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Cyclic 2-azahetaryl-3-enaminonitriles : toward synthesis of functionalized azaheterocycles, metal complexation and probes design

Olena Kuleshova

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THÈSE

En vue de l'obtention du

DOCTORAT DE L'UNIVERSITÉ DE TOULOUSE

Délivré par l'Université Toulouse 3 - Paul Sabatier

Cotutelle internationale : Taras Shevchenko National University of Kyiv

---

Présentée et soutenue par

Olena KULESHOVA

Le 20 septembre 2018

2-Azahetaryl-3-enaminonitriles cycliques pour la synthèse d'azahétérocycles fonctionnalisés, la complexation de métaux et la conception de sondes optiques.

Ecole doctorale : **SDM - SCIENCES DE LA MATIERE - Toulouse**

Spécialité : **Chimie Organométallique et de Coordination**

Unité de recherche :
LCC - Laboratoire de Chimie de Coordination

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PREFACE

This work was done in collaboration between University Toulouse III – Paul Sabatier (UPS), France (Laboratory of coordination chemistry, UPR 8241 (LCC)) and Taras Shevchenko National university of Kyiv (UNTS), Ukraine (Faculty of chemistry) between 2014 and 2018. Financial support from the French government, Ukrainian government and University Paul Sabatier are gratefully acknowledged.

I am most thankful to my supervisors Dr. Emmanuel Gras and Pr. Yulian M. Volovenko for giving me the opportunity to work within their research groups. I am grateful for all the efforts they being made for successful passing of this study, for their professional guidance and contribution of time that made me grow up professionally.

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Especially I wish to aknowledge the Mexicans whom I met during my stay in LCC: PhD Sara Ayala Mariscal (team F, LCC), PhD Alejandro Enriquez-Cabrera and MS Margarita Romero-Avila (team R, LCC and National Autonomous University of Mexico) for their friendship, understanding, encouragement, advices and for so many unforgettable moments I experienced with them.

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I wish to acknowledge the contributions several other people have made. Doctor Sonia Mallet-Ladeira (LCC), Dr. Svitlana V. Shishkina, Viktoriya V. Dyakonenko (Institute for Single Crystals, Kharkov, Ukraine) are thanked for crystal structure determinations; Dr. Yanick Coppel and Dr. Christian Bijani (Servicecommun de RMN, LCC) for the NMR experiments on *E*/*Z* isomerisation; Dr. Tetyana Ye. Keda, PhD Yuliya P. Bas, PhD student Anatolii M. Makeev and Vladyslav V. Scherban (UNTS) for studying the photophysical and coordination properties of cyclic azahetarylenaminonitriles; Pr. Volodymir M. Amirkhanov, Doctor Mikola O. Davidenko, PhD Nataliya S. Kariaka and Nataliya S. Kovalska (UNTS) for exploration of solid state structure, photophysical and photovoltaic properties of 3d-metal complexes; PhD student Valerii O. Bukhanko (LCC and UNTS) for quantum chemical calculations and their interpretation.

I want to thank my parents Alexandr and Lyudmila, my grandmother Lyubov and the other members of my big and friendly family and my husband family for their love, encouraging and supporting me.

My husband Valerii, thank you for your love, patience and firm believe in me.

Olena Kuleshova
July, 2018

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GENERAL INTRODUCTION

Among the different fields of organic chemistry, Heterocyclic Chemistry is one of the most developed both in terms of methods and applications. Indeed, many textbooks are now nicely giving a detailed overlook of the various general methods available for the building up of heterocycles, and their further functionalizations. Yet, if the preparation of the heterocycles is following well established strategies, the preparation of their precursors can be somehow a little bit tedious. This aspect is one of the major topics described in this manuscript. Indeed, we have been investigating short, efficient, in other words user friendly approaches to precursors of small heterocycles, especially pyrazoles and isoxazoles, as well as their downstream transformations. Such precursors are cyclic 2-Azahetaryl-3-enaminonitriles of general formula **A**.

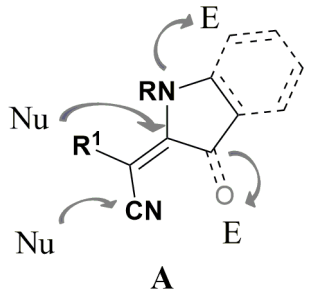


Figure GI.1. *General structure of cyclic 2-Azahetaryl-3-enaminonitriles investigated in this PhD work.*

Cyclic 2-Azahetaryl-3-enaminonitriles have been shown to exhibit different configuration around the double bond depending on their substitution. We have thoroughly investigated their behavior in order to assess the potential relationship between their configuration and their reactivities.

These compounds proved not only useful for azoles syntheses, but we found that they could undergo a further clean functionalization at the not highly reactive position 3 of the pyrrolidine ring under very specific circumstances.

Finally, we also explored the potential coordination properties of these derivatives toward boron and metals. This allowed us to characterize a wide range of new derivatives and investigate their photophysical properties.

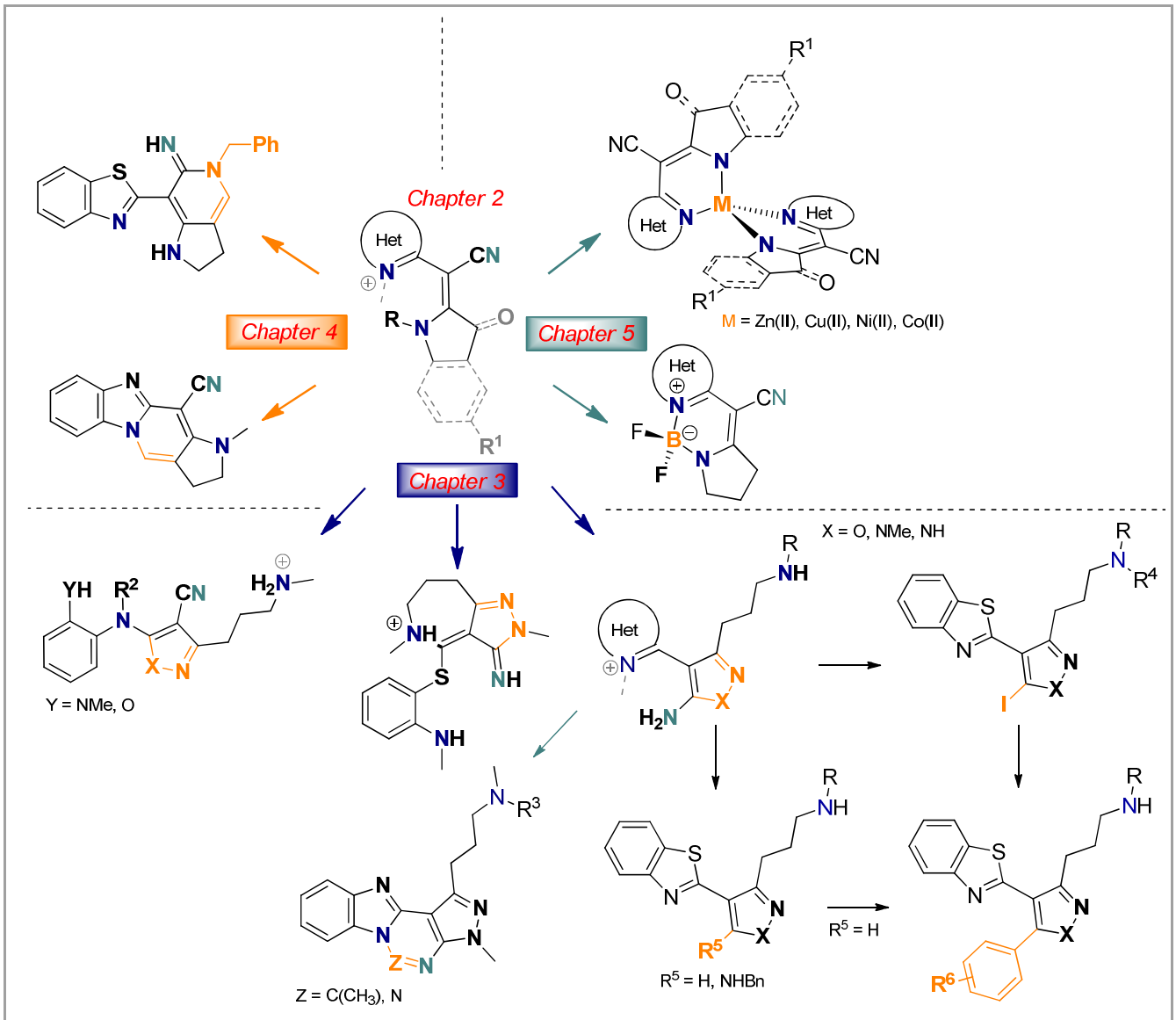


Figure GI.2. *Fate of cyclic 2-Azahetaryl-3-enaminonitriles within this manuscript.*

Thus, this manuscript describes all the experiments carried out in these different directions.

In a first chapter there is a general survey of the literature related to 2-(1-R-pyrrolidine-2-ylidene)acetonitriles and their benzo-fused analogues. Details are provided on the various synthetic approaches to these compounds. Their various reactivities depending on their cyclic or acyclic nature and substitutions are then

covered with a range of nucleophiles and with dimethylformamide acetals. A final part of this chapter describes the complexation of boron and metals by 2-(pyrrolidin-2-ylidene)acetonitrile and the applications of the complexes isolated are characterized.

A second chapter describes in details the synthesis and characterization of all the 2-azahetaryl-2-(1-R-pyrrolidin-2-ylidene)acetonitrile and 2-azahetaryl-2-(3-oxoindolin-2-ylidene)acetonitrile obtained in the course of our studies. Thorough investigation of the configuration by different analytical methods, such as X-Ray diffraction, NMR including variable temperature experiments as well as computation is then described.

Within **the third chapter** we describe the reactivity of 2-azahetaryl-2-(1-R-pyrrolidin-2-ylidene)acetonitrile as 1,3-dielectrophiles toward binucleophilic compounds, and the synthesis of differently substituted pyrazoles and isoxazoles. The downstream transformations on pyrazoles are thoroughly described and showed excellent region- and chemoselectivities.

Alternate paths observed upon modification of the hetaryl substituent are also reported highlighting the control of the reactions path in spite of the different reactive sites.

After developing the electrophilic nature of 2-azahetaryl-2-(1-R-pyrrolidin-2-ylidene)acetonitrile, we demonstrate **in chapter 4** that these adducts can also behave as nucleophile in the presence of electrophiles such as dimethylformamide acetals. A detailed investigation of the reaction outcome allowed us to propose a mechanistic rational for the very specific reactivity. Further transformation of the “formylated” adducts are then reported. This chapter is concluded by the description of the photophysical properties of a pyrrolopyridinimine obtained from these previous transformations, and more precisely its ability to react with traces amounts of water in dry organic solvents providing a simple fluorometric way to assess solvent dryness.

Finally **the fifth chapter** is devoted to the formation of (i) boron-difluoride complexes of 2-azahetaryl-2-(1*H*-pyrrolidin-2-ylidene)acetonitrile and the

photophysical properties of a range of isolated adducts; (ii) d-metal (Cu, Zn, Co, Ni) complexes, their isolation and full characterization as well as their implementation in devices to study their potent applications in solar cells and for detection of the Zn an Cu in biological fluids.

After a general conclusion, the last part of this manuscript provides the experimental details of all the products synthesized and the experiments carried out.

ABBREVIATIONS

Ac	acyl
Alk	alkyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
BODIPY	boron-dipyrromethene
CHA	cyclohexane
cat.	catalyst, catalytic
1,2-DCE	1,2-dichloroethane
DFT	density functional theory
DMAc	dimethylacetamide
DMF DMA	*N*,*N*-dimethylformamide diethyl acetal
DMF DEA	*N*,*N*-dimethylformamide dimethyl acetal
DMF	dimethylformamide
DMS	dimethyl sulfate
DMSO	dimethyl sulfoxide
E	electrophile
equiv	equivalent
Et	ethyl
ex vivo	out of the living
HRMS	high resolution mass spectrometry
IR	infrared
in situ	without isolation
in vitro	in laboratory
in vivo	in living organism
J	coupling constant, Hz
Me	methyl
mp.	melting point
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	nucleophile

one-pot	without isolation of intermediates
Ph	phenyl
PI	polarity index
ppm	parts per million
Pr	propyl
Pyr	pyrazole
rt	room temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet
VTP experiment	variable temperature experiment
XRD	X-Ray diffraction
δ	chemical shift, ppm (NMR spectroscopy)
Δ	reflux
Φ	quantum yield
$\Delta\upsilon$, cm^{-1}	Stokes shift

CHAPTER 1. SYNTHESIS, REACTIONS AND APPLICATION OF 2-(1-R-PYRROLIDIN-2-YLIDENE)ACETONITRILES AND THEIR BENZO ANALOGUES (literature review)

This chapter is devoted to a comprehensive description of the access to 2-(1-R-pyrrolidin-2-ylidene)acetonitriles (section 1.1) and their benzo analogues (section 1.2) as well as their transformations upon treatment with 1,2-binucleophiles (section 1.3) and *N*,*N*-dimethylformamide dialkyl acetals (section 1.4). These transformations provide a fast access to range of heterocyclic scaffolds due to the rich synthetic potential of starting material **A** featuring two electrophilic sites (the nitrile carbon atom and sp^2-hybridized C-2 carbon atom of the pyrrolidine moiety) and two nucleophilic sites (N-1 nitrogen atom in the case of R = H and the pyrrolidine C-3 atom) as illustrated in *Figure I.1*.

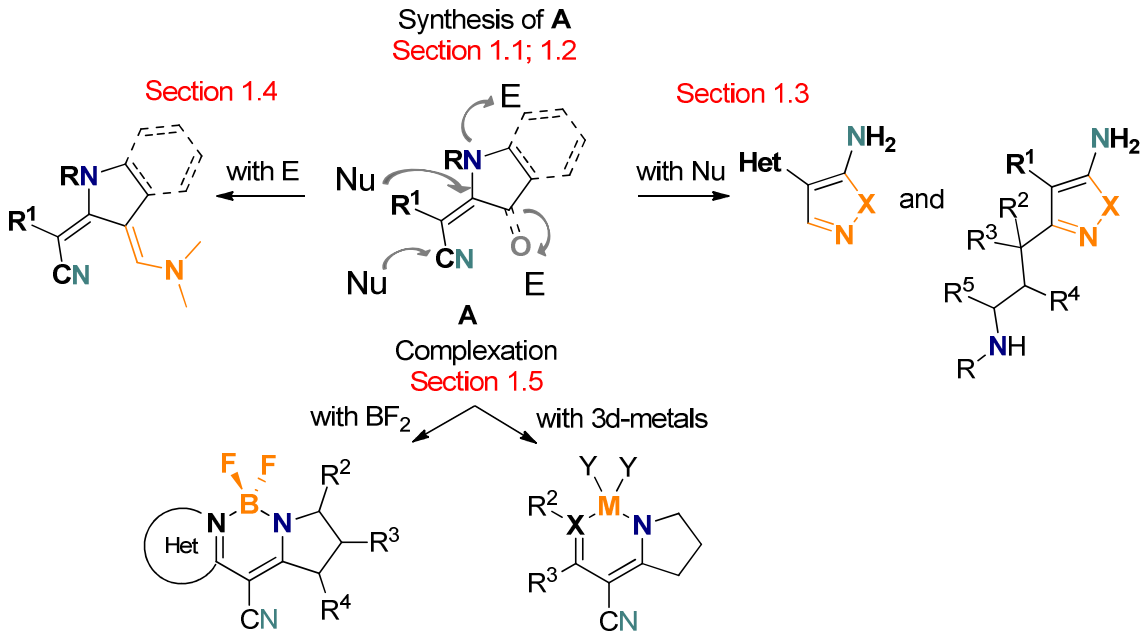
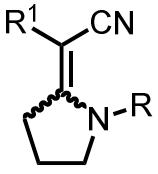


Figure I.1. *Graphical representation of the literature review.*

Moreover, when 2-(1-R-pyrrolidin-2-ylidene)acetonitriles feature extra electron donating atom (X = O, N) they are used for complexation (section 1.5). Upon complexation with boron difluoride the bright fluorescence arises allowing consider the BF_2-comlexes as BODIPY-dyes analogues (subsection 1.5.1). Coordination with

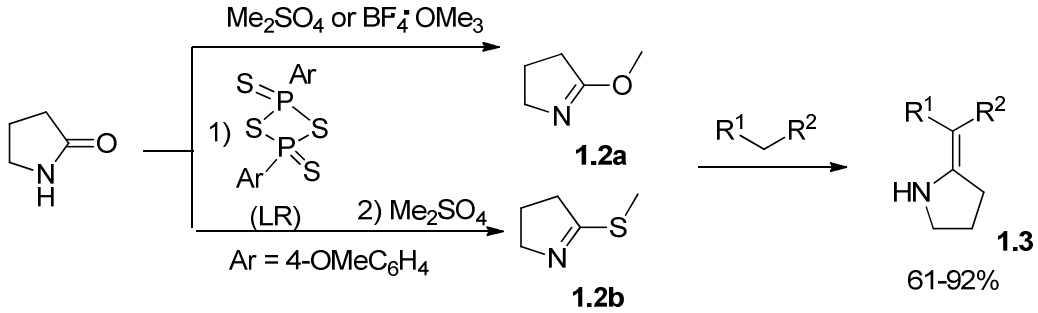
3d-metals is discussed in subsection 1.5.2. The complexes structure exploration along with their catalytic properties in enantioselective and polymerization reactions are presented.

1.1. Synthesis of 2-R[1]-2-(1-R-pyrrolidin-2-ylidene)acetonitriles



1.1

One of the most general methods for the preparation of compounds with general formula **1.1** is the condensation of 5-methoxy-3,4-dihydro-2*H*-pyrrole **1.2a** or 5-(methylthio)-3,4-dihydro-2*H*-pyrrole **1.2b** with compounds bearing the activated methylene group (*Scheme 1.1*).[1-4] The reaction to **1.3** proceeds smoothly from room temperature (rt) to reflux; the selection of reaction conditions depends on the electronegativity of the substituents connected to the methylene moiety. No additional basic catalysts are required for these reactions.

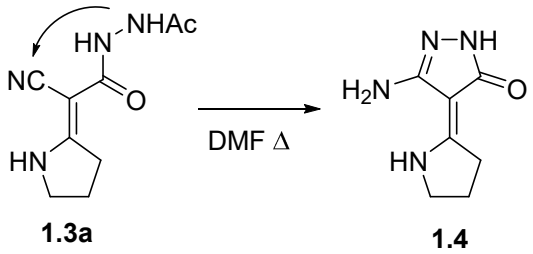


1.2a: R^1 = CN, COMe, CO_2Me, CO_2Et; R^2 = CN, COMe, CO_2Et, $CONH_2$, CONHPh, $CONHCH_2Ph$, CONHNHCOMe, R^3PhCO; R^3 = Cl, H
1.2b: R^1 = CN; R^2 = CN, CO_2Et

Scheme 1.1. *Synthesis of 2-R[1], R[2]-pyrrolidin-2-ylidenes* ***1.3****.*

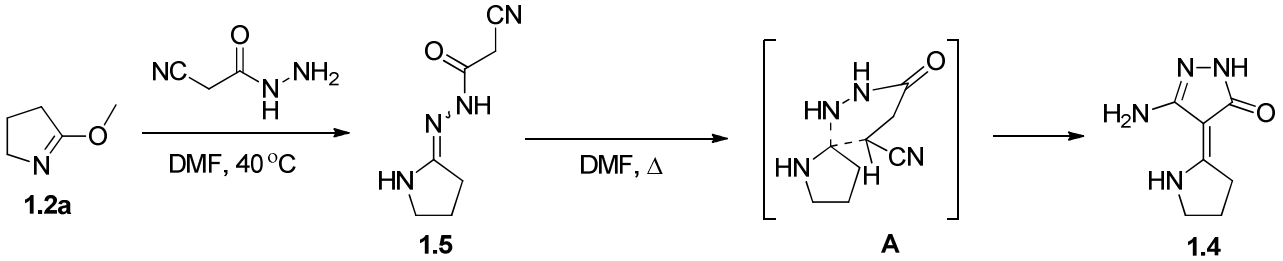
The starting material, namely methoxybutyrolactam **1.2a**, was obtained by the reaction of pyrrolide-2-one with dimethyl sulfate (Me_2SO_4, DMS) or via utilization of triethyloxonium tetrafluoroborate (Meerwein's salt).[5-6] *S*-methylthiobutyrolactam was prepared in two steps, starting with the reaction of pyrrolide-2-one and 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent, LR) followed by methylation with DMS.[7]

The structurally related pyrazolone **1.4** was synthesized *via* heating in dimethylformamide (DMF) as illustrated in *Scheme 1.2*.[1]



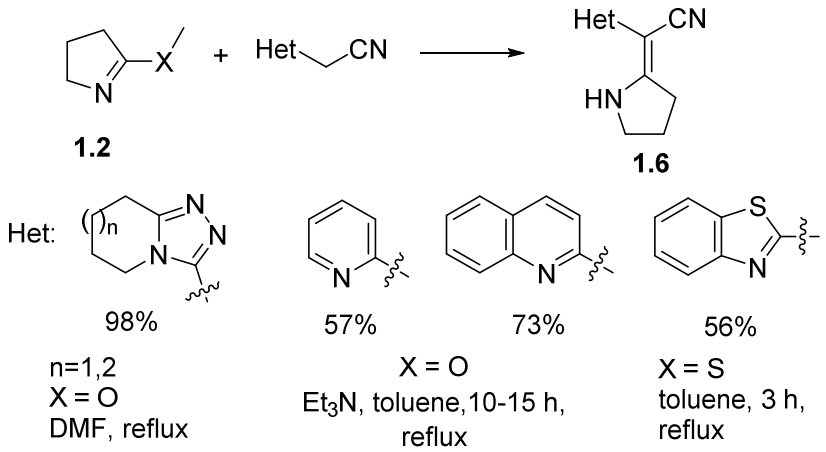
Scheme 1.2. *The cyclization of* ***1.3a*** *into the corresponding pyrazolone* ***1.4****.*

The reaction of *O*-methoxybutyrolactam **1.2a** with *N*-unsubstituted 2-cyanoacetohydrazides upon heating in DMF led to the corresponding pyrazolones **1.4** (DMF, reflux); alternatively, amidrazones **1.5** were formed under milder conditions (DMF, 40 °C.). The conversion from the open-chain form **1.5** to the cyclic one **1.4** occurs *via* the amidine-enamine rearrangement through the transition state **A** (*Scheme 1.3*).[8]



Scheme 1.3. *The reaction of O-methoxybutyrolactame* ***1.2a*** *with N-unsubstituted 2-cyanoacetohydrazides*

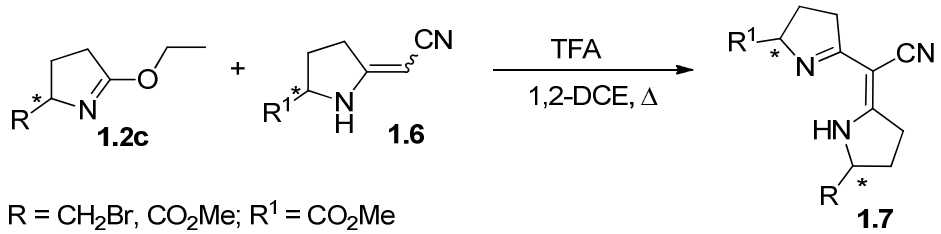
According to the scope of literature methods, only a few *β*-enaminonitriles **1.6** bearing a heterocyclic substituent are known. They were prepared by the condensation reaction of lactim ether **1.2a** or thioester **1.2b** and hetaryl acetonitriles (*Scheme 1.4*).[8-10]



Scheme 1.4. *Synthesis of enaminonitriles* ***1.6*** *bearing heterocyclic substituents.*

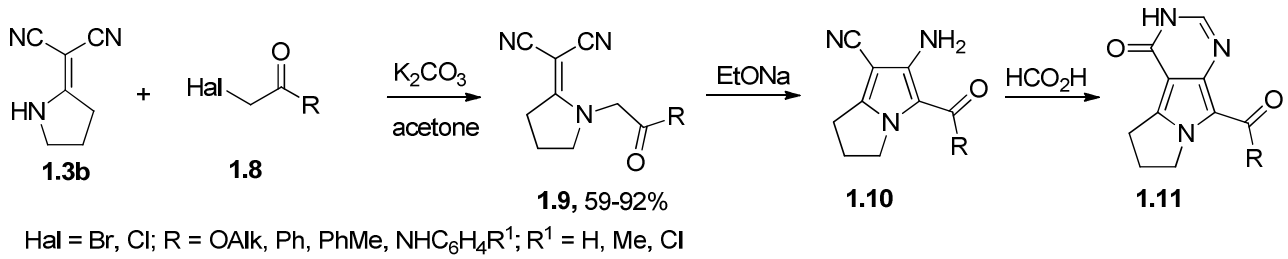
SMe is better nucleofuge, than OMe; the condensation reaction of thioester proceeds without addition of basic agents.

2-(3,4-Dihydro-2*H*-pyrrol-5-yl)-2-(pyrrolidin-2-ylidene)acetenonitrile **1.7** featuring a stereogenic centre in the position 5 of the pyrrolidine core was obtained by condensation of substituted *O*-ethoxybutyrolactame **1.2c** and enaminonitrile **1.6** under strongly acidic conditions, *i.e.* by using TFA (trifluoroacetic acid) (*Scheme 1.5*). [11-12] This approach was used for the synthesis of semicorrins[1] **1.7**.



Scheme 1.5. *Synthesis of chiral 5-(cyano(5-pyrrolidin-2-ylidene)methyl)-3,4-dihydro-2H-pyrroles* ***1.7****.*

2-(1-Alkylpyrrolidin-2-ylidene)acetonitriles were also synthesized by alkylation of their unsubstituted analogues with alkyl halides. Several examples of alkylation of *β*,*β*-pyrrolidienamalononitrile were illustrated,[13-16] in particular, with **1.3b** bromoacetic acid ester, methyl phenacyl bromide and chloroacetanilide **1.8** (*Scheme 1.6*).



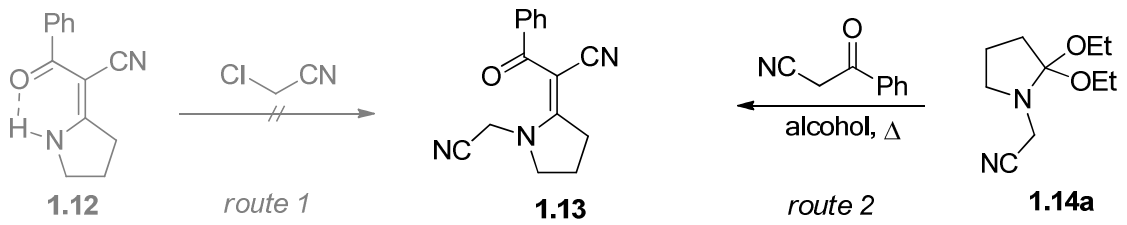
Scheme 1.6. *Synthesis of 2-(1-alkylpyrrolidin-2-ylidene)acetonitriles and their further modifications into the potentially biologically active compounds.*

The purpose of these transformations was obtaining fused systems: pyrrolizines **1.10** (Thorpe-Ziegler condensation) and pyrrolopyrimidines **1.11**, that exhibit a range of biological activities, in particular, antitumor, anti-inflammatory, antiviral. In some experiments, compound **1.9** served as an intermediate and used without isolation, but

[1] Semicorrins - nitrogen-containing ligands for enantioselective catalysis (details on their using are in section 1.5.2).

immediately transformed to the corresponding pyrrolizines **1.10**. Biological *in vitro* and *in vivo* studies were also provided.

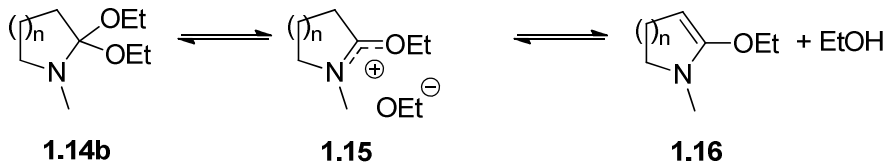
Alkylation proceeds smoothly, when the pyrrolidine's NH proton is only loosely bound. If a hydrogen bond acceptor, *e.g.* a carbonyl group, is located close to the NH moiety, then the proton become less acidic and deprotonation becomes harder preventing subsequent alkylation (*Scheme 1.7, route 1*).[16]



Scheme 1.7. *Approaches to the synthesis of 2-(1-alkylpyrrolidin-2-ylidene)acetonitriles.*

An alternative approach to the synthesis of 2-(1-alkylpyrolidine-2-ylidene)acetonitriles is the condensation of 1-alkylpyrrolidin-2-one dialkyl acetal **1.14a** with a malonate equivalent (*Scheme 1.7, route 2*).

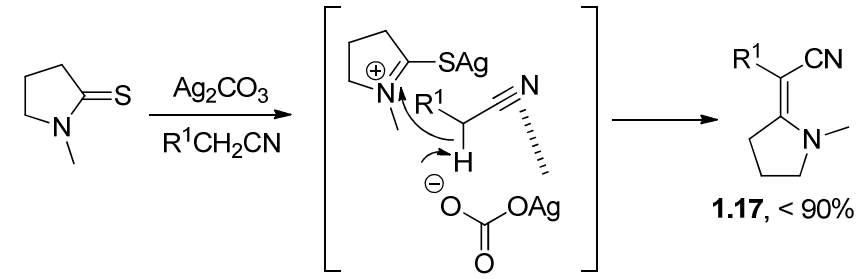
1-Methylpyrrolidin-2-one diethyl acetal **1.14b** is in equilibrium with the corresponding ambident cation **1.15** , formed by dissociation of one ethoxy from **1.14b** (*Scheme 1.8*).[17]



Scheme 1.8. *Diethyl acetal exists as an equilibrium mixture of three forms.*

At the same time, 2-ethoxyenamine **1.16** exists in equilibrium with the ambident cation **1.15**. This occurs due to the existence of a complete positive charge in compound **1.15**, which increases the proton mobility in the third position. Acetals are more reactive electrophiles than *O*-alkoxybutyrolactam **1.2a**, thus they react even with nitromethane and with other acidic CH upon milder conditions. The disadvantage of acetals is their instability and degradation with time to the starting pyrrolidin-2-one; such process accelerates upon heating.

Another method for the preparation of 2-(1-alkylpyrrolidin-2-ylidene)acetonitriles **1.17** is the condensation reaction of 1-methylpyrrolidin-2-thione and the corresponding substituted acetonitrile in the presence of Ag_2CO_3.[18] The silver salt has two significant features: first of all, it is thiophilic; secondly, it acts as a base allowing the reaction to proceed under mild conditions such as at rt (*Scheme 1.9*).

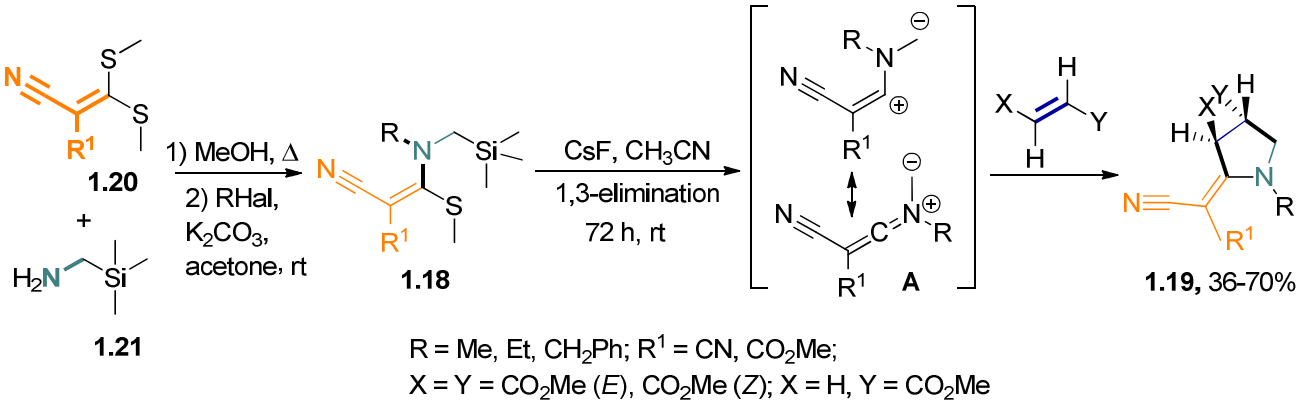


R^1 = CN, CO_2Me, CO_2t-Bu, C_6H_5CO, NO_2, $C_6H_5SO_2$, 2-pyridyl

Scheme 1.9. *Synthesis of bifunctionalized enamines* ***1.17*** *at room temperature with addition of* Ag_2CO_3.

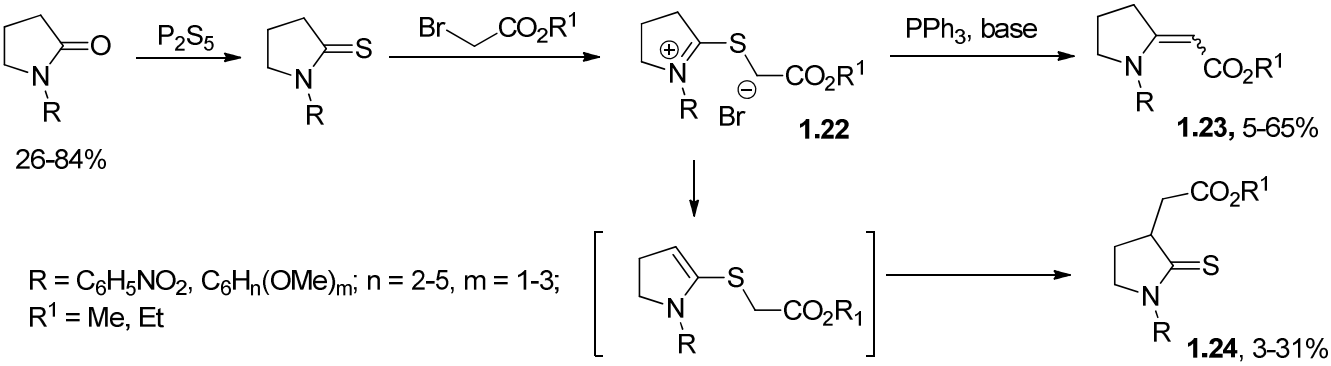
The reaction occurs with nucleophiles bearing two electron withdrawing groups, and at least one of them should be nitrile moiety. It was observed that no reaction occurs if the nitrile group was replaced with ethyl acetoacetate or dimethyl malonate, which have similar electron withdrawing properties. Also, the reaction does not take place with 1*H*-pyrrolidin-2-thione; this statement confirms the passivity of neutral silver complexes in this transformation. Solvents with coordination ability were used in above-mentioned transformations, *i.e.* acetonitrile, tetrahydrofuran.

Substituted *α*-alkylidene **1.19**, can be obtained by a [3+2] cycloaddition reaction between activated alkenes and *N*-(silylmethyl)-substituted ketene *N,S*-dithioacetals **1.18**, which serve as synthetic equivalents of alkyliden azamethine ylides (*Scheme 1.10*).[19] The reaction takes place by 1,3-elimination of (methylthio)trimethylsilane with subsequent formation of a dipole **A**, which reacts stereo- and regiospecifically with activated alkenes to form *α*-alkylidene pyrrolidines **1.19**. The reaction requires 72 h at rt. The starting *N,S*-dithioacetals are not commercially available and must be synthesized in 2 steps starting with ketene dithioacetals **1.20** and ((trimethylsilyl)methyl)amines **1.21**.



Scheme 1.10. *Synthesis of α-alkylidene-substituted [3+2] cycloadducts* ***1.19****.*

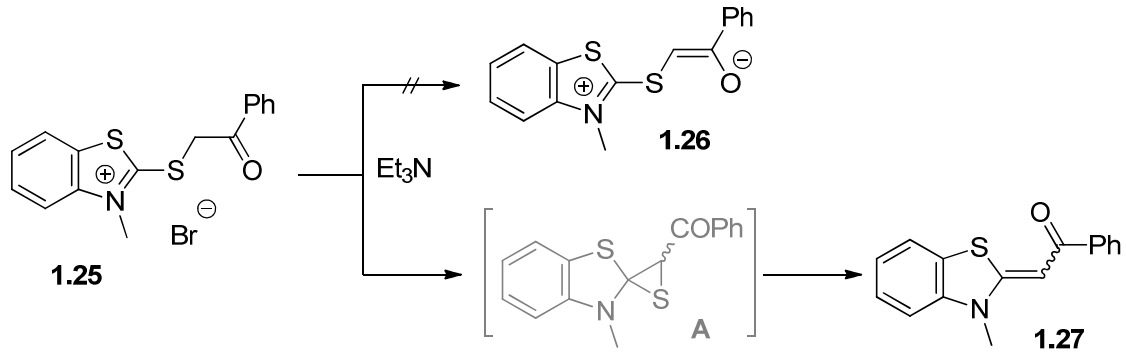
Moreover, analogues of pyrrolidinacetonitriles, *e.g.* (1-arylpyrrolidin-2-ylidene)acetates **1.23** were synthesized by alkylation of *N*-arylthiolactam with *α*-haloacetates, followed by Sulfur atom elimination and subsequent C–C bond formation (*Scheme 1.11*).[20] In the first step of the reaction, salts **1.22** were formed. Due to the conjugation of nitrogen lone pair with an aromatic ring and decreasing of the nucleophilicity of the sulfur moiety, the reaction takes place over several hours (max. 189 h for R = C_6H_4OMe), from rt to 50 °C, in the absence of a solvent (neat). The produced salts **1.22** without isolation were subjected to the next step. Yields of the target products **1.23** were low (5-65%) due to the formation of by-products such as the starting 1-arylacetate and 3-alkylthiolactam **1.24**.



Scheme 1.11. *One-pot synthesis of (1-arylpyrrolidin-2-ylidene)acetates* ***1.23*** *by alkylation of thiolactams followed by Sulfur displacement.*

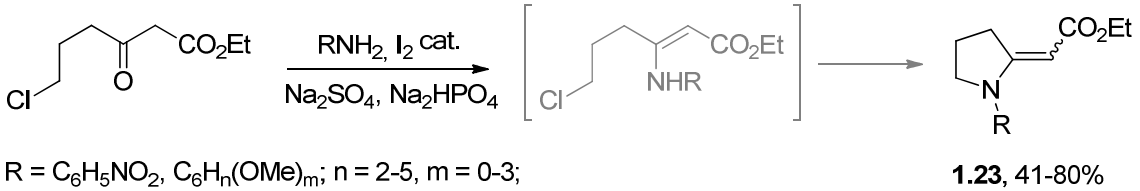
For the first time, the method for the C–C bond construction *via* Sulfur displacement was studied by Knott in his work dedicated to sulfur-containing chromophores.[21-22] In attempts to carry out the dihydrobromination reaction of (phenacylthio)benzothiazolium bromide **1.25** using triethylamine, the corresponding

unsaturated ketone **1.27** was formed instead of the expected sulfide **1.26**. The reaction passes through the episulfide intermediate **A** followed by sulfur extrusion (*Scheme 1.12*).



Scheme 1.12. *The first application of the C–C bond forming reaction via the Sulfur displacement (1955).*[21]

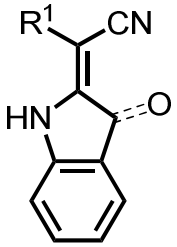
The authors of the above-described method for the synthesis of (1-arylpyrrolidin-2-ylidene)acetates **1.23** also have reported a more efficient method providing higher yields (41-80%); it consists in the condensation of 6-chlorohexanoic acid ethyl ester with aniline at 65 ^{o}C in the presence of catalytic amounts of iodine, a drying agent (Na_2SO_4) and a base (Na_2HPO_4) used to trap hydrogen chloride (*Scheme 1.13*).[20]



Scheme 1.13. *Synthesis of (1-arylpyrrolidin-2-ylidene)acetates **1.23** by condensation of 6-chlorohexanoic acid ester with aniline.*

This method was unfruitful only with *p*-nitrophenyl substituents (0% yield). However, due to the known literature procedures, condensation of nitroanilines with ethyl acetate in the presence of iodine does not occur in the desired direction.[23] The disadvantage of the method is the formation of acyclic vinylogues of urethanes, as well as condensation products of the parent ester, which significantly complicates the purification of the final product of the reaction.

1.2. Synthesis of 2-R[1]-2-(indolin/3-oxoindolin-2-ylidene)acetonitriles

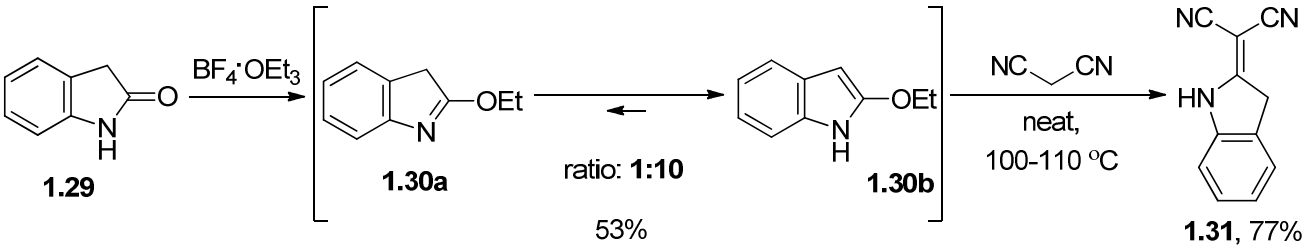


1.28a,b

1.28a – *indolin-2-ylidene*
1.28b – *3- oxoindolin -2- ylidene*

Synthesis of 2-R[1]-(indolin/3-oxoindolin-2-ylidene)acetonitriles with general formula **1.28** is not a common problem and there are exiguous ways to solve it. Application of the alkylation method for cyclic amide by utilizing DMS or Meerwein's salt followed by condensation with acidic CH (the approach used for the synthesis of pyrrolidin-2-ylidenacetonitrile **1.3**) in this case is not fruitful. Thus, isatins are mainly alkylated at the nitrogen atom; when the indolin-2-one **1.29** is alkylated with Meerwein's salt, an equilibrium mixture of 2-alkoxy-1*H*-indole **1.30a** and 2-alkoxy-3*H*-indole **1.30b** was obtained, which is passive in reactions with most of the C-nucleophiles.[24]

In the resulting tautomeric system, the equilibrium is shifted to a more thermodynamically stable isomer **1.30b** with 10π electronic aromatic system, comparing to the non-conjugated lactam ester **1.30a** (*Scheme 1.14*). According to ^{1}H NMR data, the ratio of tautomers **1.30a**:**1.30b** in the equilibrium system was 1:10.[24]. In addition, it was observed that the 2-alkoxy-3*H*-indole **1.30b** is unstable due to subsequent oxidation to the correspoding indirubin under air.[25]



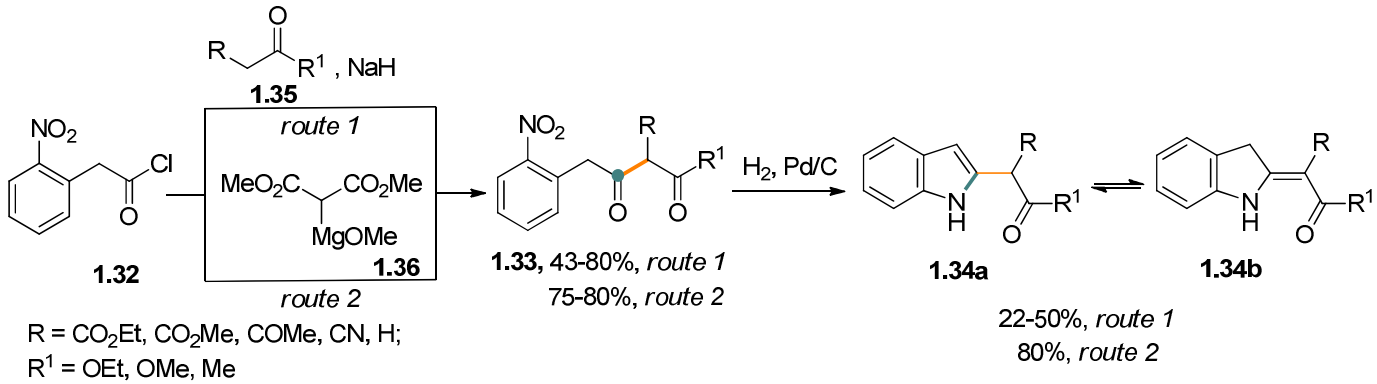
Scheme 1.14. *Synthesis of 2-(indolin-2-ylidene)malononitrile **1.31** by alkylation of indolin-2-one **1.29**.*

For the formation of systems with general formula **1.28a** *via* condensation with acidic CH, it is necessary that the equilibrium is shifted towards the lactam ether **1.30a**. For this purpose, the methylene moiety of the nucleophile must be sufficiently activated to promote the shift of equilibrium and, consequently, the reaction.[26] The target product **1.31** can only be prepared using malononitrile, which methylene group is located between two strong acceptors, *i.e.* nitrile groups (*Scheme 1.14*). The

reaction did not occur without the isolation of desired product while involving to the reaction other acidic CH, *e.g.* nitromethane, ethylcyanoacetate, ethylnitroacetate.[26]

Bearing in mind the complexity of this synthetic route, its use in the synthesis of 2-functionalized indoles is limited to one publication.[26] In section 1.4, the reactions of enaminonitrile **1.31** with C-electrophiles will be reviewed.

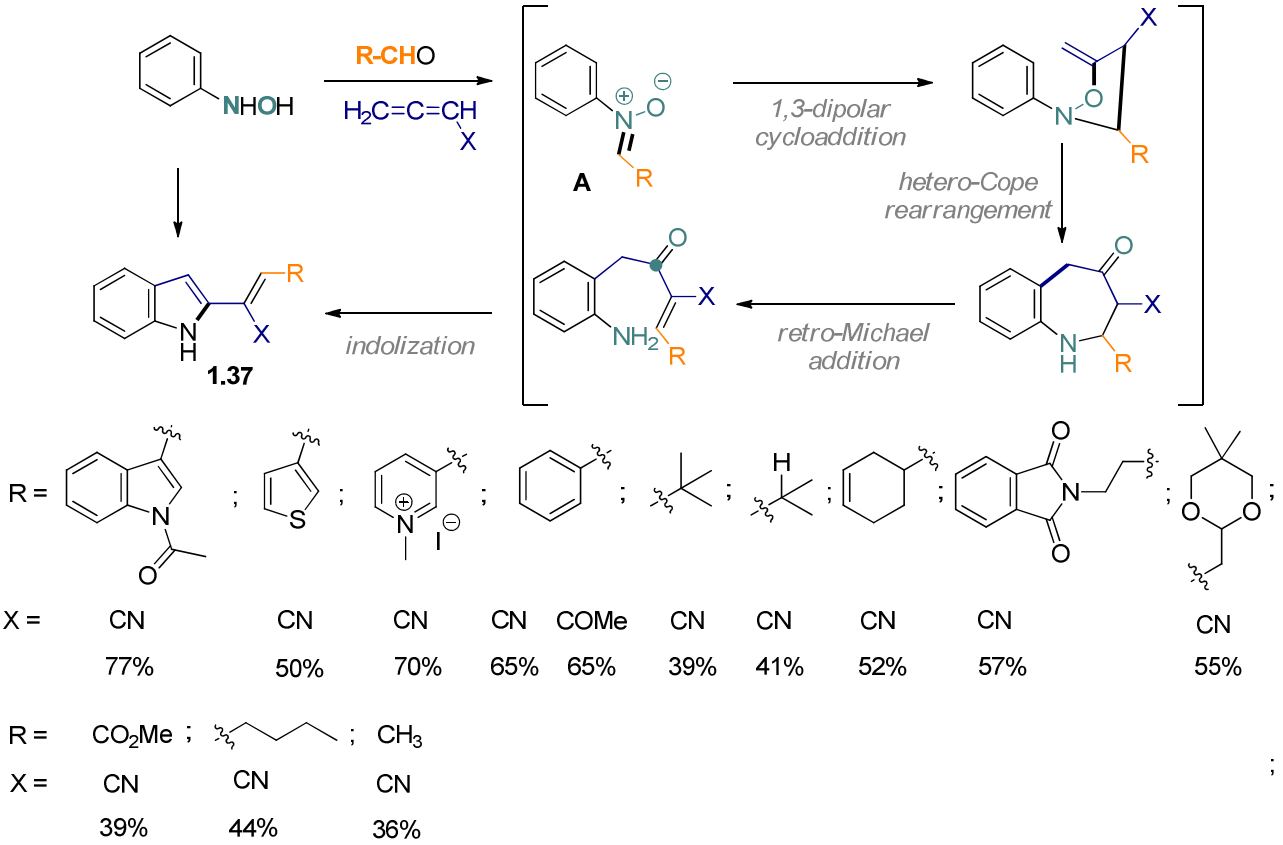
Another approach to the synthesis of compounds with general formula **1.28a** was published by German scientists (*Scheme 1.15, route 1*),[27] and subsequently improved by Swiss ones (*Scheme 1.15, route 2*);[28] those strategies were related to the reduction of *β*-diketones **1.33**.



Scheme 1.15. *Synthesis of 2-R-(indolin-2-ylidene)ketones / esters* ***1.34*** *by the reduction of β-diketone derivatives* ***1.33****.*

Compounds **1.33** were synthesized by the condensation of 2-(2-nitrophenyl)acetyl chloride **1.32** with methylene active compounds **1.35** (*Scheme 1.15, route 1*),[27] or with methoxy-magnesium derivative of dimethylmalonate **1.36**.[28]

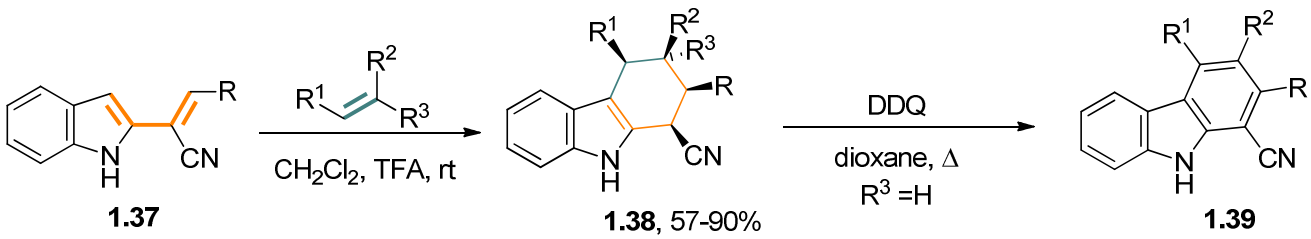
An efficient one-pot method for the synthesis of 2-vinylindole derivatives **1.37** was developed by the *S. Blechert* group.[29] The starting compounds were aldehyde, phenylhydroxylamine and cyanoallen. The reaction intermediates *N*-phenylnitrons were converted to 2-vinylindole derivatives by means of tandem reactions: 1,3-dipolar cycloaddition, Cope rearrangement, retro-Michael addition, and indolization (*Scheme 1.16*). The reaction proceeds at 20-60 °C in ethanol. According to the structure simplicity of the starting materials, as well as the number of steps, the reaction yield can be seen as satisfactory (36-77%).



Scheme 1.16. *Synthesis of 2-vinylindoles* ***1.37*** *by the tandem reactions.*

This method was applied for the synthesis of 2-vinylindoles with various substituents, *i.e.* heterocyclic and aromatic, as well as aliphatic ones. The only limitation in scope for this procedure is the availability of nitrones **A**; some of them are formed very slowly and are unstable. However, this method does not require the stage of nitrons isolation and purification; they are immediately involved into the next step with cyanoallenes, which made this approach successful.

The resulting 2-vinylindoles **1.37** proved to be a powerful source for the construction of linear carbazole cores, which are the key intermediates in the synthesis of some indole alkaloids (ellypticine, olivacine).[30] The cycloaddition reaction (Diels-Alder) with electron deficient alkenes in dichloromethane takes place at rt in the presence of TFA and ends with the formation of tetrahydrocarbazols **1.38**. The reaction proceeds with high stereo- and regioselectivity and results in the formation of endo-adducts. Tetrahydrocarbazols **1.38** can be further oxidized to carbazole **1.39** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (*Scheme 1.17*).



R^1 = H, Me; R^2 = COMe, CHO, CN; R^3 = H, Et, 2-indolyl

Scheme 1.17. *Synthesis of tetrahydrocarbazols* ***1.38*** *with 2-vinylindoles* ***1.37*** *by the Diels-Alder reaction. Oxidation of saturated compounds* ***1.38*** *into the corresponding carbazoles* ***1.39****.*

As it was mentioned above, isatins are mainly alkylated at the nitrogen atom; thus, no examples of the application of their 2-alkoxy derivatives in the construction of 2-C–C bond are reported to date.

In general, the C-2 position of isatin is passive in reactions with nucleophiles (without addition of catalysts for this process, as discussed below) in contrast to C-3, which could be functionalized by widely reported various methods.

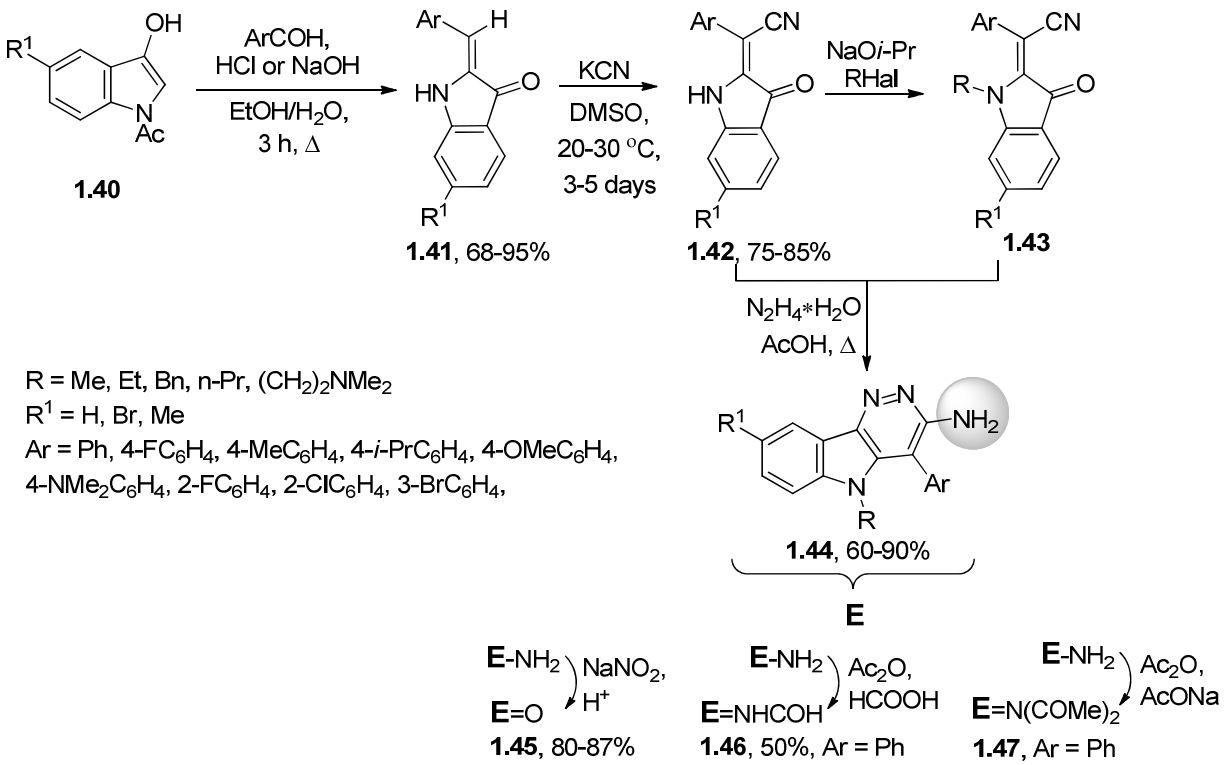
The only purposeful approach to the synthesis of **1.28b** of 2-R^1-(3-oxoindolin-2-ylidene)acetonitrile with general formula **1.28b**, in particular, 2-(6-R^1-3-oxoindolin-2-ylidene)-2-arylacetonitrile **1.42**, is the condensation of 1-acetylindoxyl **1.40** and aldehydes followed by a substitution reaction of the vinyl hydrogen atom with a cyano group. (*Scheme 1.18*).[31-32]

The reaction occurring in the first step of the synthesis is accompanied by hydrolysis of the amide bond (NAc) and the formation of the non-substituted indogenide **1.41**. In order to avoid hydrolysis, *Buzas et al.*[33] have developed the method for carrying the reaction in the presence of a less strong base, *i.e.* piperidine, upon boiling in an inert solvent (benzene/toluene)

In the reaction with potassium cyanide, *N*(1)-substituted analogues of indogenide **1.41** were found to be better substrates; thus, the modification was carried out by the introduction of an alkyl group in the third step of the synthesis, after the incorporation of nitrile moiety.

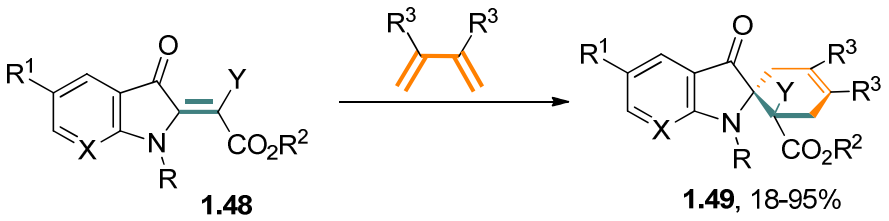
Cyanoindogenenes **1.42** and **1.43** were modified in order to obtain new potent antituberculous drugs – analogues of pyridazoindole. It is known that hydrazine derivatives exhibit activity against different strains of bacteria, in particular

M. tuberculosis H37Rv and *M. Fortuitum*, and also inhibit monoamine oxidase, an enzyme involved in the pathogen metabolism. Tricyclic pyridazoindoles **1.44** were prepared by the reaction with hydrazine hydrate; their primary amino group were modified by diazotisation-hydrolysis reactions to form pyridazinone **1.45**, formylation, which gave pyridazoamide **1.46** and subsequent acylation led to diacylaminopyridazine **1.47**.[32]



Scheme 1.18. *Synthesis of 2-R[1]-(3-oxoindolin-2-ylidene)acetonitrile and their modification in order to obtain potential anti-tuberculosis drugs.*

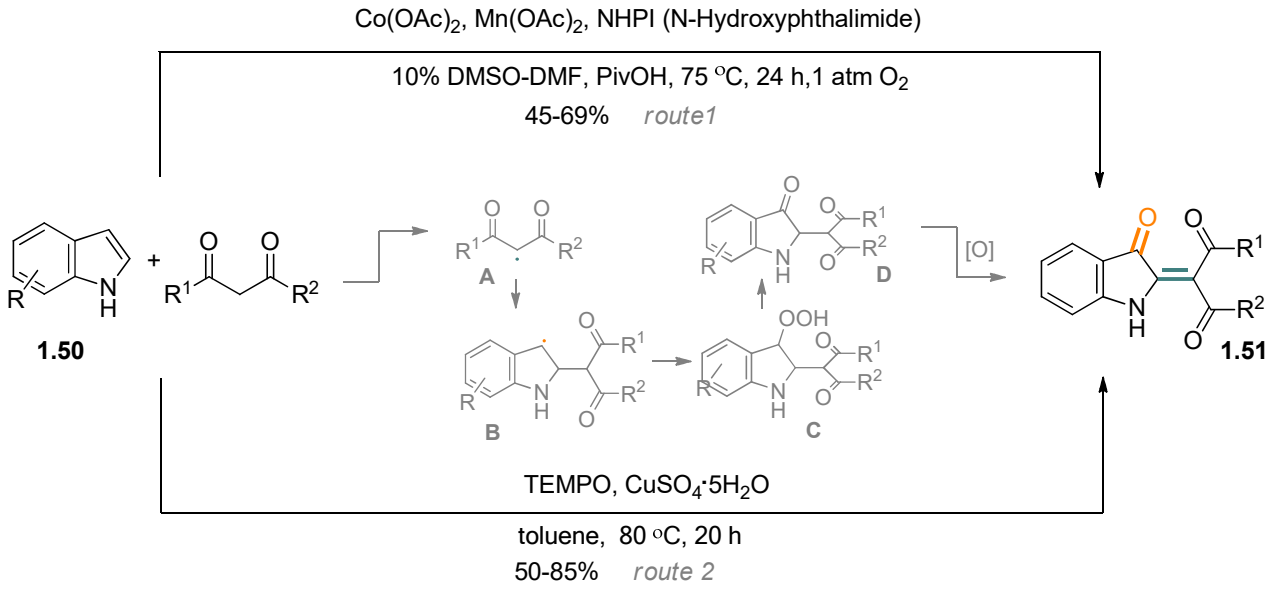
Analogues of 2-R[1]-(3-oxoindolin-2-ylidene)acetonitriles, which nitrile group was substituted by another electron-withdrawing group **1.48** were obtained by the sequence illustrated in *Scheme 1.18* (synthesis of compound **1.41**); they were acting as a dienophile in the synthesis of model cores of Aristotelía alkaloids (*Scheme 1.19*).[34]



X = H, N; Y = H, CO_2Et; R = H, Me; R^1 = H, OMe; R^2 = Me, Et; R^3 = H, Me

Scheme 1.19. *Synthesis of model cores of Aristotelía alkaloids.*

An interesting alternative approach to the synthesis of 2-R^1-(3-oxoindolin-2-ylidene)acetatoacetates **1.51** was recently published and consists in simultaneous construction of the C–C and C=O bonds using cross-coupling reaction between the indole **1.50** and *β*-ketoesters with oxygen as a mild oxidant (*Scheme 1.20*).[35-36] The reaction is tolerant to a wide range of substituents connected to the indole core and takes place both with the electron-withdrawing and the electron-donating groups. Also, the reaction is not sensitive to air humidity.



route 1
R = H, 4(5)-CO_2Et, 5-Hal, 5(7)-Me, 5-OMe;
R^1 = 3(4)-MeC_6H_4, 3(4)-ClC_6H_4; 4-BrC_6H_4, 4-FC_6H_4, 3-$OMeC_6H_4$, 4-CNC_6H_4, 2-naphtyl, Ph;
R^2 = OMe, OEt, O*i*-Pr, Me

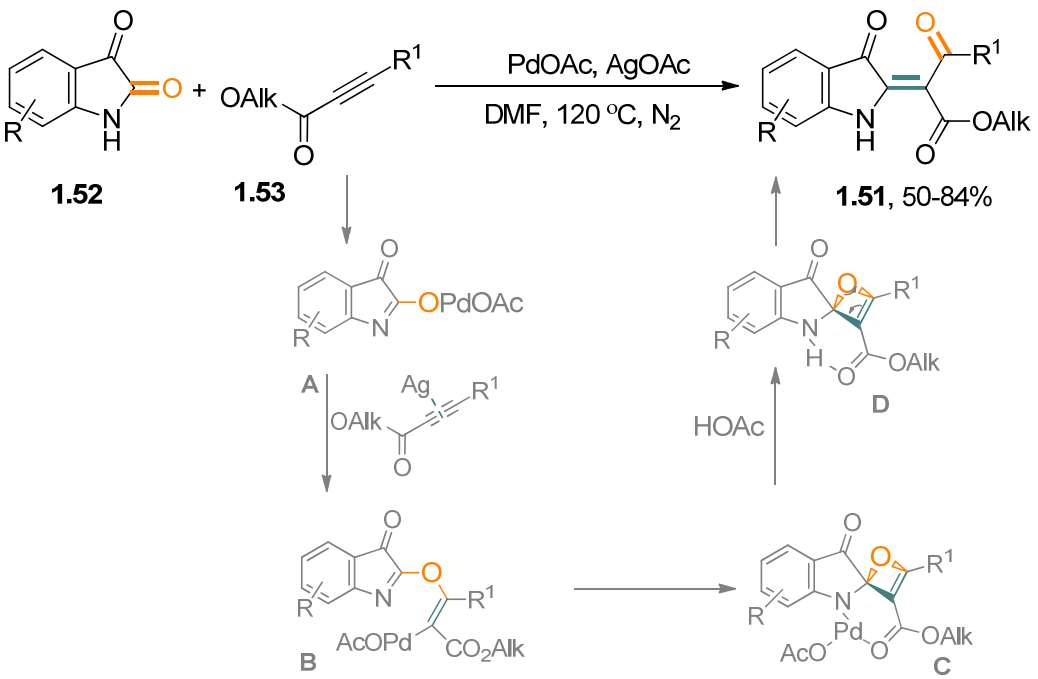
route2
R = H, 4(5)-CO_2Et, 5(6)-Hal, 5(7)-Me, 5(7)-OMe, 5(6/7)-OBn, 4(5/6)-CO_2Me, 7-Cl;
R^1 = 3(4)-MeC_6H_4, 3(4)-ClC_6H_4; 4-BrC_6H_4, 4-FC_6H_4, 3-$OMeC_6H_4$, 4-CNC_6H_4, 2-naphtyl, Ph;
R^2 = OMe, OEt, O*i*-Pr, Me

Scheme 1.20. *Oxidative cross-coupling of indoles* ***1.50*** *with β-ketoesters.*

The oxidative cross-coupling takes place regioselective with good yields of the product only with *β*-ketoesters, since the activity of the catalyst that is formed *in situ* [(1,3-diketonato)$_2$Co(II)] strongly depends on the electronic effect of 1,3-diketones. [36]

The possible reaction mechanism involves the formation of the *β*-ketoester **A** radical, which adds to the 2-position of the indole to form a stabilized radical **B**, which, in turn, reacts with the air oxygen and turns into the corresponding peroxide **C**. The latter is converted to the intermediate **D**, which transforms into the final compound during oxidative dehydrogenation **1.51**.

