize the transition state of cyclization. Therefore, our next step was to test conditions 11 (see Table 12). Under these conditions, after heating of **89a** during 10 hours, no product was observed by TLC; therefore in the beginning we presumed that our experiment failed. However later on we realized, that our product as well as starting material are electron-enriched heterocyclic derivatives, which are able to form a complex with copper (II) (Figure 23):

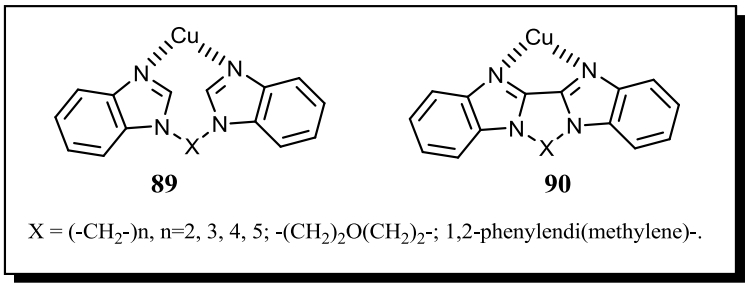
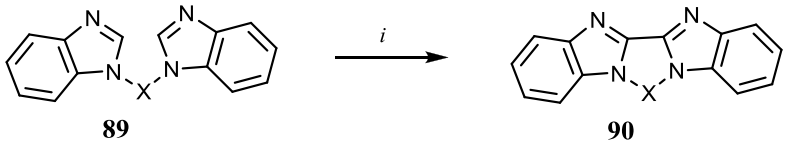


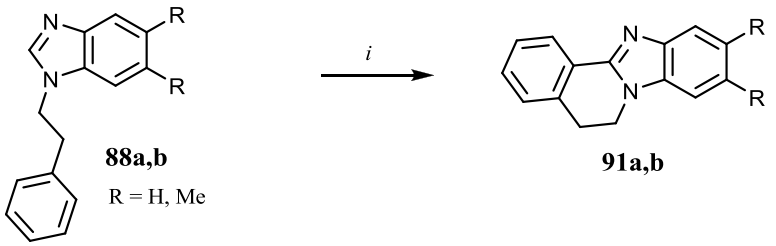
Figure 23. *Coordination of copper (II) with benzimidazole derivatives.*

To destroy the complex, that was possibly formed, we treated the sample of solution of **89a** in pivalic acid with 20% aq. solution of NaOH to neutralize the acid, and then with concentrated water solution of NH_4Cl. The color of the mixture was becoming intensively blue, indicating that copper (II) ammoniacate was forming. To our pleasure, TLC indicated almost complete conversion of starting material and product formation. In our next trial, we prolonged the reaction time to 14 hours, and after the transformation was completed, cyclized product was isolated in 52% yield. Oxidative cyclization of 89a wasn't more successful, if pure oxygen was used a co-oxidant (conditions 12 of Table 12), thus we have chosen previous conditions for the whole our following work.

All compounds **88** and **89** were tested under novel procedure (compounds **88** were put in the reactions afterwards, when all symmetrical benzimidazole derivatives were successfully prepared) All desired structures were obtained in moderate to good yields. Obviously, in case of bulky linker, product outcome was less sufficient due to sterical reasons.



X = (-CH_2-)n, n=2, 3, 4, 5; -$(CH_2)_2O(CH_2)_2$-; 1,2-phenylendi(methylene)-.



i: $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (2,5 equiv.), K_2CO_3 (2 equiv.), PivOH /air, 130°C, 8 h.

Scheme 37. *Pd-catalyzed oxidative arylation of alkylated benzimidazoles.*

Table 15. *Yields of compounds benzimidazoles **90, 91**.*

Compound	R	X	Yields of end product, (%)[a)]
90a	-	$(-CH_2-)_2$	52
90b	-	$(-CH_2-)_3$	58
90c	-	$(-CH_2-)_4$	39
90d	-	$(-CH_2-)_5$	31
90e	-	$-(CH_2)_2O(CH_2)_2-$	28
90f	-	1,2-phenylenedi(methylene)-	42
91a	H	-	58
91b	Me	-	50

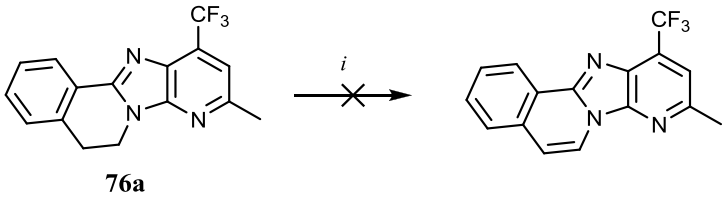
[a)] Yields of isolated products

All products were easy to identify by ^1H and ^{13}C NMR methods. Absence of peak of the H-2 proton of benzimidazole in oxidative arylation products is a clear evidence of pentacyclic species formation.

4.6 Unsuccessful trials

We were interested to achieve full aromatization of 5,6-dihydropyrido[3',2':4,5]imidazo[2,1-*a*]isoquinolines **76** by oxidation of endocyclic ethylene fragment. A bright variety of methods were tested. This includes oxidative bromination via Br_2/AcOH, oxidation with DDQ, TrOH/TFA system and

Pd/C. Unfortunately, all our experiments with compound **76a** failed, and no even traces of aromatized product was observed.

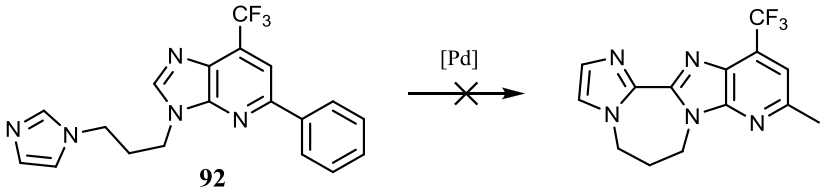


76a

i: Br_2/AcOH; TrOH/TFA; DDQ/PhH; Pd/C/Naphtalene.

Scheme 38. *Aromatization reaction attempts.*

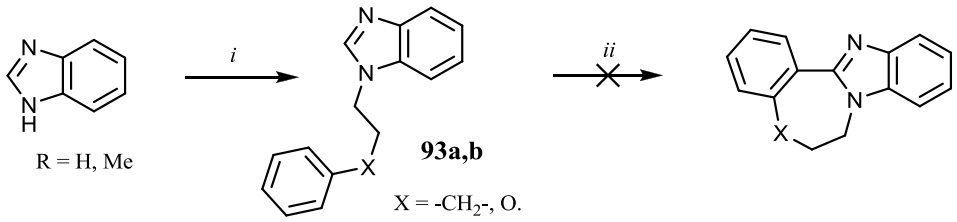
As we tested a number of oxidative reactions on fused imidazoles, another logical step would be to try it on simple 1-substituted imidazole derivatives. For this purpose imidazo[4,5-b]pyridine **92**, linked to imidazole with alkyl chain at position 3 was prepared. Disappointing, this scaffold totally decomposed under oxidative arylation conditions even in neutral solvents, such as DMF or DMSO.



92

Scheme 39. *Unsuccessful oxidative cyclization involving imidazole ring.*

Formation of 7-membered ring, fused with benzimidazole was also to no effect. Some traces of azepine in case of **93a** were observed, but couldn't be isolated pure.



i: 1 equiv. of alkylating agent, 1,1 equiv. NaH, DMF, 2h;
ii: $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (2,5 equiv.), K_2CO_3 (2 equiv.), PivOH /air, 130°C, 8 h.

Scheme 40. *Unsuccessful oxidative cyclization on benzimidazoles, aiming 7-membered ring formation .*

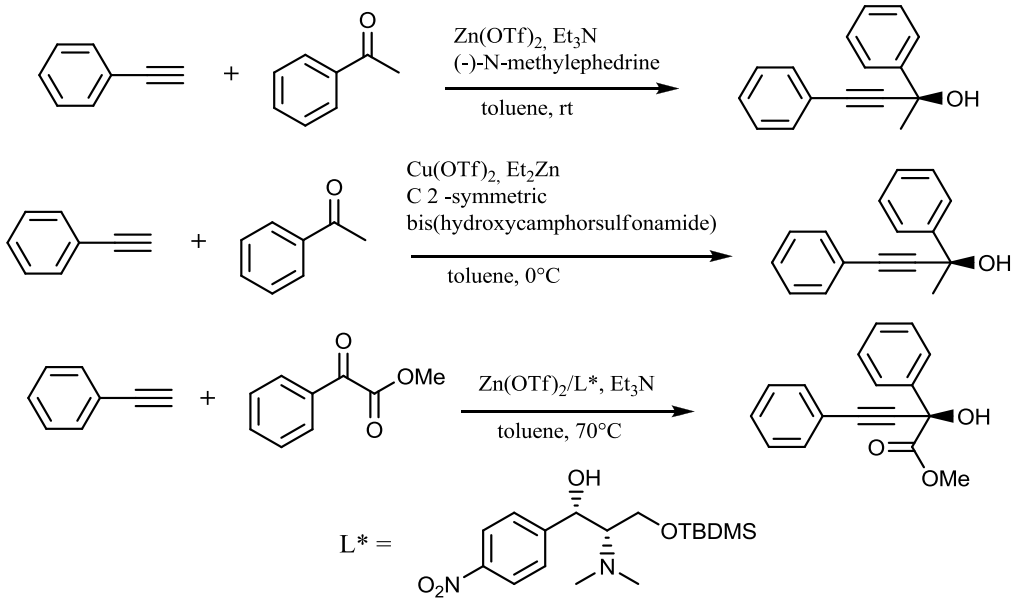
4.7 Conclusions

In conclusion, a number of routes towards fused purines, 1-desazapurines and benzimidazoles via Pd-catalyzed reactions were developed. The first oxidative-type arylation of benzimidazoles is described. Developed protocols were proven to be suitable for the formation of middle-size cycles (up to 9-membered ring). All tested compounds showed excellent regioselectivity in modifications via C-H activation, as all heterocycles tested, reacted with coupling partners at position 2 of the ring.

5. A novel method for synthesis of 4-trifluoromethyl-pyridines starting from alkynylated 1,3-diketones

5.1 Introduction

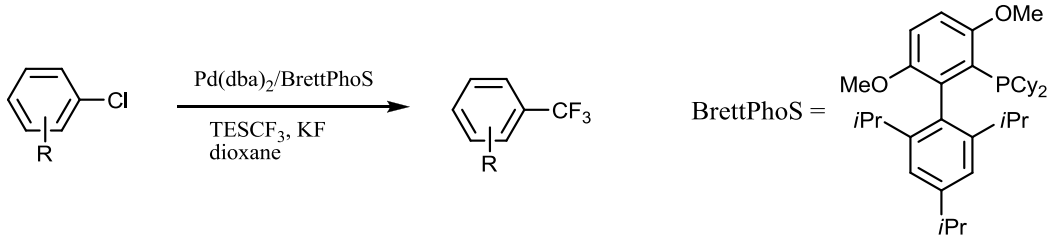
Addition of terminal alkynes to carbonyl compounds, resulting in formation of propargyl alcohols, which is also known as Favorsky reaction[63], has become a very useful synthetic tool in a context of always challenging goal of C-C bond formation. It has found its niche in chemical industry - 2-methylbut-3-yn-2-ol is a widely used precursor, which is prepared by addition of acetylene to acetone. In industry this reaction is catalyzed by potassium hydroxide and diethyl ether is used as a solvent at -40°C. For the preparative purposes, however, this method gives mediocre results and suitable only for the simplest substrates. To maintain the optimal conditions for successful alkynylation in every concrete case is an important endeavor in organic synthesis. Especially, if specific enantiomer of propargyl alcohol is desired. Generally speaking, the most famous method of alkyne addition lies in preliminary lithiation of terminal carbon, using *n*-BuLi or any other alkyllithium salt[64]. Although, this general method is not prevailing in case of enantioselective alkynylation, which usually requires Lewis acid catalysis and a chiral ligand[65]. Some notable examples of this transformation are outlined below:



Scheme 41. *Examples of asymmetric alkynylation of ketones.*

Despite the fact, that alkynylation of carbonyl group is known for more than a century, some substrates haven't been studied in this reaction by far. For example, methylene-unsubstituted 1,3-dicarbonyl compounds, to the best of our knowledge, were never modified with terminal alkynes; nevertheless, scaffolds, bearing carbonyl function and propargyl alcohol fragment could be extremely valuable in organic synthesis.

In the context of our research, dedicated to investigation of new methods of the azines preparation, we were interested in the development of a straightforward route to 4-trifluoromethyl-substituted pyridines. Theoretically, such type of compounds could be easily prepared by the same very common strategy, which was continuously implemented in this work – condensation of enamine fragment with CF_3-derived 1,3-diketones. But in the sense of diversity, some new protocols could give a better outcome, as specifically substituted pyridine core require corresponding modification of enamine, which is not a reasonable pathway sometimes. On the other hand, with development of transition metal-catalyzed reactions, direct trifluoromethylation of aromatic or heterocyclic moieties is not an extraordinary task anymore; after the pioneering work of Buchwald et al.[66] (see Scheme 42), a number of methods, based on Pd- or Cu-catalyzed trifluoromethylation with $TMSCF_3$ appeared[67].



Scheme 42. *Pioneering work of Buchwald in trifluoromethylation of aryl chlorides.*

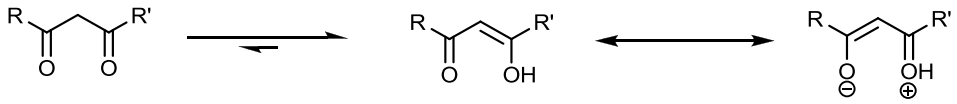
Although the progress in the field of CF_3-group introduction is imposing, the alternative methods still would be of a great privilege, as in all cases, comparatively complicated and expensive catalytic systems are required. Another possibility for 4-trifluromethylpyridine synthesis is a multi-step procedure, developed by Jiang et al., starting from ethyl trifluoroacetate and allyl bromide[68]. However, this protocol suffers from low overall yields. In this part of the work, we were happy to develop an unprecendented two-step procedure for the synthesis of trifluoromethylated pyridines starting from 1,3-diketones, terminal alkynes and urea.

5.2 Synthesis of 3-hydroxypent-4-yn-1-ones and 4-trifluoromethylpyridines

5.2.1 Concept

It occurred to us, that 3-hydroxypent-4-yn-1-ones, containing a carbonyl group and a propargylic alcohol fragment, might be attractive 1,5-dielectrophilic synthons which could form pyridines upon the reaction with a nitrogen source. This type of formal [5+1] cyclocondensation has not been previously studied to the best of our knowledge.

The starting point of this project was to develop a practical route to corresponding bielectrophiles, which is obviously would be direct alkynylation of 1,3-diketones, which (as it was pointed out) wasn't successfully accomplished before. As we have taken this problem upon close consideration, it becomes clear, that this type of transformation is not a routine problem. 1,3-Diketones, similarly to monocarbonyl compounds are being enolized in a majority of organic solvents. However, enol form of 1,3-diketones constitute an entire conjugated system, in which electrophilic properties of remaining carbonyl group are highly reduced. This could be illustrated by two resonance forms of enolized species, in which C=O group reactivity is clearly lower in comparison to the fragments, where carbonyl function is present in non-conjugated part.



Scheme 43. *Tautomeric and resonance forms of 1,3-dicarbonyl species.*

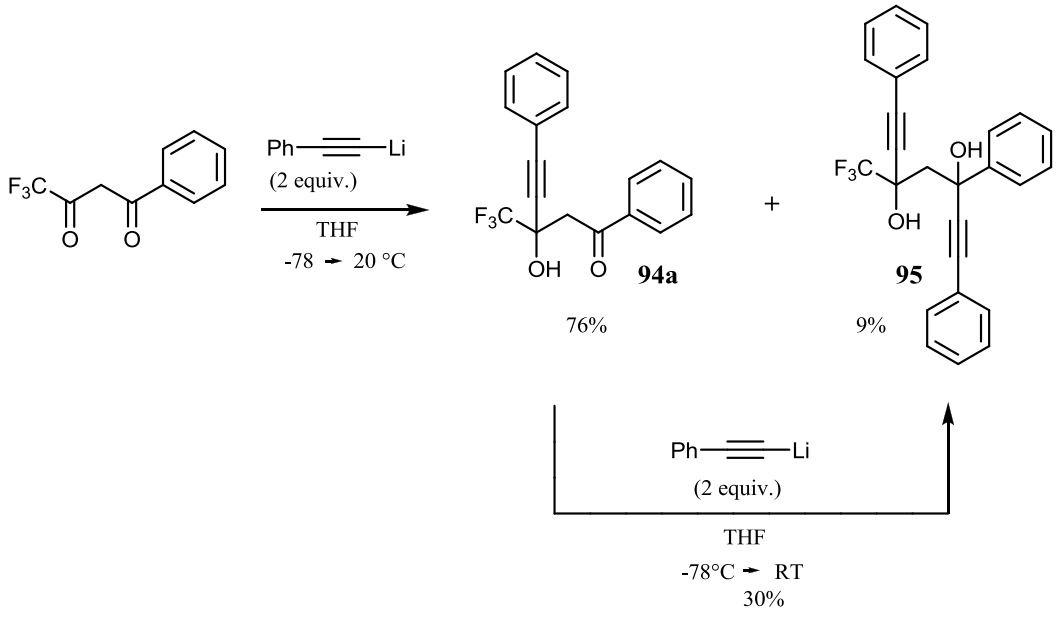
The other possible problem could be the competing deprotonation of methylene protons of diketone, in case if lithiated alkyne is used. Moreover, it is clear, that at least double amount of lithiated alkyne is necessary to use, because deprotonation of the hydroxyl group of enolized diketone is absolutely inevitable.

In our concept, introduction of strong electron-withdrawing trifluoromethyl group can increase the reactivity of the attached carbonyl group, which obviously will not enolize. Therefore, the trifluoromethyl function can facilitate the addition of nucleophile. If deprotonation of methylene part was dominant, we would implement one of the synthetic strategies, which were developed for the

assymetric synthesis of propargyl alcohols and which don't require strong bases. With this concept in mind we started our investigations.

5.2.2 Preparation of alkynylated 1,3-diketones

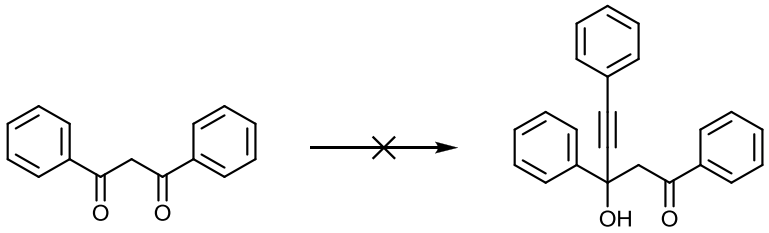
To our delight, the reaction of 2 equiv. of lithiated phenylacetylene, generated by n-BuLi, with 3-benzoyl-1,1,1-trifluoroacetone proceeded smoothly and afforded 3-hydroxy-1,5-diphenyl-3-(trifluoromethyl)pent-4-yn-1-one (**94a**) in 76% yield (Scheme 40). The formation of the product can be explained by deprotonation of the substrate by the first equivalent of the acetylide and subsequent attack of the second equivalent of the acetylide to the carbonyl group. The bis-adduct **95** was isolated as a side-product in 9% yield. The reaction of the monoadduct with 2 equiv. of lithiated phenylacetylene resulted in the formation of bis-adduct **95** in 30% yield.



Scheme 44. *Initial alkynylation of 1,3-diketone with phenylacetylene.*

With this promising result, we decided to check, if non-fluorinated diketones are reactive towards lithiated terminal alkynes. As a model substrate we have chosen dibenzoylmethane, because of its symmetrical constitution, there is no need in presumption of which keto-group will be enolized and thus product identification would be an easy task. Under the same conditions as for 3-benzoyl-1,1,1-trifluoroacetone no product formation was observed. Therefore, a number of optimizations were

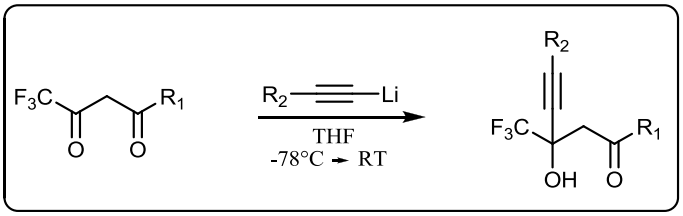
implemented. This includes refluxing the reaction mixture after addition of all reactants, performing the transformation under Lewis acid catalysis with $Zn(OTf)_2$ or $Cu(OTf)_2$ with free or lithiated alkyne. Unfortunately, all protocols were absolutely insufficient, not even traces of target compound were formed.



Scheme 45. *Unsuccessful alkynylation of dibenzoylmethane with phenylacetylene.*

These unsatisfactory results proved our concept, that simple 1,3-diketones are inert in Favorsky reaction and additional activation by electron-withdrawing group is obligatory.

With the established reaction pathway we studied the alkynylation of a number of fluorinated 1,3-diketones using different acetylene derivatives (Figure 24). Most of the products **94a-t** was isolated in good yields. The synthesis of products **94s,t**, derived from 1,1,1-trifluoroacetylacetone, required the use of 10 mol% of $Zn(OTf)_2$. All products **94** were stable, except from derivatives **94s,t** which easily decomposed during isolation by column chromatography and, thus, had to be used without purification.



Scheme 46.*Alkynylation of fluorinated 1,3-diketone with phenylacetylene*

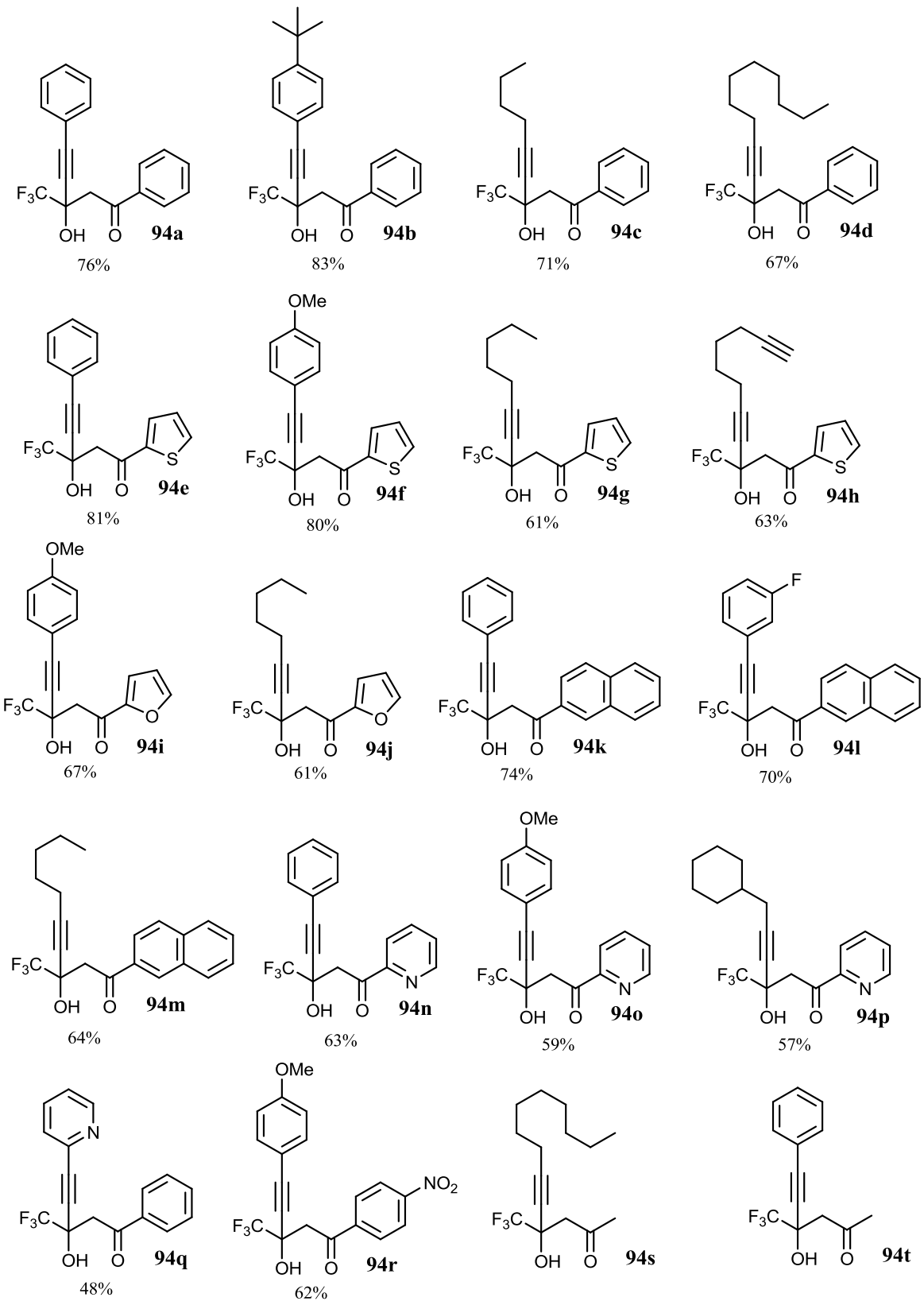


Figure 24. *Structures and yields of* ***94a-t****.*

5.2.3 Preparation of pyridines

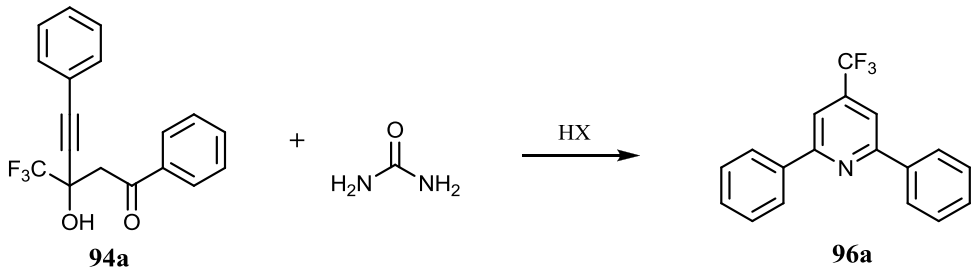
With these results in hand, we studied next the transformation of 3-hydroxy-3-(trifluoromethyl)pent-4-yn-1-ones **94** into pyridines. The first and main problem was to identify a suitable nitrogen source. In comparison to 1,5-dicarbonyl compounds, which are used in cyclocondensations with ammonia, 3-hydroxy-pent-4-yn-1-ones are reactive only in acidic media, because a propargyl cation must be formed. Therefore, the use of ammonia is not suitable, because of its natural basic properties in its free form. On the other hand, the employment of ammonium acetate is also not possible, because of low nucleophilicity of the latter. As an alternative, we turned our attention to urea, which has a number of advantages in comparison to ammonia. On the one hand, urea is much less basic than ammonia. On the other hand, it has well elucidated nucleophilic properties in its electroneutral form and also keeps some nucleophilicity in the presence of acid (as it is protonated at the oxygen atom). At the same time, its amide residue can be cleaved during the cyclization process under acidic conditions.

As we anticipated, that urea can be a good nitrogen source for our transformation, the reaction conditions needed to be evolved. Nucleophilic attack of sp^3-hybrid nitrogen on carbonyl group is a favorable process in a wide variety of solvents and can occur in acidic or basic media as well. Therefore, the main challenge for us was to find the optimal conditions for propargyl species to be active enough on the one hand, and to avoid any side reactions involving propargyl cation on the other hand.

We have studied a number of acid-promoted reactions of propargyl cations and came to a conclusion, that toluene or 1,2-dichloroethane would be the most suitable solvents for our reaction. We assumed, that implementation of nitromethane, which is also widely used in similar processes would be risky; because of its higher polarity, this solvent can facilitate a number of possible undesired reactions, involving oxygen of urea or/and oxygen of the carbonyl group.

As a starting point, we have tested the use of toluene and *p*-toluenesulfonic acid (PTSA) as solvent and catalyst, respectively. The acid was used in excess (2 equiv.). Besides its catalytic role, it also serves as a proton donor in the cyclization process, because it protonates the nitrogen source. However, reflux (up to 20 h) of a mixture of **94a**, urea (1.2 equiv.) and PTSA (2 equiv.) resulted in a poor yield of the desired pyridine (Table 16). Screening of a number of Brønsted acids revealed that trifluoroacetic acid was the most efficient. Increase of the amount of acid (3.5 equiv.) also resulted in better yields (entry 6). Employment of DCE or, especially, nitromethane, as a solvent resulted in a

drastic decrease of the yield. Notably, the current transformation appeared to be absolutely insensitive to water, as an addition of molecular sieves to the reaction mixture didn't increase the overall yield.



Scheme 47. *Formation of pyridine **96a**.*

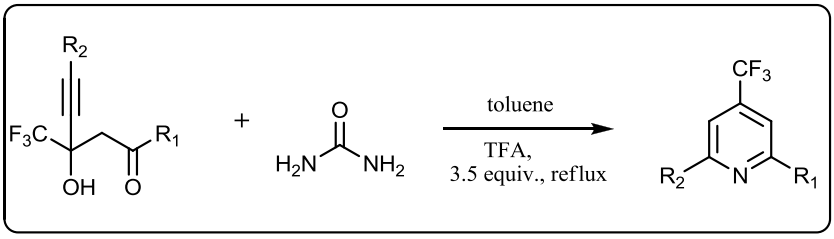
Table 16. *Optimization of reaction conditions for **96a**.*

Entry	Acid	Solvent	Time, h[b)]	Yields of end product, (%)[a)]
1	PTSA (2.0 equiv)	Toluene	20	6
2	TfOH (2.0 equiv)	Toluene	7	39
3	TFA (2.0 equiv)	Toluene	12	47
4	MsOH (2.0 equiv)	Toluene	7	34
5	AcOH (2.0 equiv)	Toluene	24	18
6	TFA (3.5 equiv)	Toluene	12	68
7	TFA (3.5 equiv)[c)]	Toluene	12	68
8	TFA (3.5 equiv)	DCE	15	41
9	TFA (3.5 equiv)	$MeNO_2$	5	9

[a)] Yields of isolated products
[b)] The reaction was stopped after the complete conversion of starting material
[c)] 4Å MS was used

The preparative scope the cyclization was next studied. The electronic properties of the substituents attached to the keto group and to the triple bond show a remarkable influence on the reaction time and yield (Figure 25). The best results were obtained when electron-rich alkynes were used and when the π-donating properties of the substituent located at the keto group are comparatively weak. Obviously, this might be explained by the carbocation stabilization in case of a π-donating group located at the triple bond and the higher reactivity of the carbonyl group attached to an electron-withdrawing substituent. This is illustrated by the fact that pyridine **96n** is obtained in 85% yield after 2 hours, starting from **94n**, while, starting from **94q**, the same product was formed in only 24% yield and

required prolonged heating up to 14 hours. Starting with **94s** and **94t**, unfortunately, no product could be isolated under various conditions, which is no surprise, as corresponding substrates were decomposing under much less acidic conditions on silica gel in column.



Scheme 48. *Formation of fluorinated pyridines.*

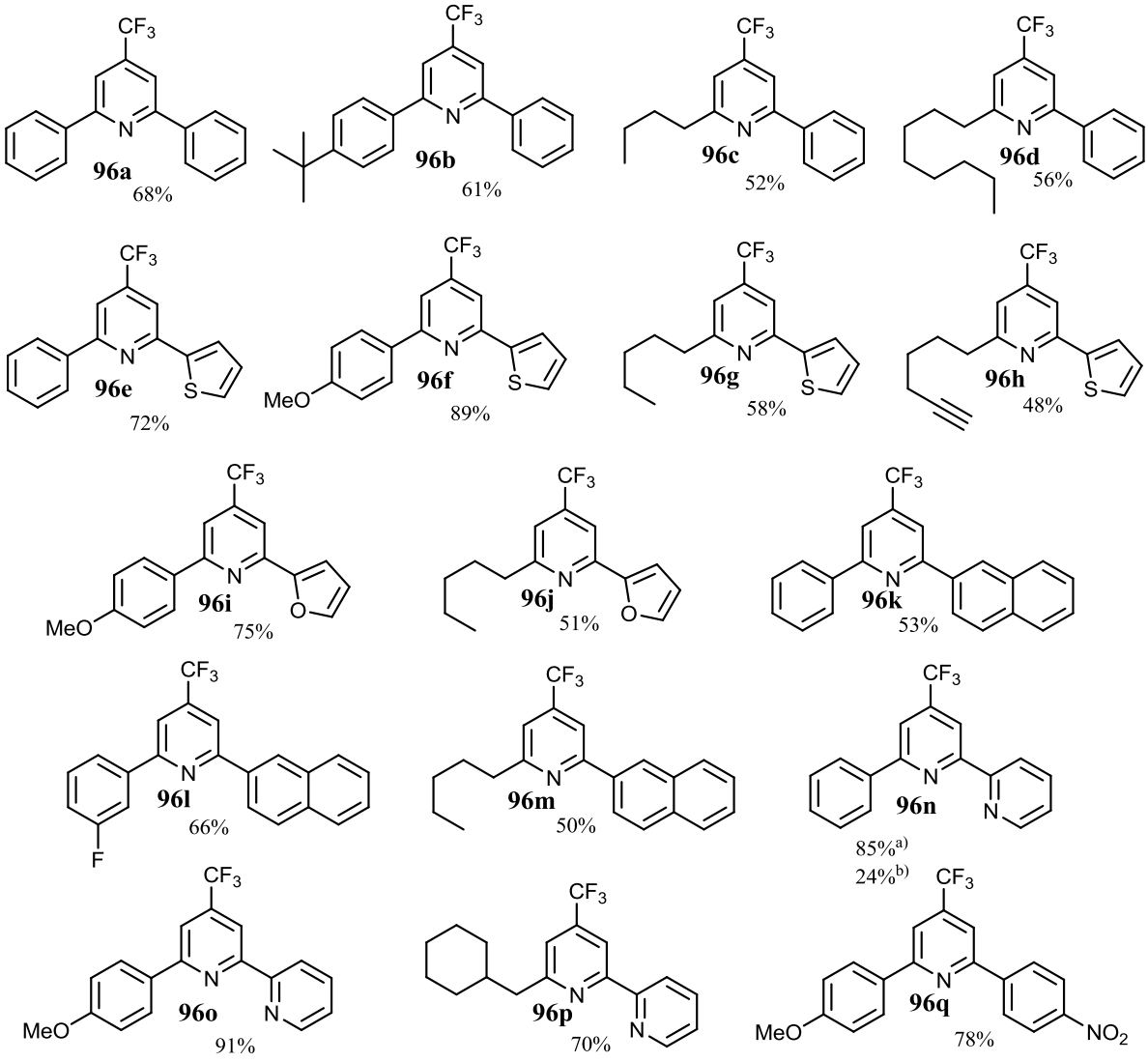


Figure 25. *Structures and yields of **64a-q**.*

The structure of compound **96q** was independently confirmed by X-ray crystal structure analysis (Figure 26). The pyridine ring and the phenyl groups are in plane.

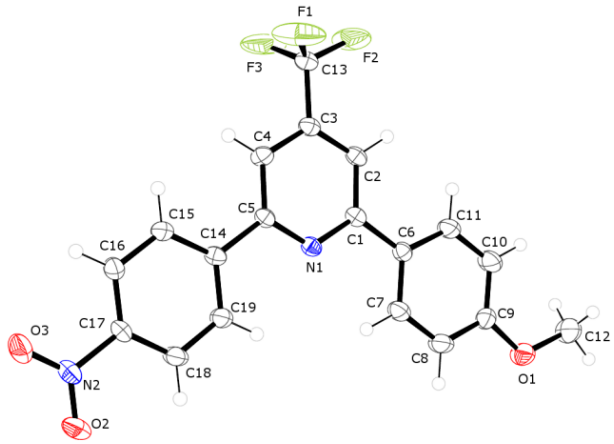


Figure 26. *Crystal structures of* ***96q***.

5.3 Mechanistic studies of developed cyclization (performed by Dr. Khurshid Ayub)

While this novel cyclization was developed, we turned our attention on the mechanistic studies. To gain mechanistic insight for the acid catalyzed formation of pyridine **96a** (Scheme 41), DFT calculations have been performed (for details, see supporting information). The starting material **1a** has two sites available for protonation, namely, the keto and alcohol oxygen atoms. Preferential protonation of the keto group would result in Schiff base formation prior to nucleophilic attack on the propargylic alcohol moiety. However, the latter would be expected in case that the alcohol oxygen atom is protonated first. Dehydration of the propargylic alcohol generates an allene cation which can be attacked by nucleophiles and eventually would deliver scrambled products similar to Meyer-Schuster[69] and Rupe[70] rearrangements. However, in our experiments, no such rearranged products have been observed which indicates that dehydration of the propargylic alcohol is not the first step. This is supported by the fact that keto-protonated isomer $\mathbf{Int_{1A}}$ is 2.85 kcal mol^{-1} more stable than the hydroxyl-protonated isomer $\mathbf{Int_{1B}}$. Nucleophilic attack of urea on $\mathbf{Int_{1A}}$, followed by proton shift of $\mathbf{Int_{2A}}$ and subsequent dehydration, generates the Schiff base intermediate $\mathbf{Int_{3A}}$ via $\mathbf{Int_{2A}}$. The overall process is thermodynamically favorable by 6.74 kcal mol^{-1}. A proton shift from the imine nitrogen to the alcohol

oxygen generates **Int$_{4A}$** in which the O-C bond is considerably weak (3.11Å) which indicates that the actual species participating in the next cyclization step is the dehydrated species **Int$_{5A}$**.

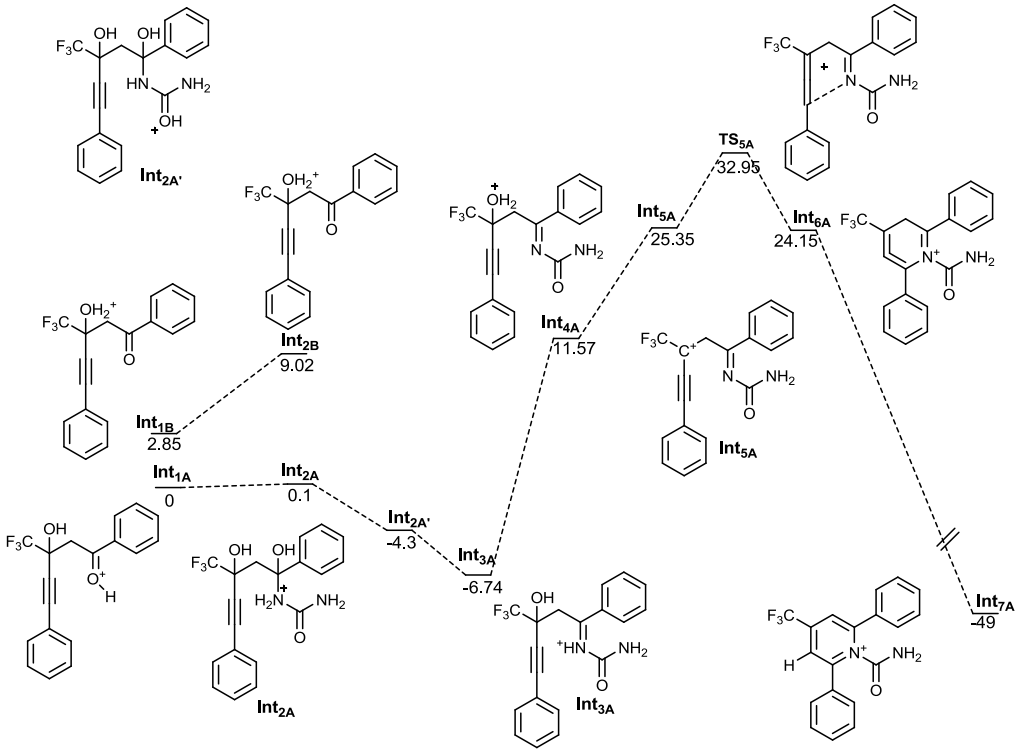


Figure 27. *Energy profile for the acid-catalyzed pyridine formation. All values are in kcal/mol and include unscaled zero point energy correction.*

A transition state for the cyclization has been located at a barrier of 7.6 kcal mol^{-1}. Although the product of cyclization is a constrained molecule with an allene-like structure, the cyclization is thermodynamically favorable by 1.2 kcal mol^{-1}. A reason for the low barrier may be the instability of the bis-allene starting material **Int$_{5A}$**. The cyclized product can undergo either an intramolecular 1,5 hydrogen shift or a deprotonation/protonation sequence to yield intermediate **Int$_{7A}$**. The kinetic barrier for the sigmatropic 1,5 shift is more than 50 kcal mol^{-1} which renders this pathway inaccessible under the experimental conditions (refluxing toluene). Therefore, the more logical pathway follows a deprotonation/protonation mechanism which was previously demonstrated by theoretical and labeling studies.[71] The weak base (trifluoroacetate) abstracts a proton and transfers it to the central atom of the allene moiety.[72] The resulting intermediate undergoes hydrolysis to afford the pyridine. The water formed during the generation of **Int$_{5A}$** may participate in the hydrolysis. Adduct **Int$_{8A}$**, which is generated by addition of water to **Int$_{7A}$**, is thermodynamically less stable than its precursor (by 14.93

kcal mol^{-1}). A transition state (**TS_{8A}**) has been located for the dissociation of carbamic acid from the pyridine moiety. The barrier is low (0.3 kcal mol^{-1}) and the cleavage is thermodynamically favorable.

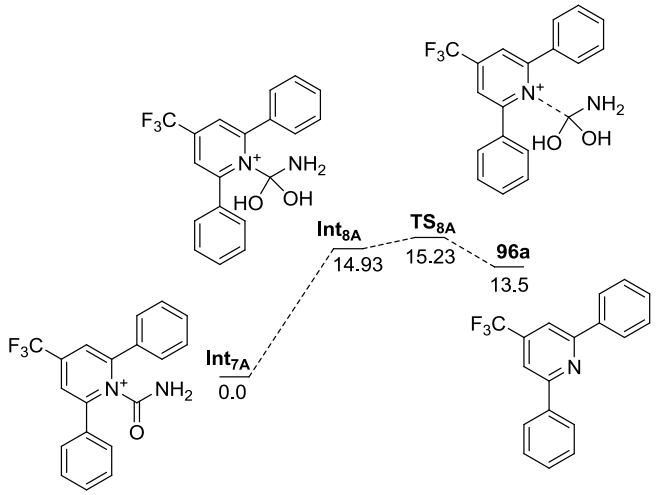


Figure 28. *Hydrosysis of intermediate **Int_{7a}**. All values are in kcal/mol and include unscaled zero point energy correction.*

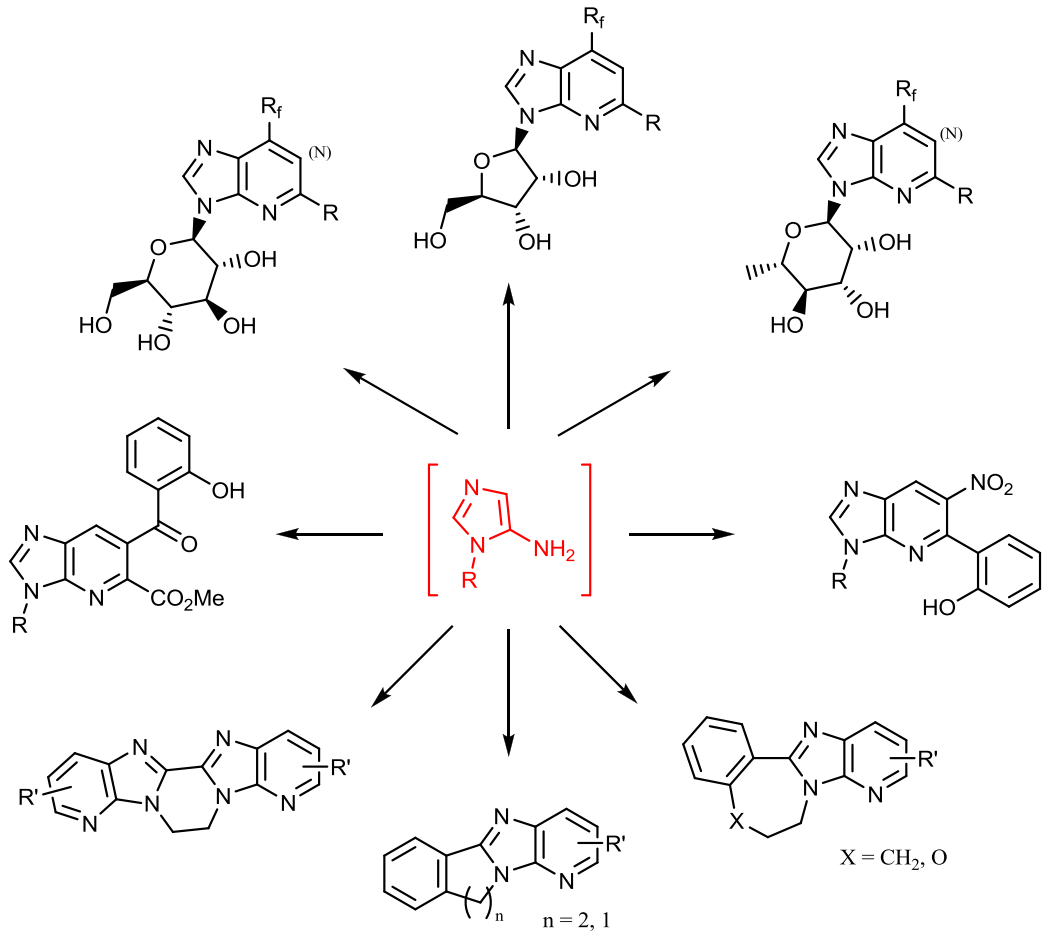
5.4 Conclusions

In a conclusion of this chapter, we have developed by far unknown method of pyridine synthesis, starting from 1,3-diketones, terminal alkynes and urea. Addition of alkynes to 1,3-diketones wasn't studied previously, however we managed to perform this transformation successfully, while introduced CF_3-group allowed to overcome most of the difficulties, related to such type of transformation. Developed [5+1] cyclization differs from the similar methods, like condensation of 1,5-dicarbonyl with urea, with its versatility, because one of nucleophilic parts (propargyl alcohol) is activated with donating species, but another part (carbonyl group) is activated with withdrawing substituents. This feature allows obtaining the target pyridine moieties from the most suitable precursor, which is not the case in other methods, where π-donating properties of the substitutents normally have the same effect on the reaction time or yield. Moreover, mechanistic studies of this novel cyclization were performed using DFT methods. All calculations were done by Dr. Khurshid Ayub (Department of Chemistry, COMSATS Institute of Information Technology, Abbottabad, 22060, Pakistan). It was indicated, that the attack of nitrogen of urea first occurs at the carbonyl part. The developed protocol can find its applications in chemical industry as an extremely cheap and simple method.

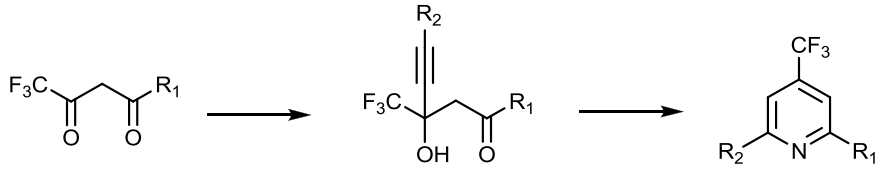
6. Summary

In this work, we successfully accomplished our research dedicated to the formation of 6-membered nitrogen-containing heterocycle ring. The well-established strategy towards pyridine synthesis, aiming condensation of enamines with 1,3-diketones was used for the preparation of imidazo[4,5-b]pyridine scaffolds starting from 1-substituted 5-amino-1*H*-imidazoles. Compounds, obtained in this manner, were utilized for the synthesis of 1-desazapurine ribosides as potential inhibitors of ADA. The preparation of these nucleosides was done according to the well-known *salvage* pathway of purine nucleoside synthesis. In addition, glucosides and rhamnosides of fluorinated purines and 1- desazapurines were synthesized in the same way. Biological evaluation of the obtained sugar-derived compounds is under investigation. Moreover, imidazo[4,5-b]pyridines and purines, which were prepared by the same methodology served as starting materials in a number of Pd-catalyzed intramolecular arylation reactions. Practical routes to fused purines and their desaza-analogues, including benzimidazoles, were developed (including optimizations for direct and oxidative cyclyzations). Extreme broad study of scope limitations in corresponding Pd-catalyzed reactions was accomplished. It indicated that our methodology featured by its versatility and simplicity, was successfully implemented for synthesis of fused benzimidazoles.

We were intrigued by a possibility of 1-desazapurine synthesis, using more complex electrophiles (in comparison with 1,3-diketones). Research, directed towards synthesis of 1-desazapurines, starting from corresponding 5-aminoimidazoles and 3-substituted chromones was performed. In case when 3-nitrochromone was used, desired 1-desazapurines were formed with excellent yields and regioselectivity, providing a set of 6-nitro- and 6-amino-imidazo[4,5-b]pyridines (the latter after reduction with H_2/Pd). While 3-methoxalylchromone provided exclusively fused α-carboxyl pyridine core, the overall yields of the target esters were moderate, despite all our attempts to increase the product outcome. Imidazo[4,5-b]pyridines, constructed in this fashion are of considerable pharmacological relevance, as the introduction of nitro-group in position 6 of heterocycle can lead to an efficient inhibition of ADA, while introduction of the carboxylic group in position 5 - to inhibition of IMPDH respectively. A number of isolated compounds were sent for further biological studies.



However we aimed not to only implement already known methods for synthesis of potentially pharmacologically valuable substances, but to establish a new protocol for synthesis of 4-trifluoromethylpyridines. Our procedure, involving 1,3-diketones, terminal alkynes and urea, constitutes only from two steps, is cheap and versatile. Moreover, any target pyridine can be prepared with a good yield by the possibility to vary substituents accordingly to discovered consistent pattern for alkynylated diketones.



7. References

1) (a) Hill, M., *Chem. Eur. J.* **2010,** *16*, 12052-12062 and references cited therein; (b) Katritzky, A. R., Al-Omran, F., Patel, R. C., Thind S. S. *J. Chem. Soc., Perkin Trans. 1* **1980,** 1890-1894; (c) Kharchenko, V. G., Promonenkov, V. K., Chalaya, S. N., Lisina S. N. *Khimiya Geterotsiklicheskikh Soedinenii* **1983,** *12*, 1691-1692; (d) Kelly, T. R., Lebedev, R. L. *J. Org. Chem.* **2002,** *67*, 2197-2205; (e) Boger, D. L., Panek, L. S. *J. Org. Chem.* **1981,** *46*, 2179-2182; (f) Lions, F., Perkin Jr., W. H., Robinson R. *J. Chem. Soc. Trans.* **1925,** *127*, 1158-1169; (g) Plaskon, A. S., Ryabukhin, S. V., Volochnyuk, D. M., Gavrilenko, K. S., Shivanyuk, A. N., Tolmachev, A. A. *J. Org. Chem.* **2008,** *73*, 6010-6013.

2) (a) Donohoe, T. J., Bower, J. F., Basutto, J. A., Fishlock, L. P., Procopiou, P. A., Callens, C. K. A. *Tetrahedron* **2009**, *65*, 8969–8980; (b) Hu, J., Zhang, Q., Yuan, H., Liu, Q. *J. Org. Chem.* **2008,** *73*, 2442–2445.

3) (a) Harschneck, T., Kirsch, S. F. *J. Org. Chem.* **2011,** *76*, 2145-2156; (b) Fananas, F. J., Arto, T., Mendoza, A., Rodrigues, F. *Org. Lett.* **2011,** *13*, 4184-4187.

4) (a) Ehlers, P., Reinmann, S., Erfle, S., Villinger, A., Langer, P. *Synlett* **2010,** *10*, 1528-1532; (b) Ehlers, P., Neubauer, S., Lochbrunner, A., Villinger, A., Langer, P. *Org. Lett.* **2011,** *13*, 1618-1621; c) Billingsley, K., Buchwald, S. L. *J. Am. Chem. Soc.* **2007,** *129*, 3358-3366.

5) (a) Clark, R. L., Pessolano, A. A., Shen, T.-Y., Jocobus, D. P., Jones, H., Lotti, V. J., Flataker, L. M. *J. Med. Chem.* **1978**, *21*, 965-978; (b) Robinson, M. M., Finch, N. U.S. Patent 3719683, **1973**; (c) Von Bebenberg, W. U.S. Patent 3819640, **1974**; (d) Lesher, G. Y., Brundage, R. P., Opalka, C. J., Page, D. F. French Patent 2,478,637, **1981**; *Chem. Abstr.* **1982,** *96*, 85551k.

6) Kuezynski, L., Mrozikiewiez, A., Poreba, K. *Pol. J. Pharmacol. Pharm.* **1982,** *34*, 229-238.

7) Bianchi, M.; Butti, A.; Rossi, S.; Barzaghi, F.; Marcaria, V. *Eur. J. Med. Chem.* **1983,** *18*, 501-506.

8) a) Vaughn, J. R. Jr. U.S. Patent 2637731, **1953;** b) Röchling, H. F. W., Büchel, K.-H., Korte, F. W. A. G. K. U.S. Patent 3459759, **1969**.

9) (a) Yawer, M.A., Hussain, I., Fischer, C., Görls, H., Langer, P. *Tetrahedron* **2008,** *64*, 894-900; (b) Appel, B., Langer, P. *Tetrahedron Lett.* **2003,** *44*, 7921-7923.

10) Wesch, T., Iaroshenko, V. O., Groth, U. *Synlett* **2008,** *10*, 1459-1462.

11) (a) Giblett, E. R., Anderson, J. E., Cohen, F., Pollara, B., Meuwissen, H. J. *Lancet* **1972,** *2*, 1067-1069; b) Hirshhorn, R. *Clin. Immunol. Immunophathol.* **1995,** *76*, 219-223.

12) (a) Saraiva da Cunha, J. G., Pereira, E., Melifo-Silvestre, A., Gaspar, E., Azevedo-Bernarda, R., Carrington da Costa, R. *Infection* **1990,** *18*, 125-128; (b) Bhatnagar, S., Beig, F. K., Malik, A. *Indian J. Clin. Biochem.* **2008,** *23*, 299-302.

13) Albera, C., Mabritto, I., Ghio, P., Solidoro, P., Marchetti, L., Pozzi, E. *Sarcoidosis* **1993,** *10*, 18-25

14) (a) Masaru, K., Masato, K., Takao, I., Nobuo, Y., Kazui, S., Tomoyuki, T. *J. Japanese Resp. Soc.* **1999,** *37*, 374-379; (b) Ocana, I., Ribera, E., Martinez-Vazquez, J. M., Ruiz, I., Bejarano, E., Pigrau, C., Pahissa, A. *Ann. Rheum. Dis.* **1988,** *47*, 394-397.

15) Chiba, S.; Matsumoto, H., Saitoh, M., Kasahara, M., Matsuya, M., Kashiwagi, M. A. *J. Neurol. Sci.* **1995,** *132*, 170-173.

16) (a) Gakis, C. *Eur. Respir. J.* **1996**, *9*, 632-633; (b) Krawczynsky, J., Raczynska, J., Jonas, S., Wencel, J., Ilowiecka, K. *Clin. Chim. Acta* **1965,** *11*, 227-232.

17) Chottiner, E. G., Cloft, H. J., Tartaglia, A. P., Mitchell, B. S. *J. Clin. Invest.* **1987,** *79*, 1001–1005.

18) (a) Demeocq, F., Viallard, J. L., Boumsell, L., Richard, Y., Chassgne, J., Plagne, R., Lemerle, J., Bernard, A. *Leuk. Res.* **1982,** *6*, 211-220. (b) Carlucci, F., Rossi, F., Di Pietro, C., Marinello, E. *Biochim. Biophys. Acta* **1997,** *1360*, 203-210.

19) Cristalli, G., Costanzi, S., Lambertucci, C., Lupidi, G., Vittori, S., Volpini, R., Camaioni, E. *Med. Res. Rev.* **2001,** *21*, 105-128.

20) (a) Shewach, D. S., Krawczyk, S. H., Acevedo, O. L., Townsend, L. B. *Biochem. Pharmacol.* **1992,** *44*, 1697-1700. (b) Frieden, C., Kurz, L. C., Gilbert, H. R. *Biochemistry* **1980,** *19*, 5303-5309.

21) (a) Seeliger, F., Blazej, S., Bernhardt, S., Makosza, M., Mayr, H. *Chem. Eur. J.* **2008,** *14*, 6108-6118. (b) Terrier, F., Chatrousse, A.-P., Schaal, R. *J. Org. Chem.* **1972,** *37*, 3010-3014.

22) (a) Takagi, K., Tanaka, M., Murakami, Y., Ogura, K., Ishii, K., Morita, H., Aotsuka, T. *J. Heterocycl. Chem.* **1987,** *24*, 1003-1007. (b) Connor, D. T., Young, P. A., von Strandtmann, M. *J. Heterocycl. Chem.* **1981,** *18*, 697-702. (c) Haas, G., Stanton, J. L., Winkler, T. *J. Heterocycl. Chem.* **1981,** *18*, 619-622.

23) Dubois, L., Evanno, Y., Gille, C., Malanda, A. WO 2009112677, **2009.**

24) Boyd, E., Brookfield, F., Gridley, J., Honold, K., Lau, R., Scheiblich, S. WO 2007014707, **2007.**

25) Mkrtchyan, S., Iaroshenko, V. O., Dudkin, S., Gevorgyan, A., Vilches-Herrera,M., Ghazaryan, G., Volochnyuk, D., Ostrovskyi, D., Ahmed, Z., Villinger, A., Sosnovskikh, V. Y., Langer, P. *Org. Biomol. Chem.* **2010,** *8*, 5280-5284.

26) Hedstrom, L. *Chem. Rev.* **2009,** *109*, 2903-2928.

27) (a) Jain, J., Almquist, S. J., Shlyakhter, D., Harding, M. V. *J. Pharm. Sci.* **2001,** *90*, 625-637; (b) Fukuda, T., Goebel, J., Thøgersen, H., Maseck, D., Cox, S., Logan, B., Sherbotie, J., Seikaly, M., Vinks, A. *J. Clin. Pharmacol.* **2011,** *51*, 309-320.

28) Franchetti, P., Grifantini, M. *Curr. Med. Chem.* **1999,** *6*, 599-614.

29) Hedstrom, L., Liechti, G., Goldberg, J. B., Gollapalli, D. R. *Curr. Med. Chem.* **2011,** *18*, 1909-1918.

30) (a) Jaharam, H. N., Cooney, D. A., Grusch, M., Krupitza, G. *Curr. Med. Chem.* **1999,** *6*, 561-574; (b) Fellenberg, J., Kunz, P., Sähr, H., Depeweg, D. *PLoS ONE,* **2010,** *5*, e12179.

31) Maidanovich, O., Beal, P. A. *Chem. Rev.* **2006,** *106*, 3397-3411.

32) Lindell, S. D., Moloney, B. A., Hewitt, B. D., Earnshaw, C. G., Dudfield, P. J., Dancer. J. E. *Bioorg. Med. Chem. Lett.* **1999,** *9*, 1985-1989.

33) Bojack, G., Earnshaw, C. G., Klein, R., Lindell, S. D., Lowinski, K., Preus, R. *Org. Lett.* **2001,** *3*, 839-842.