Another example of the cross-coupling reaction for the synthesis of 2-R^1-(3-oxoindolin-2-ylidene)acetoacetates **1.51** is the reaction between isatin **1.52** and alkanoates **1.53** (*Scheme 1.21*).[37]



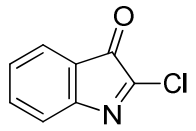
R = H, 4(5)-Cl, 4(5)-Br, 4,5,6-OMe, 5-OMe, 5-nC$_7$H$_5$; R^1= 4-BrC$_6$H$_4$, 4-PhC$_6$H$_4$, 4-OMeC$_6$H$_4$, 2-MeC$_6$H$_4$, 3,5-(CF$_3$)$_2$C$_6$H$_3$, 4-PhC$_6$H$_4$, 4-F,5-Cl-C6H$_3$, (1)2-naphtyl, Ph, Alk;

Scheme 1.21. *The coupling reaction of isatin and alkynoates, which is accompanied by the migration of oxygen atom.*

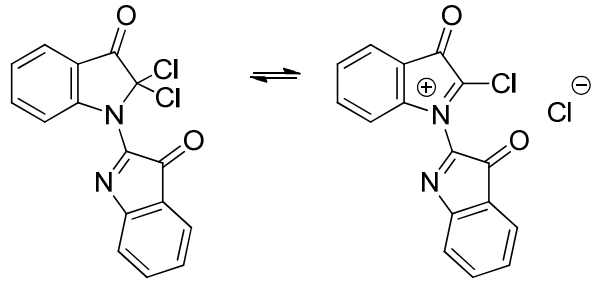
The proposed catalytic cycle starts with the palladiation of the C-2 carbonyl group of isatin **1.52** to form intermediate **A**, followed by the syn-addition to the alkyn, which ends with the formation of the vinyl-palladium complex **B**, subsequently rearranged to **C**. The catalytic cycle is completed by the release of the intermediate **D**, which oxocyclobutane undergo acid catalysed rearrangement to **1.51**. The presence of an

unsubstituted *N*(1)-isatin is compulsory to start the catalytic cycle, namely the formation of the intermediate **A**. No reaction is observed with *N*-alkyl substituted isatins.

The reaction of isatin with nucleophiles can also occur by activating the C-2 position by introducing a halogen atom. For the first time such approach was used in the *Bayer's* works devoted to the synthesis of indigo in 1878-1879 years.[38] He made the statement that the reaction of isatin with phosphorus pentachloride upon boiling in benzene led to 2-chloro-3*H*-indole-3-one **1.54** (*Figure 1.1a*), which was isolated and characterized (by methods available at that time: elemental analysis, melting point with a decomposition at 180 °C). This compound is unstable under air and hydrolyzes to the starting isatin. In 1996, the "2-chloroisatin approach" was used in 37 articles and 4 patents published by 26 scientific groups. In 1996, *Sir John Cornforth* published an article in which he provided evidence, that upon the synthesis conditions proposed by Bayer, no 2-chloroisatin was formed, as it was thougt to be for more than a century, but its dimer, namely 2-2-2-dichloro-2,3-dihydro-3-oxoindol-1-yl)3*H*-indole-3-one **1.55** (*Figure 1.1 b*).[38] The structure of the compound was confirmed by X-ray diffraction analysis.



1.54



1.55a **1.55b**

Figure 1.1. a). *2-Chloro-3H-indole-3-on – phantom.*

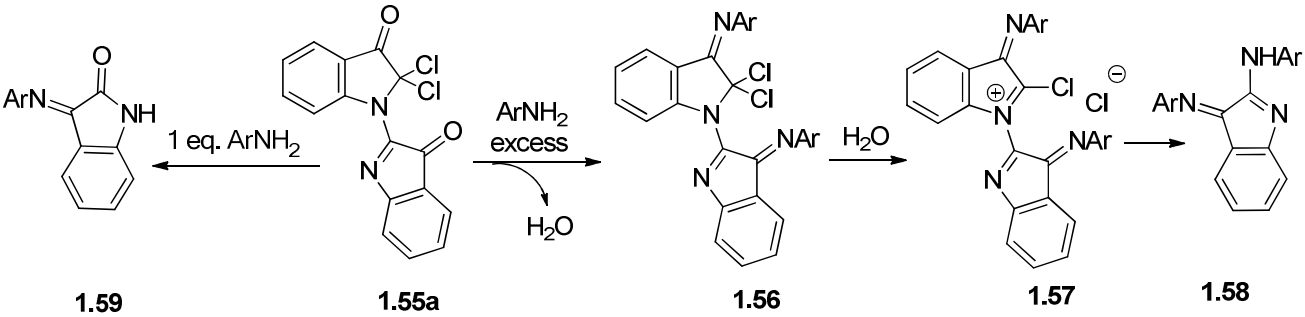
Figure 1.1. b) *2-(2,2-Dichloro-2,3-dihydro-3-oxoindol-1-yl)3H-indole-3-one - a confirmed structure.*

Using his own assumptions, *Sir John Cornforth* explained the strange features observed in the reactions of "2-chloroisatin" with nucleophiles, such as the competitive condensation at the C-3 position, which is less active than C-2, according to the proposed structure **1.54**. Prior to this, the results of these reactions were mainly

explained by the instability of 2-chloroisatin and its degradation to the starting isatin, which is an active component of the reaction.[39]

On the example of the reaction with aromatic amines, *Sir John Cornforth* explained why the structure of the formed products may depend on the amount of the starting amine.

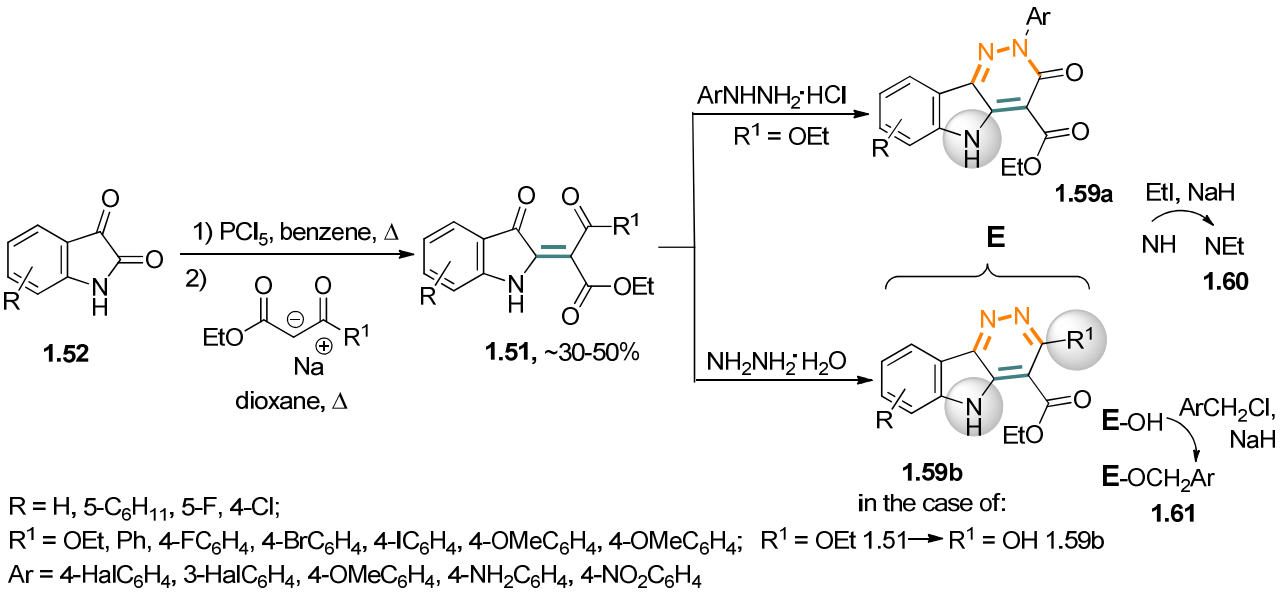
Imidochloride **1.55** predominantly exists in the non-dissociated form **1.55a**. The transition to form **1.55b** may be caused by a polar solvent. Apparently, The C-3 position of isatin is more active in the form **1.55a** (*Figure 1.1b*); thus it undergoes nucleophilic attack by amino group **1.56** (*Scheme 1.22*). Two equivalents of water released during condensation induce the dissociation of the C-Cl bond **1.57** and subsequent attack by the second amine molecule at the C-2 position of **1.58**. In the case of stoichiometric quantities of reagents, the only product of the reaction was 3-(arylimino)indolin-2-one **1.59**; the water produced during the condensation attacks at the C-2 position of imidoylchloride **1.57**.



Scheme 1.22. *Reaction of* ***1.55a*** *imidocloride with aromatic amines.*

This activation approach for the C-2 position of isatin was used to synthesize 2-R^1-(3-oxoindolin-2-ylidene)acetatoacetates **1.51** (*Scheme 1.23*).[40-42]In the first step, isatin reactes with phosphorus pentachloride. The formed imidochloride **1.55a**[2] is filtered under nitrogen and dissolved in a more polar solvent – dioxane. To the solution is added malonate salt and after a brief stirring at room temperature, C-2-functionalized isatins **1.51** were obtained in 30-50% yield .

[2] authors have not described the structure of the intermediate product and depict it in the form of imidoyl chloride **1.54**



Scheme 1.23. *Functionalization of the C-2 position of isatins via the formation of imidochloride* ***1.55a****.*

During the course of the condensation of the latter compounds with hydrazines, pyridazino[4,3-*b*]indole esters **1.59** were prepared; they have shown activity as benzodiazepine receptor ligands. A series of works by Italian scientists is devoted to synthesis and structural modifications of compounds **1.59** (alkylation with the formation of *N*-Alk **1.60** and *O*-Alk **1.61** derivatives, etc.) to pursue studies related to the structure of benzodiazepine receptors and affinity of ligands.[40-43]

1.3. Reactions of *β*-enaminonitriles with 1,2-binucleophiles for the synthesis of pyrazoles (isoxazoles)

Pyrazole is a common moiety found in many medicinal and agrochemical products (derivatives of 1-arylpyrazole are inhibitors of cyclooxygenase-2 and protein kinase, antifungal drugs, 1,5-diarylpyrazoles inhibitors of HIV-1 reverse transcriptase, etc.).[44-45] Pyrazole derivatives are also used in food and polymer chemistry (catalysts of polymerization reactions).[44] Considering the wide array of applications for pyrazoles usage, the interest in their synthesis does not fade over time. Several works of interest have recently been published on combinatorial synthesis of pyrazoles,[46] as well as cross-coupling reactions for the post-functionalization of pyrazoles[47] and modified syntheses of 4-trifluoromethyl

substituted pyrazoles.[48] Chemistry of pyrazoles,[44] their catalytic properties,[49] and therapeutic use[45] have been extensively reviewed.

There are several approaches to access the pyrazole ring. The most common is condensation between 1,3-dielectrophilic synthons and hydrazines. In this section, we focus on the synthesis of pyrazoles with the participation of cyclic or acyclic enaminonitrile having two electrophilic centres: the carbon atom of the nitrile group and the *β*-atom of the acrylonitrile fragment; therefore, these compounds may act as a 1,3-dielectrophilic agent (*Figure 1.2*).

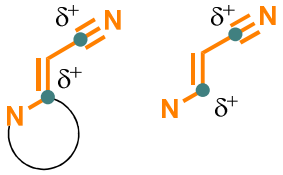


Figure 1.2. *Electrophilic sites of cyclic and acyclicenaminonitriles.*

A search in the SciFinder database revealed about 720 publications devoted to the reactions of *acyclic β*-enaminonitrile with 1,2-binucleophiles. Focusing on the nearest analogues of the systems, to which our work is devoted, namely on α-hetaryl-*β*-enaminonitrile, the range was managed to narrow down to about 20 publications, which will be discussed in subsection 1.3.1. The use of *cyclic β*-enaminonitrile derivatives in the synthesis of azoles, which will be discussed in subsection 1.3.2, has been studied scarcely and described in only 6 publications, whereas cyclic *α*-hetaryl-*β*-enaminonitrile has been used only once.

1.3.1. Reactions of acyclic α-hetaryl-β-enaminonitrile with 1,2-binucleophiles

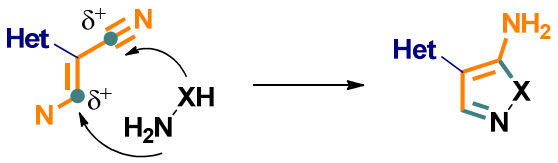
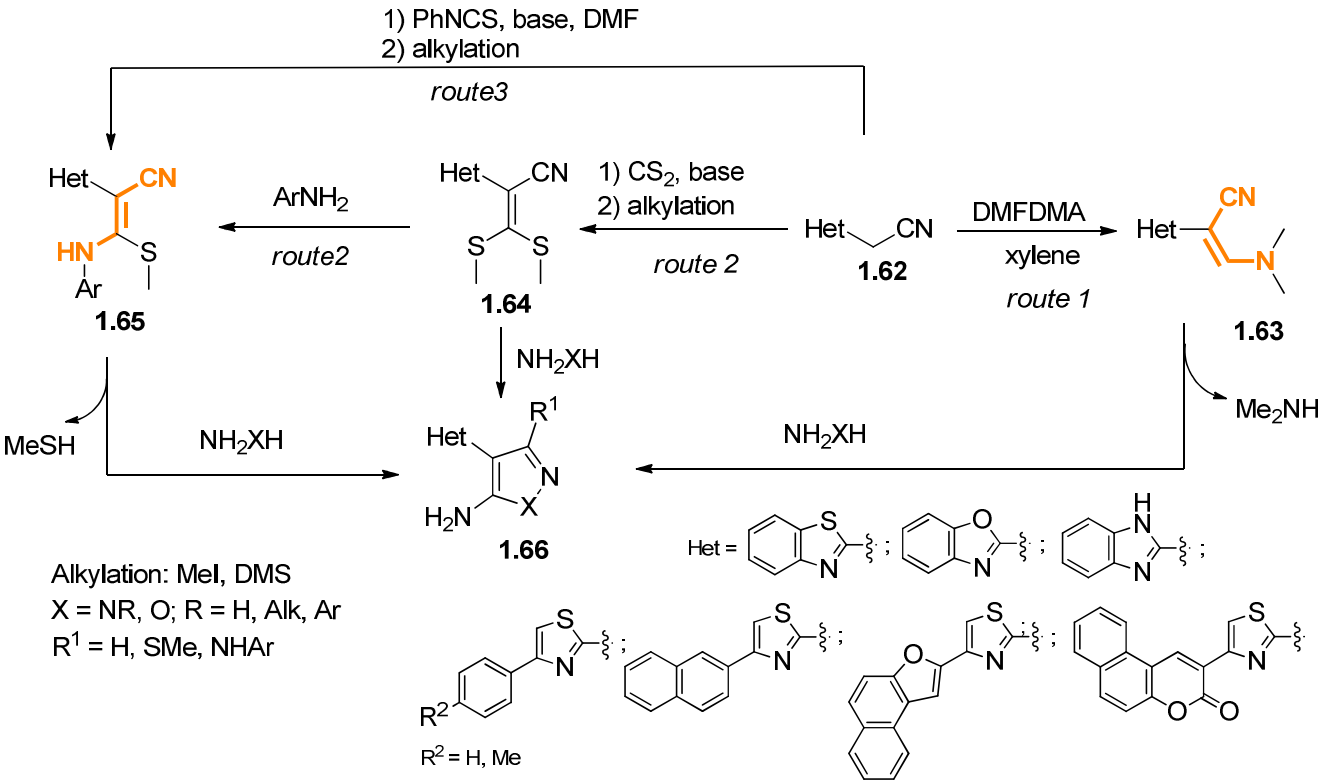


Figure 1.3. *A schematic representation of the synthesis of 4-hetaryl-5-aminopyrazoles from acyclic α-hetaryl-β-enaminonitriles.*

A series of works devoted to the synthesis of 4-hetaryl-5-aminopyrazoles from acyclic *α*-hetaryl-*β*-enaminonitriles has been reported (*Figure 1.3*).[50-57]

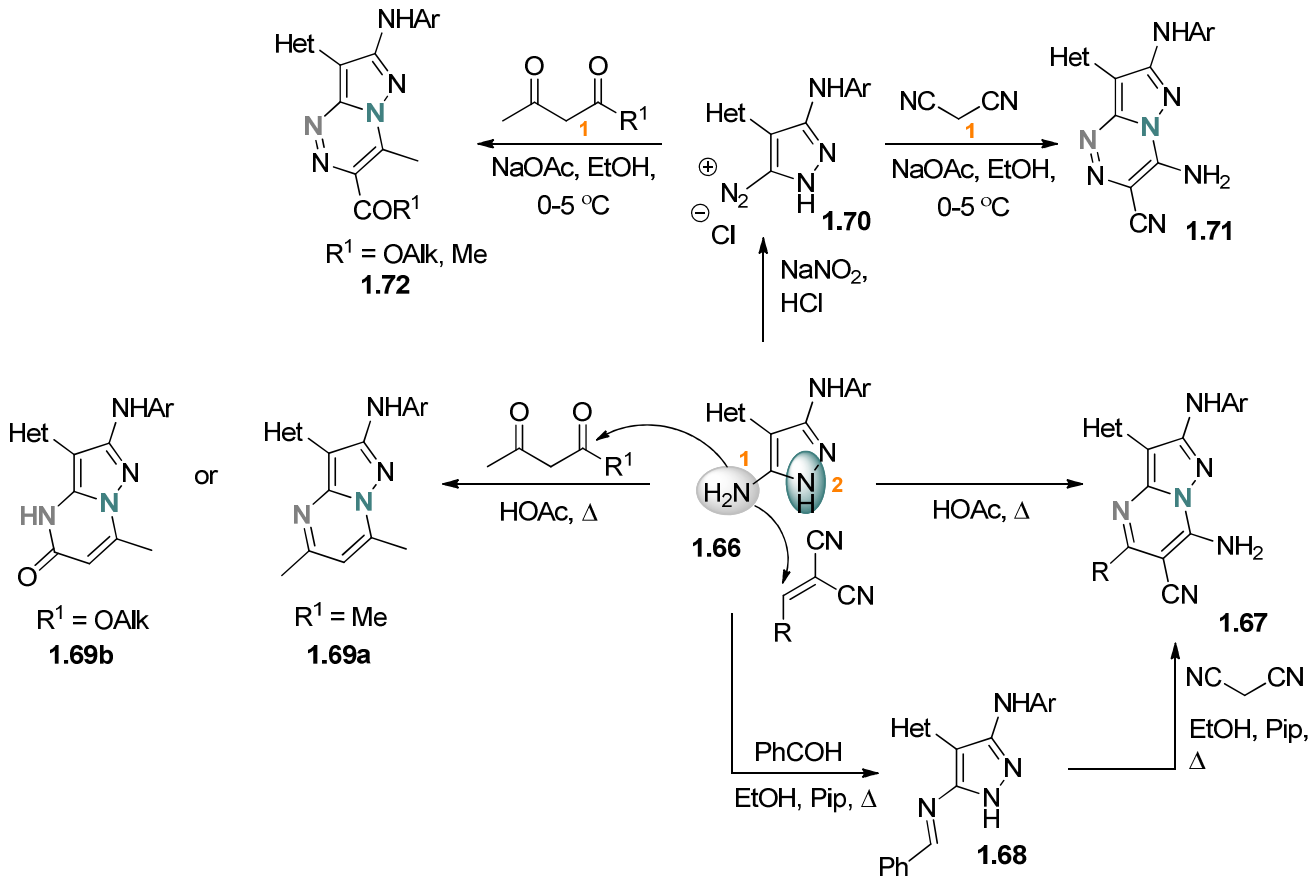
Synthesis started with the functionalization of the methylene group of hetarylacetonitrile **1.62**. The necessary precursors, *i.e.* α-hetaryl-β-enaminonitriles, can be synthesized in three ways: 1) the reaction with dimethylformamide dimethylacetal (DMF DMA) leading at 2-hetaryl-3-(dimethylamino)acrylonitrile **1.63** (*Scheme 1.24, route 1*); 2) the reaction with carbon disulfide followed by alkylation and the substitution of one methylthiol group by arylamine (*Scheme 1.24, route 2*); or 3) reaction with isothiocyanate followed by alkylation (*Scheme 1.24, route 3*) for the preparation of 2-hetaryl-3-(methylthio)-3-(phenylamino) acrylonitrile **1.65**. The subsequent cyclization with hydrazines (hydroxylamine) results in 4-hetaryl-5-amino-pyrazoles (isoxazoles) **1.66**.



Scheme 1.24. *Strategies for the preparation of 4-hetaryl-5-aminoazoles* ***1.66.***

The obtained azoles have functional groups, that can be converted into various heterocyclic frames by reactions with the appropriate reagents; thereby, this method opens a range of new ways for creating potentially biologically active compounds. Thus, in the above-mentioned works were described transformations involving the aromatic exo-amino group and the pyrazole nitrogen. The authors state that in the first step aromatic amino group was involved into the reaction, and secondly, the

cyclization occurs at the pyrazole nitrogen atom. More transformations are presented on *Scheme 1.26*.

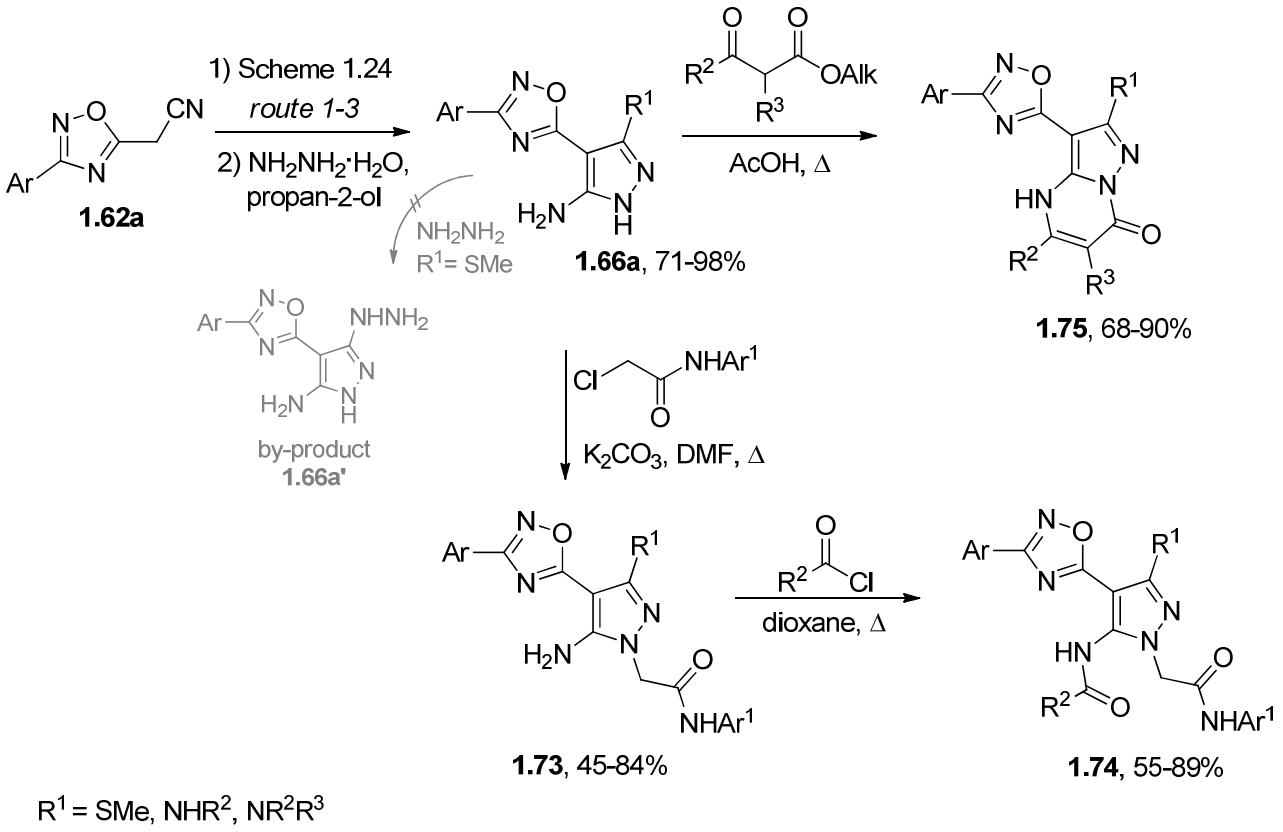


Scheme 1.26. *Modifications of pyrazoles* ***1.66****.*

5-NH_2-Group of pyrazole **1.66** adds to the activated double bond by the Michael reaction to form the pyrazolo[1,5-*a*]pyrimidine **1.67**. Alternatively, the latter can be obtained in two steps through the preparation of Schiff base **1.68**, followed by its reaction with malononitrile. Pyrazolo[1,5-*a*]pyrimidines **1.69a,b** can be prepared by reaction of pyrazoles **1.66** with *β*-diketones or *β*-ketoesters. When using the latter compound, the nucleophilic attack of the amino group occurs on the ester carbon atom. Diazonium chloride **1.70** formed by the reaction of the diazonation of the amino group, reacts with methylene active compounds to form the pyrazolo[5,1-*c*][1,2,4]triazines **1,71**, **1.72**. In this case, the diazo group such as electrophile, meanwhile *β*-diketone or *β*-ketosester acts as the nucleophile.

In 2009 report has appeared opening a way to the synthesis of combinatorial libraries of 5-(1*H*-4-pyrazolyl)-[1,2,4]oxidiazole (*Scheme 1.27*).[46] The authors of the

article synthesized more than 1000 compounds using the parallel liquid phase synthesis.



Scheme 1.27. *Parallel liquid-phase synthesis of combinatorial libraries of 5-(1H-4-pyrazolyl)-[1,2,4]oxidiazoles.*[3]

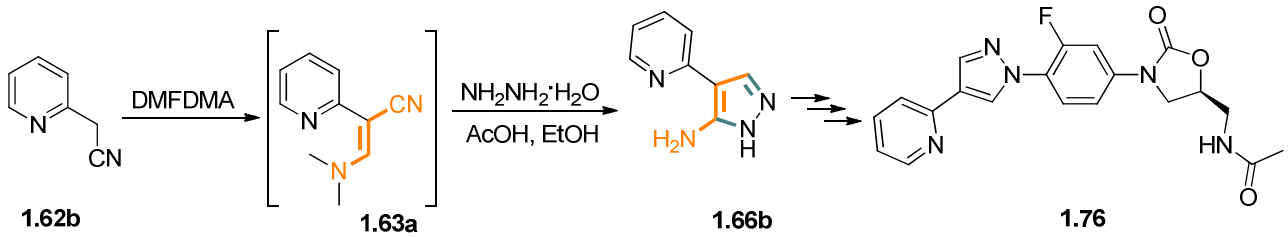
Using route 2 (*Scheme 1.24*) precursors of pyrazoles 3-(methylthio)-3-(arylamino)-2-(thiazol-2-yl)acrylonitrile **1.65** were obtained in a reaction of oxadiazolylacetonitrile **1.62** with CS_2 followed by methylation and substitution of one methylthiol group by the amino moiety. Using this approach, it is possible to synthesize pyrazoles with a large variety of 3-NR^1R^2 substituents in the core and to avoid the use of toxic isothiocyanate. The authors note, that using the excess of hydrazine hydrate in the cyclization reaction leads to the formation of a by-product **1.66a'** (in the case of R^1 = SMe) which cannot be obtained by the reaction of pyrazole **1.66a** with hydrazine. Consequently, a side reaction occurs at the stage of addition of two molecules of hydrazine to acyclic (bis(methylthio)vinyl)hetaryl **1.64**, preceding the cyclization step.

[3] The decryption of the substituents R^2-R^3, Ar^1 is not given, since the article is devoted to combinatorial synthesis with large number of variants. For more information, please refer to the article [46]

The first step of the combinatorial synthesis was a regioselective alkylation by the pyrazole N-1 position with 2-chloroacetamides, which terminates with the formation of acetamides **1.73**. The next acylation takes place on the aromatic amino group and leads to the formation of monoacyl derivative **1.74** in the case of using acyl chlorides. If anhydrides were used, no double acylation is occuring. Reaction with acetoacetates is carried out under standard conditions via boiling in acetic acid media, which led to the pyrazolo[1,5-*a*]pyrimidines **1.75**.

α-Hetaryl-*β*-enaminonitriles have also become precursors in the synthesis of new oxazolidinone compounds that are candidates for the treatment of diseases caused by resistant gram-positive bacteria, such as methicillin-resistant Staphylococcus aureus, penicillin-resistant Pneumococcus (Streptococcus pneumonia) and vancomycin-resistant Enterococcus faecalis.[58-59]

Among the synthesized compounds, the highest activity was shown by (*S*)-*N* -((3-(3-fluoro-4-(4-(pyridin-2-yl)-1*H*-pyrazol-1-yl)phenyl)-2-oxo-oxazolidine-5-yl) methyl)acetamide **1.76**;[58] for this compound, an industrial 7-stage synthetic method was developed, providing a 27.6% total yield; in this sequence, the key intermediate was 3-(dimethylamino)-2-(pyridin-2-yl)acrylonitrile **1.63a** (*Scheme 1.28*).



Scheme 1.28. *3-(Dimethylamino)-2-(pyridin-2-yl)acrylonitrile* ***1.63a*** *the key intermediate in an industrial method for a synthesis of an antibiotic* ***1.76****.*

Thus, acyclic 2-hetaryl-3-enaminonitrile were starting compounds to prepare 4-hetaryl-5-aminopyrazoles. Well-studied cyclizations, involving the exo-amino group and the pyrazole nitrogen atom, were used to obtain the compounds with potential biological activity.

1.3.2. Reactions of cyclic β-enaminonitrile with 1,2-binucleophiles

If an acyclic enaminonitrile is used, then methylthiol or dimethylamine acts as the leaving group in the course of the synthesis of pyrazoles; alternatively, in the case of cyclic analogues, the nucleofuge is *ω*-aminoalkyl (*Figure 1.4*).

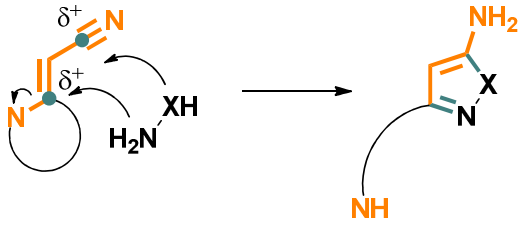
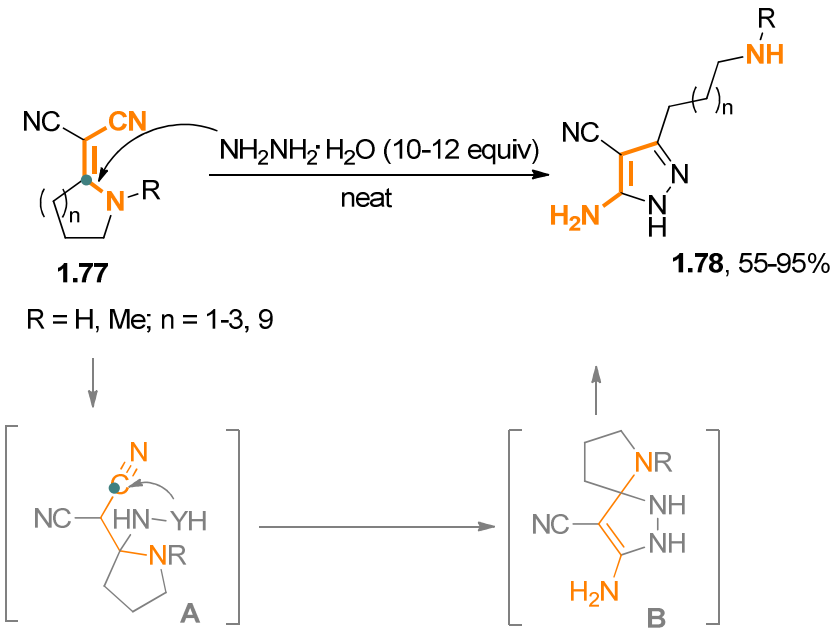


Figure 1.4. *Schematic representation of the synthesis of 3-ω-aminoalkyl-5-aminopyrazoles from cyclic β-enaminonitriles.*

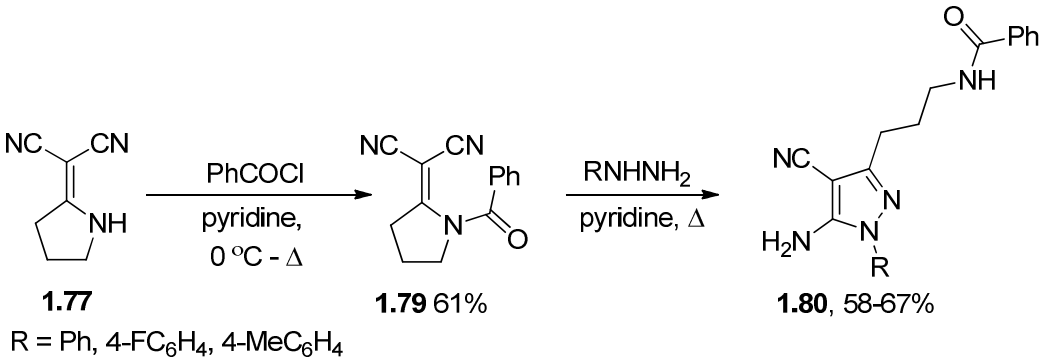
The first article, which describes the reactions of cyclic *β*-enaminonitrile with nucleophiles, was published by *M. Patzel* et al. in 1991.[60] According to the authors, the cyclic *β*-enaminonitriles are more stable than their acyclic analogues. Thus their reaction with hydrazine hydrate does not occur upon heating in alcohol, DMF, acetic acid. In all cases, the starting 2-(1-R-pyrrolidin-2-ylidene)malononitrile was isolated. Only refluxing in a 10-12-fold excess hydrazine hydrate provided 5-amino-3-(3-(R-aminopropyl)-1*H*-pyrazole-4-carbonitrile **1.78** (*Scheme 1.29*). It is also stated on that the reaction cannot be carried out either with arylhydrazines or with derivatives of **1.77**, in which one of the cyano groups is substituted by the ester moiety. It was also shown that 2-(dihydrofuran-2(3*H*)-ylidene)malononitriles undergo the same recyclization in milder conditions.

The reaction mechanism involves the nucleophilic attack of nitrogen atom of the enamine C-2 atom of pyrrolidine **A** in the first step, followed by an intramolecular attack of the second nucleophilic atom, namely carbon of the nitrile group with subsequent formation of spiro-intrameditate **B**. The pyrrolidine ring-opening step causes the aromatisation of the pyrazole core and the formation of the *ω*-aminoalkyl chain. This reaction mechanism was named ANSARO (Addition of Nucleophile – Spiro Annulation – Ring opening) (*Scheme 1.29*).[61-62]



Scheme 1.29. *The first synthesis of pyrazoles from cyclic β-enaminonitrile. The mechanism of reaction (ANSARO).*

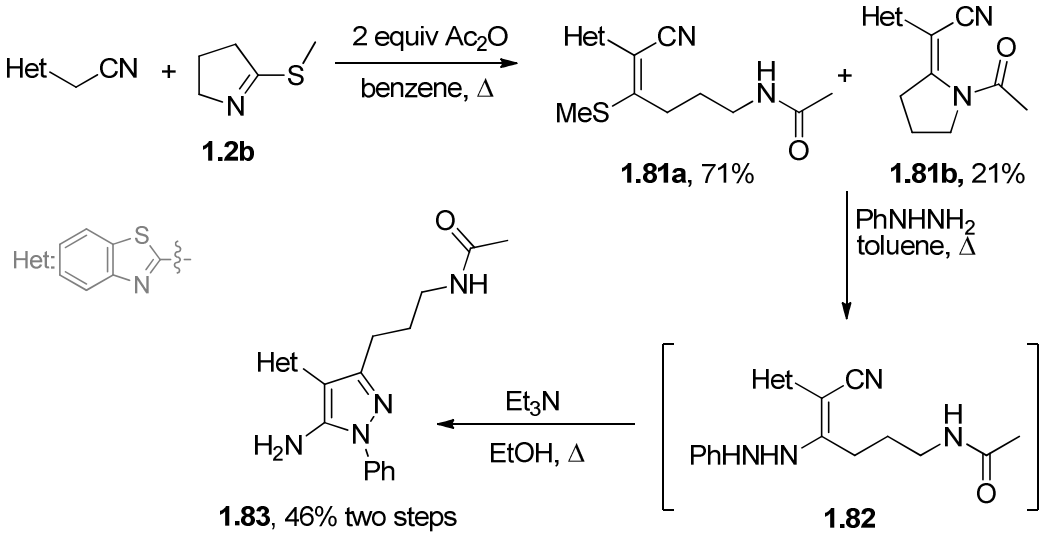
To facilitate the ring opening of cyclic *β*-enaminonitrile reactions under the action of binucleophiles, *K. Shvydenko et al.* proposed the introduction of electron-withdrawing group to pyrrolidine nitrogen atom, which was envisaged to increase the electrophilicity of the neighbour carbon atom.[63] Indeed, the *N*-benzoyl derivative of pyrrolidine **1.79** was obtained by the reaction of 2-(pyrrolidin-2-ylidene)malononitrile **1.77** with benzoyl chloride; this compound was involved in the reaction with arylhydrazines in boiling pyridine media, which gave the *ω*-benzoylaminoalkyl pyrazoles in satisfactory yields **1.80** (*Scheme 1.30*).



Scheme 1.30. *Activation of β-enaminonitrile* ***1.77*** *by introducing an electron-withdrawing substituent into the N-1 position.*

An interesting method for obtaining pyrazoles from a mixture of cyclic and acyclic *β*-enaminonitrile was presented in the work by the same authors, which consists in an *in situ* activation of the C-2 position.[10]

The reaction of thioimidate **1.2b** with benzo[*d*]thiazol-2-ylacetonitrile in the presence of 2 equiv of acetic anhydride led to the mixture of products, which are directly ending in the subsequent reaction with hydrazine (*Scheme 1.31*). The first nucleophile attack occurs at the vinyl carbon atom and is accompanied either by the substitution of the methylthio group (in the case of **1.81a**) or by the pyrrolidine ring opening (in the case of **1.81b**) to form a common intermediate with the same structure **1.82**. When the latter was boiling in ethanol in the presence of triethylamine, *N*-(3-(5-amino-4-(benzo[*d*]thiazol-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)propylacetamide was obtained **1.83**.



Scheme 1.31. *Formation of pyrazole ring* ***1.83*** *from a mixture of cyclic and acyclic β-enaminonitriles* ***1.81****.*

For the preparation of pyrazoles with the branched *ω*-aminoalkyl chain, which are potent glutamate receptor antagonists (*Figure 1.5*) *D. Young et al.*[64] also used recyclization method for the cyclic *β*-enaminonitrile bearing stereogenic centres in the 3[d] and 5th position of the pyrrolidine ring (*Scheme 1.32*).

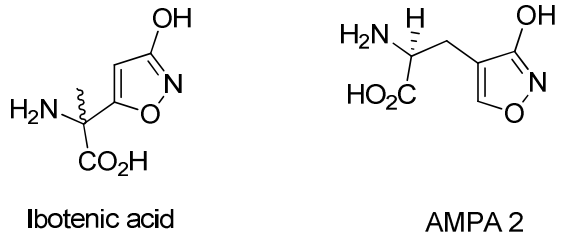


Figure 1.5. a) *Biologically active substances of glutamate receptors.*

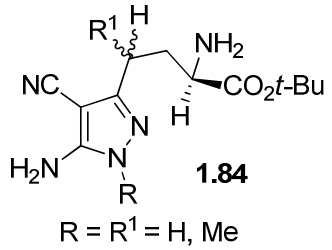
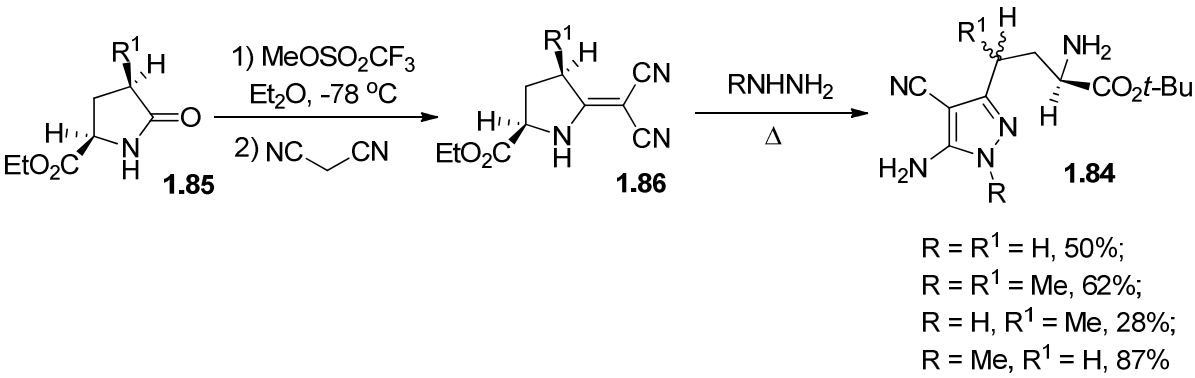


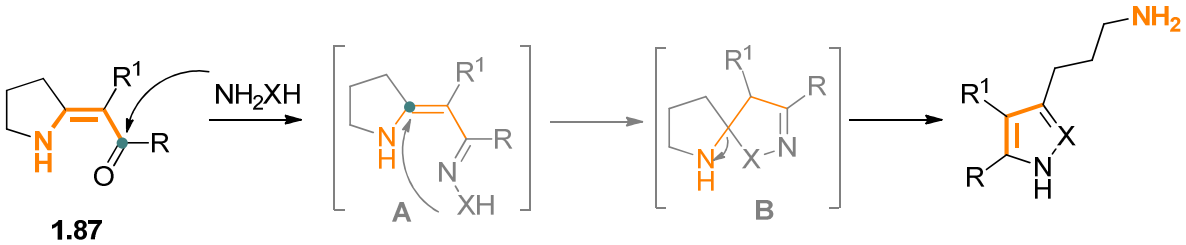
Figure 1.5. b) *Potential glutamate receptor antagonists.*



Scheme 1.32. *Synthesis of pyrazoles with branched ω-aminoalkyl chain* ***1.84****.*

In the case of 3-substituted pyrrolidines, an epimerization occurred during the reaction with hydrazine, thus, compound **1.84** was obtained as a mixture of epimers.

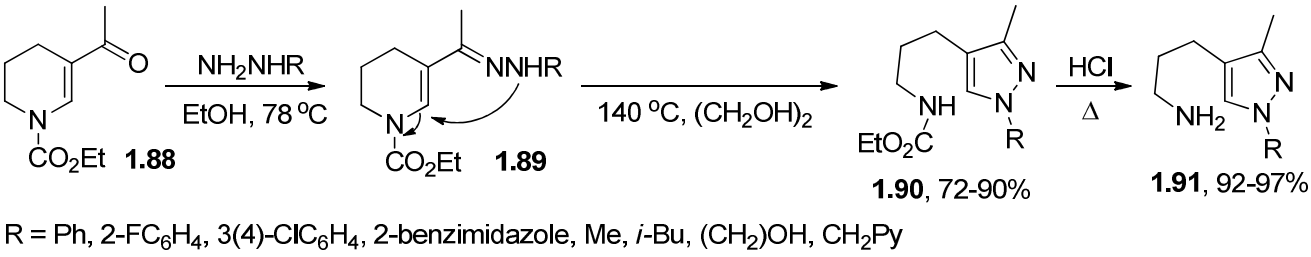
Compared to the mechanism shown in *Scheme 1.29*, another sequence of nucleophile attacks is observed for *β*-enaminones with general formula **1.87** which are analogues of *β*-enaminonitriles. First, the reaction of a 1,2-nucleophile with a carbonyl carbon atom takes place with the formation of an intermediate **A**, followed by the Michael addition of a second nucleophile atom (*Scheme 1.33*).[62, 65]Cyclic *β*-enaminones have been repeatedly used in the synthesis of 3-(*ω*-aminoalkyl/phenyl alkyl)azoles.[61, 66-67]



Scheme 1.33. *The mechanism of the reaction of β-enaminones* ***1.87*** *with 1,2-binucleophiles.*

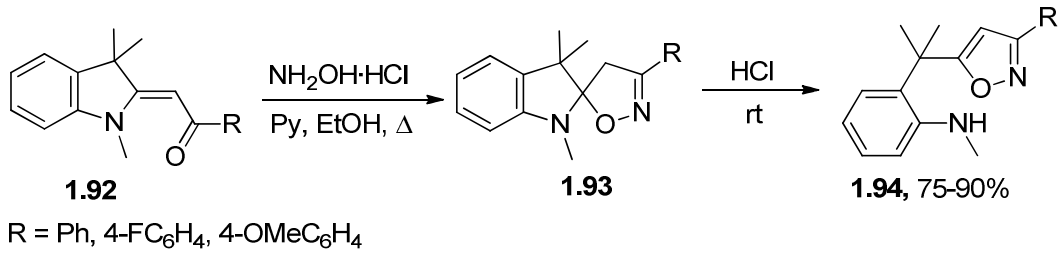
Thus, 5-acetyl-3,4-dihydropyridine **1.88** reacts with variously substituted hydrazines: aromatic, aliphatic, heterocyclic with the formation of 4-*ω*-

aminoalkylpyrazoles **1.90** (*Scheme 1.34*).[66] Cyclization occurs under harsh conditions, *i.e.* in ethylene glycol at 140 °C. By performing the reaction in ethanol at 78 °C, it is possible to isolate an intermediate hydrazone **1.89**. According to the authors, the reaction occurred regioselectively, due to *N*-ethoxycarbonyl protection of the amino group of the substrate **1.88**. Successful removal of the protective group and the formation of pyrazoles **1.91** occurred at the last step of the reaction with 92-97% yield upon heating in concentrated hydrochloric acid.



Scheme 1.34. *The regioselective transformation of β-enaminones* ***1.88*** *into 4-ω-aminoalkyl pyrazoles* ***1.90****.*

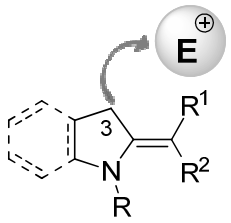
The benzo analogues of 1-aryl-2-(1,3,3-trimethyl-indolin-2-ylidene)ethanones **1.92** are converted to the corresponding dihydroisoxazole **1.93** *via* the reaction with hydroxylamine. Further treatment with concentrated hydrochloric acid, gives the products of the ring opening **1.94** with 75-90% yield (*Scheme 1.35*).[67]



Scheme 1.35. *Synthesis of aminophenylalkyl isoxazoles* ***1.94****.*

Consequently, the reactions of cyclic 3-enaminonitriles with 1,2-binucleophiles lead to the formation of *ω*-aminoalkylpyrazoles. In the absence of C-2 activation, the reaction takes place under harsh conditions (an excess of 1,2-binucleophile, at high temperatures). Reactions of cyclic 2-hetaryl-3-enaminonitriles are presented in only one publication, where they were subjected to the reactions with 1,2-binucleophiles in the presence of their acyclic analogues in the mixture.

1.4. Reactions of 2-(1-R-pyrrolidin/indolin-2-ylidene)acetonitriles with *C*-electrophiles in the synthesis of fused heterocyclic systems

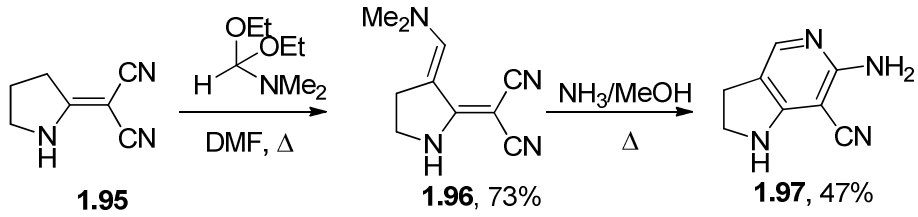


1.1 – *pyrrolidin-2-ylidene*
1.28a – *indolin-2-ylidene*

The C-3 position of the pyrrolidine ring exhibit electron-deficient character as a result of the acceptor effect of the 2-acrylonitrile fragment and can react with electrophiles via base catalysed process. 2-(1-R-Indolin-2-ylidene)acetonitriles **1.28a** are more active compared to 2-(1-R-pyrrolidin-2-ylidene)acetonitriles **1.1**. In addition to the two electron withdrawing groups in the side chain of compounds **1.28a**, they also contain a benzene ring, which additionally makes the C-3 position more acidic.[68]

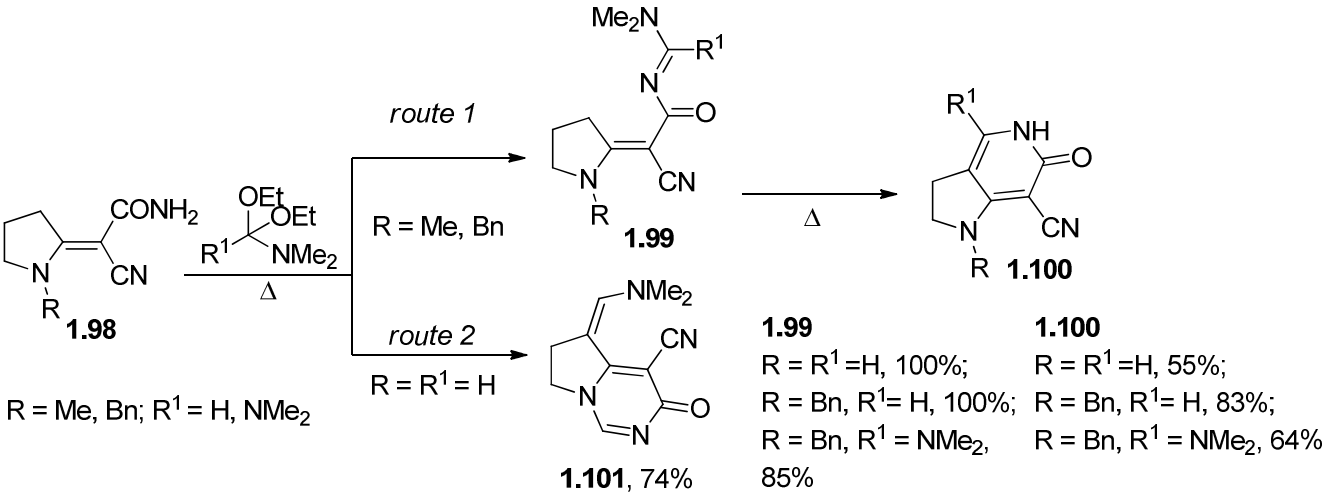
The reactions of 2-(1-R-pyrrolidin/indolin-2-ylidene)acetonitriles (**1.1**, **1.28a**) with dimethylformamide dialkylacetal and orthoesters have been studied. They result in the formation of pyrrolidines containing masked aldehyde group in the 3rd position of the cycle or in the side chain. Such systems were found to be precursors of pyrrolo[3,2-*c*]pyridines **1.97**, **1.100**, which are modified analogues of purine bases and pyrrolo-pyrimidine bases that are involved in the nucleic acid metabolism.[69]

2-(Pyrrolidin-2-ylidene)malononitrile **1.95** reacts with dimethylformamide diethylacetal (DMF DEA) to form 2-(3 -((dimethylamino)methylene)pyrrolidin-2-ylidene)malononitrile **1.96**, which upon aminolysis in the autoclave formes pyrrolo[3,2-*c*]pyridines **1.97** in 34% total yield (*Scheme 1.36*).[70] During the process, the dimethylamino group is eliminated.



Scheme 1.36. *Synthesis of pyrrolo[3,2-c]pyridines **1.97** via the formation of a derivative with the masked aldehyde group **1.96**.*

In the case of enaminoamides **1.98**, the reaction with DMF DEA or with tetramethylurea diethylacetal is taking place at the amide group of the side chain to form diene diamines **1.99** (*Scheme 1.37*).[1, 69, 71-72]

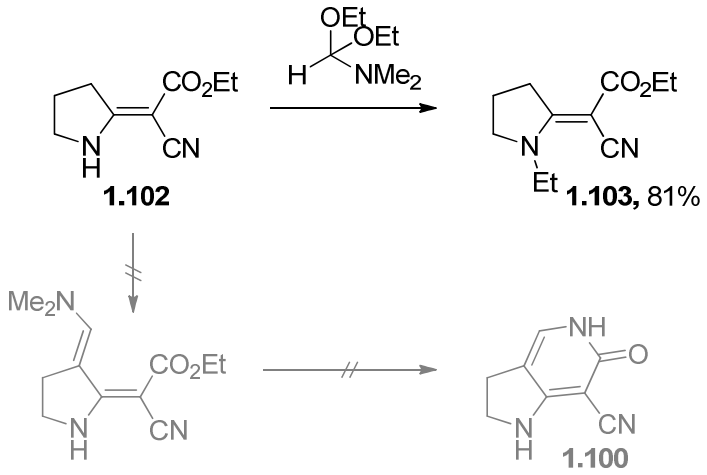


Scheme 1.37. *Reaction routes of enaminoamide* ***1.98*** *and C-electrophiles depending on the substituents at the pyrrolidine nitrogen.*

The subsequent heating contributes to the intramolecular condensation between the amidine carbon atom with the partial positive charge increased by the conjugation with the adjacent acetyl group, and activated methylene moiety of pyrrolidines. As a result of the reaction, derivatives of pyrrolo[3,2-*c*]pyridine-6-one **1.100** were obtained (*Scheme 1.37, route 1*). In the case of unsubstituted pyrrolidines **1.98** (R = H), the reaction with acetal proceeds in a different manner. Thus, the closure of the pyrimidine cycle happened in the first step by heating with DMF DEA followed by the nucleophilic attack of the pyrrolidine NH group at the amide carbon atom; the second equivalent of DMF DEA reacts with the CH_2 group at position 3.[72] In this case, the only reaction product was 5-((dimethyamino) methylene)-3-oxo-3,5,6,7-tetrahydropyrolo [1,2-*c*] pyrimidine-4-carbonitrile **1.101** obtained in 74% yield (*Scheme 1.37, route 2*).

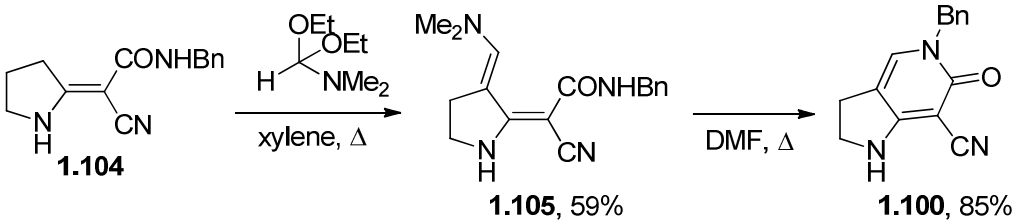
Interestingly, in an attempt to synthesize pyrrolo[3,2-*c*] pyridine-6-one **1.100** by an alternative route starting with ethyl 2-cyano-2-(pyrrolidin-2-ylidene)acetate **1.102**, the only product obtained was 1-ethylpyrrolidine **1.103** (*Scheme 1.38*).[1] Neither the temperature rise nor the increase of DMF DEA concentration result in the formation of condensation product at the third position of the pyrrolidine ring. Attempts to

introduce the acetyl protection at NH group (by reaction with acetic anhydride, acetyl chloride, methylisocyanate) resulted only in the isolation of starting enaminonitrile **1.102**.



***Scheme 1.38**. The reaction of 2-cyano-2-(pyrrolidin-2-ylidene)acetate **1.102** with DMF DEA*

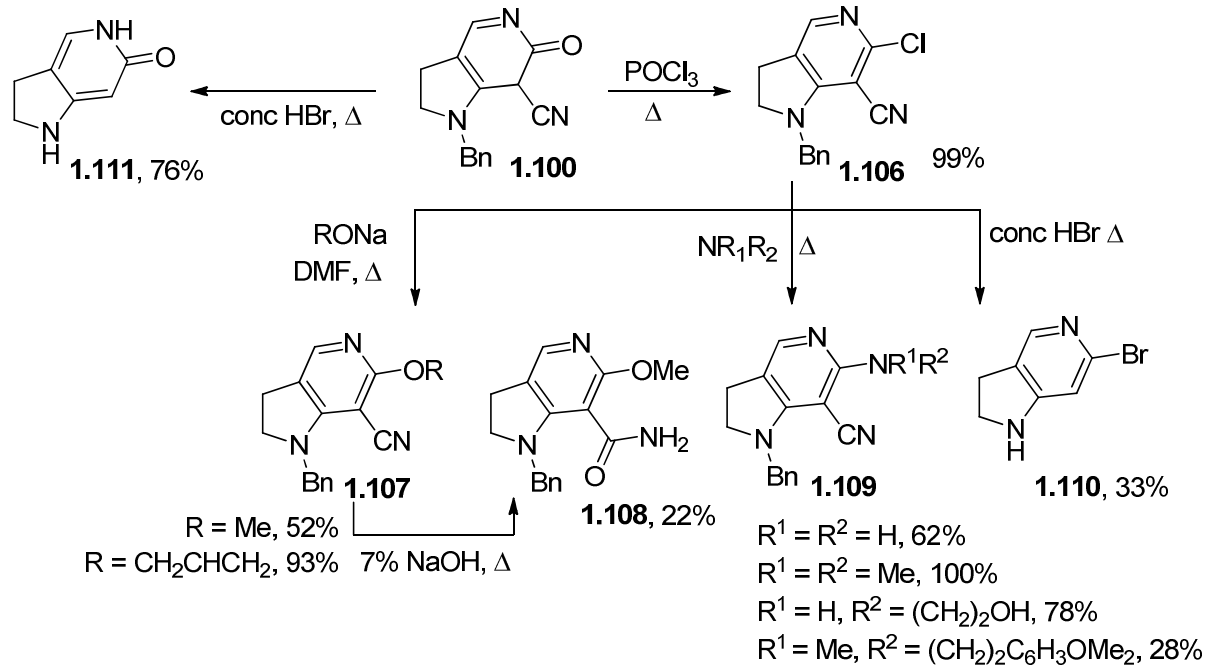
The reaction of DMF DEA with **1.104** occurs similarly to the reaction depicted in *Scheme 1.36*, namely through condensation by C-3 position of pyrrolidine to form diene diamine **1.105**, which was transformed by the condensation reaction to 5-benzyl-6-oxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-7-carbonitrile after prolonged heating. **1.100** (*Scheme 1.39*).[73]



***Scheme 1.39**. Carbamide **1.104** in the reaction with DMF DEA.*

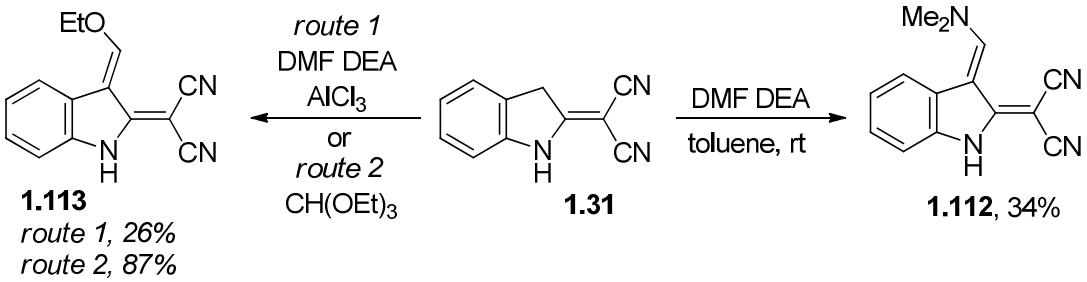
Pyrrolo[3,2-*c*]pyridin-6-ones **1.100** react with phosphorus oxychloride in order to prepare 2-chloropyridines **1.106**, which subsequently react with *O*- and *N*-nucleophiles.[1, 74] Nitrile group of 1-benzyl-6 methoxy-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine-7-carbonitrile **1.107** was hydrolized only by prolonged boiling (119 h) in a 7% NaOH solution to the correspoding amide derivative **1.108** in 22% yield. The *N*-debenzylation reaction and decyanation were carried out by boiling in concentrated

hydrobromic acid to form 6-bromopyrolo[3,2-*c*]pyridine **1.110** and pyrrolo[3,2-*c*]pyrid-6-one **1.111** (*Scheme 1.40*).



Scheme 1.40. *Modifications of pyrrolo[3,2-c]pyridine-6-one* ***1.100****.*

Reactions of benzo analogues of pyrrolidine acetonitriles with C-nucleophiles are described only for 2-(indolin-2-ylidene)malononitrile **1.31** in the *Granik et al.* publication.[26] By the reaction of the latter compound with the DMF DEA, the crude product **1.112** was obtained in 90% yield; but the amount of isolated product after thorough purification is dramatically decreased to 34% yield.

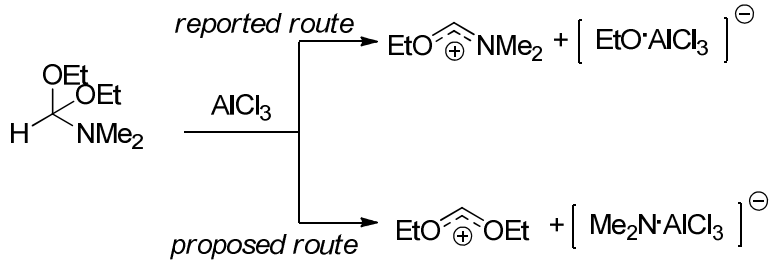


Scheme 1.41. *Reactions 2-(indolin-2-ylidene)malononitrile* ***1.31*** *with C-nucleophiles.*

Due to the low yield of the target product an $AlCl_3$ catalysis was used[75], notably, the reaction took place in a different way. In particular the formation of 3-ethoxymethylene **1.113** (26% yield) instead of 3-dimethylaminomethylene **1.112** was

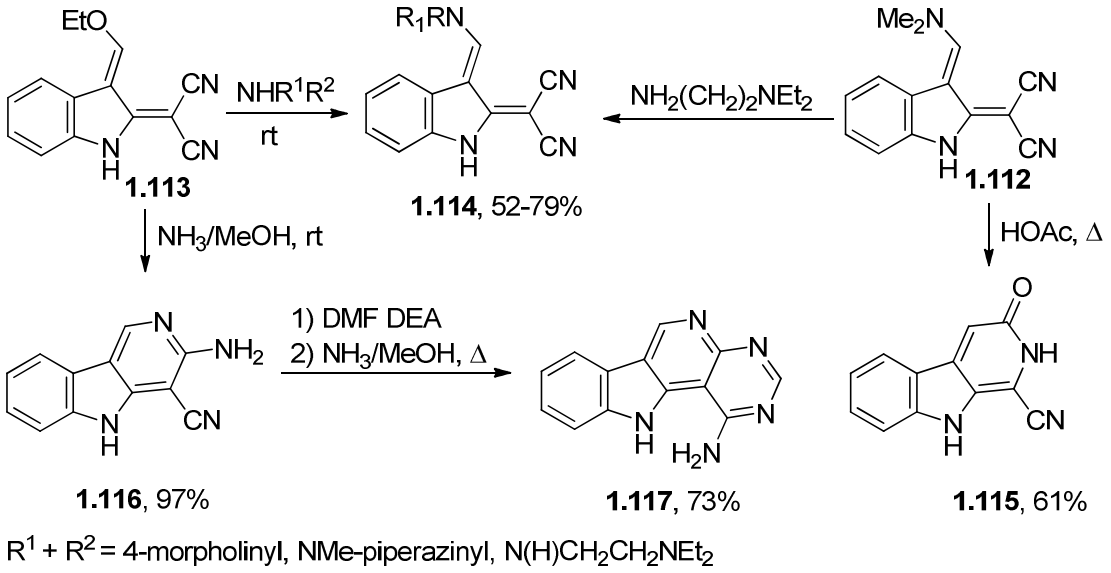
observed. The same product **1.113** was obtained by condensation reaction **1.31** with triethylorthoformiate (87% yield); *Scheme 1.41*.

It is assumed that in this case, $AlCl_3$ catalyses the cleavage of the dimethylamino group from DMF DEA, in contrast to the previously described catalytic sequence (*Scheme 1.42*).[75]



Scheme 1.42. *The mechanism of $AlCl_3$ catalysis.*

According to the known literature procedures,[76] ethoxymethylene derivatives are more active in the reactions with nucleophiles, than enamines. Thus, ethoxymethylene nitrile **1.113** reacts with primary and secondary amines in mild conditions with good yields (62-79%) providing compounds **1.114**, while dimethylmethylene derivatives are reacting only with privary amines (52%). Upon heating in acetic acid, cyclization of **1.112** led to 4-cyano-2,3-dihydropyrido[4,3-*b*]indole-3-one **1.115**.



Scheme 1.43. *Modifications of 2-(3-ethoxymethylene)* ***1.113*** */ 2-(3 -((dimethylamino)methylene)indolin-2-ylidene)malononitrile* ***1.112****.*

The reaction of **1.113** with the alcoholic ammonia solution gave 3-amino-4-cyanopyrido[4,3-*b*]indole **1.116**, which primary amino group is located in the *α*-position to the nitrile group in the pyridine ring; this makes possible to carry out cyclization reactions, that provides tetracyclic amides **1.117** (*Scheme 1.43*).

To conclude, the reactions with C-electrophiles takes place 1) at the third position of the pyrrolidine ring, followed by cyclization on the nitrile or carbonyl moiety, or 2) at the amide side chain group, followed by the cyclization at C-3 or 1-NH position of pyrrolidine. The resulting pyrolopyridines and pyrolopyrimidines can be subjected to various modifications of their functional groups allowing various decorations to pursue SAR studies.

1.5. Complexes based on 2-(pyrrolidin-2-ylidene)acetonitrile and their benzo analogues

2-(Pyrolidine-2-ylidene)acetonitriles can act as bidentate ligand due to the close spatial arrangement of two donor nitrogen atoms connected by a bridge of three carbon atoms. Such a feature is used to create BF_2-rigidified complexes that are similar to BODIPY dyes, as well as metal complexes for the asymmetric catalysis and copolymerization reactions.

1.5.1. Synthesis and application of BF_2-rigidified complexes

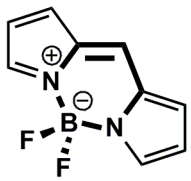


Figure 1.5. *BODIPY core*

Among heterocycles capable of forming boron-containing complexes, the dominant position is taken by dipiromethene derivatives. By the reaction with boron trifluoride diethyl etherate, the latter compounds form boron-dipiromethenes – BODIPY (*Figure 1.5*). This structural framework is based on the class of dyes, discovered by Treibs and Kreuzer in 1968.[77]

The interest of the unique properties of BODIPY-dyes (high quantum yields, stability in physiological conditions, narrow absorption and emission bands (*Figure*

1.6) has grown over time; thus, up to 2018, 4995 articles have already been published on BODIPY[4].

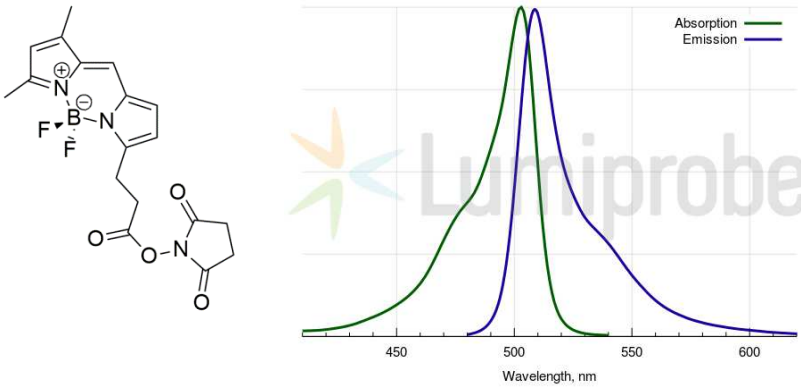


Figure 1.6. *Classic spectrum of BODIPY dye (λabs = 503 nm, λem = 509 nm, ε = 80000, Φ = 90%)*[5]

The class of BODIPY dyes is used for biomolecules labelling and for studying their distribution in cells/tissues *in vitro* and *ex vivo*. Such studies have high accuracy, since the fluorescence spectroscopy method has a high sensitivity (10^{-9}-10^{-12} M) and high spatial resolution (1 μm). On the other hand, the use of fluorescence methods for *in vivo* studies is limited to the depth of penetration of the emitted light (≤ 1 cm). The resulting signal is blurred due to the partial scattering and absorption of light by body fluids, water and tissues.[78] There are two ways to resolve the problem: 1) the synthesis of dyes, which emit the light within the optical window in the infrared spectral region (650 - 900 nm), or 2) use a method, not fluorescence based, that involves the emission of photons of greater energy, which, accordingly, increases the depth of light penetration.

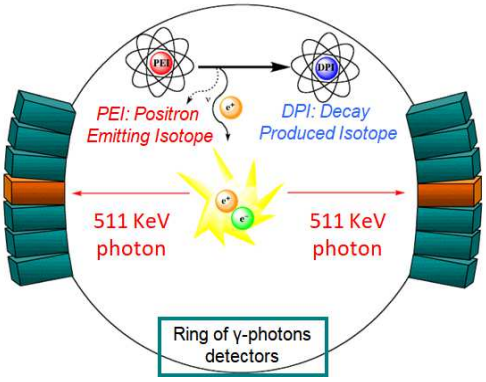


Figure 1.7. *Schematic representation of the mechanism of positron emission tomography.*

A such method is the positron emission tomography

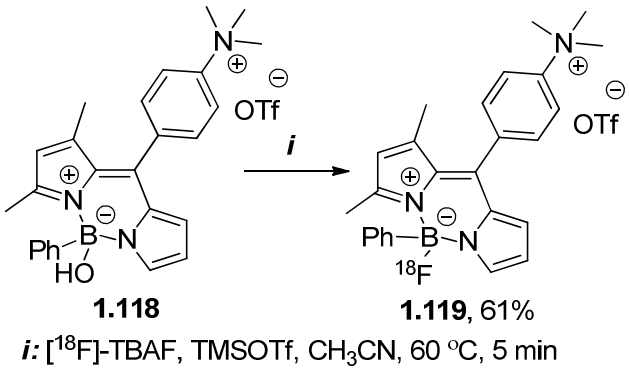
[4] according to the Web of Science portal
[5] http://www.lumiprobe.com

(PET) based on the radioactive decay of a positron-emitting nucleus (^{11}C, ^{18}F etc.). The positrons formed during decay annihilate with the electron of surrounding tissues and form two photons with 511keV energies directed at an angle of 180° to each other. High-energy particles are detected by a PET scanner (*Figure 1.7*). The method is characterized by unlimited depth of penetration, high sensitivity (10^{-11}–10^{-12} M), but lower resolution – 1-2 mm, compared with fluorescence spectroscopy of 1 μm.

The combination of PET and fluorescence spectroscopy methods offset the shortcomings of each other and is a basis for the creation of a bimodal probe.

The presence in the structure of BODIPY BF_2 group, which could be a site for introducing an isotope label – [^{18}F], makes dyes attractive bimodal probe precursors.

The idea of preparation of the bimodal probe based on BODIPY was first presented in 2011 by *Gabbai et al.*[79] The authors proposed an introduction of [^{18}F] into the compound **1.118** by exchanging the OH group connected to the boron atom with drained by azeotropic distillation tetrabutylammonium fluoride ([^{18}F]-TBAF) in the presence of a strong Lewis acid, namely trimethylsilyl trifluoromethanesulfonate (TMSOTf) (for binding water residues) in acetonitrile at 60 °C. The reaction was completed within 5 minutes with 61% yield of [^{18}F]-BODIPY **1.119** (*Scheme 1.44*).



Scheme 1.44. *Radiofluorination of BODIPY dye.*

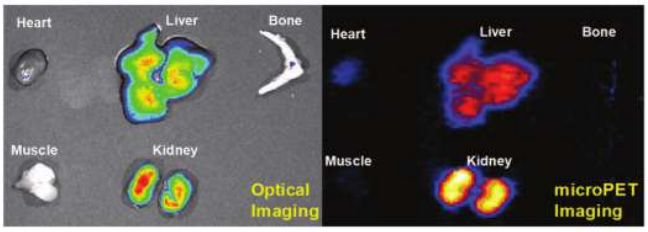


Figure 1.8. *Ex vivo mouse organ visualization by fluorescence spectroscopy (left) and microPET (right). Injection of dye* ***1.128*** *– 4 h – photo.*

The authors used the synthesized radioactive dye **1.119** to investigate its *ex vivo* binding using fluorescence spectroscopy and PET methods; consequently, they have obtained satisfactory results on the stability and selectivity of binding, as well as a

high correlation between the results of fluorescence spectroscopy and PET analysis (*Figure 1.8*).

Subsequently, novel methods have been developed, which allow the direct exchange of ^{19}F-^{18}F in BODIPY dyes in the presence of Lewis acids.[80-82] Methods, which allow avoiding azeotropic drying of fluoride ion, are developing to date. For example, cartridges containing boranes with cationic structure – fluoride-ion adherent molecules.[83]

At present, about 30 articles[6] have been published in which BODIPY-dyes are used as bimodal probes.

Despite the intense fluorescence of BODIPY-dyes in the solution, which allows them to be used for biological objects labelling, they almost do not fluoresce in solid state, which prevents their use in the field of organic electronics and photonics, including liquid crystal displays, OLEDs, solar collectors. Weak fluorescence is caused by self-absorption, which is the result of almost complete overlapping of absorption and fluorescence spectra of the dye (Stokes shift is on average 5-30 nm).[84] Small Stokes shifts can also be a problem for the correct interpretation of the signals obtained by labelling of biological objects. *In vivo* studies shows that light scattering may also occur with tissues in addition to the self-absorption; the reason is in a small difference in absorption and radiation maxima, thus, this light can be perceived as emitted one. In order to overcome this disadvantages it would be desirable to access Stokes shift over 80 nm.[85]

There are two ways to increase the Stokes shift: 1) BODIPY dye binding with a molecule capable of emitting light. In this case, BODIPY serves as the antenna that receives the signal, then excited and transmitted the signal to another fluorophore (through space or by bonds), whose wavelength of emitted light is much different from that absorbed one. Such systems are usually efficient, but they have a complex structure that requires multistage synthesis. 2) Desimetrization of the bidentant ligand in the boron complex in order to increase the distinction between the electronic

[6] according to the Web of Science portal

structure of the main and excited states. This approach is simpler in terms of synthesis.[85]

There is a large number of publications devoted to the development of desimetrized dyes based on boroaza cycle (C_3N_2B).[84] However, there are only several studies concerning the molecules containing a structural fragment of 2-functionalized-2-(pyrrolidin-2-ylidene)acetonitrile – BODIPY analogue (*Figure 1.9*).

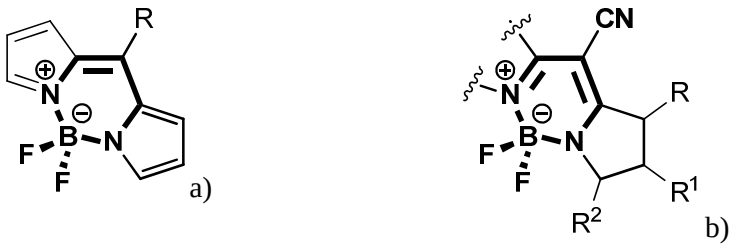


Figure 1.9. *Structural core of BODIPY (on the left) and its analogue - 2-functionalized-2-(pyrrolidin-2-ylidene)acetonitrile (right).*

Desimetrized analogues of BODIPY dyes were studied, namely BF_2 complexes with benzo[*c*,*d*]indole with *N*-heteroarenes, which are interconnected by = N– or =C(CN)– bridges **1.120**, **1.121** (*Figure 1.10*).[86] In this case, there was a large Stokes shift: about 2000 cm^{-1} for **1.129** and about 3000 cm^{-1} for **1.121**, which is much larger than the Stokes shift in BODIPY dyes within 400 – 1000 cm^{-1}.

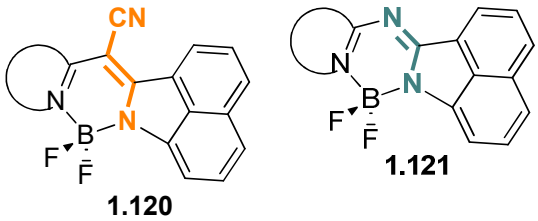
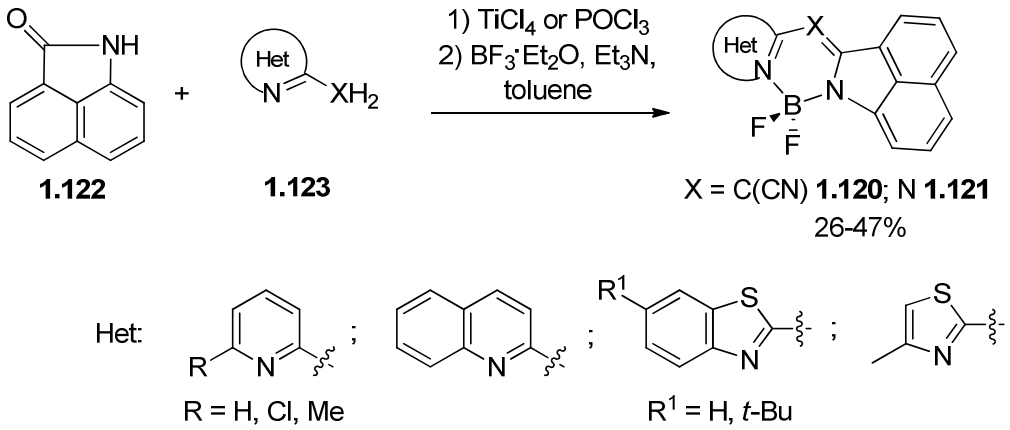


Figure 1.10. *BF_2 fixed compounds of benzo[c,d]indole of N-heteroarenes.*

The authors note that absorption and emission maxima of compounds bearing the electron-withdrawing nitrile group **1.120** is shifted by about 40-70 nm (for absorption) and 10 nm (for emission) into the infrared region comparing to compounds **1.121**. Based on the data obtained in electrochemical studies, the authors explain this shift by reducing the energy gap between HOMO–LUMO **1.120** by about 0.2eV comparing to **1.121**.

One-pot synthesis of dyes **1.120** and **1.121** have been developed by condensation of commercially available benzo[*c*,*d*]indoles **1.131** and *N*-heteroarenes **1.123** in the presence of Lewis acid ($TiCl_4$) or $POCl_3$, followed by the base and boron

trifluoride etherate treatment in the second step (26-47% yield) (*Scheme 1.45*). This approach opens the route to the rapid creation of a library of such dyes.



Scheme 1.45. *Synthesis of BODIPY-dyes analogues* ***1.120*** *and* ***1.121****.*

The introduction of the electron-donating substituent in the 6 position of the pyridine ring of dyes **1.121** increases λ_{max} of absorbtion for 30-40 nm and emission for ~ 10 nm.

XRD analysis of crystals showed that the molecules have a dense packing caused by intermolecular hydrogen bonds H···F and form aggregates with head-to-tail placement (*Figure 1.11*).

Apart from the fluorescence in the solution, the complexes also exhibit fluorescence in solid state (*Figure 1.12*), unlike the classic BODIPY. Moreover, in all cases there is a bathochromic shift in the emission spectrum ~ 40-70 nm.

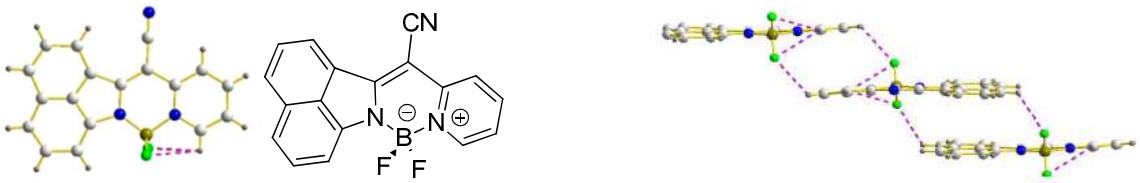


Figure 1.11. *a) X-ray structural analysis of* ***1.120.*** *b) Aggregates* ***1.120*** *with head-to-tail packing*

Synthesized complexes exhibit high photostability and also show a bathochromic shift in nonpolar solvents. Both characteristics promote their use for biovisualization. Visualization of fat droplets was reported by using the **1.121** complex (X = N, Het: 4-methylthiazole). This dye easily passes into the middle of the droplet due to the neutrality of the core and shows a bright green fluorescence.

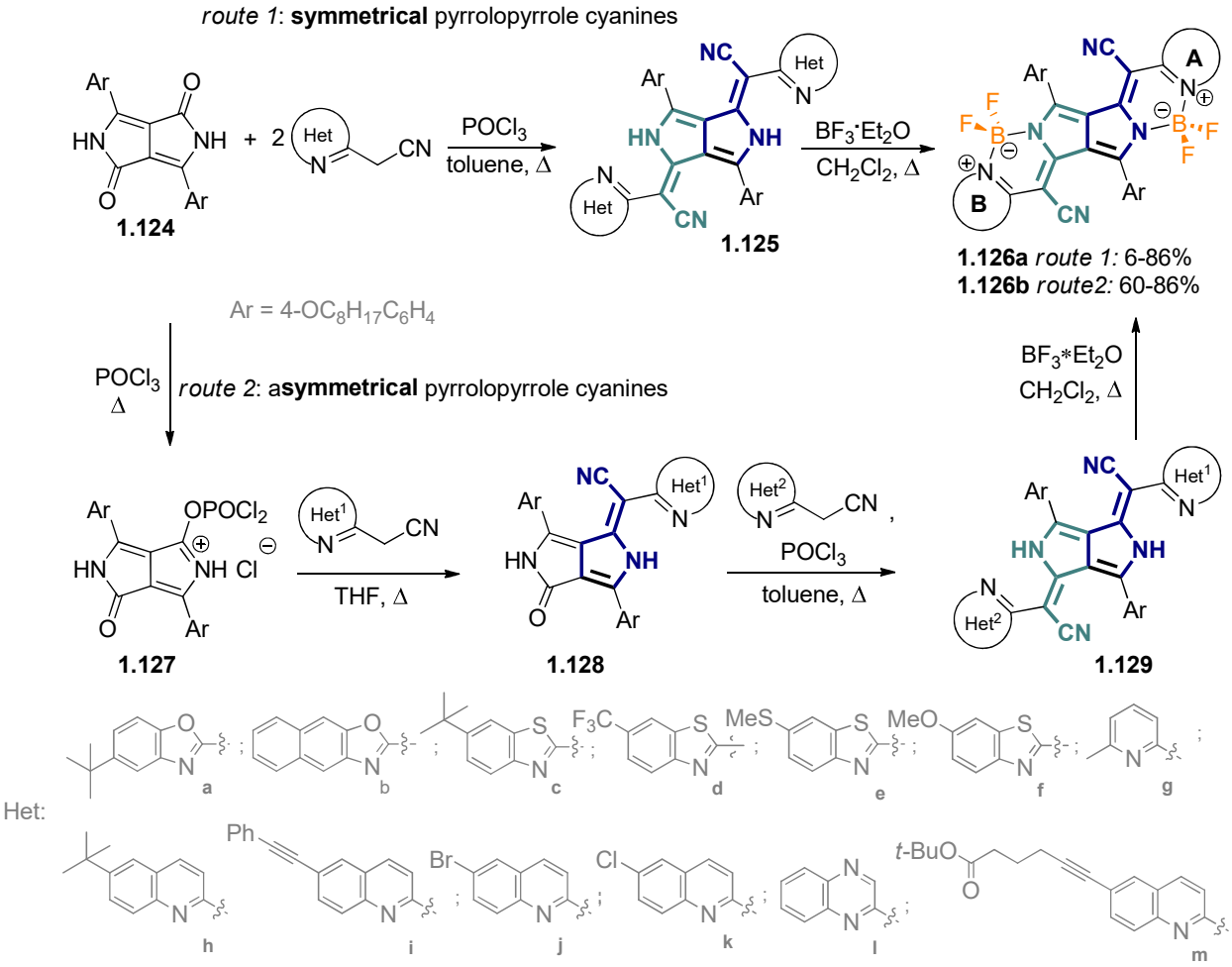
1.121 (X = N, Het: pyridine)
1.120 (X = CCN, Het: pyridine)

Figure 1.12. *Fluorescence in solid state.*

Also, the fragment of pyrrolidin-2-ylidene acetonitrile became a component of BODIPY-like dyes developed by a group of *German scientists.*[87-89] Synthesized dyes emit light (690-805 nm) within the optical window, in the near infrared (NIR) region of the spectrum. As it was noted above, substances that have such characteristics can be used for biovizualization, since biological fluids and tissues of the body do not absorb light in this region, which increases the depth of light penetration. It should be noted, that the Stokes shift for these dyes is small (within 250-500 cm^{-1}). [87-88] The authors attempted to increase the Stokes shift by synthesizing of the asymmetric dyes,[89] but they failed to achieve a sufficient deviation from C2 symmetry and Stokes shift remained within 739-786 cm^{-1}.

Synthesis of symmetric BF_2-pyrrolopyrrolocyanines (BF_2-PPC) **1.126** has been achieved by the condensation of 3,6-bis(4-octyloxyphenyl)-2,5-dihydropyrolo[3,4-*c*]pyrrole-1,4-dione **1.124** with hetaryl acetonitriles with excess $POCl_3$ in toluene at boiling point. The next reaction of PPC **1.125** with boron trifluoride etherate led to complexes **1.126** (*Scheme 1.46, route 1*). In the synthesis of asymmetric pyrrolidines, monosubstitution was achieved by evaporation of the excess $POCl_3$ in the first step of the process (*Scheme 1.46, route 2*). The resulting salt **1.127** reacted with 1 equiv of hetaryl acetonitrile and forms the mono-substituted product **1.128**. The reaction with the second equivalent of hetarylacetonitrile resulted in the asymmetric PPC **1.129**. Complex formation with $BF_3{\cdot}Et_2O$ gave the asymmetric complexes **1.126** in 60-86% yield. The authors note that mono-substituted PPC **1.128** can also form complexes

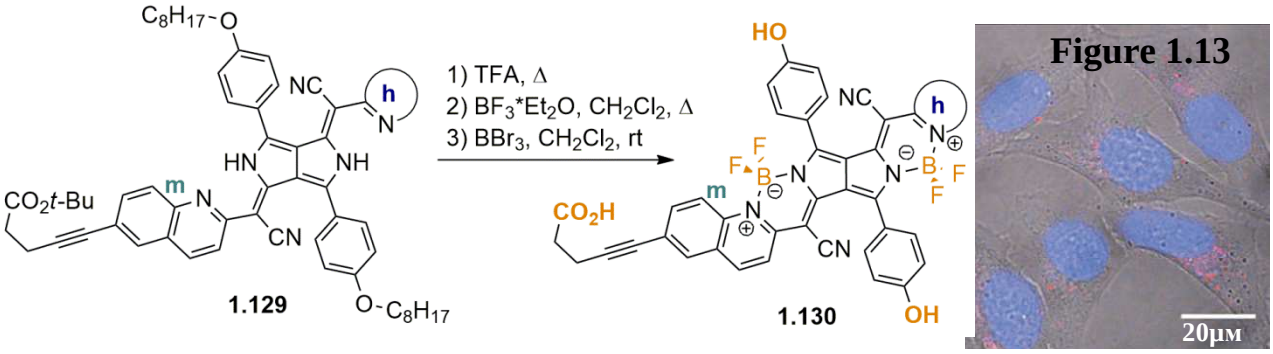
with BF_2; in this case Stokes shift reaches to 1320 cm^{-1} for **1.128c**, 1130 cm^{-1} for **1.128d**, the maximum emission was about 670 nm.



1.134, 1.135a A = B= Het = a-l; **1.137**, **1.138**, **1.135b** A = Het^1 = c, h; B = Het^2 = a, c, g-j, l-m

Scheme 1.46. *Synthesis of symmetric* ***1.126a*** *and asymmetric* ***1.126b*** *BF_2-PCC.*

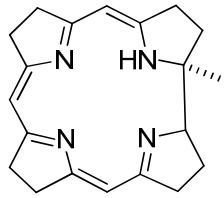
In order to show the possibility of using the synthesized complexes for biovizualization, HeLa cells were incubated with Arg_9 peptide in which the terminal amino acid was covalently bound to BF_2-PCC **1.130** (A = Het^1 = h, B = Het^2 = m). Cell nuclei are pre-painted with Hoechst 33342 fluorescent dye. A merged image of HeLa cells in which the blue fluorescence marks the nuclei stained with Hoechst 33342, while the red fluorescence indicates the position of the Arg9 peptide is shown in *Figure 1.13*. The image shows that the aggregates Arg_9-BF_2-PCC **1.130** do not penetrate into the core, but remain outside of it.



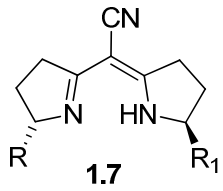
To conclude, it should be noted that the structural fragment of pyrrolide-2-ylidene acetonitriles are included to the BODIPY dyes analogues and exhibit larger Stokes shifts comparing to the classical dyes by means of the ligand desymmetrization. Other representatives emit the light in the near-infrared region of the spectrum, which allows them to be used for biovizualization (*in vitro* studies have been demonstrated). None of the articles discusses the possibility of radiofluorination of complexes with the indicated ligands for use as markers in PET, despite the fact that this opens the way for unimpeded visualization *in vivo*. Such literature data determine the relevance of research in this direction.

1.5.2. Synthesis and application of metal complexes

Many steps have already been done to create enantioselective catalysts; the necessity of developing new asymmetric catalysts is increasing with the enlargement in the number of new pharmaceutical, agro-pharmaceuticals, flavor and odor regulators, that are effective only in an enantiomerically pure form.



Corrin - *a macrocycle that is part of the structure of cobalamin (vitamin B_{12})*



Semicorrin - *Semicorrin - the name of the class of ligands, which was proposed by American scientist Stevens in the 70s*

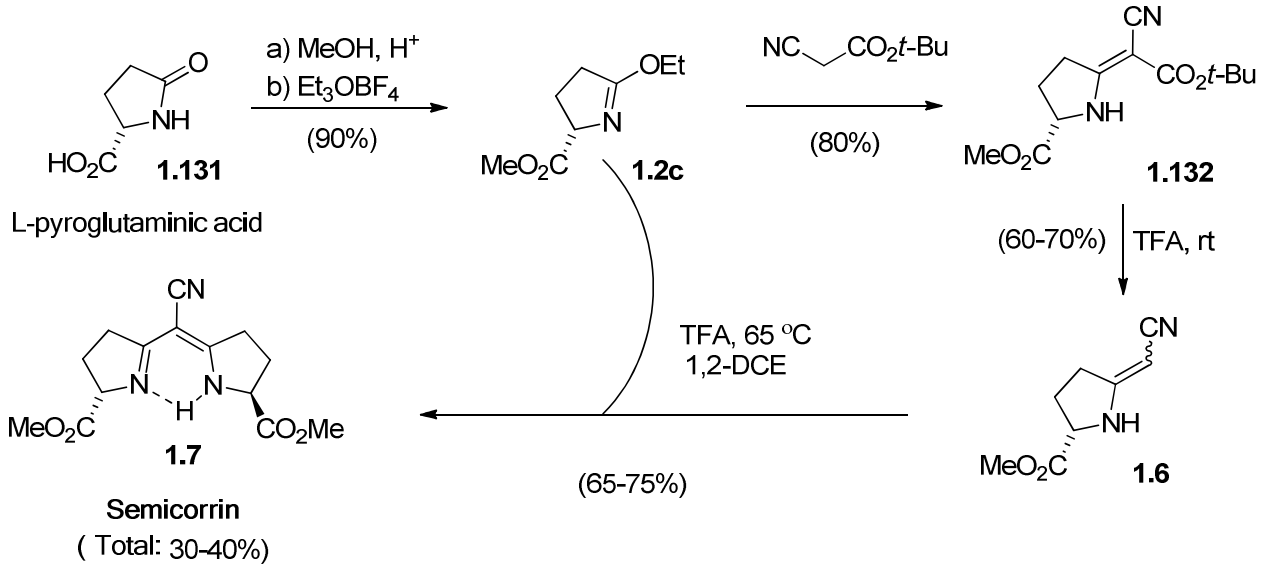
Figure 1.14

Typically, asymmetric catalysts are molecules consisting of metal and chiral ligand.

One class of ligands for asymmetric catalysis, well-studied in the 80s-90s is **semicorrins** (*Figure 1.14*). This name of compounds was proposed by Stevens in the 70s. The name is associated with the corrin (*eng*, "core" - "base") - a natural

macrocycle that is part of the cobalamin (vitamin B_{12}). The systematic name of the ligand: 5-(cyano(5-pyrrolidin-2-ylidene)methyl)-3,4-dihydro-2*H*-pyrrole.[11]

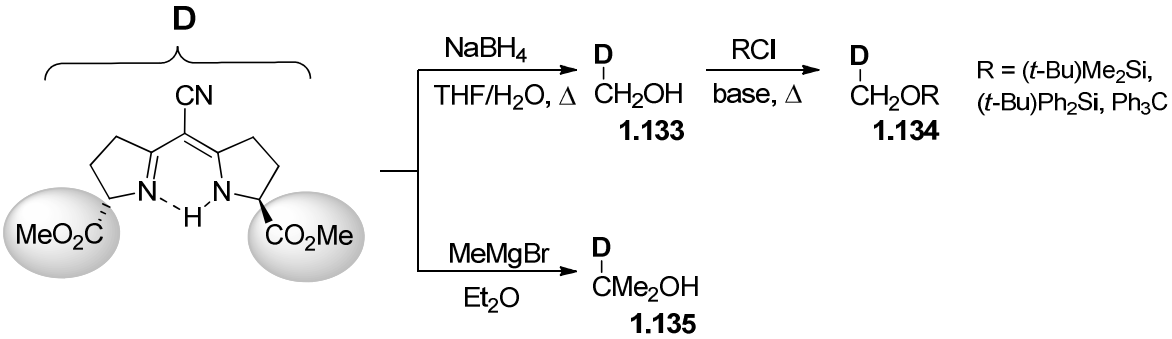
One of the advantages of semicorrins is their simple synthesis and modification of substituents at stereogenic centres. Enantiomerically pure ligands can be synthesized on multigram scale starting with commercially available L- or D-pyroglutaminic acid **1.131** with 30–40% total yield (*Scheme 1.47*).[11]



Scheme. 1.47. *Semicorrins synthesis.*

The synthesis includes the following steps: the esterification of L-pyroglutamic acid **1.131**, which is catalyzed by an ion-exchange resin, followed by alkylation with a Meerwein salt; condensation of **1.2c** with *tert*-butyl 2-cyanoacetate, which gave the enamine **1.132**; hydrolysis of *tert*-butyl ester and subsequent decarboxylation were applied for the preparation of cyanogenamine **1.6** as a mixture of *Z/E*-isomers. The last step was the hardest to implement, in particular, methods that worked on similar systems previously did not lead to the target product. Thus, an attempt to connect two monocyclic bilding blocks **1.2c** and **1.6** by carboximidate-enamine condensation was unsuccessful. In neutral or weakly basic conditions, condensation did not occur at all. Strong basic conditions could not be applied due to the potential racemization of the product. Semicorrin **1.7** can by synthesized only in the presence of TFA in 70% yield. Catalysis by other acids (AcOH, TsOH, $BF_3{\cdot}Et_2O$) gave a less satisfactory results.

Semicorrins ester groups can be easily modified by various methods (*Scheme 1.48*).



Scheme 1.48. *Structural modifications of semicorrins.*

The reaction with an excess of Grignard's reagent gave diols **1.135**. The reduction with sodium borohydride resulted in the formation of bis(hydroxymethyl)semicorrins **1.133**. Hydroxy groups can be modified with silyl or triphenylmethyl groups **1.134**.

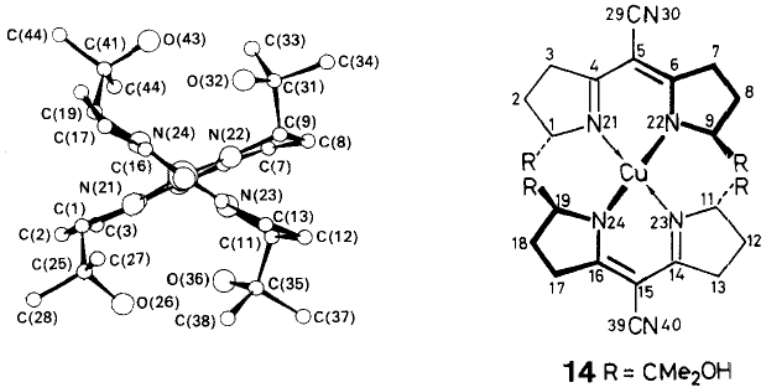


Figure 1.15. *Crystal structure, numbering and stereoscopic view of the semicorrin complex with Cu(II).* [11]

Semicorrins form stable complexes with a number of metal ions: Co(II), Rh(I), Ni(II), Pd(II), or Cu(II). Structures of some complexes were studied by X-ray diffraction analysis (*Figure 1.15*). It was observed that, depending on the metal ion, the structure of the ligand and the reaction conditions, mono- or bis(semicorrins) can be prepared.

In metal complexes with semicorrins as ligands, two substituents at the stereogenic centres of pyrrolidine are close to the coordination centre. They surround the atom of metal from two opposite sides, which should noticeably induce a control

of the stereochemistry of the reaction occurring in the coordination sphere of the complex (*Figure 1.16*).

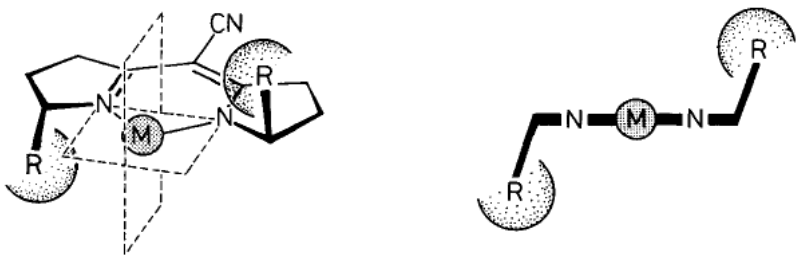


Figure 1.16. *Spatial view of the complex: 3D structure (left) and orthogonal projection (right).*[11]

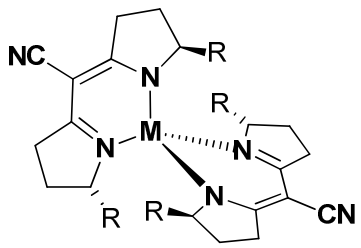
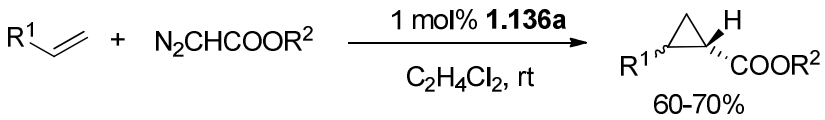


Figure 1.17. *Semicorrin complex with Cu(II)* ***(1.136a)*** *and Co(II)* ***(1.136b)****.*

Semicorrin complexes generated *in situ* or synthesized in advance with Cu(II) **1.136a** and Co (II) **1.136b** (*Figure 1.17*) were used as catalysts for enantioselective cyclopropanation of olefins by diazo compounds[90] and for reduction of *α,β*-unsaturated esters as well as amides (*Scheme 1.49 and 1.50*).[12, 91-93]

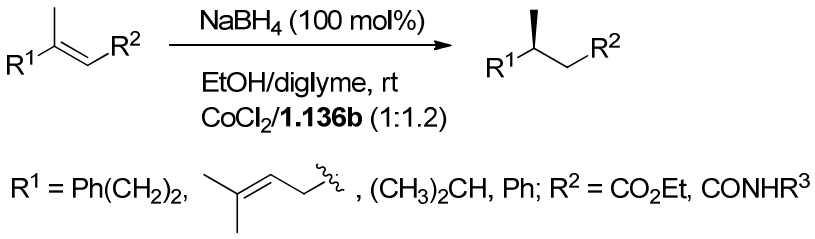


R^1 = Ph, CH_2=CH_2, *n*-pentyl; R^2 = Et, *t*-Bu, L-menthyl, D-menthyl

Scheme 1.49. *Asymmetric synthesis of cyclopropanes.*

The best enantiomeric excess (95-97%) was achieved in the case of R^1 = Ph or CH_2=CH_2; R^2 = D-menthyl; R = CMe_2OH (*Scheme 1.49*).

Reduction reactions with the Co(II) complex **1.136a** were carried out in quantitative 90-99% yield with enantiomeric excess (up to 99.9%, in the case R^1 = $Ph(CH_2)_2$, R^2=CONHMe) (*Scheme 1.48*). The solvent plays the key role in the reaction. In particular, changing the reaction media from DMF/ethanol to the diglyme/ethanol solution dramatically increased the reaction rate. According to the authors, such effect is associated with better solubility of sodium borohydride in diglyme.[91]



Scheme 1.50. *Reduction of α,β-unsaturated esters and amides.*

Notably, isolated double bond are inert in these conditions, a high chemoselectivity is achieved only with electrophilic C=C bonds conjugated with electron-withdrawing groups.

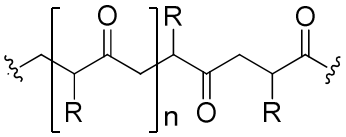


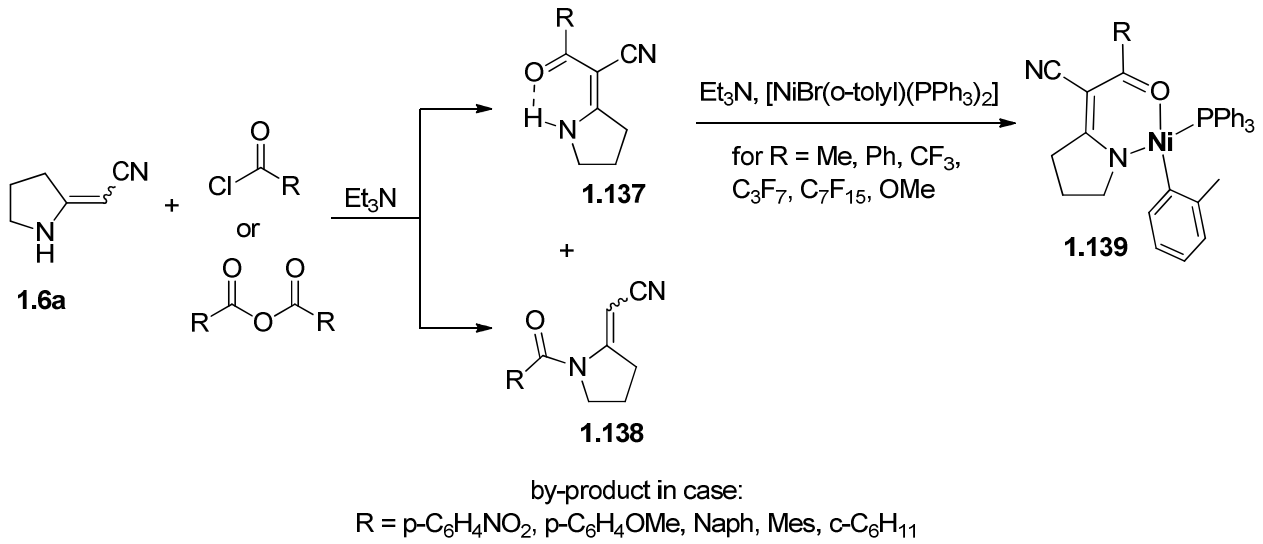
Figure 1.18. *The general structure of polyketones.*

Ni(II) complexes with pyrrolidin-2-ylidene acetonitriles have been used as polymerization catalysts to access polyketones (*Figure 1.18*), polymers with a unique combination of physico-chemical properties.[94-96]

In 1996, polyketones were first synthesized on an industrial scale and named as «Carilon».[96] The production was relied on the methodology involving palladium complex with a bidentant ligand ($Ph_2P(CH_2)_3PPh_2$) as a catalyst, which produces polyketone under mild conditions (90 °C, 45 bar) in 106 grams yield of polymer per gram of catalyst.[97-98]

The impetus for the study of complexes based on Ni(II) as cheaper Pd(II) analogue in the copolymerization of olefins and carbon monoxide (CO), was reducing the cost of the process, since catalysts can not be regenerated in the production process.[96]

The starting (*E/Z*)-(pyrrolidin-2-ylidene)acetonitrile **1.6a** was synthesized according to *Scheme 1.45* and subsequently used for the synthesis of semicorrin.[12] Upon treatment with a weak base and acylating agent (anhydride or acyl chloride), the product of acylation of *β*-enamine carbon atom **1.137** was obtained. In the case of soft acylating agents featuring bulky substituents, the product of *N*-acylation was isolated **1.138** (*Scheme 1.51*).[95]



Scheme 1.51. *Synthesis of CO and olefins copolymerization catalysts* ***1.139****.*

Ni(II) containing complexes **1.139** with N,O-chelating ligands **1.137** were obtained; these compounds were investigated in the copolymerization of ethylene and CO.[94] The highest efficiency was demonstrated by complexes **1.139** with polyfluoroalkyl substituents (R = C_3F_7, C_7F_{15}) – 11 kg of polykethone per gram of nickel were prepared. The solvent in the polymerization reaction can be dichloromethane, THF, toluene or supercritical carbon dioxide (CO_2) (environmentally friendly solvent). These complexes are the most effective of known nickel-containing catalysts. The reaction of copolymerization in their presence takes place under mild conditions: 60 °C, 40 bar, which emphasizes their promising utility

From this literature review covering synthesis, subsequent transformation using various electrophilic and nucleophilic agents, complex formation and the practical application of cyclic *β*-enaminonitrile, it is easy to find out the directions that need to be deeper investigated. Thus, there is only few information about the reactions of cyclic *β*-enaminonitriles with 1,2-binucleophiles, although they can serve as a convenient access to polyfunctional pyrazoles, which are widely used for therapeutic applications and for catalysis.

In general, syntheses and further transformations of cyclic *α*-hetaryl-*β*-enaminonitriles are scarcely studied to date. However, it is known that the heterocyclic fragment influence on the synthetic path and its presence might provide

novel methods for the construction of heterocyclic compounds. Moreover, a wide diversity of the heterocyclic substituents of starting enaminonitrile allows different biological activities of the products.

Another application of componds featuring 2-hetaryl-3-enaminonitrile moiety is the synthesis of BF_2-complexes for biovisualization purposes. Pyrrolidin-2-ylideneacetonitrile-containing structures are described in only a few articles and are characterized by the simplicity of their synthesis, practically better Stokes shifts, compared to the classical BODIPY dyes, as well as their light emission in the near infrared spectral region. Additionally, it has been shown that the nitrile group contributes to the bathochromic shift of the absorption and emission maxima.

Finally, metal complexes based on cyclic *β*-enaminonitrile are used as catalysts in the copolymerization of olefins and CO for the preparation of new materials, in particular, polyketones with unique combination of characteristics. Pyrolidine-2-ylideneacetonitrile with stereogenic centres exhibit high regio- and stereoselectivity in the cyclopropanation reaction as well as in the alkene reduction.

Therefore, the chemistry of cyclic 2-hetaryl-3-enaminonitrile is scarcely studied but is thought to be a promising topic for future developments.

CHAPTER 2. 2-AZAHETARYL-2-(1-R-PYRROLIDIN/3-OXOINDOLIN-2-YLIDENE)ACETONITRILES: SYNTHESIS AND STRUCTURE EXPLORATION

Given the promising use of derivatives of pyrrolidinylidene acetonitriles in the synthesis of functionalized azaheterocycles, our primary task was to synthesize their analogues with azaheterocyclic substituents in the position 2 of the enaminonitrile fragment (*Figure 2.1*).

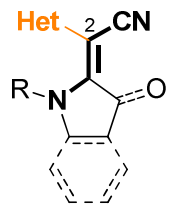


Figure 2.1. *Target molecule.*

2.1. 2-Azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles

2.1.1. Synthesis

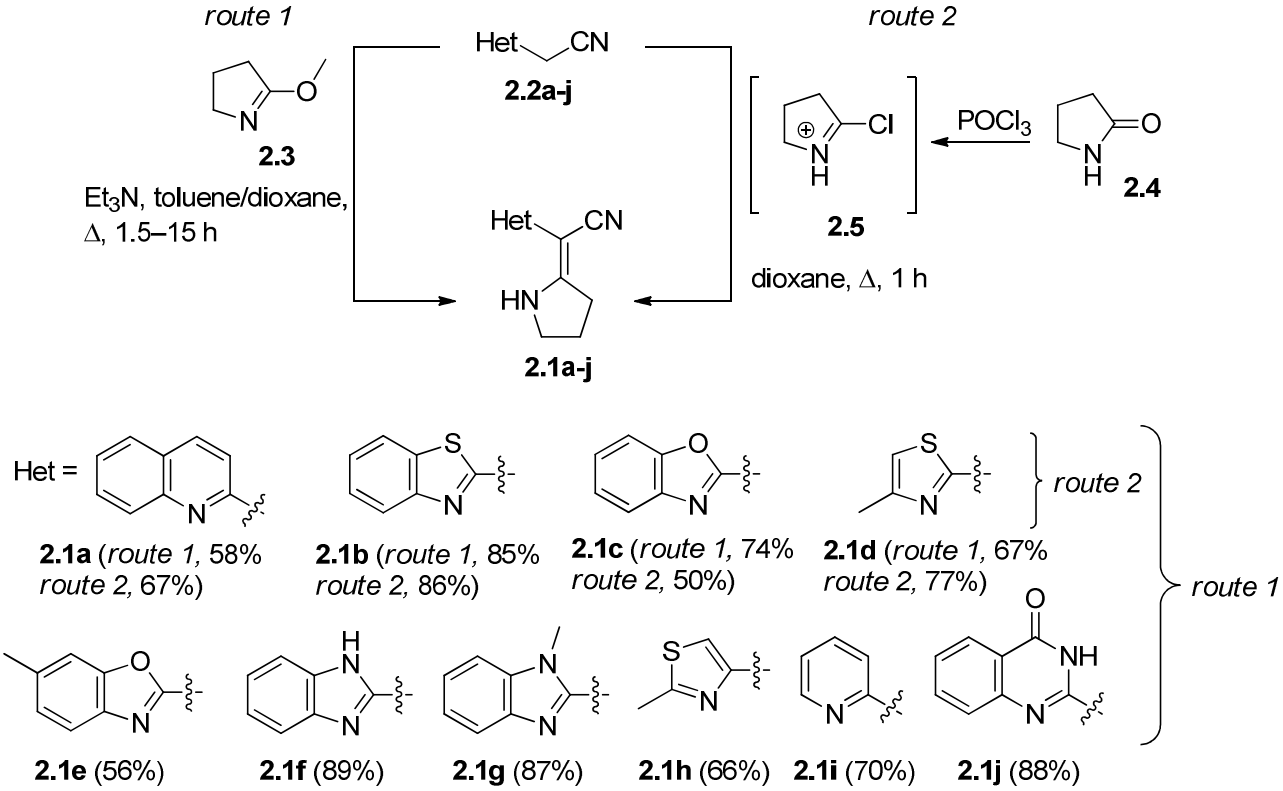
For the first time, the synthesis of 2-(pyrrolidin-2-ylidene)acetonitriles bearing heterocyclic substituents was described in 2000.[9] The method consisted in the condensation of hetarylacetonitrile **2.2** (CH-acid) with *O*-methylbutyrolactam **2.3** in the presence of Et_3N in boiling toluene. This method has been described for quinolin-2-yl **2.1a** and pyridin-2-yl **2.1i** as heterocyclic substituents.

The adjustment of the synthetic scheme allowed us to expand the number of heterocyclic substituent in 2-(pyrrolidin-2-ylidene)acetonitriles and obtain 8 new compounds **2.1b-h**,**j** depicted on the *Scheme 2.1, route 1*.

We have also developed a new method for the synthesis of enaminonitriles **2.1** by using a three-component condensation of hetarylacetonitrile **2.2**, phosphorus oxychloride, and pyrrolidin-2-one **2.4**. In contrast to the previously described method (*Scheme 2.1, route 1)* which requires the initial preparation of 5-methoxy-3,4-dihydro-2*H*-pyrroles **2.3** the proposed method is streamlined enabling *in situ* generation of 5-chloro-3,4-dihydro-2*H*-pyrrolinium cation **2.5** and preparation of the desired 2-hetaryl-2-(pyrrolidin-2-ylidene)acetonitrile **2.1** within 1 h (*Scheme 2.1. route 2*). Our method allowed us to obtain both the previously known (*E*)-2-(pyrrolidin-2-ylidene)-2-(quinolin-2-yl)acetonitrile **2.1a**[9] and (*Z*)-2-(1,3-benzothiazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile **2.1b**,[10] as well as good yields of new

compounds such as (*Z*)-2-(1,3-benzoxazol- 2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile **2.1c**, (*Z*)-2-(4-methylthiazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile **2.1d**.

The yields of known enaminonitriles are comparable or higher to those described in the literature: **2.1a** – 58% route 1, 67% route 2 and 73% according to the literature; **2.1j** – 70% route 1, 57% according to the literature;[9] **2.1b** – 85% route 1, 86% route 2 and 56% according to the literature.[10]



***Scheme 2.1**. The routes to the synthesis of 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles **2.1**.*

2.1.2. Structure exploration: XRD, ^{1}H NMR, DFT-calculations

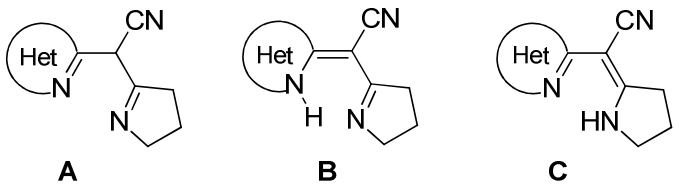


***Figure 2.2.** Tautomeric forms of enaminonitriles **2.1**.*

Theoretically, enaminonitriles **2.1** can exist in three tautomeric forms **A-C** (*Figure 2.1*). It was previously mentioned that the only form for compounds **2.1a** and **2.1i** is the enamine **C**.[9] This conclusion was made on the basis of IR spectra analysis, in which there is a stretching vibration in the region ~ 3100-3400 cm^{-1} corresponding to a NH bond and a broad signal in ^{1}H NMR

spectra in the 10-12 ppm range assigned to the chelated proton. There are also no multiplets that would appear for the spin-spin coupling of 1-H and 6-H protons for **2.1i** in tautomeric form **B**.

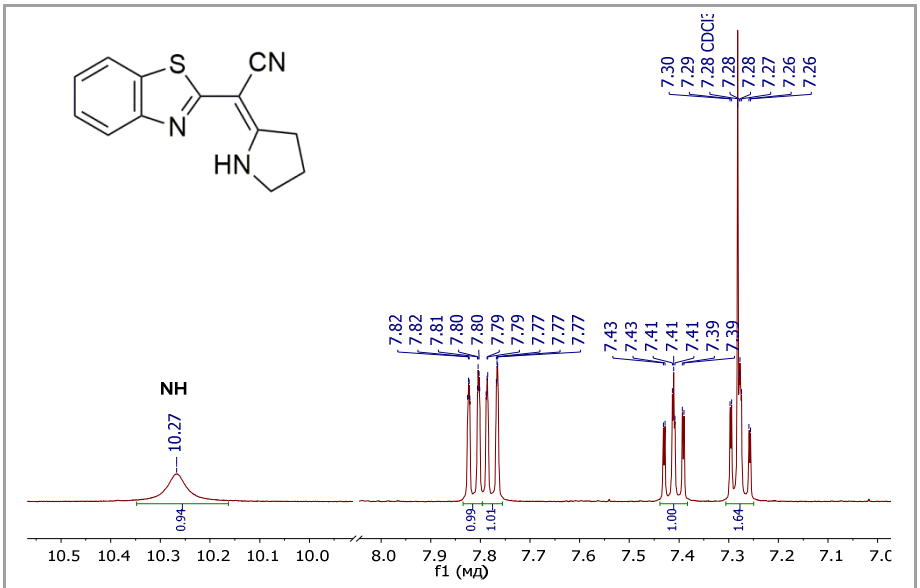


Figure 2.3. *A fragment of the ^{1}H NMR spectrum of compound* ***2.1b*** *with the highlighted shift of NH proton ($CDCl_3$, 400 MHz).*

Our results are in agreement with these statements. Thus we observe the same stretching vibrations in IR and broad signal of chelated proton in the ^{1}H NMR spectra for enaminonitriles **2.1**. (*Figure 2.3*).

Beside three tautomeric forms (*Figure 2.1*) compounds 2.1 can also exist as 2 diastereomers (*E* and *Z*). (*Figure 2.4*).

The explorations carried out indicate the existence of compounds **2.1** as *Z* isomer both in solid state and in solution with the heterocyclic substituent and the NH group of pyrrolidine in the *cis* position.

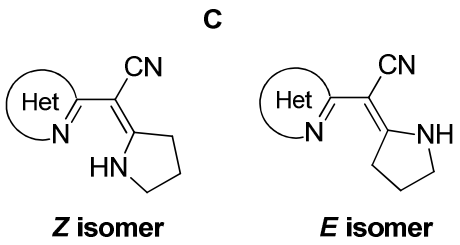


Figure 2.4*. Diastereomers of tautomer* ***C****.*

The XRD study of the compounds **2.1b** and **2.1d** has shown that molecules exist exclusively as *Z*-isomers in a crystalline state (*Figure 2.5*). XRD seems to indicate that H1 atom has a covalent bond with N1 atom of pyrrolidine (H1–N1 0.86 Å) and form the hydrogen bond with N2 (H1⋯N2 2.13 Å, N1–H1⋯N2 127.6°). The enaminonitrile **2.1b** framework is almost planar, (deviation of the pyrrolidine ring from the plane below 0.096 Å, the angle between the planes of pyrrolidine and benzothiazole is 4.91°, which is indicative of the delocalization of the enamine moiety electron density both toward the nitrile and benzothiazole. The shift promotes N1−C10 bond shortening

(1.32 Å) and C10−C8 bond elongation 1.39 Å (as compared to standard bond length values[99]) and also the deviation of the C8–C9–N3 angle (177.8°) from *sp* hybridization.

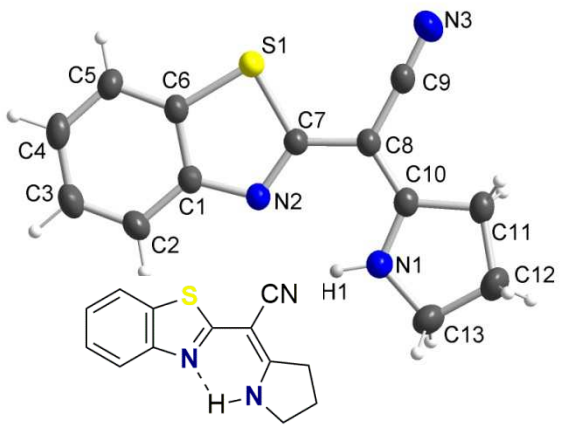
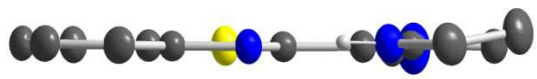


Figure 2.5. *a) Molecular structure of* ***2.1b*** *according to X-ray diffraction.*

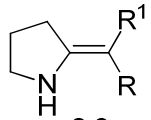


b) Orthogonal projection ***2.1b****.*

The low field shift of proton of NH group is observed in the ^{1}H NMR spectra (*table 2.1*) due to its intramolecular hydrogen bond with the nitrogen atom of the heterocycle. This bond stabilizes the *Z* isomer in the solution.

Table 2.1. *The shift of NH proton in the ^{1}H NMR spectra of enaminonitriles* ***2.1****.*

Entry	1	2	3	4	5	6	7	8	9	10
Compound	**2.1a**	**2.1b**	**2.1c**	**2.1d**	**2.1e**	**2.1f**	**2.1g**	**2.1h**	**2.1i**	**2.1j**
Shift NH, ppm	11.35	10.27	9.65	9.83	9.60	10.10	10.64	8.70	10.46	10.69
Solvent	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	dmso-d_6	$CDCl_3$	dmso-d_6	$CDCl_3$	dmso-d_6



2.6

a: R = R^1 = CN; **b**: R = R^1 = CO_2Me;
c: R = CO_2Et, R^1 = CN;
d: R = $CONH_2$, R^1 = CN;
e: R = COMe, R^1 = CO_2Et;
f: R = CO_2Me, R^1 = CN;
g: R = COPh, R^1 = CN

According to the literature data the shift of NH proton in 2-(pyrrolidin-2-ylidene)malononitrile **2.6a** is 7.52 ppm (solvent $CDCl_3$). In the latter one there is not possible to form the intramolecular hydrogen bond. By contrast the NH proton shift in 3-(pyrrolidin-2-ylidene)pentan-2,4-dione **2.6b**, where the intramolecular hydrogen bond exists (C=O···H), is 11.45 ppm (solvent $CDCl_3$).[2]

The theoretical analysis of the ratio between Z/E isomers in the solution was carried out by quantum-chemical calculations using the density functional theory (DFT).

The Gibbs free energy (ΔG) was calculated for 2 diastereomers[7] of **2.1b** in the solvents of different polarity and donor-acceptor properties. $CHCl_3$ (Polarity index (PI) = 4.1); $(CH_3)_2CO$ (PI = 5.1); CH_3OH (PI = 5.1); $(CH_3)_2SO$ (PI = 7.2). ΔG of *Z* isomer was found to be lower in all solvents than ΔG of *E* stating higher stability of *Z* form. Based on values found the ratio between isomers was calculated applying Maxwell-Boltzmann distribution (*table 2.2*).

Table 2.2. *The ratio between Z/E isomers of 2-benzo[d]thiazol-2-yl-2-(pyrrolidin-2-ylidene)acetonitrile* ***2.1b****.*

Maxwell-Boltzmann distribution: $\mathbf{N_i/N = exp(- \Delta G_i/kT)/\sum_j exp(- \Delta G_j/kT)}$*				
Compound	**2.1b**			
Ratio *Z/E*	1903	1667	1642	1630
Solvent	$CHCl_3$	$(CH_3)_2CO$	CH_3OH	$(CH_3)_2SO$

* ΔG – Gibbs free energy, J; k – Boltzmann's constant, J/K; T – temperature, K;
N – the total number of particles in the system; N_i – the number of particles with the energy ΔG_i

Quantum-chemical calculations show that the amount of *E* isomer in a diastereomeric mixture does not exceed 0.1%, which is in agreement with the experimental data we have obtained: the sensitivity of the NMR spectrometer does not allow to register the signals of *E* isomer, therefore, only one set of signals corresponding to the energetically favorable *Z* isomer is obserbed.

The theoretical data obtained by us are in agreement with the experimental observations presented in the work of *Solovea et al.*[2] for analogues with compact acceptor groups **2.6c-f** and reinforce the conclusions made by them. *Soloveva et al.* point out that nor prolonged heating of solutions **2.6c-f** at 70 ° C neither change of solvent provoke the rise of signals of the *E* isomer. Also, in the ^{1}H NMR spectra, recorded in the temperature range from -60 ° C to +60 ° C, the chemical shift of NH

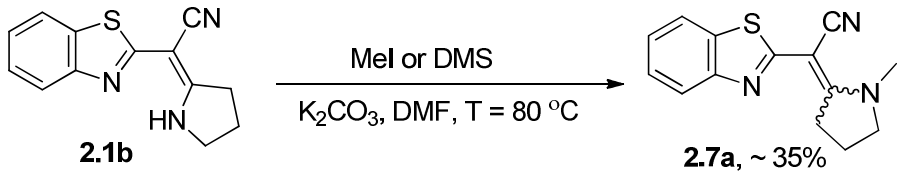
[7] only isomers with S in *cis* position to CN group were taken into account regarding the bigger size of sulfur as compared to nitrogen

proton remains almost unchanged, indicating the presence of a strong intramolecular hydrogen bond. The authors conclude that the presence of hydrogen bonding in secondary amines **2.6c-f** accounts for the lower energy of the *Z* isomer and consequently the absence of *E* form. Indeed, the calculations we made for the model enaminonitrile **2.1b** show that the Gibbs free energy is lower for the configuration *Z*: ΔG *Z* isomer = $-4.6400118 \cdot 10^{-15}$ J, ΔG *E* isomer = $-4.6399794 \cdot 10^{-15}$ J.[8]

2.2. 2-Azahetaryl-2-(1-R-pyrrolidin-2-ylidene)acetonitriles

2.2.1. Synthesis

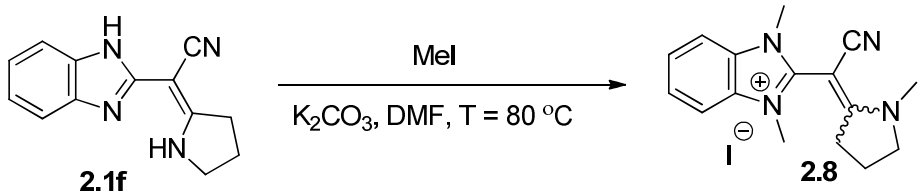
Theoretically, 2-azahetaryl-2-(1-R-pyrrolidin-2-ylidene)acetonitriles can be obtained by alkylation of their *N*-unsubstituted analogues. Using the standard alkylation conditions (MeI/DMS, K_2CO_3, DMF) for model compound **2.1b**, it was possible to obtain only a 35% yield of product **2.7a** after 36 hours of heating (*Scheme 2.2*).



Scheme 2.2. *Methylation reaction of enaminonitrile* ***2.1b****.*

The present approach is not suitable for the regioselective functionalization of NH group of pyrrolidine, in the presence of several reactive NH groups in the starting material.

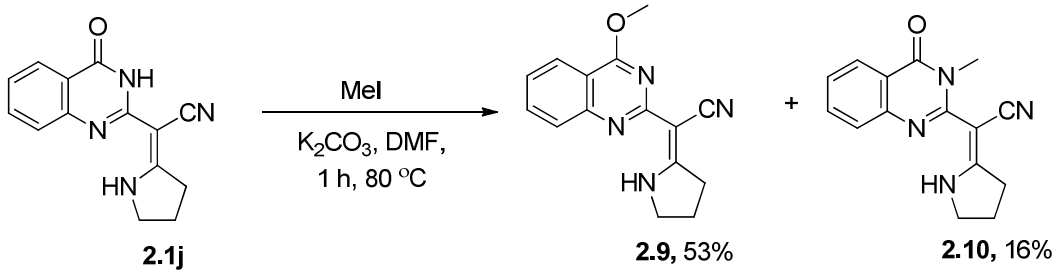
Thus in the case of benzimidazol-2-yl-2-(1*H*-pyrrolidin-2-ylidene)acetonitrile **2.1f**, the only reaction product is the 1,3-dimethylbenzimidazole salt **2.8** (*Scheme 2.3*). No intermediate alkylation products could be isolated.