34) (a) Silverman, R. B. *The Organic Chemistry of Drug Design, And Drug Action* 2nd ed., Elsevier Academic Press: Amsterdam, **2004,** p 617, ISBN 0-12-643732-7; (b) Begue, J.-P., Bonnet-Delpon, D. *Chemie Bioorganique Et Medicinal Du Fluor* EDP Sciences, **2005,** p 366, ISBN 2-86883-757-3; (c) Kirsch, P. *Modern Fluoroorganic Chemistry* VCH: Weinheim, Germany, **2004**; (d) Chambers, R. D. *Fluorine in Organic Chemistry* Blackwell Publishing CRC Press: Boca Raton, FL, **2004**.

35) (a) Hedstrom, L. *Chem. Rev.* **2009,** *109*, 2903-2928; (b) Markham, G. D., Bock, C. L., Schalk-Hihi, C. *Biochemistry* **1999,** *38*, 4433-4440.

36) (a) Rolfes, R. J. *Biochem. Soc. Trans.* **2006,** *34*, 786-790; (b) Christopherson, R. J., Lyons, S. D., Wilson, P. K. *Acc. Chem. Res.* **2002,** *35*, 961-971; (c) Zalkin, H.; Dixon, J. E. Prog. *Nucleic Acid Res. Mol. Biol.* **1992**, *42*, 259-287; (d) Manfredi, J. P., Holmes, E. W. *Annu.*

Rev. Physiol. **1985,** *47*, 691-705. (e) Berens, R. L., Krug, E. C., Marr, J. J. *Biochem. Mol. Biol. Parasites* **1995,** 89-117.

37) Bhat, B., Groziak, M. P., Leonard, N. J. *J. Am. Chem. Soc.* **1990**, *112*, 4891-4897.

38) (a) Soenen, D. R., Zimpleman, J. M., Boger, D. L. *J. Org. Chem.* **2003,** *68*, 3593-3598; (b) Zer, G., Saraolu, N., Balci, M. *J. Org. Chem.* **2003,** *68*, 7009-7015; (c) Aksenov, A. V., Aksenov, N. A., Lyakhovnenko, A. S., Aksenova, I. V. *Synthesis* **2009,** *20*, 3439-3442; (d) Hamasaki, A., Ducray, R., Boger, D. L. *J. Org. Chem.* **2006,** *71*, 185-193.

39) (a) Veliz, E. A., Stephens, O. M., Beal, P. A. *Org. Lett.* **2001,** *3*, 2969-2972; (b) Kobayashi, Y., Yamamoto, K., Asai, T., Nakano, M., Kumadaki, I. *J. Chem. Soc. Perkin Trans. 1* **1980,** *12*, 2755-2761; (c) Hockova, D., Hocek, M., Dvorakova, H., Votruba, I. *Tetrahedron* **1999,** *55*, 11109-11118; (d) Silhar, P., Pohl, R., Votruba, I., Hocek, M. *Synthesis* **2006,** 1848-1852; (e) Vorbruggen, H., Ruh-Pohlenz, C. *Handbook of Nucleoside Synthesis*; John Wiley & Sons: New York, **2001**.

40) Simons, C. *Nucleoside mimetics: their chemistry and biological properties*, CRC Press, **2001**.

41) (a) Verrier, C., Hoarau, C., Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647-650; (b) Zhang, Y. H., Shi, B. F., Yu, J. Q. *Angew. Chem.* **2009**, *121*, 6213-6216; *Angew. Chem. Int. Ed.* **2009**, *48*, 6097-6100; (c) Lapointe, D., Fagnou, K. *Org. Lett*. **2009**, *11*, 4160-4163; (d) Ackermann, L., Barfüßer, S., Pospech, J. *Org. Lett*. **2010**, *12*, 724-726; (e) Shabashov, D., Daugulis, O. *J. Am. Chem. Soc*. **2010**, *132*, 3965-3972; (f) Mukai, T., Hirano, K., Satoh, T., Miura, M. *Org. Lett.* **2010**, *12*, 1360-1363; (g) Yao, T., Hirano, K., Satoh, T., Miura, M. *Chem. Eur. J.* **2010**, *16*, 12307-12311; (h) Ackermann, L., Barfüßer, S., Kornhaaß, C., Kapdi, A. R. *Org. Lett*. **2011**, *13*, 3082-3085.

42) (a) Yamamoto, M., Matsubara, S. *Chem. Lett.* **2007**, *36*, 172-173; (b) Zhong, H. A., Labinger, J. A., Bercaw, J. E. *J. Am. Chem Soc.* **2002**, *124*, 1378-1399; (c) Hutson, A. C., Lin, M., Basickes, N., Sen, A. *J. Organomet. Chem.* **1995**, *504*, 69-74; (d) Horvath, I. T., Cook, R. A., Millar, J. M., Kiss, G. *Organometallics* **1993**, *12*, 8-10; (e) Ellis, C. S., Ess, D. H. *J. Org. Chem*. **2011**, *76*, 7180-7185; (f) Bajracharya, G. B., Pahadi, N. K., Gridnev, I. D., Yamamoto, Y. *J. Org. Chem*. **2006**, *71*, 6204-6210; (g) Tobisu, M., Nakai, H., Chatani, N. *J. Org. Chem.* **2009**, *74*, 5471-5475.

43) (a) Umeda, N., Hirano, K., Satoh, T., Shibata, N., Sato, H., Miura, M. *J. Org. Chem.* **2011**, *76*, 13-24; (b) Patureau, F. W., Besset, T., Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1064-1067; (c) Patureau, F. W., Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982-9983; (d) Hyster, T. K., Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565-10569; (e) Chen, J., Song, G., Pan, C.-L., Li, X. *Org. Lett*. **2010**, *12*, 5426-5429; (f) Wang, F., Song, G., Li, X. *Org. Lett.* **2010**, *12*, 5430-5433; (g) Stuart, D. R., Bertrand-Laperle, M., Burgess, K. M. N., Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474-16475; (h) Li, L., Brennessel, W. W., Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414-12419; (i) Ueura, K., Satoh, T., Miura, M. *Org. Lett*. **2007**, *9*, 1407-1409.

44) (a) Ackermann, L., Novak, P., Vicente, R., Hofmann, N. *Angew. Chem.* **2009**, *121*, 6161-6164; *Angew. Chem. Int. Ed.* **2009**, *48*, 6045–6048; (b) Ackermann, L., Novak, P. *Org. Lett.* **2009**, *11*, 4966–4969; (c) Ackermann, L., Hofmann, N., Vicente, R. *Org. Lett*. **2011**, *13*, 1875-1877.

45) (a) Alvarez, E., Conejero, S., Paneque, M., Petronilho, A., Poveda, M. L., Serrano, O., Carmona, E. *J. Am. Chem. Soc.* **2006**, *128*, 13060-13061; (b) Ueura, K., Satoh, T., Miura, M. *J. Org. Chem.* **2007**, *72*, 5362-5368; (c) Fujita, K.-I., Nonogawa, M., Yamaguchi, R. *Chem. Commun*. **2004**, 1926-1927; (d) De Boef, B., Pastine, S. J., Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556-6557. (e) Tsuchikama, K., Kasagawa, M., Endo, K., Shibata, T. *Org. Lett.* **2009**, *11*, 1821-1823. (h) Guo, Y., Zhao, X., Zhang, D., Murahashi, S.-I. *Angew. Chem. Int. Ed.* **2009**, *48*, 2047-2049.

46) (a) Do, H.-Q., Daugulis, O., *J. Am. Chem. Soc.* **2011**, *133*, 13577-13586; (b) Xu, W., Jin, Y., Liu, H., Jiang, Y., Fu, H. *Org. Lett.* **2011**, *13*, 1274-1277; (d) Li, Y., Xie, Y., Zhang, R., Jin, K., Wang, X., Duan, C. *J. Org. Chem.* **2011**, *76*, 5444–5449.

47) (a) Yoshikai, N., *Synlett* **2011**, 1047-1051; (b) Zhao, C., Toste, F. D., Bergman, R. G. *J. Am. Chem. Soc*. **2011**, *133*, 10787-10789; (c) Schomaker, J. M., Boyd, W. C., Stewart, I. C., Toste, F. D., Bergman, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 3777-3779; (d) Schomaker, J. M., Toste, F. D., Bergman, R. G. *Org. Lett.* **2009**, *11*, 3698-3700; (e) Boyd, W. C., Crimmin, M. R., Rosebrugh, L. E., Schomaker, J. M., Bergman, R. G., Toste, F. D. *J. Am. Chem. Soc*. **2010**, *132*, 16365-16367.

48) (a) Guihaumé, J., Halbert, S., Eisenstein, O., Perutz, R. N. *Organometallics* **2012**, *31*, 1300-1314; (b) Clot, E., Eisenstein, O., Jasim, N., Macgregor, S. A., McGrady, J. E., Perutz, R. N. *Acc. Chem. Res.* **2011**, *44*, 333–348.

49) (a) Ackermann, L., Vicente, R., Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826; (b) Gorelsky, S. I., Lapointe, D., Fagnou, K. *J. Am. Chem, Soc.* **2008**, *130*, 10848-10849.

50) (a) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866-4877; (b) Loy, R. N., Sanford, M. S., *Org. Lett.* **2011**, *13*, 2548–2551; (c) Martins, A.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 8705–8710. (d) Verrier, C., Hoarau, Ch., Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647-650; (e) Martins, A., Lautens, M. *J. Org. Chem.* **2008**, *73*, 8705–8710; (f) Oi, S., Tanaka, Y., Inoue, Y. *Organometallics* **2006**, *25*, 4773-4778.

51) (a) Xiao, F., Shuai, Q., Zhao, F., Basl, O., Deng, G., Li, C-J. *Org Lett*. **2011**, *13*, 1614-1617; (b) Jia, X., Zhang, S., Wang, W., Luo, F., Cheng, J. *Org. Lett.* **2009**, *11*, 3120-3123; (c) Fujiwara, Y., Moritani, I., Danno, S., Asano, R., Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166-7172; (d) Kochi, T., Urano, S., Seki, H., Mizushima, E., Sato, M., Kakiuchi, F. *J. Am. Chem. Soc.* **2009**, *131*, 2792-2793.

52) Zhao, X., Dimitrijevic´, E., Dong, V. M. *J. Am. Chem, Soc.* **2009**, *131*, 3466-3467.

53) (a) Stowers, K. J., Sanford, M. S. *Org. Lett.* **2009**, *11*, 4584-4587; (b) Deprez, N. R., Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234-11241; (b) Powers, D. C., Ritter, T. *Nat. Chem.* **2009**, *1*, 302-309; (c) Desai, L. V., Stowers, K. J., Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285-13293; (d) Wang, X., Mei, T. S., Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520-7524; (e) Furuya, T., Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060-10061; (f) Ball, N. D., Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796-3797.

54) Seregin, I. V., Gevorgyan, V. *Chem. Soc. Rev.* **2007,** *36*, 1173-1193.

55) Cerna, I., Pohl, R., Klepanova, B., Hocek, M. *J. Org. Chem.* **2010,** *75*, 2302-2308.

56) Cerna, I., Pohl, R., Klepanova, B., Hocek, M. *J. Org. Chem.* **2008,** *73*, 9048-9054.

57) Kielkowski, P., Pohl, R., Hocek, M. *J. Org. Chem.* **2011,** *76*, 3457-3462.

58) (a) Legraverend, M., Grierson, D. S. *Bioorg. Med. Chem.* **2006,** *14*, 3987-4006; (b) Gray, N. S., Wodicka, L., Thunnissen, A.-M., Nornam, T. C., Kwon, S., Espinoza, F. H., Morgan, D. O., Barnes, G., LeClerc, S., Meijer, L., Kim, S.-H., Lockhart, D. J., Schultz, P. G. *Science* **1998,** *281*, 533-538; (c) Wignall, S. M., Gray, N. S., Chang, Y. T., Juarez, L., Jacob, R., Burlingame, A., Schultz, P. G., Heald, R. *Chem. Biol.* **2004,** *11*, 135-146.

59) Netherton, M. R., Fu, G. C., *Org. Lett.* **2001,** *3*, 4295-4298.

60) Pintori, D. G., Greaney, M. F. *J. Am. Chem. Soc.* **2011,** *133*, 1209-1211.

61) Ackermann, L., Jeyachandran, R., Potukuchi, H. K., Novak, P., Büttner, L. *Org. Lett.* **2010,** *12*, 2056-2059.

62) (a) Lafrance, M., Fagnou, K. *J. Am. Chem. Soc.* **2006,** *128*, 16496-16497; (b) Liegault, B., Lee, D., Huestis, M. P., Stuart, D. R., Fagnou, K. *J. Org. Chem.* **2008,** *73*, 5022-5028.

63) Reutov, O. A., Kurz, A. L., Butin, K. P. *Organicheskaya Khimiya v 4 chastyakh*, Binom. Laboratoriya znaniy. Moscow, **2004**.

64) (a) Han, X., Zhang, Y., Wang K. K. *J. Org. Chem.* **2005,** *70*, 2406-2408; (b) Ma, S., Wu, B., Jiang, X., Zhao, S. *J. Org. Chem.* **2005,** *70*, 2568-2575. (c) Brandsma, L. *In Preprative acetylenic Chemistry;* Elsevier: Amsterdam, **1988**.

65) (a) Frantz, D. E., Fässler, R., Carreira, E. M. *J. Am. Chem. Soc.* **2000,** *122*, 1806-1807. (b) Jiang, B., Chen, Z., Tang, X. *Org. Lett.* **2002,** *4*, 3451-3453; (c) Lui, L., Wang, R., Kang, Y.-F., Cai, H.-Q., Chen, C. *Synlett* **2006,** *8*, 1245-1249.

66) Cho, E. J., Senecal, T. D., Kinzel, T., Zhang, Y., Watson, D. A., Buchwald, S. L. *Science* **2010,** *328*, 1679-1681.

67) (a) Jiang, X., Chu, L., Qing, F.-L. *J. Org. Chem.* **2012,** *77*, 1251-1257; (b) Dubinina, G. G., Furutachi, H., Vicic, D. A. *J. Am. Chem. Soc.* **2008,** *130*, 8600-8601; (c) Dubinina, G. G., Ogikubo, J., Vicic, D. A. *Organometallics* **2008,** *27*, 6233-6235.

68) (a) Jiang, B., Xiong, X.-N., Yang, C.-G. *Bioorg. Med. Chem. Lett.* **2001,** *11*, 475-477; (b) Jiang, B., Xiong, W., Zhang, X., Zhang., F. *Org. Proc. Res. Dev.* **2001,** *5*, 531-534.

69) Meyer, K. H., Schuster, K. *Ber*. **1922**, *55*, 819-823.

70) Rupe, H., Kambli, E. *Helv. Chim. Acta*. **1926**, *9*, 672.

71) Rodriguez, R., Navarro-Vazquez, A., Castedo, L., Dominguez, D., Saa, C. *J. Am. Chem. Soc*. **2001**, *123*, 9178-9179.

72) Gronert, S., Keeffe, J. R. *J. Org. Chem*. **2007**, *72*, 6343-6352.

Appendix 1: Experimental details

1.1 General information

Chemical shifts of the 1H and 13C NMR are reported in parts per million using the solvent internal standard (CDCl3 7.26 ppm and 77.0 ppm, DMSO-d6 2.49 ppm and 39.7 ppm). NMR spectra were recorded on a Brucker AVANCE 250 II, Brucker DPX 300 and Brucker DPX 500. Infrared spectra were recorded on a Perkin Elmer FT IR 1600 ATR apparatus. Mass spectrometric data (MS) were obtained on a "Hewlett-Packard" HP GC / MS 5890 / 5972 instrument by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). The solvents DMF, methanol, acetonitrile, acetic acid, DCM, DMA, DMSO, toluene, DCE, nitromethane, THF were purchased directly from ACROS and used without further purification. Silica gel Merck 60F254 plates were used for TLC. Column chromatography was performed using 60 A silica gel (60 – 200 mesh, Merck).

1.2 General synthetic procedures and product characterization

1.2.1 Supplement to paragraph 2

General Procedure for the Synthesis of Compounds 39a–q

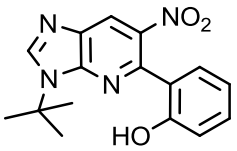
To a Schlenk flask, set with reflux, CH_2Cl_2 (2.5 mL), primary amine (1.31 mmol), and methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) were added under an argon atmosphere at r.t. The reaction mixture was refluxed during 2 h and after that, the mixture was cooled down to r.t., and then to 0°C on an ice bath. Afterwards 3-nitro-4H-chromen-4-one (250 g, 1.31 mmol) was added, and the mixture continued to stir at the same temperature for 15–20 min (the color of reaction mixture became intensively red) and then refluxed for 5 h. The formed precipitate was filtered, and the obtained solid was washed with CH_2Cl_2 and dried. In the case of homogenous solution, the solvent was evaporated to dryness, and the residue was purified by column chromatography (EtOAc : *i*-PrOH = 5:1), to give **39a–q** as light yellow crystals.

General Procedure for the Synthesis of Compounds 40a–q

To a 100 mL Schlenk flask, filled with 200 mg of corresponding imidazo[4,5-b]pyridine **39a–q** in MeOH (30 mL), Pd/C (20 mg, 10 mol%) was added. The flask was fitted with a septum, and then held under vacuum for 3 min, after that it was filled with hydrogen. Holding under vacuum was repeated one

more time, and after sequent filling with hydrogen, the reaction mixture has been stirred for 2 days under H_2 atmosphere. After the reaction was stopped, the mixture was filtered through Celite pad and filtrate was evaporated to dryness or (if necessary) was purified by column chromatography (EtOAc : *i*-PrOH = 5:1) to give **40a–q** as brown solid.

2-(3-*tert*-Butyl-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39a)



Starting from *tert*-butylamine (96 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39a** was isolated as light-yellow crystals, yield = 392 mg (96%); mp = 233 - 235°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.82 (s, 9H, *t*-Bu), 6.87 (d, 1H, H-6', ^3J = 9.0 Hz), 7.01 (t, 1H, H-4', ^3J = 9.0 Hz), 7.30 (t, 1H, H-5', ^3J = 9.2 Hz), 7.57 (d, 1H, H-3', ^3J = 9.0 Hz), 8.71 (s, 1H, H-5), 8.74 (s, 1H, H-2), 9.95 (s, 1H, OH).

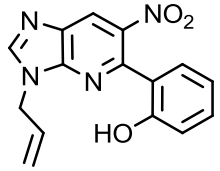
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.5 (CH_3), 57.7 ($C(CH_3)_3$), 115.1 (C-4'), 119.5 (C-6'), 123.6 (C-5'), 125.7 (C-3'), 130.2 (C-5'), 130.5 (C-1'), 133.9 (C-4), 142.8 (C-6), 144.7 (C-2), 147.1 (C-3a), 148.2 (C-7a), 154.5 (C-5).

GC-MS (EI, 70 eV): *m/z* (%): 312 (100) [M^+], 256, (14), 210 (83), 171 (20), 156 (14).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{16}H_{16}N_4O_3$: 312.1217; found: 312.1219.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3291, 3020, 1600, 1582, 1509, 1419, 1210, 1038, 967, 817.

2-(3-Allyl-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39b)



Starting from allylamine (75 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39b** was isolated as light-yellow crystals, yield = 156 mg (41%); mp = 182 - 184°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 4.97 (d, 2H, CH_2, ^3J = 2.9 Hz), 5.08 (dd, 1H, CH_2(trans), $^3J_1$ = 15.3 Hz, $^2J_2$=2.1 Hz), 5.14 (dd, 1H, CH_2(cis), $^3J_1$ = 8.7 Hz, $^2J_2$ = 2.1 Hz), 6.16 (m, 1H, CH), 6.85 (d, 1H, H-6', ^3J = 9.0 Hz), 7.00 (t, 1H, H-4', ^3J = 9.0 Hz), 7.32 (t, 1H, H-5', ^3J = 9.2 Hz), 7.63 (d, 1H, H-3', ^3J = 9.0 Hz), 8.68 (s, 1H, H-5), 8.72 (s, 1H, H-2), 9.96 (s, 1H, OH).

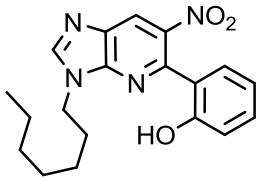
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 45.3 (CH_2), 115.0 (C-4'), 117.2 (CH_2), 119.3 (C-6'), 123.7 (C-5'), 125.7 (C-3'), 130.7 (C-5'), 131.4 (C-1'), 133.3 (CH), 133.6 (C-4), 143.9 (C-6), 144.9 (C-2), 148.4 (C-3a), 148.7 (C-7a), 154.5 (C-5).

GC-MS (EI, 70 eV): *m/z* (%): 296 (100) [M^+], 250, (34), 225 (19), 209 (50).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{15}H_{12}N_4O_3$: 296.0904; found: 296.0905.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3224, 1612, 1577, 1514, 1469, 1423, 1356, 1210, 1101, 998, 765, 721.

2-(3-Heptyl-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39c)



Starting from heptylamine (151 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39c** was isolated as light-yellow crystals, yield = 399 mg (86%); mp = 165 - 167°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 0.82 (t, 3H, CH_3, ^3J = 7.2 Hz), 1.29 (br. m, 8H, CH_2), 1.95 (m, 2H, CH_2), 4.38 (t, 2H, CH_2, ^3J = 6.6 Hz), 6.87 (d, 1H, H-6', ^3J = 8.7 Hz), 7.00 (t, 1H, H-4', ^3J = 8.7 Hz), 7.34 (t, 1H, H-5', ^3J = 9.5 Hz), 7.64 (d, 1H, H-3', ^3J = 9.2 Hz), 8.78 (s, 1H, H-5), 8.81 (s, 1H, H-2), 9.97 (s, 1H, OH).

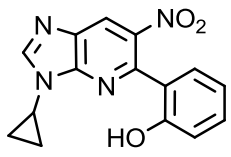
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 13.8 (CH_3), 21.9 (CH_2), 25.9 (CH_2), 28.0 (CH_2), 29.0 (CH_2), 31.0 (CH_2), 43.3 (CH_2), 115.0 (C-4'), 119.3 (C-6'), 123.8 (C-5'), 125.5 (C-3'), 130.2 (C-5'), 130.5 (C-1'), 132.6 (C-4), 143.1 (C-6), 145.8 (C-2), 148.0 (C-3a), 149.2 (C-7a), 154.4 (C-5).

GC-MS (EI, 70 eV): *m/z* (%): 354 (100) [M^+], 308 (30), 283 (15), 269 (38), 210 (55).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{19}H_{22}N_4O_3$: 354.1686; found: 354.1687.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3334, 3207, 2911, 1588, 1507, 1466, 1399, 1312, 1202, 977, 834, 766.

2-(3-Cyclopropyl-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39d)



Starting from cyclopropylamine (75 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39d** was isolated as light-yellow crystals, yield = 268 mg (69%);

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.18 (br. m, 4H, CH_2), 3.82 (m, 1H, CH), 6.88 (d, 1H, H-6', ^{3}J = 8.7 Hz), 7.02 (t, 1H, H-4', ^{3}J = 8.7 Hz), 7.33 (t, 1H, H-5', ^{3}J = 8.7 Hz), 7.61 (d, 1H, H-3', ^{3}J = 8.7 Hz), 8.70 (d, 2H, H-5, H-2), 9.89 (s, 1H, OH).

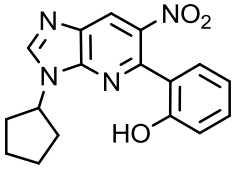
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 5.6 (CH_2), 25.6 (CH), 115.0 (C-4'), 119.3 (C-6'), 123.7 (C-5'), 125.5 (C-3'), 130.2 (C-5'), 130.6 (C-1'), 133.0 (C-4), 143.4 (C-6), 145.9 (C-2), 149.1 (C-3a), 149.2 (C-7a), 154.4 (C-5).

GC-MS (EI, 70 eV): *m/z* (%): 296 (100) [M^+], 250, (29), 222 (19), 209 (23).

HRMS (ESI): [M]$^+$ *m/z* calcd. for $C_{15}H_{12}N_4O_3$: 296.0904; found: 296.0904.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3198, 1598, 1567, 1489, 1466, 1343, 1203, 1078, 956, 723.

2-(3-Cyclopentyl-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39e)



Starting from cyclopentylamine (111 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39e** was isolated as light-yellow crystals, yield = 327 mg (77%); mp = 244 - 246°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.01 (br. m, 8H, CH_2), 5.07 (m, 1H, CH), 6.83 (d, 1H, H-6', ^{3}J = 9.0 Hz), 6.95 (t, 1H, H-4', ^{3}J = 9.0 Hz), 7.28 (t, 1H, H-5', ^{3}J = 9.0 Hz), 7.52 (d, 1H, H-3', ^{3}J = 9.0 Hz), 8.70 (s, 1H, H-5), 8.82 (s, 1H, H-2), 9.87 (s, 1H, OH).

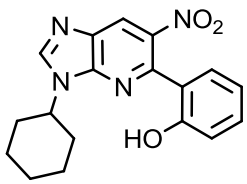
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 23.6 (CH_2), 31.9 (CH_2), 55.7 (CH), 115.0 (C-4'), 119.3 (C-6'), 123.7 (C-5'), 125.5 (C-3'), 130.2 (C-5'), 130.5 (C-1'), 133.0 (C-4), 143.1 (C-6), 145.6 (C-2), 147.6 (C-3a), 147.9 (C-7a), 154.4 (C-5).

GC-MS (EI, 70 eV): *m/z* (%): 324 (100) [M^+], 283 (13), 256 (21), 210 (81).

HRMS (ESI): [M]$^+$ *m/z* calcd. for $C_{17}H_{16}N_4O_3$: 324.1217; found: 324.1212.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3137, 1599, 1576, 1532, 1479, 1313, 1201, 1093, 987, 911, 814.

2-(3-Cyclohexyl-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39f)



Starting from cyclohexylamine (130 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39f** was isolated as light-yellow crystals, yield = 363 mg (82%); mp = 270 - 273°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.80 (br. m, 11H, CH_2), 4.57 (m, 1H, CH),

6.83 (d, 1H, H-6', ^3J = 9.3 Hz), 6.99 (t, 1H, H-4', ^3J = 9.3 Hz), 7.30 (t, 1H, H-5', ^3J = 9.3 Hz), 7.51 (d, 1H, H-3', ^3J = 9.3 Hz), 8.70 (s, 1H, H-5), 8.80 (s, 1H, H-2), 9.89 (s, 1H, OH).

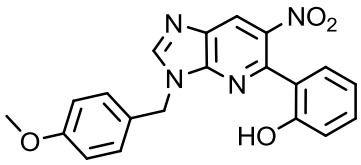
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 24.7 (CH_2), 25.0 (CH_2), 32.1 (CH_2), 53.9 (CH), 114.9 (C-4'), 119.4 (C-6'), 123.8 (C-5'), 125.5 (C-3'), 130.2 (C-5'), 130.5 (C-1'), 132.8 (C-4), 143.1 (C-6), 145.6 (C-2), 147.3 (C-3a), 147.5 (C-7a), 154.4 (C-5).

GC-MS (EI, 70 eV): *m/z* (%): 338 (100) [M^+], 292 (20), 257 (31), 210 (83).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{18}H_{18}N_4O_3$: 338.1373; found: 338.1373.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3099, 1611, 1578, 1523, 1456, 1424, 1399, 1215, 1078, 887, 854, 779.

2-(3-(4-Methoxybenzyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39g)



Starting from 4-methoxybenzylamine (179 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39g** was isolated as light-yellow crystals, yield = 419 mg (85%); mp = 224 – 226°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.74 (s, 3H, OCH_3), 5.48 (s, 2H, CH_2), 6.87 (m, 3H, H-6', H-2", H-6"), 6.99 (t, 1H, H-4', ^3J = 8.1 Hz), 7.32 (t, 1H, H-5', ^3J = 8.1 Hz), 7.41 (d, 2H, H-3", H-5", ^3J = 6.9 Hz), 7.54 (d, 1H, H-3', ^3J = 8.1 Hz), 8.77 (s, 1H, H-5), 8.83 (s, 1H, H-2), 10.00 (s, 1H, OH).

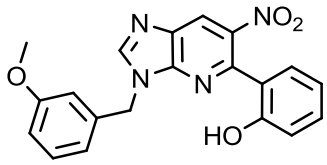
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 46.2 (CH_2), 55.1 (OCH_3), 114.1 (C-2", C-6"), 115.1 (C-4'), 119.4 (C-6'), 124.0 (C-5'), 125.4 (C-3'), 128.4 (C-4"), 129.4 (C-3", C-5"), 130.3 (C-5'), 130.5 (C-1'), 132.6 (C-4), 143.3 (C-6), 146.1 (C-2), 147.7 (C-3a), 148.9 (C-7a), 154.5 (C-5), 159.0 (C-1").

GC-MS (EI, 70 eV): *m/z* (%): 338 (37) [M^+], 121 (100).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{20}H_{16}N_4O_4$: 376.1166; found: 376.1166.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3299, 2932, 1622, 1588, 1545, 1497, 1389, 1318, 1223, 1185, 1019, 934.

2-(3-(3-Methoxybenzyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39h)



Starting from 3-methoxybenzylamine (179 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39h** was isolated as light-yellow crystals, yield = 490 mg (99%); mp = 259 - 261°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.72 (s, 3H, OCH_3), 5.52 (s, 2H, CH_2), 6.93 (br. m, 5H, H-6', H-4', H-2", H-4", H-6"), 7.29 (m, 2H, H-5', H-5"), 7.44 (d, 1H, H-3', ^{3}J = 8.4 Hz), 8.78 (s, 1H, H-5), 8.86 (s, 1H, H-2), 9.97 (s, 1H, OH).

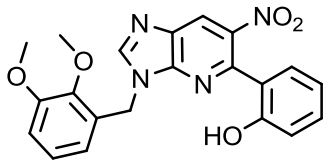
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 46.6 (CH_2), 55.0 (OCH_3), 113.3 (C-2"), 113.6 (C-4"), 115.0 (C-4'), 119.3 (C-6'), 119.8 (C-6"), 124.0 (C-5'), 125.4 (C-3'), 130.0 (C-5"), 130.3 (C-5'), 130.5 (C-1'), 132.6 (C-4), 137.9 (C-3"), 143.3 (C-6), 146.1 (C-2), 147.8 (C-3a), 149.1 (C-7a), 154.5 (C-5), 159.4 (C-1").

GC-MS (EI, 70 eV): *m/z* (%): 338 (77) [M^+], 330 (19), 121 (100).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{20}H_{16}N_4O_4$: 376.1166; found: 376.1165.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3193, 1608, 1581, 1545, 1514, 1502, 1466, 1418, 1399, 1369, 1209, 1017, 932, 866.

2-(3-(2,3-Dimethoxybenzyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39i)



Starting from 2,3-dimethoxybenzylamine (219 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39i** was isolated as light-yellow foam, yield = 463 mg (87%);

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.72 (s, 6H, OCH_3), 5.52 (s, 2H, CH_2), 6.93 (br. m, 4H, H-6', H-4', H-4", H-5"), 7.19 (d, 1H, H-4", ^{3}J = 4.8 Hz), 7.32 (t, 1H, H-5', ^{3}J = 8.1 Hz), 7.57 (d, 1H, H-3', ^{3}J = 8.1 Hz), 8.78 (s, 1H, H-5), 8.90 (s, 1H, H-2), 9.98 (s, 1H, OH).

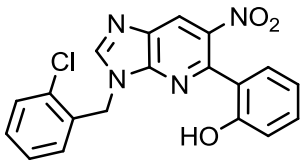
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 45.8 (CH_2), 55.0 (OCH_3), 56.3 (OCH_3), 111.7 (C-5"), 111.8 (C-4"), 115.1 (C-4'), 117.5 (C-6"), 119.3 (C-6'), 120.7 (C-3"), 124.0 (C-5'), 125.4 (C-3'), 130.3 (C-5'), 130.5 (C-1'), 132.6 (C-4), 143.2 (C-6), 146.8 (C-2), 147.8 (C-3a), 148.5 (C-7a), 154.5 (C-5), 159.4 (C-1"), 159.9 (C-2").

GC-MS (EI, 70 eV): *m/z* (%): 406 (35) [M^+], 151 (100).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{21}H_{18}N_4O_5$: 406.1272; found: 406.1274.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3035, 1587, 1559, 1518, 1471, 1432, 1394, 1356, 1201, 1108, 932, 843.

2-(3-(2-Chlorobenzyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39j)



Starting from 2-chlorobenzylamine (185 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39j** was isolated as light-yellow crystals, yield = 379 mg (76%); mp = 213 - 215°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 5.67 (s, 2H, CH_2), 6.84 (d, 1H, H-6', ^3J = 8.7 Hz), 6.99 (t, 1H, H-4', ^3J = 8.7 Hz), 7.38 (br. m, 6H, H-3', H-5', H-3", H-4", H-5", H-6"), 8.87 (s, 1H, H-5), 8.89 (s, 1H, H-2), 9.95 (s, 1H, OH).

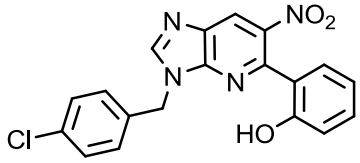
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 44.9 (CH_2), 115.0 (C-4'), 119.4 (C-6'), 124.2 (C-5'), 125.2 (C-3'), 127.5 (C-4"), 129.6 (C-6"), 129.8 (C-3"), 129.9 (C-5"), 130.2 (C-5'), 130.5 (C-1'), 132.2 (C-2"), 132.5 (C-4), 133.7 (C-1"), 143.4 (C-6), 146.1 (C-2), 147.8 (C-3a), 149.3 (C-7a), 154.4 (C-5).

GC-MS (EI, 70 eV): *m/z* (%): 380 (44) [M^+], 345 (70), 334 (13), 298 (17), 125 (100).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{19}H_{13}ClN_4O_3$: 380.0671; found: 380.0671.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2987, 1594, 1576, 1473, 1418, 1367, 1212, 1134, 1057, 869, 712.

2-(3-(4-Chlorobenzyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39k)



Starting from 4-chlorobenzylamine (185 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39k** was isolated as light-yellow crystals, yield = 394 mg (76%); mp = 190 - 192°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 5.58 (s, 2H, CH_2), 6.82 (d, 1H, H-6', ^3J = 8.7 Hz), 6.98 (t, 1H, H-4', ^3J = 8.7 Hz), 7.32 (t, 1H, H-5', ^3J = 8.7 Hz), 7.45 (m, 5H, H-3', H-2", H-6", H-3", H-5"), 8.75 (s, 1H, H-5), 8.83 (s, 1H, H-2), 9.96 (s, 1H, OH).

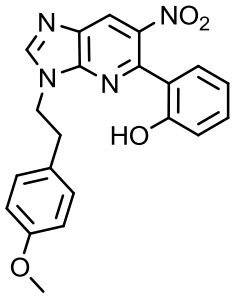
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 45.9 (CH_2), 115.0 (C-4'), 119.4 (C-6'), 124.1 (C-5'), 125.3 (C-3'), 128.7 (C-2", C-6"), 129.6 (C-3", C-5"), 130.3 (C-5'), 130.5 (C-1'), 132.6 (C-4), 135.4 (C-4"), 143.4 (C-6), 146.1 (C-2), 147.7 (C-3a), 149.0 (C-7a), 154.5 (C-5).

GC-MS (EI, 70 eV): *m/z* (%): 380 (41) [M^+], 125 (100).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{19}H_{13}ClN_4O_3$: 380.0671; found: 380.0671.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3012, 1578, 1474, 1426, 1375, 1200, 1097, 944, 823.

2-(3-(4-Methoxyphenethyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39l)



Starting from 4-methoxyphenethylamine (198 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39l** was isolated as light-yellow crystals, yield = 368 mg (72%); mp = 202 - 203°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.18 (t, 2H, CH_2, ^3J = 9.0 Hz), 3.72, (s, 3H, OCH_3), 4.58 (t, 2H, CH_2, ^3J = 9.0 Hz), 6.81 (m, 3H, H-6', H-2", H-6"), 7.01 (m, 3H, H-4', H-3", H-5"), 7.32 (t, 1H, H-5', ^3J = 8.1 Hz), 7.45 (d, 1H, H-3', ^3J = 8.1 Hz), 8.63 (s, 1H, H-5), 8.78 (s, 1H, H-2), 9.90 (s, 1H, OH).

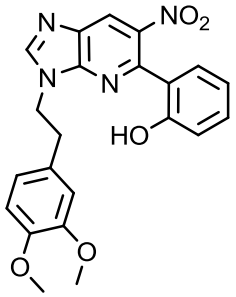
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 34.1 (CH_2), 44.9 (CH_2), 54.9 (OCH_3), 113.8 (C-2", C-6"), 115.0 (C-4'), 119.4 (C-6'), 123.8 (C-5'), 125.5 (C-3'), 129.6 (C-3", C-5"), 129.7 (C-4"), 130.2 (C-5'), 130.6 (C-1'), 132.5 (C-4), 143.1 (C-6), 145.8 (C-2), 147.9 (C-3a), 149.1 (C-7a), 154.5 (C-5), 157.9 (C-1").

GC-MS (EI, 70 eV): *m/z* (%): 390 (17) [M^+], 134 (100), 121 (16).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{21}H_{18}N_4O_4$: 390.1323; found: 390.1324.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3196, 1601, 1548, 1473, 1406, 1323, 1207, 1001, 912, 788.

2-(3-(3,4-Dimethoxyphenethyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39m)



Starting from 3,4-dimethoxyphenethylamine (216 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39m** was isolated as light-yellow crystals, yield = 500 mg (91%); mp = 176 - 178°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.17 (t, 2H, CH_2, ^3J = 8.1 Hz), 3.72, (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.65 (t, 2H, CH_2, ^3J = 8.1 Hz), 6.70 (d, 1H, H-5", ^3J = 6.9 Hz), 6.83 (m, 4H, H-6', H-4', H-3", H-6"), 7.30 (t, 1H, H-5', ^3J = 7.8 Hz), 7.49 (d, 1H, H-3', ^3J = 7.8 Hz), 8.58 (s, 1H, H-5), 8.75 (s, 1H, H-2), 9.93 (s, 1H, OH).

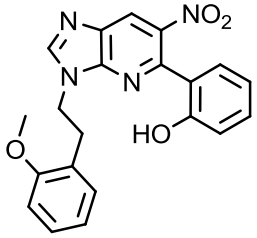
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 34.6 (CH_2), 44.8 (CH_2), 55.3 (OCH_3), 55.4 (OCH_3), 111.7 (C-5"), 112.4 (C-3"), 115.0 (C-4'), 119.3 (C-6'), 120.6 (C-6"), 123.7 (C-5'), 125.5 (C-3'), 130.1 (C-5'), 130.2 (C-4"), 130.6 (C-1'), 132.5 (C-4), 143.1 (C-6), 145.8 (C-2), 147.5 (C-1"), 148.0 (C-3a), 149.1 (C-7a), 154.5 (C-5), 161.8 (C-2").

GC-MS (EI, 70 eV): *m/z* (%): 420 (11) [M^+], 164 (100), 149 (10).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{22}H_{20}N_4O_5$: 420.1428; found: 420.1429.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3219, 1608, 1592, 1556, 1488, 1377, 1296, 1203, 1078, 943, 892.

2-(3-(4-Methoxyphenethyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39n)



Starting from 2-methoxyphenethylamine (198 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39n** was isolated as light-yellow crystals, yield = 371 mg (72%); mp = 223 - 225°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.22 (t, 2H, CH_2, ^3J = 8.7 Hz), 3.72, (s, 3H, OCH_3), 4.61 (t, 2H, CH_2, ^3J = 8.7 Hz), 6.90 (m, 5H, H-6', H-4', H-4", H-6", H-3"), 7.22 (m, 1H, H-5"), 7.31 (t, 1H, H-5', ^3J = 9.3 Hz), 7.50 (d, 1H, H-3', ^3J = 9.3 Hz), 8.52 (s, 1H, H-5), 8.69 (s, 1H, H-2), 9.93 (s, 1H, OH).

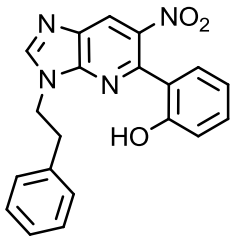
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 30.1 (CH_2), 43.4 (CH_2), 55.0 (OCH_3), 110.5 (C-4"), 115.0 (C-4'), 119.2 (C-6'), 120.2 (C-6"), 123.6 (C-5'), 125.5 (C-3', C-5"), 128.1 (C-2"), 130.1 (C-C-3"), 130.2 (C-5'), 130.6 (C-1'), 132.4 (C-4), 143.0 (C-6), 145.7 (C-2), 148.1 (C-3a), 149.1 (C-7a), 154.4 (C-5), 157.2 (C-1").

GC-MS (EI, 70 eV): *m/z* (%): 390 (50) [M^+], 134 (100), 119 (48).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{21}H_{18}N_4O_4$: 390.1323; found: 390.1320.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3087, 1589, 1545, 1472, 1419, 1369, 1298, 1203, 1043, 943, 766, 711.

2-(6-Nitro-3-phenethyl-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39o)



Starting from phenethylamine (159 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39o** was isolated as light-yellow crystals, yield = 387 mg (82%); mp = 181 - 183°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.20 (t, 2H, CH_2, ^3J = 8.7 Hz), 4.58 (t, 2H, CH_2, ^3J = 8.7 Hz), 6.82 (d, 1H, H-6', ^3J = 7.5 Hz), 7.00 (t, 1H, H-4', ^3J = 7.5 Hz), 7.22 (m, 6H, H-5', Ph), 7.47 (d, 1H, H-3', ^3J = 7.5 Hz), 8.55 (s, 1H, H-5), 8.63 (s, 1H, H-2), 9.91 (s, 1H, OH).

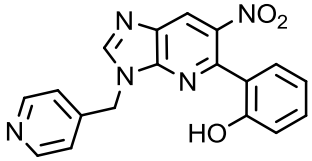
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 34.9 (CH_2), 44.6 (CH_2), 114.9 (C-4'), 119.3 (C-6'), 123.8 (C-5'), 125.5 (C-3'), 128.4 (C-3", C-5"), 128.6 (C-2", C-6", C-4"), 130.2 (C-5'), 130.6 (C-1'), 132.5 (C-4), 137.8 (C-1"), 143.1 (C-6), 145.8 (C-2), 147.9 (C-3a), 149.0 (C-7a), 154.4 (C-5).

GC-MS (EI, 70 eV): *m/z* (%): 360 (100) [M^+], 256 (35), 210 (36), 104 (57).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{20}H_{16}N_4O_3$: 360.1217; found: 360.1213.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2988, 1576, 1524, 1466, 1388, 1312, 1205, 1079, 964, 833, 776.

2-(6-Nitro-3-(pyridin-4-ylmethyl)-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39p)



Starting from (pyridin-4-yl)methylamine (141 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39p** was isolated as light-yellow crystals, yield = 345 mg (76%); mp = 270 - 273°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 5.69 (s, 2H, CH_2), 6.82 (d, 1H, H-6', ^3J = 8.7 Hz), 6.94 (t, 1H, H-4', ^3J = 8.7 Hz), 7.24 (m, 3H, H-5', H-3", H-5"), 7.42 (d, 1H, H-3', ^3J = 8.7 Hz), 8.53 (d, 2H, H-2", H-6", ^3J = 8.7 Hz), 8.78 (s, 1H, H-5), 8.90 (s, 1H, H-2), 9.92 (s, 1H, OH).

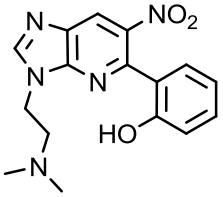
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 45.5 (CH_2), 115.0 (C-4'), 119.3 (C-6'), 122.1 (C-3", C-5"), 124.2 (C-5'), 125.2 (C-3'), 130.3 (C-5'), 130.5 (C-1'), 132.6 (C-4), 143.5 (C-6), 145.2 (C-2), 146.2 (C-4"), 147.8 (C-3a), 149.2 (C-7a), 150.0 (C-2", C-6"), 154.4 (C-5).

GC-MS (EI, 70 eV): *m/z* (%): 347 (100) [M^+], 301 (42), 209 (25).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{18}H_{13}N_5O_3$: 347.1013; found: 347.1008.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3039, 1622, 1577, 1534, 1486, 1399, 1354, 1208, 1155, 999, 823, 766.

2-(3-(2-(Dimethylamino)ethyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (39q)



Starting from 2-(dimethylamino)ethylamine (115 mg, 1.31 mmol), methyl N-(cyanomethyl)-formimidate (128 mg, 1.31 mmol) and 3-nitrochromone (250 mg, 1.31 mmol); **39q** was isolated as brown crystals, yield = 377 mg (88%); mp = 203 - 205°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.19 (s, 6H, CH_3), 2.70 (t, 2H, CH_2, 7.8 Hz), 4.43 (t, 2H, CH_2, 7.8 Hz), 6.82 (d, 1H, H-6', ^3J = 9.3 Hz), 6.98 (t, 1H, H-4', ^3J = 9.3 Hz), 7.31 (t, 1H, H-5', ^3J = 9.3 Hz), 7.52 (d, 1H, H-3', ^3J = 9.3 Hz), 8.72 (s, 1H, H-5), 8.75 (s, 1H, H-2), 9.96 (s, 1H, OH).

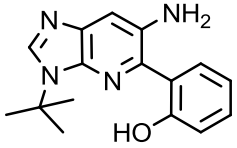
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 41.1 (CH_2), 45.0 (CH_3), 57.7 (CH_2), 115.0 (C-4'), 119.4 (C-6'), 123.8 (C-5'), 125.6 (C-3'), 130.2 (C-5'), 130.5 (C-1'), 132.5 (C-4), 143.1 (C-6), 145.8 (C-2), 148.2 (C-3a), 149.5 (C-7a), 154.5 (C-5).

GC-MS (EI, 70 eV): *m/z* (%): 257 (18), 169 (10), 140 (18), 71 (69).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{16}H_{17}N_5O_3$: 327.1326; found: 327.1335.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3276, 2988, 1578, 1545, 1466, 1371, 1299, 1209, 1118, 1056, 987, 943, 814.

2-(6-Amino-3-tert-butyl-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40a)



Starting from 2-(3-tert-butyl-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.64 mmol) **39a**; **40a** was isolated as brown crystals, yield = 166 mg (92%); mp = 187 - 189°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.75 (s, 9H, *t*-Bu), 4.86 (s, 2H, NH_2), 6.97 (t, 1H, H-4', ^3J = 9.0 Hz), 6.98 (d, 1H, H-6', ^3J = 9.0 Hz), 7.28 (t, 1H, H-5', ^3J = 9.2 Hz), 7.47 (d, 1H, H-3', ^3J = 9.0 Hz), 7.48 (s, 1H, H-5), 8.25 (s, 1H, H-2), 10.27 (s, 1H, OH).

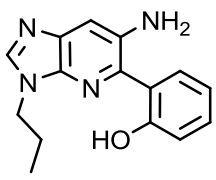
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.6 (CH_3), 56.1 ($C(CH_3)_3$), 113.5 (C-4'), 116.7 (C-6'), 119.4 (C-5'), 127.2 (C-3'), 129.1 (C-2'), 131.7 (C-1'), 136.2 (C-9), 137.5 (C-5), 140.2 (C-6), 141.0 (C-7), 142.6 (C-4), 154.6 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 282 (71) [M^+], 225 (100).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{16}H_{18}N_4O$: 282.1475; found: 282.1476.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3270, 3065, 1614, 1533, 1478, 1311, 1168, 1023, 955, 843.

2-(6-Amino-3-propyl-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40b)



Starting from 2-(3-allyl-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.68 mmol) **39b**; **40b** was isolated as brown crystals, yield = 149 mg (82%); mp = 166 - 168°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.18 (t, 3H, CH_3, ^3J = 7.2 Hz), 1.78 (m, 2H,

CH_2), 4.46 (t, 2H, CH_2, ^3J = 6.3 Hz), 4.72 (s, 2H, NH_2), 6.89 (d, 1H, H-6', ^3J = 9.0 Hz), 6.96 (t, 1H, H-4', ^3J = 9.0 Hz), 7.27 (t, 1H, H-5', ^3J = 9.2 Hz), 7.68 (d, 1H, H-3', ^3J = 9.0 Hz), 7.73 (s, 1H, H-5), 8.31 (s, 1H, H-2), 10.15 (s, 1H, OH).

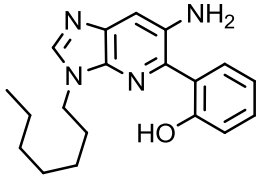
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 18.5 (CH_3), 28.9 (CH_2), 44.7 (CH_2), 113.2 (C-4'), 116.7 (C-6'), 119.0 (C-5'), 128.0 (C-3'), 128.8 (C-2'), 131.7 (C-1'), 136.2 (C-9), 137.7 (C-5), 140.2 (C-6), 142.1 (C-7), 142.9 (C-4), 154.6 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 268 (42) [M^+], 254 (19), 240 (100).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{15}H_{16}N_4O$: 268.1319; found: 268.1317.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3296, 3018, 1605, 1527, 1489, 1334, 1302, 1190, 1017, 879, 811, 766.

2-(6-Amino-3-heptyl-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40c)



Starting from 2-(3-heptyl-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.62 mmol) **39c; 40c** was isolated as brown crystals, yield = 169 mg (84%); mp = 199 - 202°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 0.85 (t, 3H, CH_3, ^3J = 7.2 Hz), 1.38 (br. m, 8H, CH_2), 1.95 (m, 2H, CH_2), 4.51 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.79 (s, 2H, NH_2), 6.86 (d, 1H, H-6', ^3J = 8.4 Hz), 7.01 (t, 1H, H-4', ^3J = 8.4 Hz), 7.33 (t, 1H, H-5', ^3J = 8.4 Hz), 7.59 (d, 1H, H-3', ^3J = 8.4 Hz), 7.68 (s, 1H, H-5), 8.22 (s, 1H, H-2), 10.17 (s, 1H, OH).

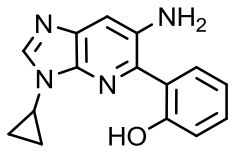
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 13.7 (CH_3), 21.9 (CH_2), 26.0 (CH_2), 28.3 (CH_2), 30.1 (CH_2), 33.4 (CH_2), 44.6 (CH_2), 113.3 (C-4'), 116.7 (C-6'), 119.0 (C-5'), 128.1 (C-3'), 128.5 (C-2'), 131.3 (C-1'), 136.4 (C-9), 137.9 (C-5), 139.9 (C-6), 142.1 (C-7), 142.8 (C-4), 154.5 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 324 (37) [M^+], 277 (21), 225 (93), 183 (17).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{19}H_{24}N_4O$: 324.1353; found: 324.1354.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3275, 3124, 2948, 1599, 1542, 1476, 1411, 1342, 1224, 1188, 1019, 932, 881.

2-(6-Amino-3-cyclopropyl-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40d)



Starting from 2-(3-cyclopropyl-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.68 mmol) **39d; 40d** was isolated as brown crystals, yield = 156 mg (86%); mp = 144 - 146°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 0.92 (m, 4H, CH_2), 3.37 (m, 1H, CH), 4.71 (s, 2H, NH_2), 6.89 (m, 2H, H-6', H-4'), 7.22 (t, 1H, H-5', ^{3}J = 8.1 Hz), 7.53 (m, 2H, H-3', H-5), 8.27 (s, 1H, H-2), 10.10 (s, 1H, OH).

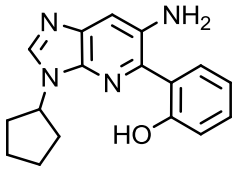
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 113.3 (C-4'), 116.7 (C-6'), 119.1 (C-5'), 127.7 (C-3'), 128.5 (C-2'), 131.9 (C-1'), 136.5 (C-9), 137.9 (C-5), 140.0 (C-6), 142.1 (C-7), 142.5 (C-4), 154.3 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 266 (100) [M^+], 249 (17), 237 (28).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{15}H_{14}N_4O$: 266.1162; found: 266.1160.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3299, 1606, 1557, 1414, 1387, 1193, 885, 711.

2-(6-Amino-3-cyclopentyl-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40e)



Starting from 2-(3-cyclopentyl-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.62 mmol) **39e; 40e** was isolated as brown crystals, yield = 168 mg (92%); mp = 191 - 193°;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.91 (br. m, 8H, CH_2), 4.90 (m, 3H, CH, NH_2), 6.91 (m, 2H, H-6', H-4'), 7.28 (t, 1H, H-5', ^{3}J = 8.1 Hz), 7.59 (d, 1H, H-3', ^{3}J = 8.1 Hz), 7.68 (s, 1H, H-5), 8.18 (s, 1H, H-2), 10.15 (s, 1H, OH).

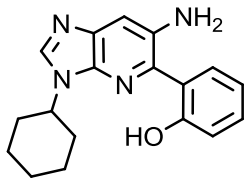
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 23.5 (CH_2), 31.2 (CH_2), 52.8 (CH), 113.4 (C-4'), 116.8 (C-6'), 119.1 (C-5'), 127.7 (C-3'), 128.6 (C-2'), 131.3 (C-1'), 136.5 (C-9), 137.9 (C-5), 139.9 (C-6), 142.1 (C-7), 142.7 (C-4), 154.4 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 294 (61) [M^+], 253 (19), 226 (100).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{17}H_{18}N_4O$: 294.1471; found: 294.1469.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3290, 1595, 1547, 1492, 1418, 1189, 1034, 992, 834, 726.

2-(6-Amino-3-cyclohexyl-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40f)



Starting from 2-(3-cyclohexyl-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.59 mmol) **39f; 40f** was isolated as bright-yellow crystals, yield = 154 mg (85%); mp = 212 - 214°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.67 (br. m, 11H, CH_2), 4.42 (m, 1H, CH),

4.70 (s, 2H, NH_2), 6.92 (m, 2H, H-6', H-4'), 7.27 (t, 1H, H-5', ^3J = 8.1 Hz), 7.50 (m, 2H, H-3', H-5), 8.19 (s, 1H, H-2), 10.17 (s, 1H, OH).

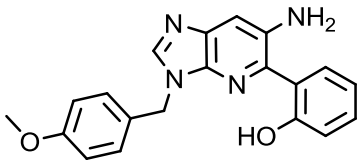
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 22.5 (CH_2), 24.7 (CH_2), 31.1 (CH_2), 52.3 (CH), 113.4 (C-4'), 116.7 (C-6'), 119.1 (C-5'), 127.5 (C-3'), 128.4 (C-2'), 131.3 (C-1'), 136.5 (C-9), 137.9 (C-5), 139.9 (C-6), 142.1 (C-7), 142.7 (C-4), 154.4 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 308 (55) [M^+], 267 (11), 226 (100), 184 (12).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{18}H_{20}N_4O$: 308.1622; found: 308.1626.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3301, 1608, 1576, 1515, 1477, 1399, 1182, 1056, 864.

2-(6-Amino-3-(4-methoxybenzyl)-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40g)



Starting from 2-(3-(4-methoxybenzyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.53 mmol) **39g**; **40g** was isolated as brown crystals, yield = 152 mg (83%); mp = 125 - 127°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.72 (s, 3H, OCH_3), 4.72 (s, 2H, NH_2), 5.42 (s, 2H, CH_2), 6.87 (d, 2H, H-2", H-6", ^3J = 8.1 Hz), 6.96 (m, 2H, H-6', H-4'), 7.23 (t, 1H, H-5', ^3J = 8.1 Hz), 7.39 (d, 2H, H-3", H-5", ^3J = 8.1 Hz), 7.48 (m, 2H, H-3', H-5), 8.28 (s, 1H, H-2), 10.14 (s, 1H, OH).

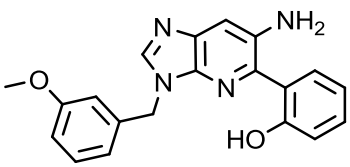
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 41.7 (CH_2), 55.0 (OCH_3), 113.4 (C-4'), 114.2 (C-2", C-6"), 116.5 (C-6'), 119.1 (C-5'), 127.5 (C-3'), 128.1 (C-4"), 128.2 (C-2'), 129.7 (C-3", C-5"), 131.6 (C-1'), 136.4 (C-9), 137.8 (C-5), 140.0 (C-6), 142.1 (C-7), 142.7 (C-4), 154.5 (C-2), 158.7 (C-1").

GC-MS (EI, 70 eV): *m/z* (%): 346 (42) [M^+], 226 (58), 121 (100).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{20}H_{18}N_4O_2$: 346.1432; found: 346.1432.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3306, 3124, 1611, 1589, 1533, 1512, 1349, 1197, 1065, 933, 766.

2-(6-Amino-3-(3-methoxybenzyl)-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40h)



Starting from 2-(3-(3-methoxybenzyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.53 mmol) **39h**; **40h** was isolated as brown crystals, yield = 150 mg (82%); mp = 137 - 139°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.69 (s, 3H, OCH_3), 4.79 (s, 2H,

NH_2), 5.40 (s, 2H, CH_2), 6.90 (m, 5H, H-2", H-4", H-6", H-6', H-4'), 7.23 (m, 2H, H-5', H-5"), 7.41 (d, 1H, H-3', ^3J = 7.8 Hz), 7.46 (s, 1H, H-5), 8.40 (s, 1H, H-2), 10.17 (s, 1H, OH).

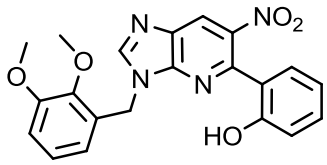
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 42.3 (CH_2), 55.1 (OCH_3), 113.3 (C-2"), 113.4 (C-4'), 113.8 (C-4"), 116.5 (C-6'), 119.2 (C-5'), 120.0 (C-6"), 127.5 (C-3'), 128.2 (C-2'), 130.2 (C-5"), 131.6 (C-1'), 136.4 (C-9), 137.1 (C-3"), 137.7 (C-5), 140.0 (C-6), 142.1 (C-7), 142.7 (C-4), 154.4 (C-2), 158.7 (C-1").

GC-MS (EI, 70 eV): *m/z* (%): 346 (100) [M^+], 121 (30).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{20}H_{18}N_4O_2$: 346.1432; found: 346.1431.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3211, 1600, 1535, 1517, 1468, 1433, 1355, 1224, 1189, 1086, 814, 758.

2-(6-Amino-3-(2,3-dimethoxybenzyl)-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40i)



Starting from 2-(3-(2,3-dimethoxybenzyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.49 mmol) **39i**; **40i** was isolated as brown crystals, yield = 155 mg (78%); mp = 121 - 123°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.72 (s, 6H, OCH_3), 4.80 (s, 2H, NH_2), 5.34 (s, 2H, CH_2), 6.93 (br. m, 4H, H-6', H-4", H-5", H-6"), 7.19 (d, 1H, H-4', ^3J = 5.4 Hz), 7.29 (t, 1H, H-5', ^3J = 6.6 Hz), 7.41 (d, 1H, H-3', ^3J = 6.6 Hz), 7.44 (s, 1H, H-5), 8.38 (s, 1H, H-2), 10.12 (s, 1H, OH).

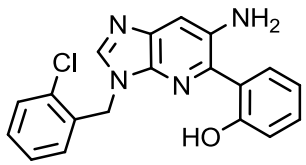
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 42.3 (CH_2), 55.1 (OCH_3), 111.8 (C-6"), 112.3 (C-4"), 113.5 (C-4'), 116.8 (C-6'), 119.2 (C-5'), 119.5 (C-5"), 122.2 (C-3"), 127.6 (C-3'), 128.2 (C-2'), 131.6 (C-1'), 136.5 (C-9), 137.8 (C-5), 139.9 (C-6), 142.1 (C-7), 142.6 (C-4), 154.5 (C-2), 159.4 (C-1"), 160.0 (C-2").