Scheme 2.3. *Methylation reaction of enaminonitrile* ***2.1f****.*

[8] The values are given for the gas phase

In the case of the quinozalinone derivative **2.1j**, methylation takes place at oxygen and nitrogen atoms leading to -OMe **2.9** and -NMe **2.10** isomers, which were separated by column chromatography (*Scheme 2.4*). The yield of -OMe product **2.9** is higher that is probably related to aromatization associated with pyrimidine cycle formation.



Scheme 2.4. *Methylation reaction of enaminonitrile* ***2.1j****.*

O. Khilya et al. pointed out that in the case of 2-azaheteryl-2- (dihydrofuran-2-ylidene)acetonitriles under similar conditions, the reaction proceeds exclusively on a more rigid nucleophilic centre to give the -OMe derivative.[100]

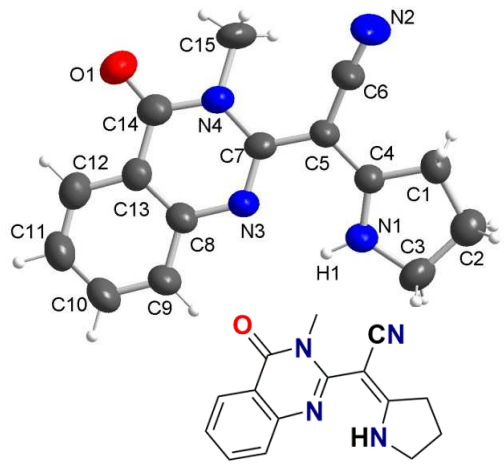


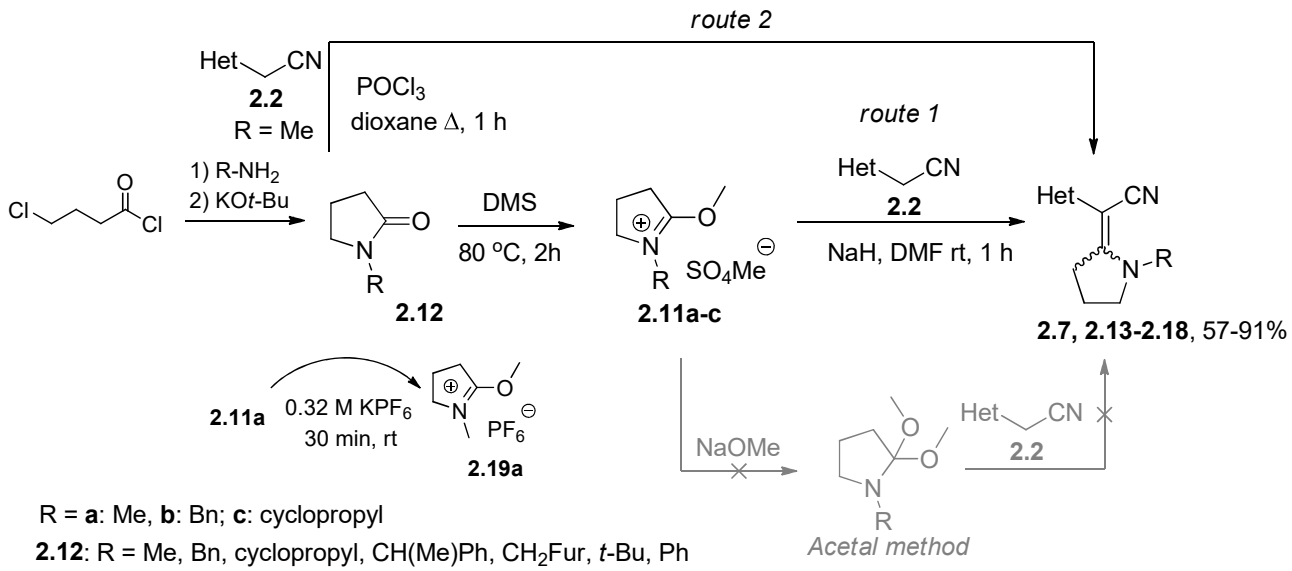
Figure 2.6. *Molecular structure of* ***2.10*** *according to X-ray diffraction.*

Structural analysis of the compounds was carried out using IR and NMR analysis including two-dimensional (2D) NMR techniques (COSY, HMQC, HMBC) and X-Ray analysis for **2.10**. In the IR spectrum of NMe-quinozalinone **2.10** there is a characteristic stretching vibration of C=O group at 1664 cm^{-1}, a vibration is absent in isomer **2.9**. Bands of the nitrile group are present in both isomers in the region of 2180-2190 cm^{-1}. The carbonyl group carbon has a chemical shift of 162.8 ppm. Noticeably, protons have different chemical shifts for the OMe and NMe groups in the ^{1}H NMR spectrum. Thus, δ_{OMe} = 4.23 ppm, δ_{NMe} = 3.86 ppm. According to X-Ray analysis, enaminonitrile **2.10** is in isomeric form Z in a crystalline state, stabilized by a hydrogen bond N1–H1···N3 (estimated bond length H1···N3 2.12 Å, N1–H1···N3 122.6 °) (Figure 2.6).

The difficulties of alkylating such secondary enamines are consistent with those described by *Mezentseva et al.*[16] for a simpler analogue **2.6g**. Thus this authors mentioned that any attempts to alkylate of (Z)-3-oxo-3-phenyl-2-(pyrrolidin-2-ylidene) propanonitrile **2.6g** in the presence of K_2CO_3, NaOEt, Na, and other bases did not lead to the desired products. This might be attributed to the presence of a strong intramolecular bond between the NH group and the oxygen of the carbonyl group stabilizes the starting material to such an extent that the deprotonation of **2.6g** is substantially hindered.

To overcome the limits of the alkylation method of pyrrolidine presented above we have developed an alternative approach to the synthesis of 2-azhetaryl-2-(1-R-pyrrolidin-2-ylidene)acetonitriles (*Scheme 2.5, route 1*).[101, 9] Such derivatives can be accessed through the condensation of the anion of 2-azahetarylacetonitriles **2.2** (obtained via deprotonation by NaH) and 5-methoxy-1-R-3,4-dihydro-2*H*-pyrrol-1-ium salt **2.11** in DMF. The starting 1-R-pyrrolidin-2-ones **2.12** have been synthesized in two steps by reaction between chloroanhydride of chlorobutiric acid and corresponding amines, and further cyclization is promoted in the presence of potassium *tert*-butoxide.[102] This approach allows us to obtain a large set of substituents on the nitrogen atom. We have managed to obtain derivatives featuring a benzyl **2.12b**, cyclopropyl **2.12c**, 1-phenylethyl **2.12d**, furan-2-ylmethyl **2.12e**, *tert*-butyl **2.12f**, phenyl **2.12g** substituent.[10]

[9] The acetal method used to synthesize simpler analogues[17], in this case, was inefficient.
[10] 1-methylpyrrolidin-2-one is cheap and commercially available substance.



2.7: benzothiazol-2-yl
2.13: benzimidazol-2-yl
2.14: quinolin-2-yl
2.15: 3,4-dihydro-4-oxoquinazolin-2-yl
2.16: 4-methylthiazol-2-yl
2.17: 1-methyl-1*H*-benzimidazol-2-yl
2.18: benzoxazol-2-yl

Route 1:
2.7a: 91%; **2.7b**: 80%; **2.7c**: 74%
2.13a: 80%; **2.13b**: 77%; **2.13c**: 60%
2.14b: 67%; **2.15a**: 75%; **2.16b**: 72%;
2.17a: 57%; **2.18a**: 88%; **2.18b**: 79%
Route 2:
2.7a: 88%

Scheme 2.5. *Synthesis of 2-azahetaryl-2-(1-R-pyrrolidin-2-ylidene)acetonitriles* ***2.7, 2.13-2.18****.*

1-R-pyrrolidin-2-ones **2.12** were reacted with DMS. Reaction was followed up by ^{1}H NMR spectroscopy through the disappearance of 1-R-pyrrolidin-2-one **2.12** signals in the crude reaction mixture. Pyrrolium salts **2.11** were directly subjected into reaction with the model compound: benzothiazol-2-ylacetonitrile **2.2**. Reactions with 1-methyl/benzyl/cyclopropylpyrrolidine-2-ones proceed with the best conversion and yield. 5-Methoxy-1-phenylethyl/*tert*-butyl-3,4-dihydro-2*H*-pyrrol-1-ium salts **2.11** react with benzothiazol-2-ylacetonitrile **2.2** only with partial conversion to the desired product most probably as a consequence of steric bulk at nitrogen. 1-Phenylpyrrolidin-2-one does not react with DMS even at elevated temperature and excess of the reagent. The reason could be a decrease of the oxygen nucleophilicity resulting from the delocalization of the nitrogen lone pair on the benzene ring. 1-Furan-2-ylmethylpyrrolidine-2-one only yielded a mixture of inseparable products.

The alternative method for the synthesis illustrated on *Scheme 2.5, route 2* is analogous to the method that was developed for the synthesis of unsubstituted enaminonitriles **2.1** (*Scheme 2.1, route 2*).

With these results in hands further 2-azahetaryl-2-(1-R-pyrrolidin-2-ylidene)acetonitriles were obtained from methyl(benzyl, cyclopropyl)-substituted pyrrolidin-2-ones. The reaction proceeded immediately at room temperature (rt) leading to the desired compounds **2.7**, **2.13-2.18** in good to excellent yields (67−91%).

Pyrrolium salts **2.11a-c** are viscous oils, which were used directly in the next step without further purification. They could be obtained as solids upon treatment with KPF_6 in water. The model compound **2.11´a** forms after the anion metathesis as a white precipitate that can be isolated by filtration (*Scheme 2.5*).

2.2.2. Structure exploration: XRD, ^{1}H NMR, DFT-calculations, VTP-experiment

As compared to the unsubstituted enaminonitriles **2.1**, which theoretically can exist in the form of three tautomers and two diastereomers (*Figure 2.1*), *N*-substituted analogues can only be in the form of Z/E isomers.

Analogously to unsubstituted enaminonitriles **2.1**, configuration and conformation of the molecules were examined using XRD, NMR and dynamic NMR, and also confirmed by the DFT.

Single crystals suitable for XRD study were obtained by solvent diffusion. The structures in the solid state of enamininitriles **2.7**, **2.13-2.16**, **2.18** revealed, as illustrated in *Figure 2.7* for **2.13b**, that the diastereomer featuring lower steric strain (*N*-alkyl and CN in the *cis* position) is preferentially formed, as expected.

In all compounds the crystalline state revealed an almost planar conformation of the pyrrolidine ring (deviation from the plane within 0.16 Å), which is coplanar with the heterocyclic substituent (dihedral angle below 9°).

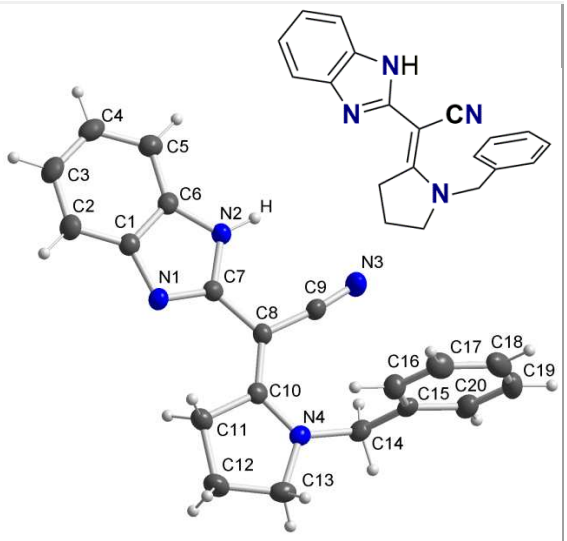
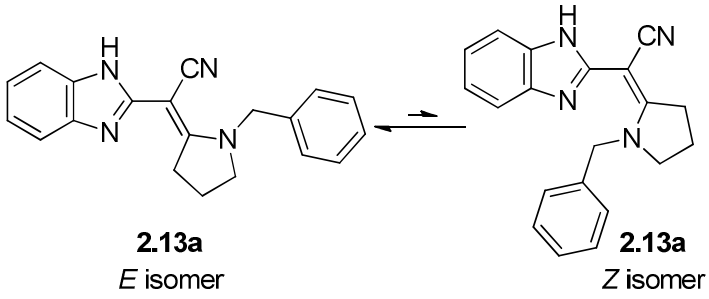


Figure 2.7. *a) Molecular structure of* ***2.13b*** *according to X-ray diffraction (E isomer).*



b) π-Diastereomerism of ***2.13b****.*

The delocalization of the electron density of the enamine moiety toward the nitrile and heterocycle promotes a general trend toward N4−C10 bond shortening and C10−C8 bond elongation, in a similar fashion as for **2.1**.

Table 2.3. *The bond lengths and C8−C9−N3 angles of selected compounds*

Entry	Compound	Length of pyrrolidine C−N bond (Å)	Length of enamine C=C bond (Å)	C8-C9-N3 angle (deg)	Dihedral angle between heterocycle and pyrrolidine ring planes (deg)	Deviation of pyrrolidine ring from plane (Å)
1	**2.7b**	1.334	1.403	176.1	5.3	0.027
2	**2.7c**	1.353	1.373	174.6	4.3	0.051
3	**2.13a**	1.328	1.382	173.7	8.8	0.161
4	**2.13b**	1.337	1.389	173.4	2.4	0.068
5	**2.14b**	1.348	1.395	175.5	5.9	0.026
6	**2.15a**	1.339	1.401	177.5	1.9	0.019
7	**2.16b**	1.342	1.389	175.5	4.9	0.024
8	**2.18b**	1.336	1.389	177.1	2.6	0.130

A clear correlation between the C8−C9−N3 angle values and the electron-withdrawing abilities of the heterocyclic substituent is observed, which implies that

both the nitrile and the heterocycle are involved in electron delocalization. For example, in the row benzoxazole **2.18b** – benzothiazole **2.7b** – benzimidazole **2.13b**, the angle C8–C9–N3 changes 177.1° –176.1° –173.4°, respectively, which reflects the decrease of the electron withdrawing abilities of the heterocyclic substituent and the displacement of the electron density toward the nitrile group (*Table 2.3*).

In previous publications[103-105] the rotation around C=C bond of such conjugated enamines was identified as a "low energy" process with the free energy for activation (ΔG*) 9-20 kcal/mol. It was also argued that energy barrier decreases as the ability of the substituents to delocalize the charge in the transition state increases.

Since azahetarylacetonitrile is a strong electron withdrawing fragment it was assumed that interchange between E/Z isomers occurs via heteropolar transition state **A** with efficient negative charge delocalization (*Figure 2.8)*.

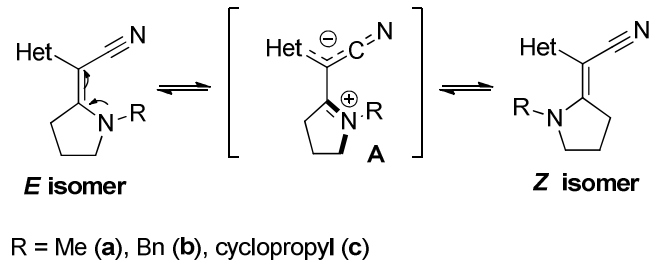


Figure 2.8. *Interchange between E and Z diastereomers* ***2.7***, ***2.13-2.18*** *via transition state* ***A***.

Bond length obtained by XRD analysis provides insight into the ability of rotation around the enamine double bond in the **2.7**, **2.13-2.18** and the literature data stated low activation energy barrier for the rotation around C=C bond in similar conjugated enamines. Taking into account the above mentioned data the presence of signals from both diastereomers *E* and *Z* was expected in the ^{1}H NMR spectra.

The ^{1}H NMR spectrum for the model compound **2.7a** recorded in $CDCl_3$, where the latter was completely soluble, showed only one set of signals. Nevertheless, the signals of N-CH_3 at 3.46 ppm and 3-CH_2 at 3.54 ppm adjacent to enamine double bond were broadened, that could be due to the fast exchange between isomers in the solution (*Figure 2.9*).

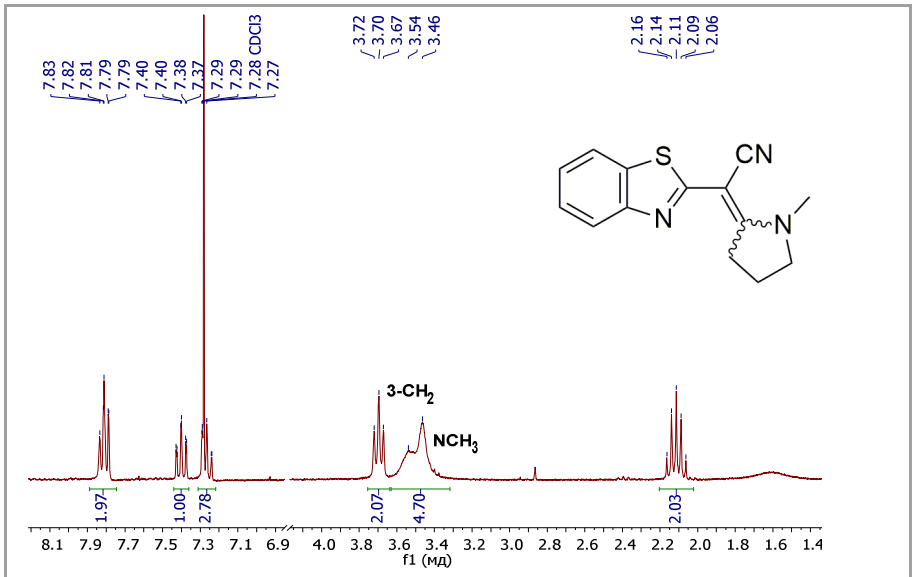


Figure 2.9. *A fragment of the ^{1}H NMR spectrum of compound **2.7a** with the highlighted shift of broadened signals of the protons of NCH_3 and 3-CH_2 moieties ($CDCl_3$, 300 MHz).*

In most of the ^{1}H NMR spectra of **2.13-2.18** recorded in $CDCl_3$ only one set of peaks is observed with broadened signals of protons adjacent to C=C bond; in rare cases the peaks of minor isomer appeared.

Minimized steric interaction in *E*, with *N*-Alk *cis* to linear nitrile group, as compared to *Z* with *cis* orientation of *N*-Alk and heterocycle substituent leads to constant prevalence of *E* isomer over *Z*. This conclusion is also substantiated by multiplets position in ^{1}H NMR spectra. Protons of *N*-Alk substituent in *E* isomer are deshielded by a neighbour-anisotropy effect of *cis* nitrile group and shifted to low field as compared to *N*-Alk protons of *Z* isomer that are located in the shielding area of heterocyclyc moiety (Δδ within 1 ppm).

Finally, assignment of the peaks either to *E* or *Z* form was made using the 2D NOESY technique (*Figure 2.10*).

The model compound **2.13a** was taken in DMSO-d_6 at 298 K. -CH_3 (δ = 2.78, 3.37 ppm) and -NH- (δ = 11.75, 12.24 ppm) protons resonance for *E* configuration gave a distinguishing positive cross peaks correlating them to the corresponding resonance of *Z* configuration. There was also a positive cross peak correlating the -NH-protons of benzimidazole to the residual water in the DMSO-d_6 solvent (δ = 3.33, 11.75, 12.24 ppm). Finally, the negative cross-peaks observed in the spectrum due to NOE between 4-CH and 3-CH_2 groups (δ = 7.40 and 3.34 ppm) belonging to isomer with higher integration value has confirmed predominance of *E* isomer (*Figure 2.11*).

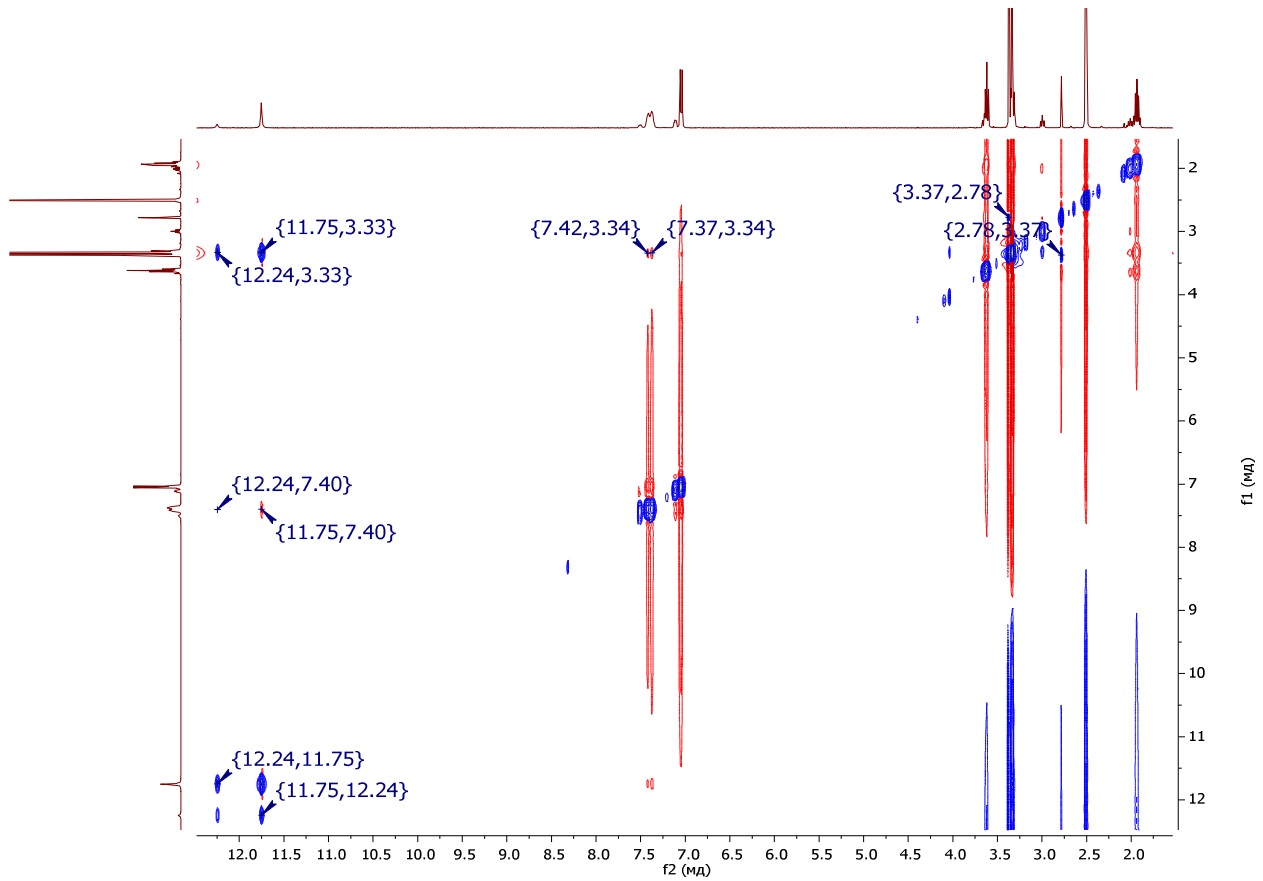


Figure 2.10. *NOESY spectrum of* ***2.13a****. Exchange processes marked with blue and NOE with red (DMSO-d_6, 500 MHz; 298 K).*

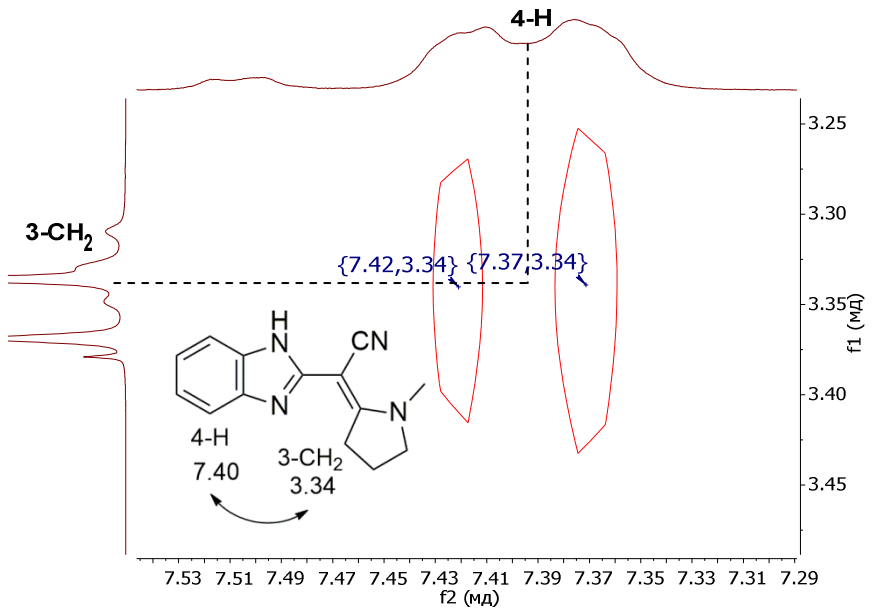


Figure 2.11. *Cross peak in NOESY spectrum which reflects the correlation between the 4-H and 3-CH_2 protons of the predominant isomer in* ***2.13a****.*

Consequently, the absence of steric hindrance in the *E* isomer makes it predominant in the diastereomeric mixture, regardless of the type of solvent and the substitution at 2-(pyrrolidin-2-ylidene)acetonitrile fragment. This experimental result is consistent with the data of the quantum-chemical calculations performed for compounds **2.7a** and **2.13a**, whereby the Gibbs free energy of the *E* isomer was smaller than the ΔG Z isomer in all the cases, indicating a greater stability of the *E* form. The relation between isomers is calculated according to the Maxwell-Boltzmann distribution and is given in *Table 2.4*.

Table 2.4. *Ratio between E/Z isomers of 2-benzo[d]thiazol-2-yl-2-(1-methylpyrrolidin-2-ylidene)acetonitrile* ***2.7 a*** *and 2-benzo[d]imidazol-2-yl-2-(1-methylpurrolidin-2-ylidene)acetonitrile* ***2.13a****.*

Compound	**2.7a**			
E/Z ratio	46	30	29	28
Solvent	$CHCl_3$	$(CH_3)_2CO$	CH_3OH	$(CH_3)_2SO$
Compound	**2.13a**			
E/Z ratio	64	22	20	19
Solvent	$CHCl_3$	$(CH_3)_2CO$	CH_3OH	$(CH_3)_2SO$

To study the dynamic behavior of those compounds in the solution VTP experiment has been conducted for compound **2.13a**. Upon cooling the solution of **2.13a** in $CDCl_3$ down to 213 K the peaks of Z isomer arise. (*table 2.5*).

Two broad singlets of 3-CH_2 (3.57 ppm) and *N*-CH_3 (3.46 ppm) signals splitted into four independent peaks upon cooling: triplet (3.48 ppm, *J* = 7.7 Hz, 3-CH_2) and singlet (3.45 ppm, *N*-CH_3) corresponded to *E* isomer and triplet (3.08 ppm, *J* = 7.5 Hz, 3-CH_2') and singlet (2.97 ppm, *N*-CH_3) corresponded to *Z* isomer (*Figure 2.12*).

Base on the spectral data the free activation energy ($\Delta G^{\neq}$) for exchange between diastereomeric species **2.13a *E*** and **2.13a *Z*** was calculated. The kinetic parameters for unequal populated isomers were identified from modified Bloch equation (1-3).[103]

$$[(\delta^2\tau^2-2)/3]^3 = (\Delta P)^2\,\delta^2\tau^2 \;(1),\quad \tau^{-1} = \tau_e^{-1} + \tau_z^{-1} \;(2),\quad p_e\tau_e^{-1} = p_z\tau_z^{-1} \;(3),$$

where δ – maximum chemical shift separation in radians, $\Delta P = p_e - p_z$, when p_e and p_z are the molar fractions of the two exchanging diastereomers, τ_e and τ_z are the life time of *E* and *Z*. Rate constants are $k_e = 1/\tau_e$, $k_z = 1/\tau_z$. Inserting the resulting rate constant

into Eyring activation function, taking transmission coefficient (t) as unity, provides the $\Delta G^{\neq}$ values: $\Delta G^{\neq}$ E→Z = 14.4 kcal/mol, $\Delta G^{\neq}$ Z→E = 13.3 kcal/mol.

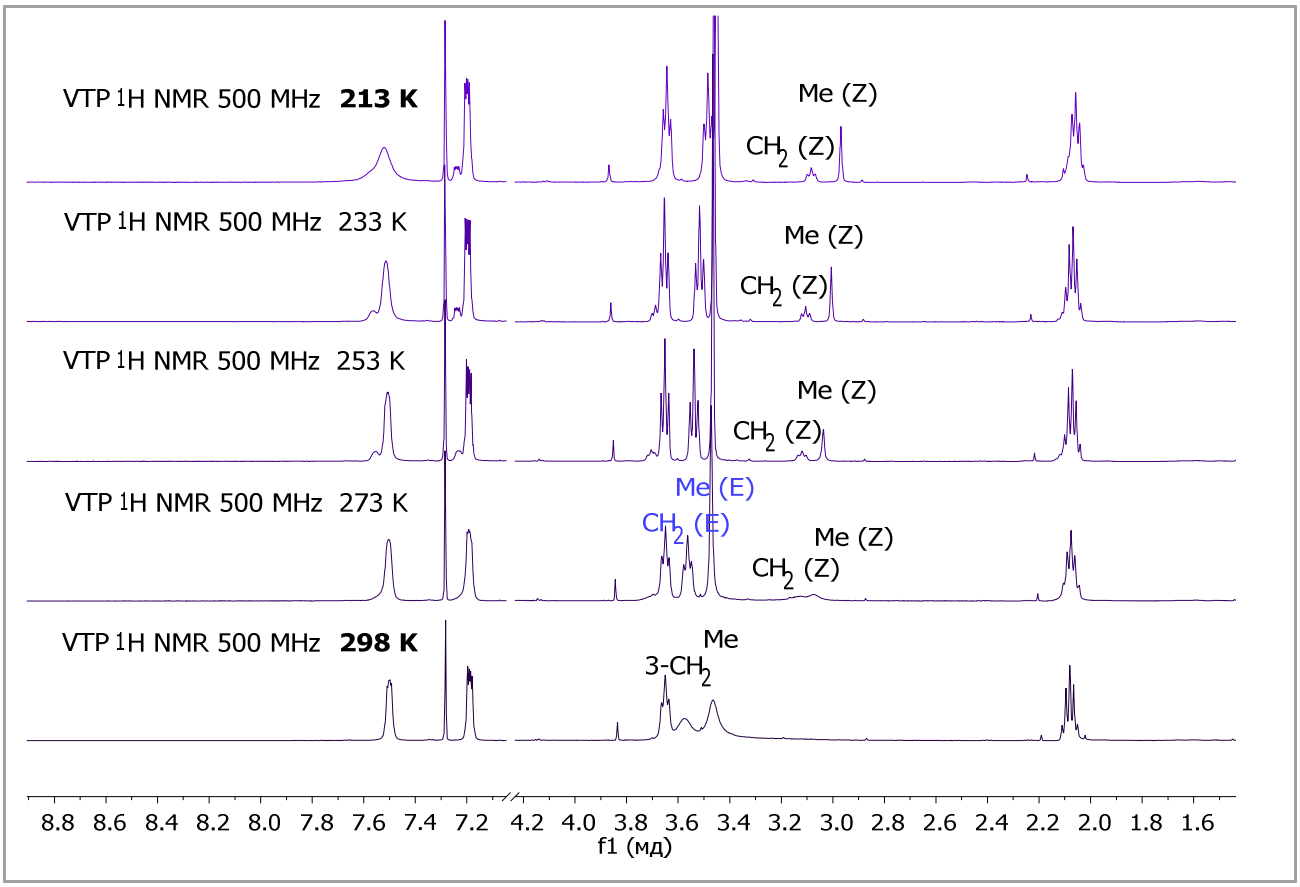
$$k = \frac{t k_B T}{h} e^{\frac{-\Delta G^{\neq}}{R T_K}} \quad (4),$$

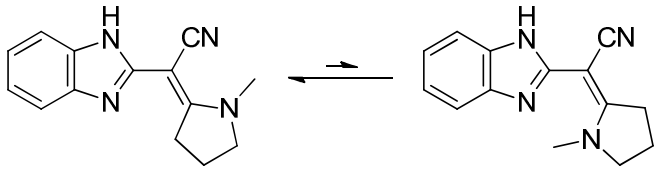
where k – rate constant, t – transmission coefficient, k_B – Boltzmann constant, h – Planck constant, T_c – coalescence temperature.

Coalescence temperature (T_c) was found as the average value of two consecutive temperatures surrounding the splitting of the signal (T_c = 285 K). Found $\Delta G^{\neq}$ values are in agreement with previous ones stated for such conjugated enamines[103-105] and characterize the isomerization process as low-energy one.

Table 2.5. *Selected chemical shifts data and ratio of isomers at different temperature observed for* ***2.13a*** *in* ^{1}*H NMR spectra (Solvent: CDCl$_3$)*

Entry	Solvent	Temp. (K)	*E*/*Z* ratio	Chemical shift (ppm)					
				N-CH_3	3-CH_2	NH	*N*-CH_3	3-CH_2	NH
1	$CDCl_3$	298	mixture	3.46	3.57	-	-	-	-
2				**2.13a *E***			**2.13a *Z***		
	$CDCl_3$	213	7:1	3.45	3.48	9.89	3.08	2.97	10.88





2.13a *E* isomer **2.13a** *Z* isomer

Figure 2.12. *Exploration of dynamic effects in enaminonitrile* ***2.13a*** *under cooling its solution in* $CDCl_3$*. Temperature imnterval 298÷213 K.*

In summary 2-azahetaryl-2-(1-R-pyrrolidin-2-ylidene)acetonitriles were synthesized by one known method and new ones, which can be used for preparative purposes. Their structure analysis was carried out using XRD, NMR, dynamic NMR and quantum-chemical calculations using DFT. Applying these techniques allowed us to show that 2-azahetaryl-2-(1*H*-pyrrolidin-2-ylidene)acetonitriles exist both in the solution and the solid state as *Z* isomers. This contrasts with 2-azahetaryl-2-(1-alkylpyrrolidin-2-ylidene)acetonitriles that exists as *Z* isomers in the solid state and as a mixture of *Z*/*E* diastereomers in the solution. The structure of *Z* isomers is stabilized by the intramolecular hydrogen bond. According to DFT-calculations the amount of *E* form in these cases is below 0.1%.

Due to the absence of steric hindrance the *E* isomer is predominant in *N*-substituted enaminonitriles, but there are also the signals of *Z* isomer in the spectra. The free activation energy of rotation at C=C double bond was calculated: $\Delta G^{\neq}$ E→Z = 14.4 kcal/mol, $\Delta G^{\neq}$ Z→E = 13.3 kcal/mol. The values found characterize this process as a low-energy one.

2.3. Synthesis of 2-(pyrrolidin-2-ylidene)acetonitriles substituted with quaternized benzazoles

It is known[63] that the introduction of an electron-withdrawing group at the nitrogen atom in the heterocycle increases the electrophilicity of the adjacent carbon atom, and resulting substrates have increased reactivity in the reactions with nucleophiles.

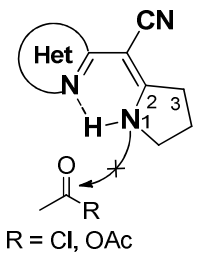
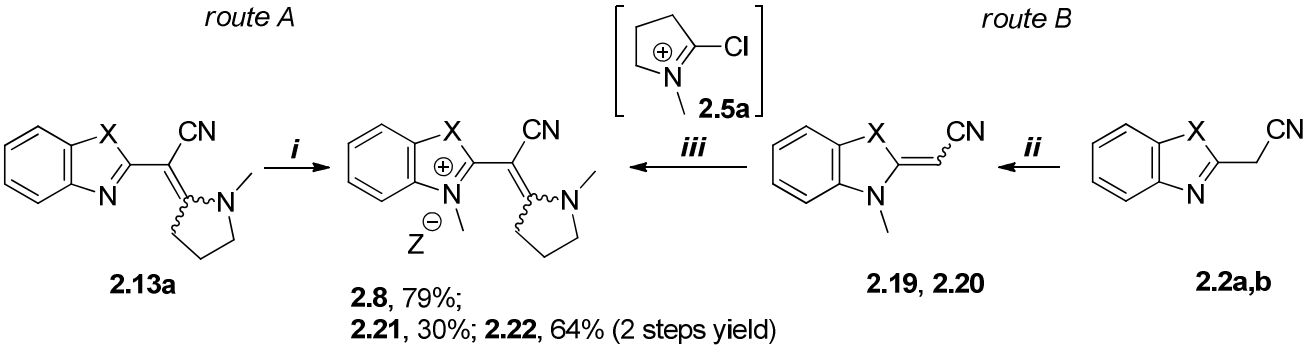


Figure 2.13. *Inactvity of compounds* ***2.1*** *in acylation reactions*

We have also attempted to use the above mentioned method to increase the electrophilicity of C-2 position of pyrrolidines, but the substrates **2.1** proved unreactive in acylation reactions (*Figure 2.13)*.

Therefore we have chosen a different approach to activate the C-2 position, which consist in increasing the charges separation in the molecule by quaternization of the nitrogen of azaheterocycle substituent.

Direct methylation of substrates **2.12** (*Scheme 2.6, route 1*) with methyliodide or DMS worked only in the case of benzimadazole **2.13a** leading to desired 2-(cyano(1-methylpyrrolidin-2-ylidene)methyl)-1,3-dimethyl-1*H*-benzo[*d*]imidazol-3-ium iodide **2.8** (*Scheme 2.6*). The structure of the product was identical to the one obtained by the reaction of **2.1f** with methyliodide (section 2.2). In the case of enamines substituted with benzoxazolyl **2.18a** and benzothiazolyl **2.7a** the starting material was quantitatively recovered under the same conditions.



i: 5 eq MeI, K_2CO_3, DMF, Δ, 2 h
X = NH (**2.13a**); X = NMe, Z = I (**2.8**)

ii: a) DMS, 70 °C, 1 h; b) NaOH
iii: a) 1-methylpyrrolidin-2-one, $POCl_3$, dioxane, Δ, 15 min; b) KPF_6
X = O, Z = PF_6 (**2.2b, 2.19, 2.21**); X = S, Z = PF_6 (**2.2c, 2.20, 2.22**)

Scheme 2.6. *Synthesis of 2-(pyrrolidin-2-ylidene)acetonitriles substituted with quaternized benzazoles* ***2.8, 2.21, 2.22****.*

Access to such charged hetarylenamines was achieved using the method described by *A. Dobrydnev et al.,*[106] which consist in methylation of initial azahetarylacetonitriles. Using this method we were able to synthesize the previously described 2-(3-methylbenzo[*d*]thiazol-2(3*H*)-ylidene)acetonitrile **2.20** [106], as well as 2-(3-methylbenzo[*d*]oxazol-2(3*H*)-ylidene)acetonitrile **2.19** (*Scheme 2.6, route 2*).

Intermediate 5-chloro-1-methyl-3,4-dihydro-2*H*-pyrrol-1-ium **2.5a** formed *in situ* upon reaction between $POCl_3$ and *N*-methylpyrrolidin-2-one undergoes addition to enamine double bond of *N*-methylhetarylacetonitriles **2.19** and **2.20** (*Scheme 2.6*). This method corresponds to the one we applied for the formation of enaminonitriles **2.1** and **2.7**.

Practically, the reaction proceeds through the formation of emulsion of salts that separates into two layers after the stirring is ceased. The bottom layer – compounds **2.19** and **2.20** were separated and solidified by anion metathesis from Cl^- to PF_6^-.

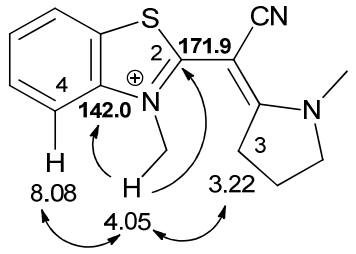


Figure 2.14. *The most indicative correlations found in NOESY and HMBC spectra of* ***2.21****.*

The ^{1}H NMR spectra of **2.21** and **2.22** are indicative of a single diastereomer. Considering the structure analysis results obtained for *N*-substituted enaminonitriles **2.7**, **2.13-2.18** (section 2.2) these signals are thought to correspond to the less steric hindered *E* isomer (all the multiplets are well resolved). Comprehensive assignment of signals of **2.21** was made by homonuclear (COSY) and hetereronuclear (HMQC, HMBC) and NOESY 2D NMR techniques. The negative cross-peaks observed in the spectrum due to NOE between CH_3 and 3-CH_2 groups (δ = 3.22, 4.05 ppm) again confirmed the *E* configuration (*Figure 2.14*).

The similarity of the chemical shifts of the corresponding protons in the ^{1}H NMR spectrum of benzoxazole derivative **2.22** also indicates *E* configuration.

For such cationic structures the existence of two resonance forms with localization of a positive charge on the nitrogen of azaheterocycle **A** or on the nitrogen atom of pyrrolidine **B** can be envisaged (*Figure 2.15)*. The signal of one of -CH_3 groups is shifted to low field (δ = 4.02 ppm vs 3.50 ppm for **2.21**; δ = 4.05 ppm vs 3.27 ppm for **2.22**) as a potential consequence of its positioning at the nitrogen bearing more positive charge. From the

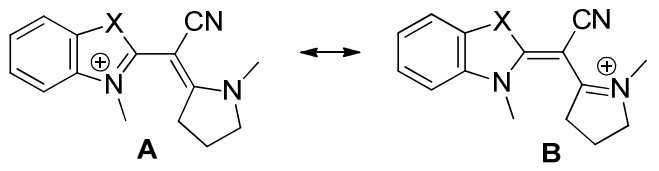


Figure 2.15. *Resonance forms of enaminonitriles* ***2.8****,* ***2.21****,* ***2.22****.*

other hand there is only minor changes in the location of -CH_3 group of pyrrolidine in cationic structure as compare to neutral one (δ = 3.38 ppm for **2.7a** vs 3.27 ppm for **2.22**; δ = 3.52 ppm for **2.18a** vs 3.50 ppm for **2.21**). Moreover, HMBC correlations with C-2 and the node carbon of benzothiazole situated next to the nitrogen (*Figure 2.14*) are providing further evidence that this CH_3 group is placed at nitrogen of benzothiazole and the predominant resonance structure is **A** (*Figure 2.15*).

In the case of **2.8**, with 1,3-dimethyl-1*H*-benzo[*d*]imidazol-3-ium (X = NMe) substituent, heterocycle is symmetric about C-2 axis and the signals of both CH_3 groups arise as one singlet (6H) in ^{1}H NMR spectrum. It has a low field shift versus *N*-CH_3 group of pyrrolidine (δ = 4.20 ppm vs 3.60 ppm), but there is also a significant low field shift of -CH_3 group of pyrrolidine as compared to the neutral analogue (δ = 2.42 ppm for **2.17a** vs 3.60 ppm for **2.8**). These evidences cannot be indicative for predominance of one resonance form over the other.

PF_6^- is evidenced by a septet in the ^{31}P NMR spectra and doublet in ^{19}F NMR spectra of compounds **2.21** and **2.22.**

As illustrated in table 2.6 the ^{13}C NMR spectrum of compound **2.8**, **2.21** and **2.22** exhibit a low field shift of C-2 atom of enaminonitrile fragment in comparison with neutral analogues. This indicates the extra deshielding related to the displacement of the electron density to the electron deficient nitrogen.

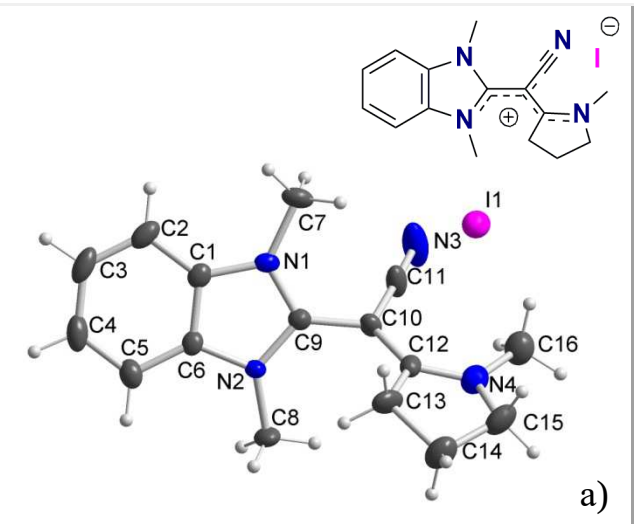
Table 2.6. *Comparison of the chemical shift of C-2 atom of enaminonitrile fragment in N-substituted uncharged enaminonitriles* ***2.13a***, ***2.7a***,***2.18a*** *and their analogues with quaternized azaheterocycles* ***2.8***, ***2.21***,***2.22***.

Entry	Compound	Chemical shift of C-2 atom of enaminonitrile fragment, (ppm)	Solvent
1	**2.13a**	167.0	$(CD_3)_2SO$
2	**2.8**	170.7	$CDCl_3$
3	**2.7a**	167.6	$(CD_3)_2SO$
4	**2.21**	170.7	$(CD_3)_2SO$
5	**2.18a**	168.0	$CDCl_3$
6	**2.22**	173.9	CD_3CN

The ^{1}H NMR spectra of compounds **2.8** (in which the azaheterocyclic substituent is 1,3-dimethyl-1*H*-benzo[*d*]imidazole-3-ium) is indicative of the presence of the 2 diastereomers, 2 sets of signals being observed . An analysis of their chemical shifts leads to conclusion that the compound exists as a mixture of *E* and *Z* isomers.[11] Interestingly the diastereomeric ratio varies with the solvent indicating equilibrium (*Table 2.7*)

Table 2.7. *Chemical shifts of N-CH_3 and 3-CH_2 groups of compound* ***2.8****, that indicate the belonging of the set of signals to E or Z isomer.*

Entry	Solvent	*E*/*Z* ratio	Chemical shift (ppm)			
			2.8 *E*		**2.8 *Z***	
			N-CH_3	3-CH_2	N-CH_3	3-CH_2
1	$CDCl_3$	1.4:1	3.60	2.94	2.76	3.36
2	CD_3CN	1:1.2	3.51	2.51	2.46	3.25



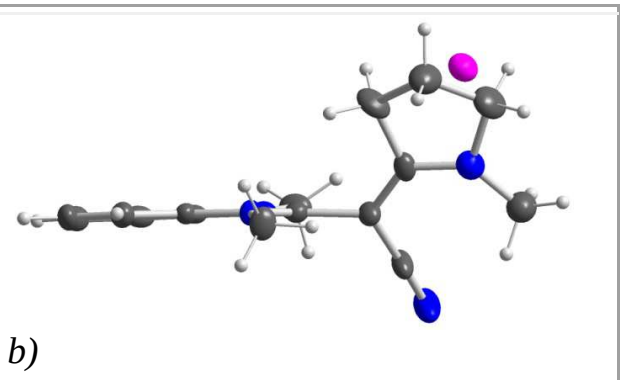


Figure 2.16. *a) Molecular structure of* ***2.8*** *according to X-ray diffraction .* *b) Orthogonal projection.*

In the crystalline structure of 2-(cyano(1-methylpyrrolidin-2-ylidene)methyl)-1,3-dimethyl-1*H*-benzo[*d*]imidazol-3-ium iodide **2.8** the dihedral angle between *N*,*N*-dimethylbenzimidazole and pyrrolidine planes is 53.0°. Nitrile group and pyrrolidine are almost coplanar (the deviation from the plane is under 0.20 Å). There is also a shortening of N4–C12 (1.33 Å) and an elongation of C12–C10 (1.39 Å) bonds that

[11] Signals that are in the shielding area of heterocycle (*N*-CH_3 *Z* isomer and 3-CH_2 *E* isomer) shifted to high field, and those which are deshielded by nitrile group (*N*-CH_3 E isomer and 3-CH_2 *Z* isomer) to low field. More detailed explanation was described in section 2.2.

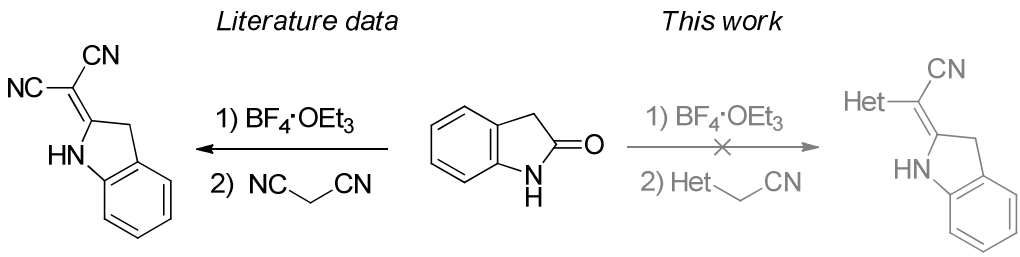
are indicative of the electron density distribution. Taking into consideration the value of dihedral angle it can be assumed that delocalization on azaheterocycle is limited by the lack of planarity with the enamine moiety. Thus delocalization toward the nitrile group is mainly occurring (*Figure 2.16*).

DFT calculation of partial charges in molecule **2.8** which has a quaternized heterocyclic substituent and its neutral analog **2.13a** indicate a partial positive charge on C-2 atom of pyrrolidine in **2.8** is equal to +0.435 whereas in **2.13a** in the same position, the charge is + 0.372. This result is in agreement with the conclusion on the increased electron deficiency of the C-2 atom, made from experimental data (low field shift of the signal of C-2 atoms in the ^{13}C NMR spectrum).

To conclude, enaminonitrile with quaternized azateterocyclic substituents can be obtained in two ways, one of which involves the introduction of the alkyl group to the hetarylacetonitrile at the first stage of synthesis and appears more versatile. The positive charge of the organic part of the molecule contributes to the charge separation and, as a result, increases the electron deficiency of the C-2 atom of the enaminonitrile fragment.

2.4. Synthesis of 2-azahetaryl-2-(5-R-3-oxoindolin-2-ylidene)acetonitriles

There is only one publication where the functionalization of the position 2 of oxindole occurs through alkylation and further condensation with CH acidic group.[26] (*Scheme 2.7*).



Scheme 2.7. *Functionalization of C-2 position of oxindole.*

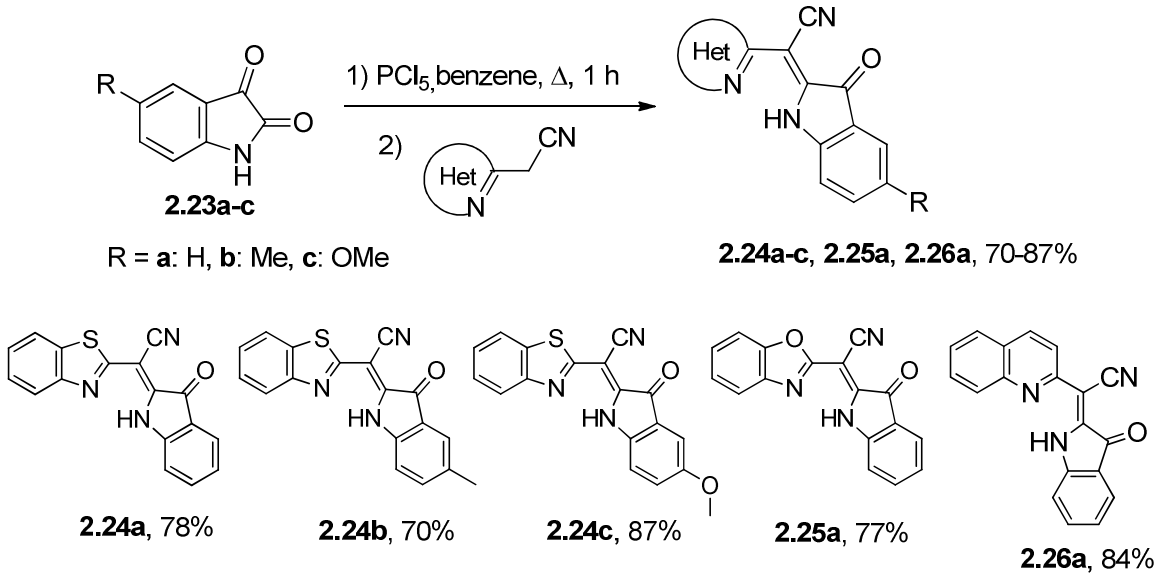
The applicability of this method is hampered by the equilibrium shift in the intermediate product of synthesis from 2-methoxy-3*H*-indole to 2-methoxy-1*H*-

indole,[24] which reduces the electrophilicity of C-2 atom (detailed description in the section 1.2).

The attempt made in this work to create the C–C bond between C-2 position of oxoindole and hetarylacetonitrile was unsucceful (*Scheme 2.7*).

To overcome the equilibrium issue we have to prevent the formation of 2-methoxy-1*H*-indole. One way to proceed is to substitute oxindole at C-3 position.

The indolin-2,3-dione **2.23** is a suitable candidate as it has a carbonyl group in the position 3 of the cycle. It is known,[38-40] that its functionalization by nucleophiles possible at the position 2 via formation of intermediate imidochloride. Usually, the later one is isolated and dissolved in a more polar to perform condensation reaction. Due to the low stability of imidochloride the yield of the reaction is always low. We have thus developed a new *one pot* approach that includes the formation of imidochloride *in situ* (~1 h, boiling in benzene) and its further condensation with hetarylacetonitrile (*Scheme 2.8*).



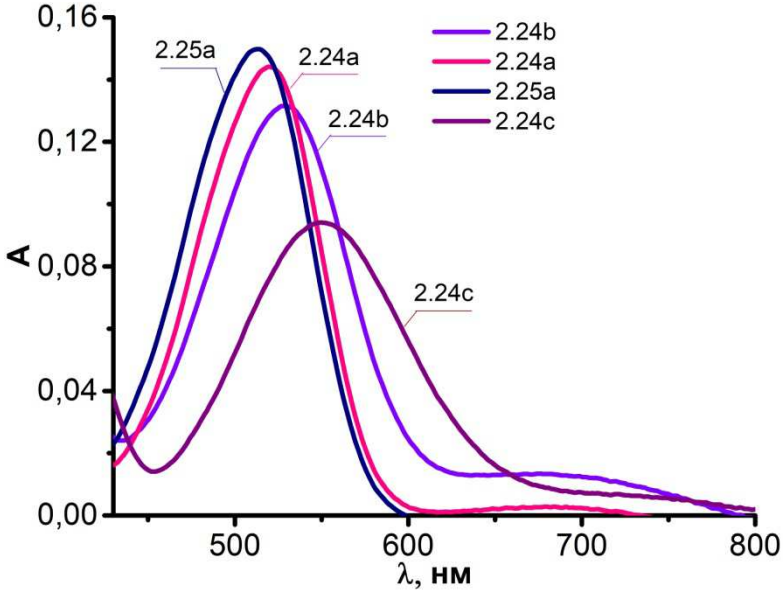
Scheme 2.8. *Synthesis of 2-azahetaryl-2-(5-R-3-oxoindolin-2-ylidene)acetonitriles* ***2.24-2.26***.

The total reaction time is around 1 h, the limiting step being the formation of imidochloride. The products are formed with high yields and purified by filtration through a plug of silica gel (eluent dichloromethane).

2-Azahetaryl-2-(5-R-3-oxoindoline-2-ylidene)acetonitriles are brightly colored compounds varying from red to violet. They exhibit low solubility in common organic solvents and water, as usually observed for the isatin's derivatives.[107-108] The compounds **2.24a-c**, **2.25a** give a long wave-length absorption band in the 515-550 nm range (*Figure 2.17, table 2.8*).

a) b)

***Figure 2.17**. Photo of **2.24b** (a) and **2.24c** (b) in the solution (DMSO) and a solid state.*

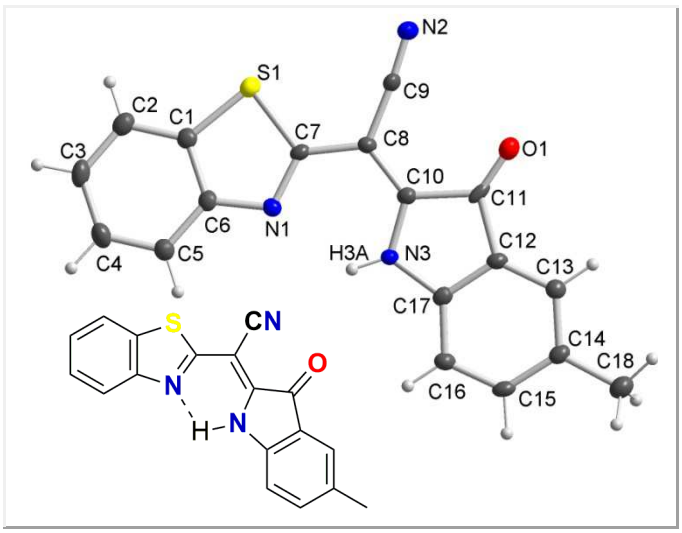


*c) Absorption spectra of **2.24a-c**, **2.25a** in DMSO. C = 10 μmol/l.*

***Table 2.8.** Spectrophotometric characteristics of compounds **2.24a-c**, **2.25** solutions.*

Entry	Compound	λ_{max}, nm	$\varepsilon^{\lambda max}$, $l \cdot mol^{-1} \cdot cm^{-1}$, 10^4
1	**2.24a**	520	1,48±0,05
2	**2.24b**	530	1,38±0,05
3	**2.24c**	550	1,03±0,05
4	**2.25a**	515	1,66±0,10

There is a predictable dependence between the increased electron donating abilities of the substituent at the position 5 of 3-oxindole (H→Me→OMe) and the bathochromic shift of λ_{max} in the absorption spectra. This occurs because of a decreased HOMO–LUMO gap.



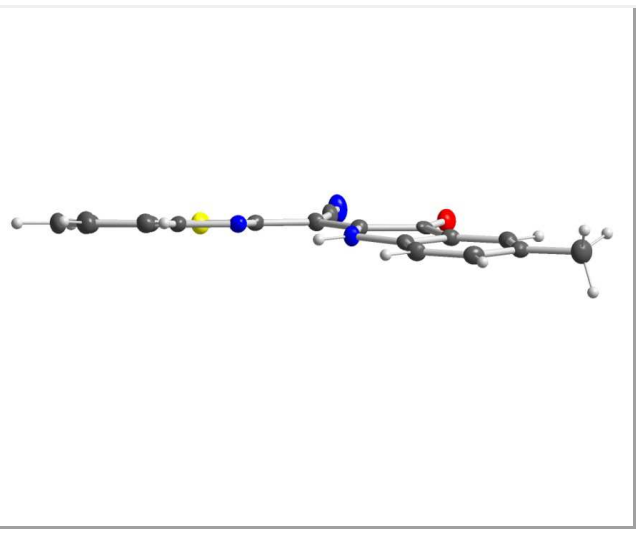


***Figure 2.18**. a) Molecular structure of **2.24b** according to X-ray diffraction.*

b) Orthogonal projection.

There is the broadened signal of NH group proton (δ = 11.4–12.0 ppm) in ^{1}H NMR spectra of **2.24-2.26** as it was observed for 2-(pyrrolidin-2-ylidene)acetonitrile derivatives **2.1**. Such low field shift caused by intramolecular hydrogen bond between nitrogen of azaheterocycle and hydrogen of pyrrolidine (NH). According to XRD estimated length of H3A···N1 hydrogen bond is 2.15 Å, the angle N3–H3A···N1 123.3° (*Figure 2.18*). The low field shift is additionally enhanced due to the deshielding effect of conjugated carbonyl group. The dihedral angle between the 3-oxindole and benzothiazole planes in **2.24b** is equal to 8.8° (*Figure 2.18, b)*), which indicates an effective delocalization of charge in the molecule.

The 2D NMR techniques (COSY, HMQC, HMBC) were used to provide a comprehensive attribution of the ^{1}H and ^{13}C NMR signals (*Figure 2.19*).

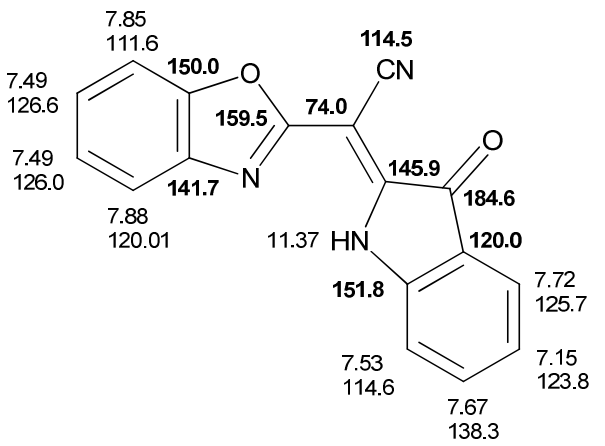
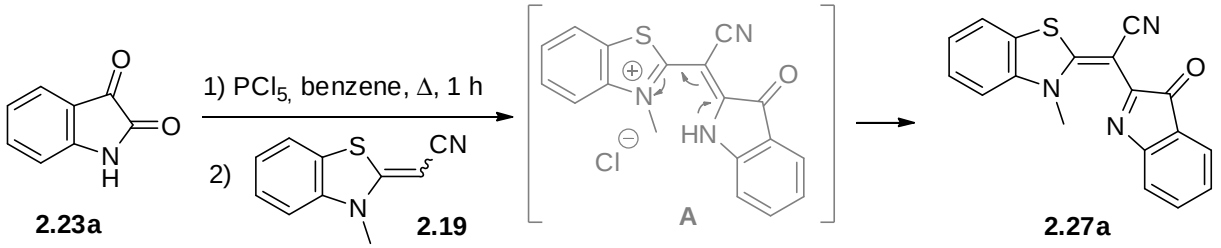


***Figure 2.19.** The chemical shifts of protons and carbons in **2.25a** found by 2D NMR spectroscopy.*

In the case of 2-(3-methylbenzo[*d*]thiazolyl-2(3*H*)-ylidene)acetonitrile **2.19** the reaction product is the base **2.27a**, but not the salt **A**, which is analogue to the one obtained in the reaction with *N*-methylpyrrolidin-2-ones (section 2.3). The imine-enamine equilibrium shift is promoted by the positive charge on the nitrogen of azaheterocycle (*Scheme 2.9*) .



Scheme 2.9. *The reaction of isatin* ***2.23a*** *with N-methylbenzothiazolylacetonitrile* ***2.19****.*

Conclusions regarding the structure of the synthesized molecule were made on the basis of IR spectrum, in which there is no characteristic vibration of the NH group, as well as ^{1}H NMR spectra, in which the signal of NH group proton is absent.

The particularity of 2-functionalized-3-oxindoles **2.24-2.26** is their behavior when changing the acidity of the medium. Absorption of **2.24b** and **2.25a** as a function of pH (from 3.8 to 11.2) were studied in DMSO:H_2O 5:1 for **2.24b** (*Figure 2.20*) and DMSO:H_2O 3:2 for **2.25a** (*Figure 2.21*).

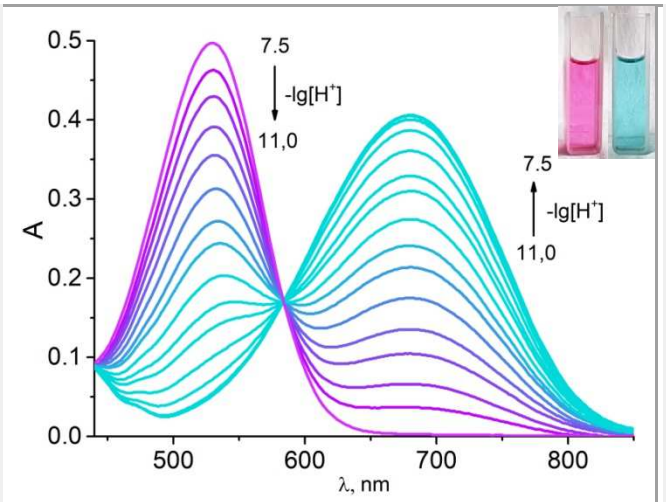


Figure 2.20. *The absorption spectra of* ***2.24b*** *in DMSO:H_2O (5:1) at different acidity of the medium.$C_{2.24b}$ = 40 μmol/l*

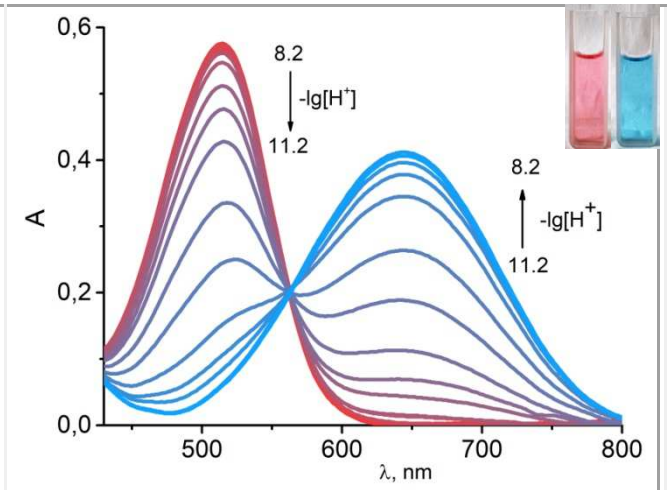
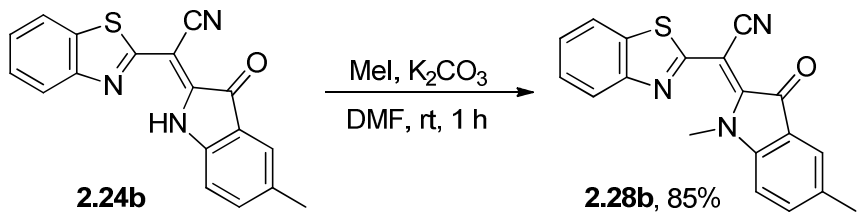


Figure 2.21. *The absorption spectra of* ***2.25a*** *in DMSO:H_2O (3:2) at different acidity of the medium. $C_{2.25a}$ = 40 μmol/l*

While increasing the basicity of the medium the batochromic shift of absorption λ_{max} is occurring, 150 nm for **2.24b** (λ_{abs}^{max} = 680 nm) and 130 nm for **2.25a** (λ_{abs}^{max} = 665 nm). Visually it is the change from purple to blue color.

The conditional dissociation constants (pKa) were calculated for **2.24b** and **2.25a** on the basis of the obtained data: $pKa_{\mathbf{2.24b}} = 10.09 \pm 0.05$; $pKa_{\mathbf{2.25a}} = 10.96 \pm 0.25$.

Considering the ease of 2-azahetaryl-2-(5-R-3-oxoindolin-2-ylidene)acetonitriles deprotonation we have tried to alkylate them. As it was mentioned earlier in the text (section 2.1) 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles **2.1** require harsh reaction conditions and even in this case the alkylation proceed only partly. In contrast methylation of **2.24b** proceed already at room temperature with stochiometric amount of K_2CO_3 (*Scheme 2.10*).

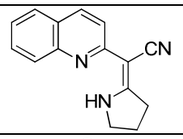
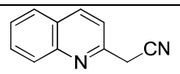
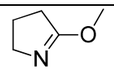
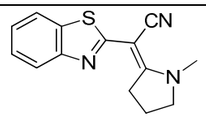
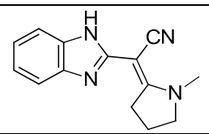
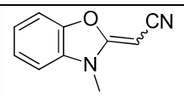
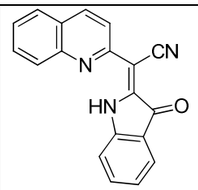
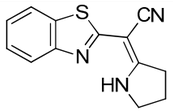
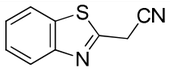
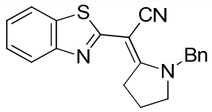
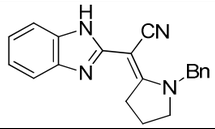
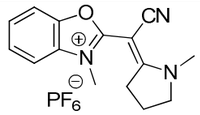
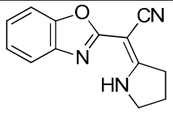
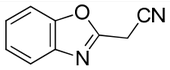
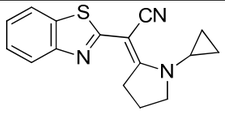
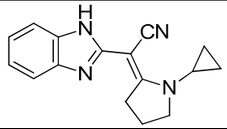
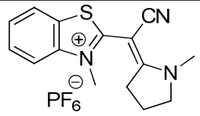
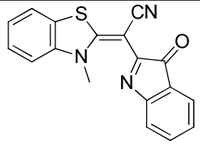
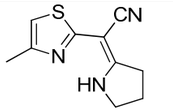
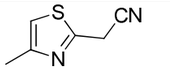
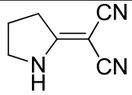
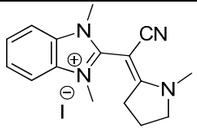
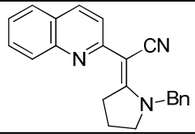
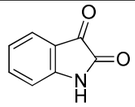
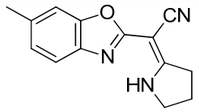
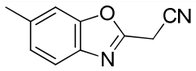
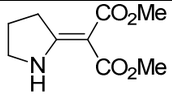
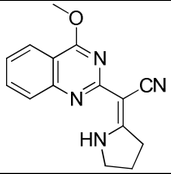
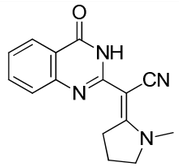
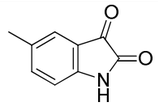
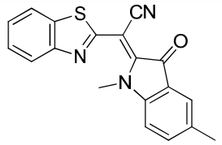
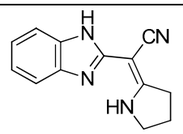
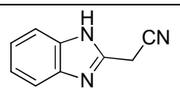
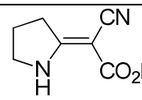
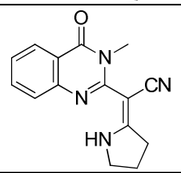
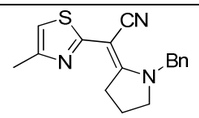
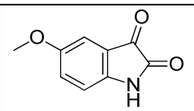
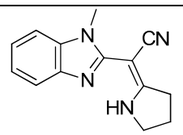
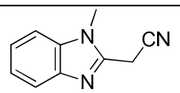
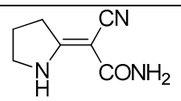
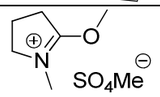
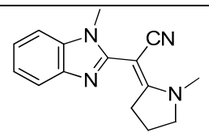
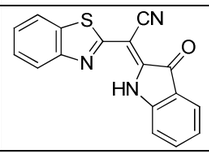
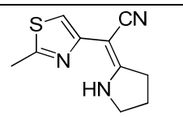
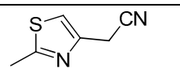
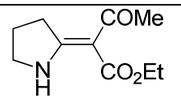
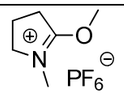
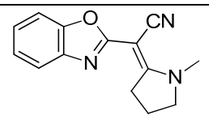
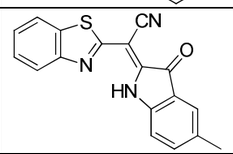
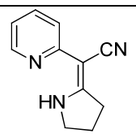
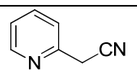
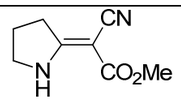
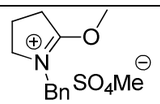
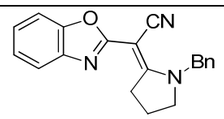
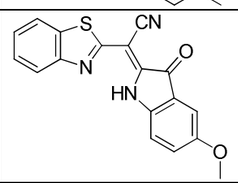
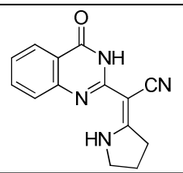
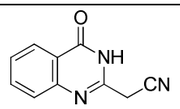
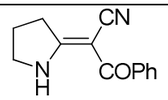
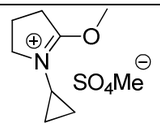
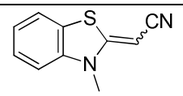
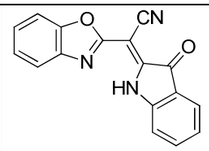


Scheme 2.10. *Alkylation of 2-benzo[d]thiazol-2-yl-2-(5-R-3-oxoindolin-2-ylidene)acetonitrile* ***2.24b***

To conclude, the preparative methods of 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles and 2-azahetaryl-2-(5-R-3-oxoindolin-2-ylidene)acetonitriles synthesis we have developed allowed to study the functionalization of their reactive centres. A thorough structure investigation gives the access to prediction of their behaviour in the reactions with nucleophiles and electrophiles.

The closely spaced location of the donor nitrogen atoms in *N*-unsubstituted pyrrolidines and 3-oxoindolines enables them to coordinate atoms with vacant orbitals. The results of the corresponding studies are presented in chapter 5.

List of samples

2.1a		**2.2a**		**2.3**		**2.7a**		**2.13a**		**2.20**		**2.26a**	
2.1b		**2.2b**		**2.4**		**2.7b**		**2.13b**		**2.21**			
2.1c		**2.2c**		**2.5**		**2.7c**		**2.13c**		**2.22**		**2.27a**	
2.1d		**2.2d**		**2.6a**		**2.8**		**2.14b**		**2.23a**			
2.1e		**2.2e**		**2.6b**		**2.9**		**2.15a**		**2.23b**		**2.28b**	
2.1f		**2.2f**		**2.6c**		**2.10**		**2.16b**		**2.23c**			
2.1g		**2.2g**		**2.6d**		**2.11a**		**2.17a**		**2.24a**			
2.1h		**2.2h**		**2.6e**		**2.11´a**		**2.18a**		**2.24b**			
2.1i		**2.2i**		**2.6f**		**2.11b**		**2.18b**		**2.24c**			
2.1j		**2.2j**		**2.6g**		**2.11c**		**2.19**		**2.25a**			

CHAPTER 3. 2-AZAHETARYL-2-(1-R-PYRROLIDIN-2-YLIDENE)ACETONITRILES AS 1,3-DIELECTROPHILES. SYNTHESIS OF PYRAZOLES/ISOXAZOLES AND THEIR CHEMICAL MODIFICATION

The delocalization of electron density of enamine moiety in 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles is driving their reactivities toward nucleophiles. We have seen in chapter 2 that both nitrile and heterocycle act as electron withdrawing groups. Such delocalization promotes a shift in the enamine-imminium equilibrium, enhancing the electrophilicity of the C-2 atom of enaminonitrile fragment and simultaneously lowering that of the nitrile group. These observations suggest that 1,3-dielectrophiles can be expected to react with binucleophiles in a very regioselective fashion. This could therefore allow an overall atom- and step-economical generation of 3-(ω-aminoalkyl)-4-hetaryl-5-aminoazoles **3.1-3.7**, that have only scarcely described[10] (*Figure 3.1*).

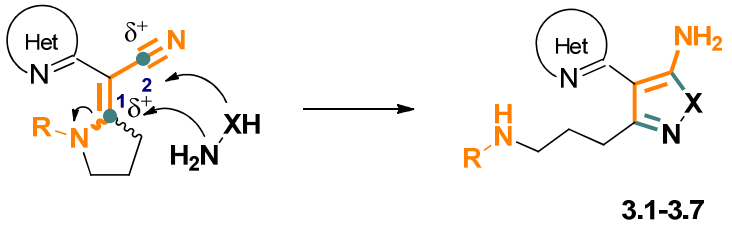


***Figure 3.1**. 2-Azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles as 1,3-dielectrophiles.*

In this chapter we report the reactions of various enaminonitriles, which exhibit different electron density distributions and the spatial structures (chapter 2) with 1,2-binucleophiles, such as hydrazines and hydroxylamine. Our aim was to explore: 1) the influence of alkyl substituent at the nitrogen of pyrrolidine (section 3.1), and 2) the influence of the nature and the substitution extent of benzazoles (section 3.2) on the reaction's path with 1,2-binucleophiles.

Synthesized polyaminoazoles were subjected into reactions of regioselective derivatization, transformation into tetracyclic azaheterocycles, Suzuki-Miyaura cross-coupling and reductive deamination with further C-H activation (subsection 3.1.1).

3.1. Reactions of 2-azahetaryl-2-(1-R-pyrrolidin-2-ylidene)acetonitriles with 1,2-binucleophiles involving C-2 atom of pyrrolidine and carbon of nitrile group

There are very few references dealing with the reactions of 2-(pyrrolidin-2-ylidene)acetonitriles with 1,2-binucleophiles. The reason for this is the lack of reactivity of the latter (subsection 1.3.2). Without activation of C-2 centre of pyrrolidine the transformation requires harsh conditions (the excess of 1,2-binucleophile, elevated temperature).

We have attempted to conduct the reaction of *N*-unsubstituted pyrrolidines **2.1** with 1,2-binucleophiles. Neither the excess of binucleophile nor the high temperature lead to the expected product. The starting material remained unchanged or the product of degradation was observed (hetarylacetonitrile was isolated).

In contrast, *N*-alkylpyrrolidines **2.7**, **2.13-2.15** that has no intramolecular hydrogen bond react with 1,2-binucleophiles successfully. The reaction proceeded smoothly in refluxing dioxane with 10−20 equiv excess of the binucleophile reagent and provided the pyrazoles and isoxazoles in moderate to good yields (*scheme3.1*).[101, 109]

The nature of the alkyl substituent on the pyrrolidine nitrogen was shown to only moderately affect the efficiency of the reaction (**3.1a-c**). Moving from methylhydrazine to hydrazine hydrate was found to promote a decrease in reaction yields (**3.1c** vs. **3.2c**), whereas no discernable effect was observed upon switching from methylhydrazine to hydroxylamine (**3.4b** vs. **3.5b**). Finally, variations in the nature of the heterocyclic moiety did not significantly affect the overall efficiency, although benzothiazole substitution systematically provided better efficiencies, all things being otherwise equivalent.

3-(ω-Aminoalkyl)-4-hetaryl-5-aminopyrazoles **3.1**–**3.4**, **3.6** and isoxazoles **3.5**, **3.7** were isolated with good analytical quality after a simple solvent evaporation and trituration in acetone or acetonitrile, or column chromatography.

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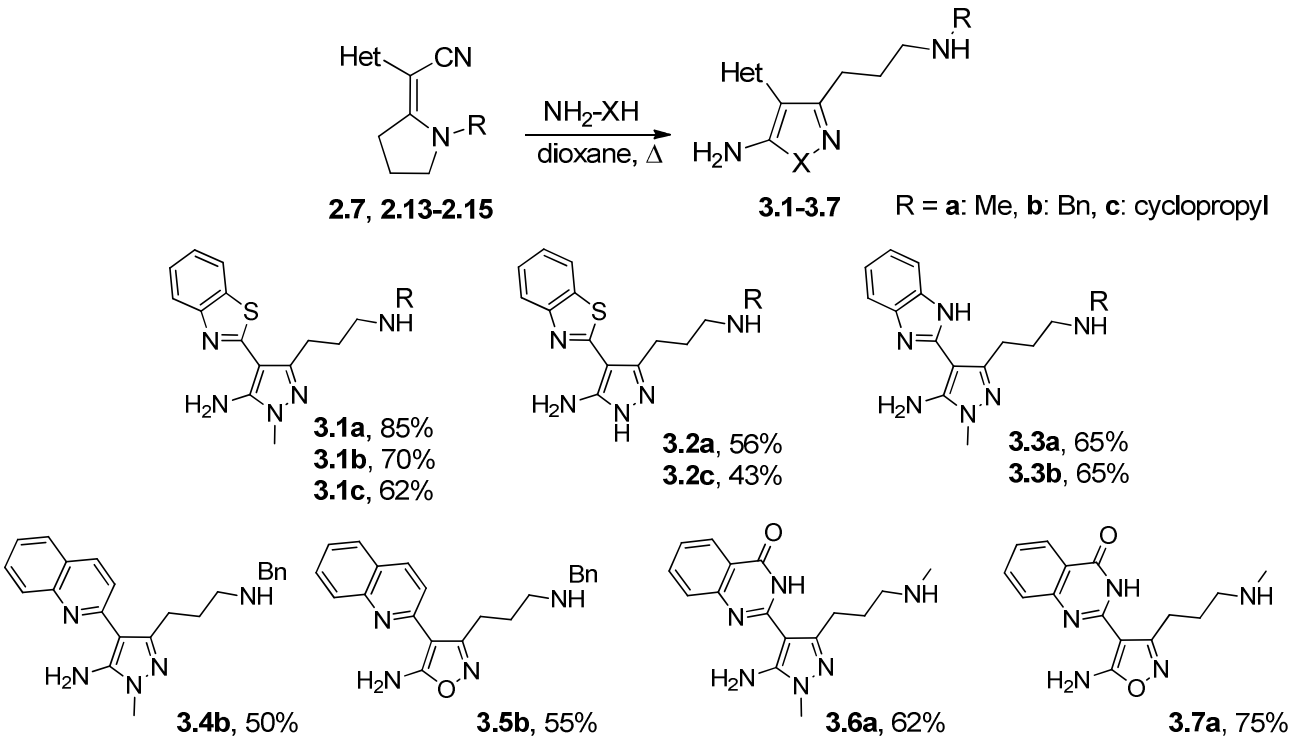


Scheme 3.1. *Reactions of 2-azahetaryl-2-(1-R-pyrrolidin-2-ylidene)acetonitriles* ***2.7***, ***2.13–2.15*** *with 1,2-binucleophiles.*

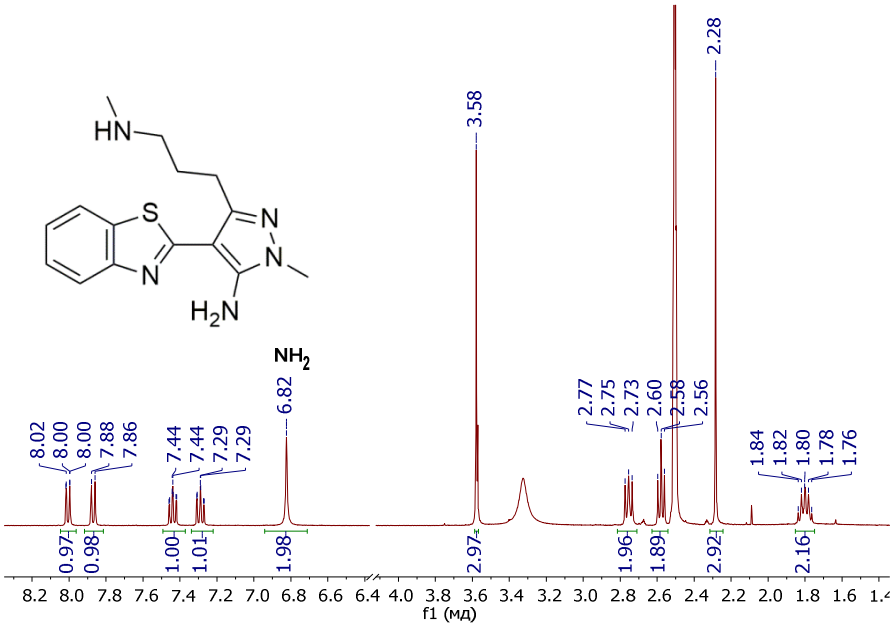


Figure 3.2. *^{1}H NMR spectrum of pyrazole* ***3.1a*** *(400 MHz, DMSO-d_6).*

The involvement of the nitrile group, initially present in **2.7**, **2.13–2.15**, in the reaction is highlighted by the disappearance of its characteristic stretching vibration absorptions in the 2198−2178 cm^{-1} range of the IR spectra.

Thorough structural analysis of the compounds was carried out using ^{1}H NMR, ^{13}C MNR, 2D NMR techniques and IR. Particularly, in DMSO-d_6, a characteristic singlet of NH_2 in the ^{1}H NMR spectrum is observed at 6.25−6.94 ppm. Interestingly, this signal is shifted up-field for isoxazoles, probably as a consequence of oxygen electronegativity

(**3.6a**, 8.04 ppm**; 3.5b**, 8.20 ppm). In both cases, addition of D_2O promotes the disappearance of these singlets, evidencing the exchangeable nature of the corresponding protons.

The ^{13}C NMR spectra of **3.1-3.7** show three signals corresponding to the carbons of the pyrazoles (isoxazoles). The first one, found at a chemical shift in the 147.1−149.0 ppm range, was assigned to the C5 atom of the pyrazole ring, and again, this signal was shifted up-field for isoxazoles (at around 169.2−170.5 ppm). The signals within the range 90.3−100.8 and 148.6−161.3 ppm correspond to C4 connected with a heterocyclic substituent and to C3 bonded with the *ω*-aminoalkyl chain, respectively.

Pleasingly, 4-hetarylaminopyrazoles **3.1a**, **3.1c** and **3.2a** formed crystals suitable for XRD study, allowing careful analysis of their structure. The benzothiazolyl substituent is almost coplanar with the pyrazole ring, with a dihedral angle of 6.48° and 1.16° for **3.1a** and **3.1c**, respectively, indicating a significant overlap of the π systems. The flattened orientation of the planar fragments is further stabilized by an intramolecular hydrogen bond between one of the protons of the amino group and the nitrogen of the benzothiazole. In the crystal lattice molecules of **3.2a** aligned antiparallel to each other and are complementary paired. Such packing stabilized by intermolecular hydrogen bonds (estimated bond length H4A···N5 2.00 Å, N4-H4A···N5 164.8°) (*Figure 3.3*).

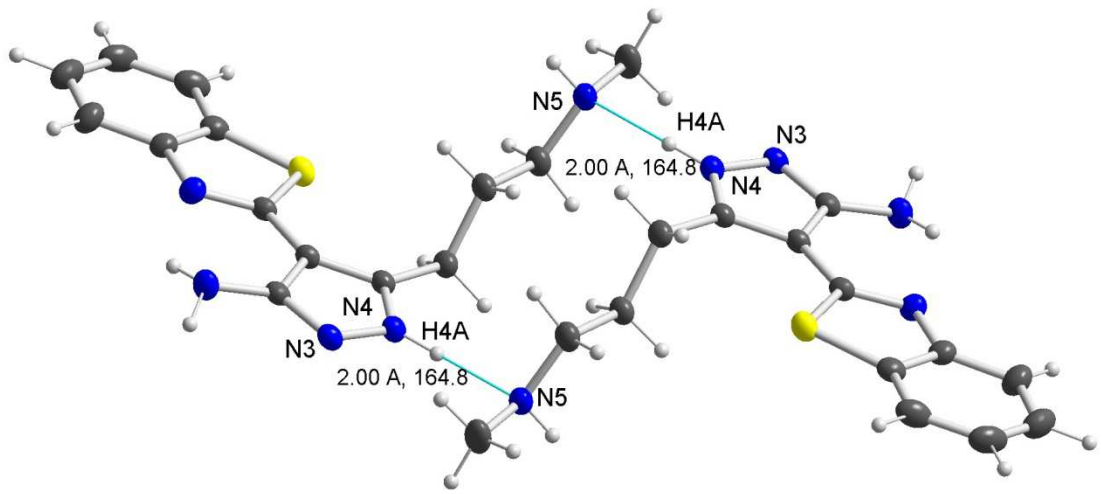


Figure 3.3. *Molecular structure of compound **3.2a** according to X-Ray diffraction. Hydrogen bonds formation in the complementary pair.*

For **3.6a** (*Figure 3.4*) featuring a quinazolinonyl substituent, distinct changes in conformation were observed. XRD data seem to indicate that **3.6a** exists as a zwitter-ion in the solid state. Indeed, the hydrogen located, initially, at N2 in **2.15a** seems to be covalently bound with the secondary amino group in the aliphatic chain of **3.6a** (N6−H6B 0.93 Å). The lone pair on N2 exhibits stronger conjugation with its adjacent carbonyl group, as shown by the shortened N2−C7 (1.340 Å) and elongated C7−O1 (1.273 Å) bond lengths, when compared to that of **2.15a** (N2−C7, 1.378 Å; C7−O1, 1.230 Å). N2 forms an intramolecular hydrogen bond with H6B (estimated bond length N2···H6B, 1.89 Å; N6−H6B···N2, 175.49°), whereas O1 forms an intermolecular hydrogen bond with H6A (estimated bond length O1···H6A, 1.78 Å; N6−H6A,···O1 170.96°) of an adjacent molecule. The positioning of the pyrazole and quinazolone planes (dihedral angle of 19.65°) in **3.6a** allows the molecule to adopt an energetically favored conformation, placing both N2−H6B and N1−H3A in close proximity (estimated bond length H3A···N1, 2.24 Å; N3−H3A···N1, 127.29°).

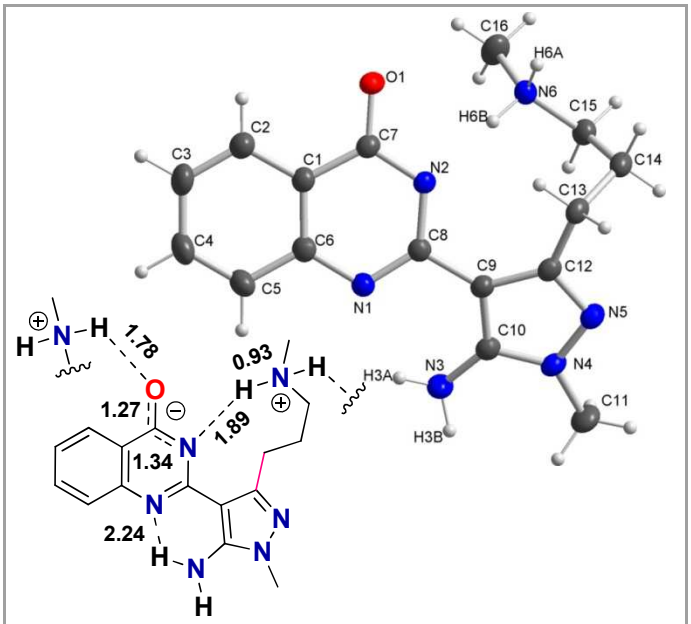
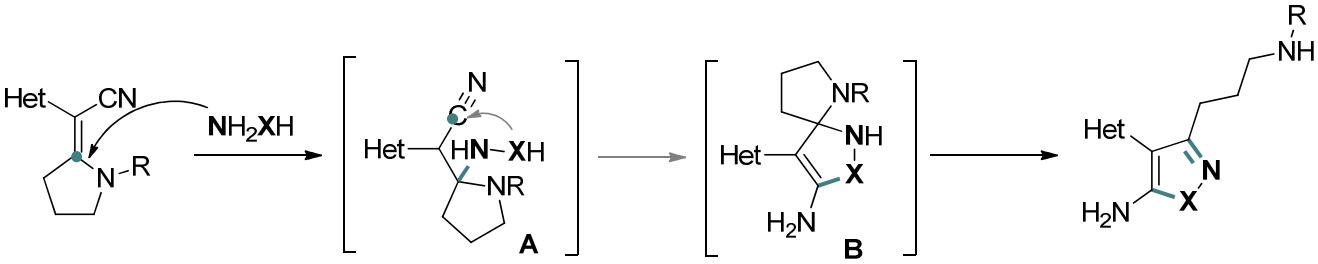


Figure 3.4. *Molecular structure of compound **3.6a** according to X-Ray diffraction.*

Considering the analytical and structural data obtained for the pyrrolidine precursors, as well as precedents from the literature,[62, 65] a ring conversion from pyrrolidine to pyrazole (or isoxazole) is expected to proceed via nucleophilic attack of the unsaturated carbon of the pyrrolidine yielding **B**; spiro intermediates **C** would then form upon attack of the second atom of the binucleophile on the nitrile group in a favored 5-exo-dig fashion. Finally, ring opening of the pyrrolidine ring promotes the aromatization of the azole ring and provides the nitrogen-substituted aliphatic

chain. Such an addition of nucleophile-spiro annulation-ring opening (ANSARO) mechanism is thought to be operative in this transformation (*Scheme 3.2*).



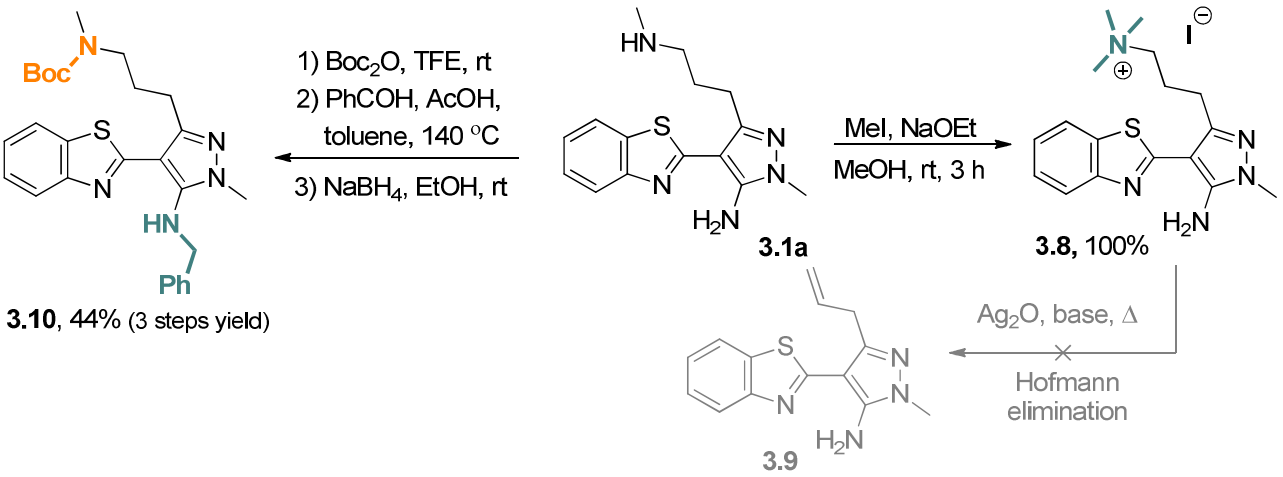
Scheme 3.2. *Proposed mechanism for the ring conversion.*

3.1.1. Regioselective functionalization of 3-(ω-aminopropyl)-4-azahetaryl-5-aminopyrazoles

Having this straightforward access to densely functionalized pyrazoles in hand, we further explored their synthetic potential by assessing the ability to selectively introduce structural variations on their reactive centres, namely, the amino groups.

The first approach was to illustrate the possibility of selectively functionalizing the amino groups substituting the pyrazole core. For that purpose, we confirmed that the secondary alkylamine is significantly more nucleophilic than the primary aromatic one. Indeed, alkylation of the secondary amino group could be achieved simply by stirring **3.1a** with 1 equiv of the base and 2.2 equiv of alkylating reagent at room temperature, leaving the primary amino group unaffected (*Scheme 3.3*). The reaction produced a white precipitate, which structure was confirmed to be **3.8** by analysis of the filtrated solid by ^{1}H, ^{13}C, and 2D NMR as well as high resolution mass spectrometry (HRMS). Expectedly, the symmetry achieved through formation of the ammonium salt significantly lowers the quadrupolar coupling constant of nitrogen, allowing observation in the ^{13}C NMR spectrum of the ^{14}N−^{13}C coupling for the methyl (J_{CN} = 4 Hz) and the methylene (J_{CN} = 3 Hz) carbons of the ammonium.

Extensive attempts to perform Hofmann elimination from **3.8** failed to provide the corresponding alkene **3.9**, leading to ammonium recovery or degradation when reaction conditions were forced.



Scheme 3.3. *Regioselective alkylation of amino groups from* ***3.1a.***

Consequently, the substitution of the primary aromatic amino group was found to require the protection of the secondary amine (*Scheme 3.3*). This could be achieved in 93% yield by simple treatment of **3.1a** with a slight excess of di-*tert*-butyl dicarbonate (Boc_2O) in trifluoroethanol[110] for 10 min at room temperature followed by column chromatography.

With this protection in place, we could perform a reductive amination of the primary amino group. It is known that for 5-aminopyrazoles such transformation does not require any acidic catalysis and proceed at 60 °C.[111]

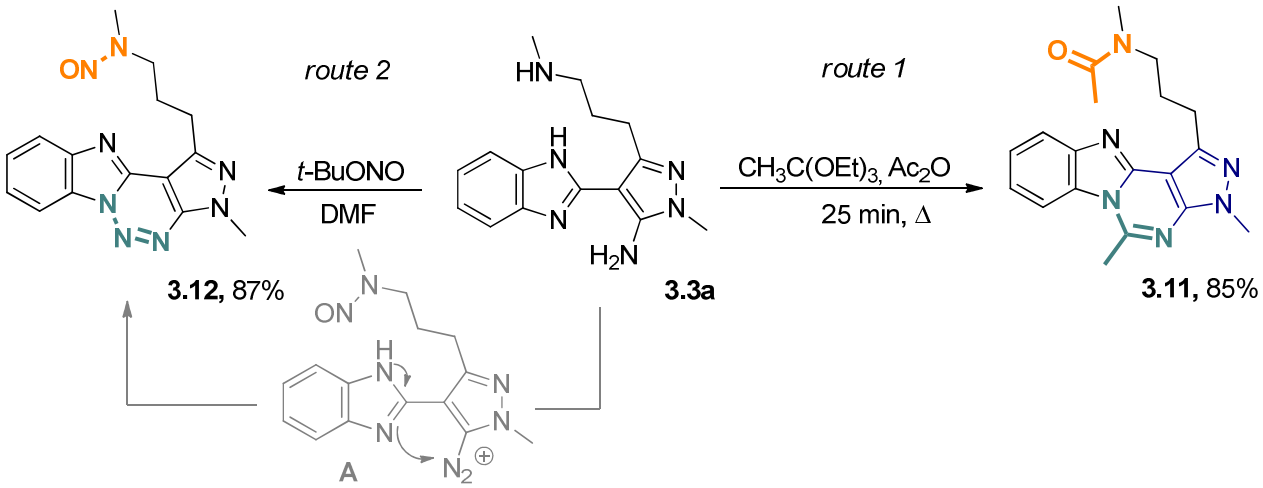
In contrast to the reference data, the primary amino group of **3.1a** reacts with aldehyde only at elevated temperature, in the presence of an acid. The produced Shiff bases are unstable and easily degrade to the starting material. After intensive efforts we have found the appropriate reaction conditions involving the use of sealed vessel and inert atmosphere to access the Shiff base. Then following reduction with sodium borohydride proceeded quickly in a protic solvent.

Compound **3.10** was isolated after column chromatography in 47% yield (44% over three steps from **3.1a**). Unreacted starting material was fully recovered (*Scheme 3.3*).

The pendant amino group on the pyrazole and proximate NH of the benzimidazole allows condensation of **3.3a** with electrophiles such as orthoesters. This approach could deliver pyrazolopyrimidine scaffolds of interest for medicinal chemistry purposes, as has been exemplified in the development of inhibitors of

glycogen synthase kinase 3, an enzyme involved in numerous diseases such as type II diabetes, Alzheimer's disease, cancer, bipolar disorder, and inflammation.[112]

Upon boiling a mixture of **3.3a** and 1,1,1-triethoxyethane in the presence of acetic anhydride, we could achieve the synthesis of 3*H*-benzo[4,5]imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine **3.11** (*Scheme 3.4, route 1*); it is important to note that a dehydrating agent is required to bring the reaction to completion. This illustrates weak stability of the formed pyrimidine ring that only tends to hydrolyze back to the acylated starting material both under strongly acidic and basic conditions.

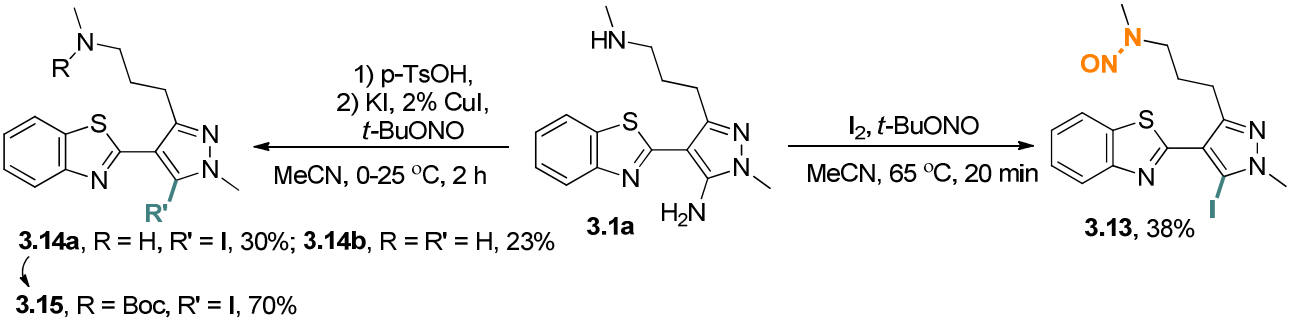


Scheme 3.4. *Straightforward access to fused tetracyclic structures* ***3.11***, ***3.12***.

Yet, under neutral conditions, **3.11** could be isolated and thoroughly characterized. The ^{1}H NMR spectrum of **3.11** in $CDCl_3$ shows two sets of peaks corresponding to two unequally populated rotamers. Moreover, the symmetry of the benzimidazole moiety initially found in **3.3a** is disrupted through this transformation, promoting the split of the two aromatic signals of **3.3a** into four signals for **3.11**, namely, two doublets at 7.94 and 8.04 ppm and two doublets of doublets at 7.41 and 7.53 ppm.

A somehow similar tetracyclic aromatic compound was also accessed by simple treatment of **3.3a** with an excess of *tert*-butyl nitrite in DMF (*Scheme 3.4, route 2*). Under these conditions, the diazonium intermediate could indeed be trapped by the imidazole nitrogen to generate the corresponding triazene **3.12**, with concomitant protection of the secondary amine as a nitrosoamine. **3.12** was isolated in 85% yield after column chromatography and fully characterized. It exhibits a unique tetracyclic

structure that has never been previously described, and as such, expands the chemical space of heterocyclic chemistry.



Scheme 3.5. *Sandmeyer iodination of the aminopyrazole core.*

Finally, following this diazotization strategy, we investigated the lability of the 5-amino group. At first, we explored the ability of these heterocyclic-substituted aminopyrazoles to undergo Sandmeyer-type reactions. After extensive investigation, we found that to avoid the formation of numerous byproducts, the reaction had to be carried out at 65 °C with excess *tert*-butyl nitrite (5 equiv) and I_2 (4.3 equiv) in acetonitrile,[113] furnishing iodopyrazole **3.13** in 38% yield (*Scheme 3.5*). As stated above for the formation of **3.12**, the secondary amine was converted to its nitrosamine derivative. We found that this could be avoided by first adding TsOH to the reaction mixture; under these acidic conditions, the secondary amine is protected as a weakly acidic ammonium salt avoiding nitrosation. Thus, only the primary aromatic ammonium formed under these conditions appears acidic enough to undergo nitrosation and water elimination to form the transient diazonium salt, which finally generates the iodopyrazole **3.14a** in 30% yield.

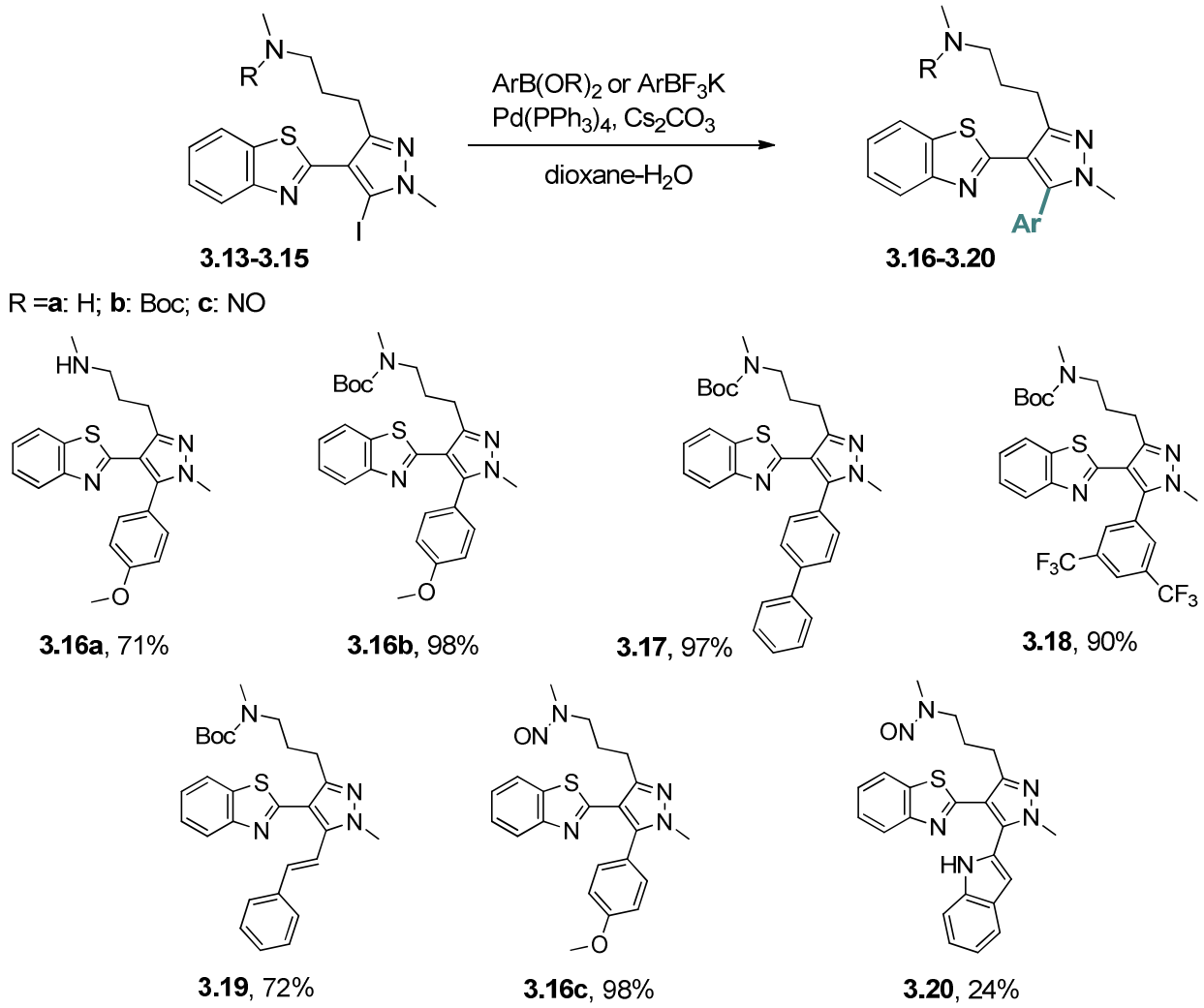
Interestingly, under these acidic conditions, the reaction proceeds with the formation of the reductive deamination byproduct **3.14b** (~1:1).

The introduction of iodine is easily monitored by the ^{13}C NMR spectrum of **3.14a** characterized by considerable shielding of C5 by the adjacent I atom (**3.1a**, 147.1 ppm; **3.14a**, 86.5 ppm).

Further, Boc protection of the secondary amine could be achieved in trifluoroethanol yielding **3.15** in 70% yield. This two step iodination−protection proved only moderately efficient (21%) that is almost two times less than *one pot*

reaction of iodination-nitrosation – 38%. The efficiency of the latter approach highlighting the nitrosamine as a potentially useful alternate protecting group, although cancerogenic properties might be found.

With these iodinated pyrazoles in hand, we explored potential C−C bond formation by way of Suzuki−Miyaura cross-coupling with a range of boronic acids (*Scheme 3.6*). A first attempt using **3.14a** and 4-methoxyboronic acid under conventional conditions (5% $Pd(PPh_3)_4$, dioxane-H_2O, Cs_2CO_3) provided the desired cross-coupling compound **3.16a** in 71% yield. Yet the presence of the secondary amine made chromatographic analysis and purification tedious.



Scheme 3.6. *Suzuki−Miyaura cross coupling of iodinated pyrazoles* ***3.13-3.15****.*

We therefore turned to **3.15** as the starting pyrazole and were pleased to achieve the cross-coupling to **3.16b** isolated in quantitative yield. We could further exemplify this reactivity by isolating **3.17** and **3.18** quantitatively, and **3.19** in 72% yield. Yet,

moving to *ortho*-substituted 2-nitrophenylboronic acid and 2,6-bis-(trifluoromethyl)phenylboronic acid fully inhibited the coupling reactivity due to the steric bulk around the reactive site of the iodopyrazole derivative.

Considering the more efficient access to **3.13** (38% vs 21% for **3.14a**), we envisaged the unprecedented use of nitrosamine as a protecting group during the Suzuki−Miyaura cross-coupling. This was found to be a successful approach because the cross-coupling leading to **3.16c** occurred in quantitative fashion (*Scheme 3.6*).We could also access the heterocyclic compound **3.20** using N-Boc-indole 2-trifluoroborate, albeit with a moderate yield and under harsher conditions (140 °C) that promoted the thermolysis of the Boc group.

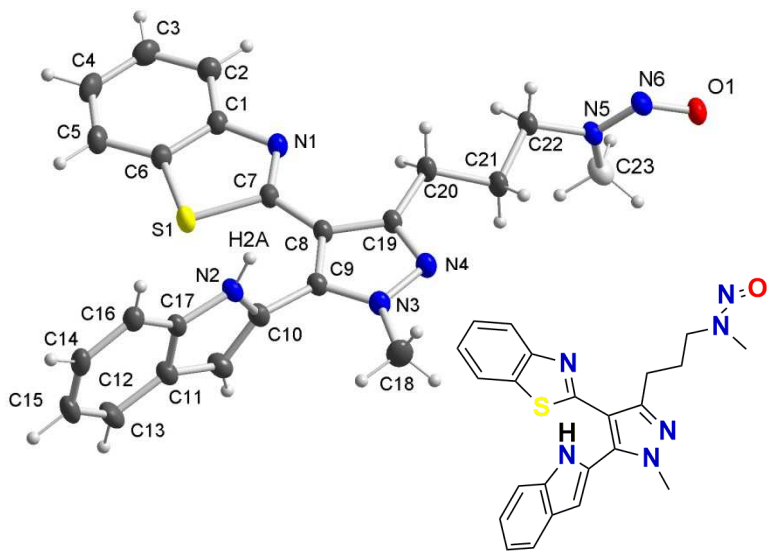


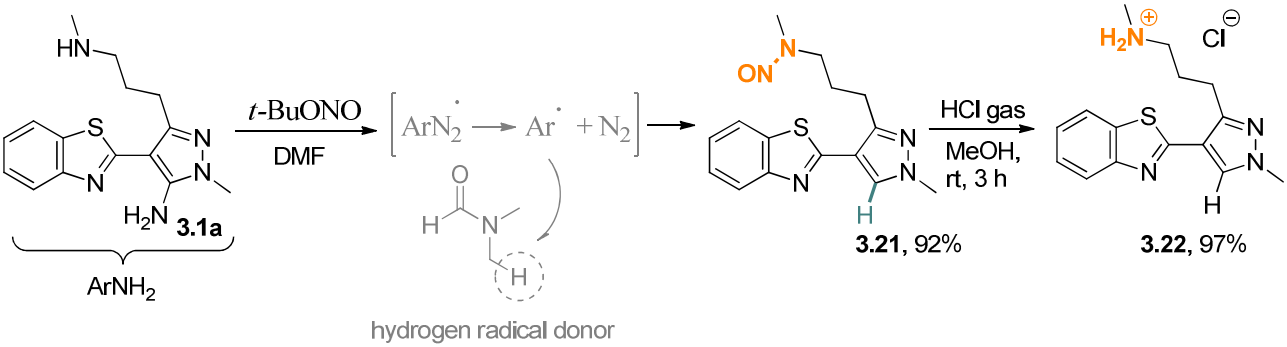
Figure 3.5. *Molecular structure of compound* ***3.20*** *according to X-Ray diffraction.*

According to XRD study in 5-indol-2-ylpyrazole **3.20** the indole and pyrazole planes are orthogonal to each other (89.7°); benzothiazole and pyrazole are almost coplanar, the dihedral angle is equal to 3.9° (*Figure 3.5*). Such a relative position of fragments stabilize by intermolecular hydrogen bonds in complementary pair, that consist of molecules of 5-indole-2-ylpyrazole aligned antiparallel to each other (H2A···O1 2.02 Å, N2–H2A···O1 171.3°).

Finally, considering the observation of reduced product **3.14b** (~1:1 relative to iodinated product **3.14a**) during the Sandmeyer reaction (*Scheme 3.4*), we investigated the possibility of performing such a reduction more efficiently.

On the basis of former reports,[114] we could achieve radical deamination of benzothiazole substituted pyrazole **3.1a** to **3.21** with *tert*-butyl nitrite in dimethylformamide (*Scheme 3.7*). Indeed, opposite to the reaction with benzimidazole **3.3a** (*Scheme 3.4*), no intramolecular trapping to the triazene can be

achieved from **3.1a**. Therefore, it is thought that the classical homolytic decomposition during diazotization allowed hydrogen abstraction from the solvent by the pyrazolyl radical to afford the desired reduced compound **3.21**. The latter was isolated and fully characterized. Similarly to the transformations described above, the reaction proceeds with concomitant nitrosation of the secondary amine.



Scheme 3.7. *Reductive deamination of 4-benzothiazol-2-ylpyrazole* ***3.1a****.*

From the mechanistic point of view, the nature of the hydrogen source is expected to be the methyl group of DMF. Indeed, it has been stated[114] that acetonitrile could also act as donor of hydrogen yet better conversions are achieved with DMF. And as tetramethylurea appears almost as efficicent as DMF it is thought that reduction occurs primarily by hydrogen transfer from the *N*-methyl group.

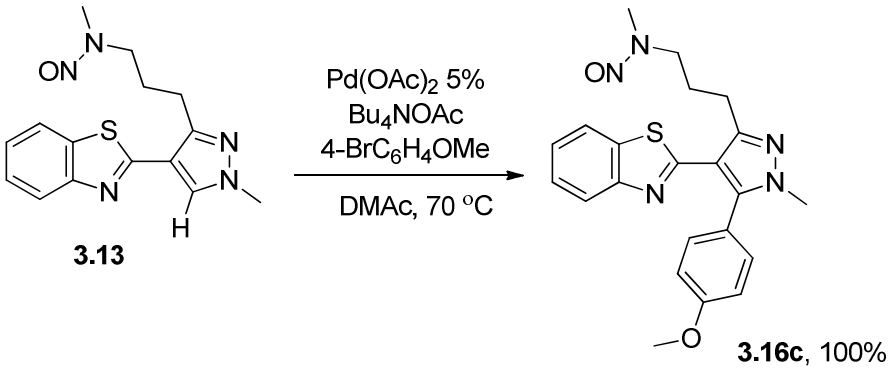
The ^{1}H NMR spectrum of **3.21** shows two sets of peaks corresponding to two unequally populated rotamers, and the characteristic singlet of the newly introduced proton arises at 7.88 ppm (in $CDCl_3$).

Deprotection of the nitrosamine to the corresponding ammonium salt could be easily achieved by bubbling HCl gas in a methanol solution of **3.21**. This two-step procedure gave 3-(4-(benzo[*d*]thiazol-2-yl)-1-methyl-1*H*-pyrazol-3-yl)-*N*-methylpropan-1-aminium chloride **3.22** in 89% overall yield. The ^{1}H NMR spectrum of **3.22** recorded in DMSO-d_6 features a broad singlet for the two protons of the ammonium at 8.94 ppm that disappeared upon D_2O addition.

Although nitrosamines are considered as having limited value as protective groups (mainly as they are considered carcinogenic),[115] we believe, through all our observations, that in this specific case, their facile generation and deprotection make them an attractive option, provided cautious experimental procedures are followed.

Moreover, nitrosamines are also known to promote the umpolung reaction of secondary amines through deprotonation, and as such, they represent an interesting functionalization of aminoalkyl chain.[116]

Having this reduced adduct in hand, we explored the possibility of further functionalization through the C−H activation reaction, as previously reported on pyrazoles.[117-118] We found that heating **3.13** at 70 °C in the presence of $Pd(OAc)_2$, 4-bromoanisole, and tetrabutylammonium acetate in dimethylacetamide (DMAc) for 24 h provided straightforward access to **3.16c** in quantitative yield (*Scheme 3.8).*



Scheme 3.8. *Functionalization of pyrazole through C−H Activation.*

Once again, this illustrates the excellent compatibility of nitrosamine protection with palladium-catalyzed cross-coupling reactions. Moreover, this reaction path provides a highly efficient approach to densely substituted pyrazoles featuring both aryl and hetaryl substituents at the 4 and 5 positions, as **3.16c** is isolated in 71% overall yield from benzothiazolylacetonitrile **2.1b** and avoids ineffective stage of 5-iodopyrazole formation (21-38%).

In summary, we have developed a two-step procedure for the synthesis of fully substituted 4-hetaryl-5-aminoazoles from readily available starting materials in a modified Knorr-type reaction. The reaction was found to be fully selective thanks to an evidenced marked difference between the two centres of the 1,3-dielectrophile. These highly functionalized azoles have been shown to represent entries to various polyheterocyclic compounds, providing a straightforward route to a wide chemical space. Indeed, further reactivity of the 4-hetaryl-5-aminopyrazoles obtained was investigated, providing highly regioselective transformations and giving access to

unknown derivatives with high nitrogen contents. Moreover, transformation of the 5-amino substituent allowed the straightforward introduction of aryl and hetaryl moieties at this position providing a four-step route to densely functionalized pyrazoles. This also illustrates the efficient nitrogen protection as a nitrosamine during the Pd-catalyzed cross-coupling reaction. We consider that this approach opens new routes to enlarge the chemical space of pyrazole-containing pharmacophores as it introduces chemical complexity in an unprecedented swift fashion from simple starting materials.

3.2. Reactions of 2-azahetaryl-2-(1-R-pyrrolidin-2-ylidene)acetonitriles with 1,2-binucleophiles involving C-2 atom of pyrrolidine and C-2 atom of azaheterocycle

To widen the scope of this kind of transformations of cyclic 2-azahetaryl-3-enaminonitriles, we turned our attention to benzoxazolyl substituted derivatives and to quaternized benzazoles substituted ones.

The similarity of the selected objects is that the C-2 atom of azaheterocycle is located between two electron-acceptor groups: the oxygen and the nitrogen in the case of benzoxazole and the corresponding heteroatom (S, N, O) and the quaternized nitrogen atom in another, which, accordingly, increases electron deficiency of above mentioned C-2 atom. Consequently, it could be predicted that the presence of one more electron deficient centre has its impact on the reaction path with 1,2-binucleophiles (*Figure 3.6*).

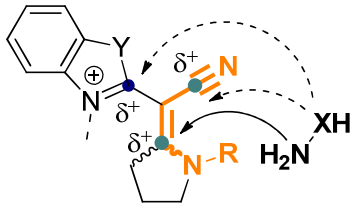


Figure 3.6. *Influence of increased electron deficiency of C-2 atom of azaheterocycle on regioselectivity of reactions with 1,2-binucleophiles.*

3.2.1. 2-Benzo[d]oxazol-2-yl-2-(1-R-pyrrolidin-2-ylidene)acetonitriles in reactions with 1,2-binucleophiles

Regioselectivity in reactions of benzoxazol-2-yl substituted pyrrolidin-2-ylidenes **2.18** with 1,2-binucleophiles was primarily explored.

After proceeding the reaction with methyl hydrazine[12] two sets of peaks with the same integral intensity were observed in ^{1}H NMR of crude reaction mixture arising as one spot on TLC. After the appropriate elution system was found ($CHCl_3$–CH_3OH–Et_3N, 20:2:1) we have separated the products and thoroughly analyze them by ^{1}H, ^{13}C and 2D NMR techniques as well as HRMS. The characteristic range for benzazoles aromatic protons is 7.1–7.7 ppm. Arising of aromatic protons in the 6.6-7.0 ppm range of one of the products might be influenced by benzoxazole ring opening (*Figure 3.7*). M + H^+ equal to 286.17 obtained by mass analysis is indicative for the presence of two isomers. Moreover, the stretching vibrations at 2218 cm^{-1} found by IR analysis unambiguously indicated that one of the isomers has still a nitrile group, thus no nucleophile attack was occurring on this centre. Considering these evidences we have suggested the structure of two isomers **3.23a** and **3.24a** and the mechanism of their formation (*Scheme 3.9*).

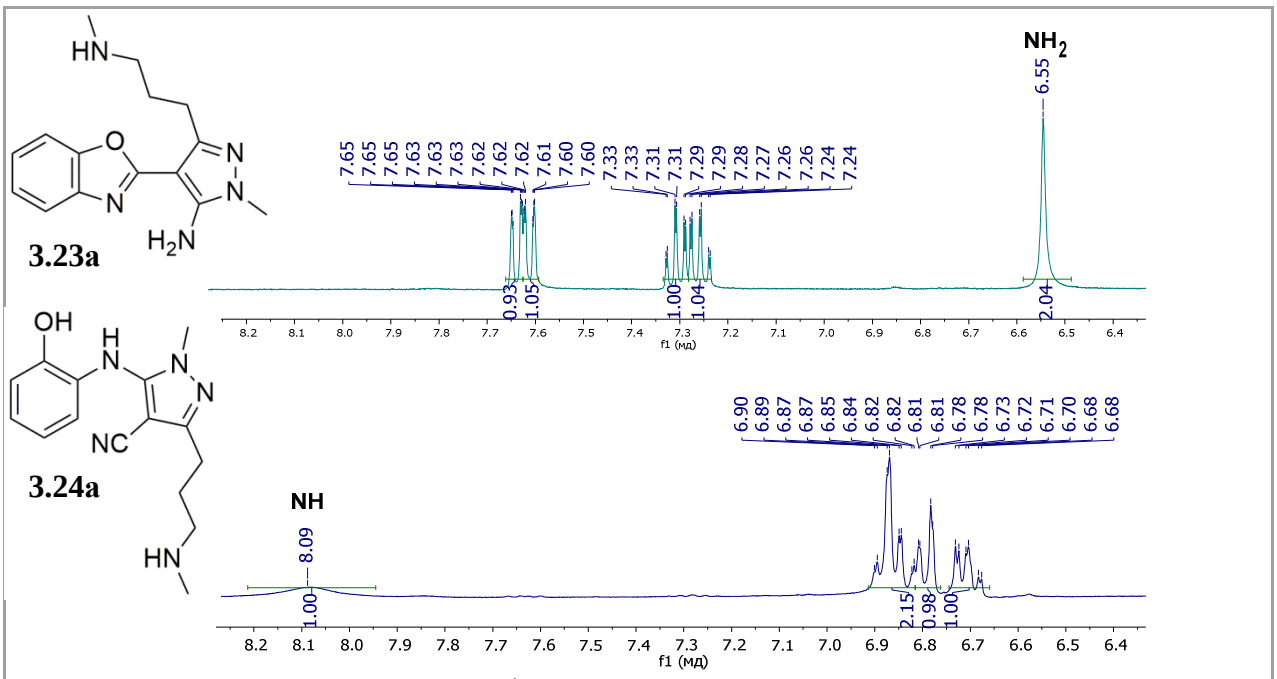
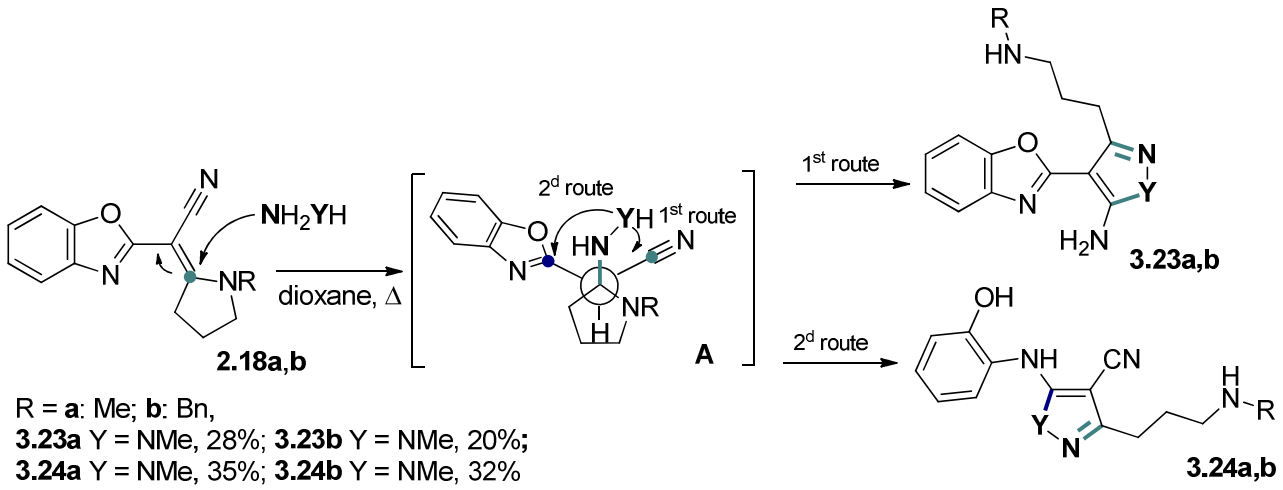


Figure 3.7. *A fragment of the ^{1}H NMR spectrum of **3.23a** and **3.24a** (Solvent: DMSO-d_6).*

[12] Reaction was performed under the same conditions applied earlier toward the synthesis of 3-(ω-aminoalkyl)-4-hetaryl-5-amino-pyrazole (or isoxazole) 3.1-3.7: refluxing in dioxane, 10-20 equiv of methylhydrazine



Scheme 3.9. *The reaction of benzoxazol-2-yl-2-(1-R-pyrrolidin-2-ylidene)acetonitriles* ***2.18*** *with methylhydrazine.*

Mechanism includes the NH attack at C2 atom of pyrrolidine ring leading to intermediate **A** in which YH is situated in the same proximity to both nitrile group and C2 atom of benzoxazole and attacks one or the other with a probability that depends directly on their electrophilicity. As stated above, the structural isomers **3.23a** and **3.24a** form with the ratio 1:1 that indicates a similar electrophilicity of C-2 atom of azaheterocycle and carbon of nitrile group in the intermediate **A**.

A similar observation was made for the reaction involving **2.18b** that afforded two structural isomers **3.23b** and **3.24b** with 1 to 1 ratio.

This 1 to 1 ratio can be explained as follow: the reaction of 2-benzoxazol-2-yl-*N*-R-pyrrolidinacetonitrile requires a 101 °C temperature to proceed (boiling point of dioxane) making this step the rate limiting one. Cyclization then proceed with no selectivity at such temperature thus promoting this 1:1 ratio. Careful follow up by TLC indicated that both products form simultaneously as soon as starting material is consumed. Moreover the relative amount of each product remaining unchanged until complete conversion of reactants.

In the ^{1}H NMR spectrum the protons of amine group of pyrazoles **3.23a,b** arise at 6.55 and 6.51 ppm correspondingly; the NH proton of aminophenol is more deshielded due to the nitrogen lone pair conjugation with benzene and pyrazole rings and as well due to formation of the hydrogen bond with Oxygen of adjacent OH; its arises at 8.09 ppm for **3.24a** and 7.89 ppm for **3.24b** (*Figure 3.7*). The proton of OH

group exchanged with deuterium and is too shrinked to observe clearly in ^{1}H NMR spectrum.

Moreover, the structure of 3-(3-(benzylamino)propyl)-5-((2-hydroxyphenyl)amino)-1-methyl-1*H*-pyrazole-4-carbonitrile **3.24b** was confirmed by XRD analysis (*Figure 3.8*). A dihedral angle between pyrazole and benzene rings in **3.24b** of 75.5° is observed. The angle C16-N5-C13 is indicative of the conjugation of N5 lone pair with a nitrile group and benzene ring (C16-N5-C13 120.9°). In the solid state molecules are aligned antiparallel to each other and are complementary paired. Such packing is stabilized by intermolecular hydrogen bonds (*Figure 3.8*).