GC-MS (EI, 70 eV): *m/z* (%): 376 (61) [M^+], 151 (100).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{21}H_{18}N_4O_5$: 376.1530; found: 376.1527.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3196, 1604, 1565, 1507, 1479, 1378, 1311, 1243, 1189, 996.

2-(6-Amino-3-(2-chlorobenzyl)-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40j)



Starting from 2-(3-(2-chlorobenzyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.53 mmol) **39j**; **40j** was isolated as brown foam, yield = 141 mg (76%); mp = 148 - 150°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 4.81 (s, 2H, NH_2), 5.56 (s, 2H, CH_2), 6.97 (br. m, 3H, H-6', H-4', H-4"), 7.21 (br. m, 5H, H-3', H-5', H-3', H-5', H-6'), 7.47 (s, 1H, H-5), 8.32 (s, 1H, H-2), 10.09 (s, 1H, OH).

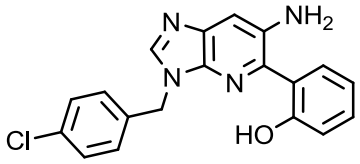
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 46.2 (CH_2), 113.5 (C-4'), 116.8 (C-6'), 119.1 (C-5'), 127.7 (C-3'), 127.4 (C-4"), 128.6 (C-2'), 129.6 (C-6"), 129.8 (C-3"), 130.2 (C-5"), 131.3 (C-1'), 132.4 (C-2"), 133.8 (C-1"), 136.4 (C-9), 137.9 (C-5), 140.1 (C-6), 142.1 (C-7), 142.7 (C-4), 154.4 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 350 (95) [M^+], 315 (100), 125 (42).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{19}H_{15}ClN_4O$: 350.0943; found: 350.0947.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3218, 1595, 1532, 1446, 1389, 1190, 1083, 1020, 992, 796, 764.

2-(6-Amino-3-(4-chlorobenzyl)-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40k)



Starting from 2-(3-(4-chlorobenzyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.53 mmol) **39k**; **40k** was isolated as brown crystals, yield = 394 mg (76%); mp = 156 - 159°;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 4.74 (s, 2H, NH_2), 5.54 (s, 2H, CH_2), 6.96 (m, 2H, H-6', H-4'), 7.23 (m, 5H, H-5', H-2", H-6", H-3", H-5"), 7.46 (m, 2H, H-3', H-5), 8.31 (s, 1H, H-2), 10.14 (s, 1H, OH).

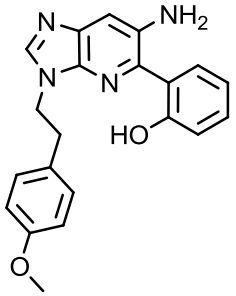
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 45.9 (CH_2), 113.4 (C-4'), 116.7 (C-6'), 119.1 (C-5'), 128.0 (C-3'), 128.5 (C-2'), 128.8 (C-2", C-6"), 129.6 (C-3", C-5"), 131.3 (C-1'), 135.2 (C-4"), 136.4 (C-9), 136.6 (C-1"), 137.9 (C-5), 139.9 (C-6), 142.3 (C-7), 142.8 (C-4), 154.4 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 350 (100) [M^+], 125 (50).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{19}H_{13}ClN_4O_3$: 350.0943; found: 350.0945.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3300, 1593, 1536, 1471, 1370, 1188, 1036, 882, 819.

2-(6-Amino-3-(4-methoxyphenethyl)-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40l)



Starting from 2-(3-(4-methoxyphenethyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.51 mmol) **39l**; **40l** was isolated as brown crystals, yield = 143 mg (78%); mp = 178 - 180°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.11 (t, 2H, CH_2, ^{3}J = 7.8 Hz), 3.74 (s, 3H, OCH_3), 4.52 (t, 2H, CH_2, ^{3}J = 7.8 Hz), 4.70 (s, 2H, NH_2), 6.88 (d, 2H, H-2", H-6", ^{3}J = 8.1 Hz), 7.00 (m, 2H, H-6', H-4'), 7.23 (t, 1H, H-5', ^{3}J = 8.7 Hz), 7.39 (d, 2H, H-3", H-5", ^{3}J = 8.7 Hz), 7.48 (m, 2H, H-3', H-5), 8.32 (s, 1H, H-2), 10.10 (s, 1H, OH).

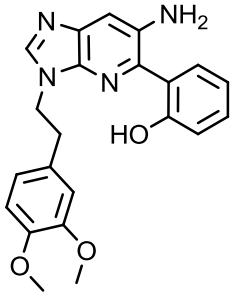
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 34.0 (CH_2), 45.4 (CH_2), 55.2 (OCH_3), 113.4 (C-4'), 114.2 (C-2", C-6"), 116.5 (C-6'), 119.1 (C-5'), 127.5 (C-3'), 128.1 (C-4"), 128.2 (C-2'), 129.7 (C-3", C-5"), 131.6 (C-1'), 136.4 (C-9), 137.8 (C-5), 140.0 (C-6), 142.1 (C-7), 142.7 (C-4), 154.5 (C-2), 158.7 (C-1").

GC-MS (EI, 70 eV): *m/z* (%): 360 (19) [M^+], 226 (100).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{21}H_{20}N_4O_2$: 360.1581; found: 360.1582.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3297, 1611, 1548, 1503, 1478, 1366, 1299, 1197, 1011, 944, 877, 753.

2-(6-Amino-3-(3,4-dimethoxyphenethyl)-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40m)



Starting from 2-(3-(3,4-dimethoxyphenethyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.48 mmol) **39m**; **40m** was isolated as brown crystals, yield = 140 mg (75%); mp = 193 -196°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.03 (t, 2H, CH_2, ^{3}J = 7.8 Hz), 3.72 (s, 6H, OCH_3), 4.56 (t, 2H, CH_2, ^{3}J = 7.8 Hz), 4.77 (s, 2H, NH_2), 6.89 (br. m, 4H, H-6', H-4", H-5", H-6"), 7.22 (d, 1H, H-4', ^{3}J = 6.9 Hz), 7.30 (t, 1H, H-5', ^{3}J = 6.9 Hz), 7.42 (m, 2H, H-3', H-5), 8.35 (s, 1H, H-2), 10.18 (s, 1H, OH).

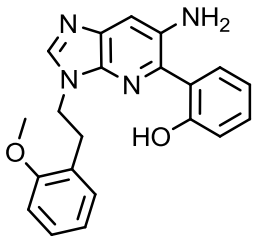
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 33.2 (CH_2), 45.3 (CH_2), 55.2 (OCH_3), 55.4 (OCH_3), 112.2 (C-6"), 112.4 (C-4"), 113.6 (C-4'), 116.8 (C-6'), 119.2 (C-5'), 119.9 (C-5"), 122.1 (C-3"), 127.6 (C-3'), 128.2 (C-2'), 131.6 (C-1'), 136.5 (C-9), 137.8 (C-5), 140.0 (C-6), 142.1 (C-7), 142.6 (C-4), 154.5 (C-2), 159.4 (C-1"), 159.8 (C-2").

GC-MS (EI, 70 eV): *m/z* (%): 390 (19) [M^+], 226 (100), 164 (30).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{22}H_{22}N_4O_3$: 390.1686; found: 390.1689.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3287, 1593, 1536, 1471, 1412, 1379, 1292, 1184, 1064, 988, 912, 845, 797.

2-(6-Amino-3-(2-methoxyphenethyl)-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40n)



Starting from 2-(3-(2-methoxyphenethyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.51 mmol) **39n**; **40n** was isolated as brown crystals, yield = 143 mg (78%); mp = 153 - 155°C

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.14 (t, 2H, CH_2, ^3J = 7.2 Hz), 3.74 (s, 3H, OCH_3), 4.42 (t, 2H, CH_2, ^3J = 7.2 Hz), 4.84 (s, 2H, NH_2), 6.79 (t, 1H, H-4', ^3J = 8.1 Hz), 6.95 (m, 4H, H-6', H-4", H-5", H-6"), 7.27 (m, 2H, H-5', H-3"), 7.42 (m, 2H, H-3', H-5), 8.11 (s, 1H, H-2), 10.24 (s, 1H, OH).

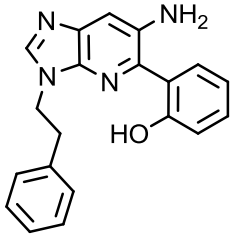
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 33.2 (CH_2), 45.8 (CH_2), 55.0 (OCH_3), 110.5 (C-4"), 113.4 (C-4'), 116.5 (C-6'), 119.1 (C-5'), 120.2 (C-6"), 125.3 (C-5"), 127.5 (C-3'), 128.2 (C-2'), 128.3 (C-2"), 129.4 (C-3"), 131.5 (C-1'), 136.5 (C-9), 137.8 (C-5), 140.0 (C-6), 142.1 (C-7), 142.7 (C-4), 154.4 (C-2), 158.9 (C-1").

GC-MS (EI, 70 eV): *m/z* (%): 360 (56) [M^+], 226 (79).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{21}H_{20}N_4O_2$: 360.1581; found: 360.1581.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3268, 1602, 1533, 1487, 1406, 1389, 1168, 1085, 1010, 818.

2-(6-Amino-3-phenethyl-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40o)



Starting from 2-(6-nitro-3-phenethyl-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.56 mmol) **39o**; **40o** was isolated as brown crystals, yield = 148 mg (80%); mp = 177 - 179°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.18 (t, 2H, CH_2, ^3J = 7.2 Hz), 4.47 (t, 2H, CH_2, ^3J = 7.2 Hz), 6.91 (d, 1H, H-6', ^3J = 7.5 Hz), 7.24 (br. m, 7H, H-4', H-5', Ph), 7.44 (m, 2H, H-3', H-5), 8.18 (s, 1H, H-2), 10.12 (s, 1H, OH).

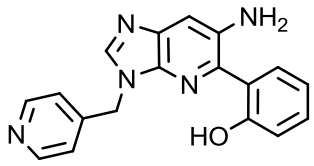
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 35.3 (CH_2), 45.8 (CH_2), 113.5 (C-4'), 116.7 (C-6'), 119.1 (C-5'), 127.7 (C-3'), 128.2 (C-3", C-5"), 128.5 (C-2", C-6", C-4"), 128.6 (C-2'), 131.4 (C-1'), 136.5 (C-9), 137.9 (C-5), 139.9 (C-6), 142.1 (C-7), 142.7 (C-4), 154.4 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 330 (50) [M^+], 226 (100).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{20}H_{18}N_4O$: 330.1523; found: 330.1523.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3276, 1605, 1591, 1558, 1463, 1387, 1319, 1171, 1068, 955, 839.

2-(6-Amino-3-(pyridin-4-ylmethyl)-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40p)



Starting from 2-(6-nitro-3-(pyridin-4-ylmethyl)-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.58 mmol) **39p**; **40p** was isolated as brown crystals, yield = 145 mg (79%); mp = 223 - 225°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 4.90 (s, 2H, NH_2), 5.69 (s, 2H, CH_2), 6.91 (m, 2H, H-6', H-4'), 7.24 (m, 4H, H-3', H-5', H-3", H-5"), 7.51 (s, 1H, H-5), 8.38 (s, 1H, H-2), 8.50 (d, 2H, H-2", H-6", ^3J = 5.7 Hz), 10.04 (s, 1H, OH).

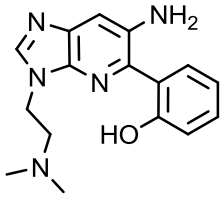
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 45.5 (CH_2), 113.6 (C-4'), 117.0 (C-6'), 119.1 (C-5'), 122.6 (C-3", C-5"), 127.9 (C-3'), 128.7 (C-2'), 131.3 (C-1'), 136.5 (C-9), 137.9 (C-5), 138.9 (C-4"), 140.1 (C-6), 142.1 (C-7), 142.7 (C-4), 149.7 (C-2", C-6"), 154.4 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 317 (100) [M^+].

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{18}H_{15}N_5O$: 317.1314; found: 317.1316.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3267, 1599, 1544, 1497, 1465, 1358, 1282, 1169, 1054, 1001, 818, 783.

2-(6-Amino-3-(2-(dimethylamino)ethyl)-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (40q)



Starting from 2-(3-(2-(dimethylamino)ethyl)-6-nitro-3*H*-imidazo[4,5-b]pyridin-5-yl)phenol (200 mg, 0.61 mmol) **39q; 40q** was isolated as dark-brown gum, yield = 147 mg (81%);

^{1}H NMR (300.13 MHz, DMSO-d_6): 2.24 (s, 6H, CH_3), 2.79 (t, 2H, CH_2, 6.3 Hz), 4.32 (t, 2H, CH_2, 6.3 Hz), 4.81 (s, 1H, NH_2), 6.90 (m, 2H, H-6', H-4'), 7.27 (t, 1H, H-5', ^3J = 8.1 Hz), 7.38 (d, 1H, H-3', ^3J = 8.1 Hz), 7.42 (s, 1H, H-5), 8.26 (s, 1H, H-2), 10.23 (s, 1H, OH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 40.8 (CH_2), 44.9 (CH_3), 54.3 (CH_2), 113.5 (C-4'), 116.9 (C-6'), 119.1 (C-5'), 127.7 (C-3'), 128.6 (C-2'), 131.5 (C-1'), 136.5 (C-9), 138.0 (C-5), 139.9 (C-6), 141.8 (C-7), 142.7 (C-4), 154.5 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 297 (23) [M^+], 248 (13), 226 (100).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{16}H_{19}N_5O$: 297.1583; found: 297.1588.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3243, 1600, 1518, 1478, 1423, 1387, 1191, 1046, 958, 788, 714.

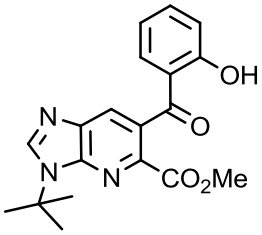
General Procedure for the Synthesis of Compounds 47a–j

To a Schlenk flask fitted with a reflux condenser, CH_2Cl_2 (2.5 mL), primary amine (3.45 mmol), and methyl N-(cyanomethyl)formimidate (338 mg 3.45 mmol) were added under an argon atmosphere at r.t. The reaction mixture was heated at reflux for 2 h then cooled down to r.t., and then to 0°C with an ice bath. 3-Methoxalylchromone (800 mg, 3.45 mmol) was added and the mixture was stirred at the same temperature for 15–20 min and then heated at reflux for 5 h. When product formation was complete, the solvent was evaporated to dryness and the residue was purified by column chromatography (EtOAc) to give **47a–j** as light-grey oily gum, which crystallized within a few hours in air.

General Procedure for the Synthesis of Compounds 48a–j

To a solution of 300 mg of corresponding ester in 20 ml methanol 2 equivalents of potassium hydroxide (30% water solution) was added. The mixture was stirring under reflux for 2 h and was led to cool down. Concentrated hydrochloric acid was added to the mixture dropwise reaching subacidic pH. The precipitate formed was filtered and washed with water, then dried to give **48a-j** as white crystals.

Methyl 3-tert-Butyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (47a)



Starting from *tert*-butylamine (252 mg, 3.45 mmol), methyl N-(cyanomethyl)-formimidate (338 mg, 3.45 mmol) and 3-methoxalylchromone (800 mg, 3.45 mmol); **47a** was isolated as light-grey powder, yield = 585 mg (48%); mp = 196 - 198°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.84 (s, 9H, *t*-Bu), 3.72 (s, 3H, OCH_3), 6.91 (t, 1H, H-4', ^3J = 9.2 Hz), 7.02 (d, 1H, H-2', ^3J = 9.2 Hz), 7.36 (d, 1H, H-5', ^3J = 9.2 Hz), 7.55 (t, 1H, H-3', ^3J = 9.2 Hz), 8.28 (s, 1H, H-4), 8.80 (s, 1H, H-2), 11.20 (s, 1H, OH).

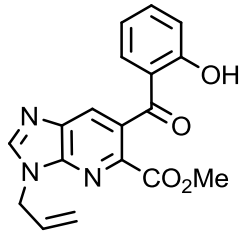
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 28.5 (CH_3), 52.6 (OCH_3), 57.6 ($C(CH_3)_3$), 117.4 (C-4'), 119.2 (C-6'), 121.7 (C-2'), 127.1 (C-5), 131.1 (C-6), 132.1 (C-3'), 135.8 (C-5'), 137.1 (C-4), 139.8 (C-9), 146.8 (C-2), 147.6 (C-7), 160.0 (C-1'), 165.6 ($COOCH_3$), 198.3 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 353 (11) $[M]^+$, 322 (10), 294 (81), 266 (20), 238 (95), 209 (10), 121 (11).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{19}H_{19}N_3O_4$: 353.1370; found: 353.1368.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1706, 1629, 1444, 1340, 1296, 1217, 1145, 911, 751, 626.

Methyl 3-allyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (47b)



Starting from allylamine (197 mg, 3.45 mmol), methyl N-(cyanomethyl)-formimidate (338 mg, 3.45 mmol) and 3-methoxalylchromone (800 mg, 3.45 mmol); **47b** was isolated as light-grey powder, yield = 512 mg (44%); mp = 163 - 165°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.69 (s, 3H, OCH_3), 5.01 (d, 2H, -CH_2-, ^{3}J = 2.9 Hz), 5.08 (dd, 1H, CH_2(trans), $^{3}J_1$ = 15.3 Hz, $^{2}J_2$=2.1 Hz), 5.25 (dd, 1H, CH_2(cis), $^{3}J_1$ = 8.7 Hz, $^{2}J_2$ = 2.1 Hz), 6.15 (m, 1H, CH), 6.88 (t, 1H, H-4', ^{3}J = 9.1 Hz), 7.00 (d, 1H, H-2',^{3}J = 9.1 Hz), 7.32 (d, 1H, H-5', ^{3}J = 9.1 Hz), 7.52 (t, 1H, H-3', ^{3}J = 9.1 Hz), 8.31 (s, 1H, H-4), 8.78 (s, 1H, H-2), 11.16 (s, 1H, -OH).

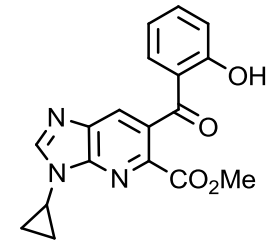
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 45.3 (CH_2), 52.6 (OCH_3), 117.5 (C-4'), 117.8 (CH_2), 119.3 (C-6'), 121.7 (C-2'), 127.5 (C-5), 131.5 (C-6), 132.1 (C-3'), 132.9 (CH), 135.7 (C-5'), 135.8 (C-4), 141.0 (C-9), 146.5 (C-2), 149.7 (C-7), 159.9 (C-1'), 165.56 (*C*$OOCH_3$), 198.2 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 337 (10) [M^+], 305 (12), 278 (100), 250 (11), 41 (11).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{18}H_{15}N_3O_4$: 338.1135; found: 338.114.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1709, 1628, 1608, 1483, 1445, 1374, 1280, 1255, 1235, 1203, 1145, 946, 907, 744, 672, 620.

Methyl 3-cyclopropyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (47c)



Starting from cyclopropylamine (197 mg, 3.45 mmol), methyl N-(cyanomethyl)-formimidate (338 mg, 3.45 mmol) and 3-methoxalylchromone (800 mg, 3.45 mmol); **47c** was isolated as light-grey powder, yield = 554 mg (47%); mp = 172 - 174°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.22 (br. m, 4H, CH_2), 3.74 (m, 4H, OCH_3, CH), 6.91 (t, 1H, H-4', ^{3}J = 9.1 Hz), 7.03 (d, 1H, H-2', ^{3}J = 9.1 Hz), 7.34 (d, 1H, H-5', ^{3}J = 9.1 Hz), 7.56 (t, 1H, H-3', ^{3}J = 9.1 Hz), 8.30 (s, 1H, H-4), 8.79 (s, 1H, H-2), 11.20 (s, 1H, OH).

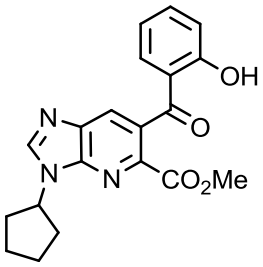
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 5.7 (CH_2), 25.6 (CH), 52.5 (OCH_3), 117.4 (C-4'), 119.2 (C-6'), 121.7 (C-2'), 127.3 (C-5), 131.6 (C-6), 132.0 (C-3'), 135.8 (C-5'), 136.2 (C-4), 140.8 (C-9), 147.8 (C-2), 149.6 (C-7), 159.9 (C-1'), 165.6 (*C*$OOCH_3$), 198.2 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 337 (12) [M^+], 304 (14), 278 (97), 250 (16), 121 (10), 65 (10).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{18}H_{15}N_3O_4$: 337.1057; found: 337.1050.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1704, 1628, 1485, 1443, 1337, 1298, 1265, 1237, 1141, 908, 759, 674, 628.

Methyl 3-cyclopentyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (47d)



Starting from cyclopentylamine (293 mg, 3.45 mmol), methyl N-(cyanomethyl)-formimidate (338 mg, 3.45 mmol) and 3-methoxalylchromone (800 mg, 3.45 mmol); **47d** was isolated as light-grey powder, yield = 579 mg (46%); mp = 161 - 163°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.01 (br. m, 8H, CH_2), 3.72 (s, 3H, OCH_3), 5.12 (m, 1H, CH), 6.90 (t, 1H, H-4', ^3J = 9.2 Hz), 7.03 (d, 1H, H-2', ^3J = 9.2 Hz), 7.34 (d, 1H, H-5', ^3J = 9.2 Hz), 7.55 (t, 1H, H-3', ^3J = 9.2 Hz), 8.31 (s, 1H, H-4), 8.92 (s, 1H, H-2), 11.18 (s, 1H, -OH).

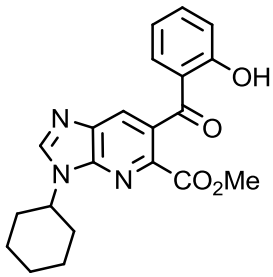
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 23.6 (CH_2), 32.2 (CH_2), 52.5 (OCH_3), 55.4 (CH), 117.4 (C-4'), 119.2 (C-6'), 121.7 (C-2'), 127.3 (C-5), 131.4 (C-6), 132.1 (C-3'), 135.8 (C-5'), 136.1 (C-4), 140.6 (C-9), 146.6 (C-2), 148.1 (C-7), 160.0 (C-1'), 165.5 (*C*$OOCH_3$), 198.3 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 365 (14) [M^+], 334 (10), 306 (97), 292 (11), 266 (21), 238 (34).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{20}H_{19}N_3O_4$: 366.1448; found: 366.1456.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 1727, 1631, 1602, 1486, 1446, 1294, 1226, 1142, 910, 797, 754, 710.

Methyl 3-cyclohexyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (47e)



Starting from cyclopentylamine (342 mg, 3.45 mmol), methyl N-(cyanomethyl)-formimidate (338 mg, 3.45 mmol) and 3-methoxalylchromone (800 mg, 3.45 mmol); **47e** was isolated as light-grey powder, yield = 667 mg (51%); mp = 143 - 145°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.74 (br. m, 10H, CH_2), 3.72 (s, 3H, OCH_3), 4.63 (m, 1H, CH), 6.90 (t, 1H, H-4', ^3J = 9.3 Hz), 7.02 (d, 1H, H-2', ^3J = 9.3 Hz), 7.34 (d, 1H, H-5', ^3J = 9.3 Hz), 7.55 (t, 1H, H-3', ^3J = 9.3 Hz), 8.30 (s, 1H, H-4), 8.95 (s, 1H, H-2), 11.18 (s, 1H, OH).

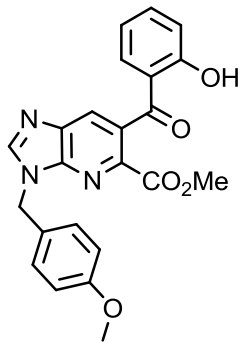
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 24.7 (CH_2), 25.0 (CH_2), 32.4 (CH_2), 52.5 (OCH_3), 53.6 (CH), 117.4 (C-4'), 119.2 (C-6'), 121.7 (C-2'), 127.4 (C-5), 131.3 (C-6), 132.1 (C-3'), 135.8 (C-5'), 135.9 (C-4), 140.8 (C-9), 146.2 (C-2), 147.8 (C-7), 159.9 (C-1'), 165.6 (*C*OOCH$_3$), 198.2 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 379 (13) [M^+], 346 (14), 320 (100), 302 (19), 266 (32), 238 (45), 207 (18).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{21}H_{21}N_3O_4$: 380.1605; found: 380.1608.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1715, 1630, 1605, 1447, 1377, 1295, 1252, 1240, 1214, 1141, 911, 796, 756, 674.

Methyl 6-(2-hydroxybenzoyl)-3-(4-methoxybenzyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (47f)



Starting from 4-methoxybenzylamine (473 mg, 3.45 mmol), methyl N-(cyanomethyl)-formimidate (338 mg, 3.45 mmol) and 3-methoxalylchromone (800 mg, 3.45 mmol); **47f** was isolated as light-grey powder, yield = 719 mg (50%); mp = 165 - 166°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.56 (s, 2 H, CH_2), 6.92 (t, 1H, H-4'', ^3J = 8.8 Hz) , 6.98 (d, 2H, H-2',H-6', ^3J =6.3 Hz), 7.06 (d, 1H, H-2'', ^3J = 8.8 Hz), 7.40 (m, 3H, H-3', H-5', H-5"), 7.57 (t, 1H, H-3'', ^3J = 8.8 Hz), 8.36 (s, 1H, H-4), 8.92 (s, 1H, H-2), 11.21 (s, 1H, OH).

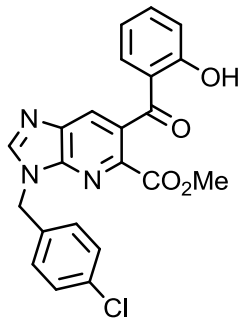
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 46.0 (CH_2), 52.9 (OCH_3), 55.1 (OCH_3), 114.1 (C-2', C-6'), 117.4 (C-4"), 119.2 (C-6"), 121.6 (C-2"), 127.5 (C-5), 128.5 (C-4'), 129.3 (C-3', C-5'), 131.5 (C-6), 132.2 (C-3"), 135.8 (C-5"), 135.8 (C-4), 141.0 (C-9), 146.5 (C-2), 149.5 (C-7), 158.9 (C-1'), 159.9 (C-1"), 165.5 (*C*OOCH$_3$), 198.2 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 385 (67), 358 (39), 281 (11), 207 (19), 121 (100), 77 (10).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{23}H_{19}N_3O_5$: 418.1397; found: 418.1395.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1715, 1627, 1601, 1448, 1348, 1282, 1239, 1142, 1034, 904, 763.

Methyl 3-(4-chlorobenzyl)-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (47g)



Starting from 4-chlorobenzylamine (488 mg, 3.45 mmol), methyl N-(cyanomethyl)-formimidate (338 mg, 3.45 mmol) and 3-methoxalylchromone (800 mg, 3.45 mmol); **47g** was isolated as light-grey powder, yield = 642 mg (44%); mp = 130 - 132°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.76 (s, 3H, OCH_3), 5.66 (s, 2H, CH_2), 6.94 (t, 1H, H-4'', ^3J = 8.9 Hz), 7.06 (d, 1H, H-2'', ^3J = 8.9 Hz), 7.40 (d, 1H, H-5'', ^3J = 8.9 Hz), 7.48 (m, 4H, H-3', H-2', H-5', H-6'), 7.59 (t, 1H, H-3'', ^3J = 8.9 Hz), 8.31 (s, 1H, H-4), 8.91 (s, 1H, H-2), 11.16 (s, 1H, OH).

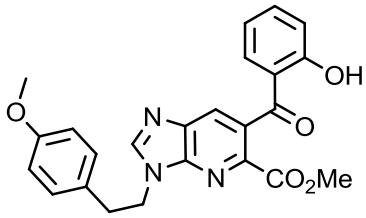
13C NMR (62.90 MHz, DMSO-d_6): δ = 45.7 (CH_2), 52.5 (OCH_3), 117.5 (C-4"), 119.2 (C-6"), 121.3 (C-2"), 126.8 (C-5), 128.7 (C-2', C-6'), 129.5 (C-3', C-5'), 131.2 (C-6), 132.3 (C-3"), 132.5 (C-4'), 135.4 (C-5"), 135.6 (C-1'), 136.1 (C-4), 141.8 (C-9), 146.2 (C-2), 149.6 (C-7), 160.0 (C-1"), 165.5 (*C*$OOCH_3$), 198.3 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 421 (10) [M^+], 390 (11), 362 (74), 125 (99), 89 (14), 65 (10).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{22}H_{16}ClN_3O_4$: 422.0902; found: 422.0904.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1715, 1622, 1602, 1445, 1349, 1288, 1237, 1142, 904, 794, 752, 663.

Methyl 6-(2-hydroxybenzoyl)-3-(4-methoxyphenethyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (47h)



Starting from 4-methoxyphenethylamine (521 mg, 3.45 mmol), methyl N-(cyanomethyl)-formimidate (338 mg, 3.45 mmol) and 3-methoxalylchromone (800 mg, 3.45 mmol); **47h** was isolated as light-grey powder, yield = 669 mg (45%); mp = 149 - 151°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.19 (t, 2H, CH_2, ^3J = 6.8 Hz), 3.71 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.59 (t, 2H, CH_2,^3J = 6.8 Hz), 6.83 (d, 2H, H-2',H-6', ^3J = 6.4 Hz), 6.91 (t, 1H, H-4'', ^3J = 9.1 Hz) , 7.03 (d, 1H, H-2'', ^3J = 9.1 Hz), 7.07 (d, 2H, H-3', H-5', ^3J = 6.4 Hz), 7.31 (d, 1H, H-5'', ^3J = 9.1 Hz), 7.55 (t, 1H, H-3'', ^3J = 9.1 Hz), 8.29 (s, 1H, H-4), 8.57 (s, 1H, H-2), 11.22 (s, 1H, -OH).

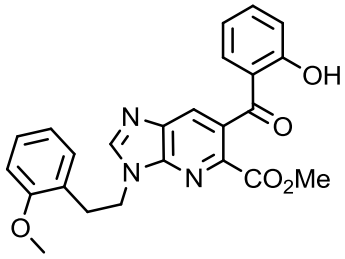
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 33.9 (CH_2), 44.8 (CH_2), 52.5 (OCH_3), 54.9 (OCH_3), 113.8 (C-2', C-6'), 117.4 (C-4"), 119.2 (C-6"), 121.6 (C-2"), 127.3 (C-5), 129.5 (C-3', C-5'), 129.6 (C-4'), 131.3 (C-6), 132.0 (C-3"), 135.8 (C-5"), 135.8 (C-4), 140.7 (C-9), 146.6 (C-2), 149.6 (C-7), 157.9 (C-1'), 160.0 (C-1"), 165.5 (*C*$OOCH_3$), 198.3 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 431 (14) [M^+], 429 (19), 372 (22), 310 (15), 134 (100), 91 (35), 65 (11).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{24}H_{21}N_3O_5$: 432.1554; found: 432.1558.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1717, 1626, 1610, 1453, 1380, 1288, 1237, 1144, 1033, 908, 761, 618.

Methyl 6-(2-hydroxybenzoyl)-3-(2-methoxyphenethyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (47i)



Starting from 2-methoxyphenethylamine (521 mg, 3.45 mmol), methyl N-(cyanomethyl)-formimidate (338 mg, 3.45 mmol) and 3-methoxalylchromone (800 mg, 3.45 mmol); **47i** was isolated as light-grey powder, yield = 743 mg (50%); mp = 138 - 140°C;

R_f = 0.75 (EtOAc).^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.19 (t, 2 H, CH_2, ^3J = 6.5 Hz), 3.67 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.61 (t, 2 H, -CH_2-, ^3J = 6.5 Hz), 6.78 (t, 1H, H-4', ^3J = 6.2 Hz), 6.91 (t, 1H, H-4'', ^3J = 9.4 Hz).6.93 (d, 1H, H-2', ^3J = 6.2 Hz), 6.94 (d, 1H, H-5', ^3J = 6.2 Hz), 7.03 (d, 1H, H-2'', ^3J = 9.4 Hz), 7.18 (t, 1H, H-3', ^3J = 6.2 Hz), 7.27 (d, 1H, H-5'', ^3J = 9.4 Hz), 7.55 (t, 1H, H-3'', ^3J = 9.4 Hz), 8.25 (s, 1H, H-4), 8.49 (s, 1H, H-2), 11.22 (s, 1H, OH).

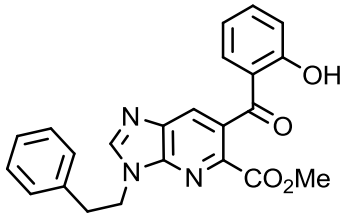
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 30.2 (CH_2), 43.3 (CH_2), 52.5 (OCH_3), 55.0 (OCH_3), 110.5 (C-4'), 117.4 (C-4"), 119.2 (C-6"), 120.1 (C-6'), 121.6 (C-2"), 125.5 (C-2'), 127.0 (C-5), 128.1 (C-3'), 130.0 (C-5'), 131.1 (C-6), 132.0 (C-3"), 135.7 (C-5"), 135.8 (C-4), 140.5 (C-9), 146.7 (C-2), 149.6 (C-7), 157.2 (C-1'), 160.0 (C-1"), 165.5 (*C*$OOCH_3$), 198.4 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 431 (15) [M^+], 400 (10), 372 (30), 134 (99), 119 (51), 91 (47), 65 (12).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{24}H_{21}N_3O_5$: 432.1554; found: 432.1559.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1713, 1626, 1601, 1497, 1443, 1380, 1285, 1249, 1142, 1034, 898, 747, 630.

Methyl 6-(2-hydroxybenzoyl)-3-phenethyl-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (47j)



Starting from phenethylamine (417 mg, 3.45 mmol), methyl N-(cyanomethyl)-formimidate (338 mg, 3.45 mmol) and 3-methoxalylchromone (800 mg, 3.45 mmol); **47j** was isolated as light-grey powder, yield = 750 mg (54%); mp = 142 - 144°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.27 (t, 2H, CH_2, ^3J = 6.4 Hz), 3.73 (s, 3H, OCH_3), 4.64 (t, 2H, CH_2, ^3J = 6.4 Hz), 6.91 (t, 1H, H-4', ^3J = 8.7 Hz), 7.02 (d, 1H, H-2', ^3J = 8.7 Hz), 7.26 (br. m, 6H, Ph, H-5'), 7.55 (t, 1H, H-3', ^3J = 8.7 Hz), 8.29 (s, 1H, H-4), 8.59 (s, 1H, H-2), 11.21 (s, 1H, OH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 34.8 (CH_2), 44.6 (CH_2), 52.5 (OCH_3), 117.5 (C-4"), 119.2 (C-6"), 121.7 (C-2"), 126.6 (C-4'), 127.3 (C-5), 128.4 (C-2', C-6'), 128.6 (C-3', C-5'), 131.3 (C-6), 132.1

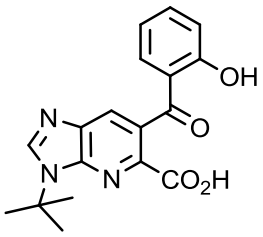
(C-3”), 135.8 (C-5”), 135.9 (C-4), 137.8 (C-1’), 140.8 (C-9), 146.6 (C-2), 149.6 (C-7), 160.0 (C-1”), 165.5 (*C*OOCH$_3$), 198.3 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 401 (16) [M$^+$], 370 (10), 342 (100), 238 (28), 207 (12), 104 (49), 91 (11).

HRMS (ESI): [M+H]$^+$ *m/z* calcd. for $C_{23}H_{19}N_3O_4$: 402.1448; found: 402.1455.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1716, 1628, 1609, 1453, 1379, 1292, 1242, 1142, 1123, 1056, 907, 759, 700, 618.

3-*tert*-Butyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylic acid (48a)



Starting from methyl 3-*tert*-Butyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (300 mg, 0.85 mmol) **47a**; **48a** was isolated as white crystals, yield = 201 mg (69%); mp = 289 - 291°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.83 (s, 9H, *t*-Bu), 6.88 (t, 1H, H-4’, ^3J = 9.2 Hz), 7.00 (d, 1H, H-2’, ^3J = 9.2 Hz), 7.29 (d, 1H, H-5’, ^3J = 9.2 Hz), 7.52 (t, 1H, H-3’, ^3J = 9.2 Hz), 8.23 (s, 1H, H-4), 8.76 (s, 1H, H-2), 11.41 (s, 1H, OH), 13.33 (s, 1H, COOH).

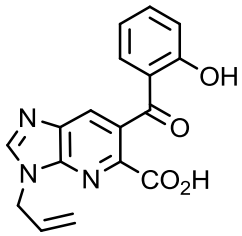
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.5 (CH_3), 57.5 (*C*(CH_3)$_3$), 117.4 (C-4’), 119.2 (C-6’), 121.3 (C-2’), 126.7 (C-5), 130.9 (C-6), 132.3 (C-3’), 135.9 (C-5’), 136.9 (C-4), 140.6 (C-9), 146.5 (C-2), 147.3 (C-7), 160.5 (C-1’), 166.5 (COOH), 199.3 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 321 (80), 294 (88), 266 (63), 237 (74), 220 (26), 205 (92), 190 (68), 177 (10), 145 (24), 117 (15), 1 57 (46).

HRMS (ESI): [M+H]$^+$ *m/z* calcd. for $C_{18}H_{17}N_3O_4$: 340.1292; found: 340.1296.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1689, 1682, 1609, 1469, 1345, 1295, 1210, 1149, 898, 750.

3-Allyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylic acid (48b)



Starting from methyl 3-allyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (300 mg, 0.89 mmol) **47b**; **48b** was isolated as white crystals, yield = 224 mg (75%); mp = 249 - 250°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 5.05 (d, 2H, CH_2, ^3J = 2.6 Hz), 5.10 (dd, 1H, CH_2 (trans), $^3J_1$ = 15.2 Hz, $^2J_2$ = 2.1 Hz), 5.28 (dd, 1H, CH_2 (cis), $^3J_1$ = 9.1 Hz, $^2J_2$ = 2.1 Hz), 6.20 (m, 1H, CH), 6.88 (t, 1H, H-4’, ^3J = 9.4 Hz), 7.03 (d, 1H, H-2’, ^3J = 9.4 Hz), 7.29 (d, 1H, H-5’, ^3J = 9.4

Hz), 7.54 (t, 1H, H-3', ^3J = 9.4 Hz), 8.30 (s, 1H, H-4), 8.79 (s, 1H, H-2), 11.42 (s, 1H, OH), 13.42 (s, 1H, COOH).

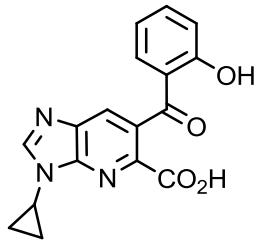
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 45.2 (CH_2), 117.5 (C-4'), 117.9 (CH_2), 119.2 (C-6'), 121.4 (C-2'), 127.0 (C-5), 131.4 (C-6), 132.3 (C-3'), 133.0 (CH), 135.6 (C-5'), 135.9 (C-4), 141.7 (C-9), 146.2 (C-2), 149.4 (C-7), 160.5 (C-1'), 166.3 (COOH), 199.2 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 305 (90), 276 (98), 260 (12), 250 (29), 237 (12), 156 (22), 92 (10), 41 (14).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{17}H_{13}N_3O_4$: 324.0979; found: 324.0979.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1633, 1613, 1488, 1445, 1354, 1244, 1186, 1151, 901, 764, 674.

3-Cyclopropyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylic acid (48c)



Starting from methyl 3-cyclopropyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (300 mg, 0.89 mmol) **47c**; **48c** was isolated as white crystals, yield = 249 mg (86%); mp = 276 - 277°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.22 (br. m, 4H, CH_2), 3.73 (m, 1H, CH), 6.88 (t, 1H, H-4', ^3J = 8.0 Hz), 7.02 (d, 1H, H-2', ^3J = 8.8 Hz), 7.27 (d, 1H, H-5', ^3J = 8.8 Hz), 7.54 (t, 1H, H-3', ^3J = 8.8 Hz), 8.25 (s, 1H, H-4), 8.76 (s, 1H, H-2), 11.42 (s, 1H, OH), 13.45 (s, 1H, COOH).

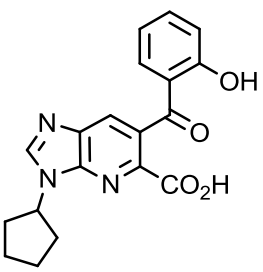
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 5.6 (CH_2), 25.6 (CH), 117.5 (C-4'), 119.2 (C-6'), 121.4 (C-2'), 126.9 (C-5), 131.4 (C-6), 132.3 (C-3'), 135.9 (C-5'), 136.1 (C-4), 141.8 (C-9), 147.6 (C-2), 149.4 (C-7), 160.5 (C-1'), 166.5 (COOH), 199.3 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 305 (91), 278 (78), 249 (34), 221 (13), 65 (10).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{17}H_{13}N_3O_4$: 324.0979; found: 324.0977.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1682, 1627, 1485, 1450, 1343, 1297, 1234, 1148, 1028, 895, 760, 708.

3-Cyclopentyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylic acid (48d)



Starting from methyl 3-cyclopentyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (300 mg, 0.82 mmol) **47d**; **48d** was isolated as white crystals, yield = 241 mg (82%); mp = 297 - 298°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.02 (br. m, 8H, CH_2), 5.12 (m, 1H, CH), 6.88 (t, 1H, H-4', ^{3}J = 9.0 Hz), 7.00 (d, 1H, H-2', ^{3}J = 9.0 Hz), 7.33 (d, 1H, H-5', ^{3}J = 9.0 Hz), 7.55 (t, 1H, H-3', ^{3}J = 9.0 Hz), 8.27 (s, 1H, H-4), 8.91 (s, 1H, H-2), 11.43 (s, 1H, OH), 13.32 (s, 1H, COOH).

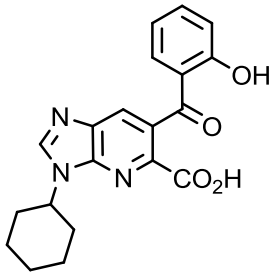
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 23.5 (CH_2), 32.1 (CH_2), 55.4 (CH), 117.4 (C-4'), 119.1 (C-6'), 121.4 (C-2'), 126.8 (C-5), 131.2 (C-6), 132.3 (C-3'), 135.9 (C-5', C-4), 141.3 (C-9), 146.3 (C-7), 147.9 (C-2), 160.5 (C-1'), 166.4 (COOH), 199.3 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 351 (11) [M^+], 332 (10), 292 (26), 282 (39), 171 (19), 69 (16).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{19}H_{17}N_3O_4$: 352.1292; found: 352.1292.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1693, 1626, 1486, 1453, 1344, 1293, 1227, 1148, 895, 763, 742, 670.

3-Cyclohexyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylic acid (48e)



Starting from methyl 3-cyclohexyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (300 mg, 0.79 mmol) **47e**; **48e** was isolated as white crystals, yield = 254 mg (87%); mp > 300°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.71 (br. m, 10H, CH_2), 4.61 (m, 1H, CH), 6.85 (t, 1H, H-4', ^{3}J = 8.9 Hz), 7.00 (d, 1H, H-2', ^{3}J = 8.9 Hz), 7.27 (d, 1H, H-5', ^{3}J = 8.9 Hz), 7.51 (t, 1H, H-3', ^{3}J = 8.9 Hz), 8.23 (s, 1H, H-4), 8.90 (s, 1H, H-2), 11.42 (s, 1H, OH).

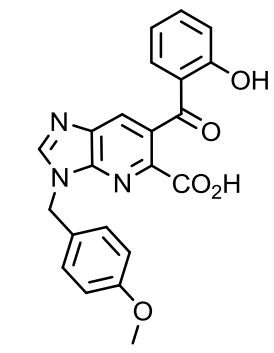
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 24.7 (CH_2), 25.1 (CH_2), 32.3 (CH_2), 53.4 (CH), 117.4 (C-4'), 119.1 (C-6'), 121.7 (C-2'), 127.6 (C-5), 131.4 (C-6), 132.1 (C-3'), 135.8 (C-5'), 135.9 (C-4), 140.8 (C-9), 146.3 (C-2), 147.6 (C-7), 160.0 (C-1'), 166.4 (COOH), 198.1 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 365 (10) [M^+], 332 (11), 306 (22), 244 (35), 184 (10), 83 (16), 59 (10).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{20}H_{19}N_3O_4$: 366.1448; found: 366.1452.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930, 1627, 1607, 1488, 1447, 1353, 1295, 1225, 1184, 1148, 895, 743, 670.

6-(2-Hydroxybenzoyl)-3-(4-methoxybenzyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylic acid (48f)



Starting from methyl 6-(2-hydroxybenzoyl)-3-(4-methoxybenzyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (300 mg, 0.72 mmol) **47f**; **48f** was isolated as white crystals, yield = 226 mg (88%); mp = 286 - 288°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.74 (s, 3H, OCH_3), 5.54 (s, 2H, CH_2), 6.87 (t, 1H, H-4'', ^{3}J = 9.2 Hz), 6.94 (d, 2H, H-2', H-6', ^{3}J = 5.7 Hz), 7.03 (d, 1H, H-2'', ^{3}J = 9.2 Hz), 7.28 (d, 1H, H-5'', ^{3}J = 9.2 Hz), 7.42 (d, 2H, H-3', H-5', ^{3}J = 5.7 Hz), 7.55 (t, 1H, H-3'', ^{3}J = 9.2 Hz), 8.29 (s, 1H, H-4), 8.89 (s, 1H, H-2), 11.40 (s, 1H, -OH), 13.43 (s, 1H, COOH).

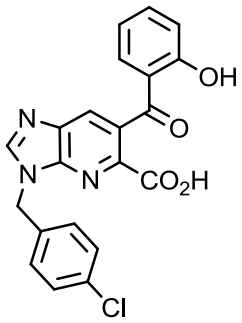
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 46.0 (CH_2), 55.1 (OCH_3), 114.1 (C-2', C-6'), 117.5 (C-4"), 119.2 (C-6"), 121.4 (C-2"), 127.0 (C-5), 128.5 (C-4'), 129.3 (C-3', C-5'), 131.4 (C-6), 132.4 (C-3"), 135.7 (C-5"), 135.9 (C-4), 141.6 (C-9), 146.2 (C-2), 149.3 (C-7), 158.9 (C-1'), 160.5 (C-1"), 166.3 (COOH), 199.2 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 403 (23) [M^+], 385 (70), 370 (11), 358 (97), 342 (16), 121 (82), 91 (12), 77 (15).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{22}H_{17}N_3O_5$: 404.1241; found: 404.1236.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1714, 1606, 1511, 1456, 1295, 1238, 1142, 1032, 911, 772, 739.

3-(4-Chlorobenzyl)-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylic acid (48g)



Starting from methyl 3-(4-chlorobenzyl)-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (300 mg, 0.71 mmol) **47g**; **48g** was isolated as white crystals, yield = 214 mg (74%); mp = 299 - 300°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ= 5.63 (s, 2H, CH_2), 6.88 (t, 1H, H-4'', ^{3}J = 9.0 Hz), 7.03 (d, 1H, H-2'', ^{3}J = 9.0 Hz), 7.30 (d, 1H, H-5'', ^{3}J = 9.0 Hz), 7.46 (m, 4H, H-3', H-2', H-5', H-6'), 7.54 (t, 1H, H-3'', ^{3}J = 9.0 Hz), 8.31 (s, 1H, H-4), 8.92 (s, 1H, H-2), 11.40 (s, 1H, OH).

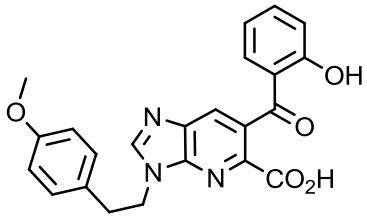
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 45.7 (CH_2), 117.4 (C-4"), 119.1 (C-6"), 121.3 (C-2"), 127.1 (C-5), 128.7 (C-2', C-6'), 129.6 (C-3', C-5'), 131.6 (C-6), 132.3 (C-3"), 132.6 (C-4'), 135.6 (C-5"), 135.7 (C-1'), 135.9 (C-4), 141.7 (C-9), 146.4 (C-2), 149.4 (C-7), 160.5 (C-1"), 166.2 (COOH), 199.1 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 389 (50), 360 (37), 250 (10), 207 (19), 125 (100), 99 (10), 89 (22), 63 (12).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{21}H_{14}ClN_3O_4$ 408.0746; found: 408.0746.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1705, 1622, 1605, 1489, 1383, 1242, 1195, 1143, 910, 774, 740, 726.

6-(2-Hydroxybenzoyl)-3-(4-methoxyphenethyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylic acid (48h):



Starting from methyl 6-(2-hydroxybenzoyl)-3-(4-methoxyphenethyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (300 mg, 0.70 mmol) **47h**; **48h** was isolated as white crystals, yield = 209 mg (73%); mp = 252 - 255°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.21 (t, 2 H, CH_2, ^{3}J = 6.3 Hz), 3.72 (s, 3H, OCH_3), 4.61 (t, 2H, CH_2, ^{3}J = 6.3 Hz), 6.84 (d, 2H, H-2',H-6', ^{3}J = 5.8 Hz), 6.90 (t, 1H, H-4'', ^{3}J = 9.0 Hz) , 7.03 (d, 1H, H-2'', ^{3}J = 9.0 Hz), 7.10 (d, 2H, H-3', H-5', ^{3}J = 5.8 Hz), 7.27 (d, 1H, H-5'', ^{3}J = 9.0 Hz), 7.55 (t, 1H, H-3'', ^{3}J = 9.0 Hz), 8.26 (s, 1H, H-4), 8.57 (s, 1H, H-2), 11.46 (s, 1H, OH).

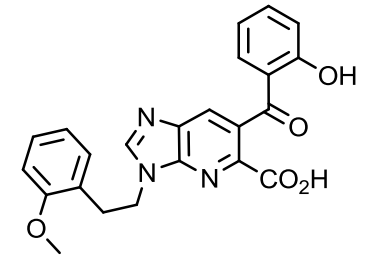
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 33.9 (CH_2), 44.9 (CH_2), 54.9 (OCH_3), 113.8 (C-2', C-6'), 117.5 (C-4"), 119.1 (C-6"), 121.3 (C-2"), 126.8 (C-5), 129.6 (C-3', C-5'), 129.6 (C-4'), 131.2 (C-6), 132.3 (C-3"), 135.7 (C-5"), 135.9 (C-4), 141.3 (C-9), 146.3 (C-2), 149.4 (C-7), 157.9 (C-1'), 160.5 (C-1"), 166.3 (COOH), 199.4 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 390 (27), 282 (20), 247 (52), 224 (10), 162 (82), 135 (95), 58 (14).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{23}H_{19}N_3O_5$: 418.1397; found: 418.1399.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1626, 1610, 1512, 1453, 1361, 1294, 1242, 1184, 1145, 1032, 893, 759, 713, 609.

6-(2-Hydroxybenzoyl)-3-(2-methoxyphenethyl)-3*H*-imidazo[4,5-b]pyridine-5-carboxylic acid (48i):



Starting from methyl 6-(2-hydroxybenzoyl)-3-(2-methoxyphenethyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (300 mg, 0.70 mmol) **47i**; **48i** was isolated as white crystals, yield = 243 mg (81%); mp = 240 - 241°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.19 (t, 2 H, CH_2, ^{3}J = 6.4 Hz), 3.67 (s, 3H, OCH_3), 4.59 (t, 2 H, CH_2, ^{3}J = 6.4 Hz), 6.77 (t, 1H, H-4', ^{3}J = 6.0 Hz), 6.92 (br.m, 4H, H-4''H-2', H-5',H-2"), 7.18 (m, 2H, H-3', H-5"), 7.53 (t, 1H, H-3'', ^{3}J = 9.1 Hz), 8.21 (s, 1H, H-4), 8.46 (s, 1H, H-2), 11.43 (s, 1H, OH), 13.37 (s, 1H, COOH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 30.1 (CH_2), 43.2 (CH_2), 55.5 (OCH_3), 110.6 (C-4'), 117.5 (C-4"), 119.1 (C-6"), 120.1 (C-6'), 121.3 (C-2"), 125.5 (C-2'), 126.6 (C-5), 128.1 (C-2'), 130.0 (C-3'),

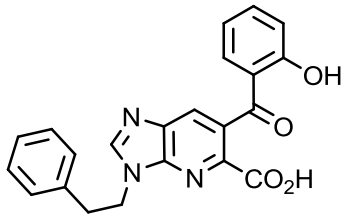
131.0 (C-6), 132.2 (C-3”), 135.6 (C-5”), 135.9 (C-4), 141.3 (C-9), 146.5 (C-2), 149.3 (C-7), 157.2 (C-1’), 160.5 (C-1”), 166.4 (COOH), 199.4 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 417 (12) [M^+], 357 (61), 324 (15), 296 (20), 221 (13), 135 (96), 105 (18), 44 (10).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{23}H_{19}N_3O_5$: 418.1397; found: 418.1400.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1632, 1485, 1453, 1296, 1235, 1181, 1147, 1035, 752, 710.

6-(2-Hydroxybenzoyl)-3-phenethyl-3*H*-imidazo[4,5-b]pyridine-5-carboxylic acid (48j):



Starting from methyl 6-(2-hydroxybenzoyl)-3-phenethyl-3*H*-imidazo[4,5-b]pyridine-5-carboxylate (300 mg, 0.75 mmol) **47j**; **48j** was isolated as white crystals, yield = 261 mg (90%); mp = 229 - 231°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.29 (t, 2H, CH_2, ^3J = 6.3 Hz), 4.66 (t, 2H, CH_2, ^3J = 6.3 Hz), 6.89 (t, 1H, H-4’, ^3J = 8.6 Hz), 7.05 (d, 1H, H-2’, ^3J = 8.6 Hz), 7.25 (br. m, 6H, Ph, H-5’), 7.55 (t, 1H, H-3’, ^3J = 8.6 Hz), 8.26 (s, 1H, H-4), 8.59 (s, 1H, H-2), 11.45 (s, 1H, OH), 13.38 (s, 1H, -COOH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 34.8 (CH_2), 44.5 (CH_2), 117.5 (C-4”), 119.1 (C-6”), 121.3 (C-2”), 126.5 (C-4’), 126.8 (C-5), 128.4 (C-2’, C-6’), 128.6 (C-3’, C-5’), 131.2 (C-6), 132.3 (C-3”), 135.7 (C-5”), 135.9 (C-4), 137.8 (C-1’), 141.3 (C-9), 146.3 (C-2), 149.3 (C-7), 160.5 (C-1”), 166.3 (COOH), 199.3 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 369 (44), 237 (10), 104 (100), 91 (12).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{22}H_{17}N_3O_4$: 388.1292; found: 388.1298.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1625, 1483, 1454, 1360, 1290, 1254, 1184, 1145, 894, 701, 611.

1.2.2 Supplement to paragraph 3

General Procedure for the Synthesis of Compounds 52a-d, 54, 56.

To a Schlenk flask, set with reflux, CH_2Cl_2 (2.5 mL) 4-methoxybenzylamine amine (754 mg, 5.5 mmol), and methyl N-(cyanomethyl)-formimidate (490 mg, 5.5 mmol) were added under an argon atmosphere at r.t. The reaction mixture was refluxed during 1 h 20 min and after that, the mixture was cooled down to room temperature. 1,3-Dicarbonyl compound was added, and the mixture continued to stir at the same temperature for 15–20 min and then refluxed for 7 h. The solvent was evaporated to

dryness and the residue was purified by column chromatography to give the desired compound. In case of **54**, the resulting mixture was refluxed for 2.5 h and formed precipitate of **54** was then filtered.

General Procedure for the Synthesis of Compound 55

To a Schlenk flask, set with reflux, CH_2Cl_2 (2.5 mL) 4-methoxybenzylamine amine (754 mg, 5.5 mmol), and methyl N-(cyanomethyl)-formimidate (490 mg, 5.5 mmol) were added under an argon atmosphere at r.t. The reaction mixture was refluxed during 1 h 20 min and after that, the mixture was cooled down to room temperature. 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (1.43 g, 5 mmol) was added, and the mixture continued to stir at the same temperature for 15–20 min and then refluxed for 5 h. The solvent was evaporated to dryness and the residue was purified by column chromatography to give the desired compound.

General Procedure for the Synthesis of Compound 53a-d, 57, 58

1.00 g of N-substituted purine isostere were dissolved in 30 ml of trifluoroacetic acid and stirred overnight at room temperature (**53a, 58**) or at 60°C (others). After the deprotection was proceeded (TLC control), the solvent was evaporated under reduced pressure, and the obtained solid was recrystallized from 2-propanol. The precipitate formed, was filtered, washed with chloroform and dried to give the corresponding unprotected purine (1-desazapurine) as white crystals.

General Procedure for the Synthesis of Compounds 59a-d, 60, 61a-c, 62, 63, 64a-c, 65, 66

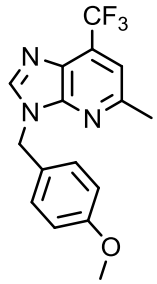
To a suspension of 300 mg of deprotected imidazo-[4,5-b]-pyridine or purine in 6 ml of dry acetonitrile 1.1 equiv. of BSA was added under argon atmosphere. The obtained clear solution was refluxed during 20 minutes and then was led to cool down to room temperature. Afterwards, the solution of 1 equiv. of corresponding acetylated sugar in dry acetonitrile and TMSOTf (0.25 eq.) were added and the reaction mixture was refluxed for 2 hours (till the color of solution has become yellow-orange). The solvent and liquid byproducts were evaporated to dryness and the residue was purified by column chromatography to give the desired glycosilated compound.

General Procedure for the Synthesis of Compounds 67a-d, 68, 69a-c, 70, 71, 72a-c, 73, 74

1 mmol of corresponding acetylated glycoside were dissolved in 15 ml of 7M ammonia solution in methanol and stirred at room temperature overnight. As the starting material completely

transformed (monitored by TLC), the solvent was evaporated and the residue was purified by sublimation of acetamide under vacuum. In case of non-complete purification, the residue was purified by column chromatography (EtOAc : i-PrOH = 5:1) to give the crude product.

3-(4-Methoxybenzyl)-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (52a)



Starting from 4-methoxybenzylamine (754 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 1,1,1-trifluoropentane-2,4-dione (770 mg, 5 mmol); **52a** was isolated as white crystals, yield = 1.09 g (68%); mp = 104 - 105°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.66 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 5.32 (s, 2H, CH_2), 6.80 (d, 2H, H-2', H-6', ^3J = 5.4 Hz), 7.20 (d, 2H, H-3', H-5', ^3J = 5.4 Hz), 7.26 (s, 1H, H-5), 7.96 (s, 1H, H-2).