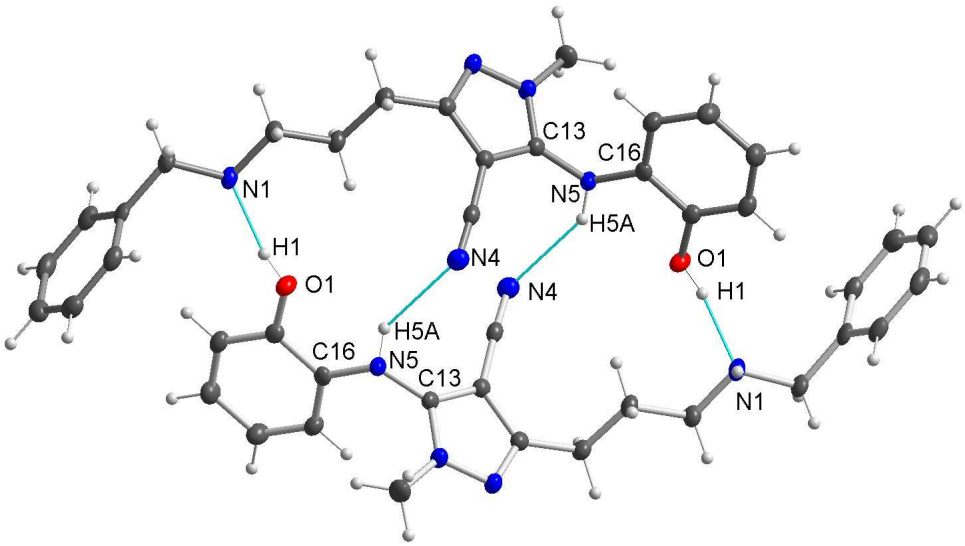
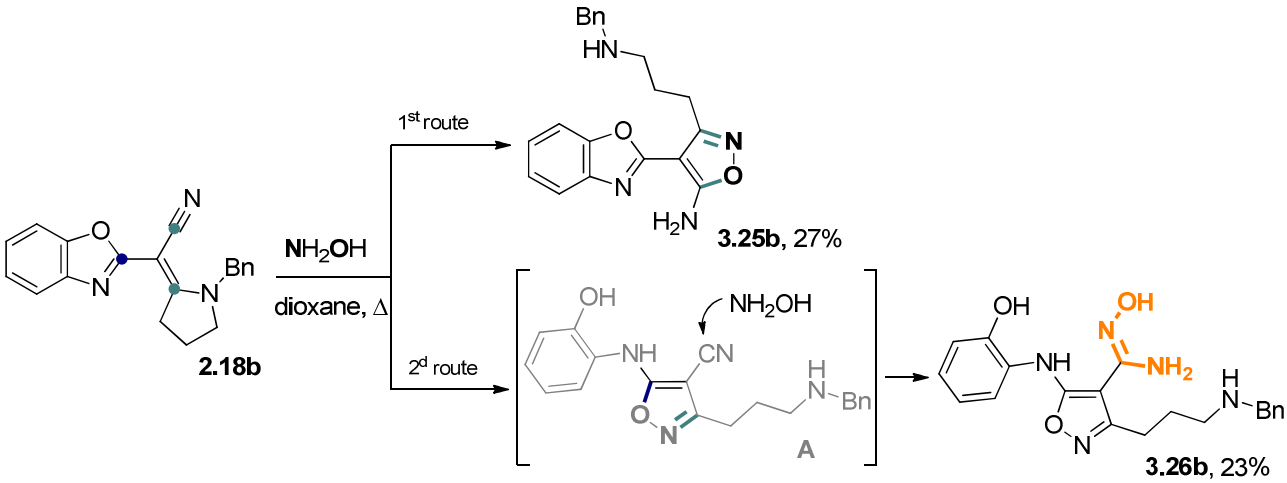


Figure 3.8. *Molecular structure of compound* ***3.24b*** *according to X-Ray diffraction. Hydrogen bonds formation in the complementary pair.*



Scheme 3.10. *Reaction of benzoxazol-2-yl-2-(1-benzylpyrrolidin-2-ylidene)acetonitrile* ***2.18b*** *with hydroxylamine.*

Under refluxing of *N*-benzylpyrrolidin-2-yledeneacetonitrile **2.18b** in dioxane with 20 equiv excess of 50% solution of NH_2OH in water, we also obtained two products (*Scheme 3.10*).

These products were separated by column chromatography and analyzed by ^{1}H, ^{13}C and 2D NMR, IR and HRMS techniques. It was established that one of the reaction products as it was expected based on previous results obtained for the reaction of **2.18b** with methylhydrazine is 4-(benzo[*d*]oxazol-2-yl)-3-(3-(benzylamino)propyl)izoxazol-5-amine **3.25b**. Unexpectedly, IR analysis of the second product did not indicate any absorption band at 2180-2230 cm^{-1} corresponding to nitrile starching vibrations. Moreover, molecular ion peak was equal to 382.17 u and differed from mass of expected product on 33 u. Nevertheless, up-field shift of aromatic protons in ^{1}H NMR spectra clearly indicated the opening of benzoxazolyl cycle. Relying on the mechanism of reaction proposed for the formation of isomers (*Scheme 2.8*), we assumed the the second atom of nucleophile attacks the C-2 centre of benzoxazole; the following attack of the second molecule of hydroxylamine (Mr of NH_2OH is 33 u) is directed at nitrile group leading to **3.26b** (*Scheme 3.10*). The proposed structure was confirmed by 2D NMR (*Figure 3.9*) and XRD (*Figure 3.10*).

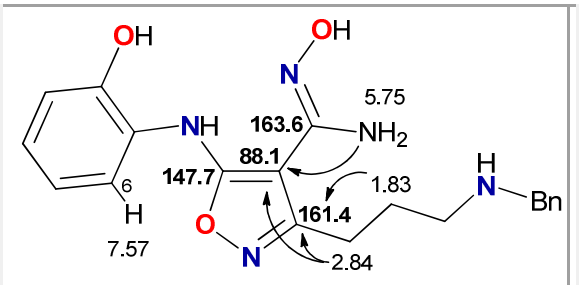


Figure 3.9. *The most indicative correlations found in HMBC spectrum of* ***3.26b****.*

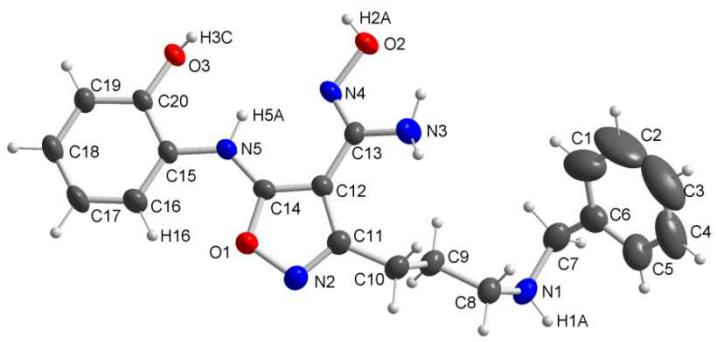


Figure 3.10. *Molecular structure of compound* ***3.26b*** *according to X-Ray diffraction.*

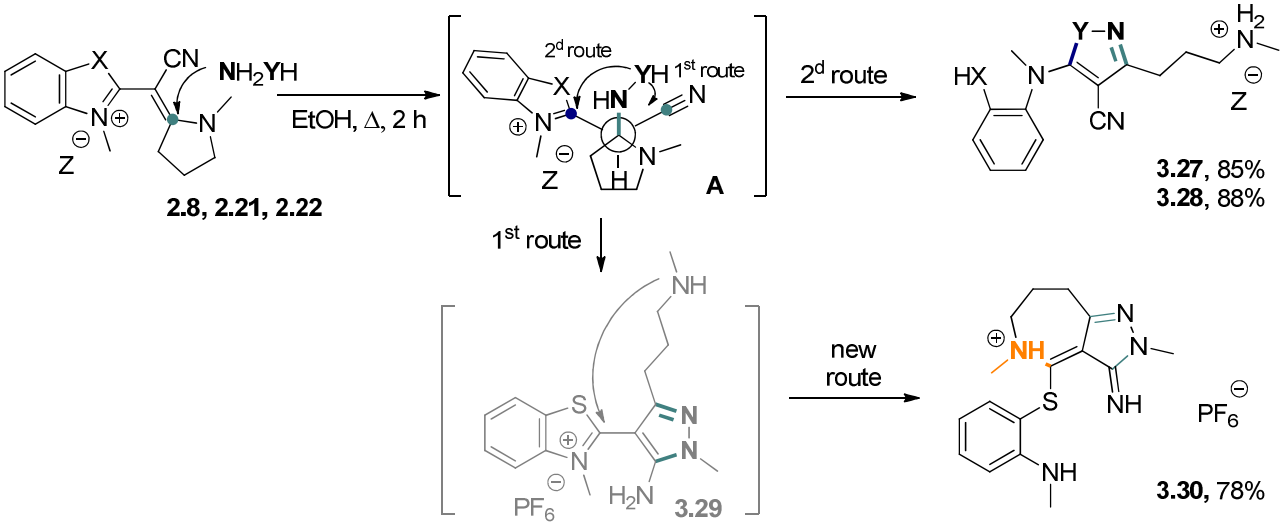
In ^{1}H NMR spectrum the signal of H-6 aromatic proton is shifted to low field (δ = 7.57 ppm). Such a shift occurred as a consequence of deshielding effect of neighbor oxygen. Indeed, according to XRD study of **3.26b** the H16 and O1 are spatially approximated (dihedral angle between benzene and isoxazole planes is 4.81°). The 4-

carboximidamide fragment is planar within 0.016 Å and turned on 17.98° toward isoxazole ring. Such orientation might allow formation of another hydrogen bond between H5A···N4 atoms.

3.2.2. Cyclic enaminonitriles substituted with quaternized benzazoles in reactions with 1,2-binucleophiles

When benzoxazole derivatives reacted with 1,2-binucleophiles three active centres were involved in reaction and the mixture of structural isomers were formed. The presence of quaternized nitrogen increases the electrophilicity of C-2 atom of heterocycle substituent (details are described in section 2.3) and thus the equilibrium of reaction should be shifted toward formation of one regioisomer – the product of the opening of azole cycle.

The stated assumption was checked by introducing the cyclic enaminonitriles substituted with quaternized azoles **2.8**, **2.21**, **2.22** in the reaction with 1,2-binucleophiles (*Scheme 3.11*).



2.8, 3.27 X=NMe, Y=N, Z=I; **2.21, 3.28** X=O, Y=NMe, Z=PF_6; **2.22** X=S, Y=NMe, Z=PF_6

Scheme 3.11. *Reaction of cyclic enaminonitriles substituted with quaternized azoles* ***2.8***, ***2.21***, ***2.22*** *with hydrazines.*

The reaction proceeds smoothly under milder conditions (refluxing ethanol, and has been finished within 2h (TLC control), most probably as a consequence of the increased reactivity associated with introducing of the positive charge.

In the case of benzimidazole **2.8** and benzoxazole **2.21** derivatives there is only one set of signals in ^{1}H NMR spectrum indicating a full regioselectivity of the reaction. After purification (recrystallization for **3.27** and column chromatography for **3.28**) the compounds were analyzed by NMR and IR spectroscopy techniques. Indicative vibration band of nitrile group absorption was found at 2214 cm^{-1} for **3.27** and at 2220 cm^{-1}for **3.28** in IR spectra; in ^{1}H NMR spectrum signals of aromatic part were shifted down field and were split into 4 signals in the case of **3.27** as a consequence of the benzimidazole moiety symmetry disruption. The combination of these facts suggests the opening of the imidazole and oxazole cycles.

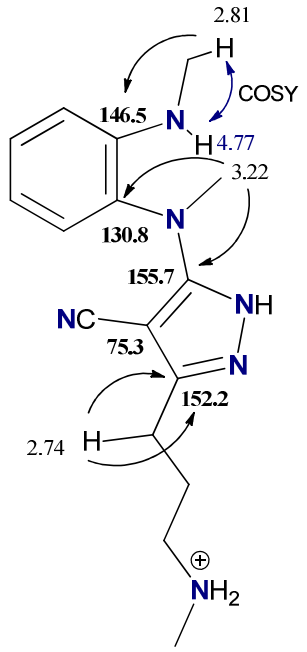


Figure 3.11**. The most indicative correlations found in HMBC, COSY spectra of **3.27.

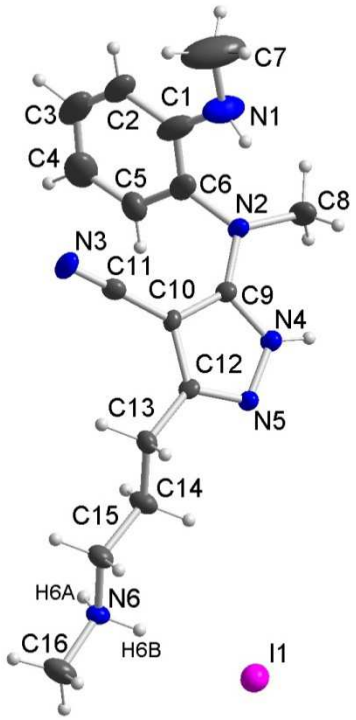


***Figure 3.12**. Molecular structure of compound **3.27** according to X-Ray diffraction.*

The generated molecules exist in the form of ammonium salts with the localization of the proton on the nitrogen atom of the *ω*-aminoalkyl chain. Such a conclusion is made on the basis of ^{1}H NMR spectra, in which the singlet of NH_2 protons is observed at 8.39 ppm in the case of **3.27** and 8.31 ppm in the case of **3.28**. An additional study was carried out using the 2D NMR method (the most indicative correlations are shown in *Figure 3.11)* and XRD (*Figure 3.12*).

An unexpected result was obtained in reaction of the benzothiazole derivative **2.22** with methylhydrazine. Instead of the expected “simple” product of the thiazole ring opening (as observed with benzimidazolyl **2.8** and benzoxazolyl **2.21**) in this case the azepine **3.30** was formed (*Scheme 3.10*). The product was obtained in 78% yield after column chromatography.

The structure of the compound was established by IR and NMR spectroscopy. Thus there is no characteristic signal of nitrile group vibration band in IR spectrum indicating its transformation during the reaction.

In the ^{1}H NMR spectra of **3.30** (*Figure 3.13*) there is down field shift of aromatic protons (δ = 7.1–7.3 ppm) indicating the opening of the thiazole ring. Doublet at 2.74 ppm (*J* = 5.0 Hz) and quadruplet at 5.31 ppm (*J* = 5.1 Hz) matching to CH_3NH protons of substituent at benzene ring. Two low field singlets at 8.97 and 8.80 ppm belong to the protons of NH groups. The intensity of these signals diminishes upon addition of D_2O. ^{31}P and ^{19}F NMR spectra are indicative for the presence of PF_6^- counterion. The molecular ion of PF_6^- group was also found by HRMS (calculated 144.9642, found 144.9649).

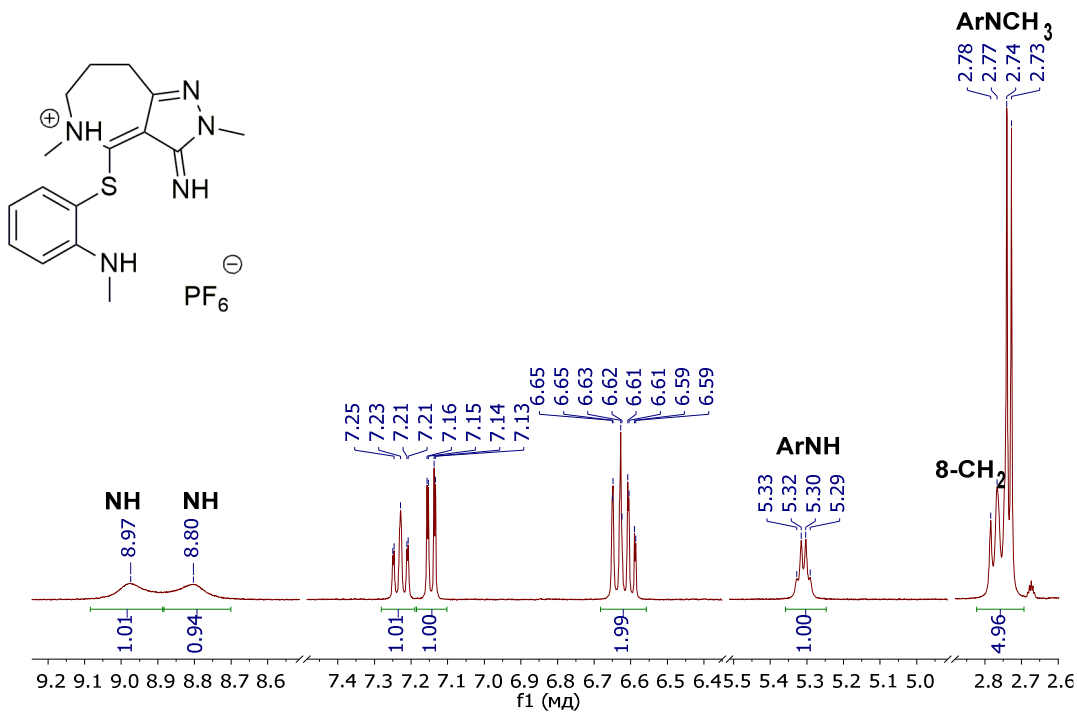


Figure 3.13. *A fragment of ^{1}H NMR spectra of* ***3.30*** *(Solvent: DMSO-d_6).*

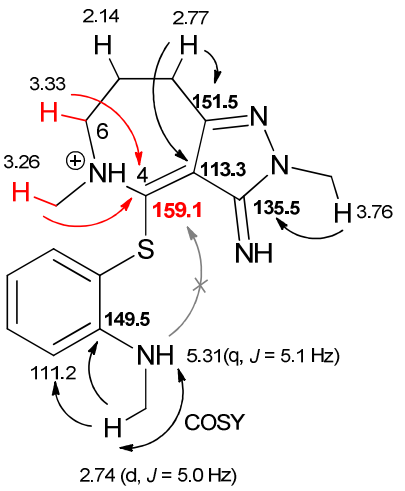
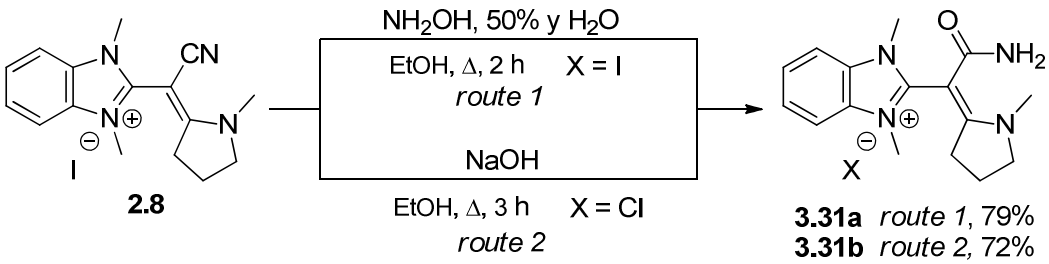


***Figure 3.14**. The most indicative correlations found in HMBC, COSY spectra of **3.30**.*

The formation of the azepine cycle is confirmed by correlations in the HMBC spectrum between the CH_3 and CH_2 protons of the aminoalkyl chain with the quaternary carbon of the C-S bond. The absence of the cross peak in HMBC spectrum for correlation between protons of CH_3NH group (substituent at benzene ring) and C-4 atom of azepine seems to be indicative for connection between thioaminophenol and azepine fragments via sulfur atom. For example, such correlation is seen in **3.27** where the connection between fragments occurred via NCH_3 group (correlation between protons of CH_3 group and C-1 atom of benzene ring, *Figure 3.11*). The most indicative correlations found in 2D NMR spectra of **3.30** depicted on *Figure 3.14*.

The formation of the azepine **3.30** probably occurs via intermediate **3.29**, which is formed by the second nitrogen atom attack at the carbon of nitrile group (the 1st route product) with the following attack of nitrogen of ω-aminoalkyl chain at C-2 position of benzothiazole (*Scheme 3.11*).

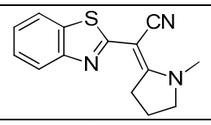
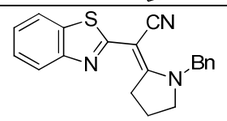
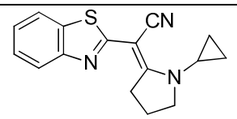
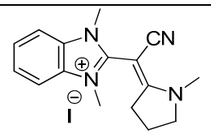
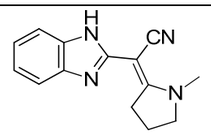
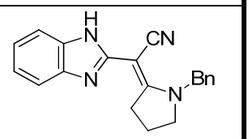
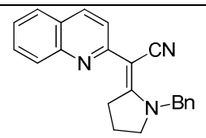
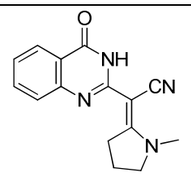
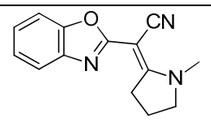
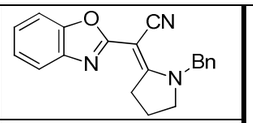
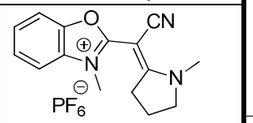
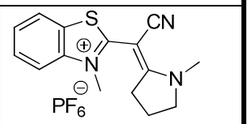
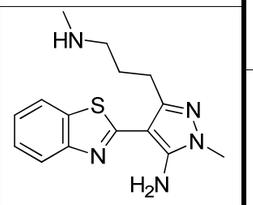
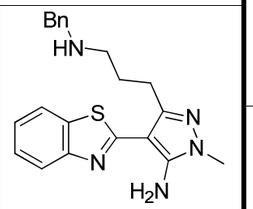
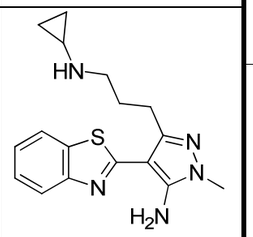
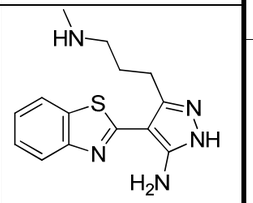
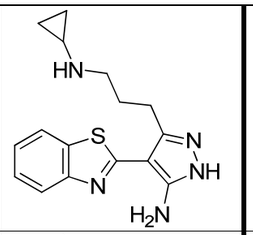
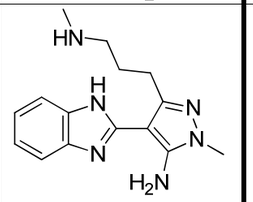
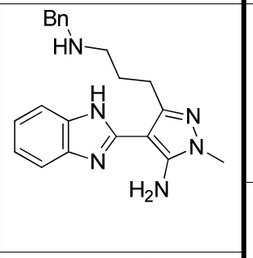
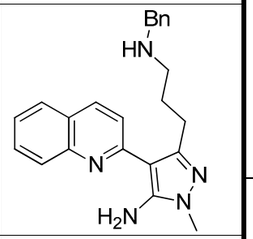
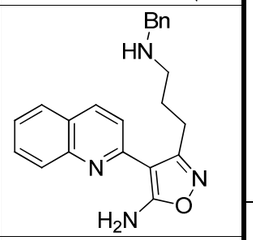
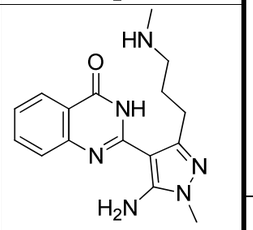
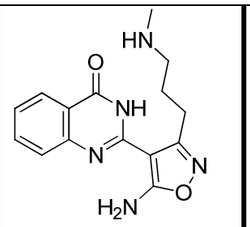
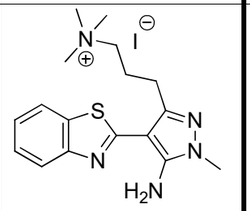
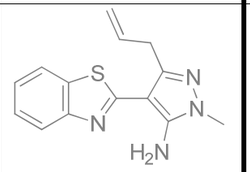
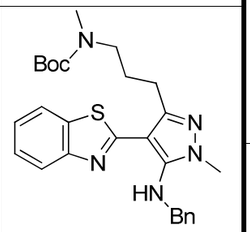
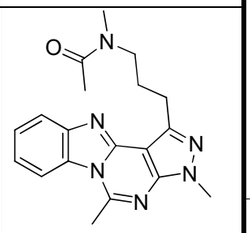
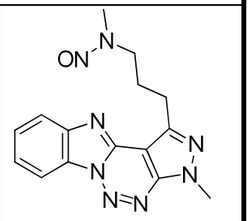
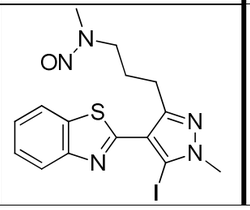
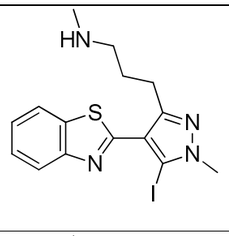
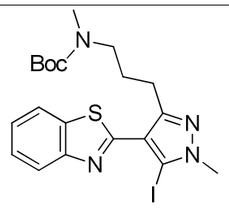
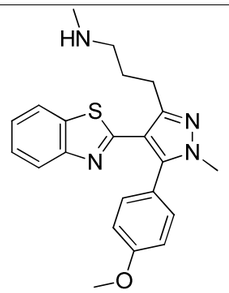
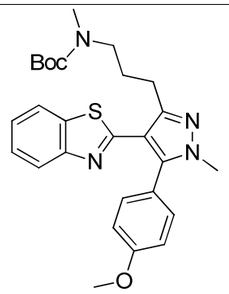
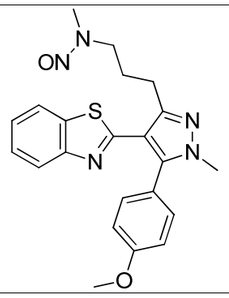
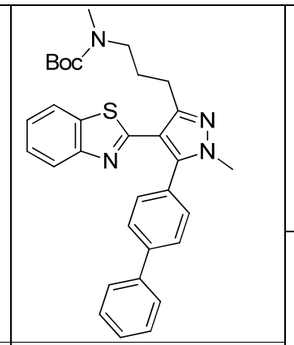
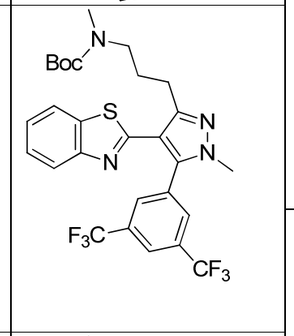
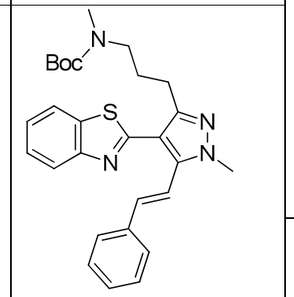
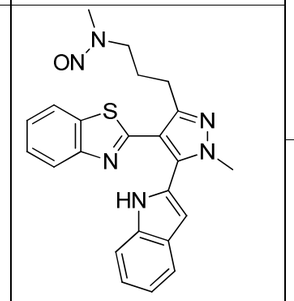
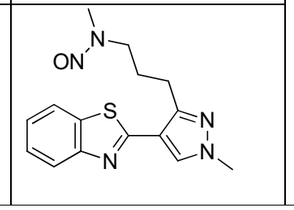
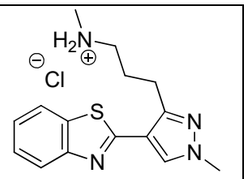
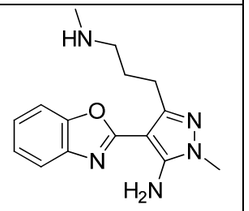
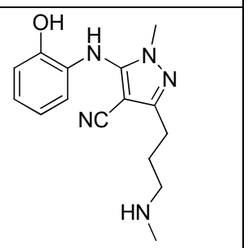
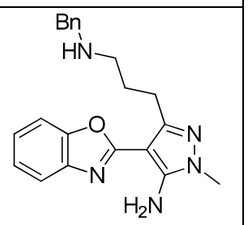
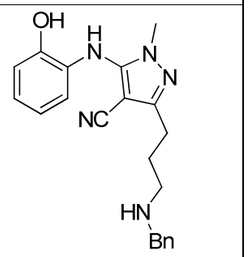
An attempt to conduct a similar reaction with benzimidazole **2.8** and hydroxylamine (50% solution NH_2OH in H_2O) only resulted in one product which was identified as the amide **3.31** (*Scheme 3.12, route 1*). The same product was obtained by hydrolysis of nitrile group under the basic conditions NaOH, EtOH-H_2O, reflux (*Scheme 3.12, route 2*).

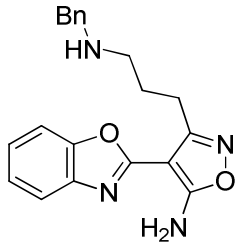
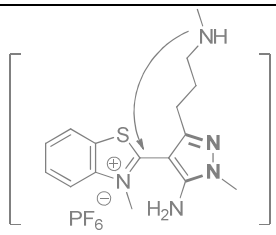
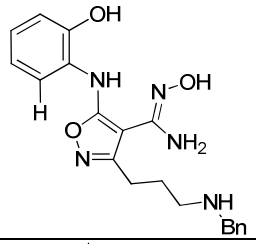
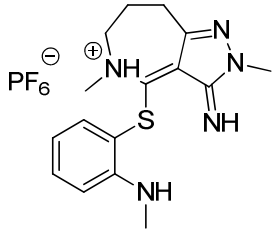
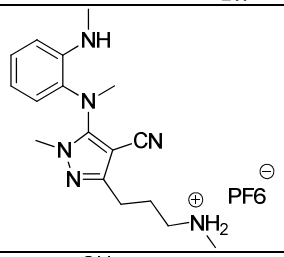
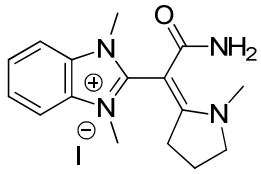
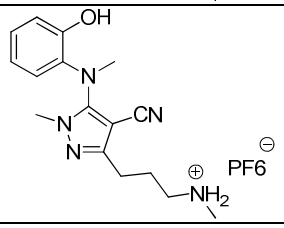
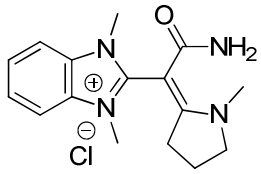


***Scheme 3.12.** The reaction of benzimidazole derivative **2.8** with hydroxylamine. The counter synthesis of amide **3.31**.*

In summary, the reactions of cyclic 2-azaheteryl-3-enaminonitriles with 1,2-binucleophiles allows the efficient formation of various pyrazoles (isoxazoles) when the nitrogen of pyrrolidine ring is substituted. The first atom attack is directed at C-2 centre of pyrrolidine, the direction of the next attack depends on the structure of azaheterocyclic substituent. Thus, in the case of *N*-alkyl substituted pyrrolidines the attack is regioselective and directed at carbon of nitrile group. In the case of benzoxazole derivatives the attack occurs both at nitrile group and with the same probability at the C-2 atom of azaheterocycle (structural isomers are formed in the ratio 1: 1). In the case of enaminonitriles substituted with quaternized benzazoles the disclosure of the azole cycle is occurring. The mechanism of transformation varies depending on the nature of azaheterocyclic substituent.

The synthetic methods developed for the synthesis of 3-(ω-aminopropyl)-4-azahetaryl-5-aminopyrazoles open new routes to enlarge the chemical space of pyrazole-containing pharmacophores as it introduces chemical complexity in an unprecedented swift fashion from simple starting materials. Tetracyclic compounds are obtained in 3 steps with the overall yield up to 45%, 5-aryl(styryl, indol-2-yl)pyrazoles in 4 steps with the overall yield up to 71%.

2.7a	
2.7b	
2.7c	
2.8	
2.13a	
2.13b	
2.14b	
2.15a	
2.18a	
2.18b	
2.21	
2.22	
3.1a	
3.1b	
3.1c	
3.2a	
3.2c	
3.3a	
3.3b	
3.4b	
3.5b	
3.6a	
3.7a	
3.8	
3.9	
3.10	
3.11	
3.12	
3.13	
3.14a	
3.15	
3.16a	
3.16b	
3.16c	
3.17	
3.18	
3.19	
3.20	
3.21	
3.22	
3.23a	
3.24a	
3.23b	
3.24b	

3.25b		**3.29**	
3.26b		**3.30**	
3.27		**3.31a**	
3.28		**3.31b**	

CHAPTER 4. REACTIONS OF 2-AZAHETARYL-2-(1-R-PYRROLIDIN-2-YLIDENE)ACETONITRILES WITH DMF DMA. PYRROLO[3,2-*c*]PYRIDIN-6-IMINE: SYNTHESIS AND PROSPECTS FOR USE

Cyclic enaminoamides derivatives are the key compounds in the synthesis of condensed pyridine systems. C–H activation at C-3 centre of pyrrolidine,[1, 69-70, 72, 74-75] indoline,[68, 119-120] 1,2,3,4-tetrahydroquinoline and 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine,[121] featuring electron withdrawing groups (cyanoacetamide, malononitrile, ethylcyanoacetate) at the C-2 position was allowed for the synthesis of 5-azaindolines, condensed pyrimidinecarbolines (pyridoindoles), pyrido[4,3-*b*]benzo[*f*]azepines (*Figure 4.1*). These scaffolds are found to be useful for the treatment of cancer, neurodegenerative diseases, as inhibitors of serotonin receptors, antihistaminics.[119, 122-123]

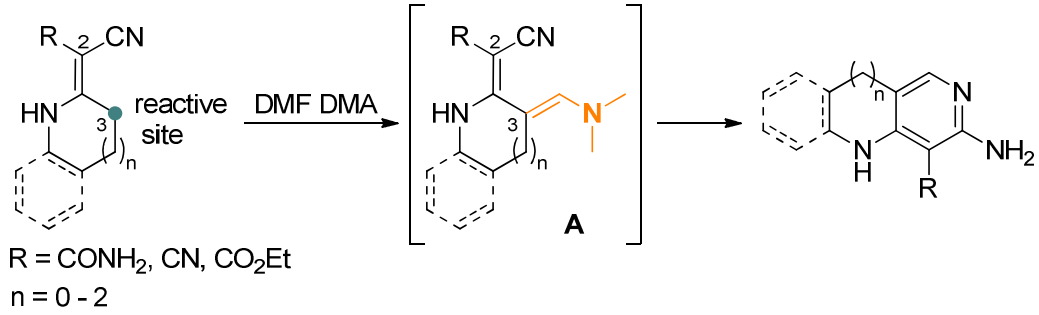


Figure 4.1. *Straightforward access to condensed pyridine systems.*

The common intermediates on the route to condensed pyridine systems are the derivatives of 3-dimethylaminomethylidenes **A**, obtaining by formylation reaction of C-3 centre of pyrrolidine ring by acetals (*Figure 4.1*).[70, 73, 75]

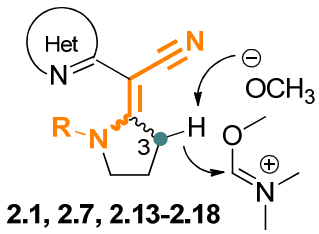


Figure 4.2. *The reactive centre (C-3) of 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles under reactions with DMF DMA*

The acidity of protons at position 3 of pyrrolidine in 2-azahetaryl-3-enaminonitriles **2.1**, **2.7**, **2.13–2.18** is enhanced by conjugation with hetarylacetonitrile fragment. Thus these compounds could also react with acetals as C-nucleophiles and provide access to functionalized azaheterocycles (*Figure 4.2*).

4.1. 2-Azahetaryl-2-(1-R-pyrrolidin-2-yliden)acetonitriles under reactions with DMF DMA

Alkylation and formylation[13] are the main types of reactions of DMF DMA **4.1.** They mainly proceed via formation of aza-oxo-stabilized Vilsmeier-Haack salt analogue **4.1A** (*Figure 4.3*).[124]

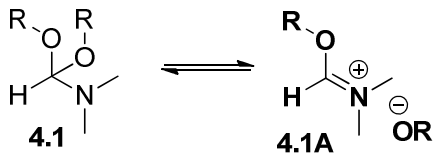


Figure 4.3. *Aza-oxo-stabilized methylene iminium salt* ***4.1A*** *– the reactive form of acetal.*

As alkylating agents, they have been used in the synthesis of esters from acids, ethers and thioethers from phenols and aromatic and heterocyclic thiols, and the alkylation of active methines. As formylating agents, formamide acetals are useful in the synthesis of enamines from active methylenes and amidines from amines and amides.[124]

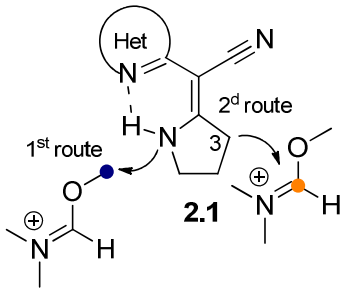


Figure 4.4. *Alternative routes to reactions of* ***2.1*** *with DMF DMA.*

Taking into account the reactivity of DMF DMA two alternative routes can be envisaged for the reaction of *N*-unsubstituted pyrrolidines (the nature of the substituent is omitted) with DMF DMA, namely, alkylation at nitrogen of pyrrolidine (*Figure 4.4, route 1*) and/or incorporation of dimethylaminomethylidene moiety at C-3 position of the ring (*Figure 4.4, route 2*).

[13] Hereafter formylation by DMF DMA stands for incorporation of dimethylaminomethylidene moiety, formyl equivalent.

In the reaction of 2-benzo[*d*]thiazol-2-yl-2-(pyrrolidin-2-ylidene)acetonitrile **2.1b** with DMF DMA the only product observed is 3-dimethylaminomethylidene **4.2a**, corresponding to a formylation product at position 3 of pyrrolidine (*Scheme 4.1*).

Scheme 4.1. *Formylation reaction of enaminonitrile* ***2.1b*** *with DMF DMA.*

The reaction proceeds by refluxing the reactants in toluene. The TLC reaction control and the ^{1}H NMR analysis did not reveal any *N*-alkylation product in the reaction mixture (*Figure 4.4, route 1*).

In the ^{1}H NMR spectra of **4.2a** there are signals of dimethylaminomethylidene moiety at 3.06 ppm (s, 6H $2CH_3$) and 7.76 ppm (t, J = 1.5 Hz, 1H, CH). The broadened singlet of NH proton of pyrrolidine is observed at 10.24 ppm (Solvent: DMSO-d_6).

According to XRD analysis the benzothiazole substituent is almost coplanar with pyrrolidine ring with the dihedral angle of 3.85°. The flattened orientation of the planar fragments is stabilized by an intramolecular hydrogen bond (the estimated bond length H3A···N1 2.00 Å, N3–H3A···N1 135.3°). The

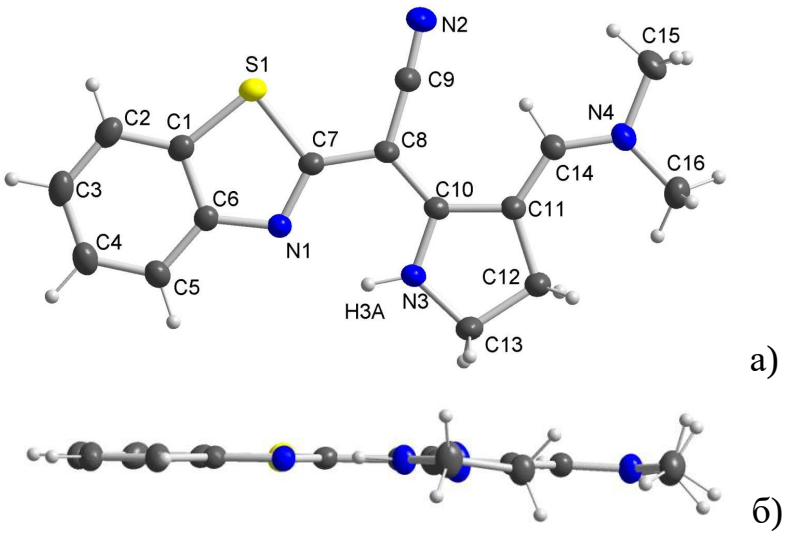
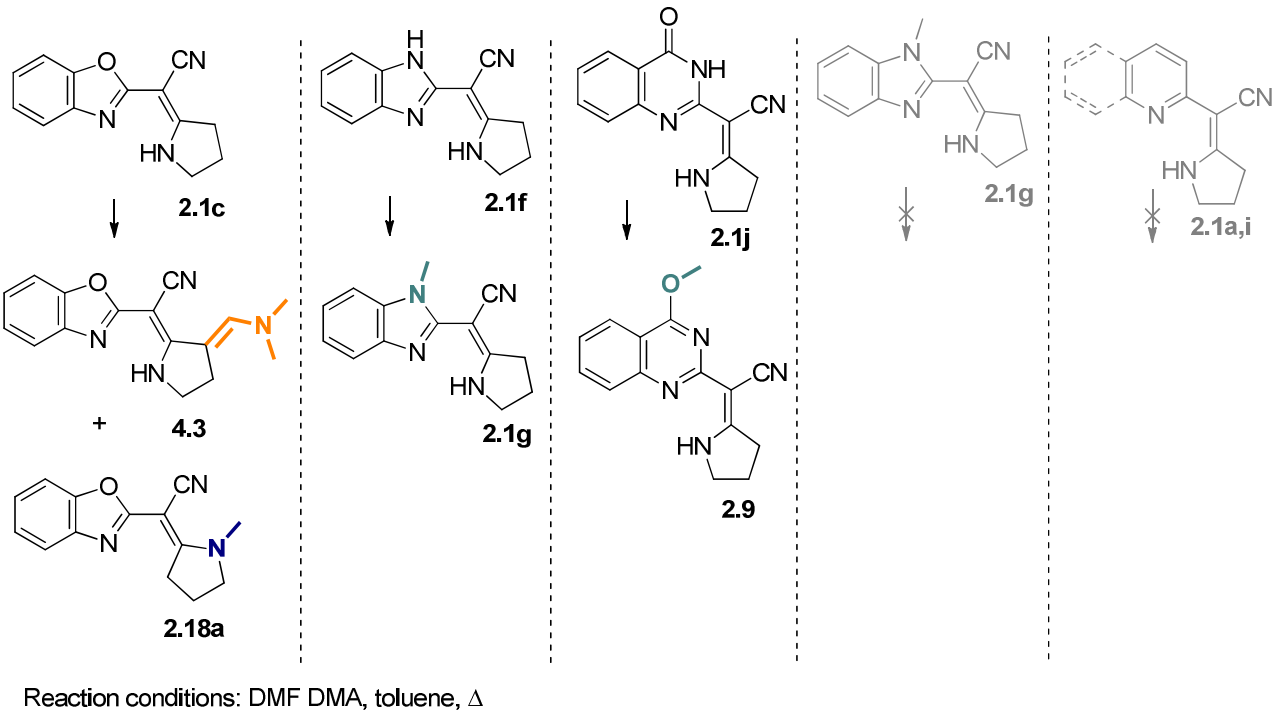


Figure 4.5*. a) Molecular structure of* ***4.2a*** *according to X-ray diffraction; b) Orthogonal projection .*

charge delocalization occur toward the hetarylacetonitrile fragment that is accompanied by N4–C14 (1.34 Å) and N3–C10 (1.34 Å) bonds shortening and C14–C11 (1.37 Å) and C10–C8 (1.42 Å) bonds elongation (*Figure 4.5*).

The reaction path appeared to be highly dependent on the nature of the heterocycle of the 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles **2.1** (*Scheme 4.2*).



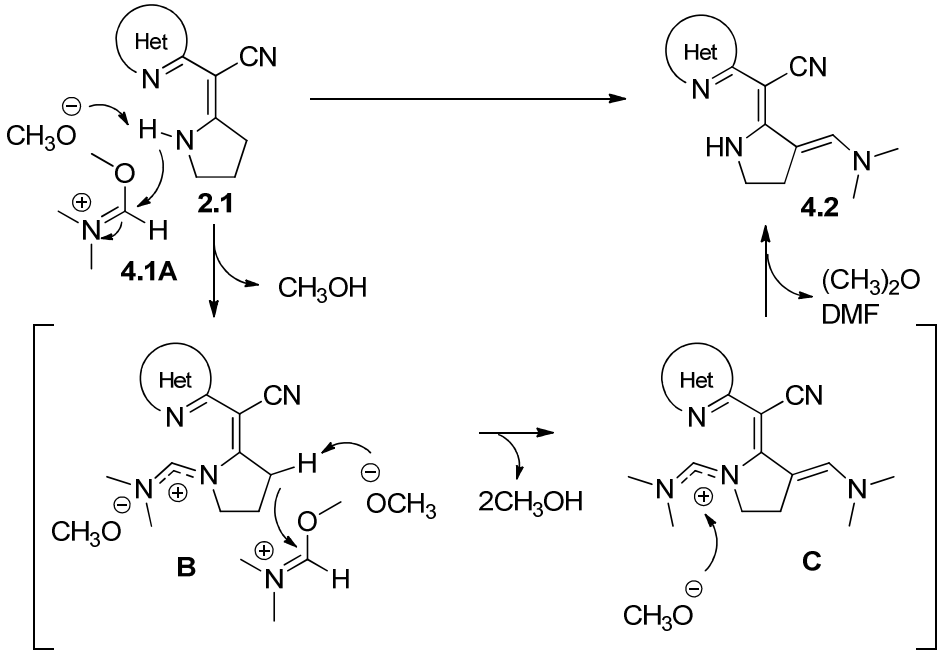
Scheme 4.2. *The dependence of reaction route on the nature of azaheterocyclic substituent in* ***2.1****.*

In the case of 2-benzoxazol-2-yl-2-(pyrrolidin-2-ylidene)acetonitrile **2.1c** the reaction proceeds with the formation of formylated product **4.3**, and methylated product **2.18a**, that was identified by analyzing the characteristic chemical shifts in ^{1}H NMR spectrum (Solvent: $CDCl_3$, mixture, ratio **2.18a**:**4.3** = 3:2; **2.18a**: δ, ppm, 2.03–2.15 (m, 2H, 4-CH_2), 3.53 (s, 3H, CH_3); **4.3**: 3.12 (s, 6H, 2CH_3), 7.96 (s, 1H, CH)). The reaction with benzimidazole **2.1f** and quinazolinone **2.1j** derivatives occurred with formation of *N*- **2.1g** and *O*-alkylated **2.9** products. The reaction does not occur in the case of *N*-methylbenzimidazole **2.1g**, pyridine **2.1i** and quinoline **2.1a** derivatives.

N-methyl-substituted pyrrolidines, namely 2-benzothiazol-2-yl-2-(1-methylpyrrolidin-2-ylidene)acetonitrile **2.7a** and 2-benzoxazol-2-yl-2-(1-

methylpyrrolidin-2-ylidene)acetonitrile **2.18a** neither react with DMF DMA that is in agreement with the results reported for ethyl 2-cyano-2-(1-ethyl(phenyl)pyrrolidin-2-ylidene)acetates.[1, 73]

The experimental data as well as precedents from the literature[1, 73] prompted us to assume that the presence of easily accessible NH group is essential in formylation of the C-3 centre of pyrrolidine allowing to propose a mechanism for this uncommon reaction (*Scheme 4.4*).



Scheme 4.4. *Proposed mechanism for reaction of 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles* ***2.1*** *with DMF DMA.*

The incorporation of dimethylmethylidene moiety proceeds in a reversible fashion via nucleophilic attack of aza-oxo-stabilized ion **4.1A** by nitrogen of pyrrolidine yielding the key intermediate **B**; the C-3 position of pyrrolidine in **B** activated by inductive effect (-I) of amidine group and enhanced mesomeric stability of the anion by the acrylonitrile moiety. Consequently deprotonation by methoxy anion and reaction with another molecule of DMF DMA can occur yielding **C**; the latter transformed into 2-azahetaryl-2-(3-(dimethylamino)methylene)pyrrolidin-2-ylidene)acetonitrile **4.3** by reversion of the first step.

The proposed mechanism not only explain failed attempts to formylate the derivatives of *N*-substituted pyrrolidines **2.7a**, **2.18a** and **1.103**, but also inactivity of

NMe-benzimizazole **2.1g**, pyridine **2.1i** and quinoline **2.1a** derivatives for which pyrrolidine NH is less accessible, and different results for the reaction with benzothiazole **2.1b** and benzoxazole **2.1c** derivatives .

Deprotonation of the NH might indeed take place when the proton is not involved in strong H bonding. Such binding is directly related to the pKa of azaheterocycles (*Figure 4.6*). In the benzazoles' row the smallest pKa has benzoxazole – 0.5, the biggest – benzimidazole 5.5, benzothiazole – pKa 1.8. Consequently, the deprotonation by a methoxy-anion is significantly restricted in the case of NMe-benzimizazole **2.1g** derivative and the key intermediate **B** cannot be accessed. For benzoxazole derivative **2.1c** deprotonation proceeds easily. Yet the hard nucleophile N^- attacks both the hard centre – methyl of methoxy-group and the soft – carbenium cation of DMF DMA. For benzothiazol derivative **2.1b** deprotonation is less favored but still achievable. In this case, a deprotonation – nucleophilic attack promotes a reaction only at the soft centre. pKa values of pyridine and quinoline are 5.2 and 4.9, respectively, H bonding in **2.1a**,**i** is stable and prevents the deprotonation.

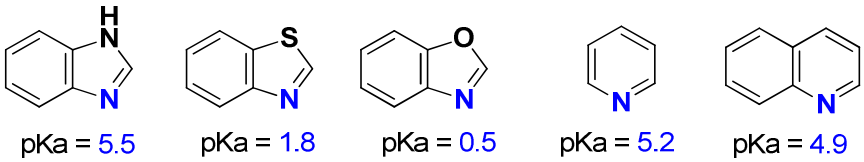
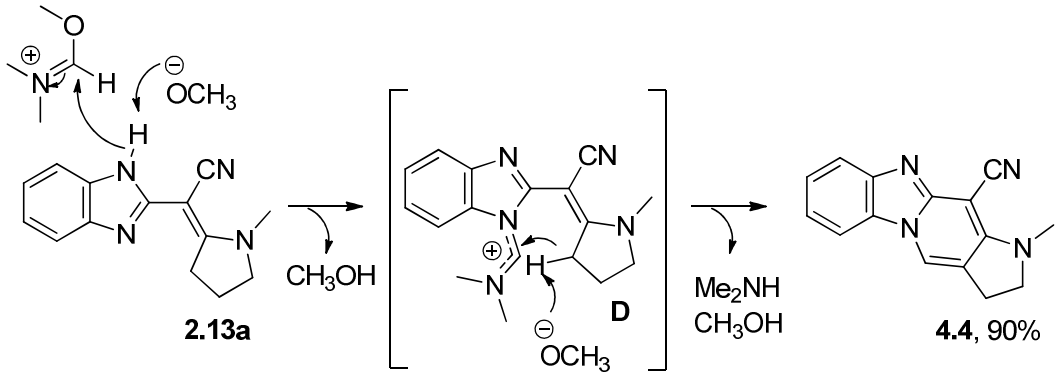


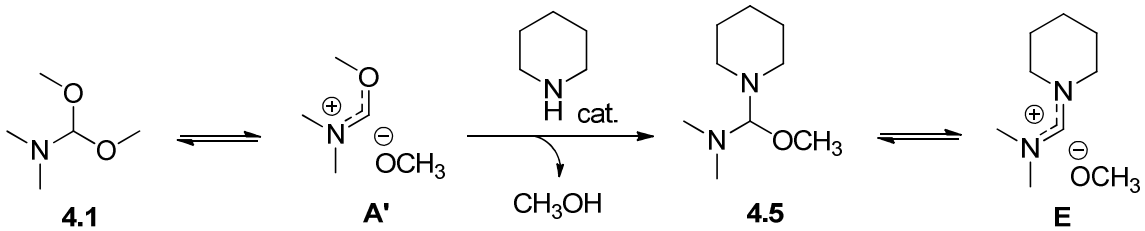
Figure 4.6. *pKa of conjugate acids of relevant azaheterocycles.*

One more evidence for amidinium ion formation in the course of reaction is the successful interaction between 2-(1*H*-benzo[*d*]imidazol-2-yl)-2-(1-methylpyrrolidin-2-ylidene)acetonitrile **2.13a** with DMF DMA in contrast to failed attempts with benzothiazole **2.7a** and benzoxazole **2.18a** derivatives. The presence of a nucleophilic nitrogen atom in the benzimidazole **2.13a** promotes reaction with the carbenium ion yielding intermediate **D**. Like in the previous case *(Scheme 4.4*), C-3 position is deprotonated upon interaction with metoxy-anion and cyclization into benzo[4,5]imidazo[1,2-*a*]pyrrolo[2,3-*d*]pyridine **4.4** occurs followed by elimination of dimethylamine.

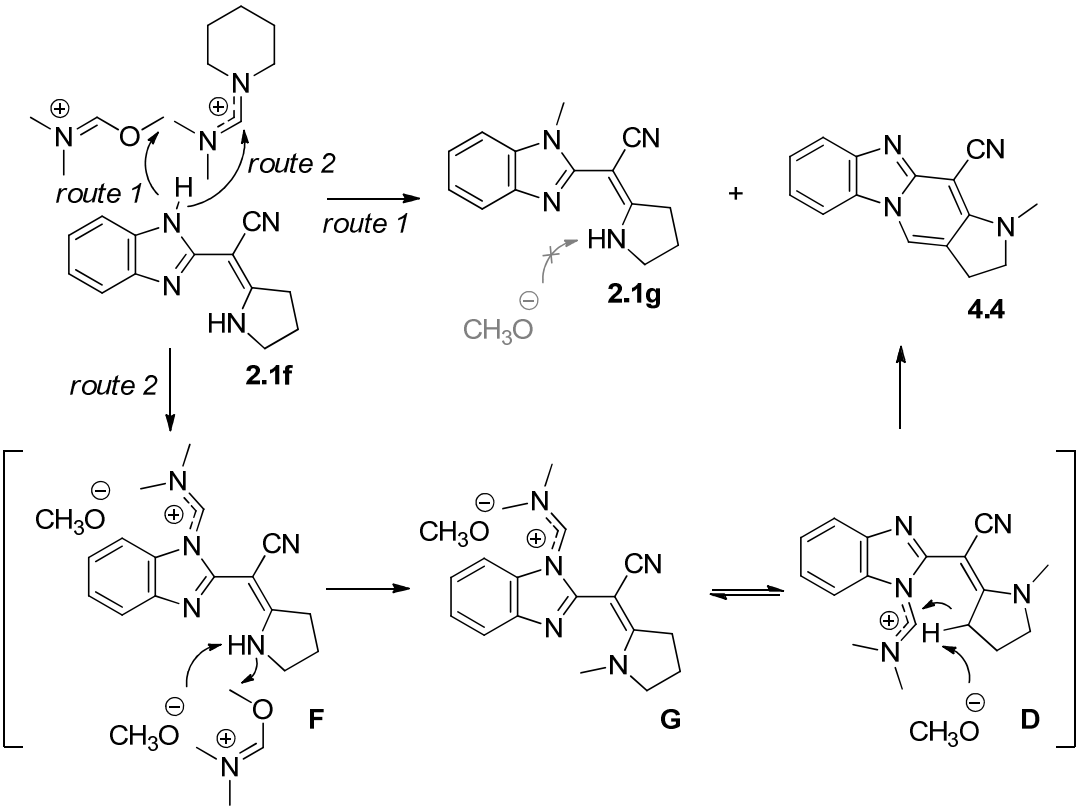


Scheme 4.4. *Proposed mechanism for reaction of 2-(1H-benzo[d]imidazol-2-yl)-2-(1-methylpyrrolidin-2-ylidene)acetonitrile* ***2.13a*** *with DMF DMA.*

Similar tetracyclic compound **4.4** in the mixture with the methylation product **2.1g** forms in the reaction of 2-(1*H*-benzo[*d*]imidazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile **2.1f** with DMF DMA in the presence of catalytic amount of piperidine (*Scheme 4.6*). *Golovko et al.*[121] use this method for formylation of 3,4-dihydroquinolin-2(1*H*)-one that is inert under usual reaction conditions (toluene, Δ). Authors notice that *N,O*-acetal **4.5**, which is formed by interaction of DMA DMF with piperidine is much more reactive than the corresponding amide acetal **4.1**, due to better stabilization of amidinium **E** as compared to iminium-ether **A´** (*Scheme 4.5*).



Scheme 4.5. *Catalytic role of piperidine.*[121]



Scheme 4.6. *Proposed mechanism for reaction of benzimidazole* ***2.1f*** *derivative with DMF DMA in the presence of catalytic amount of piperidine (****2.1g****:****4.4*** *ratio = 4:6)*

The reaction proceeds by a competitive attack of the nitrogen of benzimidazole at methyl group (*route 1*, *Scheme 4.6*) and at the carbenium ion (*route 2*, *Scheme 4.6*). As a result, compound **2.1g** is formed, which does not react with DMF DMA due to the significant stability of the chelate, as noted above, and the intermediate amidinium ion **F**. In route 2, the nitrogen lone pair participates in the positive charge distribution of amidine moiety, thus indirectly influencing on the intramolecular hydrogen bond between NH and nitrogen of benzimidazole weakening. As a consequence the deprotonation of pyrrolidine can occur. The weakening of hydrogen bond allows the isomerization of *Z*-diastereomer **G** into *E*-diastereomer **D** to proceed. Following steps are the similar to those presented in *Scheme 4.4* to yield imidazopyridine **4.4**.

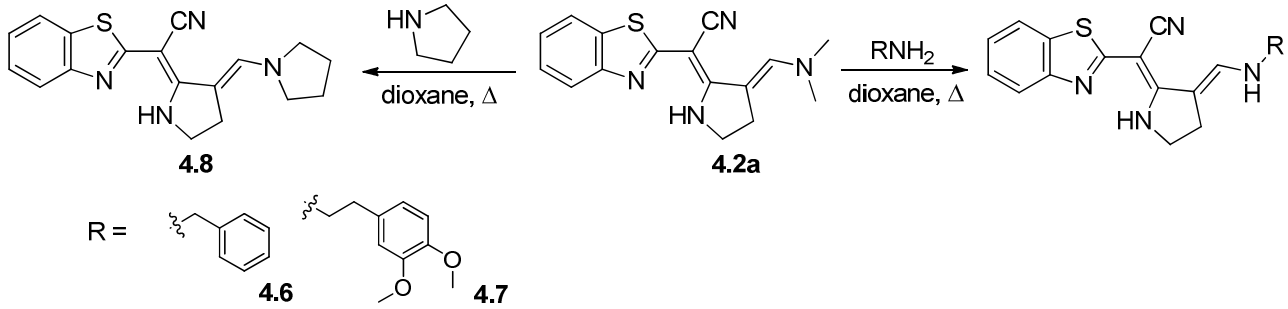
The symmetry of the benzimidazole moiety initially found in **2.1f** is disrupted through this transformation, promoting the split of the two aromatic signals of **2.1f** in ^{1}H NMR spectrum into four signals for **4.4**, namely, two doublets at 7.58 and 7.89

ppm and two doublets of doublets (J_1 = J_2) at 7.18 and 7.30 ppm. The signal of methylidene proton is shifted to low field and arises at 8.51 ppm. The formation of the pyridine ring is also confirmed by NOE which occurs between methylidene and 4-H protons: when selective irradiation of the molecule at the absorption frequency of the first, the signal of the latter increases in intensity by 7%. The IR spectrum shows there is the characteristic vibration of CN group at 2198 cm^{-1}.

In summary, individual formylation products: the 3-dimethylaminomethylidene derivative **4.2a** and benzo[4,5]imidazo[1,2-*a*]pyrrolo[2,3-*d*]pyridine **4.4**, formed only upon treatment with DMF DMA of 2-(benzo[*d*]thiazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile **2.1b** and (1*H*-benzo[*d*]imidazol-2-yl)-2-(1-methylpyrrolidin-2-ylidene)acetonitrile **2.13a**. Considering the result, compound **4.2a** became a model for further investigations of their reactivity.

4.2. Reactions of 2-(benzo[*d*]thiazol-2-yl)-2-((*E*)-3-((dimethylamino)methylene)pyrrolidine-2-ylidene)acetonitrile with amines

The benzothiazolyl 3-dimethylaminomethylidene derivative **4.2a** reacts with amines releasing dimethylamine. Successful transamination is occured with 2- (3,4-dimethoxyphenyl)ethanamine, benzylamine and pyrrolidine to form secondary **4.6**, **4.7** and tertiary amines **4.8** (*Scheme 4.7*). In the ^{1}H NMR spectra of **4.6** and **4.7** AX spin system of protons of CHNH fragment with trans constant of J = 12–13 Hz, doublet of CH_2 group (J = 5.6 Hz) and the singlet of NH proton of pyrrolidine are observed (*Figure 4.7*). Upon addition of D_2O to the solution of **4.6** in DMSO-d_6 the intensity The NH signals decreases, the doublets of methylidene (CH) and benzyl protons arise as singlets.



Scheme 4.7. *Transamination reactions of* ***4.2a.***

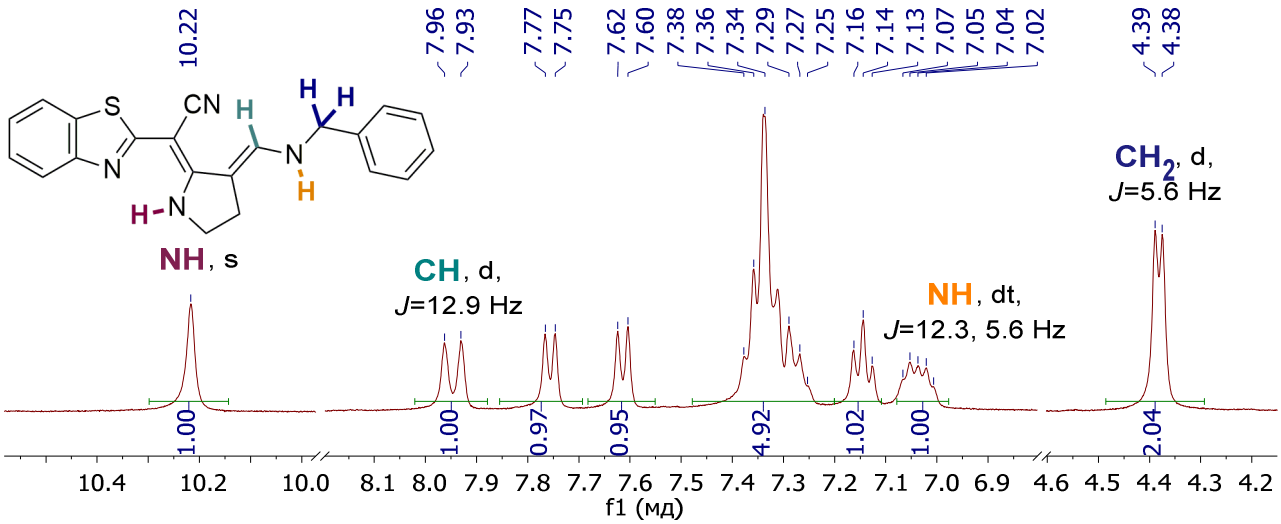


Figure 4.7. *A fragment of* ^{1}*H NMR spectrum of* ***4.6*** *(400 MHz, DMSO-*d_6*-*CCl_4*).*

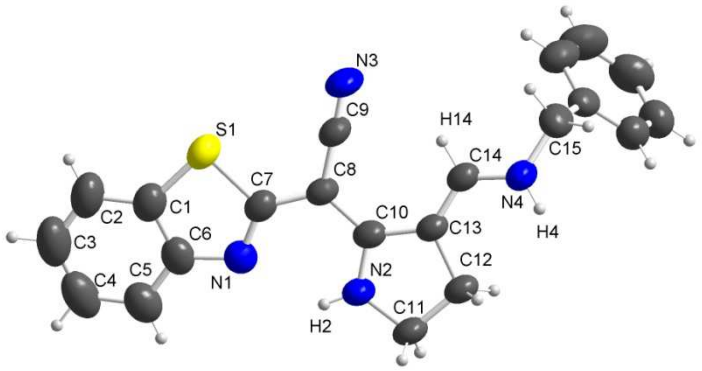


Figure 4.8. *Molecular structure of* ***4.6*** *according to X-ray diffraction.*

According to XRD the dihedral angle between benzothiazole and pyrrolidine planes is 14.5°. The estimated length of hydrogen bond is N1⋯H2 2.13 Å, angle N2–H2⋯N1 129.7°. H14 and H4 atoms are located in a trans conformation with the torsion angle of 169.8° (*Figure 4.8*).