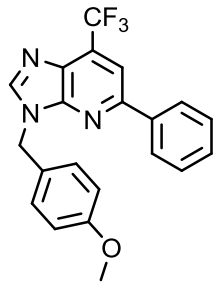
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 24.6 (CH_3), 46.78 (CH_2), 55.3 (OCH_3), 114.4 (C-2', C-6', C-5), 122.9 (q, CF_3, $^1J_{(C-F)}$= 273.2 Hz), 127.5 (C-4'), 128.6 (q, C-4, $^2J_{(C-F)}$= 33.2 Hz), 129.3 (C-3', C-5', C-6), 144.6 (C-2), 148.0 (C-3a), 154.2 (C-7a), 159.7 (C-1').

GC-MS (EI, 70 eV): *m/z* (%): 321 (70) [M^+], 306 (12), 121 (100), 77 (15).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{16}H_{14}F_3N_3O$: 321.0801; found: 321.0797.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1613, 1510, 1397, 1365, 1289, 1152, 1122, 1104, 1027, 871, 817, 762.

3-(4-Methoxybenzyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (52b)



Starting from 4-methoxybenzylamine (754 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 3-benzoyl-1,1,1-trifluoroacetone (1.08 g, 5 mmol); **52b** was isolated as white crystals, yield = 1.55 g (81%); mp = 143 - 144°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.82 (s, 3 H, OCH_3), 5.55 (s, 2H, CH_2), 6.93 (d, 2H, H-2', H-6', ^3J = 5.1Hz), 7.41 (d, 2H, H-3', H-5', ^3J = 5.1 Hz), 7.54 (br. m, 3H, Ph), 7.99 (s, 1H, H-5), 8.15 (m, 2H, Ph), 8.33 (s, 1H, H-2).

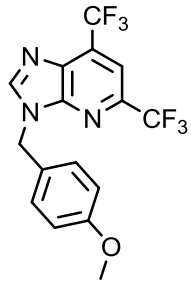
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 47.1 (CH_2), 55.3 (OCH_3), 111.9 (q, C-5, $^3J_{(C-F)}$= 2.1 Hz), 114.5 (C-2', C-6'), 123.7 (q, CF_3, $^1J_{(C-F)}$= 276.7 Hz), 127.2 (C-4"), 127.4 (C-4'), 128.9 (C-3', C-5'), 129.4 (C-3", C-5"), 129.5 (C-1"), 129.5 (q, C-4, $^2J_{(C-F)}$= 34.6 Hz), 129.7 (C-2", C-6"), 138.41 (C-6), 145.5 (C-2), 148.3 (C-3a), 153.1 (C-7a), 159.8 (C-1').

GC-MS (EI, 70 eV): *m/z* (%): 383 (78) [M^+], 368 (10), 121 (100), 77 (11).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{21}H_{16}F_3N_3O$: 383.1240; found: 383.1238.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3068, 1609, 1511, 1374, 1244, 1162, 1156, 1129, 1031, 874, 760, 632.

3-(4-Methoxybenzyl)-5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (52c)



Starting from 4-methoxybenzylamine (754 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 1,1,1,5,5,5-hexafluoropentane-2,4-dione (1.04 g, 5 mmol); **52c** was isolated as yellow crystals, yield = 1.09 g (58%); mp = 114 - 115°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.72 (s, 3H, OCH_3), 5.40 (s, 2H, CH_2), 6.82 (d, 2H, H-2', H-6', ^3J = 8.7 Hz), 7.25 (d, 2H, H-3', H-5', ^3J = 8.7 Hz), 7.80 (s, 1H, H-5), 8.22 (s, 1H, H-2).

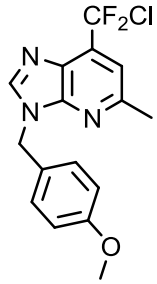
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 47.6 (CH_2), 55.3 (OCH_3), 111.5 (C-5), 114.6 (C-2', C-6'), 121.5 (q, CF_3, $^1J_{(C-F)}$= 274.0 Hz), 122.2 (q, CF_3, $^1J_{(C-F)}$= 274.0 Hz), 126.4 (C-4'), 129.5 (q, C-4, $^2J_{(C-F)}$= 35.5 Hz), 129.9 (C-3', C-5'), 133.4 (C-3a), 142.8 (q, C-6, $^2J_{(C-F)}$= 36.2 Hz), 148.0 (C-7a), 148.2 (C-2), 160.0 (C-1').

GC-MS (EI, 70 eV): *m/z* (%): 375 (77) [M^+], 360 (10), 121 (100), 78 (12).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{16}H_{11}F_6N_3O$: 375.0801; found: 375.0797.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3069, 1612, 1513, 1391, 1256, 1173, 1127, 1098, 1034, 880, 749, 655, 632.

7-[Chloro(difluoro)methyl]-3-(4-methoxybenzyl)-5-methyl-3*H*-imidazo[4,5-*b*]pyridine (52d)



Starting from 4-methoxybenzylamine (754 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 1-chloro-1,1-difluoropentane-2,4-dione (0.850 mg, 5 mmol); **52d** was isolated as yellow oil, yield = 1.23 g (73%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.66 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 5.32 (s, 2H, CH_2), 6.80 (d, 2H, H-2', H-6', ^3J = 8.7 Hz), 7.20 (d, 2H, H-3', H-5', ^3J = 8.7 Hz), 7.23 (s, 1H, H-5), 7.97 (s, 1H, H-2).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 24.6 (CH_3), 46.8 (CH_2), 55.3 (OCH_3), 112.9 (C-5), 113.1 (C-2', C-6'), 124.3 (t, CF_2Cl, $^1J_{(C-F)}$= 290.6 Hz), 127.5 (C-4'), 128.1 (C-3a), 128.9 (C-3', C-5'), 133.8 (t, C-4, $^2J_{(C-F)}$= 28.3 Hz), 144.3 (C-2), 148.1 (C-6), 154.2 (C-7a), 159.7 (C-1').

GC-MS (EI, 70 eV): *m/z* (%): 337 (41) [M^+], 302 (10), 121 (100).

HRMS (ESI): [M]$^+$ *m/z* calcd. for $C_{16}H_{14}OClF_2N_3$: 337.0788; found: 337.0789.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2910, 1626, 1499, 1365, 1288, 1067, 912, 885, 824, 702, 642.

5-Methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (53a)

Starting from 3-(4-methoxybenzyl)-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (1.00 g, 3.12 mmol) **52a**; **53a** was isolated as white crystals, yield = 376 mg (60%); mp = 243 - 244°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.64 (s, 3H, CH_3), 7.44 (s, 1H, H-5), 8.56 (s, 1H, H-2), 13.42 (s, 1H, NH).

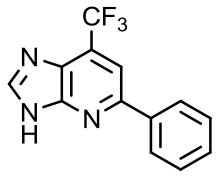
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 23.8 (CH_3), 113.0 (q, C-5, $^3J_{(C-F)}$ = 3.8 Hz), 123.0 (q, CF_3, $^1J_{(C-F)}$ = 273.6 Hz), 145.1 (C-6), 153.1 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 201 (100) [M^+], 180 (11), 154 (10), 132 (21).

HRMS (ESI): [M+H]$^+$ *m/z* calcd. for $C_8H_6F_3N_3$: 202.0587; found: 202.0588.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2759, 1613, 1418, 1386, 1360, 1243, 1118, 1029, 951, 892, 865, 811, 667, 632.

5-Phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (53b)



Starting from 3-(4-methoxybenzyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (1.00 g, 2.61 mmol) **52b**; **53b** was isolated as white crystals, yield = 577 mg (84%); mp = 262 - 264°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 7.50 (br.m, 3H, Ph), 8.08 (s, 1H, H-5), 8.20 (m, 2H, Ph), 8.69 (s, 1H, H-2), 13.72 (s, 1H, NH).

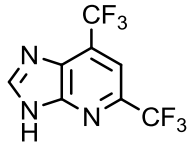
^{13}C MR (62.90 MHz, DMSO-d_6): δ = 110.6 (q, C-5, $^3J_{(C-F)}$ = 2.1 Hz), 123.3 (q, CF_3, $^1J_{(C-F)}$ = 273.3 Hz), 126.8 (C-4'), 128.8 (C-3', C-5'), 129.0 (C-1'), 129.1 (C-2', C-6'), 138.0 (C-6), 146.4 (C-2), 149.4 (C-3a), 151.5 (C-7a).

GC-MS (EI, 70 eV): *m/z* (%): 263 (100) [M^+], 242 (10).

HRMS (ESI): [M+H]$^+$ *m/z* calcd. for $C_{13}H_8F_3N_3$: 263.0665; found: 263.0666.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2783, 1472, 1384, 1260, 1183, 111, 865, 768, 614.

5,7-Bis(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (53c)



Starting from 3-(4-methoxybenzyl)-5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (1.00 g, 2.65 mmol) **52c**; **53c** was isolated as white crystals, yield = 331 mg (49%); mp = 222 - 224°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 8.06 (s, 1H, H-5), 9.01 (s, 1H, H-2), 14.20 (s, 1H, NH).

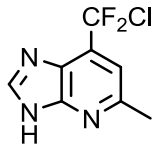
^{13}C NMR (125.76 MHz, DMSO-d_6): δ = 110.3 (C-5), 121.5 (q, CF_3, $^1J_{(C-F)}$= 271.4 Hz), 122.2 (q, CF_3, $^1J_{(C-F)}$= 273.1 Hz), 140.4 (C-6, q, $^2J_{(C-F)}$= 34.7Hz), 149.8 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 255 (100) [M^+], 236 (31), 205 (20), 186 (12), 166 (13), 69 (18).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_8H_3F_6N_3$: 256.0304; found: 256.0306.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1481, 1381, 1345, 1273, 1253, 1127, 1109, 983, 878, 729, 655.

7-[Chloro(difluoro)methyl]-5-methyl-3*H*-imidazo[4,5-*b*]pyridine (53d)



Starting from 7-[chloro(difluoro)methyl]-3-(4-methoxybenzyl)-5-methyl-3*H*-imidazo[4,5-*b*]pyridine (1.00 g, 2.97 mmol) **52d**; **53d** was isolated as white crystals, yield = 419 mg (65%); mp = 211 - 212°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.66 (s, 3H, CH_3), 7.42 (s, 1H, H-5), 8.55 (s, 1H, H-2), 13.33 (br.s, 1H, NH).

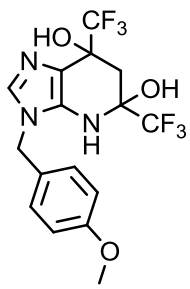
^{13}C NMR (62.90 MHz, DMSO-d_6), d= 23.9 (CH_3), 111.7 (t, C-5, $^3J_{(C-F)}$= 5.7 Hz), 124.5 (t, CF_2Cl, $^1J_{(C-F)}$= 290.0 Hz), 144.9 (C-6), 153.1 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 217 (38) [M^+], 182 (100), 128 (10).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_8H_6ClF_2N_3$: 217.0213; found: 217.0212.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2806, 1613, 1406, 1380, 1273, 1126, 1086, 997, 902, 884, 632.

3-(4-Methoxybenzyl)-5,7-bis(trifluoromethyl)-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*b*]pyridine-5,7-diol (54)



Starting from 4-methoxybenzylamine (754 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 1,1,1,5,5,5-hexafluoropentane-2,4-dione (1.04 g, 5 mmol); **54** was isolated as white crystals, yield = 1.07 g (52%); mp – dec.;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.06 (d, 1H, H-5a, ^{1}J = 13.8 Hz), 2.34 (d, 1H, H-5b, ^{1}J = 13.8 Hz), 3.75 (s, 3H, OCH_3), 5.04 (d, 1H, CH_2-a, ^{1}J = 15.3 Hz), 5.18 (d, 1H, CH_2-b, ^{1}J = 15.3 Hz), 6.33 (s, 1H, OH), 6.70 (s, 1H, NH), 6.75 (s, 1H, OH), 6.93 (d, 2H, H-2', H-6', ^{3}J = 8.7 Hz), 7.23 (d, 2H, H-3', H-5', ^{3}J = 8.7Hz), 7.25 (s, 1H, H-2).

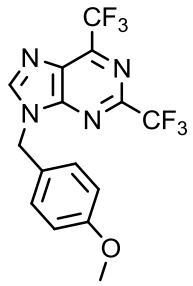
^{13}C NMR (125.76 MHz, DMSO-d_6): δ = 34.4 (C-5), 45.5 (CH_2), 55.0 (OCH_3), 68.5 (q, C-4, $^{2}J_{(C-F)}$ = 28.9 Hz), 81.0 (q, C-6, $^{2}J_{(C-F)}$ = 28.9 Hz), 113.5 (C-3a, m), 114.1 (C-2', C-6'), 123.79 (q, CF_3, $^{1}J_{(C-F)}$ = 285.5 Hz), 125.4 (q, CF_3, $^{1}J_{(C-F)}$ = 285.5 Hz), 128.8 (C-4'), 129.5 (C-3', C-5'), 131.5 (C-2), 134.3 (C-7a), 158.7 (C-1').

GC-MS (EI, 70 eV): *m/z* (%): 375 (89), 121 (100), 91 (10), 77 (14).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{16}H_{16}F_6N_3O_3$: 412.1090; found: 412.1082.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3274, 2964, 2698, 1615, 1515, 1279, 1248, 1176, 1137, 1082, 1028, 942, 805, 645 cm^{-1}

9-(4-Methoxybenzyl)-2,6-bis(trifluoromethyl)-9*H*-purine (55)



Starting from 4-methoxybenzylamine (754 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (1.43 g, 5 mmol); **55** was isolated as white crystals, yield = 1.43 g (76%); mp = 162 - 163°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.73 (s, 3 H, OCH_3), 5.41 (s, 2H, CH_2), 6.84 (d, 2H, H-2', H-6', ^{3}J = 5.7 Hz), 7.26 (d, 2H, H-3', H-5', ^{3}J = 5.7 Hz), 8.27 (s, 1H, H-8).

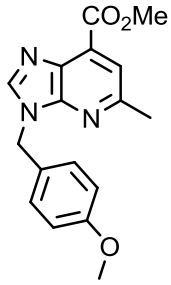
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 47.9 (CH_2), 55.3 (OCH_3), 114.8 (C-2', C-6'), 119.5 (q, CF_3, $^{1}J_{(C-F)}$ = 274.9 Hz), 120.2 (q, CF_3, $^{1}J_{(C-F)}$ = 276.1 Hz), 125.5 (C-4'), 129.9 (C-3', C-5'), 131.2 (C-5), 145.5 (q, C-6, $^{2}J_{(C-F)}$= 38.2 Hz), 149.2 (C-8), 149.8 (q, C-2, $^{2}J_{(C-F)}$= 37.6 Hz), 154.0 (C-4), 160.3 (C-1').

GC-MS (EI, 70 eV): *m/z* (%): 376 (43) [M^+], 256 (27), 121 (100), 69 (39).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{15}H_{10}F_6N_4O$: 376.0758; found: 376.0753.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1607, 1586, 1519, 1345, 1311, 1250, 1234, 1096, 976, 613.

Methyl 3-(4-methoxybenzyl)-5-methyl-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (56)



Starting from 4-methoxybenzylamine (754 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and methyl 2,4-dioxopentanoate (0.720 mg, 5 mmol); **56** was isolated as yellow crystals, yield = 949 mg (61%); mp = 91 - 93°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.66 (s, 3H, CH_3), 3.72 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 5.35 (s, 2H, CH_2), 6.80 (d, 2H, H-2', H-6', ^3J = 6.0Hz), 7.18 (d, 2H, H-3', H-5', ^3J = 6.0 Hz), 7.63 (s, 1H, H-5), 8.02 (s, 1H, H-2).

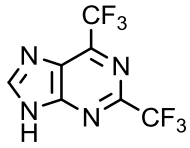
^{13}C NMR (62.90 MHz, $CDCl_3$), d= 24.3 (CH_3), 46.8 (CH_2), 52.7 (OCH_3), 55.2 (OCH_3), 114.3 (C-2', C-6'), 119.3 (C-5), 127.4 (C-4'), 128.2 (C-4), 129.4 (C-3', C-5'), 129.9 (C-6), 145.2 (C-2), 148.0 (C-3a), 154.3 (C-7a), 159.6 (C-1'), 165.7 (*C*$OOCH_3$).

GC-MS (EI, 70 eV): *m/z* (%): 311 (69) [M^+], 296 (18), 280 (11), 121 (100), 77 (14).

HRMS (ESI): $[M]^+$ *m/z* calcd. for $C_{17}H_{17}N_3O_3$: 311.1264; found: 311.1256.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2494, 1729, 1694, 1512, 1503, 1435, 1376, 1281, 1243, 1035, 990, 764.

2,6-Bis(trifluoromethyl)-9*H*-purine (57)



Starting from Methyl 3-(4-methoxybenzyl)-5-methyl-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (1.00 g, 2.66 mmol) **55**; **57** was isolated as white crystals, yield = 327 mg (48%); mp = 207 - 209°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 9.16 (s, 1H, H-8), 14.66 (br.s., 1H, NH).

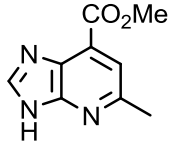
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 119.6 (q, CF_3, $^1J_{(C-F)}$ = 274.2 Hz), 120.3 (q, CF_3, $^1J_{(C-F)}$ = 274.2 Hz), 147.5 (q, C-2, $^2J_{(C-F)}$ = 37.1Hz), 151.9 (C-8).

GC-MS (EI, 70 eV): *m/z* (%): 256 (100) [M^+], 237 (22), 206 (14), 187 (40), 69 (43).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_7H_3F_6N_4$: 257.0256; found: 257.0257.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1500, 1412, 1378, 1253, 1114, 1003, 987, 919, 833, 632.

Methyl 5-methyl-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (58)



Starting from 9-(4-methoxybenzyl)-2,6-bis(trifluoromethyl)-9*H*-purine (1.00 g, 3.22 mmol) **56**; **58** was isolated as brown crystals, yield = 332 mg (54%); mp = 242 - 243°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.69 (s, 3H, CH_3), 4.03 (s, 3H, OCH_3), 7.67 (s, 1H, H-5), 8.75 (s, 1H, H-2), 12.56 (s, 1H, -NH).

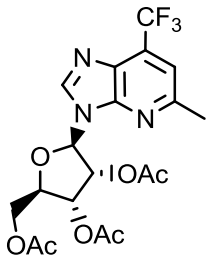
^{13}C NMR (62.90 MHz, DMSO-d_6), δ = 23.7 (CH_3), 52.7 (OCH_3), 117.4 (C-5), 121.7 (C-4), 122.5 (C-6), 147.7 (C-3a), 153.1 (C-2), 154.8 (C-7a), 164.6 (*C*$OOCH_3$).

GC-MS (EI, 70 eV): *m/z* (%): 191 (100) [M^+], 159 (20), 132 (21), 104 (10), 78 (11).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_9H_9N_3O_2$: 192.0768; found: 192.0773.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1721, 1475, 1438, 1324, 1239, 1124, 1051, 892, 762.

3-(Triacetyl-β-D-ribofuranosyl)-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (59a)



Starting from 5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (300 mg, 1.49 mmol) **53a** and tetraacetyl-β-D-ribofuranose (475 mg, 1.49 mmol); **59a** was isolated as white oil, yield = 417 mg (61%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.02 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO), 2.67 (s, 3H, CH_3), 4.30 (dd, 1H, CH_2-a, $^{3}J_1$ = 5.6Hz, $^{3}J_2$ = 3.1Hz), 4.40 (m, 2H, CH_2-b, H-5'), 5.74 (t, 1H, H-4', ^{3}J = 5.1Hz), 5.99 (t, 1H, H-3', ^{3}J = 5.4Hz), 6.18 (d, 1H, H-2', ^{3}J = 4.8Hz), 7.32 (s, 1H, H-5), 8.21 (s, 1H, H-2).

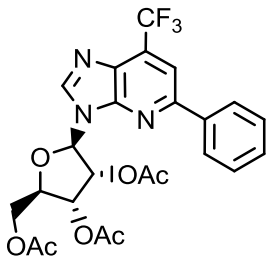
^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 20.4 (*C*H_3CO), 20.5 (*C*H_3CO), 20.7 (*C*H_3CO), 24.4 (CH_3), 63.1 (CH_2), 70.6 (C-5'), 73.0 (C-4'), 80.1 (C-3'), 86.9 (C-2'), 115.3 (d, C-5, $^{3}J_{(C-F)}$= 3.8Hz), 122.6 (q, CF_3, $^{1}J_{(C-F)}$= 274.2 Hz), 129.2 (q, C-4, $^{2}J_{(C-F)}$ = 33.9 Hz), 129.7 (C-6), 143.5 (C-2), 146.9 (C-3a), 155.1 (C-7a), 169.3 (C=O), 169.5 (C=O), 170.3 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 460 (32) [$(M+H)^+$], 306 (10), 259 (79), 244 (10), 157 (14), 139 (100), 97 (42), 43 (78).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{19}H_{21}F_3N_3O_6$: 460.1332; found: 460.1334.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1733, 1550, 1481, 1390, 1331, 1277, 1081, 968, 870.

3-(Triacetyl-β-D-ribofuranosyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (59b)



Starting from 5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (300 mg, 1.14 mmol) **53b** and tetraacetyl-β-D-ribofuranose (363 mg, 1.14 mmol); **59b** was isolated as white oil, yield = 398 mg (67%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.93 (s, 3H, CH_3CO),2.12 (s, 3H, CH_3CO), 2.18 (s, 3H, CH_3CO),4.34 (dd, 1H, CH_2-a, J_1 = 6.0Hz, J_2 = 3.0Hz), 4.47 (br. m, 2H, CH_2-b, H-5'), 5.85 (t, 1H, H-4', ^{3}J=5.1Hz), 6.21 (t, 1H, H-3', ^{3}J=5.1Hz), 6.31 (d, 1H, H-2', ^{3}J = 4.8Hz), 7.54 (br. m, 3H, Ph), 7.98 (s, 1H, H-5), 8.10 (d, 2H, Ph, ^{3}J = 9.3Hz), 8.90 (s, 1H, H-2).

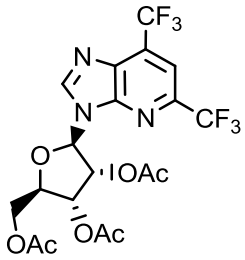
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 20.4 (CH_3CO), 20.5 (CH_3CO), 20.5 (CH_3CO), 62.6 (CH_2), 70.1 (C-5'), 73.09 (C-4'), 79.8 (C-3'), 87.3 (C-2'), 112.8 (q, C-5, $^{3}J_{(C-F)}$ = 3.0Hz), 122.6 (q, CF_3, $^{1}J_{(C-F)}$ = 272.4Hz), 127.5 (C-4"), 129.1 (C-3", C-5"), 129.6 (C-2", C-6"), 129.8 (q, C-4, $^{2}J_{(C-F)}$ = 29.1Hz), 130.9 (C-1"), 138.1 (C-6), 144.7 (C-2), 147.6 (C-3a), 154.0 (C-7a), 169.4 (C=O), 169.5 (C=O), 170.4 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 521 (32) [M^+], 306 (10), 259 (79), 244 (10), 157 (14), 139 (100), 97 (42), 43 (78).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{24}H_{23}F_3N_3O_7$: 522.1488; found: 522.1485.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1721, 1630, 1589, 1463, 1402, 1359, 1242, 1056, 761, 623.

3-(Triacetyl-β-D-ribofuranosyl)-5,7-Bis(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (59c)



Starting from 5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (300 mg, 1.18 mmol) **53c** and tetraacetyl-β-D-ribofuranose (374 mg, 1.14 mmol); **59c** was isolated as white oil, yield = 272 mg (45%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.02 (s, 3H, CH_3CO),2.03 (s, 3H, CH_3CO),2.11 (s, 3H, CH_3CO), 4.39 (br. m, 3H, CH_2, H-5'), 5.61 (t, 1H, H-4', ^{3}J = 5.1Hz), 5.83 (t, 1H, H-3', ^{3}J = 5.4 Hz), 6.25 (d, 1H, H-2', ^{3}J = 5.1Hz), 7.85 (s, 1H, H-5), 8.45 (s, 1H, H-2).

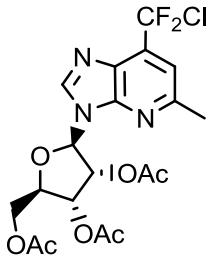
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 20.3 (CH_3CO), 20.5 (CH_3CO), 20.7 (CH_3CO), 63.0 (CH_2), 70.6 (C-5'), 73.4 (C-4'), 80.7 (C-3'), 87.3 (C-2'), 112.3 (C-5), 121.2 (q, CF_3,$^{1}J_{(C-F)}$ = 274.2Hz), 121.9 (q, CF_3, $^{1}J_{(C-F)}$ = 274.2 Hz), 130.3 (q, C-4, $^{2}J_{(C-F)}$ = 35.2 Hz), 134.2 (C-3a), 143.2 (q, C-6, $^{2}J_{(C-F)}$ = 35.9 Hz), 147.1 (C-2, C-7a).

GC-MS (EI, 70 eV): *m/z* (%): 411 (10), 351 (65), 334 (41), 256 (72), 236 (17), 156 (18), 139 (73), 97 (34).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{19}H_{18}F_6N_3O_7$: 514.1049; found: 514.1053.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1734, 1482, 1406, 1389, 1346, 1284, 1238, 1076, 911, 866, 623, 592.

3-(Triacetyl-β-D-ribofuranosyl)-7-[chloro(difluoro)methyl]-5-methyl-3*H*-imidazo[4,5-b]pyridine (59d)



Starting from 5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (300 mg, 1.38 mmol) **53d** and tetraacetyl-β-D-ribofuranose (439 mg, 1.38 mmol); **59d** was isolated as white oil, yield = 505 mg (77%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.01 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3CO),2.08 (s, 3H, CH_3CO),2.66 (s, 3H, CH_3), 4.39 (m, 3H, CH_2, H-5'), 5.75 (t, 1H, H-4', ^{3}J = 5.1 Hz), 6.00 (t, 1H, H-3', ^{3}J = 5.1 Hz), 6.18 (d, 1H, H-2', ^{3}J = 4.8 Hz), 7.27 (s, 1H, H-5), 8.19 (s, 1H, H-2).

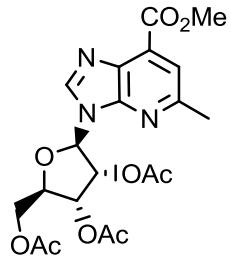
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 20.4 (*CH*$_3$CO), 20.5 (*CH*$_3$CO), 20.7 (*CH*$_3$CO), 24.2 (CH_3), 63.1 (CH_2), 70.6 (C-5'), 72.9 (C-4'), 80.1 (C-3'), 86.8 (C-2'), 113.7 (t, C-5, $^{3}J_{(C-F)}$= 5.0Hz), 123.9 (t, CF_2Cl, $^{1}J_{(C-F)}$= 291.2Hz), 129.0 (C-6), 134.5 (t, C-4, $^{2}J_{(C-F)}$ = 28.3Hz), 143.3 (C-2), 147.1 (C-3a), 154.9 (C-7a), 169.3 (C=O), 169.5 (C=O), 170.3 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 475 (11) [M^+], 416 (10), 296 (14), 259 (68), 218 (93), 182 (32), 139 (100), 97 (49).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{19}H_{21}ClF_2N_3O_6$: 476.1036; found: 476.1039.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927, 1744, 1596, 1488, 1371, 1206, 1093, 1044, 964, 820.

Methyl 3-(Triacetyl-β-D-ribofuranosyl)-5-methyl-3*H*-imidazo[4,5-b]pyridine-7-carboxylate (60)



Starting from methyl 5-methyl-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (300 mg, 1.57 mmol) **58** and tetraacetyl-β-D-ribofuranose (499 mg, 1.38 mmol); **60** was isolated as yellow oil, yield = 289 mg (41%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.00 (s, 3H, CH_3CO),2.02 (s, 3H, CH_3CO),2.08 (s, 3H, CH_3CO), 2.66 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 4.32 (dd, 1H, CH_2-a, $^{3}J_1$ = 6.9 Hz, $^{3}J_2$ = 6.0 Hz), 4.40 (m, 2H, CH_2-b, H-5'), 5.76 (t, 1H, H-4', ^{3}J = 4.8 Hz), 5.99 (t, 1H, H-3', ^{3}J = 5.4 Hz), 6.18 (d, 1H, H-2', ^{3}J = 4.8 Hz), 7.67 (s, 1H, H-5), 8.31 (s, 1H, H-2).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 20.4 (*CH*$_3$CO), 20.5 (*CH*$_3$CO), 20.7 (*CH*$_3$CO), 24.2 (CH_3), 52.9 (OCH_3), 63.1 (CH_2), 70.6 (C-5'), 73.0 (C-4'), 80.0 (C-3'), 86.9 (C-2'), 119.8 (C-5), 128.7 (C-4), 131.4

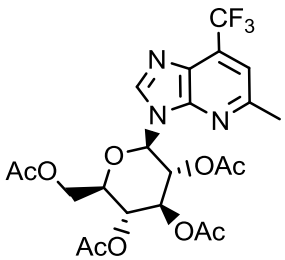
(C-6), 143.9 (C-2), 147.1 (C-3a), 154.8 (C-7a), 165.5 (*C*OOCH$_3$), 169.3 (C=O), 169.53 (C=O), 170.35 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 391 (11), 243 (24), 213 (56), 191 (78), 133 (12), 93 (22), 65 (10).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{20}H_{24}N_3O_9$: 450.1513; found: 450.1511.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1737, 1412, 1333, 1296, 1226, 1175, 1066, 1010, 762, 611 cm^{-1}.

3-(Tetra-acetyl-β-D-glucopyranosyl)-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (61a)



Starting from 5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (300 mg, 1.49 mmol) **53a** and pentaacetyl-β-D-glucopyranose (581 mg, 1.49 mmol); **61a** was isolated as white oil, yield = 396 mg (50%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.69 (s, 3H, CH_3CO),1.98 (s, 3H, CH_3CO), 2.00 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO), 2.67 (s, 3H, CH_3), 4.11 (br. m, 3H, CH_2, H-6'), 5.26 (t, 1H, H-5', ^3J = 9Hz), 5.43 (t, 1H, H-4', ^3J = 9.3Hz), 5.69 (t, 1H, H-3', ^3J = 9.6Hz), 5.98 (d, 1H, H-2', ^3J = 9.6Hz), 7.31 (s, 1H, H-6), 8.24 (s, 1H, H-2).

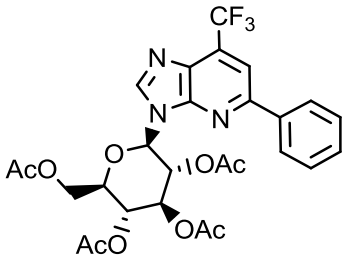
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 20.1 (*C*H_3CO), 20.5 (*C*H_3CO), 20.5 (*C*H_3CO), 20.6 (*C*H_3CO), 24.4 (Me), 61.5 (CH_2), 67.8 (C-5'), 69.9 (C-3'), 73.1 (C-4'), 74.9 (C-6'), 80.3 (C-2'), 115.4 (d, C-5, $^3J_{(C-F)}$ = 4.4 Hz), 122.5 (q, CF_3, $^1J_{(C-F)}$= 274.2 Hz), 129.0 (C-6), 129.2 (q, C-4, $^2J_{(C-F)}$ = 33.9 Hz), 142.6 (C-2), 147.4 (C-3a), 155.0 (C-7a), 168.9 (C=O), 169.3 (C=O), 169.9 (C=O), 170.5 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 531 (18) [M^+], 472 (23), 331 (24), 296 (23), 244 (23), 202 (100), 182 (13), 169 (91), 127 (21), 109 (59), 43 (97).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{22}H_{25}F_3N_3O_9$: 532.1537; found: 532.1541.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1744, 1380, 1317, 1229, 1198, 1103, 1046, 912, 643.

3-(Tetra-acetyl-β-D-glucopyranosyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine) (61b)



Starting from 5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (300 mg, 1.14 mmol) **53b** and pentaacetyl-β-D-glucopyranose (444 mg, 1.14 mmol); **61b** was isolated as white foam, yield = 352 mg (52%);

^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.69 (s, 3H, CH_3CO), 1.98 (s, 3H, CH_3CO), 1.99 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO), 4.12 (br. m, 3H, CH_2, H-6'), 5.27 (t, 1H, H-5', ^{3}J = 9.5 Hz), 5.47 (t, 1H, H-4', ^{3}J = 9.3 Hz), 5.70 (t, 1H, H-3', ^{3}J = 9.5 Hz), 6.03 (d, 1H, H-2', ^{3}J = 9.5 Hz), 7.48 (br.m, 3H, Ph), 7.91 (s, 1H, H-6), 8.03 (m, 2H, Ph), 8.32 (s, 1H, H-2).

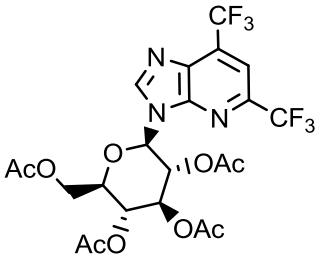
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.2 (CH_3CO), 20.5 (CH_3CO), 20.6 (CH_3CO), 20.6 (CH_3CO), 61.6 (CH_2), 67.9 (C-5'), 70.1 (C-3'), 73.1 (C-4'), 75.1 (C-6'), 80.5 (C-2'), 112.8 (d, C-5, $^{3}J_{(C-F)}$= 4.0 Hz), 122.6 (q, CF_3, $^{1}J_{(C-F)}$= 274.0 Hz), 127.2 (C-4"), 129.0 (C-3", C-5"), 129.6 (C-2", C-6"), 129.9 (q, C-4, $^{2}J_{(C-F\ )}$= 29.6 Hz), 130.0 (C-1"), 137.9 (C-6), 143.5 (C-2), 147.9 (C-3a), 153.7 (C-7a), 168.9 (C=O), 169.4 (C=O), 170.0 (C=O), 170.5 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 593 (20) [M^+], 358 (10), 331 (17), 264 (72), 169 (100), 127 (19), 109 (61), 43 (84).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{27}H_{27}F_3N_3O_9$: 594.1699; found: 594.1694.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1742, 1378, 1227, 1215, 1136, 1033, 876, 771.

3-(Tetra-acetyl-β-D-glucopyranosyl)-5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (61c).



Starting from 5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (300 mg, 1.18 mmol) **53c** and pentaacetyl-β-D-glucopyranose (460 mg, 1.18 mmol); **61c** was isolated as white oil, yield = 287 mg (43%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.69 (s, 3H, CH_3CO),1.98 (s, 3H, CH_3CO), 2.00 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO), 4.13 (br. m, 3H, CH_2, H-6'), 5.25 (t, 1H, H-5', ^{3}J = 9.9 Hz), 5.46 (t, 1H, H-4', ^{3}J = 9.6 Hz), 5.59 (t, 1H, H-3', ^{3}J = 9.3 Hz), 6.03 (d, 1H, H-2', ^{3}J = 9.3 Hz), 7.84 (s, 1H, H-5), 8.51 (s, 1H, H-2).

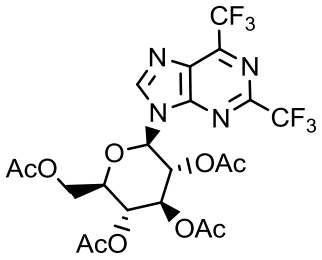
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 20.0 (CH_3CO), 20.5 (CH_3CO), 20.5 (CH_3CO), 20.6 (CH_3CO), 61.4 (CH_2), 67.7 (C-5'), 70.3 (C-3'), 72.7 (C-4'), 75.2 (C-6'), 80.7 (C-2'), 112.5 (C-5), 121.2 (q, CF_3, $^{1}J_{(C-F)}$= 274.2 Hz), 121.8 (q, CF_3, $^{1}J_{(C-F)}$= 274.2 Hz), 130.3 (q, C-4, $^{2}J_{(C-F)}$ = 35.2 Hz), 133.7 (C-3a), 143.3 (q, C-6, $^{2}J_{(C-F)}$ = 35.9Hz), 146.7 (C-2), 147.6 (C-7a), 169.0 (C=O), 169.3 (C=O), 169.8 (C=O), 170.4 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 586 (12) [$(M+H)^+$], 566 (17), 424 (14), 363 (71), 331 (16), 256 (68), 169 (71), 109 (53), 98 (34).

HRMS (ESI): $[M+Na]^+$ *m/z* calcd. for $C_{22}H_{21}F_6N_3NaO_9$: 608.1074; found: 608.1080.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1752, 1733, 1486, 1368, 1278, 1203, 1127, 1035, 962, 882, 658.

3-(Tetra-acetyl-β-D-glucopyranosyl)-2,6-bis(trifluoromethyl)-9*H*-purine (62)



Starting from 2,6-bis(trifluoromethyl)-9*H*-purine (300 mg, 1.18 mmol) **57** and pentaacetyl-β-D-glucopyranose (460 mg, 1.18 mmol); **62** was isolated as white oil, yield = 263 mg (38%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.73 (s, 3H, CH_3CO),1.99 (s, 3H, CH_3CO),2.00 (s, 3H, CH_3CO),2.03 (s, 3H, CH_3CO),4.13 (br. m, 3H, CH_2, H-6'), 5.25 (t, 1H, H-5', ^3J = 9.3 Hz), 5.47 (br.m, 2H, H-4', H-3'), 6.01 (d, 1H, H-2', ^3J = 9.0 Hz), 8.58 (s, 1H, H-8).

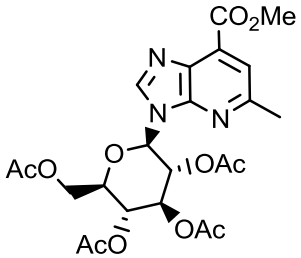
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 20.0 (*CH*$_3$CO), 20.4 (*CH*$_3$CO), 20.5 (*CH*$_3$CO), 20.5 (*CH*$_3$CO), 61.3 (CH_2), 67.5 (C-5'), 70.3 (C-3'), 72.4 (C-4'), 75.4 (C-6'), 80.9 (C-2'), 119.2 (q, CF_3, $^1J_{(C-F)}$ = 275.5 Hz), 119.9 (q, CF_3, $^1J_{(C-F)}$= 276.2 Hz), 131.1 (C-5), 146.2 (q, C-6, $^2J_{(C-F)}$ = 39.0 Hz), 147.2 (C-8), 150.4 (q, C-2, $^2J_{(C-F)}$ = 38.6 Hz), 154.0 (C-4), 169.1 (C=O), 169.3 (C=O), 169.7 (C=O), 170.4 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 424 (12), 364 (73), 351 (42), 257 (38), 169 (44), 157 (13), 115 (23), 69 (11).

HRMS (ESI): $[M+Na]^+$ *m/z* calcd. for $C_{21}H_{20}F_6N_4NaO_9$: 609.1027; found: 609.1025.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1752, 1728, 1418, 1379, 1208, 1093, 946, 724, 677.

Methyl 3-(Tetra-acetyl-β-D-glucopyranosyl)-5-methyl-3*H*-imidazo[4,5-b]pyridine-7-carboxylate (63)



Starting from methyl 5-methyl-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (300 mg, 1.57 mmol) **58** and pentaacetyl-β-D-glucopyranose (612 mg, 1.57 mmol); **63** was isolated as white oil, yield = 442 mg (54%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.65 (s, 3H, CH_3CO),1.97 (s, 3H, CH_3CO), 2.00 (s, 3H, CH_3CO), 2.01 (s, 3H, CH_3CO),2.65 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 4.11 (br. m, 3H, CH_2, H-6'), 5.25 (t, 1H, H-5', ^3J = 9.6 Hz), 5.42 (t, 1H, H-4', ^3J = 9.3 Hz), 5.66 (t, 1H, H-3', ^3J = 9.6 Hz), 5.98 (d, 1H, H-2', ^3J = 9.6 Hz), 7.65 (s, 1H, H-6), 8.25 (s, 1H, H-2).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 20.1 (*CH*$_3$CO), 20.5 (*CH*$_3$CO), 20.5 (*CH*$_3$CO), 20.6 (*CH*$_3$CO), 24.3 (CH_3), 52.9 (OCH_3), 61.5 (CH_2), 67.9 (C-5'), 69.9 (C-3'), 73.1 (C-4'), 74.9 (C-6'), 80.2 (C-2'), 120.0

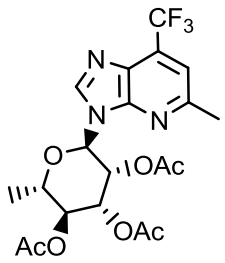
(C-5), 129.0 (C-4), 130.8 (C-6), 142.6 (C-2), 147.7 (C-3a), 154.7 (C-7a), 165.5 (*C*OOCH$_3$), 168.8 (C=O), 169.4 (C=O), 169.9 (C=O), 170.5 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 443 (13), 376 (10), 332 (29), 297 (32), 212 (12), 192 (46), 92 (53), 65 (16).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. Calcd. for $C_{23}H_{28}N_3O_{11}$: 522.1724; found: 522.1719.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1743, 1366, 1210, 1032, 908, 761, 599.

3-(Triacetyl-α-L-rhamnosyl)-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (64a)



Starting from 5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (300 mg, 1.49 mmol) **53a** and tetraacetyl-α-L-rhamnose (495 mg, 1.49 mmol); **64a** was isolated as white oil, yield = 388 mg (55%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.32 (d, 3H, CH_3, ^3J = 6.6 Hz), 1.99 (s, 3H, CH_3CO),2.05 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 2.67 (s, 3H, CH_3), 3.99 (m, 1H, H-6'), 5.02 (t, 1H, H-5', ^3J = 6.6 Hz), 5.64 (dd, 1H, H-4', $^3J_1$ = 3.6 Hz, $^3J_2$ = 3 Hz), 6.08 (d, 1H, H-2', ^3J = 5.1 Hz), 6.31 (dd, 1H, H-3', $^3J_1$ = 3.9 Hz, $^3J_2$ = 1.2 Hz), 7.31 (s, 1H, H-5), 8.22 (s, 1H, H-2).

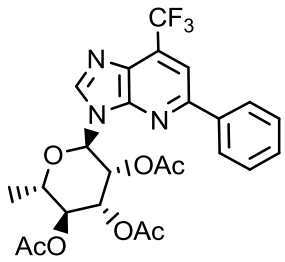
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 17.0 (CH_3), 20.6 (*C*H_3CO), 20.7 (*C*H_3CO), 20.8 (*C*H_3CO), 24.5 (CH_3), 67.6 (C-5'), 69.1 (C-4'), 71.1 (C-6'), 71.6 (C-3'), 79.5 (C-2'), 115.1 (d, C-5, $^3J_{(C-F)}$ = 4.0 Hz), 122.7 (q, CF_3, $^1J_{(C-F)}$= 274.0 Hz), 129.1 (q, C-4, $^2J_{(C-F)}$ = 34.0 Hz), 129.4 (C-6), 143.7 (C-2), 147.5 (C-3a), 155.1 (C-7a), 169.5 (C=O), 169.6 (C=O), 169.8 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 414 (30), 353 (41), 310 (13), 294 (25), 273 (17), 244 (18), 202 (83), 153 (94), 11 (82), 83 (25), 43 (100).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{20}H_{23}F_3N_3O_7$: 474.1488; found: 474.1485.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1737, 1401, 1351, 1322, 1223, 1134, 1064, 870, 653.

3-(Triacetyl-α-L-rhamnosyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (64b)



Starting from 5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (300 mg, 1.14 mmol) **53b** and tetraacetyl-α-L-rhamnose (385 mg, 1.14 mmol); **64b** was isolated as white oil, yield = 323 mg (53%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.40 (d, 3H, CH_3, ^{3}J = 6.6 Hz), 1.94 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO),4.23 (m, 1H, H-6'), 5.01 (t, 1H, H-5', ^{3}J = 5.7 Hz), 5.54 (dd, 1H, H-4', $^{3}J_1$ = 3.3 Hz, $^{3}J_2$ = 2.4 Hz), 6.18 (d, 1H, H-2', ^{3}J = 6.3 Hz), 6.50 (dd, 1H, H-3', $^{3}J_1$ = 3.6 Hz, $^{3}J_2$ = 2.7 Hz), 7.42 (br.m, 3H, Ph), 7.92 (s, 1H, H-5), 8.03 (m, 2H, Ph), 8.28 (s, 1H, H-2).

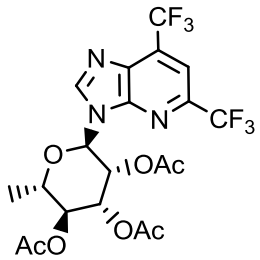
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 17.0 (CH_3), 20.6 (CH_3CO), 20.7 (CH_3CO), 20.9 (CH_3CO), 67.1 (C-5'), 69.1 (C-4'), 71.8 (C-6'), 71.9 (C-3'), 79.0 (C-2'), 112.6 (d, C-5, $^{3}J_{(C-F)}$= 4.5 Hz), 122.7 (q, CF_3, $^{1}J_{(C-F)}$= 274.0 Hz), 127.2 (C-4"), 128.9 (C-3", C-5"), 129.7 (C-2", C-6"), 129.7 (q, C-4, $^{2}J_{(C-F)}$= 34.0 Hz), 130.7 (C-1"), 138.0 (C-6), 144.7 (C-2), 147.9 (C-3a), 153.6 (C-7a) 169.4 (C=O), 169.5 (C=O), 169.7 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 535 (14) [M^+], 518 (11), 458 (48), 346 (31), 288 (11), 273 (53), 263 (80), 185 (39), 77 (87).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{25}H_{25}F_3N_3O_7$: 536.1644; found: 536.1643.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 1732, 1575, 1490, 1378, 1334, 1284, 1219, 1214, 1158, 1020, 943, 862, 614.

3-(Triacetyl-α-L-rhamnosyl)-5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (64c)



Starting from 5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (300 mg, 1.18 mmol) **53c** and tetraacetyl-α-L-rhamnose (399 mg, 1.18 mmol); **64c** was isolated as white oil, yield = 305 mg (49%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.42 (d, 3H, CH_3, ^{3}J = 6.6Hz), 1.88 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO), 2.13 (s, 3H, CH_3CO), 4.20 (m, 1H, H-6'), 4.96 (t, 1H, H-5', ^{3}J = 5.1 Hz), 5.50 (dd, 1H, H-4', $^{3}J_1$ = 3.3 Hz, $^{3}J_2$ = 1.8 Hz), 6.04 (dd, 1H, H-3', $^{3}J_1$ = 3.6 Hz, $^{3}J_2$ = 3.5 Hz), 6.21 (d, 1H, H-2', ^{3}J = 7.2 Hz), 7.85 (s, 1H, H-5), 8.48 (s, 1H, H-2).

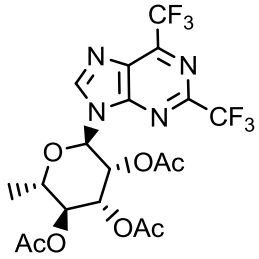
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.66 (CH_3), 20.40 (CH_3CO), 20.70 (CH_3CO), 20.85 (CH_3CO), 67.19 (C-5'), 68.86 (C-4'), 71.63 (C-6'), 72.57 (C-3'), 78.09 (C-2'), 112.28 (C-5), 121.21 (q, CF_3, $^{1}J_{(C-F)}$ = 274.0 Hz), 121.95 (q, CF_3, $^{1}J_{(C-F)}$ = 274.0 Hz), 130.18 (q, C-4, $^{2}J_{(C-F)}$ = 35.5 Hz), 134.26 (C-3a), 143.23 (q, C-6, $^{2}J_{(C-F)}$ = 36.2 Hz), 147.13 (C-2), 147.60 (C-7a), 169.30 (C=O), 169.32 (C=O), 169.67 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 437 (12), 318 (10), 255 (64), 206 (38), 145 (23), 109 (42), 74 (18).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{20}H_{20}F_6N_3O_7$: 528.1205; found: 528.1208.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1756, 1454, 1385, 1211, 1188, 1107, 1019, 693.

3-(Triacetyl-α-L-rhamnosyl)-2,6-bis(trifluoromethyl)-9*H*-purine (65)



Starting from 2,6-bis(trifluoromethyl)-9H-purine (300 mg, 1.18 mmol) **57** and tetraacetyl-α-L-rhamnose (399 mg, 1.18 mmol); **65** was isolated as white oil, yield = 301 mg (48%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.45 (d, 3H, CH_3, ^{3}J = 6.9Hz), 1.86 (s, 3H, CH_3CO), 2.11 (s, 3H, CH_3CO), 2.15 (s, 3H, CH_3CO), 4.21 (m, 1H, H-6'), 4.95 (t, 1H, H-5', ^{3}J = 4.5 Hz), 5.48 (t, 1H, H-4', ^{3}J = 4.2 Hz), 5.92 (dd, 1H, H-3', $^{3}J_1$ = 3.9 Hz, $^{3}J_2$ = 3.6 Hz), 6.22 (d, 1H, H-2', ^{3}J = 7.5 Hz), 8.54 (s, 1H, H-8).

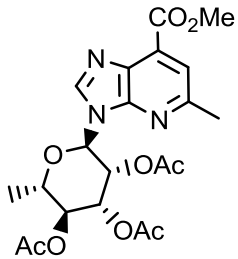
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 16.7 (CH_3), 20.3 (CH_3CO), 20.7 (CH_3CO), 20.8 (CH_3CO), 67.1 (C-5'), 68.6 (C-4'), 71.4 (C-6'), 73.1 (C-3'), 77.9 (C-2'), 119.3 (q, CF_3, $^{1}J_{(C-F)}$= 274.7 Hz), 120.0 (q, CF_3, $^{1}J_{(C-F)}$= 276.2 Hz), 131.4 (C-5), 146.2 (q, C-6, $^{2}J_{(C-F)}$ = 39.2 Hz), 147.9 (C-8), 150.4 (q, C-2, $^{2}J_{(C-F)}$ = 38.5 Hz), 154.0 (C-4), 169.2 (C=O), 169.3 (C=O), 169.6 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 408 (29), 366 (54), 323 (17), 257 (28), 171 (10), 153 (33), 111 (38).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{19}H_{19}F_6N_4O_7$: 529.1152; found: 529.1150.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1748, 1543, 1466, 1398, 1309, 1211, 1186, 1124, 908, 767, 698.

Methyl 3-(Triacetyl-α-L-rhamnosyl)-5-methyl-3*H*-imidazo[4,5-b]pyridine-7-carboxylate (66)



Starting from methyl 5-methyl-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (300 mg, 1.57 mmol) **58** and tetraacetyl-α-L-rhamnose (531 mg, 1.57 mmol); **66** was isolated as white oil, yield = 393 mg (54%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.56 (d, 3H, CH_3, ^{3}J = 6.6 Hz), 2.16 (s, 3H, CH_3CO), 2.28 (s, 3H, CH_3CO), 2.31 (s, 3H, CH_3CO), 2.90 (s, 3H, CH_3), 4.28 (m, 4H, H-6', OCH_3), 5.22 (t, 1H, H-5', ^{3}J = 6.3 Hz), 5.82 (dd, 1H, H-4', $^{3}J_1$ = 3.3 Hz, $^{3}J_2$ = 2.7 Hz), 6.35 (d, 1H, H-2', ^{3}J = 5.7 Hz), 6.47 (dd, 1H, H-3', $^{3}J_1$ = 3.6 Hz, $^{3}J_2$ = 2.1 Hz), 7.94 (s, 1H, H-5), 8.74 (s, 1H, H-2).

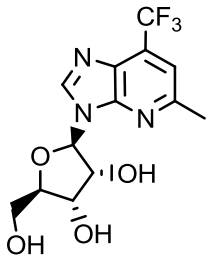
^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 16.9 (CH_3), 20.6 (CH_3CO), 20.7 (CH_3CO), 20.9 (CH_3CO), 24.4 (CH_3), 53.1 (OCH_3), 67.5 (C-5'), 69.1 (C-4'), 71.4 (C-6'), 71.6 (C-3'), 79.4 (C-2'), 120.0 (C-5), 128.5 (C-4), 130.2 (C-6), 143.9 (C-2), 147.4 (C-3a), 153.4 (C-7a), 165.5 (CO_2Me), 169.4 (C=O), 169.5 (C=O), 169.8 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 432 (18), 403 (11), 287 (21), 191 (78), 132 (34), 92 (23).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{21}H_{26}N_3O_{19}$: 464.1667; found: 464.1670.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1745, 1727, 1371, 1212, 1160, 1031, 760, 639.

l-(β-D-Ribofuranosyl)-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (67a)



Starting from 3-(Triacetyl-β-D-ribofuranosyl)-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (459 mg, 1.00 mmol) **59a**; **67a** was isolated as white powder, yield = 332 mg (99%); mp = 156-158°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.69 (s, 3H, CH_3), 3.66 (br.m, 2H, CH_2), 4.01 (m, 1H, H-5'), 4.21 (dd, 1H, H-4', $^3J_1$ = 5.1 Hz, $^3J_2$ = 3.3 Hz), 4.67 (dd, 1H, H-3', $^3J_1$ = 6.0 Hz, $^3J_2$ = 5.1 Hz), 5.16 (t, 1H, OH-4', ^3J = 4.2 Hz), 5.25 (d, 1H, CH_2-*OH*, ^3J = 4.8 Hz), 5.50 (d, 1H, OH-3', ^3J = 6.0 Hz), 6.11 (d, 1H, H-2', ^3J = 6.0 Hz), 7.58 (s, 1H, H-5), 8.84 (s, 1H, H-2).

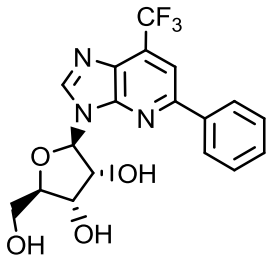
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 29.1 (CH_3), 66.6 (CH_2), 75.7 (C-4'), 78.8 (C-3'), 91.0 (C-5'), 92.7 (C-2'), 119.5 (d, C-5, $^3J_{(C-F)}$= 4.5 Hz), 128.1 (q, CF_3, $^1J_{(C-F)}$= 273.6 Hz), 132.6 (q, C-4, $^2J_{(C-F)}$ = 33.2 Hz), 134.3 (C-6), 150.4 (C-2), 152.7 (C-3a), 159.1 (C-7a).

GC-MS (EI, 70 eV): *m/z* (%): 274 (10), 201 (100), 180 (12), 154 (10), 132 (17), 126 (10).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{13}H_{15}F_3N_3O_4$: 334.1009; found: 334.1010.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3288, 1602, 1501, 1387, 1365, 1235, 1205, 1167, 1143, 1084, 1056, 896, 866, 723.

l-(β-D-Ribofuranosyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (67b)

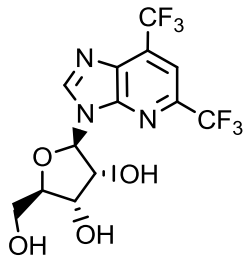


Starting from 3-(Triacetyl-β-D-ribofuranosyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (521 mg, 1.00 mmol) **59b**; **67b** was isolated as light-brown gum, yield = 381 mg (96%);

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.70 (br.m, 2H, CH_2), 4.00 (m, 1H, H-5'), 4.26 (dd, 1H, H-4', $^3J_1$ = 4.8 Hz, $^3J_2$ = 3.6 Hz), 4.75 (dd, 1H, H-3', $^3J_1$ = 5.1 Hz, $^3J_2$ = 3.9 Hz), 5.04 (br.s, 1H, OH-4'), 5.28 (br.s., 1H, CH_2-*OH*), 5.56 (d, 1H, OH-3', ^3J = 3.6Hz), 6.22 (d, 1H, H-2', ^3J = 5.4Hz), 7.54 (br.m, 3H, Ph), 8.17 (s, 1H, H-5), 8.24 (br.m, 2H, Ph), 8.95 (s, 1H, H-2).

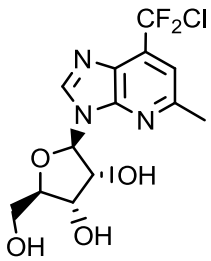
^{13}C NMR (125.76 MHz, DMSO-d_6): δ = 61.2 (CH_2), 70.3 (C-4'), 73.7 (C-3'), 85.5 (C-5'), 87.5 (C-2'), 111.5 (C-5), 122.8 (q, CF_3, $^1J_{(C-F)}$= 274.2 Hz), 126.9 (C-4"), 127.3 (q, C-4, $^2J_{(C-F)}$= 34.0 Hz), 128.9 (C-3", C-5"), 129.5 (C-2", C-6"), 130.2 (C-1"), 137.6 (C-6), 146.5 (C-2), 148.0 (C-3a), 151.8 (C-7a).
GC-MS (EI, 70 eV): *m/z* (%): 334 (18), 312 (26), 263 (88), 148 (11), 77 (66).
HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{18}H_{17}F_3N_3O_4$: 396.1171; found: 396.1166.
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925, 1604, 1491, 1376, 1209, 1134, 1044, 875, 770, 693, 615.

3-(β-D-Ribofuranosyl)-5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (67c)



Starting from 3-(Triacetyl-β-D-ribofuranosyl)-5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (513 mg, 1.00 mmol) **59c**; **67c** was isolated as light-brown powder, yield = 365 mg (94%); mp = 139 - 142°C;
^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.71 (br.m, 2H, CH_2), 4.08 (m, 1H, H-5'), 4.29 (dd, 1H, H-4', $^3J_1$ = 4.8 Hz, $^3J_2$ = 3.9 Hz), 4.74 (dd, 1H, H-3', $^3J_1$ = 5.4 Hz, $^3J_2$ = 5.4 Hz), 5.09 (t, 1H, OH-4', ^3J = 5.4 Hz), 5.35 (d, 1H, CH_2-*OH*, ^3J = 5.1 Hz), 5.63 (d, 1H, OH-3', ^3J = 5.7 Hz), 6.21 (d, 1H, H-2', ^3J = 5.7 Hz), 8.20 (s, 1H, H-5), 9.31 (s, 1H, H-2).
^{13}C NMR (125.76 MHz, DMSO-d_6): δ = 61.0 (CH_2), 70.2 (C-4'), 73.7 (C-3'), 85.8 (C-5'), 87.8 (C-2'), 111.6 (C-5), 121.4 (q, CF_3, $^1J_{(C-F)}$= 274.2 Hz), 122.1 (q, CF_3, $^1J_{(C-F)}$= 272.9 Hz), 127.7 (q, C-4, $^2J_{(C-F)}$ = 34.0 Hz), 133.8 (C-3a), 140.7 (q, C-6, $^2J_{(C-F)}$ = 35.2 Hz), 147.7 (C-2), 149.6 (C-7a).
GC-MS (EI, 70 eV): *m/z* (%): 298 (11), 284 (100), 255 (68), 236 (63), 205 (19), 166 (15), 73 (22).
HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{13}H_{12}F_6N_3O_4$: 388.0727; found: 388.0719.
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3317, 1568, 1493, 1411, 1354, 1246, 1238, 1180, 1043, 818.