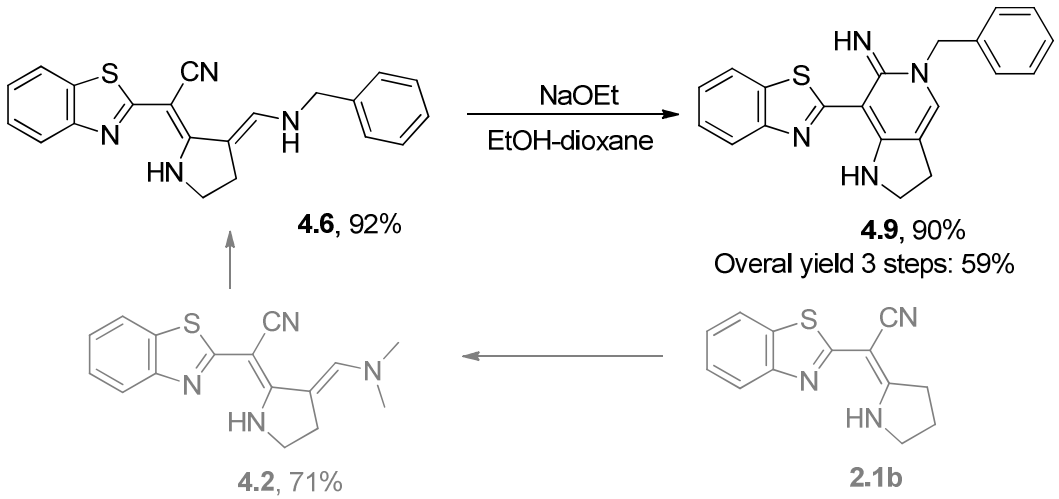
Compound **4.2a** was also reacted with propylamine, 4-metoxyaniline and *β*-aminoethylpropanoate but the formed amines were not stable in solution preventing their characterization.

4.3. Synthesis of pyrrolo[3,2-*c*]pyridin-6-imine, physicochemical study and prospects for use

Intramolecular rection between the nitrile and amino groups provides access to a wide range of nitrogen-containing heterocycles, namely, azines, azoles, quinolines, pyridines, pyrimidines, azepines.[125] Such rection is carried out by treatment with acids, bases or thermally and usually proceeds irreversibly.

Numerous reports from *Granik V.G.* are devoted to the synthesis of pyrimidines and pyridines from derivatives of pyrrolidinylidenes creating C–N bond formation with such methods.[1, 68-73, 75, 119-121]

Following on these reports we were able to conduct intramolecular condensation of the derivative of 3-((benzylamino)methylene) pyrrolidine-2-ylidene)acetonitrile **4.6** by action of sodium ethylate to access pyrrolo[3,2-*c*]pyrimidine (*Scheme 4.8*). The overall yield of three-steps synthesis of **4.9** starting from **2.1b** is 59% (51%, starting from 2-(benzo[*d*]thiazol-2-yl)acetonitrile).



Scheme 4.8. *Synthesis of pyrrolo[3,2-c]pyrimidine* ***4.9****.*

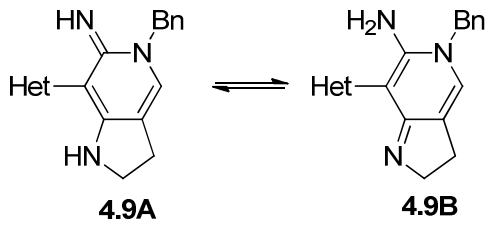


Figure 4.9. *Imine-enamine tautomerism of* ***4.9****.*

It is known,[120, 126-127] that for the structures of **4.9** type the imine-enamine tautomerism is characteristic (*Figure 4.9*). Thus, in the ^{1}H NMR spectrum of **4.9** recorded in $CDCl_3$ there is broadened NH protons signals in the region 5.69-10.34 ppm, which may indicate a fast proton transfer on the NMR time scale. When changing the solvent to DMSO-d_6, the transition between the tautomers is slowing down and signals are observed in the spectrum both for the imine **4.9A** and the enamine **4.9B** tautomeric forms (*Figure 4.10*).

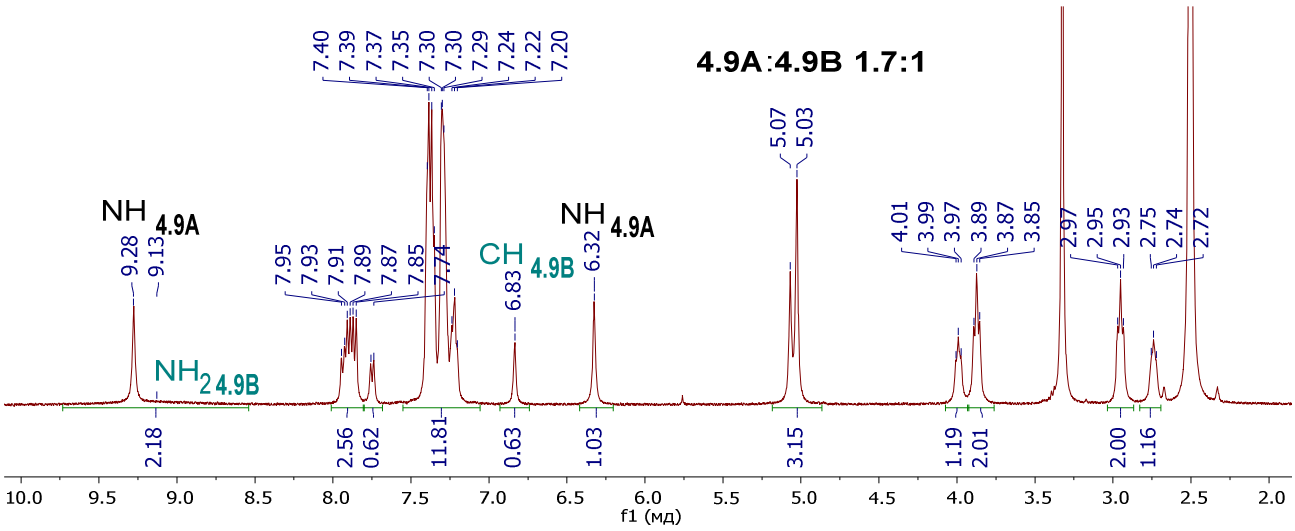


Figure 4.10. *^{1}H NMR spectrum of **4.9** in DMSO-d_6.*

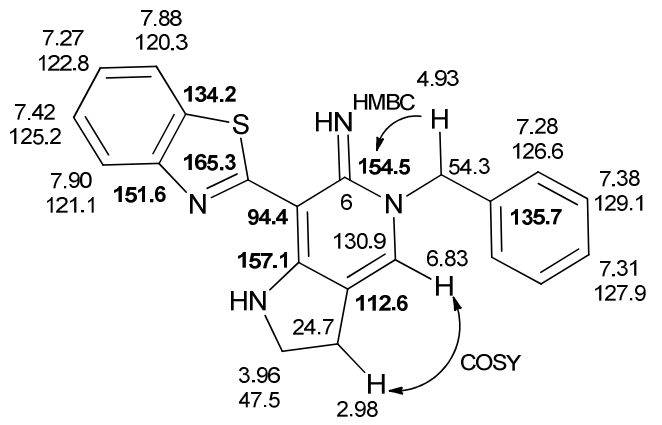


Figure 4.11. *The compound **4.9** structure according to 2D NMR (400 MHz, $CDCl_3$) (the arbitrary tautomer is depicted).*

Thorough structural analysis of **4.9** was carried out using 2D NMR, namely, COSY, HMQC, HMBC (*Figure 4*.11). The pyridine ring closure was confirmed by correlation in HMBC between protons of methylene group of benzyl substituent and quaternary carbon C-6 of pyrrolopyridine fragment (cross peak δ = 4.93, 154.5 ppm). Coupling is observed between vinyl CH proton and 3-CH_2 protons of pyrrolidine ring (J^3 = 1.6 Hz) in ^{1}H NMR spectrum and is confirmed by cross peaks in COSY (*Figure 4.11*). Cross peaks are also seen between NH–2-CH_2 and NCH_2–2,6-H_{Ph}.

The structure of **4.9** was also confirmed by XRD analysis (*Figure 4.12, a*). In contrast to the solution in the solid state there is only the imine form of the molecule **4.9A**. This form is stabilized by the intramolecular hydrogen bond between nitrogen of benzothiazole and hydrogen of pyrrolidine (estimated bond length N1⋯H2 2.14 Å, angle N2–H2⋯N1 125.1°, dihedral angle between the benzothiazole and pyrrolopyridine planes is 6.3°). The bond length in the vinamidine systems of **4.9** are indicative of an open-chain push-pull conjugated π-system rather than of π-

delocalization (*Figure 4.12, b*).[128-129] The electron density from donor to acceptors imino group and benzothiazole seems arising to a greater extent from the nitrogen of pyrrolidine rather than the nitrogen of pyridine. This evidenced by smaller bond length of N2–C19 1.32 Å in contrast to the bonds N3–C14 1.41 Å and N3–C13 1.38 Å.

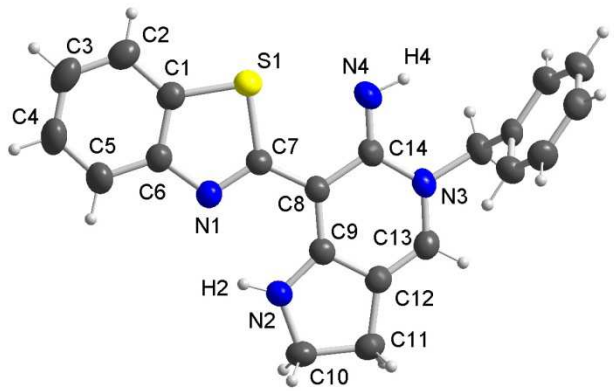
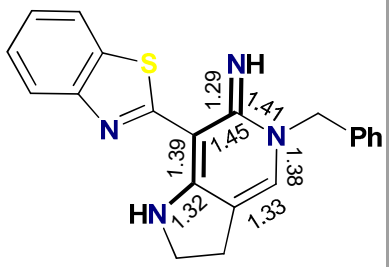
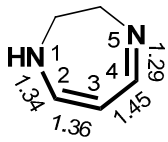


Figure 4.12. *a) Molecular structure of* ***4.9*** *according to X-ray diffraction.*



b) The bonds length in pyrrolopyrimidine fragment according to XRD.

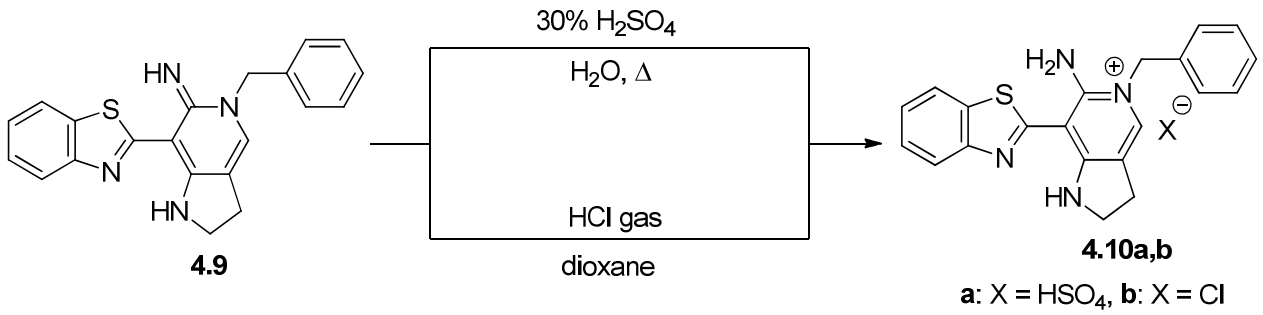


c) The bonds length in diazepine according to XRD.[129]

These data correlate with ones given for diazepines *(Figure 4.12, c*). The small difference in the bond length of N2–C9 and C9–C8 from the corresponding bonds in diazepine N1–C2 and C2–C3 might it be due to the electron delocalization in **4.9** toward benzothiazole substituent.

When attempting to convert pyrrolopyridin-6-imine into pyrolopyrid-6-one by acid hydrolysis with a 30% solution of H_2SO_4 in a water-dioxane mixture, the only reaction product was the salt **4.10a** (*Scheme 4.9*). The protonation promotes the aromatization to the pyridinium thus preventing hydrolysis.

Compound **4.10b**, which only differs by the nature of the conteranion, was accessed by HCl bubbling in the solution of **4.9** in dioxane. The ^{1}H NMR spectra for both compounds were almost identical (supplementary information).



Scheme 4.9. *The interaction of pyrrolo[3,2-c]pyridine derivative* ***4.9*** *with acids.*

In the ^{1}H NMR spectrum of compounds **4.10**, the singlets of amino groups protons are clearly distinguished. The NH proton of pyrrolidine comes out at 8.57 ppm for **4.10a** and at 8.61 ppm for **4.10b** (s, 1H) and signal of NH_2 protons at 8.68 and 8.76 ppm (s, 2H), respectively. The significant low field shift of CH_2 protons of benzyl substituent ($\Delta\delta$ ~ 0.4 ppm) and almost constant position of 2-CH_2 signal ($\Delta\delta$ = 0.02 ppm), as compare to initial pyrrolopyridine **4.9**, are indicative of localization of a positive charge on the nitrogen of pyridine ring rather than on the nitrogen of pyrrolidine. These confirm the structure proposed for **4.10b** as do further 2D-NMR: COSY, HMQC, HMBC (*Figure 4.13*).

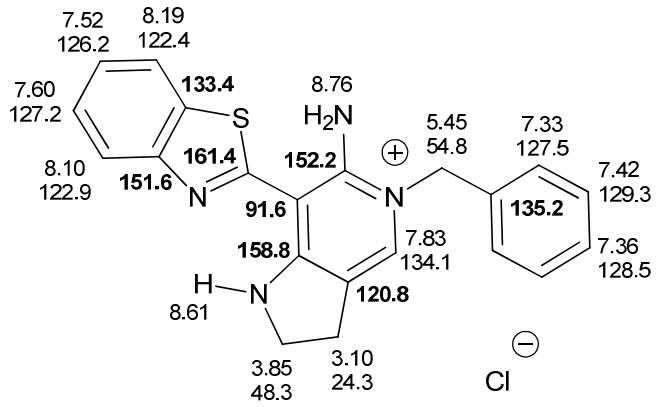
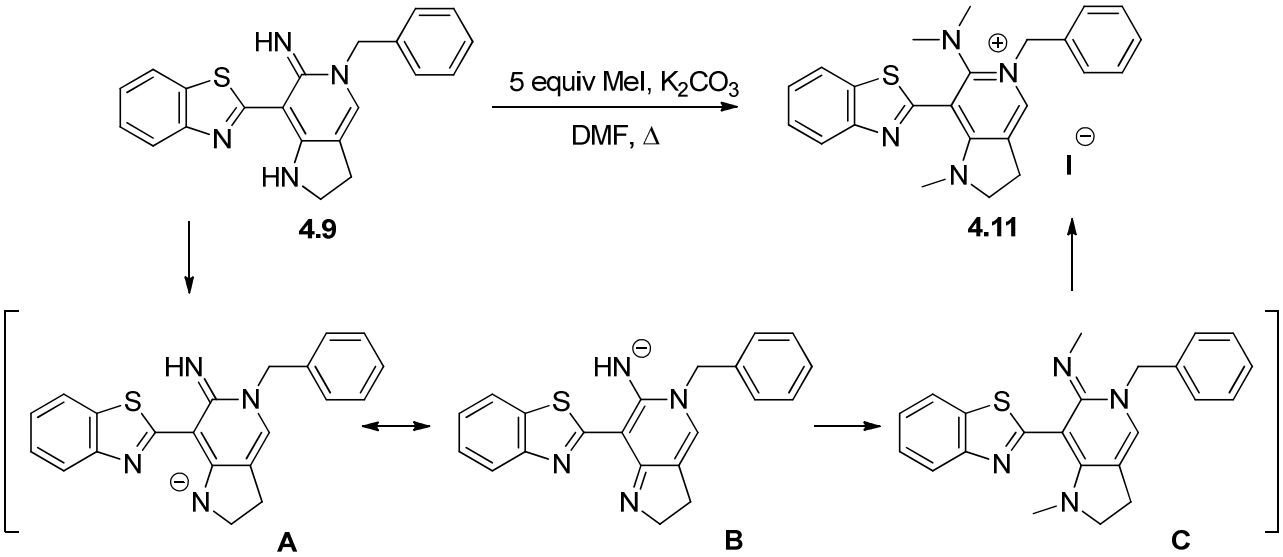


Figure 4.13. *The compound* ***4.10b*** *structure according to 2D NMR (400 MHz, DMSO-d$_6$).*

Pyrrolo[3,2-*c*]pyridine-6-imine **4.9** alkylation with the excess of MeI and in the presence of K_2CO_3 leads to the permethylated product **4.11** (*Scheme 4.10*). It is known[127], that the formation of permethylated derivatives for similar compounds – 2-imino-*β*-carbolines occurs via formation of a dimethylated product at endo- and exocyclic nitrogen atoms. Taking into account precedents from the literature we propose the mechanism for the formation of **4.11**. The mechanism involves the deprotonation of **4.9** leading to intermediate **A↔B**, followed by its methylation leading to **C**. Finally the methylation at methylamino group occurs yielding **4.11**.



Scheme 4.10. *Permethylation of pyrrolo[3,2-c]pyridin-6-imine* ***4.9****.*

The structure of trimethyl-derivative **4.11** was confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. In the ^{1}H NMR spectrum the singlet of NMe_2 arises at 2.34 ppm (6H), the signals of another CH_3 group has the same shift as the residual peak of DMSO-d_6 in ^{1}H NMR spectrum but in ^{13}C NMR spectrum arises separately at 35.4 ppm; peaks of NMe_2 carbons located at 42.4 ppm (Solvent: DMSO-d_6). The values found for the molecular mass correspond to the calculated values for the cation of compound **4.11** – calculated 401.1800, found 401.1800 and iodide – calculated 126.9045, found 126.9047.

It was noted that in the presence of acid pyrrolo[3,2-*c*]pyridin-6-imine **4.9** is protonated at the imino group yielding the salt **4.10**. The protonation process can be monitored by spectrophotometric titration of $1.5 \cdot 10^{-6}$ M solution of **4.9** in acetonitrile by HCl solution. Under increase of acid concentration there is the hypochromic effect within the range of 370–440 nm, however, hyperchromic within the range of 310–370 nm (*Figure 4.14*). After adding the equimolar amount (curves 10-11), further acid additives do not cause significant changes in the spectra (curves 12-13). From *Figure 4.16* it is seen that the shape of absorption band of **4.10b** in acetonitrile (curve 7) is similar to those obtained by titration of **4.9** by HCl at stoichiometric point (curve 6).

Similar trends are observed upon addition of water from 0.5 to 11.8% to the solution of **4.9** in acetonitrile (*Figure 4.15*).

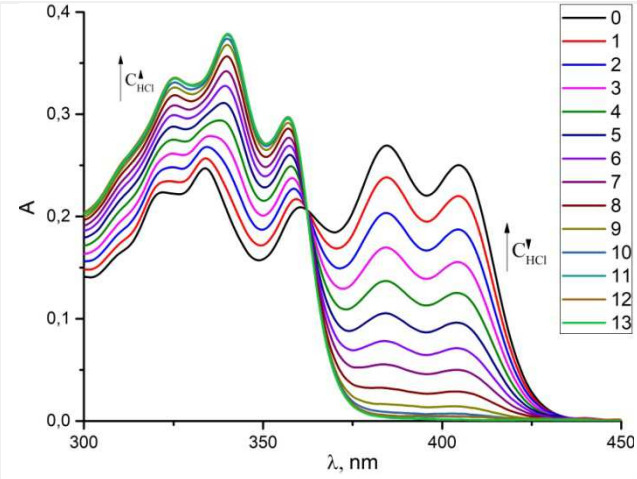


Figure 4.14. *Evolution of the absorption spectra of* ***4.9*** *upon titration with HCl solution (starting solution of 4.9 (0) with HCl additives (1-13)).* $C_{4.9} = 1.5 \cdot 10^{-5}$ *mol/l.* $C_{HCl} = 1.4 \cdot 10^{-6} - 2.4 \cdot 10^{-5}$ *mol/l.* φ_{H_2O} = 2.5% (in total).

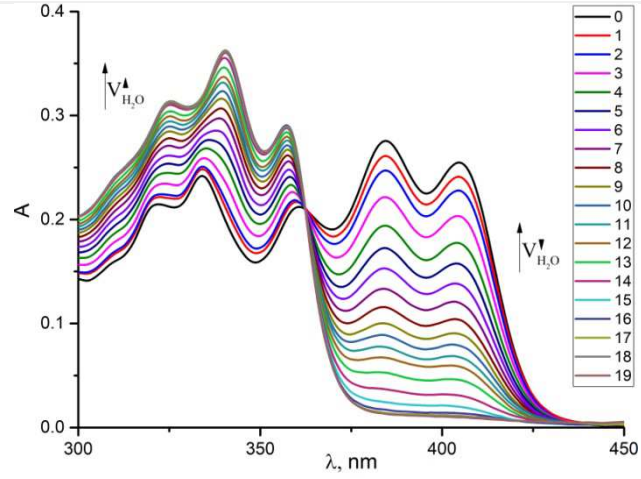


Figure 4.15. *Evolution of the absorption spectra of* ***4.9*** *upon titration with* H_2O *(starting solution of 4.9 (0) with* H_2O *additives (1-19)).* $C_{4.9} = 1.5 \cdot 10^{-5} - 1.3 \cdot 10^{-5}$ *mol/l.* φ_{H_2O} = 11.8% (in total).

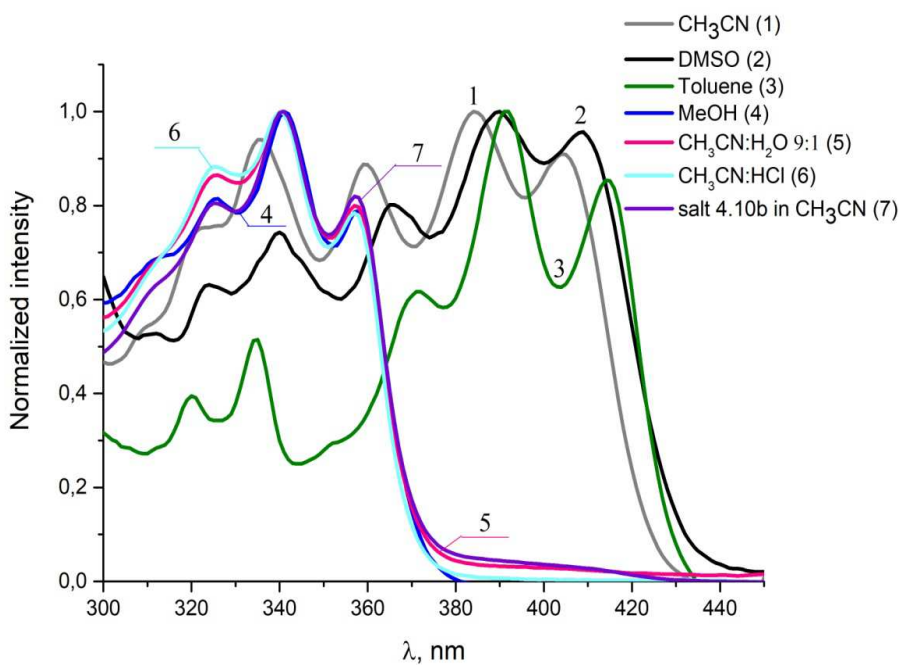


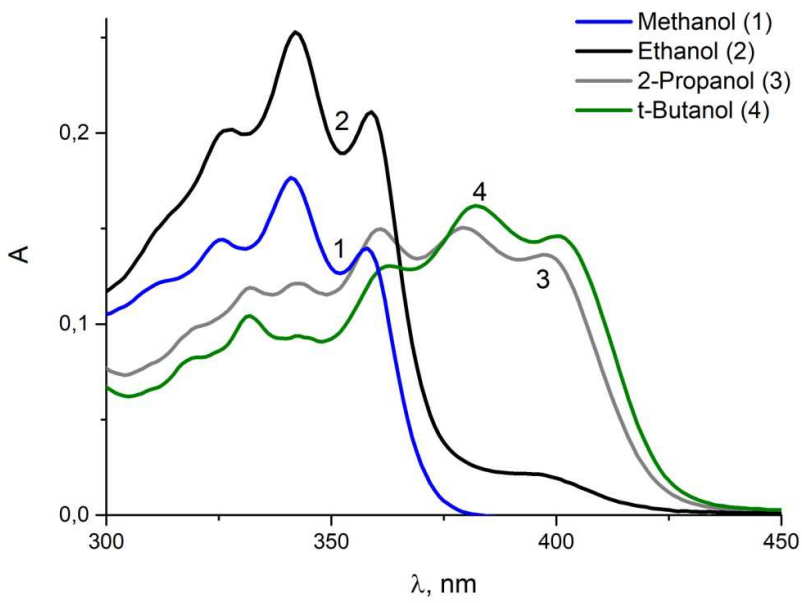
Figure 4.16. *Normalized absorption spectra of pyrrolo[3,2-c]pyridin-6-imine* ***4.9*** *in the solvents of different polarity and proton donating abilities. The absorption spectrum of* ***4.10b*** *in* CH_3CN *(7).*

From *Figure 4.16* it can be seen that the absorption spectrum of **4.9** in protic solvent – freshly distilled methanol (curve 4), is similar to the spectra in acetonitrile with acid and water additives (curves 5,6) and has a maxima around 340 nm while in the aprotic solvents of different polarity, namely, CH_3CN, DMSO, toluene (curves 1 – 3 respectively) there are maxima in the range of 310 – 440 nm.[130]
Spectrophotometric characteristics of **4.9** is presented in the *Table 4.1*.

Table 4.1. *Spectrophotometric characteristics of* ***4.9***.

Solvent	λ_{max} of absorption, nm	ε_{max}, 10^4 $l/mol \cdot cm$	Solvent	λ_{max} of absorption, nm	ε_{max}, 10^4 $l/mol \cdot cm$	Solvent	λ_{max} of absorption, nm	ε_{max}, 10^4 $l/mol \cdot cm$
DMSO	324	0.46±0,02	CH_3CN	323	1.05±0,01	Toluene	320	0.42±0,02
	339	0.54±0,02		335	1.31±0,02		335	0.56±0,02
	366	0.59±0,02		360	1.25±0,04		372	0.71±0,05
	390	0.72±0,09		384	1.46±0,19		391	1.15±0,07
	409	0.69±0,09		404	1.33±0,18		414	0.99±0,07
CH_3CN :HCl CH_3CN :H_2O	325	2.15±0,07	CH_3OH	326	0.92±0,07	Ethanol *	328	1.35
	340	2.47±0,06		341	1.11±0,08		342	1.69
	357	1.95±0,02		358	0.90±0,06		359	1.41
Propan -2-ol*	332	0.79	*tert*- Buthanol*	319	0.55		397	0.14
	342	0.79		332	0.70	* The molar absorption coefficient is calculated for the solution with $C_{\mathbf{4.9}}$=1.5•10^{-5} mol/l		
	361	1.00		363	0.87			
	379	1.00		382	1.08			
	397	0.91		400	0.97			

With a decrease of pKa of the solvents[131] and their ability to act as donors of hydrogen bond, characterized by alpha coefficient,[132] moving from methanol to ethanol, propan-2-ol and t*ert*-buthanol induced a significant decrease of the donor solvent effect and the spectra in *tert*-butanol and propan-2-ol being close to the ones in aprotic solvents (*Figure 4.17*).



α-scale
0.990 – methanol
0.850 – ethanol
0.687 – propan-2-ol
0.436 – *tert*-butanol

pKa
15.2 – methanol
16.0 – ethanol
16.5 – propan-2-ol
17.0 – *tert*-butanol

Figure 4.17. *The absorbtion spectra of pyrrolo[3,2-c]pyridin-6-imine* ***4.9*** *in alcohols: methanol–ethanol–propan-2-ol–tert-buthanol;* $C_{4.9}$ *= 15 μmol/l.*

Taking into account the experimental data and the calculated $pKa_{4.9}$ value of 10.9 leads to the conclusion that at concentration required for spectrophotometric measurements, in solvents such as water, methanol and ethanol most of the molecules are in protonated state (estimated value 99% in water and methanol and about 95% in ethanol). Thus, the UV-spectra of pyrrolopyridine in the mentioned solvents and the spectrum on the salt **4.10** are similar.

According to ^{1}H NMR spectra of **4.9** recorded in DMSO-d_6 and $CDCl_3$ compound **4.9** exist as a mixture of imine **4.9A** and enamine **4.9B** forms in solution. Thus the spectra in aprotic solvents show a broad absorption band within the range of 310–440 nm reflecting the absorption of a mixture of tautomers.

Pyrrolo[3,2-*c*]pyridine **4.9** has an intense (quantum yield of 61% in CH_3CN; standard – quinine sulfate) with λ_{max} of emission 460 nm. The emission intensity increases with the increase of concentration up to 1 μmol/l, the effect of the internal filter in the spectra does not appear (*Figure 4.18*).

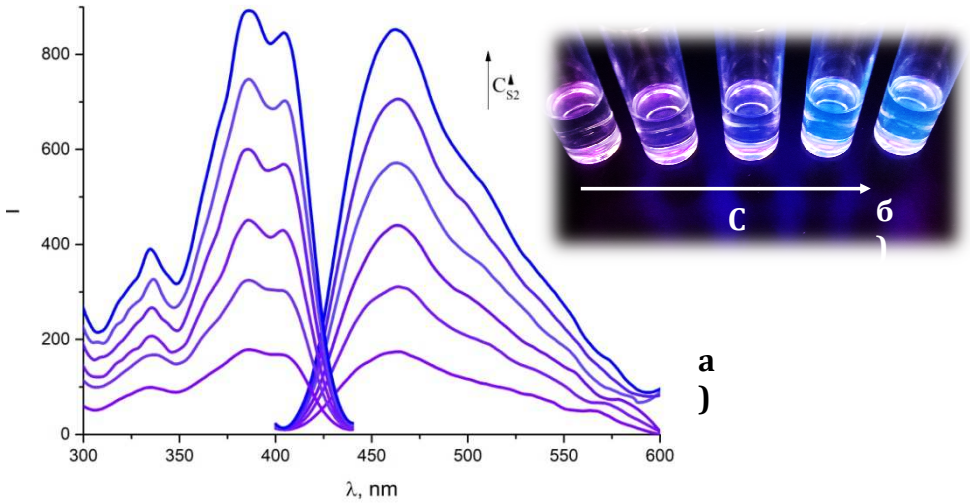


***Figure 4.18**. **a)** The spectra of excitation and emission of **4.9** in DMSO. $C_{4.9}$ = 9.3•10^{-8} -5.6•10^{-7} mol/l (λ_{ex} = 380 nm, λ_{fl} = 460 nm). **b)** Picture of fluorescence of compound **4.9** solutions of different concentrations in DMSO under irradiation with a UV lamp (λ_{ex} = 365 nm).*

Such sensitivity of pyrrolo[3,2-*c*]pyridin-6-imine **4.9** to protonation along with high fluorescence quantum yield could be useful to develop an unprecedented water detection test for aprotic solvents.

We have demonstrated, that upon water adding to the solution of **4.9** in DMSO the fluorescence quenching is occurring (*Figure 4.19*). The calibration graph equation is ΔI_{max} = (-2±2) + (96.0±0.9)·φ(H_2O), %, R^2 = 0.999, n = 13. Limit of water detection by 3S-criterion is 0.068 %.

The pyrrolo[3,2-*c*]pyridine-6-imine based procedure therefore represents a convenient alternative to Karl Fischer titration as it does not require any specific equipment and can be used wherever fluorometer is available. The limit of detection of 0.068 % is sufficient to determine the water content in DMSO. Standard of DMSO anhydrous is DMSO with less than 0.1 % H_2O[133] Moreover, the fast measurement prevents an increase of the water content in the sample associated with a contact with wet air.

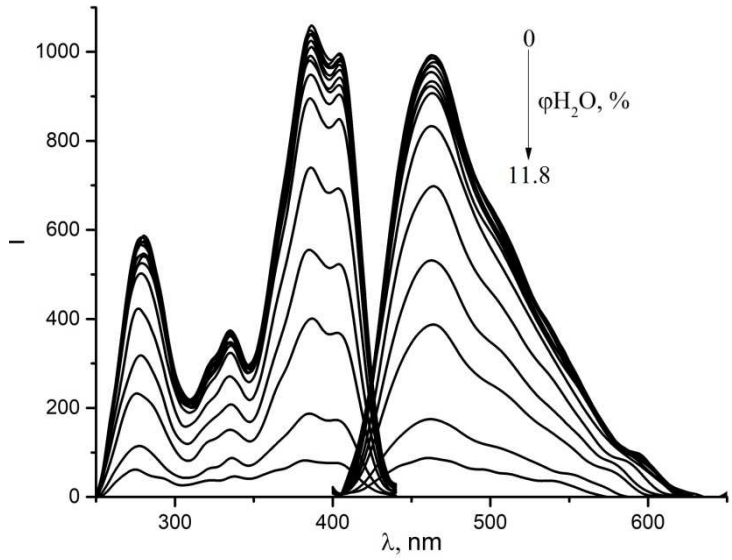
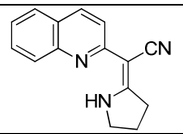
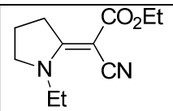
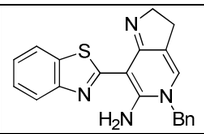
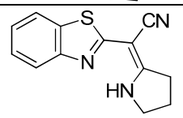
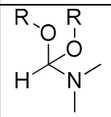
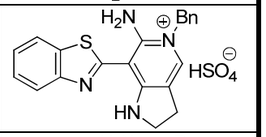
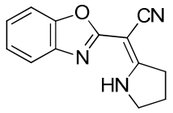
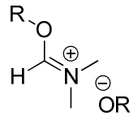
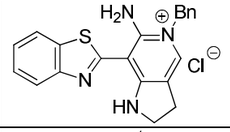
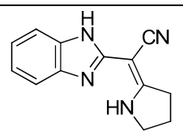
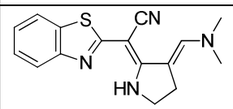
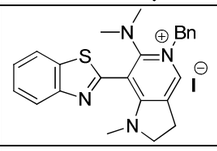
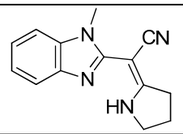
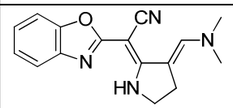
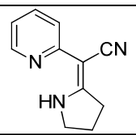
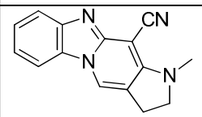
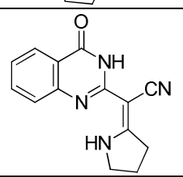
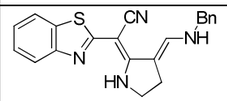
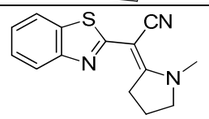
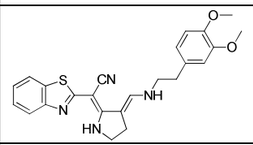
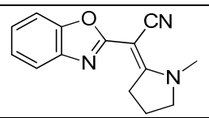
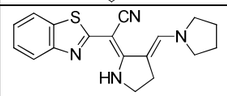
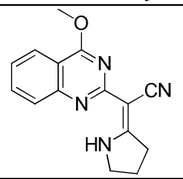
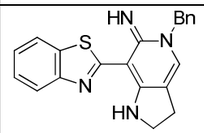


Figure 4.19. *The spectra of excitation and emission of* ***4.9*** *in DMSO with and without water additives (φ).*

In summary, 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles react with DMF DMA yielding both the methylated products **2.18a**, **2.1g**, **2.9** and formylated ones **4.2a**, **4.3, 4.4**. Pyrrolidinacetonitriles, that does not feature a NH group with a labile proton do not react with DMF DMA **2.1a**,**i 2.7a**, **2.18a.** These observations prompted us to assume that the presence of easily accessible NH group is essential in formylation of the C-3 centre of pyrrolidine allowing to propose a mechanism for this uncommon reaction.

Formylation reaction of 2-(benzo[*d*]thiazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile with DMF DMA, followed by further transamination and cyclization under basic conditions gave rise to pyrrolo[3,2-*c*]pyridine-6-imine **4.9**, a compound that exhibits a high fluorescent quantum yield (Φ = 61%) and proved to be very sensitive to protonation. Both characteristics are expected to be useful to develop an unprecedented water detection test for aprotic solvents. We have demonstrated that such a fluorometric method for determining water content in DMSO presents a limit of detection of 0.068%.

List of samples

2.1a		**1.103**		**4.9B**	
2.1b		**4.1**		**4.10a**	
2.1c		**4.1A**		**4.10b**	
2.1f		**4.2a**		**4.11**	
2.1g		**4.3**			
2.1i		**4.4**			
2.1j		**4.6**			
2.7a		**4.7**			
2.18a		**4.8**			
2.9		**4.9A**			

CHAPTER 5. COMPLEXES ON THE BASE OF 2-AZHETARYL-2-PYRROLIDIN/5-R-3-OXOINDOLIN-2-YLIDENE)ACETONITRILES

We have so far demonstrated numerous synthetic transformations of cyclic 2-azahetaryl-3-enaminonitriles. They also may be considered as bidentate ligands due to the presence of two proximate electron donating nitrogen atom allowed to consider their photophysical properties upon binding to boron and their coordination chemistry toward 3d-metals.

5.1. BF_2-rigidified complexes on the base of 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles

The BF_2 complexes of 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles **5.1** feature structural analogues with BODIPY-dyes, namely, the boroazacycle. This similarity allows us to consider newly synthesized complexes **5.1** as desimetrized analogues of BODIPY-dyes (*Figure 5.1*).

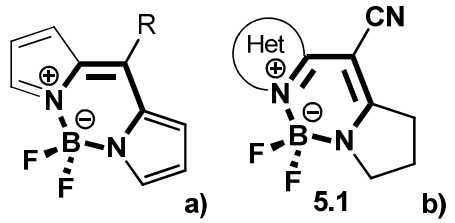
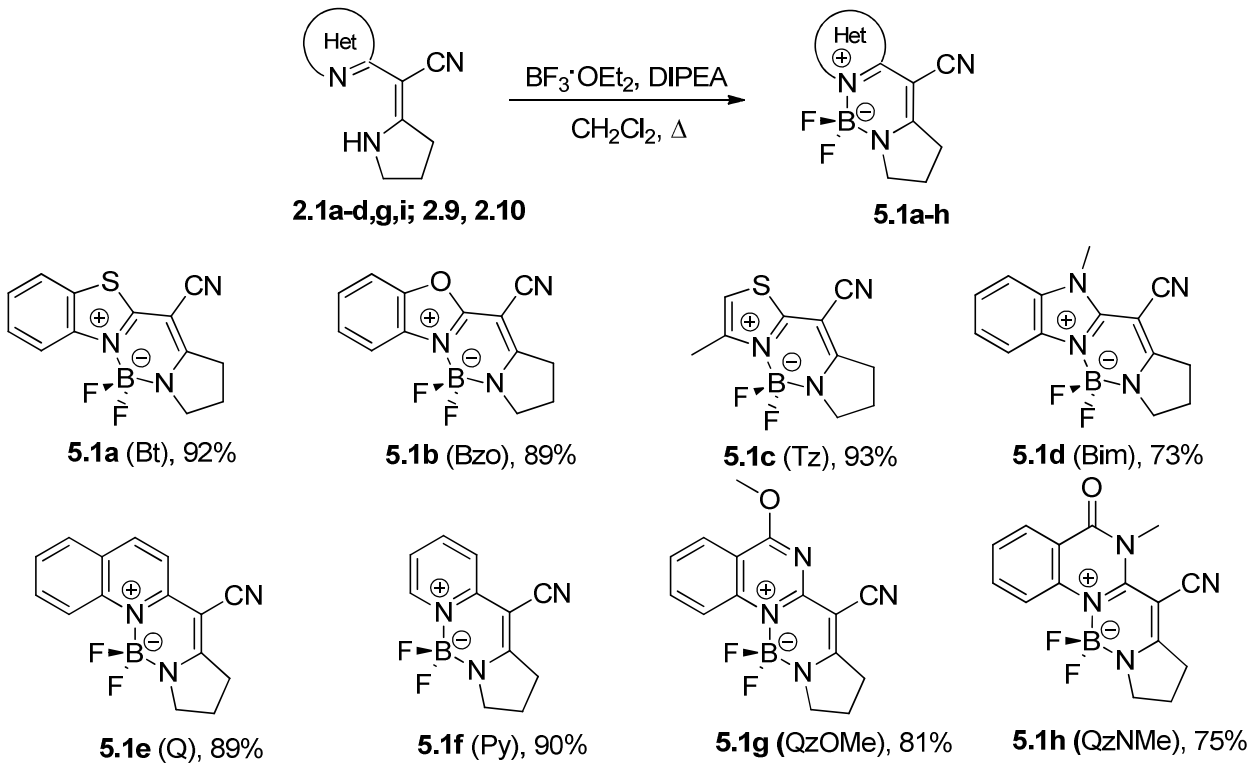


Figure 5.1. a) *Central core of BODIPY-dyes* ***b)*** *Desimetrized analogues of BODIPY-dyes.*

BF_2 complexes **5.1** were obtained from 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles **2.1** (*Scheme 5.1*). As these compounds are easily accessible starting material (section 2.1) it can be expected that a large structural versatility of dyes might be accessed from these precursors. Indeed, complexes are obtained in excellent yields 73–93% by treatment of the mixture of enaminonitrile **2.1**, **2.9**, **2.10** and *N,N*-diisopropylethylamine (DIPEA) with $BF_3{\cdot}OEt_2$ in refluxing dichloromethane. Complexes **5.1** are stable to hydrolysis in slightly acidic or basic media and could be purified by aqueous work up followed by column chromatography on silica gel.



Scheme 5.1. *Synthesis of BF_2-rigidified complexes* ***5.1****.*

Benzimidazole **2.1f** and 4-oxo-3,4-dihydroquinazoline **2.1j** derivatives did not provide the desired complexes **5.1.** The presence of several acidic NH protons in these molecules most probably hamper a regioselectivity of complexation. An attempt to isolate individual products from the reaction mixture, according to TLC control, failed. Changing NH to N-CH_3 group allowed the isolation of the complexes **5.1d**,**g-h**.

The ^{1}H NMR spectra of complexes **5.1** exhibit the disappearance of the NH signal that was observed in starting material (δ = 8.5–11.5 ppm); the significant low field shift of aromatic (Δδ = 0.2–0.8 ppm) and 5-CH_2 (Δδ = 0.2–0.25 ppm) protons, arising from the close proximity to fluorine and induced by magnetic anisotropy effect of B–F bond and electronegativity of F (*Figure 5.2, Table 5.1*). For quinoline **5.1e** and quinazoline **5.1g,h** derivatives the low field shift is larger than for benzazoles; for pyridine **5.1f** derivative the 6-H proton is shielded and shifted up field by 0.05 ppm (*Table 5.1*).

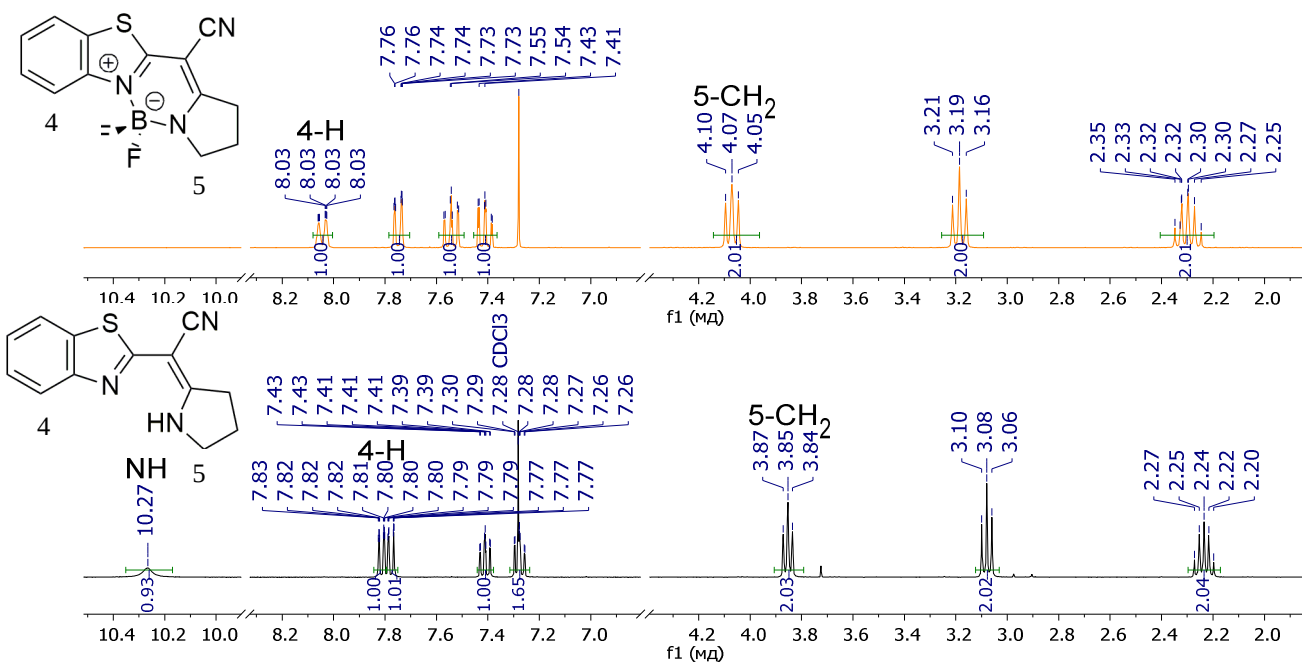


Figure 5.2. *^{1}H NMR spectra of ligand **2.1b** (bottom) and complexe **5.1a** (top).*

Table 5.1. *^{1}H NMR chemical shifts of protons modified by complex formation and corresponding protons in initial hetarylenaminonitriles **2.1**(Solvent: $CDCl_3$).*

Compound	δ of aromatic proton, ppm	δ of 5-CH_2-protons, ppm	Compound	δ of corresponding aromatic proton, ppm	δ corresponding CH_2-protons
5.1a	8.05	4.07	**2.1b**	7.81	3.85
5.1b	7.71	4.06	**2.1c**	7.52	3.85
5.1c	2.51 (CH_3)	3.98	**2.1d**	2.37 (CH_3)	3.76
5.1d	7.82	4.03	**2.1g**	7.57	3.82
5.1e	8.61	4.10	**2.1a**	7.84	3.85
5.1f	8.31	3.98	**2.1i**	8.36	3.75
5.1g	8.38	4.05	**2.9**	7.67	3.85
5.1h	8.28	4.10	**2.10**	7.47	3.86

The complexes formation could be also confirmed by ^{11}B NMR and ^{19}F NMR spectra where the triplet and quartet arise respectively due to spin-spin interaction between ^{11}B (the spin is $^{3}/_{2}$) and ^{19}F (the spin is $^{1}/_{2}$) nuclei (J_{BF} = 29–33 Hz).

The stability of the complexes was checked by ^{1}H, ^{11}B and ^{19}F NMR in $CDCl_3$, CD_3CN and for **5.1a** and **5.1c** in CD_3OD. The NMR spectra were recorded: directly after preparation the solutions, in 3h, in 1 day and in 1 week. None of the compounds

degraded under these conditions. Addition of a drop of water to the solutions in CD_3CN and CD_3OD and another set of NMR spectra was recorded immediately and after 1 day. No degradation of complexes occurred. The stability of complexes was also checked in electron donating solvents: deuterated pyridine and tetrahydrofuran for compounds **5.1a** and **5.1c**. The graduate formation of another set of signals was observed only in aliphatic region in pyridine solution for compound **5.1a**. The ^{11}B and ^{19}F NMR spectra showed no variation with time. Such change could be due to competitive coordination of pyridine to boron atom. The compound **5.1c** stayed unaffected in pyridine solution. Tetrahydrofuran does not influence anyhow on the structure of complexes.

Crystals suitable for X-ray analysis were obtained by slow diffusion of hexane into their dichloromethane solutions at room temperature. XRD shows a dihedral angle between azaheterocycle and pyrrolidine is within the range of 2.5–13.9°. The boron atom has distorted tetrahedral geometry $[N_2F_2]$ (angles around B vary from 105.8° to 112.0°). The dyes are well ordered and packed densely due to C–H···F and π-π interactions. The same packing is observed for other BF_2-carrying compounds $[N_2F_2]$[86] and $[NOF_2]$[134] reported in the literature. The structure of complexes (*Figure 5.2a*), orthogonal projection (*Figure 5.2b*) and packing (*Figure 5.2c,d*) for the representative complex **5.1d** are shown at *Figure 5.2*.

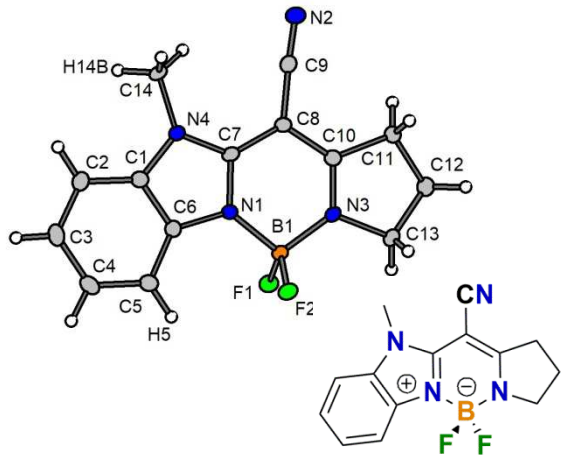
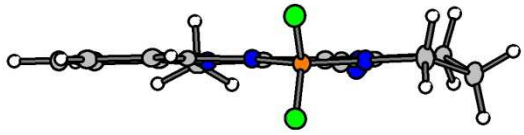
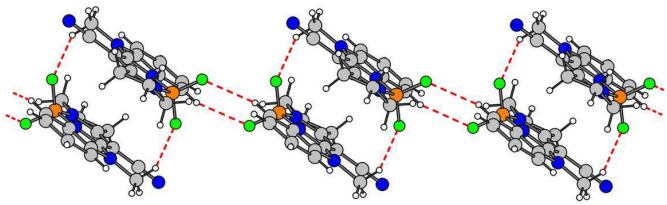


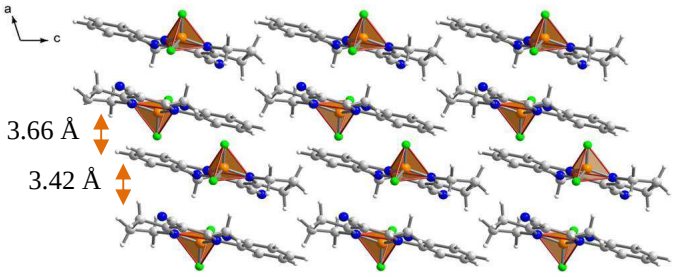
Figure 5.2. *a) Molecular structure of compound* ***5.1d*** *according to X-Ray diffraction.*



b) Orthogonal projection.



c) Dimerization of the layers (H14···F2 2.42 Å, C14–H14···F2 128.2°, H5···F1 2.52 Å, C5–H5···F1 143.4°).



d) Layered crystalline structure (the average distance between layers is 3.54 Å).

Absorption spectra are represented at *Figure 5.3*.[135]

In the near UV and visible range there are bands resulting from transitions within aromatic fragments that are conjugated with heteroatoms lone pairs (n→π*, π→π* transitions). Most absorption maxima are located within the range of 320 – 400 nm (*Table 5.2*), except for quinoline derivative **5.1e**, which exhibits a λ_{max} = 420 nm, (Solvent: CH_3CN); this is in agreement with the data reported in the literature for BF_2-rigidified pyrrolopyrrole cyanines for which λ_{max} increase in order benzoxazol-2-yl→pyridin-2-yl→benzothiazol-2-yl→quinolin-2-yl (754 nm)[87], and for BF_2-benzo[*c*,*d*]indole *N*-

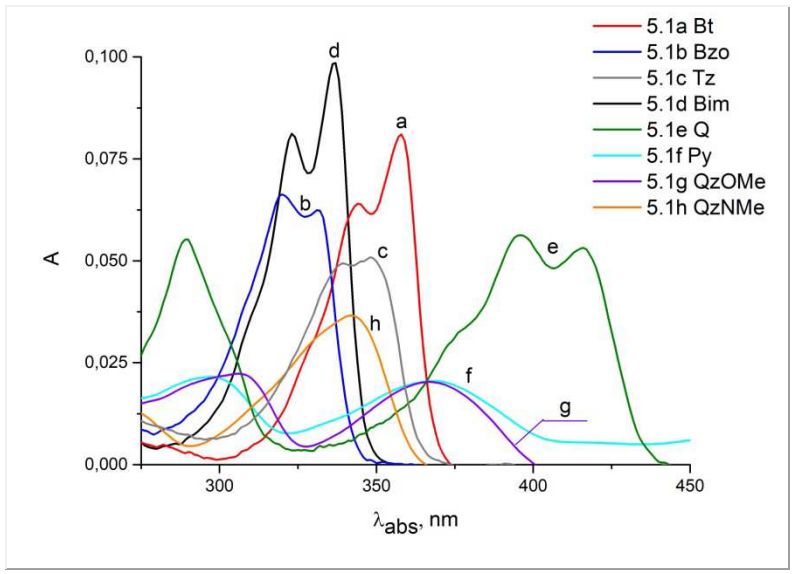


Figure 5.3. *Absorption spectra of complexes* ***5.1a-h*** *in CH_3CN with concentration of 1.6 μmol/l.*

heteroarenes in order pyridin-2-yl→thiazol-2-yl→benzothiazol-2-yl→quinolin-2-yl (455 nm)[86].

The decrease of energy gap between HOMO–LUMO is reflected in bathochromic shift of the absorption maximum of complexes **5.1** (9–50 nm) as compared to **2.1** (*Table 5.2*).

4-Metoxyquinazoline derivative **5.1g** has a batochromic shift of long wavelength maximum (λ_{abs}^{max}) relative to its structural isomer, namely, the derivative of 3-methyl-4-oxo-3,4-dihydroquinazoline **5.1h** (CH_3CN). This arise from the elongation of p,π-conjugation chain (*Figure 5.3, Table 5.2*).

The absence of isosbestic points in the normalized absorption spectra (A/Amax) of the same complex at different concentrations indicates that there is no self-association in the solution.

When increasing the structure's rigidity the amount of radiationless transition decreases. Consequently, all BF_2-rigidified complexes **5.1** have brighter fluorescence as compared to initial hetarylenaminonitriles **2.1**, **2.9**, **2.10**, which florescence intensity in the same conditions of spectra recording is within the range of 20 – 40 relative units. The fluorescence quantum yields (*Φ*) of **5.1** are varied from 6% (**5.1h**) to 90% (**5.1a**) in DMSO (*Figure 5.4*).

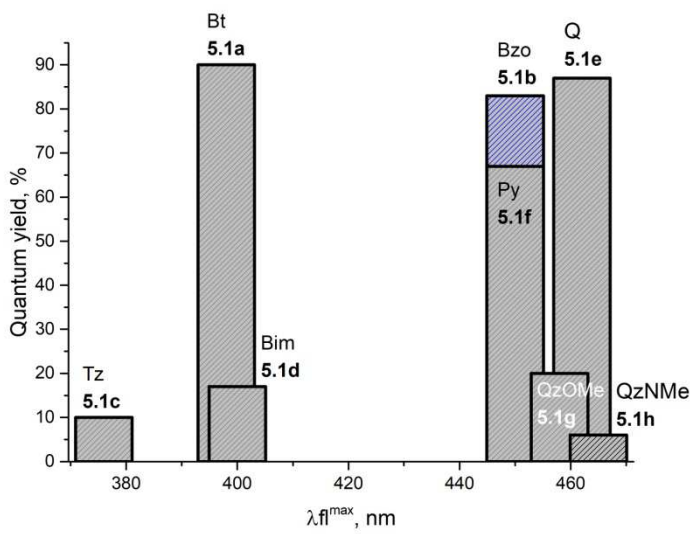


***Figure5.4**. Diagram of distribution of complexes **5.1** depending on quantum yield and λ_{fl}^{max}.*

Desimetrization of the ligand around boroazacycle increases the distinction between the electron distribution in the ground and excited states, thus increasing the Stokes shift of **5.1** (≈ 2000–9000 cm^{-1}) as compared to classical BODIPY dyes (the average value of the Stokes shift is in the range of 400–1000 cm^{-1}[86])

Table 5.2. *Photophysical characteristics of complexes* ***5.1a-h*** *and the ligands* ***2.1a-d,g,i; 2.9, 2.10*** *in various solvents.*

Compound	Solvent	λ_{abs} (nm)	ε_{abs}^{max} (M^{-1}•cm^{-1})	λ_{fl} (nm)	$\Delta\upsilon$, (cm^{-1})	*Φ*, DMSO, %	ε× Φ (M^{-1}•cm^{-1})
2.1b	$CHCl_3$	336	20 000				
5.1a	DMSO	360	96 000	398	2652	90	86 400
	CH_3CN	358	52 700	398	2807		
	$CHCl_3$	361	43 300	393	2256		
	Толуен	364	42 100	392	1361		
	Solid state			406, 423			
2.1c	DMSO	323	43 000				
5.1b	DMSO	322	84 800	450	8 834	83	70 400
	CH_3CN	320	40 600	447	8 879		
	$CHCl_3$	323	31 900	406	6 329		
	Toluene	325	31 300	382	4 591		
2.1d	DMSO	327	33 900				
5.1c	DMSO	349	28 000	400	3653	10	2 800
	CH_3CN	349	30 900	430	5397		
	$CHCl_3$	349	13 900	395	3337		
	Toluene	355	34 100	386	2262		
	Solid state			434			
2.1g	DMSO	325, 338	26 900				
5.1d	DMSO	339	46 000	370, 382	3321	17	7800
	CH_3CN	337	63 800	431	6472		
	$CHCl_3$	339	14 900	453	7423		
	Toluene	342	36 700	366	1917		
	Solid state			376, 396			
2.1a	DMSO	380	24 100				
5.1e	DMSO	398, 417	38 100 35 900	462	3 481	87	33 100
	CH_3CN	396, 416	35 000 33 700	459	3 466		
	$CHCl_3$	397, 420	22 400 22 200				
	Toluene	400, 424	19 200 19 600	441	9 092		
	Solid state			496			
2.1i	DMSO	295, 334	18 600				

5.1f	DMSO	369	34 700	450	4 878	67	10 200
	CH_3CN	367	15 300	447	4 877		
	$CHCl_3$	369	10 600	434	4 059		
	Toluene	375	7 000	437	3 783		
	Solid state			Fluorescence is in the range of 20 units			
2.9	DMSO	320	28 000				
5.1g	DMSO	370	62 200	458	5 193	20	12 400
	CH_3CN	367	12 500	455	5 270		
	$CHCl_3$	368	21 000	437	4 291		
	Toluene	374	26 100	440	4 011		
	Solid state						
2.10	DMSO	337	15 100				
5.1h	DMSO	346	78 800	465	7 396	6	4 700
	CH_3CN	345	23 000	431	5 784		
	$CHCl_3$	347	28 500	457	6 937		
	Toluene	350	10 400	437	5 688		
	Solid state						

Polar solvents exhibit a better solvation of the excited state compared to the ground state. This is reflected in the bathochromic shift of the maximum of excitation when switching from toluene to DMSO (Δλ up to 68 nm). Solvatochromism in absorption spectra is negligible, shift of absorption maxima upon changing the solvent polarity being within 7 nm.

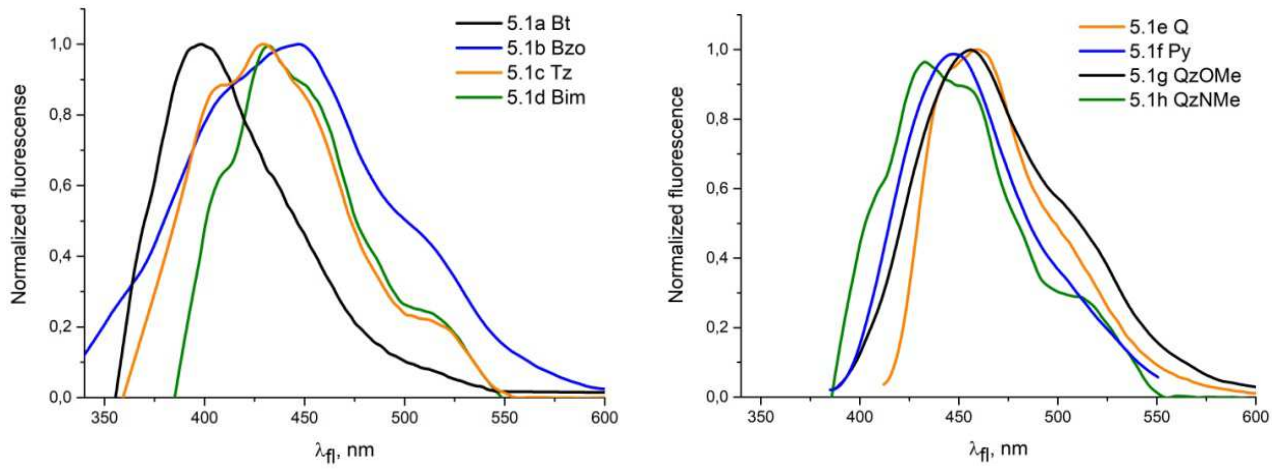


Figure 5.5. *Normalized spectra of fluorescence of complexes substituted with azole* ***5.1c*** *and benzazoles* ***5.1a,b,d*** *(left) and quinoline* ***5.1e****, pyridine* ***5.1a*** *and azines* ***5.1g,h*** *(right) (Solvent: CH_3CN).*

The optical properties of the compounds in solution remain constant for at least a month upon storage in unprotected from air and humidity conditions.

In contrast to BODIPY dyes which are not usually fluorescent in the solid state due to small Stokes,[84, 86] complexes **5.1** have a bright fluorescence in the solid state that could be even detected with a naked eye (*Figure 5.6*).

Solid-state luminescence usually arises from luminescent dyes carrying peripheral bulky groups that prevent close packing and subsequent aggregation-induced fluorescence annihilation. On the other hand, aggregation-induced fluorescence is sometimes observed for dyes due to the restriction of intramolecular rotation in the solid state compared to solution.[134, 136-137] This phemomenon called "aggregation-induced emission" is probably the case for complexes **5.1**, which are characterized by numerous intermolecular C–H···F hydrogen bonds and strong packing, governed by π-π interactions with interlayer distances of 3.36–3.99 Å.

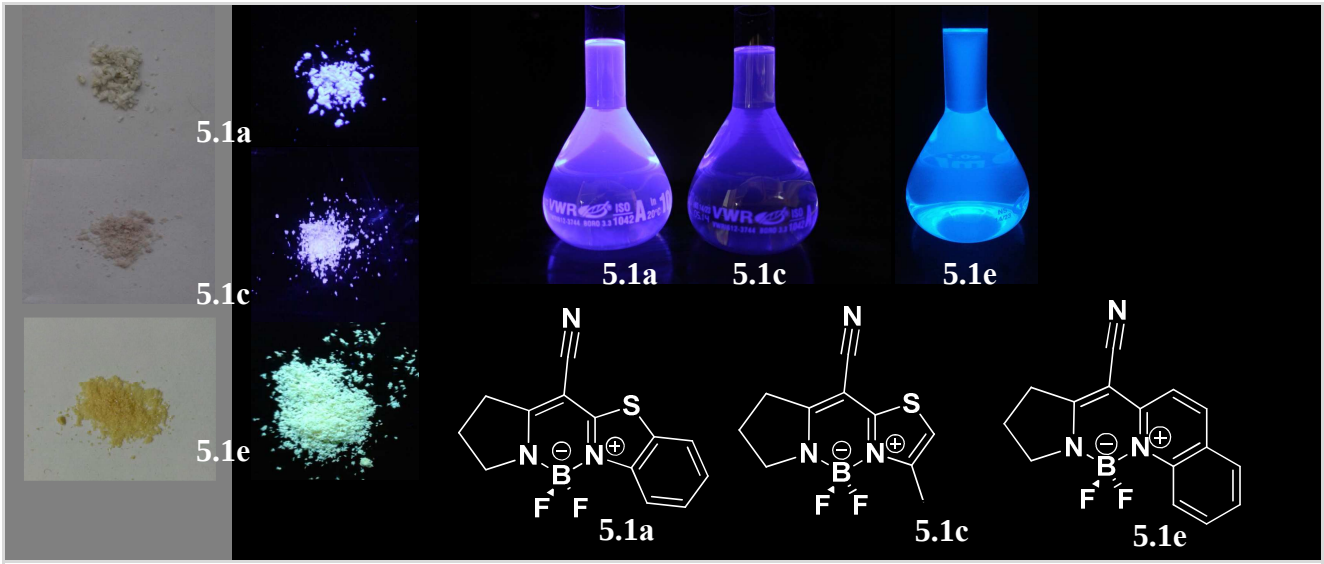


Figure 5.6. *Photographs of borate complexes as amorphous powders* ***5.1a,c,e****; powders and solutions under bench UV lamp (irradiation* λ_{ex}*=365 nm).*

In summary, BF_2-rigidified complexes that are easily accessible by two-steps approach from azahetarylacetonitriles have advantageous over BODIPY dyes: 1) Stokes shift up to 9000 cm^{-1} due to the desimetrization of the ligand around boroazacycle; 2) emission at violet-blue range that is not covered by BODIPY-dyes; 3) fluorescence both in solution (*Φ* up to 90%) and crystalline state.