3-(β-D-Ribofuranosyl)-7-[chloro(difluoro)methyl]-5-methyl-3*H*-imidazo[4,5-b]pyridine (67d)



Starting from 3-(Triacetyl-β-D-ribofuranosyl)-7-[chloro(difluoro)methyl]-5-methyl-3*H*-imidazo[4,5-b]pyridine (475 mg, 1.00 mmol) **59d**; **67d** was isolated as white oil, yield = 332 mg (95%);
^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.69 (s, 3H, CH_3), 3.68 (br.m, 2H, CH_2), 4.01 (m, 1H, H-5'), 4.21 (dd, 1H, H-4', $^3J_1$ = 4.8 Hz, $^3J_2$ = 3.3 Hz), 4.67 (dd, 1H, H-3', $^3J_1$

= 6.0 Hz, $^{3}J_{2}$ = 5.7 Hz), 5.16 (t, 1H, OH-4', ^{3}J = 5.4 Hz), 5.25 (d, 1H, CH_2-*OH*, ^{3}J = 4.8 Hz), 5.51 (d, 1H, OH-3', ^{3}J = 6.0 Hz), 6.10 (d, 1H, H-2', ^{3}J = 6.3 Hz), 7.53 (s, 1H, H-5), 8.82 (s, 1H, H-2).

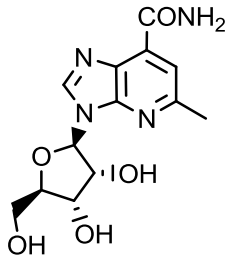
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 23.9 (CH_3), 61.4 (-CH_2-), 70.5 (C-4'), 73.5 (C-3'), 85.8 (C-5'), 87.4 (C-2'), 112.7 (t, C-5, $^{3}J_{(C-F)}$= 5.3 Hz), 124.2 (t, CF_2Cl, $^{1}J_{(C-F)}$= 289.8 Hz), 128.2 (C-6), 132.6 (t, C-4, $^{2}J_{(C-F)}$ = 27.9 Hz), 144.9 (C-2), 147.6 (C-3a), 153.8 (C-7a).

GC-MS (EI, 70 eV): *m/z* (%): 246 (100), 218 (56), 182 (62), 73 (11), 57 (10).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{13}H_{15}ClF_2N_3O_4$: 350.0719; found: 350.0712.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3251, 2922, 1598, 1489, 1385, 1355, 1301, 1203, 1079, 965, 824, 634.

l-(β-D-Ribofuranosyl)-5-methyl-3*H*-imidazo[4,5-b]pyridine-7-carboxamide (68)



Starting from 3-(Triacetyl-β-D-ribofuranosyl)-5-methyl-3*H*-imidazo[4,5-b]pyridine-7-carboxylate (449 mg, 1.00 mmol) **60**; **68** was isolated as white powder, yield = 306 mg (99%); mp = 245 - 247°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.65 (s, 3H, CH_3), 3.64 (br.m, 2H, CH_2), 4.01 (m, 1H, H-5'), 4.20 (dd, 1H, H-4', $^{3}J_{1}$ = 4.8 Hz, $^{3}J_{2}$ = 3.3 Hz), 4.67 (dd, 1H, H-3', $^{3}J_{1}$ = 6.0 Hz, $^{3}J_{2}$ = 5.1 Hz), 5.23 (m, 2H, OH-4', CH_2-*OH*), 5.48 (d, 1H, OH-3', ^{3}J = 6.0 Hz), 6.08 (d, 1H, H-2', ^{3}J = 6.0 Hz), 7.68 (s, 1H, H-5), 8.13 (s, 1H, $CONH_2$), 8.72 (s, 1H, $CONH_2$), 8.84 (s, 1H, H-2).

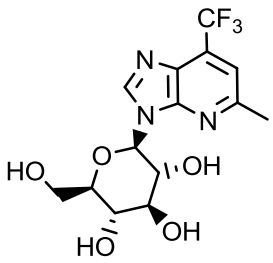
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 23.8 (CH_3), 61.44 (CH_2), 70.2 (C-4'), 73.4 (C-3'), 85.8 (C-5'), 87.7 (C-2'), 117.3 (C-5), 130.6 (C-4, C-6), 144.2 (C-2), 146.8 (C-3a), 153.6 (C-7a), 164.3 (*C*ONH_2).

GC-MS (EI, 70 eV): *m/z* (%): 308 (10), [M^+], 193 (18), 176 (68), 160 (19), 131 (10), 91 (26).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{13}H_{17}N_4O_5$: 309.1193; found: 309.1196.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3259, 1683, 1662, 1580, 1486, 1414, 1297, 1203, 1123, 1071, 1045, 862, 740.

3-(β-D-Glucopyranosyl)-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (69a)



Starting from 3-(Tetra-acetyl-β-D-glucopyranosyl)-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (449 mg, 1.00 mmol) **61a**; **69a** was isolated as white oil, yield = 345 mg (95%);

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.74 (s, 3H, CH_3), 3.36 (dd, 1H, H-5', $^{3}J_1$ = 5.4 Hz, $^{3}J_2$ = 3.3 Hz), 3.53 (br.m, 3H, H-6', H-4', CH_2-a), 3.76 (dd, 1H, CH_2-b, $^{3}J_1$ = 6.0 Hz, $^{3}J_2$ = 3.9 Hz), 4.06 (dt, 1H, H-3', $^{3}J_1$ = 6.0 Hz, $^{3}J_2$ = 5.4 Hz), 4.63 (d, 1H, CH_2-*OH*, ^{3}J = 2.7 Hz), 5.22 (d, 1H, OH-5', ^{3}J = 5.4 Hz), 5.37 (d, 1H, OH-4', ^{3}J = 4.5 Hz), 5.43 (d, 1H, OH-3', ^{3}J = 5.4 Hz), 5.68 (d, 1H, H-2', ^{3}J = 9.3 Hz), 7.61 (s, 1H, H-5), 8.86 (s,1H, H-2).

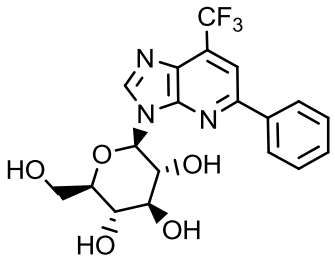
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 23.9 (CH_3), 60.9 (CH_2), 69.7 (C-5'), 71.6 (C-3'), 77.03 (C-6'), 80.0 (C-4'), 82.5 (C-2'), 114.2 (d, C-5, $^{3}J_{(C-F)}$= 4.4 Hz), 122.9 (q, CF_3, $^{1}J_{(C-F)}$= 273.6 Hz), 126.1 (q, C-4, $^{2}J_{(C-F)}$ = 32.7 Hz), 128.4 (C-6), 145.2 (C-2), 147.9 (C-3a), 153.9 (C-7a).

GC-MS (EI, 70 eV): *m/z* (%): 255 (10), 201 (100), 180 (14), 154 (10), 132 (16).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{14}H_{17}F_3N_3O_5$: 364.1115; found: 364.1122.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3385, 3280, 1601, 1511, 1387, 1366, 1264, 1239, 1172, 1126, 1074, 1036, 893, 790, 725.

3-(β-D-Glucopyranosyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (69b)



Starting from 3-(Tetra-acetyl-β-D-glucopyranosyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (593 mg, 1.00 mmol) **61b**; **69b** was isolated as white oil, yield = 416 mg (98%);

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.49 (br. m, 3H, H-6', H-4', CH_2-a), 3.74 (dd, 1H, CH_2-b, $^{3}J_1$ = 5.7 Hz, $^{3}J_2$ = 4.8 Hz), 4.16 (dt, 1H, H-3', $^{3}J_1$ = 5.7 Hz, $^{3}J_2$ = 5.4 Hz), 4.59 (t, 1H, CH_2-*OH*, ^{3}J = 5.1 Hz), 5.18 (d, 1H, OH-5', ^{3}J = 5.4 Hz), 5.34 (d, 1H, OH-4', ^{3}J = 4.5 Hz), 5.43 (d, 1H, OH-3', ^{3}J = 5.4 Hz), 5.75 (d, 1H, H-2', ^{3}J = 9.3 Hz), 7.54 (m, 3H, Ph), 8.18 (s, 1H, H-5), 8.25 (m, 2H, Ph), 8.92 (s,1H, H-2).

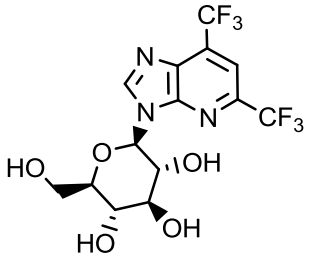
^{13}C NMR (125.76 MHz, DMSO-d_6): δ = 60.9 (CH_2), 69.8 (C-5'), 71.4 (C-3'), 77.0 (C-6'), 80.0 (C-4'), 83.1 (C-2'), 111.3 (C-5), 122.9 (q, CF_3, $^{1}J_{(C-F)}$= 274.2Hz), 127.0 (C-4"), 127.5 (q, C-4, $^{2}J_{(C-F)}$= 33.3Hz), 128.9 (C-3", C-5"), 129.5 (C-2", C-6"), 129.8 (C-1"), 137.6 (C-6), 146.8 (C-2), 148.3 (C-3a), 151.7 (C-7a).

GC-MS (EI, 70 eV): *m/z* (%): 425 (40), [M^+], 306 (34), 292 (97), 276 (59), 264 (100), 244 (32), 140 (11), 60 (20).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{19}H_{19}F_3N_3O_5$: 426.1271; found: 426.1277.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3238, 1606, 1499, 1376, 1261, 1130, 1088, 1019, 878, 769, 688, 616.

3-(β-D-Glucopyranosyl)-5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (69c)



Starting from 3-(Tetra-acetyl-β-D-glucopyranosyl)-5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (585 mg, 1.00 mmol) **61c**; **69c** was isolated as white oil, yield = 403 mg (97%);

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.35 (dd, 1H, H-5', $^{3}J_1$ = 5.7 Hz, $^{3}J_2$ = 3.6 Hz), 3.52 (br.m, 3H, H-6', H-4', CH_2-a), 3.75 (dd, 1H, CH_2-b, $^{3}J_1$ = 5.4 Hz, $^{3}J_2$ = 5.1 Hz), 4.06 (dt, 1H, H-3', $^{3}J_1$ = 5.4 Hz, $^{3}J_2$ = 3.6 Hz), 4.60 (d, 1H, CH_2-*OH*, ^{3}J = 6.0 Hz), 5.21 (d, 1H, OH-5', ^{3}J = 5.4 Hz), 5.38 (d, 1H, OH-4', ^{3}J = 4.5 Hz), 5.45 (d, 1H, OH-3', ^{3}J = 5.4 Hz), 5.70 (d, 1H, H-2', ^{3}J = 9.3 Hz), 8.16 (s, 1H, H-5), 9.26 (s,1H, H-2).

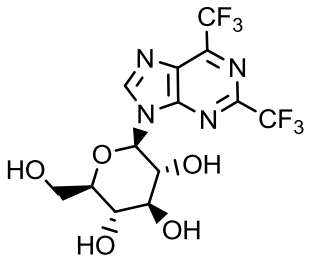
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 60.9 (CH_2), 69.6 (C-5'), 71.7 (C-3'), 76.7 (C-6'), 80.1 (C-4'), 83.2 (C-2'), 111.7 (C-5), 121.4 (q, CF_3, $^{1}J_{(C-F)}$= 274.2 Hz), 122.1 (q, CF_3, $^{1}J_{(C-F)}$= 273.6 Hz), 127.7 (q, C-4, $^{2}J_{(C-F)}$ = 34.6 Hz), 133.3 (C-3a), 140.8 (q, C-6, $^{2}J_{(C-F)}$ = 35.9 Hz), 148.0 (C-2), 150.0 (C-7a).

GC-MS (EI, 70 eV): *m/z* (%): 323 (21), 280 (18), 256 (59), 190 (11), 149 (17), 77 (36).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{14}H_{14}F_6N_3O_5$: 418.0832; found: 418.0831.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3288, 1602, 1492, 1405, 1273, 1129, 1103, 1054, 880, 658.

3-(β-D-Glucopyranosyl)-2,6-bis(trifluoromethyl)-9*H*-purine (70)



Starting from 3-(Tetraacetyl-β-D-glucopyranosyl)-2,6-bis(trifluoromethyl)-9*H*-purine (586 mg, 1.00 mmol) **62**; **70** was isolated as pink gum, yield = 395 mg (95%);

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.53 (br.m, 4H, H-5', H-6', H-4', CH_2-a), 3.76 (dd, 1H, CH_2-b, $^{3}J_1$ = 5.4 Hz, $^{3}J_2$ = 5.1 Hz), 4.04 (dt, 1H, H-3', $^{3}J_1$ = 5.1 Hz, $^{3}J_2$ = 3.9 Hz), 4.59 (t, 1H, CH_2-*OH*, ^{3}J = 5.4 Hz), 5.24 (d, 1H, OH-5', ^{3}J = 5.4 Hz), 5.37 (d, 1H, OH-4', ^{3}J = 4.5 Hz), 5.41 (t, 1H, OH-3', ^{3}J = 5.1 Hz), 5.73 (d, 1H, H-2', ^{3}J = 9.0 Hz), 9.26 (s,1H, H-8).

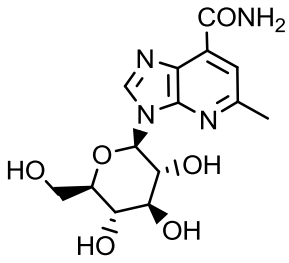
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 60.8 (CH_2), 69.5 (C-5'), 71.9 (C-3'), 76.3 (C-6'), 80.2 (C-4'), 83.7 (C-2'), 119.5 (q, CF_3, $^{1}J_{(C-F)}$= 274.9 Hz), 120.3 (q, CF_3, $^{1}J_{(C-F)}$= 275.5 Hz), 131.5 (C-5), 143.0 (q, C-6, $^{2}J_{(C-F)}$ = 37.7 Hz), 147.8 (q, C-2, $^{2}J_{(C-F)}$ = 37.0 Hz), 151.3 (C-8), 154.5 (C-4).

GC-MS (EI, 70 eV): *m/z* (%): 383 (15), 353(14), 332 (43), 294 (87), 266 (34), 238 (100), 209 (13), 69 (17).

HRMS (ESI): $[M-H]^+$ *m/z* calcd. for $C_{13}H_{11}F_6N_4O_4$: 417.0639; found: 417.0648.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3322, 1577, 1511, 1463, 1250, 1127, 1079, 1054, 919, 887, 644.

3-(β-D-Glucopyranosyl)-5-methyl-3*H*-imidazo[4,5-b]pyridine-7-carboxamide (71)



Starting from methyl 3-(Tetra-acetyl-β-D-glucopyranosyl)-5-methyl-3*H*-imidazo[4,5-b]pyridine-7-carboxylate (521 mg, 1.00 mmol) **63**; **70** was isolated as yellow oil, yield = 329 mg (97%); mp – dec.;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.68 (s, 3H,CH_3), 3.46 (br.m, 3H, H-6', H-4', CH_2-a), 3.73 (dd, 1H, CH_2-b, $^3J_1$ = 5.7 Hz, $^3J_2$ = 4.5 Hz), 4.04 (dt, 1H, H-3', $^3J_1$ = 5.7 Hz, $^3J_2$ = 3.3 Hz), 4.60 (t, 1H, CH_2-*OH*, ^3J = 3.3 Hz), 5.17 (d, 1H, OH-5', ^3J = 5.4 Hz), 5.33 (d, 1H, OH-4', ^3J = 4.5 Hz), 5.37 (d, 1H, OH-3', ^3J = 5.7 Hz), 5.64 (d, 1H, H-2', ^3J = 9.3 Hz), 7.69 (s, 1H, H-5), 8.13 (d, 1H, $CONH_2$, ^2J = 1.8 Hz), 8.76 (d, 1H, $CONH_2$, ^2J = 1.8 Hz), 8.85 (s,1H, H-2).

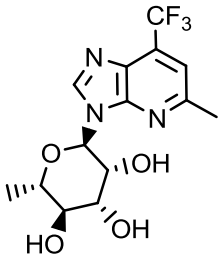
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 24.0 (CH_3), 60.9 (CH_2), 69.7 (C-5'), 71.6 (C-3'), 77.1 (C-6'), 80.0 (C-4'), 82.5 (C-2'), 117.3 (C-5), 129.9 (C-4), 130.2 (C-6), 144.1 (C-2), 147.3 (C-3a), 153.8 (C-7a), 164.5 (*C*$CONH_2$).

GC-MS (EI, 70 eV): *m/z* (%): 219 (10), 205 (100), 177 (83), 160 (20), 133 (49), 78 (12), 63 (10).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{14}H_{19}N_4O_6$: 339.1299; found: 339.1306.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3306, 3179, 1668, 1622, 1584, 1490, 1248, 1093, 1075, 1064, 996, 662.

3-(α-L-Rhamnosyl)-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (72a)



Starting from 3-(Triacetyl-α-L-Rhamnosyl)-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (473 mg, 1.00 mmol) **64a**; **72a** was isolated as light-yellow oil, yield = 326 mg (94%);

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.40 (d, 3H, CH_3, ^3J = 6.9 Hz), 2.74 (s, 3H, CH_3), 3.60 (t, 1H, H-5', ^3J = 4.2 Hz), 3.99 (m, 2H, H-4', H-6'), 4.65 (dt, 1H, H-3', $^3J_1$ = 5.7 Hz, $^3J_2$ = 3.3 Hz), 5.24 (m, 3H, OH), 6.16 (d, 1H, H-2', ^3J = 8.4 Hz), 7.61 (s, 1H, H-5), 8.82 (s, 1H, H-2).

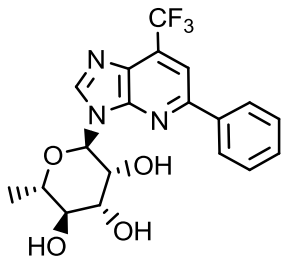
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 17.5 (CH_3), 24.0 (CH_3), 66.5 (C-5'), 72.6 (C-6'), 73.4 (C-4'), 74.2 (C-3'), 78.2 (C-2'), 114.0 (d, C-5, $^3J_{(C-F)}$ = 4.4 Hz), 122.9 (q, CF_3, $^1J_{(C-F)}$= 273.6 Hz), 126.6 (q, C-4, $^2J_{(C-F)}$= 33.3 Hz), 128.5 (C-6), 145.3 (C-2), 147.9 (C-3a), 153.7 (C-7a).

GC-MS (EI, 70 eV): *m/z* (%): 289 (10), 201 (97), 180 (12), 154 (10), 132 (19), 91 (14).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{14}H_{17}F_3N_3O_4$: 348.1166; found: 348.1172.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3311, 1600, 1490, 1386, 1365, 1238, 1129, 1086, 1052, 895, 782, 723.

3-(α-L-Rhamnosyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (72b)



Starting from 3-(Triacetyl-α-L-Rhamnosyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (535 mg, 1.00 mmol) **64b**; **72b** was isolated as light-yellow powder, yield = 404 mg (99%); mp – dec.;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.40 (d, 3H, CH_3, ^3J = 6.3 Hz), 3.60 (t, 1H, H-5', ^3J = 3.9 Hz), 3.97 (dd, 1H, H-4', $^3J_1$ = 3.6 Hz, $^3J_2$ = 3.6 Hz), 4.07 (m, 1H, H-6'), 4.82 (dt, 1H, H-3', $^3J_1$ = 4.5Hz, $^3J_2$ = 3.3 Hz), 5.27 (br.m, 3H, OH), 6.21 (d, 1H, H-2', ^3J = 7.8 Hz), 7.53 (br.m, 3H, Ph), 8.20 (s, 1H, H-5), 8.27 (m, 2H, Ph), 8.91 (s, 1H, H-2).

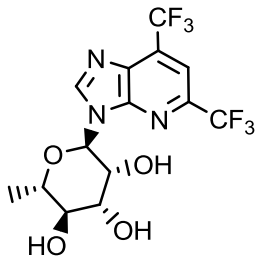
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 17.5 (CH_3), 66.3 (C-5'), 72.6 (C-6'), 73.6 (C-4'), 74.2 (C-3'), 79.3 (C-2'), 111.2 (d, C-5, $^3J_{(C-F)}$ = 4.4 Hz), 122.9 (q, CF_3, $^1J_{(C-F)}$= 274.2 Hz), 126.9 (C-4"), 127.3 (q, C-4, $^2J_{(C-F)}$= 33.3 Hz), 128.9 (C-3", C-5"), 129.4 (C-2", C-6"), 130.0 (C-1"), 137.6 (C-6), 147.0 (C-2), 148.3 (C-3a), 151.5 (C-7a).

GC-MS (EI, 70 eV): *m/z* (%): 409 (10), [M^+], 306 (10), 292 (43), 263 (100), 244 (13).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{19}H_{18}F_3N_3O_4$: 410.1322; found: 410.1328.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3459, 3372, 1600, 1489, 1372, 1260, 1134, 1112, 1081, 1051, 850, 770, 690.

3-(α-L-Rhamnosyl)-5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (72c)



Starting from 3-(Triacetyl-α-L-Rhamnosyl)-5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (527 mg, 1.00 mmol) **64c**; **72c** was isolated as light-brown powder, yield = 387 mg (97%); mp – dec.;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.40 (d, 3H, CH_3, ^3J = 6.9 Hz), 3.63 (t, 1H, H-5', ^3J = 4.2 Hz), 3.97 (dd, 1H, H-4', $^3J_1$ = 3.6 Hz, $^3J_2$ = 3.3 Hz), 4.08 (m,

1H, H-6'), 4.70 (dt, 1H, H-3', $^{3}J_{1}$ = 5.7 Hz, $^{3}J_{2}$ = 3.0 Hz), 5.31 (br.m, 3H, OH), 6.19 (d, 1H, H-2', ^{3}J = 8.4 Hz), 8.18 (s, 1H, H-5), 9.26 (s, 1H, H-2).

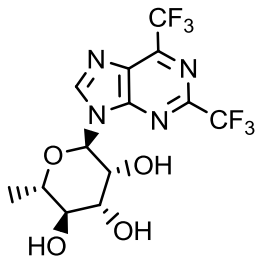
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 17.3 (CH_3), 66.3 (C-5'), 72.6 (C-6'), 73.5 (C-4'), 74.4 (C-3'), 79.2 (C-2'), 111.5 (C-5), 121.4 (q, CF_3, $^{1}J_{(C-F)}$= 273.6 Hz), 122.2 (q, CF_3, $^{1}J_{(C-F)}$= 273.6 Hz), 127.5 (q, C-4, $^{2}J_{(C-F)}$ = 34.0 Hz), 133.5 (C-3a), 140.6 (q, C-6, $^{2}J_{(C-F)}$ = 35.2 Hz), 148.1 (C-2), 150.0 (C-7a).

GC-MS (EI, 70 eV): *m/z* (%): 298 (10), 284 (100), 256 (31), 236 (29), 111 (11), 85 (15), 60 (38).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{14}H_{14}F_6N_3O_4$: 402.0883; found: 402.0892.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3310, 1485, 1317, 1274, 1138, 1126, 1092, 1034, 954, 883, 736, 658.

3-(α-L-Rhamnosyl)-2,6-bis(trifluoromethyl)-9*H*-purine (73)



Starting from 3-(Triacetyl-α-L-rhamnosyl)-2,6-bis(trifluoromethyl)-9*H*-purine (528 mg, 1.00 mmol) **65**; **73** was isolated as white oil, yield = 382 mg (96%);

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.38 (d, 3H, CH_3, ^{3}J = 6.9 Hz), 3.59 (dd, 1H, H-5', $^{3}J_{1}$ = 4.5 Hz, , $^{3}J_{2}$ = 4.5 Hz), 3.98 (br. m, 2H, H-4',H-6'), 4.66 (dt, 1H, H-3', $^{3}J_{1}$ = 5.4 Hz, $^{3}J_{2}$ = 3.0 Hz), 5.25 (br. m, 3H, OH), 6.14 (d, 1H, H-2', ^{3}J = 8.1 Hz), 9.37 (s, 1H, H-8).

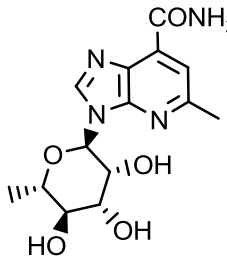
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 17.3 (CH_3), 66.5 (C-5'), 72.3 (C-6'), 73.3 (C-4'), 74.6 (C-3'), 80.2 (C-2'), 119.5 (q, CF_3, $^{1}J_{(C-F)}$= 274.9 Hz), 120.3 (q, CF_3, $^{1}J_{(C-F)}$= 275.5 Hz), 131.7 (C-5), 142.8 (q, C-6, $^{2}J_{(C-F)}$ = 36.9 Hz), 147.6 (q, C-2, $^{2}J_{(C-F)}$ = 36.5 Hz), 151.4 (C-8), 154.6 (C-4).

GC-MS (EI, 70 eV): *m/z* (%): 366 (10), 323 (22), 299 (28), 285 (100), 257 (60), 237 (60), 187 (21), 146 (32), 111 (28).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{13}H_{13}F_6N_4O_4$: 403.0836; found: 403.0837.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3318, 1516, 1444, 1286, 1271, 1126, 1068, 1029, 966, 883, 647.

3-(α-L-Rhamnosyl)-5-methyl-3*H*-imidazo[4,5-b]pyridine-7-carboxamide (74)



Starting from methyl 3-(triacetyl-α-L-rhamnosyl)-5-methyl-3*H*-imidazo[4,5-b]pyridine-7-carboxylate (463 mg, 1.00 mmol) **66**; **74** was isolated as white powder, yield = 316 mg (98%); mp – dec.;

^{1}H NMR (250.13 MHz, DMSO-d_6): δ = 1.28 (d, 3H, CH_3, ^{3}J = 6.9 Hz), 2.59 (s, 3H, CH_3), 3.63 (t, 1H, H-5', ^{3}J = 3.5 Hz), 3.48 (dd, 1H, H-4', $^{3}J_1$ = 4.5 Hz, $^{3}J_2$ = 4.2 Hz), 3.90 (m, 1H, H-6'), 4.56 (dt, 1H, H-3', $^{3}J_1$ = 3.8 Hz, $^{3}J_2$ = 3.0 Hz), 5.10 (br. m, 3H, OH), 6.03 (d, 1H, H-2', ^{3}J = 8.0 Hz), 7.60 (s, 1H, H-5), 8.05 (s, 1H, $CONH_2$), 8.72 (br. s., 2H, H-2, $CONH_2$).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 17.5 (CH_3), 24.1 (CH_3), 66.5 (C-5'), 72.6 (C-6'), 73.4 (C-4'), 74.2 (C-3'), 78.4 (C-2'), 117.1 (C-5), 130.0 (C-4), 130.2 (C-6), 144.2 (C-2), 147.4 (C-3a), 153.6 (C-7a), 164.5 (*C*ONH_2).

GC-MS (EI, 70 eV): *m/z* (%): 205 (12), 176 (87), 133 (97), 106 (22), 92 (56), 65 (18), 52 (14).

HRMS (ESI): $[M+H]^+$ *m/z* calcd. for $C_{14}H_{19}N_4O_5$: 323.1350; found: 323.1352.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3317, 1662, 1620, 1580, 1489, 1410, 1283, 1245, 1144, 1105, 1039, 911, 865, 785, 604.

1.2.3 Supplement to paragraph 4

General Procedure for the Synthesis of Compounds 75a–p, 79a-d, 92

To a Schlenk flask, set with reflux, CH_2Cl_2 (3 mL), corresponding amine (0.0055 mol), and methyl N-(cyanomethyl)-formimidate (0.005 mol) were added under an argon atmosphere at r.t. The reaction mixture was refluxed during 1 h 20 min and after that, the mixture was cooled down to room temperature. 1,3-Dicarbonyl compound was added, and the mixture continued to stir at the same temperature for 15–20 min and then refluxed for 6 h. The solvent was evaporated to dryness and the residue was purified by column chromatography to give the desired compound.

General Procedure for the Synthesis of Compounds 77a–d

To a Schlenk flask, set with reflux, CH_2Cl_2 (3 mL), corresponding amine (0.0055 mol), and methyl N-(cyanomethyl)-formimidate (0.005 mol) were added under an argon atmosphere at r.t. The reaction mixture was refluxed during 1 h 20 min and after that, the mixture was cooled down to room temperature, and then to 0 °C on an ice bath. Afterwards, corresponding 1,3,5-triazine was added, and the mixture continued to stir at the same temperature for 15–20 min and then refluxed for 7 h. The solvent was evaporated to dryness and the residue was purified by column chromatography to give the desired compound.

General Procedure for the Synthesis of Compounds 76a–k, 76o, 78a-c

To an argon-purged pressure tube, filled with 200 mg of corresponding substrates **5** or **8** , $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), and base (2 or 2,5 equiv.) 3,5 ml of dry DMF were added. Pressure tube was capped and reaction mixture was heated at required temperature (mentioned in body manuscript). After the reaction is complete, the solution was diluted with 20 ml of chloroform, and liquid residues were evaporated under vacuum. The crude product was isolated via column chromatography.

General Procedure for the Synthesis of Compounds 76a, 76c (alternative oxidative arylation), 80a-b, 82, 87a-b

200 mg (1 equiv.) of corresponding imidazo[4,5-b]pyridine was dissolved in 4 ml of acetic acid. Afterwards $Pd(OAc)_2$ (10 mol %) and anhydrous $Cu(OAc)_2$ (2,5 equiv.) or AgOAc (2,5 equiv.) (in case of 87b) were added and reaction mixture was heated up to 110°C under air athmosphere during 8 h. As reaction is completed, the solvent was evaporated under vacuum, the residue was treated with water (30 ml). Organic residues were extracted with EtOAc (3x 100 ml), washed with water and dried over sodium sulphate. After evaporation of solvent, the desirable product was isolated by column chromatography.

General Procedure for the Synthesis of Compounds 81a-b, 83, 84, 86a-b, 88a-b, 89a-f, 93a-b

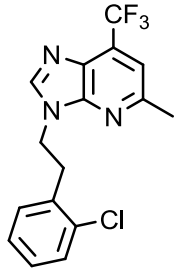
To the solution of -NH- containing heterocycle (300 mg, 1 equiv.) in dry DMF (4 ml) sodium hydride (1.1 equiv.) was added portionwise. After hydrogen evolution was over, corresponding alkylating agent (1 equiv.) was added. The mixture was stirred at r.t. during 2 hours, and then was poured into water. The mixture was extracted with EtOAc (3x 100 ml), organic layers were washed with water and dried over sodium sulphate. After evaporation of solvent, the residue was purified by column chromatography (in case of **88a**, product was recrystalized from 60% aq. ethanol).

General Procedure for the Synthesis of Compounds 90a-f, 91a-b

200 mg (1 equiv.) of corresponding benzimidazole was dissolved in 4 ml of pivalic acid. Afterwards $Pd(OAc)_2$ (10 mol %), anhydrous $Cu(OAc)_2$ (2,5 equiv.), K_2CO_3 (2 equiv.) were added and reaction mixture was heated up to 140°C under air athmosphere during 14 h. As reaction is completed, the crude mixture was treated with 20% aq. NaOH, till the full neutralisation of acid and then with conc. aq. NH_4Cl (50 ml) and left to stay for 1 hour. Organic residues were extracted with EtOAc (3x 150 ml),

washed with water and dried over sodium sulphate. After evaporation of solvent, the desirable product was isolated by column chromatography.

3-[2-(2-Chlorophenyl)ethyl]-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (75a)



Starting from 2-(2-chlorophenyl)ethylamine (856 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 1,1,1-trifluoropentane-2,4-dione (770 mg, 5 mmol); **75a** was isolated as light-yellow crystals, yield = 1.48 g (80%); mp = 86 - 89°C;

^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 2.66 (s, 3H, CH_3), 3.27 (t, 2H, CH_2, ^{3}J = 7.0 Hz), 4.52 (t, 2H, CH_2, ^{3}J = 7.0 Hz), 6.84 (dd, 1H, H-6', ^{3}J = 6.0 Hz, ^{4}J = 1.5 Hz), 7.09 (br. m, 4H, H-3', H-4', H-5', H-6), 7.68 (s, 1H, H-2).

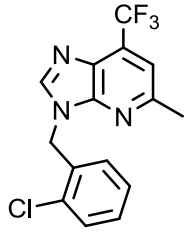
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 23.5 (CH_3), 33.1 (CH_2), 42.3 (CH_2), 113.2 (d, C-6, $^{3}J_{C-F}$ = 4.4 Hz), 121.9 (q, CF_3, $^{1}J_{C-F}$ = 273.6 Hz), 126.1 (C-6'), 127.5 (q, C-7, $^{2}J_{C-F}$ = 34.0 Hz), 127.7 (C-4'), 128.8 (C-3'), 130.0 (C-5'), 133.0 (C-2'), 134.0 (C-1'), 143.8 (C-2), 146.9 (C-7a), 153.0 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 339 (59) [M^+], 214 (39), 201 (100), 138 (39).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{14}ClF_3N_3$: 340.0823; found: 340.0828.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1600, 1493, 1477, 1392, 1363, 1295, 1271, 1252, 1205, 1156, 1123, 1102, 892, 861, 753, 665 .

3-(2-Chlorobenzyl)-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (75b)



Starting from 2-chlorobenzylamine (779 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 1,1,1-trifluoropentane-2,4-dione (770 mg, 5 mmol); **75b** was isolated as light-yellow crystals, yield = 1.22 g (68%); mp = 101 - 102°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.66 (s, 3H, CH_3), 5.53 (s, 2H, CH_2), 7.21 (br. m, 5H, H-6, H-3', H-4', H-5', H-6'), 8.08 (s, 1H, H-2).

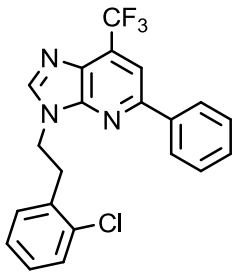
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 24.5 (CH_3), 44.8 (CH_2), 114.5 (q, C-6, $^{3}J_{C-F}$ = 4.5 Hz), 122.8 (q, CF_3, $^{1}J_{C-F}$ = 274.0 Hz), 127.4 (C -6'), 128.8 (q, C-7, $^{2}J_{C-F}$ = 34.0 Hz), 129.4 (C-4', C-5'), 130.2 (C-3'), 133.1 (C-2'), 133.5 (C-5), 144.8 (C-2), 145.0 (C-3a), 148.0 (C-7a), 154.4 (C-1').

GC-MS (EI, 70 eV): *m/z* (%): 290 (100), 125 (14).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}ClF_3N_3$: 326.0666; found: 326.0671.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1488, 1441, 1402, 1364, 1290, 1273, 1125, 1041, 895, 754.

3-[2-(2-Chlorophenyl)ethyl]-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (75c)



Starting from 2-(2-chlorophenyl)ethylamine (856 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 3-benzoyl-1,1,1-trifluoroacetone (1.08 g, 5 mmol); **75c** was isolated as light-red crystals, yield = 1.81 g (82%); mp = 122 - 125°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.35 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.61 (t, 2H, CH_2, ^3J = 6.9 Hz), 6.87 (dd, 1H, H-6“, ^3J = 5.7 Hz, ^4J = 1.8 Hz), 7.06 (br. m, 2H, H-4”, H-5”), 7.31 (dd, 1H, H-3”, ^3J = 6.6 Hz, ^4J = 1.5 Hz), 7.45 (br. m, 3H, H-3’, H-4’, H-5’), 7.82 (s, 1H, H-6), 7.86 (s, 1H, H-2), 8.04 (m, 2H, H-2’, H-6’).

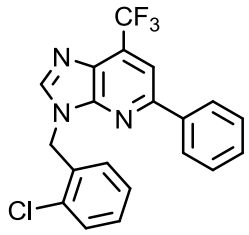
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 34.3 (CH_2), 43.5 (CH_2), 111.6 (d, C-6, $^3J_{C-F}$ = 4.4 Hz), 122.9 (q, CF_3, $^1J_{C-F}$ = 273.6 Hz), 127.1 (C-3’, C-5’), 127.17 (C-4”), 128.5 (q, C-7, $^2J_{C-F}$ = 35.5 Hz), 128.7 (C-4’), 128.9 (C-2’, C-6’), 129.4 (C-6”), 129.8 (C-5”), 130.2 (C-2”), 131.0 (C-3”), 134.0 (C-1’), 135.0 (C-1”), 138.4 (C-5), 145.8 (C-2), 148.4 (C-7a), 152.8 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 401 (23) [M^+], 263 (100).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}ClF_3N_3$: 402.0979; found: 402.0988.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3071, 1605, 1475, 1375, 1289, 1261, 1200, 1119, 941, 864, 741, 687.

3-(2-Chlorobenzyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (75d)



Starting from 2-chlorobenzylamine (779 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 3-benzoyl-1,1,1-trifluoroacetone (1.08 g, 5 mmol); **75d** was isolated as light-pink crystals, yield = 1.53 g (72%); mp = 152 - 154°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.59 (CH_2), 7.37 (br. m, 7H, H-3’, H-4’, H-5’, H-3”, H-4”, H-5”, H-6”), 7.86 (s, 1H, H-6), 8.01 (dd, 2H, H-2’, H-6’, ^3J = 5.1 Hz, ^4J = 1.8 Hz), 8.03 (s, 1H, H-2).

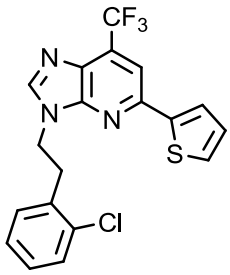
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 45.1 (CH_2), 111.9 (q, C-6, $^{3}J_{C-F}$ = 4.5 Hz), 122.9 (q, CF_3, $^{1}J_{C-F}$ = 274.0 Hz), 127.2 (C-4"), 127.4 (C-6"), 128.8 (q, C-7, $^{2}J_{C-F}$ = 34.7 Hz), 129.0 (C-5"), 129.4 (C-3"), 129.7 (C-2"), 129.9 (C-1"), 130.0 (C-3', C-5'), 130.1 (C-4'), 130.7 (C-2', C-6'), 133.0 (C-1'), 138.4 (C-5), 146.1 (C-2), 148.5 (C-7a), 153.1 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 387 (68) [M^+], 306 (32), 263 (100), 125 (44), 91 (14).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{20}H_{13}ClF_3N_3$: 387.0796; found: 387.0789.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3068, 1602, 1481, 1445, 1373, 1288, 1256, 1208, 1124, 1054, 949, 874, 748, 678, 634.

3-[2-(2-Chlorophenyl)ethyl]-5-(2-thienyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (75e)



Starting from 2-(2-chlorophenyl)ethylamine (856 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (1.11 g, 5 mmol); **75e** was isolated as light-yellow crystals, yield = 1.86 g (87%); mp = 110 - 111°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.33 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 4.55 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 6.91 (dd, 1H, H-4', ^{3}J = 5.7 Hz, ^{4}J = 1.8 Hz), 7.06 (br.m, 3H, H-3', H-4", H-6"), 7.30 (m, 1H, H-5"), 7.37 (dd, 1H, H-3", ^{3}J = 4.2 Hz, ^{4}J = 0.9 Hz), 7.61 (dd, 1H, H-5', $^{3}J_1$ = 3.6 Hz, $^{3}J_2$ = 1.2 Hz), 7.73 (s, 1H, H-6), 7.74 (s, 1H. H-2).

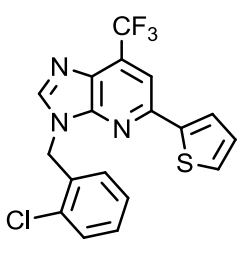
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 34.3 (CH_2), 43.6 (CH_2), 110.5 (d, C-6, $^{3}J_{C-F}$ = 4.5 Hz), 123.1 (q, CF_3, $^{1}J_{C-F}$ = 274.0 Hz), 125.5 (C-4'), 127.2 (C-3'), 128.2 (C-6"), 128.3 (C-4"), 129.7 (q, C-7, $^{2}J_{C-F}$ = 34.7 Hz), 129.9 (C-5"), 130.0 (C-5'), 131.1 (C-3"), 134.1 (C-2"), 134.9 (C-2'), 144.0 (C-5), 145.5 (C-2), 148.0 (C-7a), 148.2 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 407 (29) [M^+], 269 (100).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{19}H_{13}ClF_3N_3S$: 407.0465; found: 407.0464.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1598, 1537, 1496, 1430, 1375, 1257, 1202, 1116, 935, 866, 706.

3-(2-Chlorobenzyl)-5-(2-thienyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (75f)



Starting from 2-chlorobenzylamine (779 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-

dione (1.11 g, 5 mmol); **75f** was isolated as light-yellow crystals, yield = 1.36 g (63%); mp = 116 - 117°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.54 (s, 2H, CH_2), 7.06 (dd, 1H, H-4', $^3J_1$ = 4.8 Hz, $^3J_2$ = 1.2 Hz), 7.20 (m, 2H, H-3', H-6"), 7.35 (m, 2H, H-4", H-5"), 7.50 (dd, 1H, H-3", ^3J = 3.0 Hz, ^4J = 1.2 Hz), 7.59 (dd, 1H, H-5', ^3J = 3.3 Hz, ^4J = 1.2 Hz), 7.74 (s, 1H, H-6), 8.18 (s, 1H, H-2).

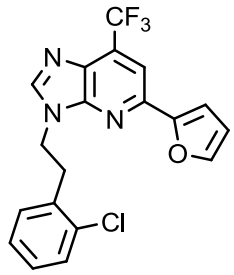
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 45.3 (CH_2), 110.6 (d, C-6, $^3J_{C-F}$ = 4.5 Hz), 122.7 (q, CF_3, $^1J_{C-F}$ = 274.0 Hz), 125.5 (C-4'), 127.4 (C-3'), 128.2 (C-6"), 128.3 (C-4"), 129.3 (q, C-7, $^2J_{C-F}$ = 34.7 Hz), 130.0 (C-5"), 130.2 (C-5'), 131.4 (C-3"), 132.8 (C-2"), 133.9 (C-2'), 144.1 (C-5), 145.7 (C-2), 148.1 (C-7a), 148.3 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 393 (33) [M^+], 358 (100), 125 (32).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{12}ClF_3N_3S$: 394.0378; found: 394.0392.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2985, 1596, 1495, 1431, 1349, 1263, 1131, 939, 866, 745.

3-[2-(2-Chlorophenyl)ethyl]-5-(2-furyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (75g)



Starting from 2-(2-chlorophenyl)ethylamine (856 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione (1.03 g, 5 mmol); **75g** was isolated as light-brown crystals, yield = 1.53 g (71%); mp = 120 - 121°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.36 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.64 (t, 2H, CH_2, ^3J = 6.9 Hz), 6.72 (dd, 1H, H-4', $^3J_1$ = 1.8 Hz, $^3J_2$ = 1.8 Hz), 7.23 (br. m, 4H, H-3", H-4", H-3', H-6"), 7.39 (m, 1H, H-5"), 7.83 (s, 1H, H-6), 7.90 (dd, 1H, H-5', $^3J_1$ = 1.2 Hz, $^3J_2$ = 1.2 Hz), 8.54 (s, 1H, H-2).

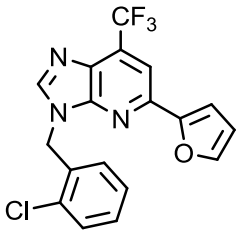
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 33.1 (CH_2), 42.9 (CH_2), 108.8 (d, C-6, $^3J_{C-F}$ = 4.5 Hz), 109.6 (C-4'), 112.5 (C-3'), 122.7 (q, CF_3, $^1J_{C-F}$ = 273.2 Hz), 126.6 (q, C-7, $^2J_{C-F}$ = 33.2 Hz), 127.2 (C-4"), 128.2 (C-2"), 128.6 (C-6"), 129.2 (C-5"), 131.1 (C-3"), 133.3 (C-2'), 135.3 (C-5), 143.5 (C-7a), 144.6 (C-5'), 147.8 (C-2), 148.3 (C-3a), 152.2 (C-1").

GC-MS (EI, 70 eV): *m/z* (%): 391 (33) [M^+], 253 (100).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{19}H_{13}ClF_3N_3O$: 391.0292; found: 391.0289.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3084, 1602, 1493, 1363, 1255, 1205, 1125, 1007, 953, 861, 815, 732, 665.

3-(2-Chlorobenzyl)-5-(2-furyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (75h)



Starting from 2-chlorobenzylamine (779 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione (1.03 g, 5 mmol); **75h** was isolated as brown crystals, yield = 1.22 g (59%); mp = 137 - 139°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.57 (s, 2H, CH_2), 6.51 (dd, 1H, H-4', $^3J_1$ = 1.8 Hz, $^3J_2$ = 1.8 Hz), 7.09 (dd, 1H, H-3', ^3J = 2.7 Hz, ^4J = 0.9 Hz), 7.30 (br.m, 4H, H-3", H-4", H-5", H-6"), 7.51 (dd, 1H, H-5', ^3J = 1.2 Hz, ^4J = 0.6 Hz), 7.86 (s, 1H, H-6), 8.16 (s, 1H, H-2).

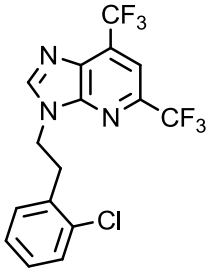
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 45.01 (CH_2), 109.4 (C-4'), 110.4 (q, C-6, $^3J_{C-F}$ = 4.4 Hz), 112.3 (C-3'), 122.7 (q, CF_3, $^1J_{C-F}$ = 273.6 Hz), 127.4 (C-6"), 129.3 (q, C-7, $^2J_{C-F}$ = 34.0 Hz), 130.0 (C-4"), 130.1 (C-3"), 130.6 (C-5"), 132.9 (C-2"), 133.7 (C-1"), 143.8 (C-2), 145.0 (C-5'), 145.6 (C-2'), 148.2 (C-7a), 153.1 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 377 (34) [M^+], 342 (100), 125 (32).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{12}ClF_3N_3O$: 378.0616; found: 378.0613.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1603, 1479, 1455, 1384, 1261, 1230, 1120, 971, 870, 769, 688.

3-[2-(2-Chlorophenyl)ethyl]-5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (75i)



Starting from 2-(2-chlorophenyl)ethylamine (856 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 1,1,1,5,5,5-hexafluoropentane-2,4-dione (1.04 g, 5 mmol); **75i** was isolated as light-brown crystals, yield = 1.19 g (55%); mp = 94 - 95°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.30 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.61 (t, 2H, CH_2, ^3J = 6.9 Hz), 6.83 (dd, 1H, H-6',^3J = 5.7 Hz, ^4J = 1.8 Hz), 7.09 (br.m, 2H, H-4', H-5'), 7.29 (dd, 1H, H-3', ^3J = 6.6 Hz, ^4J = 1.8 Hz), 7.78 (s, 1H, H-6), 7.96 (s, 1H, H-2).

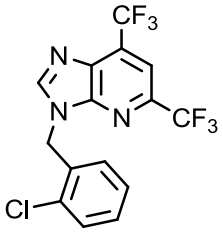
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 34.0 (-CH_2-), 43.9 (-CH_2-), 111.4 (C-6), 121.4 (q, CF_3, $^1J_{C-F}$ = 274.0 Hz), 122.1 (q, CF_3, $^1J_{C-F}$ = 274.7 Hz), 127.3 (C-6'), 129.0 (C-4'), 129.4 (q, C-7, $^2J_{C-F}$ = 35.5 Hz), 130.0 (C-5'), 131.0 (C-3'), 133.2 (C-2'), 134.1 (C-1'), 134.5 (C-2), 142.7 (q, C-5, $^2J_{C-F}$ = 35.8 Hz), 148.0 (C-7a), 148.6 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 393 (44) [M^+], 268 (13), 248 (14), 138 (100), 125 (34), 103 (17).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{11}ClF_6N_3$: 394.0540; found: 394.0544.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3087, 1657, 1602, 1489, 1477, 1399, 1270, 1248, 1131, 879, 749, 655.

3-(2-Chlorobenzyl)-5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (75j)



Starting from 2-chlorobenzylamine (779 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 1,1,1,5,5,5-hexafluoropentane-2,4-dione (1.04 g, 5 mmol); **75j** was isolated as brown crystals, yield = 1.19 g (57%); mp = 109 - 111°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.59 (s, 2H, CH_2), 7.22 (br. m, 2H, H-4', H-6'), 7.38 (br. m, 2H, H-3', H-5'), 7.79 (s, 1H, H-6), 8.38 (s, 1H, H-2).

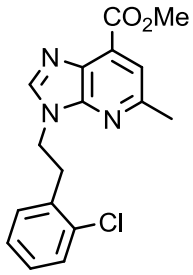
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 45.6 (CH_2), 111.6 (q, C-6, $^3J_{C-F}$ = 3.0 Hz), 121.4 (q, CF_3, $^1J_{C-F}$ = 274.0 Hz), 122.1 (q, CF_3, $^1J_{C-F}$ = 274.0 Hz), 127.6 (C-4'), 129.6 (q, C-7, $^2J_{C-F}$ = 34.7 Hz), 130.1 (C-6'), 130.6 (C-5'), 131.4 (C-3'), 132.0 (C-2'), 133.2 (C-1'), 133.9 (C-7a), 142.8 (q, C-5, $^2J_{C-F}$ = 34.7 Hz), 148.1 (C-3a), 148.6 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 344 (100), 125 (23).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_9ClF_6N_3$: 380.0384; found: 380.0383.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3073, 1486, 1397, 1285, 1260, 1176, 1130, 1108, 1053, 961, 881, 745, 657.

Methyl 3-[2-(2-chlorophenyl)ethyl]-5-methyl-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (75k)



Starting from 2-(2-chlorophenyl)ethylamine (856 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and methyl 2,4-dioxopentanoate (720 mg, 5 mmol); **75k** was isolated as yellow powder, yield = 1.10 g (61%); mp = 77 - 79°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.74 (s, 3H, CH_3), 3.38 (t, 2H, CH_2, ^3J = 6.6 Hz), 4.11 (s, 3H, OCH_3), 4.66 (t, 2H, CH_2, ^3J = 6.9 Hz), 6.90 (dd, 1H, H-6', ^3J = 5.7 Hz, ^4J = 1.8 Hz), 7.09 (m, 1H, H-4'), 7.19 (m, 1H, H-5'), 7.39 (dd, 1H, H-3', ^3J = 6.6 Hz, ^4J = 1.2 Hz), 7.74 (s, 1H, H-6), 7.97 (s, 1H, H-2).

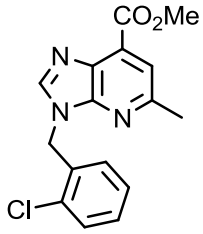
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 24.3 (CH_3), 34.0 (CH_2), 43.3 (CH_2-, 52.8 (-OCH_3), 118.9 (C-6), 127.1 (C-6'), 128.3 (C-7), 128.6 (C-4'), 129.8 (C-3'), 131.0 (C-5'), 131.1 (C-2'), 134.0 (C-5), 135.1 (C-1'), 145.0 (C-2), 148.2 (C-7a), 153.8 (C-3a), 166.0 (-*C*$OOCH_3$).

GC-MS (EI, 70 eV): *m/z* (%): 329 (45) [M^+], 204 (15), 172 (12), 133 (100), 103 (11).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}ClN_3O_2$: 330.1004; found: 330.1003.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3050, 2946, 1717, 1583, 1503, 1474, 1430, 1377, 1351, 1243, 1150, 757.

Methyl 3-(2-chlorobenzyl)-5-methyl-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (75l)



Starting from 2-chlorobenzylamine (779 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and methyl 2,4-dioxopentanoate (720 mg, 5 mmol); **75l** was isolated as yellow powder, yield = 952 mg (55%); mp = 93 - 94°C;

^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 2.65 (s, 3H, CH_3), 4.02 (s, 3H, OCH_3), 5.54 (s, 2H, CH_2), 7.19 (br. m, 4H, H-3', H-4', H-5', H-6'), 7.65 (s, 1H, H-6), 8.13 (s, 1H, H-2).

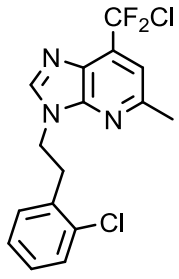
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 24.4 (CH_3), 44.9 (CH_2), 52.9 (OCH_3), 119.4 (C-6), 127.3 (C-6'), 128.5 (C-7), 129.8 (C-3', C-4'), 129.9 (C-2'), 130.0 (C-5'), 133.2 (C-1'), 133.4 (C-5), 144.9 (C-2), 148.2 (C-7a), 154.4 (C-3a), 165.8 (-*C*$OOCH_3$).

GC-MS (EI, 70 eV): *m/z* (%): 280 (100), 125 (17).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}ClN_3O_2$: 316.0847; found: 316.0846.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1712, 1582, 1484, 1381, 1354, 1246, 1226, 1127, 1039, 998, 758, 628.

7-[Chloro(difluoro)methyl]-3-[2-(2-chlorophenyl)ethyl]-5-methyl-3*H*-imidazo[4,5-*b*]pyridine (75m)



Starting from 2-(2-chlorophenyl)ethylamine (856 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 1-chloro-1,1-difluoropentane-2,4-dione (850 mg, 5 mmol); **75m** was isolated as yellow oil, yield = 1.64 g (84%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.65 (s, 3H, CH_3), 3.27 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.51 (t, 2H, CH_2, ^3J = 6.9 Hz), 6.85 (dd, 1H, H-6', ^3J = 5.7 Hz, ^4J = 1.8 Hz), 7.09 (br. m, 4H, H-3', H-4', H-5', H-6), 7.72 (s, 1H, H-2).

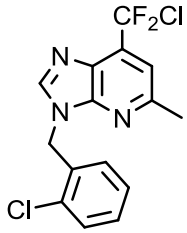
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 24.5 (CH_3), 34.1 (CH_2), 43.3 (CH_2), 112.9 (t, C-6, $^{3}J_{C-F}$ = 5.7 Hz), 124.3 (t, CF_2Cl, $^{1}J_{C-F}$ = 291.3 Hz), 127.1 (C-4'), 128.2 (C-2'), 128.6 (C-6'), 129.8 (C-5'), 131.0 (C-3'), 133.9 (t, C-7, $^{2}J_{C-F}$ = 28.3 Hz), 134.0 (C-5), 135.0 (C-1'), 144.5 (C-2), 148.1 (C-7a), 154.0 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 355 (75) [M^+], 320 (34), 217 (100), 182 (80), 138 (38), 103 (17).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{14}Cl_2F_2N_3$: 356.0527; found: 356.0527.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3002, 1594, 1477, 1413, 1322, 1223, 1201, 1020, 877, 744.

3-(2-Chlorobenzyl)-7-[chloro(difluoro)methyl]-5-methyl-3*H*-imidazo[4,5-*b*]pyridine (75n)



Starting from 2-chlorobenzylamine (779 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 1-chloro-1,1-difluoropentane-2,4-dione (850 mg, 5 mmol); **75n** was isolated as yellow powder, yield = 1.44 g (77%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.64 (s, 3H, CH_3), 5.51 (s, 2H, CH_2), 7.19 (br. m, H-6, H-3', H-4', H-5', H-6'), 8.08 (s, 1H, H-2).

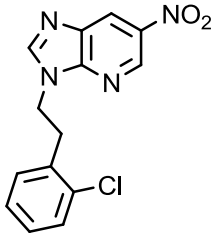
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 23.6 (CH_3), 43.7 (CH_2), 112.2 (t, C-6, $^{3}J_{C-F}$ = 5.3 Hz), 123.2 (t, CF_2Cl, $^{1}J_{C-F}$ = 291.3 Hz), 126.4 (C-4'), 128.2 (C-2'), 128.5 (C-6'), 128.9 (C-5'), 129.2 (C-3'), 132.1 (C-5), 133.0 (t, C-7, $^{2}J_{C-F}$ = 27.9 Hz), 137.5 (C-1'), 143.5 (C-2), 147.1 (C-7a), 153.4 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 306 (100), 271 (10), 125 (22).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}Cl_2F_2N_3$: 342.0371; found: 342.0365.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3067, 1593, 1486, 1444, 1351, 1291, 1198, 1095, 967, 822, 805, 748, 636.

3-[2-(2-Chlorophenyl)ethyl]-6-nitro-3*H*-imidazo[4,5-*b*]pyridine (75o)



Starting from 2-(2-chlorophenyl)ethylamine (856 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 2-nitromalonaldehyde (580 mg, 5 mmol); **75o** was isolated as dark brown crystals, yield = 727 mg (44%); mp = 81 - 83°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.30 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 4.59 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 6.82 (dd, 1H, H-6', ^{3}J = 6.3 Hz, ^{4}J = 1.2 Hz), 7.11 (br. m, 2H, H-4', H-5'), 7.30 (dd, 1H, H-3', ^{3}J = 7.5 Hz, ^{4}J = 0.9 Hz), 7.81 (s, 1H, H-2), 8.79 (d, 1H, H-7, ^{4}J = 2.1 Hz), 9.27 (d, 1H, H-5, ^{4}J = 1.8 Hz).

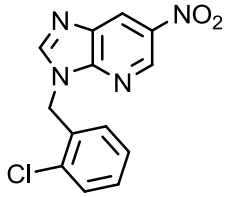
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 33.9 (CH_2), 43.9 (CH_2), 123.8 (C-2'), 127.3 (C-4'), 128.9 (C-6'), 129.9 (C-5'), 130.9 (C-3'), 134.0 (C-1'), 134.2 (C-7a), 134.6 (C-2), 140.9 (C-7), 141.1 (C-5), 147.8 (C-3a), 150.1 (C-6).

GC-MS (EI, 70 eV): *m/z* (%): 267 (100), 138 (37), 125 (17), 103 (13).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{12}ClN_4O_2$: 303.0643; found: 303.0647.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3078, 2964, 1597, 1514, 1441, 1344, 1199, 1051, 915, 760, 642.

3-(2-Chlorobenzyl)-6-nitro-3*H*-imidazo[4,5-*b*]pyridine (75p)



Starting from 2-chlorobenzylamine (779 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 2-nitromalonaldehyde (580 mg, 5 mmol); **75p** was isolated as dark brown crystals, yield = 684 mg (43%); mp = 105 - 107°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.57 (s, 2H, CH_2), 7.28 (br. m, 4H, H-3', H-4', H-5', H-6'), 8.26 (s, 1H, H-2), 8.82 (d, 1H, H-7, ^4J = 1.8 Hz), 9.29 (d, 1H, H-5, ^4J = 1.8 Hz).

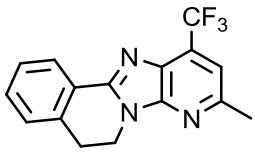
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 45.4 (CH_2), 123.9 (C-2'), 127.5 (C-4'), 130.1 (C-6'), 130.4 (C-5'), 130.7 (C-3'), 132.3 (C-1'), 133.7 (C-7a), 134.1 (C-2), 140.9 (C-7), 141.1 (C-5), 147.9 (C-3a), 150.2 (C-6).

GC-MS (EI, 70 eV): *m/z* (%): 253 (100), 207 (41), 125 (29), 89 (14).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{10}ClN_4O_2$: 289.0487; found: 289.0493.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3076, 1596, 1525, 1467, 1441, 1402, 1345, 1199, 1041, 921, 793, 748, 675, 634.

9-Methyl-11-(trifluoromethyl)-5,6-dihydropyrido[3',2':4,5]imidazo[2,1-*a*]isoquinoline (76a)



Starting from 3-[2-(2-chlorophenyl)ethyl]-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.59 mmol) **75a** or 5-methyl-3-(2-phenylethyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.66 mmol) **79a**; **76a** was isolated as white flakes, yield = 167 mg (93%) (in case of **75a**); yield = 110 mg (61%) (in case of **79a**); mp = 212 - 214°C;

^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 2.64 (s, 3H, CH_3), 3.20 (t, 2H, CH_2, ^3J = 6.8 Hz), 4.42 (t, 2H, CH_2, ^3J = 6.8 Hz), 7.32 (br. m, 4H, H-2, H-3, H-4, H-10), 8.28 (m, 1H, H-1).

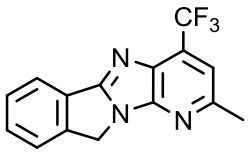
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 24.4 (CH_3), 27.9 (C-5), 39.3 (C-6), 114.1 (d, C-10, $^3J_{C-F}$ = 4.4 Hz), 123.0 (q, CF_3, $^1J_{C-F}$ = 273.6 Hz), 125.8 (C-4a), 126.2 (C-2), 126.9 (q, C-11, $^2J_{C-F}$ = 34.0 Hz), 127.6 (C-4), 128.1 (C-3), 130.5 (C-12b), 131.1 (C-1), 135.2 (C-9), 148.6 (C-11a), 151.2 (C-7a), 152.9 (C-12a).

GC-MS (EI, 70 eV): *m/z* (%): 303 (100) [M^+], 282 (17).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}F_3N_3$: 304.1056; found: 304.1060.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953, 1601, 1484, 1455, 1382, 1364, 1274, 1226, 1125, 1080, 896, 854, 715, 699.

2-Methyl-4-(trifluoromethyl)-10*H*-pyrido[3',2':4,5]imidazo[2,1-*a*]isoindole (76b)



Starting from 3-(2-chlorobenzyl)-5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.62 mmol) **75b**; **76b** was isolated as light-brown crystals, yield = 119 mg (67%); mp = 227 - 229°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.67 (s, 3H, CH_3), 5.15 (s, 2H, CH_2), 7.26 (d, 1H, H-9, ^3J = 3.9 Hz), 7.51 (br. m, 3H, H-3, H-7, H-8), 8.14 (br. s, 1H, H-6).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 23.4 (CH_3), 46.0 (C-10), 113.0 (C-3, d, $^3J_{C-F}$ = 4.4 Hz), 122.0 (C-9), 123.1 (C-8), 122.7 (q, CF_3, $^1J_{C-F}$ = 274.0 Hz), 126.9 (C-4, q, $^2J_{C-F}$ = 34.0 Hz), 127.5 (C-9a), 128.0 (C-7), 129.7 (C-6), 133.7 (C-5b), 135.4 (C-2), 142.8 (C-4a), 151.9 (C-11a), 152.3 (C-5a).

GC-MS (EI, 70 eV): *m/z* (%): 289 (100) [M^+], 269 (24).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{10}F_3N_3$: 290.0900; found: 290.0901.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2926, 1607, 1529, 1446, 1386, 1360, 1267, 1240, 1167, 1117, 900, 775, 727

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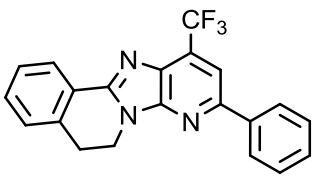
9-Phenyl-11-(trifluoromethyl)-5,6-dihydropyrido[3',2':4,5]imidazo[2,1-*a*]isoquinoline (76c)



Starting from 3-[2-(2-chlorophenyl)ethyl]-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.50 mmol) **75c** or 5-phenyl-3-(2-phenylethyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.54 mmol) **79b**; **76c** was isolated as white flakes, yield = 173 mg (95%) (in case of **75c**); yield = 95 mg (52%) (in case of **79b**); mp = 233 - 234°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.25 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.54 (t, 2H, CH_2, ^3J = 6.9 Hz), 7.42 (br.m, 6H, H-3', H-4', H-5', H-2, H-3, H-4), 7.82 (s, 1H, H-10), 8.05 (dt, 2H, H-2', H-6', ^3J = 4.8 Hz, ^4J = 1.5 Hz), 8.33 (m, 1H, H-1).

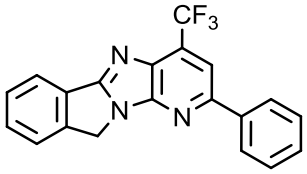
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 28.0 (C-5), 39.4 (C-6), 111.7 (d, C-10, $^{3}J_{C\text{-}F}$ = 4.4 Hz), 123.1 (q, CF_3, $^{1}J_{C\text{-}F}$ = 273.6 Hz), 125.7 (C-1'), 126.4 (C-4), 127.0 (C-3', C-5'), 127.8 (C-3) , 127.8 (q, C-11, $^{2}J_{C\text{-}F}$ = 33.3 Hz), 128.2 (C-2), 128.9 (C-2', C-6'), 129.1 (C-4'), 131.4 (C-1), 131.7 (C-4a), 135.4 (C-11a), 138.6 (C-9), 149.1 (C-11a), 151.9 (C-7a), 152.2 (C-12a).

GC-MS (EI, 70 eV): *m/z* (%): 365 (100) [M^+], 344 (11).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{15}F_3N_3$: 366.1213; found: 366.1209.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3012, 1598, 1490, 1475, 1401, 1386, 1322, 1118, 955, 877, 773, 702.

2-Phenyl-4-(trifluoromethyl)-10*H*-pyrido[3',2':4,5]imidazo[2,1-*a*]isoindole (76d)



Starting from methyl 3-(2-chlorobenzyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.52 mmol) **75d**; **76d** was isolated as pink crystals, yield = 138 mg (76%); mp = 244 - 246°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.21 (s, 2H, CH_2), 7.51 (br. m, 6H, Ph, H-8), 7.83 (s, 1H, H-3), 8.01 (m, 2H, H-7, H-9), 8.17 (dd, 1H, H-6, ^{3}J = 4.5 Hz, ^{4}J = 1.5 Hz).

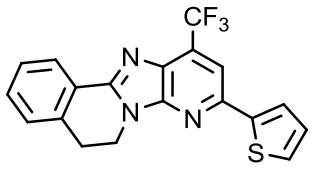
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 47.2 (C-10), 111.6 (d, C-3, $^{3}J_{C\text{-}F}$ = 4.5 Hz), 122.9 (q, CF_3, $^{1}J_{C\text{-}F}$ = 274.2 Hz), 123.1 (C-9), 124.1 (C-8), 127.1 (C-3', C-5'), 128.0 (q, C-4, $^{2}J_{C\text{-}F}$ = 34.7 Hz), 128.8 (C-1'), 128.9 (C-2', C-6'), 129.0 (C-4'), 129.2 (C-7), 130.9 (C-6), 135.5 (C-9a), 138.5 (C-2), 144.0 (C-5b), 147.4 (C-4a), 151.9 (C-11a), 161.5 (C-5a).

GC-MS (EI, 70 eV): *m/z* (%): 351 (100) [M^+], 331 (13).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{13}F_3N_3$: 352.1056; found: 352.1052.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3054, 1613, 1602, 1531, 1474, 1455, 1375, 1265, 1233, 1204, 1120, 973, 871, 770, 729, 685, 613.

9-(2-Thienyl)-11-(trifluoromethyl)-5,6-dihydropyrido[3',2':4,5]imidazo[2,1-*a*]isoquinoline (76e)



Starting from methyl 3-[2-(2-chlorophenyl)ethyl]-5-(2-thienyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.50 mmol) **75e**; **76e** was isolated as light-yellow crystals, yield = 160 mg (88%); mp = 224 - 226°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.23 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 4.49 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 7.06 (dd, 1H, H-4', $^{3}J_1$ = 3.6 Hz, $^{3}J_2$ = 1.2 Hz), 7.34 (br. m, 4H, H-2, H-3, H-4, H-3'), 7.58 (dd, 1H, H-5', $^{3}J_1$ = 2.7 Hz, ^{4}J = 1.2 Hz), 7.70 (s, 1H, H-10), 8.28 (dd, 1H, H-1, ^{3}J = 5.7 Hz, ^{4}J = 3.0 Hz).

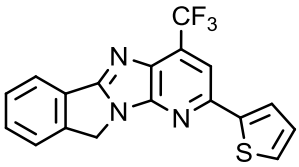
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 28.0 (C-5), 39.4 (C-6), 110.5 (d, C-10, $^{3}J_{C-F}$ = 4.5 Hz), 122.9 (q, CF_3, $^{1}J_{C-F}$ = 274.0 Hz), 125.1 (C-4'), 125.7 (C-4a), 126.4 (C-3'), 127.7 (C-4), 127.8 (C-3), 128.7 (q, C-11, $^{2}J_{C-F}$ = 34.7 Hz), 128.2 (C-2), 128.2 (C-5'), 131.4 (C-1), 131.7 (C-12b), 135.4 (C-11a), 144.3 (C-9), 147.2 (C-11a), 148.8 (C-7a), 152.1 (C-12a).

GC-MS (EI, 70 eV): *m/z* (%): 371 (100) [M^+], 350 (10).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{13}ClF_3N_3S$: 372.0777; found: 372.0782.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3468, 1537, 1487, 1379, 1282, 1257, 1123, 866, 700.

2-(2-Thienyl)-4-(trifluoromethyl)-10*H*-pyrido[3',2':4,5]imidazo[2,1-*a*]isoindole (76f)



Starting from methyl 3-(2-chlorobenzyl)-5-(2-thienyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.51 mmol) **75f**; **76f** was isolated as yellow crystals, yield = 125 mg (69%); mp = 231 - 233°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.29 (s, 2H, CH_2), 7.17 (dd, 1H, H-4', $^{3}J_1$ = 3.6 Hz, $^{3}J_2$ = 1.5 Hz), 7.46 (dd, 1H, H-3', ^{3}J = 3.6 Hz, ^{4}J = 1.2 Hz), 7.68 (br. m, 4H, H-5', H-7, H-8, H-9), 7.83 (s, 1H, H-3), 8.24 (m, 1H, H-6).

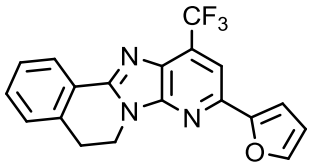
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 47.3 (C-10), 110.3 (q, C-3, $^{3}J_{C-F}$ = 4.4 Hz), 122.6 (q, CF_3, $^{1}J_{C-F}$ = 273.6 Hz),123.1 (C-4'), 124.1 (C-3'), 125.3 (C-9), 127.8 (C-8), 128.3 (C-7), 128.5 (q, C-4, $^{2}J_{C-F}$ = 34.0 Hz),129.0 (C-5'), 130.8 (C-2'), 134.2 (C-2), 144.0 (C-6), 147.1 (C-5b), 152.2 (C-4a), 156.2 (C-11a), 161.3 (C-5a).

GC-MS (EI, 70 eV): *m/z* (%): 357 (100) [M^+].

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{11}F_3N_3S$: 358.0620; found: 358.0623.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1605, 1527, 1456, 1422, 1362, 1266, 1241, 1127, 1009, 977, 880, 726.

9-(2-Furyl)-11-(trifluoromethyl)-5,6-dihydropyrido[3',2':4,5]imidazo[2,1-*a*]isoquinoline (76g)



Starting from methyl 3-[2-(2-chlorophenyl)ethyl]-5-(2-furyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.52 mmol) **75g**; **76g** was isolated as yellow crystals, yield = 143 mg (79%); mp = 230 - 231°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.24 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.49 (t, 2H, CH_2, ^3J = 6.9 Hz), 6.50 (dd, 1H, H-4', $^3J_1$ = 1.8 Hz, $^3J_2$ = 1.8 Hz), 7.05 (dd, 1H, H-3', ^3J = 2.4 Hz, ^4J = 0.9 Hz), 7.36 (br.m, 3H, H-2, H-3, H-4), 7.51 (dd, 1H, H-5', ^3J =1.2 Hz, ^4J = 1.2 Hz), 7.80 (s, 1H, H-10), 8.31 (dd, 1H, H-1, ^3J = 3.6 Hz, ^4J = 2.4 Hz).

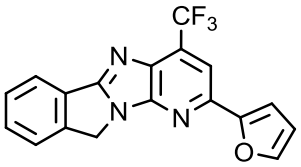
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 27.9 (C-5), 39.4 (C-6), 108.9 (C-4'), 110.4 (d, C-10, $^3J_{C-F}$ = 4.4 Hz), 112.3 (C-3'), 122.9 (q, CF_3, $^1J_{C-F}$ = 273.6 Hz), 125.6 (C-4a), 126.5 (C-4), 127.8 (q, C-11, $^2J_{C-F}$ = 34.0 Hz), 127.8 (C-3), 128.2 (C-2), 131.4 (C-5'), 131.6 (C-9), 135.3 (C-1a), 143.6 (C-1), 143.8 (C-2'), 148.9 (C-11a), 152.2 (C-7a), 153.3 (C-12a).

GC-MS (EI, 70 eV): *m/z* (%): 355 (100) [M^+], 326 (10).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{13}F_3N_3O$: 356.1005; found: 356.1011.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3121, 1599, 1504, 1488, 1454, 1384, 1283, 1151, 1117, 922, 871, 750, 731, 709, 682.

2-(2-Furyl)-4-(trifluoromethyl)-10*H*-pyrido[3',2':4,5]imidazo[2,1-*a*]isoindole (76h)



Starting from methyl 3-(2-chlorobenzyl)-5-(2-furyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.54 mmol) **75h**; **76h** was isolated as yellow needles, yield = 94 mg (52%); mp = 250 - 252°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.28 (s, 2H, CH_2), 6.61 (dd, 1H, H-4', $^3J_1$ = 1.8 Hz, $^3J_2$ = 1.8 Hz), 7.15 (dd, 1H, H-3', ^3J = 2.7 Hz, ^4J = 0.6 Hz), 7.61 (br.m, 4H, H-7, H-8, H-9, H-5'), 7.89 (s, 1H, H-3), 8.22 (dd, 1H, H-6, ^3J = 6.0 Hz, ^4J = 1.5 Hz).

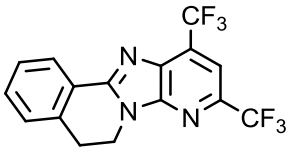
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 47.7 (C-6), 109.1 (C-4'), 110.0 (q, C-3, $^3J_{C-F}$ = 4.5 Hz), 112.3 (C-3'), 122.8 (q, CF_3, $^1J_{C-F}$ = 273.6 Hz), 123.0 (C-9), 124.1 (C-8), 128.3 (C-9a), 128.5 (q, C-4, $^2J_{C-F}$ = 34.0 Hz), 128.9 (C-7), 130.8 (C-5'), 135.6 (C-2), 143.6 (C-6), 143.7 (C-5b), 144.0 (C-2'), 147.2 (C-4a), 153.0 (C-11a), 161.4 (C-5a).

GC-MS (EI, 70 eV): *m/z* (%): 341 (100) [M^+], 312 (11).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{11}F_3N_3O$: 342.0849; found: 342.0851.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3064, 1605, 1527, 1455, 1428, 1378, 1269, 1243, 1203, 1132, 1081, 961, 728.

9,11-bis(Trifluoromethyl)-5,6-dihydropyrido[3',2':4,5]imidazo[2,1-*a*]isoquinoline (76i)



Starting from methyl 3-[2-(2-chlorophenyl)ethyl]-5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.51 mmol) **75i**; **76i** was isolated as white crystals, yield = 160 mg (88%); mp = 237 - 239°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.27 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.52 (t, 2H, CH_2, ^3J = 6.9 Hz), 7.41 (br.m, 3H, H-2, H-3, H-4), 7.74 (s, 1H, H-10), 8.34 (dd, 1H, H-1, ^3J = 7.5 Hz, ^4J = 1.2 Hz),

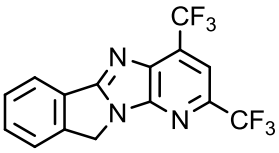
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 27.7 (C-5), 39.8 (C-6), 111.4 (C-10), 121.7 (q, CF_3, $^1J_{C-F}$ = 273.2 Hz), 122.4 (q, CF_3, $^1J_{C-F}$ = 274.0 Hz), 125.0 (C-4a), 127.0 (C-4), 127.8 (q, C-11, $^2J_{C-F}$ = 35.5 Hz), 128.0 (C-3), 128.4 (C-2), 132.4 (C-1), 134.9 (C-11a), 135.8 (C-12b), 141.3 (q, C-9, $^2J_{C-F}$ = 35.9 Hz), 148.9 (C-7a), 155.0 (C-12a).

GC-MS (EI, 70 eV): *m/z* (%): 357 (100) $[M^+]$, 336 (39).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{10}F_6N_3$: 358.0773; found: 358.0783.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961, 1602, 1527, 1485, 1456, 1323, 1271, 1255, 1214, 1133, 1103, 989, 875, 671.

2,4-bis(Trifluoromethyl)-10*H*-pyrido[3',2':4,5]imidazo[2,1-*a*]isoindole (76j)



Starting from methyl 3-(2-chlorobenzyl)-5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.53 mmol) **75j**; **76j** was isolated as light-grey crystals, yield = 116 mg (64%); mp = 240 - 242°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.34 (s, 2H, CH_2), 7.68 (br.m, 3H, H-7, H-8, H-9), 7.88 (s, 1H, H-3), 8.28 (dd, 1H, H-6, ^3J = 3.9 Hz, ^4J = 1.8 Hz).

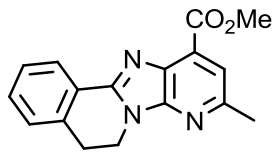
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 47.7 (C-10), 111.2 (d, C-3, $^3J_{C-F}$ = 4.5 Hz), 121.4 (q, CF_3, $^1J_{C-F}$ = 276.2 Hz), 122.0 (q, CF_3, $^1J_{C-F}$ = 276.2 Hz), 123.7 (C-9), 124.3 (C-8), 127.5 (C-9a), 128.5 (q, C-4, $^2J_{C-F}$ = 35.2 Hz), 129.3 (C-7), 131.9 (C-6), 140.2 (q, C-2, $^2J_{C-F}$ = 35.2 Hz), 144.3 (C-5b), 145.1 (C-4a), 147.2 (C-11a), 164.3 (C-5a).

GC-MS (EI, 70 eV): *m/z* (%): 343 (100) $[M^+]$, 323 (55).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_8F_6N_3$: 344.0617; found: 344.0619.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1630, 1528, 1473, 1419, 1366, 1279, 1242, 1126, 978, 883, 732, 672.

Methyl 9-methyl-5,6-dihydropyrido[3',2':4,5]imidazo[2,1-*a*]isoquinoline-11-carboxylate (76k)



Starting from methyl 3-[2-(2-chlorophenyl)ethyl]-5-methyl-3*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (200 mg, 0.61 mmol) **75k**; **76k** was isolated as yellow crystals, yield = 69 mg (39%); mp = 179 - 181°C

^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 2.65 (s, 3H, CH_3), 3.23 (t, 2H, CH_2, ^3J = 6.8 Hz), 4.05 (s, 3H, OCH_3), 4.46 (t, 2H, CH_2, ^3J = 6.8 Hz), 7.37 (br. m, 3H, H-2, H-3, H-4), 7.60 (s, 1H, H-10), 8.44 (m, 1H, H-1).

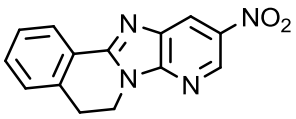
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 24.2 (CH_3), 28.0 (C-5), 39.4 (C-6), 52.8 (OCH_3), 118.9 (C-10), 125.7 (C-11), 126.6 (C-4), 127.7 (C-3), 128.1 (C-2), 131.2 (C-1), 132.2 (C-12b), 135.3 (C-9), 148.8 (C-11a), 151.4 (C-7a) 153.0 (C-12a), 166.0 (*C*OOCH$_3$).

GC-MS (EI, 70 eV): *m/z* (%): 293 (75) [M^+],235 (100), 130 (14).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}N_3O_2$: 294.1237; found: 294.1234.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2948, 1732, 1706, 1591, 1486, 1454, 1424, 1374, 1215, 1088, 713.

10-Nitro-5,6-dihydropyrido[3',2':4,5]imidazo[2,1-*a*]isoquinoline (76o)



Starting from 3-[2-(2-chlorophenyl)ethyl]-6-nitro-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.66 mmol) **75o**; **76o** was isolated as dark-yellow crystals, yield = 91 mg (69%); mp = 279 - 281°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.39 (t, 2H, -CH_2-, ^3J = 6.9 Hz), 4.56 (t, 2H, -CH_2-, ^3J = 6.9 Hz), 7.57 (br. m, 3H, H-2, H-3, H-4), 8.25 (dd, 1H, H-1, ^3J = 3.6 Hz, ^4J = 2.4 Hz), 8.84 (d, 1H, H-11, ^4J = 2.4 Hz), 9.24 (d, 1H, H-9, ^4J = 2.4 Hz).

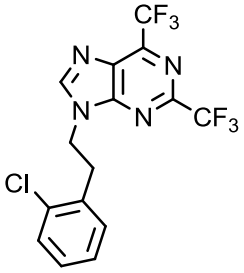
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 26.9 (C-5), 39.4 (C-6), 121.7 (C-11), 125.1 (C-4a), 125.5 (C-1), 127.6 (C-4), 128.7 (C-3), 131.8 (C-2), 134.9 (C-12b), 136.4 (C-11a), 139.7 (C-9), 141.0 (C-7a), 150.8 (C-12a), 153.8 (C-10).

GC-MS (EI, 70 eV): *m/z* (%): 266 (100) [M^+], 220 (36), 208 (13), 130 (11).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{11}N_4O_2$: 267.0877; found: 267.0878.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3073, 1584, 1525, 1454, 1319, 821, 774, 747, 734.

9-[2-(2-Chlorophenyl)ethyl]-2,6-bis(trifluoromethyl)-9*H*-purine (77a)



Starting from 2-(2-chlorophenyl)ethylamine (856 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (1.43 g, 5 mmol); **77b** was isolated as light-brown crystals, yield = 1.47 g (68%); mp = 122 - 124°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.30 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 4.65 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 6.84 (dd, 1H, H-6‘, ^{3}J = 6.0 Hz, ^{4}J = 1.8 Hz), 7.04 (m, 1H, H-4’), 7.16 (m, 1H, H-5’), 7.30 (dd, 1H, H-3’, ^{3}J = 6.4 Hz, ^{4}J = 1.5 Hz), 7.97 (s, 1H, H-8).

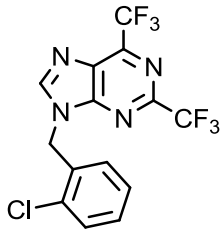
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 32.9 (CH_2), 43.2 (CH_2), 118.4 (q, CF_3, $^{1}J_{C\text{-}F}$ = 274.7 Hz), 119.2 (q, CF_3, $^{1}J_{C\text{-}F}$ = 276.2 Hz), 126.4 (C-6’), 128.2 (C-4’), 129.0 (C-3’), 129.9 (C-5’), 133.0 (C-2’), 144.4 (q, C-6, $^{2}J_{C\text{-}F}$ = 38.5 Hz), 148.6 (C-8), 148.6 (q, C-2, $^{2}J_{C\text{-}F}$ = 37.7 Hz), 153.2 (C-1’).

GC-MS (EI, 70 eV): *m/z* (%): 394 (13) [M^+], 138 (100), 125 (31), 103 (15), 89 (10).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{10}ClF_6N_4$: 395.0493; found: 395.0498.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1601, 1506, 1454, 1442, 1403, 1305, 1271, 1198, 1124, 888, 760, 737, 639.

9-(2-Chlorobenzyl)-2,6-bis(trifluoromethyl)-9*H*-purine (77b)



Starting from 2-chlorobenzylamine (779 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (1.43 g, 5 mmol); **77b** was isolated as light-brown crystals, yield = 1.44 g (69%); mp = 135 - 137°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.60 (s, 2H, CH_2), 7.32 (br. m, 4H, H-3’, H-4’, H-5’, H-6’), 8.44 (s, 1H, H-8).

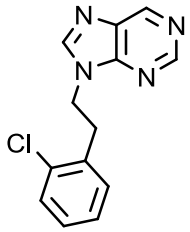
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 46.1 (CH_2), 119.4 (q, CF_3, $^{1}J_{C\text{-}F}$ = 274.9 Hz), 120.2 (q, CF_3, $^{1}J_{C\text{-}F}$ = 276.1 Hz), 127.8 (C-6’), 130.3 (C-4’), 131.02 (C-3’), 131.6 (C-5’), 134.0 (C-2’), 145.6 (q, C-6, $^{2}J_{C\text{-}F}$ = 38.5 Hz), 149.5 (C-8), 150.0 (q, C-2, $^{2}J_{C\text{-}F}$ = 37.7 Hz), 154.2 (C-1’).

GC-MS (EI, 70 eV): *m/z* (%): 361 (14), 345 (100), 125 (84), 89 (23).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_8ClF_6N_4$: 381.0336; found: 381.0340.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3087, 1598, 1500, 1455, 1403, 1309, 1270, 1188, 1125, 1055, 962, 889, 753, 658, 640.

9-[2-(2-Chlorophenyl)ethyl]-9*H*-purine (77c)



Starting from 2-(2-chlorophenyl)ethylamine (856 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 1,3,5-triazine (405 mg, 5 mmol); **77c** was isolated as light-brown crystals, yield = 506 mg (36%); mp = 141 - 143°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.37 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.61 (t, 2H, CH_2, ^3J = 6.9 Hz), 6.90 (dd, 1H, H-6', $^3J_1$ = 6.0 Hz, $^3J_2$ = 1.5 Hz), 7.14 (br.m, 2H, H-4', H-5'), 7.40 (dd, 1H, H-3', $^3J_1$ = 6.6 Hz, $^3J_2$ = 1.5 Hz), 7.73 (s, 1H, H-8), 9.03 (s, 1H, H-6), 9.15 (s, 1H, H-2).

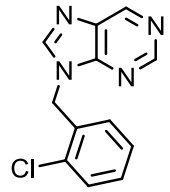
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 33.9 (CH_2), 43.3 (CH_2), 127.2 (C-4'), 128.8 (C-6'), 129.8 (C-3'), 131.1 (C-5'), 134.0 (C-2'), 134.6 (C-1'), 145.2 (C-8), 148.5 (C-6), 151.3 (C-4), 152.5 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 223 (100), 138 (35), 103 (12).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{12}ClN_4$: 259.0745; found: 259.0748.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3081, 1628, 1595, 1579, 1498, 1474, 1409, 1346, 1303, 1200, 1096, 1051, 793, 741.

9-(2-Chlorobenzyl)-9*H*-purine (77d)



Starting from 2-chlorobenzylamine (779 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 1,3,5-triazine (405 mg, 5 mmol); **77d** was isolated as light-brown crystals, yield = 524 mg (39%); mp = 155 - 157°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.51 (s, 2H, CH_2), 7.26 (br.m, 4H, H-3', H-4', H-5', H-6'), 8.10 (s, 1H, H-8), 8.95 (s, 1H, H-6), 9.09 (s, 1H, H-2).

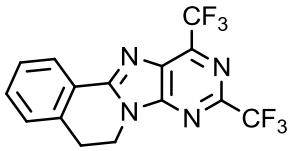
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 44.9 (CH_2), 127.6 (C-4'), 130.1 (C-6'), 130.3 (C-5'), 130.6 (C-3'), 132.5 (C-2'), 133.7 (C-1'), 133.9 (C-5), 145.3 (C-8), 148.8 (C-6), 151.5 (C-4), 152.9 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 209 (100), 125 (15).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{10}ClN_4$: 245.0589; found: 245.0589.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961, 1592, 1579, 1498, 1409, 1347, 1303, 1199, 1162, 1039, 763, 634.

9,11-bis(Trifluoromethyl)-5,6-dihydropurino[8,9-*a*]isoquinoline (78a)



Starting from 9-[2-(2-chlorophenyl)ethyl]-2,6-bis(trifluoromethyl)-9*H*-purine (200 mg, 0.51 mmol) **77a**; **78a** was isolated as white flakes, yield = 164 mg (90%); mp = 253 - 255°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.50 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 4.69 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 7.76 (br.m, 3H, H-2, H-3, H-4), 8.40 (d, 1H, H-1, ^{3}J = 6.6 Hz).

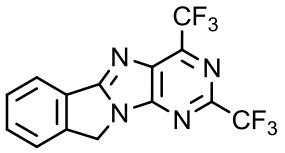
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 26.5 (C-5), 40.0 (C-6), 119.7 (q, CF_3, $^{1}J_{C-F}$ = 274.8 Hz), 120.6 (q, CF_3, $^{1}J_{C-F}$ = 274.8 Hz), 124.0 (C-4a), 126.4 (C-4), 127.7 (C-3), 128.8 (C-2), 132.6 (C-12b), 133.1 (C-1), 137.5 (C-11a), 140.9 (q, C-11, $^{2}J_{C-F}$ = 37.7 Hz), 147.0 (q, C-9, $^{2}J_{C-F}$ = 37.7 Hz), 153.3 (C-7a), 156.5 (C-12a).

GC-MS (EI, 70 eV): *m/z* (%): 358 (100) [M^+], 337 (29).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{10}F_6N_3$: 359.0726; found: 359.0724.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1614, 1524, 1491, 1468, 1427, 1378, 1266, 1190, 1131, 1080, 992, 890, 731, 676.

2,4-bis(Trifluoromethyl)-10*H*-isoindolo[2,1-*e*]purine (78b)



Starting from 9-(2-chlorobenzyl)-2,6-bis(trifluoromethyl)-9*H*-purine (200 mg, 0.53 mmol) **77b**; **78b** was isolated as brown crystals, yield = 85 mg (47%); mp = 260 - 263°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.27 (s, 2H, CH_2), 7.64 (br.m, 3H, H-7, H-8, H-9), 8.21 (dd, 1H, H-6, ^{3}J = 6.0 Hz, ^{4}J = 1.2 Hz).

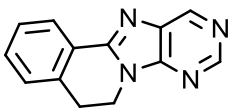
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 48.2 (C-10), 119.7 (q, CF_3, $^{1}J_{C-F}$ = 274.7 Hz), 120.6 (q, CF_3, $^{1}J_{C-F}$ = 275.5 Hz), 123.4 (C-9), 125.2 (C-8), 125.9 (C-9a), 128.7 (q, C-4, $^{2}J_{C-F}$ = 33.2 Hz), 129.3 (C-7), 132.9 (C-6), 140.8 (q, C-2, $^{2}J_{C-F}$ = 34.0 Hz), 146.4 (C-5b), 152.3 (C-4a), 152.3 (C-11a), 165.9 (C-5a).

GC-MS (EI, 70 eV): *m/z* (%): 344 (100) [M^+], 324 (39).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_7F_6N_4$: 345.0569; found: 345.0572.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930, 1626, 1449, 1245, 1209, 1129, 983, 888, 785, 737.

5,6-Dihydropurino[8,9-*a*]isoquinoline (78c)



Starting from 9-[2-(2-chlorophenyl)ethyl]-9*H*-purine (200 mg, 0.78 mmol) **77c**; **78c** was isolated as brown crystals, yield = 165 mg (96%); mp = 280 - 282°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.26 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 4.44 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 7.42 (br. m, 3H, H-2, H-3, H-4), 8.25 (dd, 1H, H-1, ^{3}J = 4.5 Hz, ^{4}J = 1.8 Hz), 8.89 (s, 1H, H-11), 9.04 (s, 1H, H-9).

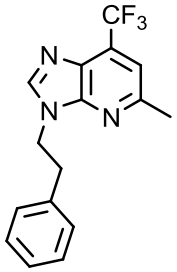
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 27.8 (C-5), 39.2 (C-6), 125.4 (C-11), 126.1 (C-4a), 128.0 (C-1), 128.4 (C-4), 128.9 (C-3), 131.8 (C-2), 135.0 (C-12b), 135.6 (C-11a), 147.1 (C-9), 151.4 (C-7a), 151.9 (C-12a).

GC-MS (EI, 70 eV): *m/z* (%): 222 (100) [M^+].

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}N_4$: 223.0978; found: 223.0981.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963, 1598, 1487, 1456, 1348, 1332, 1298, 1229, 1098, 894, 779, 727, 616.

5-Methyl-3-(2-phenylethyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (6a)



Starting from phenethylamine (666 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 1,1,1-trifluoropentane-2,4-dione (770 mg, 5 mmol); **79c** was isolated as light-yellow crystals, yield = 1.20 g (72%); mp = 83 - 85°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.66 (s, 3H, CH_3), 3.13 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 4.56 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 7.18 (br.m, 6H, H-6, -Ph), 7.69 (s, 1H, H-2).

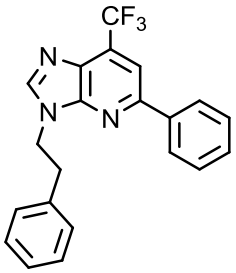
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 19.2 (CH_3), 36.1 (CH_2), 45.3 (CH_2), 114.2 (q, C-6, $^{3}J_{C-F}$ = 4.4 Hz), 122.9 (q, CF_3, $^{1}J_{C-F}$ = 273.6 Hz), 127.0 (C-4'), 128.4 (q, C-7, $^{2}J_{C-F}$ = 34.0 Hz), 128.7 (C-2', C-6'), 128.8 (C-3', C-5'), 129.0 (C-1'), 137.4 (C-5), 144.9 (C-2), 147.9 (C-7a), 154.0 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 305 (97) [M^+],286 (12), 214 (33), 201 (79), 104 (100), 91 (27).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}F_3N_3$: 306.1213 found: 306.1221.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2938, 1596, 1496, 1362, 1255, 1123, 893, 865, 699.

5-Phenyl-3-(2-phenylethyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (79b)



Starting from phenethylamine (666 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 3-benzoyl-1,1,1-trifluoroacetone (1.08 g, 5 mmol); **79b** was isolated as light-red gum, yield = 1.37 g (68%); mp = 111 - 113°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.21 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.56 (t, 2H, CH_2, ^3J = 6.9 Hz), 7.05 (dd, 1H, H-4“, ^3J = 6.6 Hz, ^4J = 1.5 Hz), 7.20 (br. m, 4H, H-2”, H3”, H-5”, H-6”), 7.42 (br.m, 3H, H-3’, H-4’, H-5’), 7.81 (s, 1H, H-6), 7.86 (s, 1H, H-2), 8.02 (dd, 2H, H-2’, H-6’, ^3J = 2.7 Hz, ^4J = 1.8 Hz).

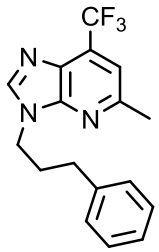
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 36.2 (CH_2), 45.6 (CH_2), 111.7 (d, C-6, $^3J_{C-F}$ = 3.8 Hz), 122.9 (q, CF_3, $^1J_{C-F}$ = 273.6 Hz), 127.1 (C-4”), 127.2 (C-2”, C-6”), 128.1 (q, C-7, $^2J_{C-F}$ = 34.0 Hz), 128.7 (C-3”, C-5”), 128.9 (C-4’), 128.9 (C-3’, C-5’), 129.4 (C-2’, C-6’), 130.2 (C-1”), 137.4 (C-1’), 138.5 (C-5), 145.9 (C-2), 148.3 (C-7a), 152.9 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 367 (34) [M^+], 263 (100).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}F_3N_3$: 368.1369; found: 368.1375.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3066, 1603, 1497, 1373, 1265, 1212, 1119, 871, 767, 686, 621.

5-Methyl-3-(3-phenylpropyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (79c)



Starting from 3-phenylpropan-1-amine (743 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 1,1,1-trifluoropentane-2,4-dione (770 mg, 5 mmol); **79c** was isolated as light-yellow crystals, yield = 1.21 g (69%); mp = 73 - 76°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.23 (t, 2H, CH_2, ^3J = 7.2 Hz), 2.61 (t, 2H, CH_2, ^3J = 7.2 Hz), 2.65 (s, 3H, CH_3), 4.25 (t, 2H, CH_2, ^3J = 7.2 Hz), 7.18 (br. m, 6H, H-6, Ph), 7.99 (s, 1H, H-2).

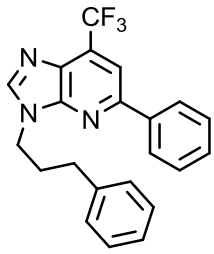
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 24.5 (CH_3), 31.0 (CH_2), 32.7 (CH_2), 43.3 (CH_2), 114.2 (q, C-6, $^3J_{C-F}$ = 4.4 Hz), 122.9 (q, CF_3-, $^1J_{C-F}$ = 273.6 Hz), 126.3 (C-4’), 128.3 (C-3’, C-5’), 128.5 (q, C-2, $^2J_{C-F}$ = 34.0 Hz), 128.6 (C-2’, C-6’), 129.3 (C-1’), 140.2 (C-5), 144.8 (C-2), 148.1 (C-7a), 154.0 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 319 (33) [M^+], 214 (100), 91 (16) .

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}F_3N_3$: 320.1369 found: 320.1370.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3080, 1597, 1497, 1387, 1364, 1302, 1205, 1124, 894, 870, 746, 693.

5-Phenyl-3-(3-phenylpropyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (79d)



Starting from 3-phenylpropan-1-amine (743 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 3-benzoyl-1,1,1-trifluoroacetone (1.08 g, 5 mmol); **79d** was isolated as light-red gum, yield = 1.12 g (53%); mp = 98 - 100°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.35 (t, 2H, CH_2, ^{3}J = 7.2 Hz), 2.73 (t, 2H, CH_2, ^{3}J = 7.2 Hz), 4.48 (t, 2H, CH_2, ^{3}J = 7.2 Hz), 7.27 (br. m, 5H, Ph), 7.58 (br. m, 3H, H-3', H-4', H-5'), 8.17 (s, 1H, H-6), 8.26 (dd, 2H, H-2', H-6', ^{3}J = 6.9 Hz, ^{4}J = 1.2 Hz), 8.79 (s, 1H, H-2).

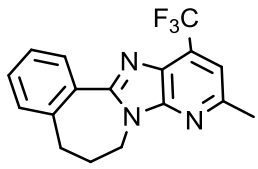
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 30.5 (CH_2), 32.1 (CH_2), 42.9 (CH_2), 110.7 (d, C-6, $^{3}J_{C-F}$ = 4.4 Hz), 122.9 (q, CF_3, $^{1}J_{C-F}$ = 274.2 Hz), 125.8 (C-4"), 126.9 (C-4'), 127.7 (q, C-7, $^{2}J_{C-F}$ = 35.5 Hz), 128.2 (C-2", C-6"), 128.5 (C-3", C-5"), 128.8 (C-3', C-5'), 129.3 (C-2', C-6'), 129.7 (C-1"), 137.7 (C-1'), 140.7 (C-5), 147.9 (C-2), 148.4 (C-7a), 151.2 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 381 (32) [M^+], 276 (100).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}F_3N_3$: 382.1526 found: 382.1525.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079, 1615, 1496, 1378, 1288, 1266, 1122, 944, 868, 770, 688.

10-Methyl-12-(trifluoromethyl)-6,7-dihydro-5*H*-pyrido[3',2':4,5]imidazo[2,1-*a*][2]benzazepine (80a)



Starting from 5-methyl-3-(3-phenylpropyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (200 mg, 0.63 mmol) **79a**; **80a** was isolated as light-yellow crystals, yield = 113 mg (57%); mp = 199 - 201°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.38 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 2.66 (s, 3H, CH_3), 2.75 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 4.25 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 7.38 (br. m, 4H, H-2, H-3, H-4, H-11), 7.95 (dd, 1H, H-1, ^{3}J = 5.4 Hz, ^{4}J = 1.5 Hz).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 24.5 (CH_3), 30.3 (C-6), 30.8 (C-5), 39.7 (C-7), 114.7 (d, C-11, $^{3}J_{C-F}$ = 4.4 Hz), 123.1 (q, CF_3, $^{1}J_{C-F}$ = 273.9 Hz), 127.4 (C-4), 127.8 (q, C-12, $^{2}J_{C-F}$ = 33.2 Hz), 129.6 (C-3),

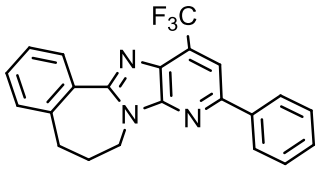
129.7 (C-4a), 130.0 (C-2), 130.1 (C-10), 131.0 (C-1), 139.2 (C-13b), 149.2 (C-12a), 152.9 (C-8a), 156.7 (C-13a).

GC-MS (EI, 70 eV): *m/z* (%): 317 (100) [M^+], 302 (14) .

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{17}H_{15}F_3N_3$: 318.1213 found: 318.1218.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2933, 1479, 1427, 1387, 1309, 1242, 1120, 897, 849, 768, 732, 697, 634.

10-Phenyl-12-(trifluoromethyl)-6,7-dihydro-5*H*-pyrido[3',2':4,5]imidazo[2,1-*a*][2]benzazepine (80b)



Starting from 5-phenyl-3-(3-phenylpropyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (200 mg, 0.52 mmol) **79b**; **80b** was isolated as yellow crystals, yield = 96 mg (48%); mp = 231 - 233°C;

^{1}H NMR (250.13 MHz, DMSO-d_6): δ = 2.42 (m, 2H, CH_2), 2.85 (t, 2H, CH_2, ^3J = 6.8 Hz), 4.37 (t, 2H, CH_2, ^3J = 7.0 Hz), 7.55 (br. m, 6H, Ph, H-3), 7.97 (m, 1H, H-2), 8.15 (s, 1H, H-11), 8.28 (m, 2H, H-1, H-4).

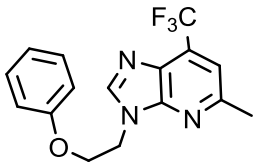
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 29.1 (C-6), 30.8 (C-5), 40.6 (C-7), 111.1 (q, C-11, $^3J_{C-F}$ = 4.4 Hz), 123.1 (q, CF_3, $^1J_{C-F}$ = 274.2 Hz), 126.9 (C-3', C-5'), 127.0 (C-4'), 128.0 (q, C-12, $^2J_{C-F}$ = 34.0 Hz),128.8 (C-2', C-6'), 129.1 (C-4), 129.4 (C-1'), 129.6 (C-3), 130.0 (C-2), 131.1 (C-1), 138.1 (C-10), 139.8 (C-4a), 149.6 (C-13b), 149.8 (C-12a), 151.0 (C-8a), 157.4 (C-13a)

GC-MS (EI, 70 eV): *m/z* (%): 379 (100) [M^+].

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{22}H_{17}F_3N_3$: 380.1369 found: 380.1376.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 1598, 1478, 1428, 1381, 1260, 1220, 1141, 1120, 872, 769, 688.

5-Methyl-3-(2-phenoxyethyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (81a)



Starting from 5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (300 mg, 1.49 mmol) **53a** and (2-bromoethoxy)benzene (300 mg, 1.49 mmol); **81a** was isolated as white crystals, yield = 345 mg (72%); mp = 106 - 109°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.64 (s, 3H, CH_3), 4.27 (t, 2H, CH_2, ^3J = 5.1 Hz), 4.56 (t, 2H, CH_2, ^3J = 5.1 Hz), 6.84 (br. m, 3H, H-2', H-4', H-6'), 7.21 (m, 3H, H-3', H-5', H-6), 8.24 (s, 1H, H-2).

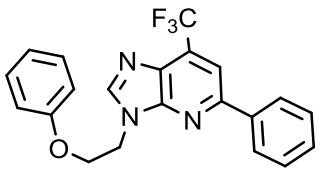
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 24.4 (CH_3), 43.1 (CH_2), 65.7 (CH_2), 114.3 (q, C-6, $^3J_{C-F}$ = 4.4 Hz), 114.5 (C-4'), 121.6 (C-2', C-6'), 122.8 (q, CF_3, $^1J_{C-F}$ = 273.6 Hz), 128.7 (q, C-7, $^2J_{C-F}$ = 33.3 Hz), 129.1 (C-5), 129.5 (C-3', C-5'), 145.8 (C-2), 147.8 (C-7a), 154.0 (C-3a), 157.8 (C-1').

GC-MS (EI, 70 eV): *m/z* (%): 321 (14) [M^+], 302 (12), 228 (76), 215 (40), 201 (34), 120 (100), 91 (28).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}F_3N_3O$: 322.1162; found: 322.1163.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924, 1598, 1495, 1385, 1286, 1229, 1140, 1039, 892, 866, 752, 690.

3-(2-Phenoxyethyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (81b)



Starting from 5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (300 mg, 1.14 mmol) **53b** and (2-bromoethoxy)benzene (228 mg, 1.14 mmol); **81b** was isolated as light-yellow crystals, yield = 297 mg (68%); mp = 118 - 119°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 4.34 (t, 2H, CH_2, ^3J = 5.1 Hz), 4.73 (t, 2H, CH_2, ^3J = 5.1 Hz), 6.86 (br. m, 3H, H-2", H-6", H-4"), 7.19 (m, 2H, H-3", H-5"), 7.43 (br. m, 3H, H-3', H-4', H-5'), 7.86 (s, 1H, H-6), 7.99 (m, 2H, H-2', H-6'), 8.34 (s, 1H, H-2).

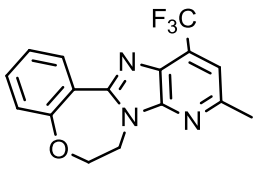
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 42.2 (CH_2), 64.6 (CH_2), 110.8 (q, C-6, $^3J_{C-F}$ = 4.4 Hz), 113.4 (C-4"), 120.6 (C-2", C-6"), 121.9 (q, CF_3, $^1J_{C-F}$ = 274.2 Hz), 126.1 (C-3", C-5"), 127.8 (q, C-7, $^2J_{C-F}$ = 33.3 Hz), 127.9 (C-4'), 128.4 (C-3', C-5'), 128.6 (C-2', C-6'), 129.2 (C-1'), 137.4 (C-5), 145.7 (C-2), 147.2 (C-7a), 152.0 (C-3a), 156.8 (C-1").

GC-MS (EI, 70 eV): *m/z* (%): 383 (13) [M^+],290 (43), 277 (23), 263 (100), 120 (24).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}F_3N_3O$: 384.1318 found: 384.1322.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2951, 1601, 1498, 1376, 1262, 1227, 1158, 1125, 1048, 868, 796, 684.

10-Methyl-12-(trifluoromethyl)-6,7-dihydropyrido[3',2':4,5]imidazo[1,2-*d*][1,4]benzoxazepine (82a)



Starting from 5-methyl-3-(2-phenoxyethyl)-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.62 mmol) **81a**; **82b** was isolated as light-yellow crystals, yield = 137 mg (69%); mp = 220 - 222°C;

^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 2.65 (s, 3H, CH_3), 4.51 (m, 2H, CH_2), 4.65

(m, 2H, CH_2), 7.19 (br.m, 4H, H-2, H-3, H-4, H-11), 8.76 (dd, 1H, H-1, ^3J = 7.8 Hz, ^4J = 2.1 Hz).

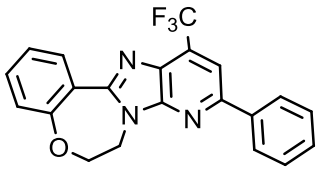
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 24.4 (CH_3), 45.8 (C-7), 68.8 (C-6), 114.7 (q, C-11, $^3J_{C-F}$ = 4.4 Hz), 117.2 (C-13b), 120.8 (C-4), 122.9 (C-2), 123.2 (q, CF_3, $^1J_{C-F}$ = 273.0 Hz), 127.5 (q, C-12, $^2J_{C-F}$ = 34.0 Hz), 129.1 (C-10), 131.9 (C-3), 132.3 (C-11), 149.7 (C-12a), 152.3 (C-8a), 153.0 (C-13a), 157.1 (C-4a).

GC-MS (EI, 70 eV): *m/z* (%): 319 (100) [M^+], 290 (15).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}F_3N_3O$: 320.1005; found: 320.1014.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924, 1741, 1599, 1478, 1386, 1234, 1132, 1055, 896, 770, 696.

10-Phenyl-12-(trifluoromethyl)-6,7-dihydropyrido[3',2':4,5]imidazo[1,2-*d*][1,4]benzoxazepine (82b)



Starting from 3-(2-phenoxyethyl)-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (200 mg, 0.52 mmol) **81b**; **82b** was isolated as yellow crystals, yield = 105 mg (53%); mp = 239 - 241°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 4.56 (m, 2H, CH_2), 4.77 (m, 2H, CH_2), 7.14 (br m, 2H, H-2, H-4), 7.38 (br. m, 4H, H-3, H-3', H-4', H-5'), 7.87 (s, 1H, H-11), 8.03 (m, 2H, H-2', H-6'), 8.81 (dd, 1H, H-1, ^3J = 6.6 Hz, ^4J = 1.5 Hz).

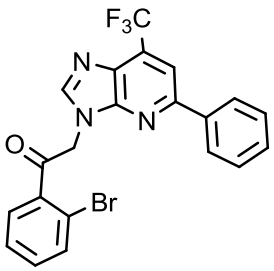
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 42.2 (C-7), 64.6 (C-6), 112.2 (q, C-11, $^3J_{C-F}$ = 4.4 Hz), 117.1 (C-13b), 120.9 (C-2), 122.9 (C-4), 123.0 (q, CF_3, $^1J_{C-F}$ = 273.6 Hz), 127.0 (C-3', C-5'), 127.2 (q, C-12, $^2J_{C-F}$ = 34.2 Hz), 128.2 (C-1'), 128.9 (C-2', C-6'), 129.2 (C-4'), 132.0 (C-3), 132.6 (C-1), 138.6 (C-10), 150.1 (C-12a), 151.8 (C-8a), 157.2 (C-13a).

GC-MS (EI, 70 eV): *m/z* (%): 381 (100) [M^+].

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{15}F_3N_3O$: 382.1162 found: 382.1170.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1603, 1478, 1443, 1386, 1257, 1120, 874, 766, 688.

1-(2-Bromophenyl)-2-[5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]ethanone (83)



Starting from 5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (300 mg, 1.14 mmol) **53b** and 2-bromo-1-(2-bromophenyl)ethanone (317 mg, 1.14 mmol); **83** was isolated as yellow crystals, yield = 387 mg (74%);

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 6.05 (s, 2H, CH_2), 7.62 (br. m, 5H, H-3', H-4', H-5', H-4", H-6"), 7.89 (m, 1H, H-5"), 8.09 (m, 1H, H-3"), 8.25 (br., m, 3H, H-6, H-2', H-6'), 8.29 (s, 1H, H-2).

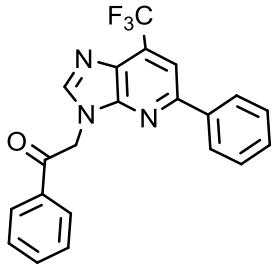
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 51.7 (CH_2), 111.1 (d, C-6, $^{3}J_{C\text{-}F}$ = 4.5 Hz), 118.8 (C-2"), 122.9 (q, CF_3, $^{1}J_{C\text{-}F}$ = 274.0 Hz), 127.0 (C-4"), 127.5 (q, C-7, $^{2}J_{C\text{-}F}$ = 33.2 Hz), 128.0 (C-6"), 128.4 (C-1"), 128.8 (C-4'), 129.5 (C-3', C-5'), 129.9 (C-2', C-6'), 133.4 (C-5"), 134.2 (C-3"), 137.0 (C-2"), 137.5 (C-5), 148.4 (C-7a), 148.5 (C-2), 151.7 (C-3a), 195.4 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 459 (28) [M^+], 183 (100), 157 (14).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{14}BrF_3N_3O$: 460.0267 found: 460.0275.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2919, 1720, 1593, 1496, 1406, 1378, 1344, 1300, 1261, 1209, 1171, 1124, 990, 953, 869, 749, 685, 670.

1-Phenyl-2-[5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]ethanone (84)



Starting from 5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (300 mg, 1.14 mmol) **53b** and 2-bromo-1-phenylethanone (228 mg, 1.14 mmol); **84** was isolated as yellow crystals, yield = 274 mg (63%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.81 (s, 2H, CH_2), 7.40 (br. m, 6H, H-3', H-4', H-5', H-3", H-4", H-5"), 7.87 (s, 1H, H-6), 7.95 (m, 2H, H-2", H-6"), 8.03 (m, 2H, H-2', H-6'), 8.26 (s, 1H, H-2).

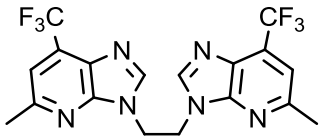
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 48.8 (CH_2), 112.1 (C-6), 123.1 (q, CF_3-,$^{1}J_{C\text{-}F}$ = 273.6 Hz),127.2 (C-3', C-5'), 127.7 (q, C-7, $^{2}J_{C\text{-}F}$ = 34.0 Hz), 128.2 (C-3", C-5"), 128.9 (C-4'), 129.1 (C-2', C-6'), 129.4 (C-4"), 134.1 (C-1'), 134.6 (C-2", C-6"), 138.3 (C-4), 146.8 (C-1"), 148.5 (C-7a), 153.1 (C-3a), 191.1 (C=O).

GC-MS (EI, 70 eV): *m/z* (%): 381 (22) [M^+], 105 (100), 77 (42).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{21}H_{14}F_3N_3O$: 381.1147 found: 381.1139.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2935, 1685, 1594, 1496, 1446, 1374, 1292, 1374, 1292, 1263, 1229, 1124, 1000, 873, 750, 686.

3,3'-Ethane-1,2-diylbis[5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine] (86a)



Starting from 5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (300 mg, 1.49 mmol) **53a** and 1,2-dibromoethane (110 mg, 0.59 mmol); **86a** was isolated as white crystals, yield = 192 mg (60%); mp = 243 - 246°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.30 (s, 6H, CH_3), 4.77 (s, 4H, CH_2), 7.26 (s, 2H, H-6, H-6'), 8.42 (s, 2H, H-2, H-2').

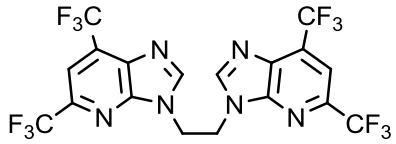
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 23.3 (CH_3), 43.6 (CH_2), 113.0 (d, C-6, C-6', $^{3}J_{C-F}$ = 4.4 Hz), 122.9 (q, CF_3, $^{1}J_{C-F}$ = 274.0 Hz), 126.4 (q, C-7, C-7', $^{2}J_{C-F}$ = 32.5 Hz), 128.3 (C-5, C-5'), 146.2 (C-2, C-2'), 148.1 (C-7a, C-7a'), 153.0 (C-3a, C-3a').

GC-MS (EI, 70 eV): *m/z* (%): 428 (100) [M^+], 409 (14), 228 (84), 214 (20), 200 (54).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}F_6N_6$: 429.1257; found: 429.1262.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3076, 1600, 1495, 1383, 1364, 1271, 1209, 1124, 893, 871, 738, 666.

3,3'-Ethane-1,2-diylbis[5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine] (86b)



Starting from 5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-b]pyridine (300 mg, 1.17 mmol) **53c** and 1,2-dibromoethane (110 mg, 0.59 mmol); **86b** was isolated as white crystals, yield = 175 mg (56%); mp = 255 - 257°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 4.94 (s, 2H, CH_2), 7.88 (s, 1H, H-6), 8.86 (s, 1H, H-2).

^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 44.2 (CH_2), 110.6 (d, C-6, C-6' $^{3}J_{C-F}$ = 4.4 Hz), 121.0 (q, CF_3, $^{1}J_{C-F}$ = 273.6 Hz), 122.0 (q, CF_3, $^{1}J_{C-F}$ = 274.2 Hz), 127.3 (q, C-7, C-7' $^{2}J_{C-F}$ = 34.6 Hz), 132.9 (C-7a, C-7a'), 140.2 (q, C-5, C-5' $^{2}J_{C-F}$ = 35.9 Hz), 148.0 (C-2, C-2'), 151.0 (C-3a, C-3a').

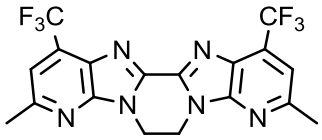
GC-MS (EI, 70 eV): *m/z* (%): 536 (30) [M^+], 517 (27), 282 (73), 268 (39), 254 (100), 214 (18), 69 (32).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_9F_{12}N_6$: 537.0692 found: 537.0702.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3089, 1488, 1269, 1140, 1103, 926, 891, 738, 655, 628

.

3,10-Dimethyl-1,12-bis(trifluoromethyl)-6,7-dihydrobispyrido[3',2':4,5]imidazo[1,2-*a*:2',1'-*c*]pyrazine (87a)



Starting from 3,3'-ethane-1,2-diylbis[5-methyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine] (200 mg, 0.47 mmol) **86a**; **87a** was isolated as white crystals, yield = 150 mg (75%); mp > 300°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.68 (s, 6H, CH_3), 4.80 (s, 4H, CH_2), 7.29 (s, 2H, H-2, H-11).

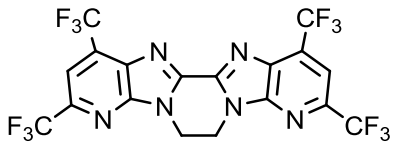
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 24.6 (CH_3), 39.7 (C-6, C-7), 115.7 (d, C-2, C-11, $^3J_{C-F}$ = 4.4 Hz), 122.3 (q, CF_3, $^1J_{C-F}$ = 274.0 Hz), 129.4 (q, C-1, C-12, $^2J_{C-F}$ = 34.7 Hz), 129.9 (C-3, C-10), 141.9 (C-12a, C-14a), 147.4 (C-4a, C-8a), 156.3 (C-13a, C-13b).

GC-MS (EI, 70 eV): *m/z* (%): 426 (100) [M^+].

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{18}H_{12}F_6N_6$: 426.1022 found: 426.1020.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3398, 1597, 1493, 1426, 1377, 1311, 1248, 1225, 1200, 1110, 872

1,3,10,12-Tetrakis(trifluoromethyl)-6,7-dihydrobispyrido[3',2':4,5]imidazo[1,2-*a*:2',1'-*c*]pyrazine (87b)



Starting from 3,3'-ethane-1,2-diylbis[5,7-bis(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine] (200 mg, 0.37 mmol) **86b**; **87b** was isolated as white crystals, yield = 175 mg (88%); mp > 300°C;

^{1}H NMR (300.13 MHz, acetone-d_6): δ = 5.13 (s, 4H, CH_2), 8.04 (s, 2H, H-2, H-11).

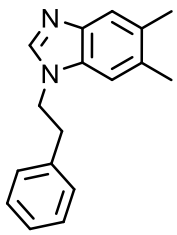
^{13}C NMR (62.90 MHz, acetone-d_6): δ = 41.3 (C-6, C-7), 113.4 (C-2, C-11), 122.3 (q, CF_3, $^1J_{C-F}$ = 273.6 Hz), 123.3 (q, CF_3, $^1J_{C-F}$ = 273.6 Hz), 130.0 (q, C-1, C-12, $^2J_{C-F}$ = 33.3 Hz), 135.1 (C-12a, C-14a), 144.4 (q, C-3, C-10, $^2J_{C-F}$ = 34.0 Hz), 147.2 (C-4a, C-8a), 149.1 (C-13a, C-13b).

GC-MS (EI, 70 eV): *m/z* (%): 534 (100) [M^+], 513 (20).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_6F_{12}N_6$: 535.0535 found: 535.0547.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3492, 1667, 1607, 1441, 1377, 1352, 1270, 1194, 1129, 1105, 889, 666 cm^{-1}.

5,6-Dimethyl-1-phenethyl-1*H*-benzimidazole (88b)



Starting from benzimidazole (300 mg, 2.54 mmol) and phenethylbromide (470 mg, 2.54 mmol); **88b** was isolated as white crystals, yield = 362 mg (64%); mp = 110 - 112°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.15 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.37 (t, 2H, CH_2, ^3J = 6.9 Hz), 7.07 (dd, 2H, H-2', H-6', ^3J = 6.0 Hz, ^4J = 1.5 Hz), 7.17 (s, 1H, H-7), 7.28 (m , 3H, H-3', H-4', H-5'), 7.53 (s, 1H, H-4), 7.59 (s, 1H, H-2).

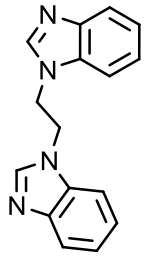
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 20.3 (CH_3), 20.6 (CH_3), 36.2 (CH_2), 46.6 (CH_2-, 109.8 (C-7), 120.4 (C-4), 127.0 (C-4'), 127.3 (C-1'), 128.7 (C-3', C-5'), 128.8 (C-2', C-6'), 130.9 (C-5), 132.1 (C-6), 137.7 (C-7a), 142.3 (C-2), 142.5 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 250 (48) [M^+], 159 (100) .

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}N_2$: 251.1543 found: 251.1542.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2932, 2864, 1490, 1452, 1358, 1329, 1219, 1152, 1028, 1000, 864, 747, 700.

1,1'-Ethane-1,2-diylbis-1*H*-benzimidazole (89a)



Starting from benzimidazole (300 mg, 2.54 mmol) and 1,5-dibromoethane (220 mg, 1.17 mmol); **89a** was isolated as white crystals, yield = 200 mg (60%); mp = 236 - 238°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ =4.74 (s, 4H, CH_2), 7.18 (m, 4H, H-5, H-5', H-6, H-6'), 7.42 (m, 2H, H-7, H-7'), 7.61 (m, 2H, H-4, H-4'), 7.92 (s, 2H, H-2, H-2').

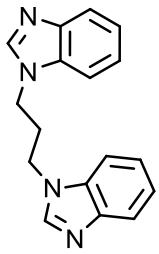
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 43.8 (CH_2), 109.9 (C-5, C-5'), 119.4 (C-6, C-6'), 121.5 (C-7, C-7'), 122.3 (C-4, C-4'), 133.6 (C-7a, C-7a'), 143.2 (C-3a, C-3a'), 143.8 (C-2, C-2').

GC-MS (EI, 70 eV): *m/z* (%): 262 (89) [M^+], 131 (100), 104 (14), 77 (25).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}N_4$: 263.1291 found: 263.1288.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3091, 3053, 1609, 1488, 1457, 1361, 1332, 1287, 1260, 1201, 1170, 882, 743, 625.

1,1'-Propane-1,3-diylbis-1*H*-benzimidazole (89b)



Starting from benzimidazole (300 mg, 2.54 mmol) and 1,5-dibromopropane (236 mg, 1.17 mmol); **89b** was isolated as light-yellow crystals, yield = 245 mg (76%); mp = 277 - 279°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.40 (t, 2H, CH_2, ^3J = 7.2 Hz), 4.33 (t, 4H, CH_2, ^3J = 7.2 Hz), 7.24 (br. m, 4H, H-5, H-6, H-5‘, H-6‘), 7.59 (br. m, 4H, H-4, H-7, H-4‘, H-7‘), 8.27 (s, 2H, H-2, H-2‘).

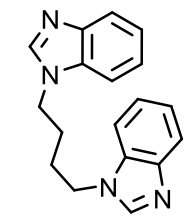
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 29.6 (CH_2), 41.7 (CH_2), 110.2 (C-5, C-5‘), 119.5 (C-6, C-6‘), 121.5 (C-7, C-7‘), 122.3 (C-4, C-4‘), 133.7 (C-7a, C-7a‘), 143.5 (C-3a, C-3a’), 143.9 (C-2, C-2’).

GC-MS (EI, 70 eV): *m/z* (%): 276 (67) [M^+], 131 (100), 77 (18).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}N_4$: 277.1448 found: 277.1445.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3051, 2982, 1612, 1494, 1459, 1440, 1357, 1323, 1285, 1253, 1200, 1007, 741.

1,1'-Butane-1,4-diylbis-1*H*-benzimidazole (89c)



Starting from benzimidazole (300 mg, 2.54 mmol) and 1,5-dibromobutane (253 mg, 1.17 mmol); **89c** was isolated as light-yellow crystals, yield = 254 mg (69%); mp = 265 - 266°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.80 (t, 4H, CH_2, ^3J = 2.7 Hz), 4.29 (t, 4H, CH_2, ^3J = 2.7 Hz), 7.23 (br. m, 4H, H-5, H-6, H-5‘, H-6‘), 7.60 (br. m, 4H, H-4, H-7, H-4‘, H-7‘), 8.24 (s, 2H, H-2, H-2‘).

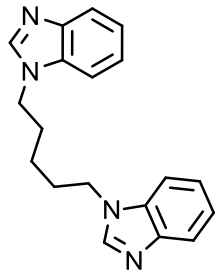
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 26.7 (CH_2), 43.5 (CH_2), 110.3 (C-5, C-5‘), 119.4 (C-6, C-6‘), 121.4 (C-7, C-7‘), 122.2 (C-4, C-4‘), 133.7 (C-7a, C-7a‘), 143.4 (C-3a, C-3a’), 143.9 (C-2, C-2’).

GC-MS (EI, 70 eV): *m/z* (%): 290 (100) [M^+], 173 (29), 159 (60), 145 (29), 131 (100), 118 (33), 77 (39).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{18}H_{18}N_4$: 290.1526 found: 290.1525.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3418, 2942, 1611, 1488, 1441, 1382, 1360, 1256, 1163, 883, 743, 633.

1,1'-Pentane-1,5-diylbis-1*H*-benzimidazole (89d)



Starting from benzimidazole (300 mg, 2.54 mmol) and 1,5-dibromopentane (269 mg, 1.17 mmol); **89d** was isolated as grey crystals, yield = 238 mg (67%); mp = 249 - 251°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.27 (m, 2H, CH_2), 1.84 (m, 4H, CH_2), 4.27 (t, 4H, CH_2, ^3J = 7.2 Hz), 7.24 (br. m, 4H, H-5, H-6, H-5‘, H-6‘), 7.60 (br. m, 4H, H-4, H-7, H-4‘, H-7‘), 8.22 (s, 2H, H-2, H-2‘).

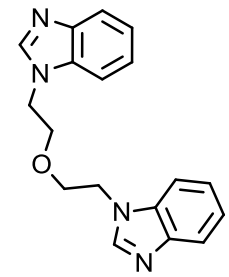
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 23.4 (CH_2), 28.9 (CH_2), 43.9 (CH_2), 110.4 (C-5, C-5‘), 119.4 (C-6, C-6‘), 121.3 (C-7, C-7‘), 122.2 (C-4, C-4‘), 133.8 (C-7a, C-7a‘), 143.4 (C-3a, C-3a’), 143.9 (C-2, C-2’).

GC-MS (EI, 70 eV): *m/z* (%): 304 (82) [M^+], 187 (19), 173 (100), 159 (32), 145 (27), 131 (97), 118 (33), 104 (22), 90 (17), 77 (46).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{19}H_{20}N_4$: 304.1683 found: 304.1687.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3094, 2927, 1614, 1495, 1452, 1369, 1331, 1289, 1244, 1201, 1154, 730.

1,1'-[Oxybis(ethane-2,1-diyl)]bis-1*H*-benzimidazole (89e)



Starting from benzimidazole (300 mg, 2.54 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (270 mg, 1.17 mmol); **89e** was isolated as grey crystals, yield = 272 mg (76%); mp = 247 - 249°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.71 (t, 4H, CH_2, ^3J = 5.1 Hz), 4.27 (t, 4H, CH_2, ^3J = 5.1 Hz), 7.33 (br. m, 6H, H-5, H-6, H-7, H-5‘, H-6‘, H-7‘), 7.86 (m, 4H, H-4, H-4’, H-2, H-2’).

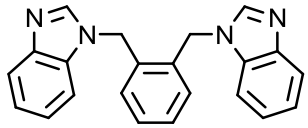
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 44.0 (CH_2), 68.8 (CH_2), 110.4 (C-5, C-5‘), 119.3 (C-6, C-6‘), 121.3 (C-7, C-7‘), 122.1 (C-4, C-4‘), 133.9 (C-7a, C-7a‘), 143.3 (C-3a, C-3a’), 144.2 (C-2, C-2’).

GC-MS (EI, 70 eV): *m/z* (%): 306 (79) [M^+], 191 (18), 147 (39), 131 (100), 118 (44), 77 (39).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}N_4O$: 307.1553 found: 307.1557.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3390, 3020, 2894, 2866, 1614, 1494, 1457, 1435, 1362, 1280, 1203, 1116, 1055, 882, 746.

1,1'-[1,2-Phenylenedi(methylene)]bis-1*H*-benzimidazole (89f)



Starting from benzimidazole (300 mg, 2.54 mmol) and 1,3-bis(bromomethyl)benzene (335 mg, 1.17 mmol); **89f** was isolated as light-brown crystals, yield = 357 mg (83%); mp = 289 - 291°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 5.76 (s, 4H, CH_2), 6.76 (dd, 2H, H-3, H-6, ^3J = 3.3 Hz, ^4J = 2.7 Hz), 7.24 (br. m, 6H, H-5', H-6', H-7', H-5", H-6", H-7"), 7.43 (dd, 2H, H-4, H-5, ^3J = 5.4 Hz, ^4J = 2.7 Hz), 7.76 (m, 2H, H-4', H-4"), 8.40 (s, 2H, H-2', H-2").

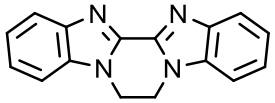
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 45.0 (CH_2), 110.7 (C-5', C-5"), 119.6 (C-6', C-6"), 121.9 (C-7', C-7"), 122.5 (C-4', C-4"), 126.8 (C-3, C-6), 127.9 (C-4, C-5), 133.9 (C-7a', C-7a"), 134.4 (C-1, C-2), 143.5 (C-3a', C-3a"), 144.6 (C-2', C-2").

GC-MS (EI, 70 eV): *m/z* (%): 338 (32) [M^+], 219 (100).

HRMS (ESI): *m/z* [M]$^+$ calcd for $C_{22}H_{18}N_4$: 338.1526 found: 338.1528.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3271, 1656, 1614, 1497, 1456, 1361, 1287, 1264, 1188, 766, 746.

6,7-Dihydrobenzimidazo[2',1':3,4]pyrazino[1,2-*a*]benzimidazole (90a)



Starting from 1,1'-ethane-1,5-diylbis-1*H*-benzimidazole (200 mg, 0.76 mmol) **89a**; **90a** was isolated as white powder, yield = 103 mg (52%); mp > 300°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 4.85 (s, 4H, CH_2), 7.40 (br. m, 4H, H-2, H-3, H-10, H-11), 7.82 (m, 4H, H-1, H-4, H-9, H-12).

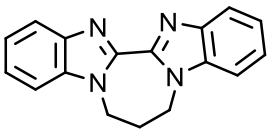
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 40.4 (C-6, C-7), 110.8 (C-2, C-11), 120.0 (C-3, C-10), 122.8 (C-4, C-9), 123.7 (C-1, C-12), 134.2 (C-4a, C-8a), 141.6 (C-12a, C-14a), 143.3 (C-13a, C-13b).

GC-MS (EI, 70 eV): *m/z* (%): 260 (100) [M^+], 144 (14).

HRMS (ESI): *m/z* [M]$^+$ calcd for $C_{16}H_{12}N_4$: 260.1178 found: 260.1182.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3189, 2943, 1584, 1499, 1465, 1400, 1312, 1202, 1001, 819, 765, 720.

7,8-Dihydro-6*H*-benzimidazo[2',1':3,4][1,4]diazepino[1,2-*a*]benzimidazole (90b)



Starting from 1,1'-propane-1,5-diylbis-1*H*-benzimidazole (200 mg, 0.72 mmol) **89b**; **90b** was isolated as white powder, yield = 115 mg (58%); mp > 300°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.62 (br. s, 2H, CH_2), 4.61 (t, 4H, CH_2, ^{3}J = 5.7 Hz), 7.37 (br. m, 4H, H-2, H-3, H-11, H-12), 7.70 (br. m, 4H, H-1, H-4, H-10, H-13).

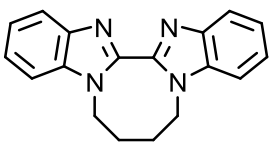
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 26.6 (C-7), 43.8 (C-6, C-8), 110.8 (C-2, C-12), 119.8 (C-3, C-11), 122.7 (C-4, C-10), 123.5 (C-1, C-13), 134.2 (C-4a, C-9a), 142.7 (C-13a, C-15a), 144.0 (C-14a, C-14b).

GC-MS (EI, 70 eV): *m/z* (%): 274 (100) [M^+], 207 (11), 129 (13).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{17}H_{14}N_4$: 274.1213 found: 274.1211.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2988, 1598, 1488, 1413, 1387, 1366, 1303, 1254, 1208, 787, 690.

6,7,8,9-Tetrahydrobenzimidazo[2',1':3,4][1,4]diazocino[1,2-*a*]benzimidazole (90c)



Starting from 1,1'-butane-1,5-diylbis-1*H*-benzimidazole (200 mg, 0.69 mmol) **89c**; **90c** was isolated as light-yellow powder, yield = 77 mg (39%); mp = 271 - 273°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.02 (br. s, 4H, CH_2), 4.20 (br. s, 4H, CH_2), 7.41 (br. m, 4H, H-2, H-3, H-12, H-13), 7.82 (br. m, 4H, H-1, H-4, H-11, H-14).

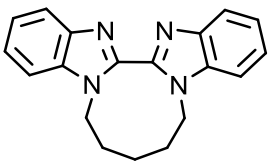
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 27.4 (C-7, C-8), 43.6 (C-6, C-9), 110.8 (C-2, C-13), 120.0 (C-3, C-12), 122.7 (C-4, C-11), 123.6 (C-1, C-14), 134.9 (C-4a, C-10a), 142.7 (C-15a, C-15b), 143.5 (C-14a, C-16a).

GC-MS (EI, 70 eV): *m/z* (%): 288 (100) [M^+], 259 (36), 144 (11).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{16}H_{16}N_4$: 288.1409 found: 288.1413.

IR (ATR, cm^{-1}): $\tilde{\nu}$ =3050, 2967, 1606, 1455, 1402, 1344, 1292, 1267, 1118, 1003, 890, 744.

7,8,9,10-Tetrahydro-6*H*-benzimidazo[2',1':3,4][1,4]diazonino[1,2-*a*]benzimidazole (90d)



Starting from 1,1'-pentane-1,5-diylbis-1*H*-benzimidazole (200 mg, 0.66 mmol) **89d**; **90d** was isolated as light-yellow powder, yield = 62 mg (31%); mp = 266 - 268°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.29 (br. S, 2H, CH_2), 1.80 (m, 4H, CH_2), 4.07 (t, 4H, CH_2, ^{3}J = 5.7 Hz), 7.44 (br. m, 4H, H-2, H-3, H-13, H-14), 7.86 (br. m, 4H, H-1, H-4, H-12, H-15).

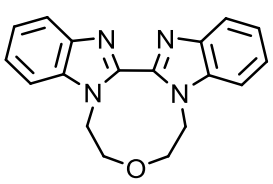
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 24.5 (C-8), 26.3 (C-7, C-9), 44.9 (C-6, C-10), 111.1 (C-2, C-14), 120.0 (C-3, C-13), 122.7 (C-4, C-12), 123.7 (C-1, C-15), 134.5 (C-4a, C-11a), 142.5 (C-16a, C-16b), 143.8 (C-15a, C-17a).

GC-MS (EI, 70 eV): *m/z* (%): 302 (100) [M^+], 275 (39), 249 (33), 236 (16), 173 (17), 144 (33).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{19}H_{18}N_4$: 302.1514 found: 302.1519.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3129, 1534, 1491, 1466, 1388, 1305, 1226, 1193, 1132, 1090, 865, 754.

6,7,9,10-Tetrahydrobenzimidazo[2',1':6,7][1,4,7]oxadiazonino[4,5-*a*]benzimidazole (90e)



Starting from 1,1'-[oxybis(ethane-2,1-diyl)]bis-1*H*-benzimidazole (200 mg, 0.65 mmol) **89e**; **90e** was isolated as yellow powder, yield = 56 mg (28%); mp = 242 - 244°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.85 (t, 4H, CH_2, ^3J = 4.5 Hz), 4.22 (br. s, 4H, CH_2), 7.44 (br. m, 4H, H-2, H-3, H-13, H-14), 7.85 (br. m, 4H, H-1, H-4, H-12, H-15).

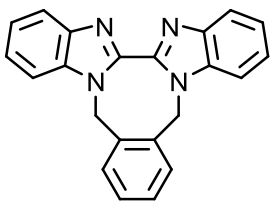
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 45.5 (C-6, C-10), 67.0 (C-7, C-9), 111.2 (C-3, C-14), 120.0 (C-3, C-13), 122.7 (C-4, C-12), 123.6 (C-1, C-15), 134.4 (C-4a, C-11a), 142.4 (C-16a, C-16b), 143.2 (C-15a, C-17a).

GC-MS (EI, 70 eV): *m/z* (%): 304 (56) [M^+], 275 (28), 261 (14), 248 (100), 209 (46), 144 (30).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{18}H_{16}N_4O$: 304.1319 found: 304.1317.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3211, 3012, 1522, 1478, 1398, 1333, 1218, 1124, 1078, 1030, 987, 814, 778, 721, 690.

6,11-Dihydrobisbenzimidazo[1,2-*b*:2',1'-*d*][2,5]benzodiazocine (90f)



Starting from 1,1'-[1,2-phenylenedi(methylene)]bis-1*H*-benzimidazole (200 mg, 0.59 mmol) **89f**; **90f** was isolated as light-yellow powder, yield = 84 mg (42%); mp > 300°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 5.33 (s, 4H, CH_2), 7.45 (br. m, 6H, H-2, H-3, H-8, H-9, H-14, H-15), 7.79 (br. m, 6H, H-1, H-4, H-7, H-10, H-13, H-16).

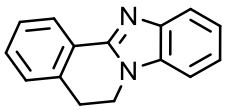
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 47.2 (C-6, C-11), 110.8 (C-2, C-15), 120.3 (C-3, C-14), 122.9 (C-4, C-13), 123.9 (C-1, C-16), 128.8 (C-8, C-9), 130.1 (C-7, C-10), 133.6 (C-6a, C-10a), 135.1 (C-4a, C-12a), 142.8 (C-17a, C-17b), 144.8 (C-16a, C-18a).

GC-MS (EI, 70 eV): *m/z* (%): 336 (96) [M^+], 220 (20) .

HRMS (ESI): *m/z* [$M]^+$ calcd for $C_{22}H_{16}N_4$: 336.1370 found: 336.1361.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2974, 1587, 1502, 1466, 1344, 1293, 1240, 1176, 1076, 1020, 942, 812, 732.

5,6-Dihydrobenzimidazo[2,1-*a*]isoquinoline (91a)



Starting from 1-phenethyl-1*H*-benzimidazole (200 mg, 0.90 mmol) **88a**; **91a** was isolated as light-yellow powder, yield = 116 mg (58%); mp = 229 - 231°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.20 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.25 (t, 2H, CH_2, ^3J = 6.9 Hz), 7.29 (br.m, 6H, H-2, H-3, H-4, H-8, H-9, H-10), 7.76 (m, 1H, H-11), 8.24 (dd, 1H, H-1, ^3J = 6.0 Hz, ^4J = 1.8 Hz).

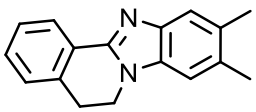
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 27.2 (C-5), 39.4 (C-6), 108.0 (C-10), 118.6 (C-9), 121.6 (C-4), 121.8 (C-3), 124.8 (C-2), 125.4 (C-4a), 126.8 (C-8), 127.1 (C-11), 129.2 (C-1), 133.3 (C-12b), 133.5 (C-7a), 142.5 (c-11a), 148.0 (C-12a).

GC-MS (EI, 70 eV): *m/z* (%): 220 (100) [M^+], 110 (11) .

HRMS (ESI): *m/z* [$M]^+$ calcd for $C_{15}H_{12}N_2$: 220.0995 found: 220.0991.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2917, 1616, 1481, 1447, 1408, 1325, 1263, 732 cm^{-1}.

9,10-Dimethyl-5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline (91b)



Starting from 5,6-dimethyl-1-phenethyl-1*H*-benzimidazole (200 mg, 0.80 mmol) **88b**; **91b** was isolated as light-yellow powder, yield = 100 mg (50%); mp = 244 – 246°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.32 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.19 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.21 (t, 2H, CH_2, ^3J = 6.9 Hz), 7.06 (s, 1H, H-8), 7.29 (br. m, 3H, H-2, H-3, H-4), 7.51 (s, 1H, H-11), 8.22 (dd, 1H, H-1, ^3J = 6.0 Hz, ^4J = 2.1 Hz).

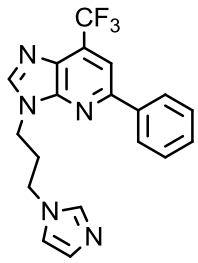
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 20.0 (CH_3), 20.1 (CH_3), 27.4 (C-5), 39.8 (C-6), 108.0 (C-8), 119.0 (C-11), 126.1 (C-10), 126.5 (C-9), 127.2 (C-4), 128.2 (C-4a), 128.4 (C-3), 128.7 (C-2), 129.7 (C-1), 130.2 (C-12b), 131.0 (C-7a), 134.8 (C-11a), 142.0 (C-12a).

GC-MS (EI, 70 eV): *m/z* (%): 248 (100) [M^+], 233 (32), 116 (13) .

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{17}H_{16}N_2$: 248.1314 found: 248.1310.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2917, 1486, 1449, 1409, 1321, 1020, 844, 729, 704 cm^{-1}.

3-[3-(1*H*-imidazol-1-yl)propyl]-5-phenyl-7-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridine (92)



Starting from 3-(1*H*-imidazol-1-yl)propan-1-amine (688 mg, 5.5 mmol), methyl N-(cyanomethyl)-formimidate (490 mg, 5 mmol) and 3-benzoyl-1,1,1-trifluoroacetone (1.08 g, 5 mmol); **92** was isolated as brown crystals, yield = 1.15 g (62%); mp = 127 - 129°C;

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.46 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.10 (t, 2H, CH_2, ^3J = 6.9 Hz), 4.40 (t, 2H, CH_2, ^3J = 6.9 Hz), 6.92 (t, 1H, H-5“, ^3J = 1.2 Hz), 7.25 (t, 1H, H-4“, ^3J = 1.2 Hz), 7.54 (br. m, 3H, H-3‘, H-4‘, H-5‘), 7.68 (s, 1H, H-2”), 8.14 (s, 1H, H-6), 8.22 (m, 2H, H-2’, H-6’), 8.73 (s, 1H, H-2).

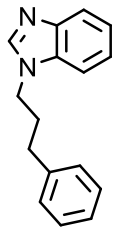
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 30.6 (CH_2), 40.8 (CH_2), 43.5 (CH_2), 110.8 (d, C-6, $^3J_{C-F}$ = 4.4 Hz), 119.2 (C-4”), 122.8 (CF_3-, q, $^1J_{C-F}$ = 273.6 Hz), 127.0 (C-5”), 127.3 (C-7, q, $^2J_{C-F}$ = 33.3 Hz), 128.4 (C-3’, C-5’), 128.8 (C-2’, C-6’), 129.3 (C-4’), 129.8 (C-1’), 137.3 (C-2”), 137.7 (C-5), 147.9 (C-2), 148.4 (C-7a), 151.3 (C-3a).

GC-MS (EI, 70 eV): *m/z* (%): 303 (59), 276 (86), 95 (100).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{17}F_3N_5$: 372.1431 found: 372.1437.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3086, 1504, 1376, 1264, 1226, 1154, 1121, 925, 911, 871, 827, 766, 686, 668, 628.

1-(3-Phenylpropyl)-1*H*-benzimidazole (93a)



Starting from benzimidazole (300 mg, 2.54 mmol) and (3-bromopropyl)benzene (505 mg, 2.54 mmol); **93b** was isolated as light-brown crystals, yield = 462 mg (77%); mp = 80 - 82°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.17 (m, 2H, CH_2), 2.57 (t, 2H, CH_2, ^3J = 7.2 Hz), 4.09 (t, 2H, CH_2, ^3J = 6.9 Hz), 7.22 (br. m, 8H, H-5, H-6, H-7, Ph), 7.84 (d, 1H, H-4, ^3J = 5.1 Hz), 7.90 (s, 1H, H-2).

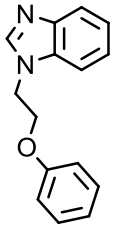
^{13}C NMR (62.90 MHz, DMSO-*d*$_6$): δ = 31.0 (CH_2), 32.2 (CH_2), 43.8 (CH_2), 110.3 (C-5), 119.4 (C-6), 121.4 (C-7), 122.2 (C-4), 125.9 (C-4'), 128.2 (C-2', C-6'), 128.3 (C-3', C-5'), 133.8 (C-1'), 140.9 (C-7a), 143.5 (C-3a), 143.9 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 236 (39) [M^+], 120 (84) .

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{16}H_{17}N_2$: 237.1386 found: 237.1388.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2948, 1614, 1494, 1454, 1439, 1358, 1259, 893, 745, 732, 699.

1-(2-Phenoxyethyl)-1*H*-benzimidazole (93b)



Starting from benzimidazole (300 mg, 2.54 mmol) and (2-bromoethoxy)benzene (511 mg, 2.54 mmol); **93b** was isolated as white crystals, yield = 417 mg (69%); mp = 89 - 91°C;

^{1}H NMR (300.13 MHz, DMSO-*d*$_6$): δ =4.34 (t, 2H, CH_2, ^3J = 5.4 Hz), 4.68 (t, 2H, CH_2, ^3J = 5.4 Hz), 6.91 (m, 3H, H-2', H-4', H-6'), 7.25 (br. m, 4H, H-3', H-5', H-5, H-6), 7.69 (m, 2H, H-4, H-7), 8.29 (s, 1H, H-2).

^{13}C NMR (62.90 MHz, DMSO-*d*$_6$): δ = 43.7 (CH_2), 66.2 (CH_2), 110.6 (C-5), 114.4 (C-2', C-6'), 119.3 (C-6), 120.9 (C-4'), 121.4 (C-7), 122.2 (C-4), 129.5 (C-3', C-5'), 133.9 (C-7a), 143.3 (C-3a), 144.4 (C-2), 157.9 (C-1').

GC-MS (EI, 70 eV): *m/z* (%): 238 (100) [M^+], 145 (53), 131 (82), 77 (34).

HRMS (ESI): *m/z* [M]$^+$ calcd for $C_{15}H_{14}N_2O$: 238.1101 found: 238.1103.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3100, 2957, 1598, 1587, 1493, 1454, 1356, 1285, 1244, 1207, 1043, 910, 877, 740, 686.

1.2.4 Supplement to paragraph 5

General procedure for the synthesis of 3-hydroxy-pent-4-yn-1-ones compounds 94a-r.

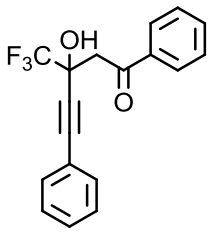
A Schlenk flask, containing solution of terminal alkyne (5.5 mmol) in 6 ml of dry THF was cooled down to -78°C and equimolar amount of n-BuLi was added dropwise. After addition, the reaction mixture was allowed to warm up to room temperature during 1,5 hours and then cooled down again. CF_3-derived diketone (2.5 mmol), dissolved in 2,5 ml of dry THF was then added dropwise to the mixture and reaction was warmed up during 3 hours this time. Afterwards, solution of 7.5 mmol of NH_4Cl in 5 ml of water was added and the mixture was stirred during 15 min. Organic residues were extracted with EtOAc (3x50 ml), organic layers were combined, washed with water and dried over Na_2SO_4. The

solvent was evaporated on vacuum and the residue was purified by column chromatography to give desired compounds.

General procedure for preparation of 4-trifluoromethylpyridines compounds 96a-q.

1 mmol of corrersponding 3-hydroxy-pent-4-yn-1-one **94** was dissolved in 3,5 ml of toluene and 72 mg (1.2 mmol) of urea and 400 mg (3.5 mmol) of trifluoroacetic acid were added to the formed solution. The mixture was heated under reflux till the full conversion of starting material (monitored by TLC). Afterwards 0.404 mg (4 mmol) of triethylamine was added, and the formed solution was evaporated under vacuum. The crude mixture was then purified by column chromatography to give desired pyridines.

3-Hydroxy-1,5-diphenyl-3-(trifluoromethyl)pent-4-yn-1-one (94a)



Starting from 3-benzoyl-1,1,1-trifluoroacetone (540 mg, 2.5 mmol) and phenylacetylene (561 mg, 5.5 mmol); **94a** was isolated as light-yellow powder, yield = 604 mg (76%); mp – dec.;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.34 (d, 1H, H-2a, ^{2}J = 16.8 Hz), 3.70 (d, 1H, H-2b, ^{2}J = 16.8 Hz), 5.35 (s, 1H, OH), 7.17 (br. m, 5H, -Ph), 7.43 (m, 2H, H-3', H-5'), 7.55 (d, 1H, H-4', ^{3}J = 7.5 Hz), 7.91 (dd, 2H, H-2', H-6', $^{3}J_1$ = 7.2 Hz, $^{3}J_2$ = 1.2 Hz).

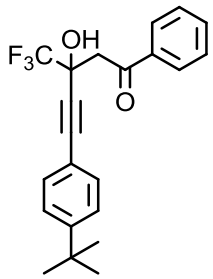
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 43.0 (C-2), 68.8 (q, C-3, $^{2}J_{C-F}$ = 31.5 Hz), 84.3 (C-4), 86.7 (C-5), 120.1 (C-4'), 124.1 (q, CF_3, $^{1}J_{C-F}$ = 286.2 Hz), 128.5 (C-2', C-6'), 128.6 (C-3", C-5"), 128.7 (C-3', C-5'), 129.4 (C-1'), 131.4 (C-2", C-6"), 133.2 (C-4"), 137.2 (C-1"), 194.5 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 318 (14) [M^+], 300 (15), 249 (48), 207 (41), 178 (25), 129 (76), 105 (100), 77 (68).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{14}F_3O_2$: 319.0940; found: 319.0945.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3398, 2955, 2222, 1622, 1599, 1575, 1512, 1453, 1403, 1167, 1045, 996, 832, 633.

5-(4-*Tert*-butylphenyl)-3-hydroxy-1-phenyl-3-(trifluoromethyl)pent-4-yn-1-one (94b)



Starting from 3-benzoyl-1,1,1-trifluoroacetone (540 mg, 2.5 mmol) and 4-*tert*-butylphenylacetylene (869 mg, 5.5 mmol); **94b** was isolated as light-yellow liquid, yield = 776 mg (83%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.19 (s, 9H, *t*-Bu), 3.34 (d, 1H, H-2a, ^{2}J = 16.8 Hz), 3.73 (d, 1H, H-2b, ^{2}J = 16.8 Hz), 5.37 (s, 1H, OH), 7.21 (br. s, 4H, H-2', H-3', H-5', H-6'), 7.44 (m, 2H, H-3", H-5"), 7.57 (m, 1H, H-4"), 7.92 (m, 2H, H-2", H-6").

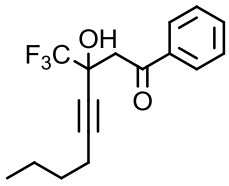
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 31.1 (CH_3), 34.8 ((CH_3)$_3$*C*), 41.7 (C-2), 70.6 (q, C-3, $^{2}J_{C-F}$ = 32.6 Hz), 82.7 (C-4), 87.0 (C-5), 118.0 (C-4'), 123.3 (q, CF_3, $^{1}J_{C-F}$ = 284.3 Hz), 125.3 (C-2', C-6'), 128.4 (C-3', C-5'), 128.9 (C-3", C-5"), 131.7 (C-2", C-6"), 134.4 (C-4"), 136.3 (C-1'), 152.6 (C-1"), 198.6 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 359 (49), 341 (60), 254 (21), 239 (100), 185 (35), 105 (76), 77 (56).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}F_3O_2$: 375.1566; found: 375.1563.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3327, 2983, 2230, 1670, 1578, 1576, 1497, 1469, 1447, 1211, 1039, 843, 779, 765.

3-Hydroxy-1-phenyl-3-(trifluoromethyl)non-4-yn-1-one (94c)



Starting from 3-benzoyl-1,1,1-trifluoroacetone (540 mg, 2.5 mmol) and 1-hexyne (451 mg, 5.5 mmol); **94c** was isolated as colorless liquid, yield = 529 mg (71%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.76 (t, 3H, CH_3, ^{3}J = 7.2 Hz), 1.30 (m, 4H, CH_2), 2.08 (t, 2H, CH_2, ^{3}J = 7.2 Hz), 3.30 (d, 1H, H-2a, ^{2}J = 16.2 Hz), 3.60 (d, 1H, H-2b, ^{2}J = 16.2 Hz), 5.20 (s, 1H, OH), 7.55 (br. m, 3H, H-2', H-4', H-6'), 7.90 (dd, 2H, H-3', H-5', $^{3}J_1$ = 5.1 Hz, $^{3}J_2$ = 0.9 Hz).

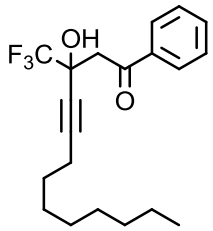
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 13.4 (C-9), 18.2 (C-8), 21.7 (C-7), 30.0 (C-6), 41.7 (C-2), 70.2 (q, C-3, $^{2}J_{C-F}$ = 32.1 Hz), 75.0 (C-4), 88.3 (C-5), 123.3 (q, CF_3, $^{1}J_{C-F}$ = 283.7 Hz), 128.4 (C-3', C-5'), 128.9 (C-2', C-6'), 134.3 (C-4'), 136.4 (C-1'), 198.7 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 256 (10), 187 (10), 105 (100), 77 (46).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}F_3O_2$: 299.1253; found: 299.1247.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3217, 2219, 1658, 1529, 1456, 1389, 1286, 1214, 1000, 922, 866, 786, 619.

3-Hydroxy-1-phenyl-3-(trifluoromethyl)tridec-4-yn-1-one (94d)



Starting from 3-benzoyl-1,1,1-trifluoroacetone (540 mg, 2.5 mmol) and 1-decyne (759 mg, 5.5 mmol); **94d** was isolated as colorless liquid, yield = 593 mg (67%);

^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 0.76 (t, 3H, CH_3, ^{3}J = 7.5 Hz), 1.29 (m, 12H, CH_2), 2.07 (t, 2H, CH_2, ^{3}J = 7.0 Hz), 3.23 (d, 1H, H-2a, ^{2}J = 16.8 Hz), 3.60 (d, 1H, H-2b, ^{2}J = 16.8 Hz), 5.21 (s, 1H, OH), 7.47 (br. m, 3H, H-2', H-4', H-6'), 7.91 (dd, 2H, H-3', H-5', $^{3}J_1$ = 1.5 Hz, $^{3}J_2$ = 1.0 Hz).

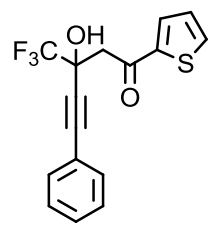
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.0 (C-13), 18.5 (C-12), 22.6 (C-11), 27.9 (C-10), 28.6 (C-9), 28.9 (C-8), 29.0 (C-7), 31.8 (C-6), 41.7 (C-2), 70.1 (q, C-3, $^{2}J_{C-F}$ = 32.7 Hz), 75.0 (C-4), 88.3 (C-5), 123.3 (q, CF_3, $^{1}J_{C-F}$ = 283.1 Hz), 128.4 (C-3', C-5'), 128.9 (C-2', C-6'), 134.3 (C-4'), 136.6 (C-1'), 198.7 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 285 (10), 238 (10), 105 (100), 77 (44).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{26}F_3O_2$: 355.1879; found: 355.1880.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3437, 2925, 2855, 2240, 1674, 1597, 1450, 1348, 1173, 1002, 755, 686, 624.

3-Hydroxy-5-phenyl-1-(thiophen-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (94e)



Starting from 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (555 mg, 2.5 mmol) and phenylacetylene (561 mg, 5.5 mmol); **94e** was isolated as light-grey powder, yield = 656 mg (81%); mp – dec.;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.32 (d, 1H, H-2a, ^{2}J = 16.5 Hz), 3.61 (d, 1H, H-2b, ^{2}J = 16.5 Hz), 5.34 (s, 1H, OH), 7.26 (br. m, 6H, H-2', H-4', H-6', H-3", H-4", H-5"), 7.75 (m, 2H, H-3', H-5').

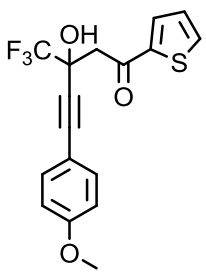
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 42.4 (C-2), 70.6 (q, C-3, $^{2}J_{C-F}$ = 32.7 Hz), 83.1 (C-4), 87.1 (C-5), 123.2 (q, CF_3, $^{1}J_{C-F}$ = 283.7 Hz), 128.3 (C-2', C-6'), 128.6 (C-4'), 129.3 (C-4"), 131.8 (C-1'), 132.0 (C-3', C-5'), 134.0 (C-3"), 136.1 (C-5"), 143.3 (C-2"), 190.7 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 323 (21) $[M-H^+]$, 255 (23), 237 (18), 184 (43), 129 (99), 111 (100).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{12}F_3O_2S$: 325.0505; found: 325.0508.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3297, 2918, 2229, 1661, 1587, 1522, 1496, 1423, 1398, 1233, 1098, 1010, 954, 812.

3-Hydroxy-5-(4-methoxyphenyl)-1-(thiophen-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (94f)



Starting from 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (555 mg, 2.5 mmol) and 4-methoxyphenylacetylene (726 mg, 5.5 mmol); **94f** was isolated as light-yellow powder, yield = 708 mg (80%); mp – dec.;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.30 (d, 1H, H-2a, ^{2}J = 16.5 Hz), 3.58 (d, 1H, H-2b, ^{2}J = 16.5 Hz), 3.71 (s, 3H, OCH_3), 5.29 (s, 1H, OH), 6.71 (d, 2H, H-2', H-6', ^{3}J = 4.8 Hz), 7.19 (m, 3H, H-3', H-5', H-4), 7.47 (m, 2H, H-3", H-5").

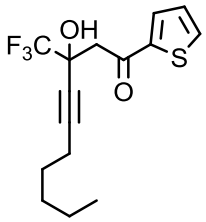
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 42.5 (OCH_3), 55.3 (C-2), 70.7 (q, C-3, $^{2}J_{C-F}$ = 32.5 Hz), 81.9 (C-4), 87.3 (C-5), 113.0 (C-4"), 113.9 (C-2', C-6'), 122.9 (q, CF_3, $^{1}J_{C-F}$ = 283.7 Hz), 128.9 (C-3"), 133.1 (C-3', C-5'), 134.0 (C-4"), 136.0 (C-5"), 143.4 (C-2"), 160.3 (C-1'), 190.8 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 428 (93), 409 (11), 228 (100), 214 (23), 200 (71).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{14}F_3O_3S$: 355.0160; found: 355.0163.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3350, 3018, 2897, 1653, 1598, 1524, 1447, 1229, 1210, 1143, 1018, 859, 687.

3-Hydroxy-1-(thiophen-2-yl)-3-(trifluoromethyl)dec-4-yn-1-one (94g)



Starting from 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (555 mg, 2.5 mmol) and 1-heptyne (528 mg, 5.5 mmol); **94g** was isolated as yellow liquid, yield = 485 mg (61%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.83 (t, 3H, CH_3, ^{3}J = 2.4 Hz), 1.17 (br. m, 6H, CH_2), 2.08 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 3.18 (d, 1H, H-2a, ^{2}J = 15.9 Hz), 3.48 (d, 1H, H-2b, ^{2}J = 15.9 Hz), 5.17 (s, 1H, OH), 7.13 (m, 1H, H-4'), 7.71 (m, 2H, H-3', H-5').

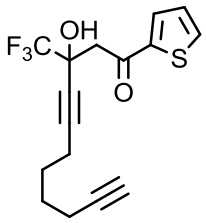
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 13.8 (C-10), 18.4 (C-9), 22.0 (C-8), 27.6 (C-7), 30.7 (C-6), 42.4 (C-2), 70.1 (q, C-3, $^{2}J_{C-F}$ = 32.1 Hz), 74.7 (C-4), 88.6 (C-5), 123.2 (q, CF_3, $^{1}J_{C-F}$ = 283.7 Hz), 128.6 (C-4'), 133.9 (C-3'), 135.9 (C-5'), 143.4 (C-2'), 191.0 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 257 (31), 244 (100), 231 (24), 216 (12), 189 (10), 147 (13), 111 (21).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{18}F_3O_2S$: 319.0974; found: 319.0972.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3405, 2840, 2233, 1645, 1605, 1509, 1411, 1243, 1168, 1072, 831, 726, 628.

3-Hydroxy-1-(thiophen-2-yl)-3-(trifluoromethyl)undeca-4,10-diyn-1-one (94h)



Starting from 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (555 mg, 2.5 mmol) and 1,7-octadiyne (583 mg, 5.5 mmol); **94h** was isolated as yellow liquid, yield = 0,517 g (63%);

^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 1.46 (m, 4H, CH_2), 1.85 (t, 1H, H-11, ^{3}J = 3.0 Hz), 2.06 (m, 4H, CH_2), 3.19 (d, 1H, H-2a, ^{2}J = 19.2 Hz), 3.48 (d, 1H, H-2b, ^{2}J = 19.2 Hz), 5.20 (s, 1H, OH), 7.13 (dd, 1H, H-4', $^{3}J_1$ = 3.6 Hz, $^{3}J_2$ = 1.2 Hz), 7.20 (m, 2H, H-3', H-5').

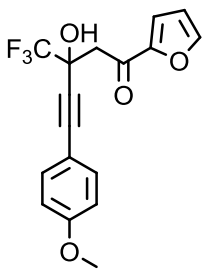
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 17.8 (C-8), 18.0 (C-7), 26.8 (C-9), 27.2 (C-6), 42.4 (C-2), 68.6 (C-11), 70.1 (q, C-3, $^{2}J_{C-F}$ = 32.5 Hz), 75.2 (C-10), 83.9 (C-4), 88.0 (C-5), 123.2 (q, CF_3, $^{1}J_{C-F}$ = 283.8 Hz), 128.6 (C-4'), 133.9 (C-3'), 136.0 (C-5'), 143.4 (C-2'), 190.9 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 302 (14), 243 (43), 202 (28), 144 (100), 128 (19).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{16}F_3O_2S$: 329.0786; found: 329.0782.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3369, 3288, 2237, 2196, 1629, 1587, 1506, 1468, 1387, 1241, 1176, 1033, 954, 814, 682.

1-(Furan-2-yl)-3-hydroxy-5-(4-methoxyphenyl)-3-(trifluoromethyl)pent-4-yn-1-one (94i)



Starting from 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione (515 mg, 2.5 mmol) and 4-methoxyphenylacetylene (726 mg, 5.5 mmol); **94i** was isolated as light-yellow flakes, yield = 566 mg (67%); mp – dec.;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.23 (d, 1H, H-2a, ^{2}J = 16.2 Hz), 3.56 (d, 1H, H-2b, ^{2}J = 16.2 Hz), 3.71 (s, 3H, OCH_3), 5.17 (s, 1H, -OH), 6.54 (dd, 1H, H-4" $^{3}J_1$ = 1.8 Hz, $^{3}J_2$ = 1.8 Hz), 6.72 (m, 2H, H-2', H-6'), 7.24 (m, 3H, H-3', H-5', H-3"), 7.60 (d, 1H, H-5", ^{3}J = 0.9 Hz).

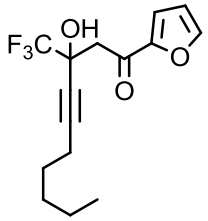
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 41.7 (OCH_3), 55.3 (C-2), 70.6 (q, C-3, $^{2}J_{C-F}$ = 32.5 Hz), 81.8 (C-4), 87.2 (C-5), 113.1 (C-4"), 113.9 (C-2', C-6'), 119.5 (C-3"), 123.3 (q, CF_3, $^{1}J_{C-F}$ = 284.5 Hz), 133.1 (C-3', C-5'), 148.0 (C-4'), 152.1 (C-1"), 160.3 (C-1'), 186.4 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 338 (18) $[M^+]$, 228 (15), 198 (11), 159 (100), 144 (17), 95 (52).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{17}H_{13}F_3O_4$: 338.0760; found: 338.0761.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3386, 2964, 2198, 1673, 1575, 1524, 1497, 1446, 1389, 1221, 1075, 849, 712.

1-(Furan-2-yl)-3-hydroxy-3-(trifluoromethyl)dec-4-yn-1-one (94j)



Starting from 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione (515 mg, 2.5 mmol) and 1-heptyne (528 mg, 5.5 mmol); **94j** was isolated as orange liquid, yield = 461 mg (61%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.78 (t, 3H, CH_3, ^{3}J = 2.1 Hz), 1.21 (br. m, 6H, CH_2), 2.08 (t, 2H, CH_2, ^{3}J = 6.6 Hz), 3.11 (d, 1H, H-2a, ^{2}J = 16.2 Hz), 3.45 (d, 1H, H-2b, ^{2}J = 16.2 Hz), 5.05 (s, 1H, OH), 6.55 (dd, 1H, H-4', $^{3}J_1$ = 2.1 Hz, $^{3}J_2$ = 2.1 Hz), 7.27 (dd, 1H, H-3', $^{3}J_1$ = 3.3 Hz, $^{3}J_2$ = 0.4 Hz), 7.60 (t, 1H, H-5', ^{3}J = 0.6 Hz).

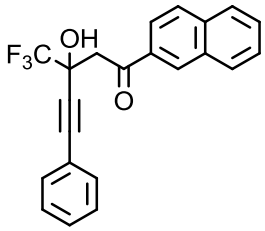
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 13.8 (C-10), 18.4 (C-9), 22.0 (C-8), 27.6 (C-7), 30.7 (C-6), 41.6 (C-2), 70.0 (q, C-3, $^{2}J_{C-F}$ = 32.5 Hz), 74.5 (C-4), 88.6 (C-5), 113.0 (C-4'), 119.4 (C-3'), 123.2 (q, CF_3, $^{1}J_{C-F}$ = 284.5 Hz), 147.9 (C-5'), 152.1 (C-1'), 186.6 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 274 (100), 144 (11), 44 (14).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{18}F_3O_3$: 303.1203; found: 303.1198.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3424, 2933, 2242, 1658, 1569, 1465, 1175, 1100, 1004, 883, 765, 653.

3-Hydroxy-1-(naphthalen-2-yl)-5-phenyl-3-(trifluoromethyl)pent-4-yn-1-one (94k)



Starting from 4,4,4-trifluoro-1-(naphtalen-2-yl)butane-1,3-dione (665 mg, 2.5 mmol) and phenylacetylene (561 mg, 5.5 mmol); **94k** was isolated as light-yellow powder, yield = 0,681 g (74%); mp – dec.;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.48 (d, 1H, H-2a, ^{2}J = 16.5 Hz), 3.87 (d, 1H, H-2b, ^{2}J = 16.5 Hz), 5.49 (s, 1H, OH), 7.18 (br. m, 5H, -Ph), 7.55 (m, 2H, H-5', H-7'), 7.91 (br. m, 4H, H-3', H-4', H-6', H-8'), 8.43 (s, 1H, H-1').

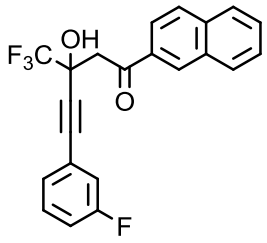
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 41.7 (C-2), 70.7 (q, C-3, $^{2}J_{C-F}$ = 32.5 Hz), 83.4 (C-4), 86.9 (C-5), 123.4 (q, CF_3, $^{1}J_{C-F}$ = 284.5 Hz), 123.4 (C-5"), 127.2 (C-7"), 127.9 (C-8"), 128.3 (C-3', C-5'), 129.0 (C-6"), 129.2 (C-4"), 129.3 (C-3"), 129.8 (C-1"), 130.9 (C-4'), 131.9 (C-1'), 132.0 (C-2', C-6'), 132.4 (C-8a"), 133.6 (C-4a"), 136.2 (C-2"), 198.4 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 368 (55) $[M^+]$, 350 (20), 299 (24), 281 (26), 228 (56), 170 (36), 155 (98), 127 (100), 101 (15).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{22}H_{15}F_3O_2$: 368.1019; found: 368.1019.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3399, 3077, 2223, 1678, 1597, 1464, 1431, 1229, 1163, 1055, 987, 963, 879, 787, 679.

5-(3-Fluorophenyl)-3-hydroxy-1-(naphthalen-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (94l)



Starting from 4,4,4-trifluoro-1-(naphtalen-2-yl)butane-1,3-dione (665 mg, 2.5 mmol) and 3-fluorophenylacetylene (660 mg, 5.5 mmol); **94l** was isolated as light-yellow powder, yield = 676 mg (70%); mp – dec.;

^{1}H NMR (500.13 MHz, CD_2Cl_2): δ = 3.47 (d, 1H, H-2a, ^{2}J = 16.5 Hz), 3.87 (d, 1H, H-2b, ^{2}J = 16.5 Hz), 5.46 (s, 1H, OH), 6.94 (m, 2H, H-2', H-4'), 7.05 (m, 1H, H-6'), 7.13 (dd, 1H, H-5', $^{3}J_1$ = 5.5 Hz, $^{3}J_2$ = 1.0 Hz), 7.49 (dd, 1H, H-6", $^{3}J_1$ = 7.0 Hz, $^{3}J_2$ = 1.0 Hz), 7.55 (dd, 1H, H-7", $^{3}J_1$ = 7.0 Hz, $^{3}J_2$ = 1.0 Hz), 7.85 (br. m, 4H, H-3", H-4", H-5", H-8"), 8.42 (d, 1H, H-1", ^{3}J = 1.0 Hz).

^{13}C NMR (125.76 MHz, CD_2Cl_2): δ = 42.1 (C-2), 71.0 (q, C-3, $^{2}J_{C-F}$ = 32.7 Hz), 84.8 (C-4), 85.7 (d, C-5, $^{4}J_{C-F}$ = 3.8 Hz), 117.0 (d, C-2', $^{2}J_{C-F}$ = 23.9 Hz), 119.0 (d, C-4', $^{2}J_{C-F}$ = 23.9 Hz), 123.2 (q, CF_3, $^{1}J_{C-F}$ = 284.1 Hz),

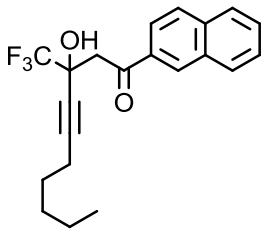
123.7 (C-6'), 127.7 (C-5"), 128.3 (d, 1H, C-4', $^{3}J_{C-F}$ = 7.6 Hz), 129.0 (C-7"), 129.3 (C-6"), 129.6 (C-8"), 130.2 (C-4"), 130.5 (C-3"), 131.0 (C-4a", C-8a"), 131.3 (C-1"), 132.8 (d, C-1', $^{3}J_{C-F}$ = 8.8 Hz), 136.6 (C-2"), 162.5 (d, C-3', $^{1}J_{C-F}$ = 246.9 Hz), 198.7 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 368 (100), 299 (38), 270 (59), 246 (21), 220 (22), 152 (53), 144 (25), 127 (66).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{22}H_{14}F_4O_2$: 386.0924; found: 386.0927.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3457, 3077, 2229, 2201, 1674, 1580, 1485, 1470, 1435, 1367, 1339, 1233, 1163, 1070, 955, 933, 860, 832, 777, 741, 673, 561.

3-Hydroxy-1-(naphthalen-2-yl)-3-(trifluoromethyl)dec-4-yn-1-one (94m)



Starting from 4,4,4-trifluoro-1-(naphtalen-2-yl)butane-1,3-dione (665 mg, 2.5 mmol) and 1-heptyne (528 mg, 5.5 mmol); **94m** was isolated as colorless liquid, yield = 579 mg (64%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.70 (t, 3H, CH_3, ^{3}J = 2.4 Hz), 1.16 (br. m, 6H, CH_2), 2.06 (t, 2H, CH_2, ^{3}J = 6.9 Hz), 3.35 (d, 1H, H-2a, ^{2}J = 16.5 Hz), 3.75 (d, 1H, H-2b, ^{2}J = 16.5 Hz), 5.30 (s, 1H, OH), 7.55 (m, 2H, H-5', H-7'), 7.88 (br. m, 4H, H-3', H-4', H-6', H-8'), 8.41 (s, 1H, H-1').

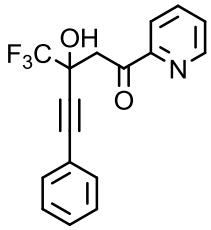
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 13.8 (C-10), 18.5 (C-9), 22.0 (C-8), 27.6 (C-7), 30.7 (C-6), 41.7 (C-2), 70.3 (q, C-3, $^{2}J_{C-F}$ = 32.7 Hz), 75.0 (C-4), 88.4 (C-5), 123.3 (q, CF_3, $^{1}J_{C-F}$ = 283.7 Hz), 123.4 (C-5'), 127.2 (C-7'), 127.9 (C-8'), 128.8 (C-6'), 129.2 (C-4'), 129.8 (C-3'), 130.1 (C-1'), 132.3 (C-8a'), 133.7 (C-4a'), 136.1 (C-2'), 198.6 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 345 (15), 288 (12), 170 (32), 155 (100), 127 (94).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{21}H_{21}F_3O_2$: 362.1488; found: 362.1483.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3437, 2930, 2238, 1667, 1469, 1356, 1242, 1171, 1100, 822, 746, 671.

3-Hydroxy-5-phenyl-1-(pyridin-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (94n)



Starting from 4,4,4-trifluoro-1-(pyridin-2-yl)butane-1,3-dione (543 mg, 2.5 mmol) and phenylacetylene (561 mg, 5.5 mmol); **94n** was isolated as violet liquid, yield = 502 mg (63%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.61 (d, 1H, H-2a, ^{2}J = 14.4 Hz), 3.71 (d, 1H, H-2b, ^{2}J = 14.4 Hz), 7.23 (br. m, 5H, Ph), 7.53 (m, 1H, H-5'), 7.90 (m, 1H, H-3"), 8.10 (m, 1H, H-4'), 8.63 (s, 1H, H-6').

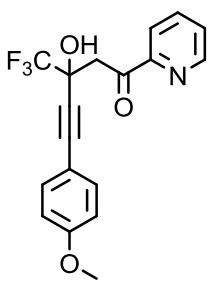
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 46.5 (C-2), 69.7 (q, C-3, $^{2}J_{C-F}$ = 32.7 Hz), 83.4 (C-4), 87.3 (C-5), 121.2 (C-1'), 123.2 (C-5") 123.7 (q, CF_3, $^{1}J_{C-F}$ = 284.9 Hz), 128.0 (C-4'), 128.2 (C-2', C-6'), 129.1 (C-3"), 132.0 (C-3', C-5'), 138.3 (C-4"), 148.2 (C-6"), 152.1 (C-2"), 196.0 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 319 (11) $[M^+]$, 250 (18), 222 (17), 198 (11), 129 (100), 121 (21), 78 (29).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{17}H_{12}F_3NO_2$: 319.0815; found: 319.0816.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3414, 2876, 2234, 1700, 1596, 1579, 1512, 1498, 1287, 1153, 1012, 913, 846, 655.

3-Hydroxy-5-(4-methoxyphenyl)-1-(pyridin-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (94o)



Starting from 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione (543 mg, 2.5 mmol) and 4-methoxyphenylacetylene (726 mg, 5.5 mmol); **94o** was isolated as light-green liquid, yield = 497 mg (59%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.54 (d, 1H, H-2a, ^{2}J = 14.1 Hz), 3.66 (d, 1H, H-2b, ^{2}J = 14.1 Hz), 3.69 (s, 3H, OCH_3), 6.72 (m, 2H, H-2', H-6'), 7.20 (m, 2H, H-3', H-5'), 7.53 (m ,1H, H-5"), 7.89 (m, 2H, H-3", OH), 8.06 (m, 1H, H-4"), 8.61 (m, 1H, H-6").

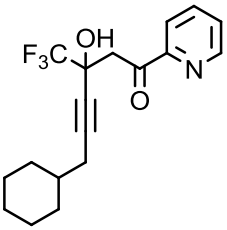
^{13}C NMR (62.90 MHz, CD_2Cl_2): δ = 47.0 (C-2), 55.7 (OCH_3), 70.0 (q, C-3, $^{2}J_{C-F}$ = 32.7 Hz), 82.7 (C-4), 87.6 (C-5), 113.4 (C-4'), 114.3 (C-2', C-6'), 123.4 (C-5"), 124.2 (q, CF_3, $^{1}J_{C-F}$ = 284.9 Hz), 128.5 (C-3"), 133.7 (C-3', C-5'), 138.8 (C-4"), 148.7 (C-6"), 152.6 (C-2"), 160.8 (C-1'), 196.4 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 228 (28), 159 (100), 144 (20), 116 (18), 88 (14).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}F_3NO_3$: 350.0999; found: 350.0993.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3391, 2935, 2840, 2232, 1698, 1605, 1509, 1247, 1169, 1107, 1027, 832, 617.

6-Cyclohexyl-3-hydroxy-1-(pyridin-2-yl)-3-(trifluoromethyl)hex-4-yn-1-one (94p)



Starting from 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione (543 mg, 2.5 mmol) and 3-cyclohexyl-prop-1-yne (671 mg, 5.5 mmol); **94p** was isolated as light-violet liquid, yield = 483 mg (57%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.81 (br.m, 6H, Cy), 1.04 (m, 5H, Cy), 1.95 (d, 2H, H-6, ^{3}J = 5.4 Hz), 3.51 (d, 1H, H-2a, ^{2}J = 15.3 Hz), 3.55 (d, 1H, H-2b, ^{2}J = 15.3 Hz), 7.52 (m, 1H, H-5'), 7.90 (m, 1H, H-3"), 8.08 (m, 1H, H-4'), 8.62 (m, 1H, H-6').

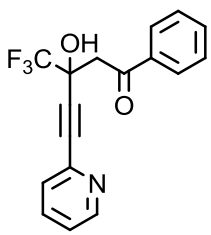
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 26.1 (CH_2), 26.2 (CH_2), 32.3 (CH_2), 36.8 (CH), 46.6 (C-6), 68.8 (q, C-3, $^{2}J_{C-F}$ = 32.7 Hz), 75.8 (C-4), 87.7 (C-5), 123.3 (C-3'), 124.6 (q, CF_3, $^{1}J_{C-F}$ = 284.3 Hz), 127.3 (C-5'), 138.2 (C-4'), 148.2 (C-6'), 152.2 (C-2'), 196.3 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 338 (14) $[M-H^+]$, 310 (16), 256 (46), 188 (35), 149 (29), 121 (80), 83 (100).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{21}F_3NO_2$: 340.1519; found: 340.1524.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923, 2851, 2240, 1699, 1587, 1449, 1262, 1173, 1104, 617.

3-Hydroxy-1-phenyl-5-(pyridin-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (94q)



Starting from 3-benzoyl-1,1,1-trifluoroacetone (540 mg, 2.5 mmol) and 2-ethynylpyridine (567 mg, 5.5 mmol); **94q** was isolated as dark-green powder, yield = 383 mg (48%); mp – dec.;

^{1}H NMR (300.13 MHz, CD_2Cl_2): δ = 3.57 (d, 1H, H-2a, ^{2}J = 18.0 Hz), 3.87 (d, 1H, H-2b, ^{2}J = 18.0 Hz), 5.78 (s, 1H, OH), 7.59 (br. m, 6H, H-3', H-4', H-5', H-2", H-4", H-6"), 8.04 (dd, 2H, H-3", H-5", $^{3}J_1$ = 3.6 Hz, $^{3}J_2$ = 3.0 Hz), 8.58 (m, 1H, H-6').

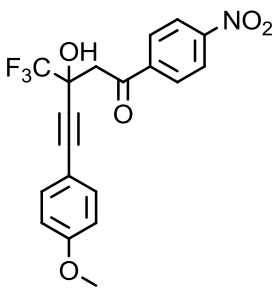
^{13}C NMR (62.90 MHz, CD_2Cl_2): δ = 42.3 (C-2), 70.7 (q, C-3, $^{2}J_{C-F}$ = 32.7 Hz), 83.3 (C-4), 86.1 (C-5), 123.8 (q, CF_3, $^{1}J_{C-F}$ = 284.3 Hz), 123.9 (C-3'), 124.2 (C-5'), 128.0 (C-4"), 128.8 (C-2", C-6"), 129.3 (C-3", C-5"), 134.7 (C-4'), 136.6 (C-6'), 141.8 (C-1"), 150.4 (C-1"), 198.2 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 318 (46) [M-H$^+$], 250 (14), 222 (18), 180 (51), 130 (44), 105 (100), 77 (69).

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{17}H_{13}F_3NO_2$: 320.0893; found: 320.0890.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3086, 2790, 2239, 1689, 1586, 1470, 1430, 1371, 1268, 1167, 1114, 1084, 976, 763, 688, 623.

3-Hydroxy-5-(4-methoxyphenyl)-1-(4-nitrophenyl)-3-(trifluoromethyl)pent-4-yn-1-one (94r)



Starting from 3-(4-nitrobenzoyl)-1,1,1-trifluoroacetone (653 mg, 2.5 mmol) and 4-methoxyphenylacetylene (726 mg, 5.5 mmol); **94r** was isolated as yellow gum, yield = 609 mg (62%);

^{1}H NMR (300.13 MHz, CD_2Cl_2): δ = 3.46 (d, 1H, H-2a, ^{2}J = 15.2 Hz), 3.70 (s, 3H, OCH_3), 3.73 (d, 1H, H-2b, ^{2}J = 15.2 Hz), 4.66 (s, 1H, OH), 6.74 (dd, 2H, H-2', H-6", $^{3}J_1$ = 4.5 Hz, $^{3}J_2$ = 2.1 Hz), 7.22 (dd, 2H, H-3', H-5', $^{3}J_1$ = 4.5 Hz, $^{3}J_2$ = 2.1 Hz), 8.08 (dd, 2H, H-3", H-5", $^{3}J_1$ = 4.8 Hz, $^{3}J_2$ = 2.1 Hz), 8.27 (dd, 2H, H-2", H-6", $^{3}J_1$ = 4.8 Hz, $^{3}J_2$ = 2.1 Hz),

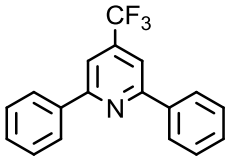
^{13}C NMR (62.90 MHz, CD_2Cl_2): δ = 43.2 (C-2), 55.6 (OCH_3), 70.5 (q, C-3, $^{2}J_{C-F}$ = 32.7 Hz), 81.8 (C-4), 87.8 (C-5), 114.3 (C-2', C-6'), 123.4 (q, CF_3, $^{1}J_{C-F}$ = 284.9 Hz), 124.1 (C-3', C-5'), 129.8 (C-3", C-5"), 133.7 (C-2", C-6"), 135.8 (C-1'), 141.0 (C-4"), 151.2 (C-1'), 160.9 (C-1"), 196.8 (C-1).

GC-MS (EI, 70 eV): *m/z* (%): 281 (78), 253 (20), 159 (100).

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{19}H_{15}F_3NO_5$: 394.0897; found: 394.0892.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3489, 3110, 2912, 2235, 1683, 1603, 1511, 1401, 1344, 1230, 1178, 1077, 1030, 947, 840, 747, 688, 639.

2,6-Diphenyl-4-(trifluoromethyl)pyridine (96a)



Starting from 3-hydroxy-1,5-diphenyl-3-(trifluoromethyl)pent-4-yn-1-one (318 mg, 1 mmol) **94a** and urea (72 mg, 1.2 mmol); **96a** was isolated as light-yellow powder, yield = 203 mg (68%); mp = 62- 64°C;

^{1}H NMR (250.13 MHz, DMSO-d_6): δ = 7.49 (m, 6H, H-3', H-4', H-5', H-3", H-4", H-5"), 8.25 (m, 6H, H-3, H-5, H-2', H-6', H-2", H-6").

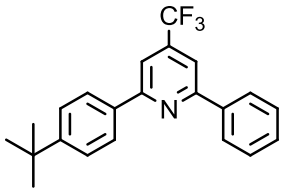
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 112.6 (q, C-3, C-5, $^{3}J_{C-F}$ = 3.1 Hz), 121.6 (q, CF_3, $^{1}J_{C-F}$ = 274.2 Hz), 125.5 (C-3', C-5', C-3", C-5"), 127.4 (C-2', C-6', C-2", C-6"), 128.5 (C-4', C-4"), 135.8 (C-1', C-1"), 137.7 (q, C-4, $^{2}J_{C-F}$ = 33.3 Hz), 155.8 (C-2, C-6).

GC-MS (EI, 70 eV): *m/z* (%): 299 (100) [M^+], 230 (11).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{13}F_3N$: 300.0995; found: 300.0992.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2890, 1589, 1566, 1518, 1466, 1376, 1255, 1180, 1162, 1084, 877, 696.

2-(4-*Tert*-butylphenyl)-6-phenyl-4-(trifluoromethyl)pyridine (96b)



Starting from 5-(4-tert-butylphenyl)-3-hydroxy-1-phenyl-3-(trifluoromethyl)pent-4-yn-1-one (374 mg, 1 mmol) **94b** and urea (72 mg, 1.2 mmol); **96b** was isolated as light-yellow liquid, yield = 216 mg (61%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.30 (s, 9H, *t*-Bu), 7.46 (br. m, 5H, -Ph), 7.77 (s, 2H, H-3, H-5), 8.08 (br, m, 4H, H-2", H-3", H-5", H-6").

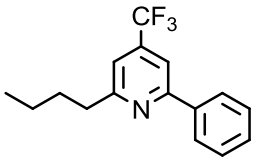
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 31.3 (CH_3), 34.8 ((CH_3)$_3$*C*), 113.6 (d, C-5, $^{3}J_{C-F}$ = 3.8 Hz), 113.8 (d, C-3, $^{3}J_{C-F}$ = 3.8 Hz), 122.9 (q, CF_3, $^{1}J_{C-F}$ = 273.2 Hz), 125.9 (C-3", C-5"), 126.9 (C-2', C-6'), 127.1 (C-3', C-5'), 128.9 (C-2", C-6"), 129.8 (C-4"), 135.5 (C-1'), 138.3 (C-1"), 139.9 (q, C-4, $^{2}J_{C-F}$ = 34.0 Hz), 153.1 (C-4'), 158.1 (C-6), 158.3 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 355 (42) [M^+], 340 (100), 312 (14), 156 (20).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{20}H_{20}F_3N$: 355.1542; found: 355.1537.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962, 1611, 1574, 1562, 1412, 1371, 1263, 1168, 1132, 1106, 877, 840, 772, 687.

2-Butyl-6-phenyl-4-(trifluoromethyl)pyridine (96c)



Starting from 3-hydroxy-1-phenyl-3-(trifluoromethyl)non-4-yn-1-one (298 mg, 1 mmol) **94c** and urea (72 mg, 1.2 mmol); **96c** was isolated as light-orange liquid, yield = 145 mg (52%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.90 (t, 3H, CH_3, ^3J = 7.2 Hz), 1.39 (m, 2H, CH_2), 1.73 (m, 2H, CH_2), 2.86 (t, 2H, CH_2, ^3J = 7.8 Hz), 7.18 (d, 1H, H-4‘, ^3J = 8.4 Hz), 7.39 (m, 3H, H-3, H-3’, H-5’), 7.65 (s, 1H, H-5), 7.95 (m, 2H, H-2’, H-6’).

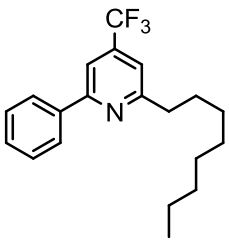
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 13.9 (CH_3), 22.5 (CH_2), 31.7 (CH_2), 38.3 (CH_2), 113.2 (q, C-3, $^3J_{C-F}$ = 3.8 Hz), 116.4 (q, C-5, $^3J_{C-F}$ = 3.8 Hz), 123.2 (q, CF_3, $^1J_{C-F}$ = 273.6 Hz), 127.1 (C-3’, C-5’), 128.8 (C-2’, C-6’), 129.5 (C-4’), 138.5 (C-1’), 139.2 (q, C-4, $^2J_{C-F}$ = 33.3 Hz), 158.1 (C-6), 164.0 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 250 (21), 237 (100).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{17}F_3N$: 280.1308; found: 280.1310.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2930, 1573, 1459, 1412, 1372, 1261, 1166, 1131, 1103, 867, 773, 691, 639.

2-Octyl-6-phenyl-4-(trifluoromethyl)pyridine (96d)



Starting from 3-hydroxy-1-phenyl-3-(trifluoromethyl)tridec-4-yn-1-one (354 mg, 1 mmol) **94d** and urea (72 mg, 1.2 mmol); **96d** was isolated as light-orange liquid, yield = 188 mg (56%);

^{1}H NMR (300.13 MHz, CD_2Cl_2): δ = 0.79 (t, 3H, CH_3, ^3J = 6.0 Hz), 1.27 (m, 10H, CH_2), 1.72 (dd, 2H, CH_2 , $^3J_1$ = 10.5 Hz, $^3J_2$ = 7.8 Hz), 2.84 (t, 2H, CH_2, ^3J = 7.8 Hz), 7.23 (s, 1H, H-3), 7.41 (m, 3H, H-3‘, H-4‘, H-5‘), 7.68 (s, 1H, H-5), 7.98 (m, 2H, H-2‘, H-6‘).

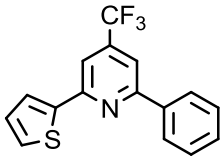
^{13}C NMR (75.47 MHz, CD_2Cl_2): δ = 13.3 (CH_3), 22.2 (CH_2), 28.7 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 31.4 (CH_2), 37.9 (CH_2), 112.4 (q, C-3, $^3J_{C-F}$ = 3.8 Hz), 115.9 (q, C-5, $^3J_{C-F}$ = 3.8 Hz), 122.9 (q, CF_3, $^1J_{C-F}$ = 273.2 Hz), 126.4 (C-3‘, C-5‘), 128.3 (C-2‘, C-6‘), 129.1 (C-4‘), 137.8 (C-1‘), 138.5 (q, C-4, $^2J_{C-F}$ = 33.2 Hz), 157.2 (C-2), 163.6 (C-6).

GC-MS (EI, 70 eV): *m/z* (%): 264 (10), 250 (19), 237 (100).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{20}H_{24}F_3N$: 335.1855; found: 335.1847.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925, 1573, 1412, 1372, 1261, 1134, 879, 773, 691, 639.

2-Phenyl-6-(thiophen-2-yl)-4-(trifluoromethyl)pyridine (96e)



Starting from 3-hydroxy-5-phenyl-1-(thiophen-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (324 mg, 1 mmol) **94e** and urea (72 mg, 1.2 mmol); **96e** was isolated as light-orange crystals, yield = 220 mg (72%); mp = 104 - 107°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.08 (dd, 1H, H-4", $^{3}J_1$ = 3.6 Hz, $^{3}J_2$ = 1.5 Hz), 7.45 (br. m, 4H, H-3', H-4', H-5', H-3"), 7.66 (m, 3H, H-2', H-6', H-5"), 8.06 (m, 2H, H-3, H-5).

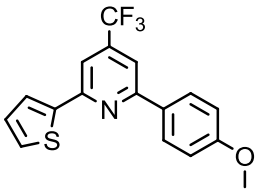
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 112.4 (q, C-5, $^{3}J_{C-F}$ = 3.8 Hz), 113.5 (q, C-3, $^{3}J_{C-F}$ = 3.8 Hz), 123.0 (q, CF_3, $^{1}J_{C-F}$ = 273.9 Hz), 125.7 (C-4"), 127.1 (C-3', C-5'), 128.2 (C-3"), 128.9 (C-2', C-4', C-6'), 130.0 (C-5"), 137.7 (C-1'), 140.0 (q, C-4, $^{2}J_{C-F}$ = 33.2 Hz), 144.0 (C-1"), 153.5 (C-2), 158.1 (C-6).

GC-MS (EI, 70 eV): *m/z* (%): 305 (100) [M^+].

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{10}F_3NS$: 306.0559; found: 306.0558.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3068, 1568, 1436, 1403, 1373, 1337, 1264, 1167, 1126, 870, 833, 773, 714, 689, 633.

2-(4-Methoxyphenyl)-6-(thiophen-2-yl)-4-(trifluoromethyl)pyridine (96f)



Starting from 3-hydroxy-5-(4-methoxyphenyl)-1-(thiophen-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (354 mg, 1 mmol) **94f** and urea (72 mg, 1.2 mmol); **96f** was isolated as white crystals, yield = 298 mg (89%); mp = 69 - 71°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.81 (s, 3H, OCH_3), 6.95 (m, 2H, H-2', H-6'), 7.07 (dd, 1H, H-4", $^{3}J_1$ = 2.4 Hz, $^{3}J_2$ = 1.2 Hz), 7.38 (dd, 1H, H-3", $^{3}J_1$ = 4.2 Hz, $^{4}J_2$ = 0.9 Hz), 7.62 (m, 3H, H-5, H-3', H-5'), 8.03 (m, 2H, H-3, H-5").

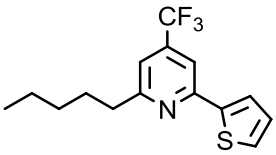
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 111.5 (q, C-3, $^{3}J_{C-F}$ = 3.8 Hz), 112.6 (q, C-5, $^{3}J_{C-F}$ = 3.8 Hz), 114.2 (C-2', C-6'), 123.1 (q, CF_3, $^{1}J_{C-F}$ = 273.2 Hz), 125.5 (C-4"), 128.1 (C-3"), 128.4 (C-3', C-5'), 128.7 (C-5"), 130.3 (C-4'), 139.8 (q, C-4, $^{2}J_{C-F}$ = 33.2 Hz), 144.2 (C-2"), 153.3 (C-2), 157.7 (C-6), 161.2 (C-1').

GC-MS (EI, 70 eV): *m/z* (%): 335 (100) [M^+], 320 (12), 292 (35), 223 (11).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}F_3NOS$: 336.0665; found: 336.0663.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3093, 3015, 2968, 2840, 1608, 1562, 1516, 1435, 1411, 1371, 1337, 1265, 1162, 1127, 1105, 1025, 870, 831. 713, 690, 581.

2-Pentyl-6-(thiophen-2-yl)-4-(trifluoromethyl)pyridine (96g)



Starting from 3-hydroxy-1-(thiophen-2-yl)-3-(trifluoromethyl)dec-4-yn-1-one (318 mg, 1 mmol) **94g** and urea (72 mg, 1.2 mmol); **96g** was isolated as light-red powder, yield = 173 mg (58%); mp = 47 - 49°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.84 (t, 3H, CH_3-, ^3J = 6.9 Hz), 1.31 (m, 4H, -CH_2-), 1.72 (m, 2H, CH_2), 2.79 (t, 2H, CH_2, ^3J = 7.8 Hz), 7.06 (m, 2H, H-3‘, H-4‘), 7.33 (s, 1H, H-3), 7.56 (m, 2H, H-5, H-5’).

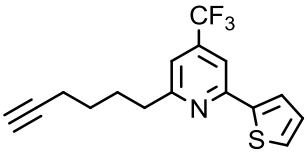
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5 (CH_2), 29.0 (CH_2), 31.5 (CH_2), 38.2 (CH_2), 111.4 (q, C-3, $^3J_{C-F}$ = 3.8 Hz), 116.1 (q, C-5, $^3J_{C-F}$ = 3.8 Hz), 121.8 (q, CF_3, $^1J_{C-F}$ = 273.2 Hz), 125.4 (C-4’), 128.4 (C-3’), 128.5 (C-5’), 139.6 (q, C-4, $^2J_{C-F}$ = 33.2 Hz), 144.1 (C-1’), 153.1 (C-6), 164.0 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 270 (28), 256 (42), 243 (100).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{17}F_3NS$: 300.1028; found: 300.1025.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963, 2930, 1608, 1569, 1440, 1410, 1375, 1335, 1256, 1164, 1123, 870, 833, 794, 709, 694.

2-(Hex-5-ynyl)-6-(thiophen-2-yl)-4-(trifluoromethyl)pyridine (96h)



Starting from 3-hydroxy-1-(thiophen-2-yl)-3-(trifluoromethyl)undeca-4,10-diyn-1-one (328 mg) **94h** and urea (72 mg, 1.2 mmol); **96h** was isolated as yellow liquid, yield = 148 mg (48%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.59 (t, 2H, CH_2, ^3J = 6.9 Hz), 1.88 (m, 3H, CH_2, H-6‘), 2.20 (m, 2H, CH_2), 2.82 (t, 2H, CH_2, ^3J = 7.5 Hz), 7.18 (m, 2H, H-4”, H-3”), 7.35 (s, 1H, H-3), 7.56 (m, 2H, H-5, H-5”).

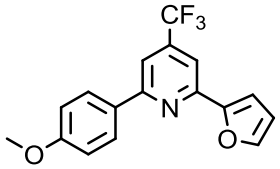
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 18.3 (C-3’), 27.9 (C-2’), 28.1 (C-4’), 37.5 (C-1’), 68.5 (C-6’), 84.2 (C-5’), 111.6 (q, C-3, $^3J_{C-F}$ = 3.8 Hz), 116.1 (q, C-5, $^3J_{C-F}$ = 3.8 Hz), 123.0 (q, CF_3, $^1J_{C-F}$ = 273.2 Hz), 125.5 (C-4”), 128.4 (C-3”), 128.6 (C-5”), 139.2 (q, C-4, $^2J_{C-F}$ = 33.2 Hz), 144.0 (C-2”), 153.2 (C-2), 163.3 (C-6).

GC-MS (EI, 70 eV): *m/z* (%): 308 (20), 280 (19), 256 (25), 243 (100).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}F_3NS$: 310.0872; found: 310.0867.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3305, 2937, 2117, 1610, 1572, 1439, 1410, 1375, 1336, 1256, 1167, 1130, 873, 695, 629.

2-(Furan-2-yl)-6-(4-methoxyphenyl)-4-(trifluoromethyl)pyridine (96i)



Starting from 1-(furan-2-yl)-3-hydroxy-5-(4-methoxyphenyl)-3-(trifluoromethyl)pent-4-yn-1-one (338 mg, 1 mmol) **94i** and urea (72 mg, 1.2 mmol); **96i** was isolated as yellow powder, yield = 239 mg (75%); mp = 89 - 92°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OCH_3), 6.49 (dd, 1H, H-4", $^3J_1$ = 1.8 Hz, $^3J_2$ = 1.8 Hz), 6.93 (m, 2H, H-3', H-5'), 7.17 (dd, 1H, H-3", $^3J_1$ = 1.8 Hz, $^3J_2$ = 0.6 Hz), 7.49 (dd, 1H, H-5", $^3J_1$ = 1.8 Hz, $^3J_2$ = 0.6 Hz), 7.62 (s, 1H, H-3), 7.67 (s, 1H, H-5), 7.96 (m, 2H, H-2', H-6').

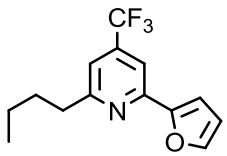
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 110.0 (C-4"), 111.4 (q, C-3, $^3J_{C-F}$ = 3.8 Hz), 112.3 (C-3"), 112.9 (q, C-3, $^3J_{C-F}$ = 3.8 Hz), 114.2 (C-2', C-6'), 123.1 (q, CF_3, $^1J_{C-F}$ = 273.2 Hz), 128.4 (C-3', C-5'), 130.5 (C-4'), 139.8 (q, C-4, $^2J_{C-F}$ = 33.7 Hz), 143.9 (C-5"), 150.1 (C-2"), 153.2 (C-2), 157.9 (C-6), 161.2 (C-1').

GC-MS (EI, 70 eV): *m/z* (%): 319 (100) [M^+], 276 (16), 246 (12).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{17}H_{12}F_3NO_2$: 319.0815; found: 319.0819.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3101, 1608, 1564, 1400, 1379, 1361, 1246, 1131, 1105, 1016, 874, 837, 753, 690, 586.

2-(Furan-2-yl)-6-pentyl-4-(trifluoromethyl)pyridine (96j)



Starting from 1-(furan-2-yl)-3-hydroxy-3-(trifluoromethyl)dec-4-yn-1-one (302 mg, 1 mmol) **94j** and urea (72 mg, 1.2 mmol); **96j** was isolated as red liquid, yield = 144 mg (51%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.94 (t, 3H, CH_3, ^3J = 1.8 Hz), 1.38 (m, 4H, -CH_2-), 1.78 (m, 2H, CH_2), 2.88 (t, 2H, CH_2, ^3J = 7.8 Hz), 6.55 (dd, 1H, H-4', $^3J_1$ = 1.8 Hz, $^3J_2$ = 0.6 Hz), 7.20 (m, 2H, H-3', H-5'), 7.25 (s, 1H, H-5), 7.70 (s, 1H, H-3).

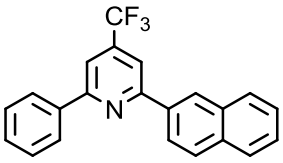
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.4 (CH_2), 29.2 (CH_2), 31.5 (CH_2), 38.3 (CH_2), 110.0 (C-4'), 111.4 (d, C-5, $^3J_{C\text{-}F}$ = 3.8 Hz), 112.7 (C-3'), 116.1 (d, C-3, $^3J_{C\text{-}F}$ = 3.8 Hz), 122.9 (q, CF_3, $^1J_{C\text{-}F}$ = 273.6 Hz), 139.2 (q, C-4, $^2J_{C\text{-}F}$ = 33.7 Hz), 143.9 (C-5'), 149.8 (C-2'), 152.8 (C-2), 164.0 (C-6).

GC-MS (EI, 70 eV): *m/z* (%): 254 (11), 240 (19), 227 (100), 198 (10).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{15}H_{16}F_3NO$: 283.1179; found: 283.1175.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930, 2860, 1575, 1494, 1382, 1361, 1260, 1134, 1008, 884, 740, 695.

2-(Naphthalen-2-yl)-6-phenyl-4-(trifluoromethyl)pyridine (96k)



Starting from 3-hydroxy-1-(naphthalen-2-yl)-5-phenyl-3-(trifluoromethyl)pent-4-yn-1-one (368 mg, 1 mmol) **94k** and urea (72 mg, 1.2 mmol); **96k** was isolated as light-yellow powder, yield = 185 mg (53%); mp = 97 - 99°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.44 (m, 5H, H-3', H-4', H-5', H-6", H-7"), 7.88 (br. m, 5H, H-1", H-4", H-5", H-8", H-5), 8.13 (m, 2H, H-2', H-6'), 8.23 (dd, 1H, H-3", $^3J_1$ = 6.9 Hz, $^3J_2$ = 1.8 Hz), 8.54 (s, 1H, H-3').

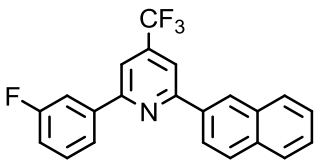
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 113.0 (q, C-3, $^3J_{C\text{-}F}$ = 3.8 Hz), 113.2 (q, C-5, $^3J_{C\text{-}F}$ = 3.8 Hz), 122.2 (q, CF_3, $^1J_{C\text{-}F}$ = 273.2 Hz), 123.4 (C-7"), 125.5 (C-5"), 125.8 (C-6"), 125.9 (C-3', C-5'), 126.1 (C-8"), 126.7 (C-4'), 127.6 (C-2', C-6'), 127.8 (C-1", C-4"), 128.8 (C-3"), 132.3 (C-8a"), 133.0 (C-4a"), 134.4 (C-1'), 137.2 (C-2"), 139.0 (q, C-4, $^2J_{C\text{-}F}$ = 33.2 Hz), 157.0 (C-6), 157.3 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 349 (100) $[M^+]$.

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{22}H_{14}F_3N$: 349.1073; found: 349.1066.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962, 1598, 1412, 1373, 1260, 1175, 1125, 1104, 1015, 796, 768, 755, 690.

2-(3-Fluorophenyl)-6-(naphthalen-2-yl)-4-(trifluoromethyl)pyridine (96l)



Starting from 5-(3-fluorophenyl)-3-hydroxy-1-(naphthalen-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (386 mg, 1 mmol) **94l** and urea (72 mg, 1.2 mmol); **96l** was isolated as light-yellow powder, yield = 242 mg (66%); mp = 84 - 86°C;

^{1}H NMR (300.13 MHz, CD_2Cl_2): δ = 7.13 (m, 1H, H-4‘), 7.47 (m, 3H, H-2‘, H-5‘, H-6‘), 7.90 (m, 6H, H-1“, H-4“, H-5“, H-6“, H-7“, H-8“), 7.96 (s, 1H, H-3), 8.24 (d, 1H, H-3“ ^{3}J = 6.0 Hz), 8.56 (s, 1H, H-5).

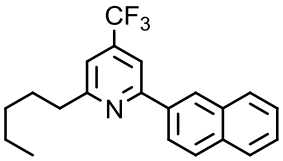
^{13}C NMR (62.90 MHz, CD_2Cl_2): δ = 114.4 (d, C-2’, $^{2}J_{C-F}$ = 23.3 Hz), 114.5 (d, C-5, $^{3}J_{C-F}$ = 3.8 Hz), 115.3 (d, C-3, $^{3}J_{C-F}$ = 3.8 Hz), 119.0 (d, C-4’, $^{2}J_{C-F}$ = 21.4 Hz), 123.0 (d, C-5’, $^{3}J_{C-F}$ = 3.1 Hz), 123.6 (q, CF_3, $^{1}J_{C-F}$ = 273.6 Hz), 124.7 (C-6”), 127.0 (C-5”), 127.2 (C-7”), 127.5 (C-8”), 128.0 (C-6”), 129.0 (C-4”), 129.2 (C-1”), 130.8 (C-3”), 133.8 (C-8a”), 134.5 (C-4a”), 135.5 (C-2”), 140.8 (d, C-1’, $^{3}J_{C-F}$ = 4.9 Hz), 141.0 (q, C-4, $^{2}J_{C-F}$ = 34.0 Hz), 157.1 (d, C-2, $^{4}J_{C-F}$ = 1.9 Hz), 158.5 (C-6), 163.7 (d, C-3’, $^{1}J_{C-F}$ = 245.3 Hz).

GC-MS (EI, 70 eV): *m/z* (%): 367 (100) [M^+].

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{22}H_{13}F_4N$: 367.0979; found: 367.0974.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3065, 1565, 1459, 1410, 1370, 1270, 1126, 861, 822, 782, 756, 694, 680.

2-(Naphthalen-2-yl)-6-pentyl-4-(trifluoromethyl)pyridine (96m)



Starting from 3-hydroxy-1-(naphthalen-2-yl)-3-(trifluoromethyl)dec-4-yn-1-one (362 mg, 1 mmol) **94m** and urea (72 mg, 1.2 mmol); **96m** was isolated as light-yellow liquid, yield = 173 mg (50%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.86 (m, 3H, CH_3), 1.36 (m, 4H, CH_2), 1.80 (m, 2H, CH_2), 2.89 (t, 2H, CH_2, ^{3}J = 7.8 Hz), 7.24 (s, 1H, H-5‘), 7.47 (m, 2H, H-1‘, H-4‘), 7.86 (m, 4H, H-5‘, H-6‘, H-7‘, H-8‘), 8.11 (dd, 1H, H-3‘,$^{3}J_1$ = 6.9 Hz, $^{3}J_2$ = 1.8 Hz), 8.43 (s, 1H, H-3).

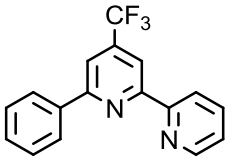
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.0 (CH_3), 25.5 (CH_2), 29.3 (CH_2), 31.6 (CH_2), 38.6 (CH_2), 113.4 (q, C-3, $^{3}J_{C-F}$ = 3.8 Hz), 116.4 (q, C-5, $^{3}J_{C-F}$ = 3.8 Hz), 123.2 (q, CF_3, $^{1}J_{C-F}$ = 273.6 Hz), 124.5 (C-5’), 126.4 (C-7’), 126.8 (C-8’, C-6’), 127.7 (C-4’), 128.6 (C-1’), 128.8 (C-3’), 133.4 (C-8a’), 133.9 (C-4a’), 135.8 (C-2’), 139.3 (q, C-4, $^{2}J_{C-F}$ = 34.0 Hz), 157.9 (C-6), 164.1 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 343 (14) [M^+], 314 (33), 300 (50), 287 (100).

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{21}H_{20}F_3N$: 343.1542; found: 343.1540.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3059, 2928, 2858, 1573, 1413, 1375, 1261, 1166, 1130, 857, 815, 740, 698.

6-Phenyl-4-(trifluoromethyl)-2,2'-bipyridine (96n)



Starting from 3-hydroxy-5-phenyl-1-(pyridin-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (319 mg, 1 mmol) **94n** or 3-hydroxy-1-phenyl-5-(pyridin-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (319 mg, 1 mmol) **94q** and urea (72 mg, 1.2 mmol); **96n** was isolated as grey powder, yield = 255 mg (85%) (in case of **94n**); yield = 72 mg (24%) (in case of **94q**); mp = 76 - 78°C;

^{1}H NMR (300.13 MHz, CD_2Cl_2): δ = 7.32 (m, 1H, H-5"), 7.43 (m, 3H, H-3', H-4', H-5'), 7.81 (m, 1H, H-3"), 7.90 (s, 1H, H-5), 8.10 (m, 2H, H-2', H-6'), 8.58 (m, 3H, H-3, H-4", H-6").

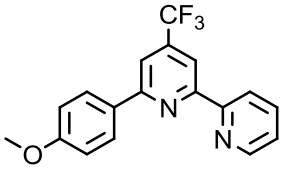
^{13}C NMR (62.90 MHz, CD_2Cl_2): δ = 115.3 (d, C-3, $^{3}J_{C-F}$ = 3.8 Hz), 116.0 (d, C-5, $^{3}J_{C-F}$ = 3.1 Hz), 121.7 (C-5"), 123.7 (q, CF_3, $^{1}J_{C-F}$ = 266.1 Hz), 125.0 (C-3"), 127.4 (C-3', C-5'), 129.3 (C-2', C-6'), 130.3 (C-4'), 137.5 (C-4"), 138.4 (C-4'), 140.4 (q, C-4, $^{2}J_{C-F}$ = 34.0 Hz), 149.6 (C-2"), 155.2 (C-2"), 157.6 (C-6), 158.1 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 300 (100) [M^+], 231 (18).

HRMS (ESI): *m/z* [$M]^+$ calcd for $C_{17}H_{11}F_3N_2$: 300.0869; found: 330.0866.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3060, 1585, 1567, 1405, 1370, 1263, 1120, 1059, 879, 772, 688, 661.

6-(4-Methoxyphenyl)-4-(trifluoromethyl)-2,2'-bipyridine (96o)



Starting from 3-hydroxy-5-(4-methoxyphenyl)-1-(pyridin-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (349 mg, 1 mmol) **94o** and urea (72 mg, 1.2 mmol); **96o** was isolated as white crystals, yield = 300 mg (91%); mp = 66 - 69°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.82 (s, 3H, OCH_3), 6.97 (m, 2H, H-2', H-6'), 7.30 (m, 1H, H-5"), 7.80 (m, 2H, H-5, H-3"), 8.06 (m, 2H, H-3', H-5'), 8.50 (s, 1H, H-3), 8.56 (d, 1H, H-6", ^{3}J = 9.0 Hz), 8.65 (dd, 1H, H-4", $^{3}J_1$ = 3.0 Hz, $^{3}J_2$ = 3.0 Hz).

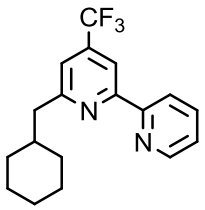
^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 114.3 (C-2', C-6'), 114.8 (d, C-3, C-5, $^{3}J_{C-F}$ = 3.8 Hz), 121.4 (C-3"), 123.2 (q, CF_3, $^{1}J_{C-F}$ = 273.6 Hz), 124.4 (C-5"), 128.4 (C-3', C-5'), 130.7 (C-4'), 137.0 (C-4"), 140.1 (q, C-4, $^{2}J_{C-F}$ = 34.0 Hz), 149.2 (C-2"), 155.0 (C-6), 156.9 (C-2), 161.2 (C-1').

GC-MS (EI, 70 eV): *m/z* (%): 330 (100) [M^+], 315 (12), 287 (12).

HRMS (ESI): *m/z* [$M]^+$ calcd for $C_{18}H_{13}F_3N_2O$: 330.0975; found: 330.0975.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962, 1607, 1585, 1562, 1515, 1408, 1372, 1262, 1245, 1121, 1029, 837, 793, 660.

6-(Cyclohexylmethyl)-4-(trifluoromethyl)-2,2'-bipyridine (96p)



Starting from 6-cyclohexyl-3-hydroxy-1-(pyridin-2-yl)-3-(trifluoromethyl)hex-4-yn-1-one (339 mg, 1 mmol) **94p** and urea (72 mg, 1.2 mmol); **96p** was isolated as greenish liquid, yield = 224 mg (70%);

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.15 (m, 5H, Cy), 1.79 (m, 6H, Cy), 2.74 (d, 2H, CH_2, ^{3}J = 6.0 Hz), 7.24 (s, 1H, H-5), 7.27 (m, 1H, H-5‘), 7.77 (m, 1H, H-3‘), 8.42 (m, 2H, H-3, H-6‘), 8.63 (m, 1H, H-4‘).

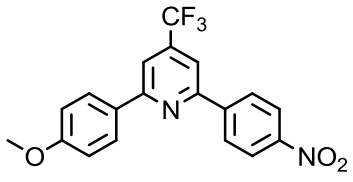
^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 26.2 (CH_2), 26.4 (CH_2), 33.1 (CH_2), 38.4 (CH), 46.2 (CH_2), 114.0 (d, C-3, $^{3}J_{C\text{-}F}$ = 3.1 Hz), 118.8 (d, C-5, $^{3}J_{C\text{-}F}$ = 3.1 Hz), 121.4 (C-5’), 123.2 (q, CF_3, $^{1}J_{C\text{-}F}$ = 270.9 Hz), 124.2 (C-3’), 137.0 (C-4’), 139.2 (q, C-4, $^{2}J_{C\text{-}F}$ = 34.0 Hz), 149.2 (C-6’), 155.2 (C-2”), 156.8 (C-6), 162.3 (C-2).

GC-MS (EI, 70 eV): *m/z* (%): 238 (100).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}F_3N_2$: 321.1570; found: 321.1570.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922, 2850, 1586, 1568, 1449, 1408, 1372, 1263, 1165, 1131, 793, 661.

2-(4-Methoxyphenyl)-6-(4-nitrophenyl)-4-(trifluoromethyl)pyridine (96q)



Starting from 3-hydroxy-5-(4-methoxyphenyl)-1-(4-nitrophenyl)-3-(trifluoromethyl)pent-4-yn-1-one (393 mg, 1 mmol) **94r** and urea (72 mg, 1.2 mmol); **96q** was isolated as brown crystals, yield = 292 mg (78%); mp = 136 - 139°C;

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.83 (s, 3H, OCH_3), 6.99 (d, 2H, H-2’, H-6’, ^{3}J = 6.0 Hz), 7.80 (s, 1H, H-3), 7.84 (s, 1H, H-5), 8.06 (d, 2H, H-3’, H-5’, ^{3}J = 6.0 Hz), 8.28 (m, 4H, H-2“, H-3“, H-5“, H-6“).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 113.9 (q, C-5, $^{3}J_{C\text{-}F}$ = 3.1 Hz), 114.3 (C-2’, C-6’), 114.6 (q, C-3, $^{3}J_{C\text{-}F}$ = 3.1 Hz), 123.3 (q, CF_3, $^{1}J_{C\text{-}F}$ = 273.6 Hz), 124.1 (C-3”, C-5”), 127.9 (C-3’, C-5’), 128.5 (C-2”, C-6”), 130.1 (C-4’), 140.3 (q, C-4, $^{2}J_{C\text{-}F}$ = 34.0 Hz), 144.0 (C-4”), 148.6 (C-1”), 155.5 (C-2), 158.4 (C-6), 161.5 (C-1’).

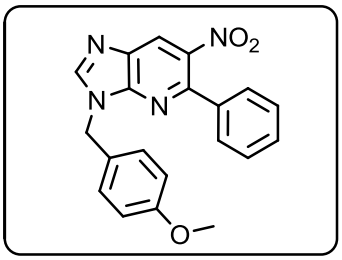
GC-MS (EI, 70 eV): *m/z* (%): 374 (100) [M^+], 328 (17), 284 (13).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{14}F_3N_2O_3$: 375.0951; found: 375.0954.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2845, 1682, 1607, 1563, 1525, 1368, 1348, 1246, 1162, 1128, 1028, 861, 827, 696.

Appendix 2: Crystallographic data

Crystal data and structure refinement for **39g**



Identification code **vy-3**

Empirical formula: $C_{20}H_{16}N_4O_4$

Formula weight: 376.37

Temperature: 173 K

Wavelength: 0.71073 Å

Crystal system, space group: Orthorhombic, $P2_12_12_1$

Unit cell dimensions: a = 7.0116 (3) Å α = 90.00°

b = 11.7207 (5) Å β = 90.00°

c = 21.8253 (9) Å γ = 90.00°

Volume: 1793.6 (1) $Å^3$

Z = 4

Calculated density: 1.394 mg/m^3

Absorption coefficient: 0.13 mm^{-1}

F(000) = 784

Crystal size: 0.32 x 0.29 x 0.11 mm

Θ range for data collection: 5.10° to 64.90°

Limiting indices: -10<=h<=19, -17<=k<=11, -29<=l<=32

Reflections collected / unique: 15102 / 6422 [R(int) = 0.0261]

Completeness to Θ = 29.95°

Absorption correction: None

Refinement method: Full-matrix least-squares on F^2

Data / restraints / parameters: 6442 / 0 / 258

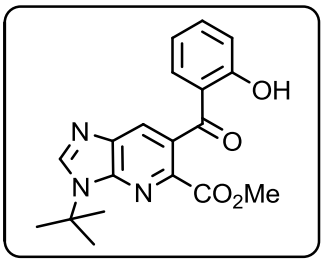
Goodness-of-fit on F^2: 1.045

Final R indices [I>2sigma(I)]: R1 = 0.0644, wR2 = 0.1133

R indices (all data) R1 = 0.0451, wR2 = 0.1055

Largest diff. peak and hole: 0.46 e. and -0.34 e. $Å^{-3}$

Crystal data and structure refinement for **47a**



Identification code **tbu-4**

Empirical formula: $C_{19}H_{19}N_3O_4$

Formula weight: 353.37

Temperature: 173 K

Wavelength: 0.71073 Å

Crystal system, space group: Orthorhombic, *Pbca*

Unit cell dimensions: a = 10.7884 (5) Å α = 90.00°

b = 14.2328 (6) Å β = 90.00°

c = 22.7013 (12) Å γ = 90.00°

Volume: 3485.8 (3) $Å^3$

Z = 2

Calculated density: 1.347 mg/m^3

Absorption coefficient: 0.10 mm^{-1}

F(000) = 336

Crystal size: 0.63 x 0.42 x 0.13 mm

Θ range for data collection: 5.06° to 62.67°

Limiting indices: -14<=h<=15, -19<=k<=18, -31<=l<=31

Reflections collected / unique: 39154 / 5074 [R(int) = 0.0460]

Completeness to Θ = 27.47°

Absorption correction: None

Refinement method: Full-matrix least-squares on F^2

Data / restraints / parameters: 5074 / 0 / 243

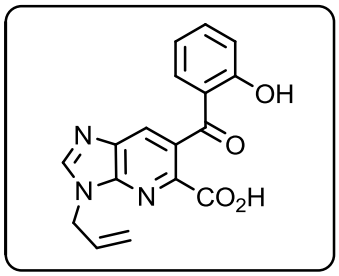
Goodness-of-fit on F^2: 1.064

Final R indices [I>2sigma(I)]: R1 = 0.0422, wR2 = 0.1104

R indices (all data) R1 = 0.0622, wR2 = 0.1205

Largest diff. peak and hole: 0.39 e. and -0.22 e. $Å^{-3}$

Crystal data and structure refinement for **48b**



Identification code **od202**

Empirical formula: $C_{17}H_{13}N_3O_4 \cdot 0.5(C_3H_7NO)$

Formula weight: 359.85

Temperature: 173 K

Wavelength: 0.71073 Å

Crystal system, space group: Triclinic, P_i

Unit cell dimensions: a = 8.6842 (3) Å α = 69.895 (2)°

b = 13.5724 (5) Å β = 80.582 (2)°

c = 15.7795 (6) Å γ = 87.279 (2)°

Volume: 1722.91 (11) $Å^3$

Z = 4

Calculated density: 1.387 mg/m^3

Absorption coefficient: 0.10 mm^{-1}

F(000) = 752

Crystal size: 0.99 x 0.16 x 0.06 mm

Θ range for data collection: 4.76° to 64.59°

Limiting indices: -12<=h<=12, -19<=k<=17, -22<=l<=22

Reflections collected / unique: 39263 / 10831 [R(int) = 0.0365]

Completeness to Θ = 28.62°

Absorption correction: None

Refinement method: Full-matrix least-squares on F^2

Data / restraints / parameters: 10831 / 1/ 503

Goodness-of-fit on F^2: 1.043

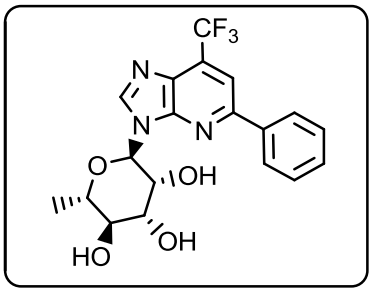
Final R indices [I>2sigma(I)]: R1 = 0.0920, wR2 = 0.1328

R indices (all data) R1 = 0.0503, wR2 = 0.1197

Largest diff. peak and hole: 0.36 e. and -0.33 e. $Å^{-3}$

Crystal data and structure refinement for **72b**

Identification code **ap054**



Empirical formula: $C_{19}H_{18}F_3N_3O_4$

Formula weight: 409.36

Temperature: 173 K

Wavelength: 0.71073 Å

Crystal system, space group: Orthorhombic, $P2_12_12_1$

Unit cell dimensions: a = 6.1794 (4) Å α = 90.00°

b = 10.3600 (7) Å β = 90.00°

c = 27.9401 (6) Å γ = 90.00°

Volume: 1788.7 (2) $Å^3$

Z = 4

Calculated density: 1.520 mg/m^3

Absorption coefficient: 0.13 mm^{-1}

F(000) = 848

Crystal size: 0.80 x 0.15 x 0.15 mm

Θ range for data collection: 4.90° to 63.85°

Limiting indices: -9<=h<=4, -15<=k<=15, -41<=l<=40

Reflections collected / unique: 22219 / 5927 [R(int) = 0.0281]

Completeness to Θ = 29.04°

Absorption correction: None

Refinement method: Full-matrix least-squares on F^2

Data / restraints / parameters: 5927 / 0/ 289

Goodness-of-fit on F^2: 1.043

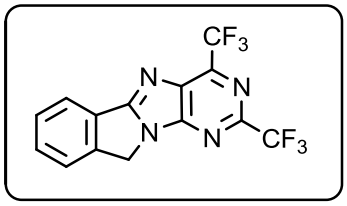
Final R indices [I>2sigma(I)]: R1 = 0.0474, wR2 = 0.0928

R indices (all data) R1 = 0.0374, wR2 = 0.0880

Largest diff. peak and hole: 0.27 e. and -0.21 e. $Å^{-3}$

Crystal data and structure refinement for **78b**

Identification code **od366**



Empirical formula: $C_{14}H_6F_6N_4$

Formula weight: 344.23

Temperature: 173 K

Wavelength: 0.71073 Å

Crystal system, space group: Triclinic, P_i

Unit cell dimensions: a = 7.1131 (7) Å α = 103.847 (5)°

b = 8.9701 (10) Å β = 100.067 (5)°

c = 10.7667 (13) Å γ = 91.888 (5)°

Volume: 654.73 (13) $Å^3$

Z = 2

Calculated density: 1.746 mg/m^3

Absorption coefficient: 0.17 mm^{-1}

F(000) = 344

Crystal size: 0.96 x 0.12 x 0.09 mm

Θ range for data collection: 5.34° to 59.32°

Limiting indices: -9<=h<=9, -12<=k<=12, -14<=l<=14

Reflections collected / unique: 13065 / 3441 [R(int) = 0.0307]

Completeness to Θ = 26.65°

Absorption correction: None

Refinement method: Full-matrix least-squares on F^2

Data / restraints / parameters: 3441 / 3/ 245

Goodness-of-fit on F^2: 1.061

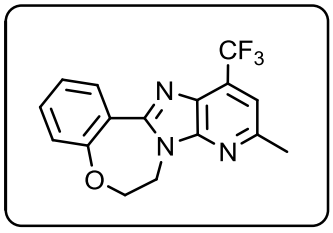
Final R indices [I>2sigma(I)]: R1 = 0.0621, wR2 = 0.1179

R indices (all data) R1 = 0.0436, wR2 = 0.1105

Largest diff. peak and hole: 0.36 e. and -0.28 e. $Å^{-3}$

Crystal data and structure refinement for **82a**

Identification code **od403**



Empirical formula: $C_{16}H_{12}F_3N_3O$

Formula weight: 319.29

Temperature: 173 K

Wavelength: 0.71073 Å

Crystal system, space group: Triclinic, P_i

Unit cell dimensions: a = 7.1700 (4) Å α = 96.965 (2)°

b = 8.1493 (4) Å β = 96.286 (3)°

c = 12.4415 (6) Å γ = 105.096 (2)°

Volume: 689.11 (6) $Å^3$

Z = 2

Calculated density: 1.539 mg/m^3

Absorption coefficient: 0.13 mm^{-1}

F(000) = 328

Crystal size: 0.66 x 0.24 x 0.10 mm

Θ range for data collection: 5.76° to 58.50°

Limiting indices: -9<=h<=8, -11<=k<=11, -16<=l<=16

Reflections collected / unique: 17393 / 3655 [R(int) = 0.0411]

Completeness to Θ = 26.38°

Absorption correction: None

Refinement method: Full-matrix least-squares on F^2

Data / restraints / parameters: 3655 / 0/ 220

Goodness-of-fit on F^2: 1.086

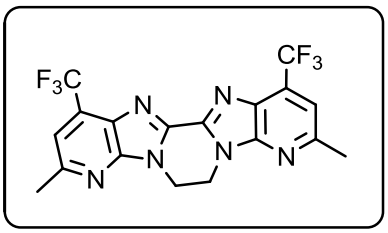
Final R indices [I>2sigma(I)]: R1 = 0.0726, wR2 = 0.1380

R indices (all data) R1 = 0.0487, wR2 = 0.1264

Largest diff. peak and hole: 0.35 e. and -0.34 e. $Å^{-3}$

Crystal data and structure refinement for **87a**

Identification code **od406**



Empirical formula: $C_{18}H_{12}F_6N_6$

Formula weight: 426.34

Temperature: 173 K

Wavelength: 0.71073 Å

Crystal system, space group: Monoclinic $P2_1/n$

Unit cell dimensions: a = 7.1502 (3) Å α = 90.00°

b = 18.1510 (7) Å β = 97.473 (2)°

c = 13.2630 (5) Å γ = 90.00°

Volume: 1706.70 (12) $Å^3$

Z = 4

Calculated density: 1.659 mg/m^3

Absorption coefficient: 0.15 mm^{-1}

F(000) = 864

Crystal size: 0.35 x 0.21 x 0.17 mm

Θ range for data collection: 5.45° to 57.80°

Limiting indices: -10<=h<=10, -25<=k<=25, -18<=l<=18

Reflections collected / unique: 19152 / 4968 [R(int) = 0.0420]

Completeness to Θ = 27.27°

Absorption correction: None

Refinement method: Full-matrix least-squares on F^2

Data / restraints / parameters: 4968 / 0/ 280

Goodness-of-fit on F^2: 1.037

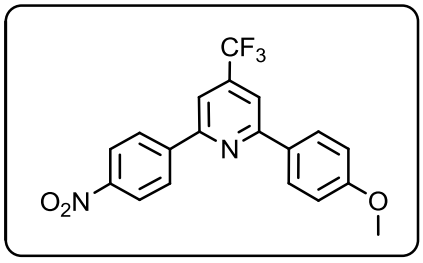
Final R indices [I>2sigma(I)]: R1 = 0.0756, wR2 = 0.1230

R indices (all data) R1 = 0.0446, wR2 = 0.1112

Largest diff. peak and hole: 0.34 e. and -0.26 e. $Å^{-3}$

Crystal data and structure refinement for **96q**

Identification code **ax0200**



Empirical formula: $C_{19}H_{13}F_3N_2O_3$

Formula weight: 374.31

Temperature: 150 K

Wavelength: 0.71073 Å

Crystal system, space group: Orthorhombic, $P2_12_12_1$

Unit cell dimensions: a = 12.7231 (2) Å α = 90.00°

b = 6.6173 (6) Å β = 90.00°

c = 19.4361 (4) Å γ = 90.00°

Volume: 1636.4 (5) $Å^3$

Z = 4

Calculated density: 1.519 mg/m^3

Absorption coefficient: 0.13 mm^{-1}

F(000) = 768

Crystal size: 0.47 x 0.24 x 0.16 mm

Θ range for data collection: 2.64° to 28.73°

Limiting indices: -17<=h<=17, -7<=k<=8, -26<=l<=26

Reflections collected / unique: 35609 / 4240 [R(int) = 0.0316]

Completeness to Θ = 26.86°

Absorption correction: None

Refinement method: Full-matrix least-squares on F^2

Data / restraints / parameters: 4240 / 0 / 245

Goodness-of-fit on F^2: 1.054

Final R indices [I>2sigma(I)]: R1 = 0.0674, wR2 = 0.1514

R indices (all data) R1 = 0.0497, wR2 = 0.1343

Largest diff. peak and hole: 0.52 e. and -0.46 e. $Å^{-3}$

List of abbreviations

Ac	Acetyl
ADA	Adenosine deaminase
All	Allyl
ATR	Attenuated total reflection
Bn	Benzyl
BSA	N,O-bis(trimethylsilyl)acetamide
coe	Cyclooctene
COSY	Correlation spectroscopy
Cy	Cyclohexyl
Cys	Cysteine
d	Days
dba	Dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DMA	N,N-dimethylacetamide
DMF	N,N-dimethylformamide
DMSO	Dimethylsulphoxide
DNA	Desoxyribonucleic acid
EHNA	Erythro-9-(2-hydroxy-3-nonyl)adenine
EI	Electron ionization
ESI	Electron spray ionization
Et	Ethyl
EWG	Electron withdrawing group
GS	Gas chromatography
h	Hours
HRMS	High resolution mass spectroscopy
IMPDH	Inosine monophosphate dehydrogenase
i-Pr	Isopropyl
IR	Infrared
Me	Methyl

min	minutes
MS	Mass spectroscopy
Ms	Mesyl
n-BuLi	*n*-Butyllithium
NAD	Nicotineamide adenine dinucleotide
NADP	Nicotineamide adenine dinucleotide phosphate
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
p-DMAPH	*p*-Dimethylaminophenyl
Ph	Phenyl
Piv	Pivaloyl
PMB	*p*-methoxybenzyl
PTSA	*p*-toluenesulphonic acid
PVP	Polyvinyl pyridine
py	Pyridine
RNA	Ribonucleic acid
t-Bu	*tert*-Butyl
TBDMS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
Tf	Triflate
TFA	Trifluoroacetic acid
TFE	Tetrafluroethylene
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluromethanesulphonate
TLC	Thin layer chromatography
TrOH	Triphenylmethanol

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Dmytro Ostrovskyi, Rostock, 19.07.2012

Curriculum vitae and list of publications

Persönliche Daten

Geburtstag	07.06.1986
Geburtsort	Vyshneve, Ukraine
Staatsangehörigkeit	Ukrainisch
Familienstand	ledig

Schulbildung

09.1993 – 06.2000	Schüler, Gymnasium №136, Kiew, Ukraine
09.2000 – 06.2004	Schüler, wissenschaftlich Lyceum №145, Kiew, Ukraine

Studium

09.2004 – 06.2008	Student, "Kiev National Taras Shevchenko University", Kiew, Ukraine. Abschluss: Bachelorarbeit "The new method of synthesis of 4-(3-thienyl)-coumarins" unter der Leitung von Prof. Dr. Volodymyr Khiliya; "rotes diploma" Auszeichnung.
09.2008 – 06.2009	Student, "Kiev National Taras Shevchenko University", Kiew, Ukraine. Abschluss: Masterarbeit "The synthesis of derivatives of hydrazones of 5-phenylfuro[3,2-g]-chromen-7-ones" unter der Leitung von Prof. Dr. Volodymyr Khiliya; "rotes diploma" Auszeichnung.
Seit 10.2009	Doktorarbeit unter der Leitung von Prof. Dr. Dr. h.c. Peter Langer, Institut für Chemie an der Universität Rostock, Rosctok, Deutschland; Finanzierung durch ein Stipendium des Landesgraduiertenförderung.

List of publications:

1) **Iaroshenko, V. O.*, Ostrovskyi, D., Ayub, K., Spannenber, A., Langer, P*.** "Straightforward route to 4-trifluoromethylpyridines by Brønsted acid promoted [5+1] cyclization of 3-hydroxy-pent-4-yn-1-ones with urea", *manuscript in preparation.*
2) **Iaroshenko, V. O.*, Ostrovskyi, D., Milyutina, M., Maalik, A., Villinger, A., Tolmachev, A., Volochnyuk, D. M., Langer, P*.** "Design and Synthesis of Polycyclic Imidazole-Containing N-heterocycles based on C-H Activation / Cyclization Reactions." *Adv. Synth. Cat.* in print.

3) **Iaroshenko, V. O*., Maalik, A., Ostrovskyi, D., Villinger, A., Spannenberg, A., Langer, P*.** "Efficient synthesis of purines by inverse electron-demand Diels-Alder reactions of 1-substituted-1*H*-imidazole-5-amines with 1,3,5-triazines." *Tetrahedron,* **2011,** 67, 8321-8330.
4) **Iaroshenko, V.O.*; Specowius, V.; Vlach, K.; Vilches-Herreira, M.; Ostrovskyi, D.; Mkrtchyan, S.; Villinger, A.; Langer, P*.** "A general strategy for the synthesis of difluoromethyl-containing pyrazoles, pyridines and pyrimidines", *Tetrahedron*, **2011,** 67, 5663-5677**.**
5) **Iaroshenko, V.O.*; Ostrovskyi, D.; Petrosyan, A.; Villinger, A.; Langer, P*.** "Synthesis of fluorinated purine and 1-dezazapurine glycosides as potential inhibitors of adenosine deaminase", *J. Org. Chem.,* **2011,** 76, 2899-2903.
6) **Iaroshenko, V. O.*; Mkrtchyan, S.; Ghazaryan, G.; Hakobyan, A.; Maalik, A.; Supe, L.; Villinger, A.; Tolmachev, A. A.; Ostrovskyi, D.; Sosnovskikh, V. Y.; Ghochikyan, T.; Langer, P*.** "3-(Dichloroacetyl)chromone: A new building block for the synthesis of formylated purine isosteres: design and synthesis of fused α-(formyl)pyridines", *Synthesis*, **2011,** 3, 469-479.
7) **Ostrovskyi, D.; Iaroshenko, V.O.*; Iftikhar, A; Mkrtchyan, S.; Villinger, A.; Tolmachev, A. A.; Langer, P*.** "3-Methoxalylchromone – a versatile reagent fro regioselective synthesis of 1-dezazapurines", *Synthesis,* **2011,** 1, 133-141.
8) **Mkrtchyan, S.; Iaroshenko, V. O.*; Dudkin, S.; Gevorgyan, A.; Vilches-Herreira, M.; Ghazaryan, G.; Volochnyuk, D. M.; Ostrovskyi, D.; Zeeshan, A.; Villinger, A.; Sosnovskikh, V. Y.; Langer, P*.** "3-Methoxalylchromone – a novel versatile reagent for regioselective purine isostere synthesis", *Org. Biomol. Chem.,* **2010,** 8, 5280-5284.
9) **Ostrovskyi, D.; Iaroshenko, V.O.*; Petrosyan, A.; Dudkin, S; Iftikhar, A; Villinger, A.; Tolmachev, A. A.; Langer, P*.** " An efficient synthesis of 6-Nitro- and 6-Amino-3*H*-imidazo-[4,5-b]-pyridines by cyclocondensation of 1-substituted 1*H*-Imidazole-5-amines with 3-Nitro-4*H*-chromen-4-one", *Synlett,* **2010,** 15, 2239-2303.
10) **Iaroshenko, V. O.*; Mkrtchyan, S.; Volochnyuk, D. M.; Langer, P.; Sosnovskikh, V. Y.; Ostrovskyi, D.; Dudkin, S.; Kotlyarov, A. V.; Miliutina M.; Savych, I.; Tolmachev, A. A.** "3-Formylchromones, acylpyruvates and chalcone as valuable substrates for the synthesis of fused pyridines", *Synthesis*, **2010,** 16, 2749-2758.

11) **Ostrovskiy , D.P. ; Ya. L. Garazd, M. M. Garazd, V. P. Khilya*** "The synthesis of derivatives of hydrazones of 5-phenylfuro[3,2-g]-chromen-7-ones"**,** *Chemistry of Heterocyclic compounds*, **2011**, 46, 11, 1318-1324.

Attendance at conferences:

1) **Ostrovskyi, D.; Iaroshenko, V.O.; Mkrtchyan, S.; Gevorgyan, A.; Vilches-Herreira, M.; Langer, P.** " Synthesis of fused pyridines via cyclocondensation of electron-enriched aminoheterocycles and anilines with 3-substituted chromones", "JCF Frühjahrssymposium", **Erlangen, Germany, 2011,** poster.
2) **Ostrovskiy , D.P. ; Ya. L. Garazd, V. P. Khilya** "New method of synthesis of 4-(3-thienyl)-coumarins", "Ukrainian chemical conference of students and postgraduates", **Kiev, Ukraine, 2008,** oral presentation.