The brightness of these molecules, especially benzothiazole (86400 $M^{-1}\cdot см^{-1}$) and benzoxazole (70400 $M^{-1}\cdot см^{-1}$) derivatives, matches the brightness of BODIPY dyes (for example, BODIPY-FL[14] 86 000 $M^{-1}\cdot см^{-1}$) and is one of the largest at violet-blue range among the dyes that are used for biovizualization (quinine – 3000 $M^{-1}\cdot см^{-1}$, Hoechst 33342 (the dye of dibenzimidazole group) – 17000 $M^{-1}\cdot см^{-1}$, 7-hydroxy-4-methylcumarin – 11000 $M^{-1}\cdot см^{-1}$).[138] The brightness of these dyes is sufficient for *in vitro* studies, but their emission (400 – 460 nm) is out of the optical window (650 – 900 nm) required for *in vivo* studies. Nevertheless, the presence of BF_2 group could be used for incorporation of radioactive label [^{18}F] and would provide these probes a bimodal character.

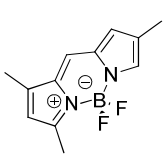
An important characteristic for biovizualization is neutrality of such probes allowing crossing through the cell membrane.

5.2. Complexes of 2-azahetaryl-2-(pyrrolidin/5-R-3-oxoindolin-2-ylidene)acetonitriles with 3d-metals: synthesis, structure and prospects for use

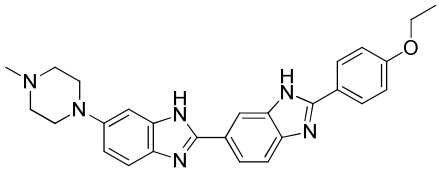
One of the tasks of modern coordination chemistry is the search for new ligands that can form thermodynamically and kinetically stable metal complexes. Bidentate-chelating ligands are one of the most studied types due to their ability to coordinate both d- and f-metals.[139]

The use of complexes of chiral *β*-enaminonitriles with Co(II), Cu(II), Zn(II), Ni(II) as catalysts for asymmetric synthesis and copolymerization is reported (subsection 1.5.2). We have investigated the prospect for use of metal complexes on the base of *β*-enaminonitriles in the synthesis of films of polymeric composites (FPC) that exhibit photovoltaic effect (subsection 5.2.1) and optical probes for Zn(II) and Cu(II) determination (subsection 5.2.2).

14



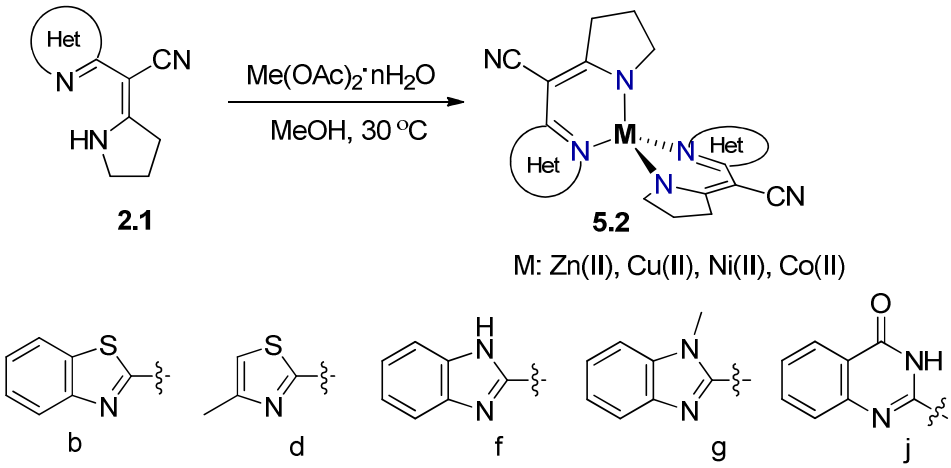
BODIPY-FL



Hoechst 33342

5.2.1. Complexes on the base of 2-azahetaryl-(2-pyrrolidin-2-ylidene)acetonitriles

On the base of new ligands of enaminonitrile type (HL) **2.1** the method to access complexes ML_2 was established yielding **5.2** with 60–65%.[139]



Scheme 5.2. *Synthesis of transition metals coordination compounds with heterocyclic enaminonitriles* ***5.2****.*

The IR spectra of **5.2** show no absorption band for NH group assessing the coordination of ligands. The absence of significant changes in the vibrations of CN and C=O (in the case of **5.2j**) indicates that these groups do not participate in the coordination of metal ions.

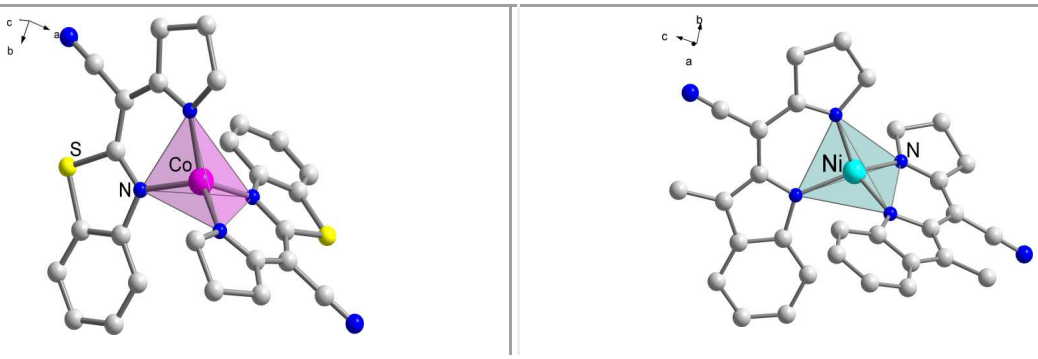


Figure 5.7. *Molecular structure of compound* ***5.2b*** *with Co(II) (left) and* ***5.2g*** *with Ni(II) (right) according to X-Ray diffraction.*

Coordination of ligands in deprotonated form is also confirmed by the absence of signals of NH group proton in ^{1}H NMR spectra of complexes with Zn(II). For the remaining protons, there is a general tendency for an up field shift, which can be explained by the increase of the electron density on the ligand due to its

deprotonation. XRD shows that the central 3d-metal in **5.2** takes tetrahedral geometry with four coordinating nitrogen atoms (*Figure 5.7*).

The photovoltaic and photoconductive properties of film composites of a copolymer of styrene with octyl methacrylate (COM) and additions of the complexes of **5.2d** with Co(II), Cu(II), Ni(II) were investigated (*Figure 5.8*).[140] In the samples with a free surface the photovoltaic effect was found. The value of electric potential of the surface (V_{PH}^{max}) increases in a row CuL_2 (80 mV), NiL_2 (120 mV), CoL_2 (180 mV), (concentrations of these additives in the SOM smaller than 50 wt.%). It was established that these composites have hole-type photoconductivity and upon increase of the magnetic moment of the metal ions (Cu(II) 1.8, Ni(II) 3.3, Co(II) 5.4) the efficiency of photogeneration of free charge carriers increases, which consequently causes the increase of the photovoltaic effect.

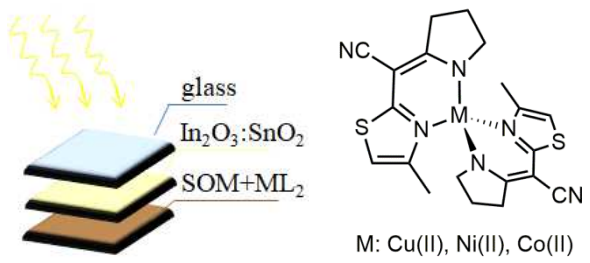
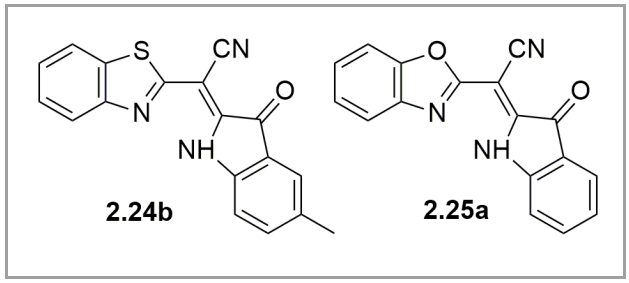


Figure 5.8. *Films composites of a copolymer of styrene with octyl methacrylate and additions of the* ***5.2d*** *with Co(II), Cu(II), Ni(II).*

5.2.2. Complexes on the base of 2-azahetaryl-2-(5-R-3-oxoindolin-2-ylidene)acetonitriles

As indicated in Section 2.4, 2-azahetharyl-2-(5-R-3-oxoindolin-2-ylidene) acetonitriles **2.24a-c**, **2.25a** are compounds having a bright purple color. Their absorption spectra in DMSO are characterized by bands with λ_{max} in the range of 515 – 550 nm.

Taking into account the λ_{max} position in the visible range of the spectrum, as well as the tendency of compounds to form chelate complexes, we have studied their photophysical properties in the presence of 3d-metal ions.[141]



Two model compounds that characterized by the highest extinction coefficient and λ_{max} of absorption (section 2.4) were selected, namely benzothiazole derivative **2.24b** and benzoxazole derivative **2.25a**. A spectrophotometric study showed that with a gradual addition to the solutions of compounds **2.24b** and **2.25a** in DMSO:H_2O Cu(II) and Zn(II) acetates in a buffer solution (Tris, pH = 7.2), a significant bathochromic shift of the absorption maxima occurs (*Figure 5.8 , Table 5.3*), which indicates the high visibility of these compounds as chromophore reagents ($\Delta\lambda \geq 70$ nm).

Table 5.3. *The influence of Zn(II) and Cu(II) on spectrophotometric characteristics of **2.24b** (DMSO 83%) and **2.25a** (DMSO 70%) in solution DMSO-H_2O.*

Entry	Compound	λ_{max} of absorption of reagent, nm	The influence of metal ion			
			Zn(II)		Cu(II)	
			λ_{max}, nm	$\Delta\lambda$, nm	λ_{max}, nm	$\Delta\lambda$, nm
1	**2.24b**	530	600	70	605	75
2	**2.25a**	515	590	75	590	75

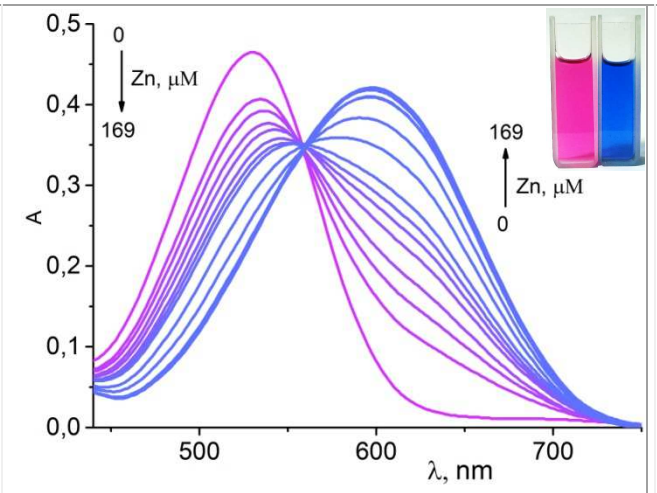
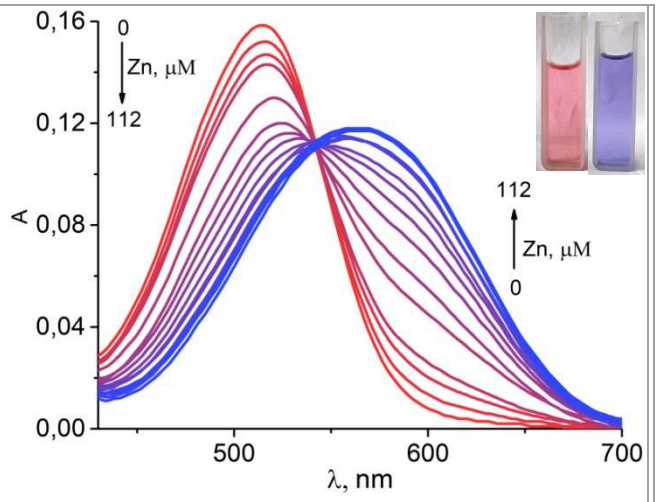


Figure 5.8. a) *The absorption spectra of* ***2.24b*** *with and without Zn(II).*
φ(DMSO) = 83 %,
$C_{2.24b}$ *= 38 μmol/l.*



b) *The absorption spectra of* ***2.25a*** *with and without Zn(II).*
φ(DMSO) = 70 %,
$C_{2.25a}$ *= 10 μmol/l.*

Applying the limited logarithmic method for the investigation of complexes[142] we have established that the complexes of the simplest composition 1:1 exist in the solution. The stability constant of lgK **2.24b**Zn(II) = 7.88±0.02, lgK **2.24b**Cu(II) = 7.51±0.05, **2.25a**Zn(II) = 8.66±0.05, indicates the formation of complex of average stability. The reagents are sensitive showing limit of ions detection (LD) calculated by 3S-criterion below 1 μmol/l (*Table 5.4*).

Table 5.4. *Limit of detection of Zn(II) and Cu(II) by* ***2.24b*** *and* ***2.25a****.*

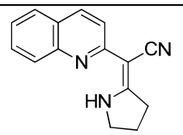
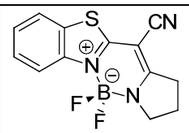
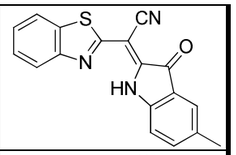
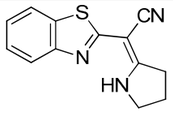
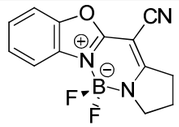
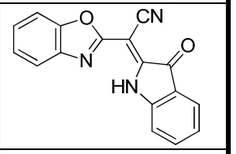
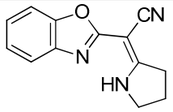
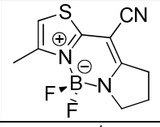
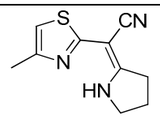
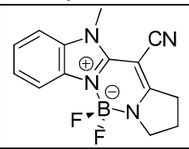
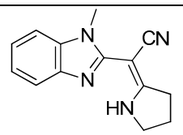
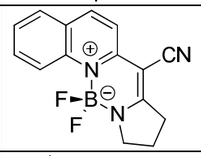
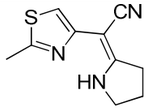
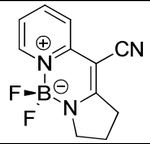
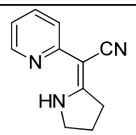
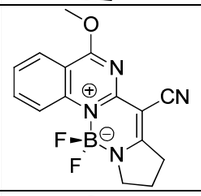
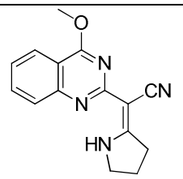
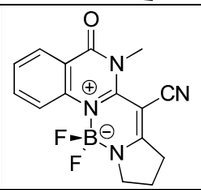
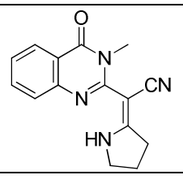
Entry	Compound	Ion	$\Delta A_{\lambda max}$	LD (3S), (μmol/l)
1	**2.24b**	Zn(II)	ΔA_{600}	0.54
2		Cu(II)	ΔA_{605}	0.97
3	**2.25a**	Zn(II)	ΔA_{590}	0.94
4		Cu(II)	ΔA_{590}	0.40

Complex formation occurs slowly with other 3d metals under conditions of interaction with Zn(II) and Cu(II), as in the case of Co(II) or does not occur in the case of Ni(II). For the selective determination of Zn(II), the Cu(II) ions can be masked by thiosulphate ions.

Thus at the pH of biological fluids, the spectrophotometric determination of the microquantities of Zn(II) and Cu(II) can be carried out using 2-azahetaryl-2-(5-R-3-oxoindoline-2-ylidene)acetonitriles as chromophore reagents, as they has a low limit of detection of metal ions (0.4-1 μmol/l) with large λ_{max} shift ($\Delta\lambda \geq 70$ nm).

Compared with the method of determining Zn(II) and Cu(II) with the use of porphyrin derivatives[143] (prototype), while maintaining the sensitivity our method is less laborious and energy saving (no need to heat up to 100 ° C). Moreover, the optimal pH corresponds to the acidity of biological fluids as opposed to the prototype, where the determination is carried out in an acid or alkaline medium. These facts indicate the promising use of the developed chromophore reagents for the analysis of biological fluids.

List of samples

2.1a		**5.1a**		**2.24b**	
2.1b		**5.1b**		**2.25a**	
2.1c		**5.1c**			
2.1d		**5.1d**			
2.1g		**5.1e**			
2.1h		**5.1f**			
2.1i		**5.1g**			
2.9		**5.1h**			
2.10					

GENERAL CONCLUSIONS

The work carried out within this PhD project has allowed the development of preparative methods of 2-azahetaryl-2-(1-R-pyrrolidine-2-ylidene)acetonitriles featuring azaheterocyclic substituents of neutral and cationic nature and 2-azahetaryl-2-(5-R-3-oxoindolin-2-ylidene)acetonitriles. The method to access 2-azahetaryl-2-(1*H*-pyrrolidine-2-ylidene)acetonitriles has been optimized, allowing a significant broadening of the scope of the reaction to numerous azaheterocyclic substituents (up to 12, starting from 2).

We have established that 2-azahetaryl-2-(1*H*-pyrrolidine-2-ylidene)acetonitriles exist both in the solution and the solid state as *Z* isomers in contrast to 2-azahetaryl-2-(1-alkylpyrrolidin-2-ylidene)acetonitriles that exists as *Z* isomers in the solid state and as a mixture of *Z*/*E* diastereomers in the solution. The free activation energy of rotation at C=C double bond has been calculated: $\Delta G^{\neq}$ E→Z = 14.4 kcal/mol, $\Delta G^{\neq}$ Z→E = 13.3 kcal/mol, a value that is characteristic of low-energy processes.

In our investigation on the reaction of 2-azahetaryl-2-(1-R-pyrrolidine-2-ylidene)acetonitriles with binucleophilic moieties, such as hydrazines and hydroxylamine we obseved a complete regioselectivity. Indeed it was established that the first nucleophilic attack is directed at C-2 atom of pyrrolidine. The orientation of the following attack is determined by the nature of azaheterocylic substituent:

- in the case of neutral azaheterocyclic substituents (beside benzoxazole) the attack is directed at the carbon of nitrile group leading to 3-(*ω*-aminopropyl)-4-azahetaryl-5-aminopyrazoles;
- in the case of benzoxazole derivatives the attack occurs both at nitrile group and with the same probability at the C-2 atom of azaheterocycle leading to the structural isomers: 4-benzo[*d*]oxazol-2-yl-3-(*ω*-aminopropyl)-1*H*-azol-5-amines and 5-((2-hydroxyphenyl)amino)-3-(3-(R-amino)propyl)-1*H*-pyrazol-4-carbonitriles (4-carboxydiimide in the case of hydroxylamine);

- in the case of quaternized benzoxazole and benzimidazole the attack is directed at C-2 atom of azaheterocycle leading to protonated 3-(4-cyano-5-((2-R-phenyl)methyamino)-1-R^1-1*H*-pyrazol-3-yl)-*N*-methylpropan-1-amines. With quaternized benzothiazole the first attack is directed at carbon of nitrile group followed by next nitrogen of *ω*-aminopropyl chain attack at C-2 atom of *N*-methylbenzothiazole leading to an original azepine derivative.

Starting from 3-(*ω*-aminopropyl)-4-azahetaryl-5-aminopyrazoles, we investigated methods for regioselective functionalization of their amino groups, condensation in tetracyclic compounds, namely, benzo[4,5]imidazo[1,2-*c*]pyrazolo[4,3-*e*]*pyrimidine* and *[1,2,3]triazine* derivatives with up to 87% overall yield; and deamination via diazotization step followed by Suzuki-Miyaura arylation and C–H activation leading to 5-aryl(styryl, indol-2-yl)-substituted pyrazoles with up to 92% overall yield were developed.

We also explored the properties of 2-azahetaryl-2-(1-R-pyrrolidine-2-ylidene)acetonitriles in reaction with DMF DMA. It was established that the presence of easily accessible NH group is essential in “formylation” of the C-3 centre of pyrrolidine. The method of the synthesis of pyrrolo[3,2-*c*]pyridine-6-imine (PP) with 59% over 3 steps was developed. The prospect use of PP for water content determination in aprotic organic solvents by fluorometric assay was developed for DMSO presenting a limit of detection of 0.068%.

Finally, we studied the structure and photophysical properties of complexes of 2-azahetaryl-2-(pyrrolidin/3-oxoindolin-2-ylidene)acetonitriles with 3d-metals and boron.

This allowed us to establish their potent usefulness since:

- The key characteristics of BF_2 complexes based on 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles are the big Stokes shifts (up to 9000 cm^{-1}), high brightness (up to 86400 $l \cdot mol^{-1} \cdot cm^{-1}$), positive solvatofluorochromy, fluorescence in the solid state and water stability.

- Films of polymeric composites with additions of metal complexes of 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles with Co(II), Cu(II), Ni(II) (ML_2)

exhibite photovoltaic effect. Electric potential of the surface attain the biggest value of 180 mV in the case of CoL_2.

- 2-Azahetaryl-2-(5-R-3-oxoindolin-2-ylidene)acetonitriles have demonstrated the high visibility when chelating Zn(II) and Cu(II): $\Delta\lambda \geq 70$ nm, $\lambda ligand^{max}$ = 515–530 nm (red-purple), $\lambda complex^{max}$ = 590–605 nm (blue), at the pH of biological fluids. Limit of ions detection is 0.4-1.0 µmol/l.

Therefore this work illustrates the wide potential developments that can be achieved based on an efficienty synthetic approach of polyfunctionnal heterocycles. We have shown that synthetic efforts are not only allowing new accesses to densely functionnalized compounds, but also providing straightforward molecular tools for photophysical studies that allow new development in a wide array of fields. As such this work contributes to the establish the molecule as the centre of any scientific development in chemical sciences.

EXPERIMENTAL PART

Instrumentation. For monitoring reaction progress, analytical thin layer chromatography (TLC) was performed using precoated Merck glass or alumina backed silica gel plates (Silica gel 60 F254).

Preparative chromatography was performed either manually with silica gel (63−200 μm) or with an automated flash chromatography Interchim Puriflash medium-pressure liquid chromatography system using Interchim high-purity grade silica gel (30 or 50 μm) prepacked columns.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 400 (400 and 101 MHz respectively) in DMSO-d_6–CCl_4, internal standard TMS; a Bruker Avance 300 (300 and 75 MHz respectively) or a Bruker Avance III 400 (400 and 101 MHz respectively) spectrometer, the internal standard is the residual peaks of deuterated solvents $CDCl_3$: 7.28 for ^{1}H and 77.0 ppm for ^{13}C; DMSO-d_6: 2.50 for ^{1}H and 40.0 ppm for ^{13}C; CD_3OD: 3.31 for ^{1}H and 47.6 ppm for ^{13}C, $(CD_3)_2CO$: 2.06 ppm for ^{1}H; CD_3CN: 1.97 ppm for ^{1}H and 117.3 ppm for ^{13}C. The degree of carbon atom substitution was determined by NMR spectra acquired according to the DEPT-135 or JMOD methods. Two-dimensional (2D) (COSY, HMQC, HMBC) spectra were recorded on a Bruker Avance III 400 (400 MHz) spectrometer and Bruker Avance 500 (500 MHz). VTP experiment was run on Bruker Avance 500 (500 MHz). All spectra were recorded at ambient temperature (298 K) unless otherwise stated. Coupling constants (*J*), are reported in Hz, chemical shift (δ) in ppm. The multiplicity of signals is indicated using the following abbreviations: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets, and m = multiplet.

IR spectra recorded on FT-IR spectrometries Perkin Elmer in KBr plates and neat films.

High resolution mass spectra (HRMS) were recorded on GCT Premier spectrometer upon electron spray ionization (ESI) or chemical ionization (DCI, CH_4).

Elemental analysis was performed on “CHNOS elementar vario MICRO Cube” analizator.

The melting points Melting points were determined on a Boetius micro hot stage apparatus with VEB Analytik 1399RNMK 05 observation lens or on Stuart melting point apparatus SMP10.

X-Ray diffraction was performed on on single crystal diffractometers: Agilent Gemini, Bruker Nonius, Bruker Kappa Apex II, and Xcalibur 3. All crystals were grown by the gas diffusion method or slow crystallization from solution.

The absorption spectra recorded on UV-Vis spectrometer UV-240IPC (Shimadzu). The excitation and emission spectra recorded on fluorescent spectrometer Perkin Elmer ls55. Weighing of samples was carried out on analytical scales VPK, VLR-200.

Fluorescence quantum yield (Φ_x) for BF_2-rigidified complexes was measured in diluted solution in DMSO with absorption maxima of A = 0.05 and calculated using the equation 1.

$$\Phi_x = \Phi_r \times \frac{F_x}{F_r} \times \frac{1-10^{A_r(\lambda_{ex})}}{1-10^{A_x(\lambda_{ex})}} \times \frac{n_x^2}{n_r^2} \quad (1)$$

F – the integral of the emission spectrum; A – absorption at maximum of excitation wavelenghth; n – refractive index. “r” – standard, “x” – test sample. The standard for complexes is the solution of 7-(diethylamino)-4-methyl-2*H*-chromen-2-oney (λ_{abs}^{max} = 330 nm, Φ_r = 0.73) in ethanol.[144] Measurements were made on the UV-3100 spectrophotometer and the SM-3500 spectrofluorometer.

Quantum-chemical calculations were performed using DFT at B3LYP/6-31G* level of theory. Conformations of *Z* and *E* isomers in stationary points corresponded to the minima on the potential energy surfaces that was confirmed by vibrational analyses performed at the same level of theory - no negative vibration frequency was found.

General Consideration. Reactions were performed in oven-dried, round-bottom flasks equipped with a reflux condenser and protected from humidity by a $CaCl_2$ tube unless otherwise noted.

The ratio between compounds in a reaction mixture and the ratio between *Z* and *E* stereoisomers were found by comparing the integration sum under the peaks in the ^{1}H NMR spectrum of the reaction mixture.

The distance between layers in the crystal lattice of BF_2-complexes was calculated as the distance between the molecule plain from the layer *n* and centroid of the molecule from the layer *n+1*.

General procedure for 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles 2.1a-f synthesis.

*Route 1 (for **2.1a-f**).* 5-Methoxy-3,4-dihydro-2*H*-pyrrole (0.15 г, 1.5 mmol) was added to a hot stirred solution of hetarylacetonitrile **2.2** (1 mmol) and triethylamine (0.21 ml, *d* = 0.726 g/ml, 1.5 mmol) in toluene. The reaction mixture was refluxed for 3-20 h (TLC control, elution system: CH_2Cl_2-CH_3OH 95:5) and after the reaction ceased was cooled down to room temperature and concentrated under reduced pressure.Compounds were purified by column chromatography (for enaminionitriles **2.1a**,**i**), or recrystallization from ethanol (for enaminonitriles **2.1b**,**d**,**e**,**h**) or mixture *i*-PrOH–dioxane (for enaminonitriles **2.1c**,**f**,**j**), or $CHCl_3$ (**2.1g**) in the presence of activated charcoal.

*Route 2 (for **2.1a-d**).* A vigorously stirred solution of hetarylacetonitrile **2** (2 mmol) and pyrrolidinone **4** (3 mmol) in dioxane (8 ml) was treated by dropwise addition of $POCl_3$ (0.28 ml, *d*=1.64 g/mlл, 3 mmol) and then refluxed for 1 h. The mixture was then cooled, treated with H_2O, and stirred for 30 min at 10° C. The obtained precipitate was filtered off and recrystallized from EtOH (in the case of pyrrolidines **2.1a,b,d**) or from *i*-PrOH−dioxane mixture (for pyrrolidine **2.1c**) in the presence of activated charcoal.

Synthesis of 2-(cyano(1-methylpyrrolidin-2-ylidene)methyl)-1,3-dimethyl-1*H*-benzo[*d*]imidazol-3-ium iodide (2.8).

A suspension of 2-(benzoimidazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile **2.1f** 449 mg, 2 mmol) or або 2-benzoimidazolyl-2-(1-methylpyrrolidin-2-ylidene)acetonitrile **2.13a** (450 mg, 2 mmol), iodomethane (0.3 ml, d = 2.28 g/cm^3, 5

mmol) and potassium carbonate (690 mg, 5mmol) in anhydrous DMF (5 ml) was heated to 80 °C over a 1 h period (TLC elution system: $CHCl_3$–CH_3OH, 95:5) The reaction mixture was then concentrated under reduced pressure ant triturated with CH_2Cl_2. The solid was filtered off and the filtrate was concentrated. Purification was made by triturating of solid residual with a minimal quantity of CH_3CN and further filtration. Yield 630 mg (1.6 mmol, 79 %) in the case of **2.1f**; Yield 654 mg (1.66 mmol, 83 %) in the case of **2.13a**. Light brown powder (mp 197 °C).

Synthesis of (*Z*)-2-(4-methoxyquinazolin-2-yl)- 2-(pyrrolidin-2-ylidene)acetonitrile (2.9) and (*Z*)-2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile (2.10).

A suspension of (*Z*)-2-(4-oxo-3,4-dihydroquinazolin-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile **1g** (505 mg, 2 mmol), iodomethane (0.3 ml, d = 2.28 g/cm^3,5 mmol) and potassium carbonate (690 mg, 5mmol) in anhydrous DMF (5 ml) was heated to 80 °C over a 1 h period (TLC elution system: EtOAc–CH_2Cl_2, 1:10. The reaction mixture was then concentrated under reduced pressure ant triturated with CH_2Cl_2. The solid was filtered off and the filtrate was concentrated. Products were separated by manual column chromatography (elution system: EtOAc-CH_2Cl_2,1:10, R_f **2.9** = 0.58, R_f **2.10** = 0.18).

General procedure for 1-R-pyrrolidin-2-ones 2.12 synthesis.

New 1-R-pyrrolidin-2-ones **2.12b**,**c**,**d**,**e**,**g** were obtained according to a reported procedure.[102] Their characteristics are listed below.

*1-benzylpyrrolidin-2-one (**2.12b**).* Yield 89%, colorless viscous liquid. **^{1}H NMR** (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 1.93−2.10 (m, 2H, 4-CH_2), 2.44 (t, J = 8.1, 2H, 3-CH_2), 3.26 (t, J = 7.1, 2H, 5-CH_2), 4.45 (s, 2H, Bn–CH_2), 7.21−7.38 (m, 5H, Ar-H).

*1-cyclopropylpyrrolidin-2-one (**2.12c**).* Yield 53%, colorless viscous liquid. **^{1}H NMR** (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 0.61−0.69 (m, 2H, NCHC$\underline{H_2}$), 0.69−0.78

(m, 2H, NCHC$\underline{H_2}$), 1.88−2.00 (m, 2H, 4-CH_2), 2.35 (t, *J* = 8.1, 2H, 3-CH_2), 2.56−2.70 (m, 1H, CH), 3.28 (t, *J* = 7.0, 2H, 5-CH_2).

*(R)-1-phenylethylpyrrolidin-2-one (**2.12d**).* Yield 81%, colorless viscous liquid. **^{1}H NMR** (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.54 (d, J = 7.1, 3H, CH_3), 1.89–2.04 (m, 2H, 4-CH_2), 2.35–2.51 (m, 2H), 3.00 (ddd, *J* = 9.6, 8.4, 5.3, 1H, 3-CH_2), 3.34 (ddd, *J* = 9.6, 8.2, 6.2, 1H, 3-CH_2), 5.52 (q, *J* = 7.2, 1H, CH), 7.25 – 7.39 (m, 5H, Ar–H).

*1-(furan-2-ylmethyl)pyrrolidin-2-one (**2.12e**).* Yield 83%, colorless viscous liquid. **^{1}H NMR** (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.95–2.08 (m, 2H, 4-CH_2), 2.43 (t, *J* = 8.1, 2H, 5-CH_2), 3.34–3.41 (t, *J* = 7.1, 2H, 3-CH_2), 4.47 (s, 2H, CH_2), 6.25–6.27 (m, 1H, 3-H), 6.32–6.36 (m, 1H, 4-H), 7.36–7.40 (m, 1H, 5-H).

*1-phenylpyrrolidin-2-ylidene (**2.12g**).* Yield 70%, yellowish powder. **^{1}H NMR** (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.10–2.26 (m, 2H, 4-CH_2), 2.55–2.70 (m, 2H, 3-CH_2), 3.81–3.95 (m, 2H, 5-CH_2), 7.12–7.21 (m, 1H, 4-H), 7.34–7.43 (m, 2H, 3,6-H), 7.59–7.66 (m, 2H, 2,6-H).

General procedure for 5-methoxy-1-R-3,4-dihydro-2H-pyrrol-1-ium methylsulfate salt synthesis (2.11).

1-Alkyl-pyrrolidin-2-one (50 mmol) and dimethyl sulfate (4.74 ml, 55 mmol) were stirred for 2 h at 80 °C to give the desired pyrrolium salt as a viscous oil, which was used directly in the next step without further purification. Reaction progress was controlled by ^{1}H NMR spectroscopy through the disappearance of 1-R-pyrrolidin-2-one in the crude reaction mixture.

Alternatively, such pyrrolium salts could be obtained as solids upon treatment with KPF_6 in water.

5-Methoxy-1-methyl-3,4-dihydro-2H-pyrrol-1-ium hexafluorophospate salt 2.11´a.

5-Methoxy-1-R-3,4-dihydro-2H-pyrrol-1-ium methylsulfate salt **2.11a** (1g, 4.4 mmol) was added dropwise to a strongly stirred solution of KPF_6 (1.47 g, 8 mmol) in

water (25 ml) at rt. The suspension was allowed to stir for 30 min. The white precipitate was filtrated off to yield 0.65 g of the title compound (2.5 mmol, 56%) as a white solid.

^{1}H NMR (300 MHz, acetone-d_6), δ, ppm (*J*, Hz): 2.33−2.55 (m, 2H, 4-CH_2), 3.24 (s, 3H, NCH_3), 3.35−3.44 (m, 2H, 3-CH_2), 4.02−4.10 (m, 2H, 5-CH_2), 4.43 (s, 3H, OCH_3). ^{31}P NMR (121 MHz, acetone-d_6), δ, ppm (*J*, Hz): −144.37 (sept, *J* = 707.5).

General procedure for 2-hetaryl-N-R-pyrrolidin-2-ylideneacetonitrile synthesis 2.7, 2.13–2.18.

Route 1. A solution of hetarylacetonitrile (4 mmol) in DMF (10 ml) was added dropwise to a strongly stirred suspension of NaH (107 mg, 4 mmol) in DMF (5 mL), and the reaction mixture was stirred for 10 min until complete evolution of gas had occurred. A solution of 5-methoxy-1-R-3,4-dihydro-2H-pyrrol-1-ium salt (6 mmol) in DMF (3 mL) was subsequently added to the reaction mixture, and stirring was pursued until complete conversion of the starting material had occurred (TLC control). Water was then added to the mixture, promoting precipitation. The suspension was additionally stirred for 30 min, and the precipitate was then filtered and washed with cyclohexane. Further precipitation was achieved by concentration of the initial mother liquid (water, DMF) and trituration of the residues at 0 °C with water, filtration, and subsequent washing with cyclohexane. Substances do not require additional purification (**2.7c**, **2.18a**) or purified by column chromatography (**2.7b**, **2.14b**, **2.16b, 2.17a**) or by recrystallization from EtOH (**2.7a**, **2.15a**), *i*-PrOH (**2.13a**,**b**), EtOH-dioxane (**2.18b**). The products are obtained as a mixture of *Z* and *E* stereoisomers.

Note: 1) the aliquot for TLC was taken from the crude reaction mixture followed by addition of water and extraction with EtOAc. 2) for **2.13a-c**, **2.15a** NaH (2.1 equiv, 0.336 g, 8.4 mmol) were used to deprotonate the methylene group in the presence of the benzimidazole or 4-oxodihydroquinazolone substituent.

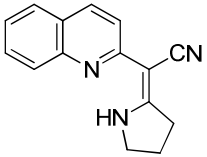
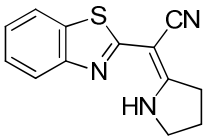
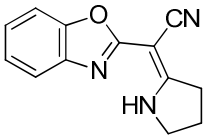
Route 2. General procedure for 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles **2.1a-f** synthesis, route 2 was used to access 2-benzothiazole-2-(1-methyl-2-pyrrolidin-2-ylidene)acetonitrile **2.7a.** Yield 900 mg (88%), white powder, mp 186 °C.

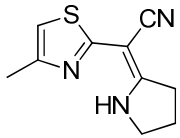
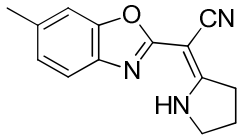
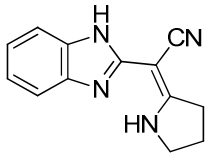
General procedure for the synthesis of 2-(cyano(1-methylpyrrolidin-2-ylidene)methyl)-3-methylbenzo[d]oxazol/thiazol-3-ium hexafluorophosphate (2.21, 2.22).

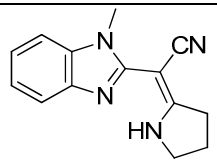
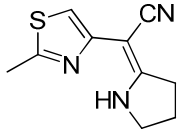
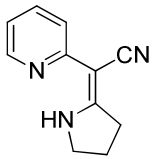
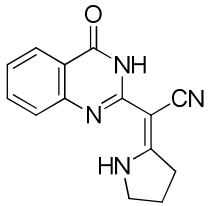
A mixture of appropriate hetarylacetonitrile (1.5 mmol) and dimethyl sulfate (1.71 ml, d = 1.33g/cm^3, 18 mmol) was stirred for 40 min at 70°C. Then the reaction mixture was poured into water (10 ml) and a solution of NaOH (5% solution in water) was added with stirring. a) The solution was neutralized with 2M HCl to pH = 7 and extracted with EtOAc (3 times). The combined extracts were evaporated under reduced pressure and the solid residual was purified by column chromatography (elution system: CHA–EtOAc, 3:1) to give **2.21** as a yellow solid (MS (ESI) m/z: [M + H]$^+$ Found for $C_{10}H_9N_2O$ 173.11); b) The precipitate formed was filtered off, washed with cold water and recrystallized from ethanol to give **2.22** as a yellow solid. (^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.36 (br.s, 3H, CH_3), 6.95 (d, *J* = 8.1, 1H, H-4), 7.07–7.13 (m, 1H, H-6), 7.28–7.33 (m, 1H, H-5), 7.42 (d, *J* = 7.8, 1H, H-7).

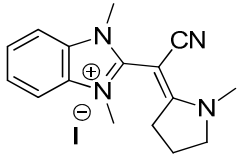
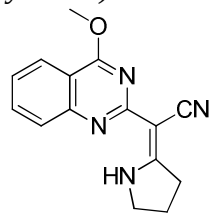
The obtained compounds were used in the next step without any further characterization. A solution of 2-(3-methylbenzo[d]oxazol/thiazol-2(3H)-ylidene)acetonitrile **2.21** or **2.22** and *N*-methylpyrrolidin-2-one **2.12a** (1.2 equiv) in dioxane (5 ml) was heated up to reflux and $POCl_3$ (1.2 equiv) was added to the reaction mixture dropwise. In 5 min the stirring was ceased and emulsion of the formed salts in dioxane separated into 2 layers. The viscous oil of the bottom layer was gathered with Pasteur pipette and dropped into solution of KPF_6 (2 equiv) in water (5 ml) with stirring. The formed precipitate was filtrated off, dried and characterized.

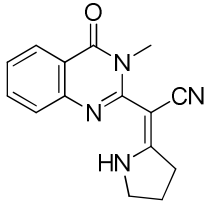
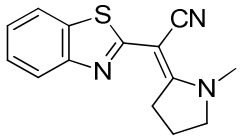
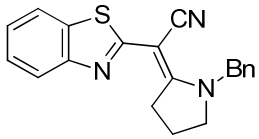
Table 6.1. Physico-chemical characteristics of 2-azahetaryl-2-(1-R-pyrrolidin-2-ylidene)acetonitriles **2.1a-f**, **2.7-2.10, 2.13-2.18, 2.21, 2.22**

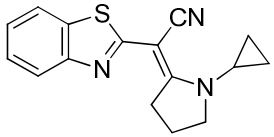
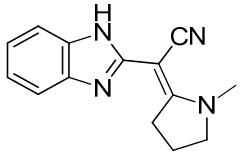
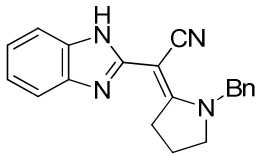
Compound	**IUPAC name**	**IR, ν, cm^{-1}**	**^{1}H NMR**	**^{13}C NMR**	**HRMS/MS, elemental analysis**
2.1a	*(E)-2-(pyrrolidin-2-ylidene)-2-(quinolin-2-yl)acetonitrile* 	KBr 3468 (NH), 2182 (C≡N), 1588 (C=N, C=C).	(400 MHz, DMSO-d_6–CCl_4), δ, ppm (*J*, Hz): 2.08– 2.22 (м, 2H, 4-CH_2); 3.03 (t, *J* = 7.8, 2H, 3-CH_2); 3.84 (t, *J* = 7.1, 2H, 5-CH_2); 7.34–7.40 (м, 1H, H-6); 7.42 (d, *J* = 8.8, 1H, H-3); 7.57–7.63 (м, 1H, H-7); 7.75 (d, *J* = 8.0, 1H, H-8); 7.97 (d, *J* = 8.4, 1H, H-5); 8.12 (d, *J* = 8.8, 1H, H-4); 11.14 (с, 1H, NH).	(101 MHz, DMSO-d_6–CCl_4), δ, ppm: 21.2 (CH_2); 33.9 (CH_2); 49.4 (CH_2); 72.5 (C); 118.0 (CH); 121.4 (CN); 124.4 (CH); 124.7 (C); 127.4 (CH); 127.6 (CH); 129.4 (CH); 136.3 (CH); 146.8 (C); 156.3 (C); 168.1 (C).	**Found, %**: C 76.59; H 5.68; N 17.88. $C_{15}H_{13}N_3$. **Calculated, %**: C 76.57; H 5.57; N 17.86.
Route 1: yield 136 mg (0.58 mmol, 58%), yellow powder (elution system for column chromatography: gradient $CHCl_3$ 100% to $CHCl_3$–CH_3OH, 49:1). *Route 2*: yield 315 mg (1.34 mmol, 67%), yellow powder (mp 207–208 °C, 207 °C[9]).					
2.1b	*(Z)-2-(benzo[d]thiazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile* 	KBr 3450 (NH), 2189 (C≡N), 1595 (C=N, C=C).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.18– 2.30 (м, 2H, 4-CH_2); 3.08 (t, *J* = 7.9, 2H, 3-CH_2); 3.85 (t, *J* = 7.1, 2H, 5-CH_2); 7.28 (ddd, *J* = 7.9, 7.3, 1.3, 1H, H-6); 7.41 (ddd, *J* = 8.0, 7.3, 1.2, 1H, H-5); 7.78 (ddd, *J* = 8.0, 1.3, 0.5, 1H, H-7); 7.81 (ddd, *J* = 7.9, 1.2, 0.5, 1H, H-4); 10.27 (s, 1H, NH).	(101 MHz, $CDCl_3$), δ, ppm: 21.7 (CH_2); 33.0 (CH_2); 49.1 (CH_2); 70.6 (C); 120.3 (CN); 120.4 (CH); 121.4 (CH); 123.6 (CH); 125.9 (CH); 132.7 (C); 153.4 (C); 166.4 (C); 167.9 (C).	**Found, %**: C 64.98; H 4.87; N 17.23; S 13.73. $C_{13}H_{11}N_3S$. **Calculated, %**: C 64.71; H 4.59; N 17.41; S 13.29.
Route 1: yield 205 mg (0.85 mmol, 85 %), white powder. *Route 2*: yield 415 mg (1.72 mmol, 86%), white powder (mp 226 °C, 223–224 °C[10]).					
2.1c	*(Z)-2-(benzo[d]oxazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile* 	KBr 3437 (NH), 2203 (C≡N), 1602, 1547 (C=N, C=C).	(400 MHz, DMSO-d_6–CCl_4), δ, ppm (*J*, Hz): 2.19 (quint, *J* = 7.3, 2H, 4-CH_2); 3.06 (t, *J* = 7.5, 2H, 3-CH_2); 3.83 (t, *J* = 7.1, 2H, 5-CH_2); 7.16–7.30 (м, 2H, H-5,6); 7.50 (d, *J* = 7.6, 1H, H-7); 7.54 (d, *J* = 7.5, 1H, H-4); 9.60 (s,1H, NH).	(101 MHz, DMSO-d_6–CCl_4), δ, ppm: 21.4 (CH_2); 33.5 (CH_2); 49.8 (CH_2); 61.9 (C); 110.0 (CH); 117.5 (CH); 118.0 (CN); 123.3 (CH); 124.2 (CH); 141.8 (C); 148.7 (C); 162.6 (C); 169.7 (C).	**Found, %**: C 69.33; H 4.25; N 18.53. $C_{13}H_{11}N_3O$. **Calculated, %**: C 69.32; H 4.92; N 18.66.

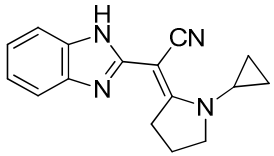
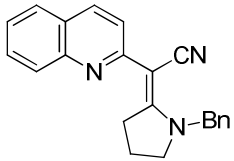
Route 1: yield 167 mg (0.74 mmol, 74 %), white powder. *Route 2*: yield 225 mg (1 mmol, 50%), white powder (mp 230 °C).					
2.1d	*(Z)-2-(4-methylthiazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile* 	KBr 3475 (NH), 2179 (C≡N), 1603 (C=N, C=C).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.08–2.25 (м, 2H, 4-CH_2); 2.37 (d, *J* = 1.0, 3H, CH_3); 2.99 (t, *J* = 7.8, 2H, 3-CH_2); 3.70–3.81 (м, 2H, 5-CH_2); 6.56 (q, *J* = 1.0, 1H, H-5); 9.83 (s, 1H, NH).	(101 MHz, $CDCl_3$), δ, ppm: 17.2 (CH_3); 21.9 (CH_2); 32.6 (CH_2); 48.7 (CH_2); 70.3 (C); 108.4 (CH); 120.7 (CN); 151.4 (C); 165.8 (2C).	**Found, %**: C 58.33; H 5.33; N 20.12; S 15.15. $C_{10}H_{11}N_3S$. **Calculated, %**: C 58.51; H 5.40; N 20.47; S 15.62.
Route 1: yield 138 mg (0.67 mmol, 67 %), white powder. *Route 2*: yield 316 mg (1.54 mmol, 77%), white powder (mp 150–151 °C).					
2.1e	*(Z)-2-(6-methylbenzo[d]oxazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile* 	Neat film 3224 (NH), 2210 (C≡N), 1613, 1559 (C=N, C=C,), 1255 (C–O).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): δ 2.25 (quint, *J* = 7.6, 2H, 4-CH_2), 2.48 (s, 3H, CH_3) 3.10 (t, *J* = 7.9, 2H, 3-CH_2), 3.84 (t, *J* = 7.1, 2H, 5-CH_2), 7.07 – 7.11 (м, 2H, 4-H), 7.31 (d d, *J* = 1.5, 0.7, 1H, 7-H), 7.39 (d, *J* = 8.0, 1H, 5-H), 9.60 (s, 1H, NH).	(101 MHz, $CDCl_3$), δ, ppm: 21.7 (CH_3), 21.8 (CH_2), 32.9 (CH_2), 49.1 (CH_2), 63.3 (C), 110.6 (CH), 116.8 (CH), 118.4 (C), 125.2 (CH), 133.8 (C), 139.4 (C), 149.3 (C), 162.2 (C), 169.5 (C).	**HRMS** (ESI) Calculated for $C_{14}H_{14}N_3O$ (M + H^+) 240.1137, Found 240.1143.
Yield 134 mg (0.56 mmol, 56 %), white powder.					
2.1f	*(Z)-2-(benzo[d]imidazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile* 	K Br 3226 (NH), 2197 (C≡N), 1608 (C=N, C=C).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.08 (p, *J* = 7.6, 2H, 4-CH_2), 2.96 (t, *J* = 7.8, 1H, 3-CH_2), 3.73 (t, *J* = 7.1, 1H, 5-CH_2), 7.05–7.12 (м, 2H, 5,6-H), 7.33–7.39 (м, 1H, Ar H), 7.43–7.49 (м, 1H, Ar H), 10.10 (s, 1H, NH), 12.00 (s, 1H, NH_{Het}).	(101 MHz, DMSO-d_6), δ, ppm: δ 21.7 (CH_2), 33.2 (CH_2), 49.4 (CH_2), 62.6 (C), 111.1 (CH), 117.0 (CH), 120.6 (C), 121.5 (2CH), 134.1 (C), 143.6 (C), 151.7 (C), 168.5 (C).	**Found, %**: C, 69.85; H, 6.08; N, 25.08. $C_{13}H_{12}N_4$. **Calculated, %**: C, 69.62; H, 5.39; N, 24.98.
Yield 200 mg (0.89 mmol, 89 %), white powder (mp 292–293 °C).					
2.1g	*(Z)-2-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-(pyrrolidin-2-ylidene)*	KBr 3448 (NH), 2187 (C≡N), 1609 (C=N, C=C).	(300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.13–2.30 (м, 2H, 4-CH_2), 3.10 (t, *J* = 7.9, 2H, 3-CH_2), 3.76 – 3.88 (t, *J* = 7.9, 2H, 5-CH_2), 4.02 (s, 3H, CH_3), 7.34–7.15 (м, 3H, Ar H), 7.64–7.51	(75 MHz, $CDCl_3$), δ, ppm: CH_2: 21.9 (CH_2), 31.1 (CH_3), 33.3 (CH_2), 49.0 (CH_2), 62.4 (C), 108.7 (CH), 117.2 (CH), 121.4 (C), 121.6 (CH), 121.8 (CH), 135.3 (C), 141.8 (C), 150.8 (C),	**MS (ESI)** m/z: [M + H]+ Found for $C_{14}H_{15}N_4$: 239.1. **Calculated, %:**

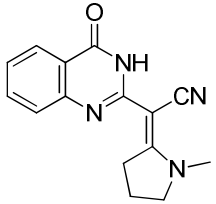
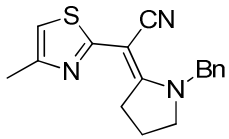
			(m, 1H, Ar H), 10.64 (s, 1H, NH).	170.3 (C).	C, 70.57; H, 5.92; N, 23.51. $C_{14}H_{14}N_4$. **Found, %**: C, 70.76; H, 6.14; N, 24.06.
Yield 207 mg (0.87 mmol, 87 %), white powder (mp 184–185 °C).					
2.1h	*(E)-2-(2-methylthiazol-4-yl)-2-(pyrrolidin-2-ylidene)acetonitrile* 	KBr 3449 (NH), 2180 (C≡N), 1602, 1511 (C=C, C=N).	(400 MHz, DMSO-d_6–CCl_4), δ, ppm (*J*, Hz): 2.10 (quint, *J* = 7.2, 2H, 4-CH_2), 2.72 (s, 3H, CH_3), 2.89 (t, *J* = 7.7, 2H, 3-CH_2), 3.66 (t, *J* = 6.8, 2H, 5-CH_2), 6.71 (s, 1H, 5-H), 8.70 (s, 1H, NH).	(101 MHz, DMSO-d_6–CCl_4), δ, ppm: 19.3 (CH_3), 22.1 (CH_2), 32.7 (CH_2), 48.4 (CH_2), 68.3 (C), 105.8 (CH), 121.2 (C), 151.8 (C), 162.7 (C), 165.0 (C).	**Calculated, %:** C, 58.51; H, 5.40; N, 20.47. $C_{10}H_{11}N_3S$. **Found, %**: C, 58.33; H, 5.33; N, 20.12.
Yield 135 mg (0.66 mmol, 66 %), white powder (mp 124 °C).					
2.1i	*(E)-2-(pyridin-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile* 	KBr 3439 (NH), 2189 (C≡N), 1578 (C=N, C=C).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.13 (quint, *J* = 7.5, 2H, 4-CH_2), 3.05 (t, *J* = 7.9, 2H, 3-CH_2), 3.75 (t, *J* = 7.0, 2H, 5-CH_2), 6.92 (ddd, *J* = 7.5, 7.3, 1.1, 1H, 5-H), 7.41 (d, *J* = 8.2, 1H, 3-H), 7.61 (ddd, *J* = 8.2, 7.3, 1.8, 1H, 4-H), 8.32–8.40 (м, 1H, 6-H), 10.46 (s, 1H, NH).	(101 MHz, $CDCl_3$), δ, ppm: 21.5 (CH_2), 33.5 (CH_2), 48.7 (CH_2), 72.5 (C), 117.7 (CH), 118.7 (CH), 122.0 (C), 136.4 (CH), 147.0 (CH), 156.6 (C), 167.1 (C).	**Calculated, %**: C 71.33, H 5.99, N 22.69. $C_{11}H_{11}N_3$. **Found, %**: C 71.65, H 6.34, N 23.13.
Eluent for automatic column chromatography: CH_2Cl_2-CHA, 7:3. Yield 130 mg (0.7 mmol, 70%), white powder (mp 97 °C, 97 °C[9]).					
2.1j	*(Z)-2-(4-oxo-3,4-dihydroquinazolin-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile* 	KBr 3462, 3339 (NH), 2192 (C≡N), 1669 (C=O), 1617, 1561, 1546 (C=N, C=C).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.98 – 2.13 (м, 2H, 4-CH_2), 2.97 (t, *J* = 7.7, 2H, 3-CH_2), 3.77 (t, *J* = 7.1, 2H, 5-CH_2), 7.33 (t, *J* = 7.1, 1H, 6-H), 7. 60–7.86 (м, 2H, 7, 8-H), 7.99 (d, *J* = 8.0, 1H, 5-H), 10.69 (s, 1H, NH), 10.74 (s, 1H, NH).	(101 MHz, DMSO-d_6), δ, ppm: 20.9 (CH_2), 34.8 (CH_2), 50.5 (CH_2), 66.1 (C), 119.5 (C), 119.6 (C), 125.0 (CH), 126.1 (CH), 126.4 (CH), 134.8 (CH), 149.1 (C), 152.4 (C), 161.7 (C), 171.2 (C).	**MS (ESI)** m/z: $[M + H]^+$ Found for $C_{14}H_{13}N_4O$: 253.1. **Calculated, %:** C, 66.66; H, 4.79; N, 22.21. $C_{14}H_{12}N_4O$. **Found, %:** C,

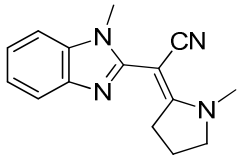
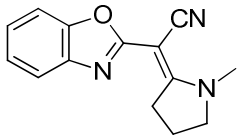
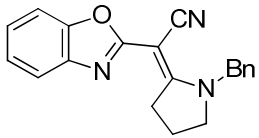
					66.95; H, 5.14; N, 22.72.
Yield 222 mg (0.88 mmol, 88%), white powder (mp 286–287 °C).					
2.8	*2-(cyano(1-methylpyrrolidin-2-ylidene)methyl)-1,3-dimethyl-1H-benzo[d]imidazol-3-ium iodide* 	Neat film 2188 (C≡N), 1598, 1531 (C=N, C=C).	$CDCl_3$: ratio *E*:*Z* = 1:0.75		**HRMS** (ESI) Calculated for $C_{16}H_{19}N_4$ (M + H^+): 267.1610, Found: 267.1613.
			(300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): *E* isomer: 2.23–2.14 (м, 2H, 4-CH_2), 2.95 (t, *J* = 7.8, 1H, 3-CH_2), 3.60 (s, 3H, NCH_3), 3.94 (t, *J* = 7.3, 2H, 5-CH_2), 4.20 (s, 6H, 2NCH_3), 7.64–7.72 (м, 2H, 5,6-H), 7.72–7.79 (м, 2H, 4,7-H); *Z* isomer: 2.23–2.34 (м, 2H, 4-CH_2), 2.76 (s, 3H, NCH_3), 3.36 (t, *J* = 7.9, 2H, 3-CH_2), 4.07 (t, *J* = 7.3, 2H, 5-CH_2), 4.15 (s, 6H, 2NCH_3), 7.72–7.64 (м, 2H, 5,6-H), 7.86–7.79 (м, 2H, 4,7-H).	(75 MHz, $CDCl_3$), δ, ppm: *E* isomer: 20.0 (CH_2), 34.6 (2CH_3), 36.3 (CH_3), 36.5 (CH_2), 49.1 (C), 59.7 (CH_2), 113.0 (2CH), 116.8 (C), 127.5 (2CH), 131.7 (2C), 148.3 (C), 168.5 (C). *Z* isomer: 20.2 (CH_2), 34.6 (2CH_3), 37.2 (CH_2), 37.4 (CH_3), 50.5 (C), 60.8 (CH_2), 113.1 (CH), 117.6 (C), 127.6 (CH), 131.5 (2C), 146.7 (C), 170.7 (C).	
Yield 630 mg (1.6 mmol, 79 %) for **2.1f**; Yield 654 mg (1.66 mmol, 83 %) for **2.13a**, light brown powder (mp 197 °C).					
2.9	*(Z)-2-(4-methoxyquinazolin-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile* 	KBr 3436 (NH), 2196 (C≡N), 1628, 1573 (C=N, C=C).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.20 (quint, *J* = 7.3, 2H, 4-CH_2), 3.13 (t, *J* = 8.0, 2H, 3-CH_2), 3.85 (t, *J* = 7.0, 2H, 5-CH_2), 4.23 (s, 3H, OCH_3), 7.38 (ddd, *J* = 8.1, 6.7, 1.4, 1H, 6-H), 7.67 (d, *J* = 7.9, 1H, 8-H), 7.72 (ddd, *J* = 8.2, 6.7. 1.5, 1H, 7-H), 8.06 (d d, *J* = 8.0, 1.4, 1H, 5-H), 10.77 (s, 1H, NH).	(101 MHz, $CDCl_3$), δ, ppm: 21.6 (CH_2), 33.7 (CH_2), 49.1 (CH_2), 54.3 (CH_3), 75.1 (C), 113.6 (C), 121.3 (C), 123.7 (CH), 124.7 (CH), 125.5 (CH), 133.4 (CH), 150.8 (C), 161.5 (C), 166.2 (C), 169.8 (C).	**HRMS** (ESI) Calculated for $C_{15}H_{15}N_4O$ (M + H^+): 267.1246, Found: 267.1249.
Yield 282 mg (1.06 mmol, 53%), white powder (mp 185–186 °C).					
2.10	*(Z)-2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(pyrrolidin-2-*	KBr 3432 (NH), 2184 (C≡N), 1664 (C=O), 1612,	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.23 (quint, *J* = 7.5, 2H, 4-CH_2), 3.13 (t, *J* = 7.9, 2H, 3-CH_2), 3.86 (t, *J* = 7.2, 2H, 5-CH_2), 3.86 (s, 3H, NCH_3), 7.36	(101 MHz, $CDCl_3$), δ, ppm: 21.2 (CH_2), 33.9 (CH_3), 34.5 (CH_2), 49.4 (CH_2), 67.8 (C), 119.1 (C), 120.7 (C), 125.1 (CH), 125.4 (CH), 127.1 (CH),	**HRMS** (ESI) Calculated for $C_{15}H_{15}N_4O$ (M + H^+): 267.1246,

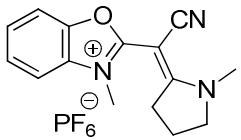
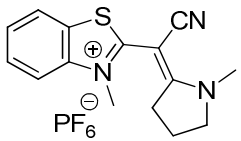
	ylidene)acetonitrile 	1523 (C=N, C=C).	(ddd, *J* = 8.3, 7.5, 1.0, 1H, 6-H), 7.47 (d, *J* = 7.5, 1H, 8-H), 7.68 (ddd, *J* = 8.4, 7.6. 1.7, 1H, 7-H), 8.25 (d d, *J* = 7.9, 1.3, 1H, 5-H), 10.49 (s, 1H, NH).	134.1 (CH), 146.6 (C), 153.6 (C), 162.8 (C), 172.6 (C).	Found: 267.1249.
Yield 85 mg (0.32 mmol, 16%), white powder (mp 244–245 °C).					
2.7a	*2-(Benzo[d]thiazol-2-yl)-2-(1-methylpyrrolidin-2-ylidene)acetonitrile* 	KBr 2178 (C≡N), 1573 (C=N, C=C).	(300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.99 (quint, *J* = 7.5, 2H, 4-CH_2), 3.38 (s, 3H, CH_3), 3.43 (t, *J* =7.5, 2H, 3-CH_2), 3.68 (t, *J* = 7.3, 2H, 5-CH_2), 7.25 (t, *J* = 7.7, 1H, H-6), 7.39 (t, J = 7.7, 1H, H-5), 7.72 (d, *J* = 7.7, 1H, H-7), 7.93 (d, *J* = 7.7, 1H, H-4).	(75 MHz, DMSO-d_6), δ, ppm: 20.0 (CH_2), 36.2 (CH_3), 37.2 (CH_2), 58.1(CH_2), 68.4 (C), 120.9 (CH), 121.4 (C), 121.7 (CH), 123.6 (CH), 126.4 (CH) 133.1 (C), 154.6 (C), 167.3 (C), 167.6 (C)	**HRMS** (ESI) Calculated for $C_{14}H_{13}N_3S$ (M + H^+): 256.0908, Found: 256.0909
Route 1: yield 900 mg (3.52 mmol, 88%), white powder. The reaction was directly scaled up to 10.45 g of starting material affording 13.94 g (91% yield) of the desired product. *Route 2*: yield 450 mg (1.76 mmol, 88%), white powder (mp186 °C).					
2.7b	*2-(Benzo[d]thiazol-2-yl)-2-(1-benzylpyrrolidin-2-ylidene)acetonitrile* 	Neat film 2183 (C≡N), 1588, 1559 (C=N, C=C).	DMSO-d_6: *E* isomer, *Z* isomer traces (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.02 (quint, *J* = 7.4, 2H, 4-CH_2), 3.56 (t, *J* = 7.6, 2H, 3-CH_2), 3.63 (t, *J* = 7.2, 2H, 5-CH_2), 5.13 (s, 2H, CH_2), 7.26 (t, *J* = 7.6, 1H, H-6), 7.36−7.49 (м, 6H, H-5,Ar), 7.74 (d, *J* = 8.1, 1H, H-7), 7.93 (d, J = 7.8, 1H, H-4).	(101 MHz, DMSO-d_6), δ, ppm: 20.1 (CH_2), 37.6 (CH_2), 51.0 (CH_2), 56.2 (CH_2), 68.6 (C), 120.9 (C), 121.2 (CH), 121.8 (CH), 123.9 (CH), 126.5 (CH), 127.5 (2CH), 128.0 (CH), 129.3 (2CH), 133.2 (C), 136.2 (C), 154.5 (C), 167.2 (C), 167.4 (C).	**HRMS** (ESI) Calculated for $C_{20}H_{18}N_3S$ (M + H^+): 332.1221, Found: 332.1212.
Yield 1.06 g (3.6 mmol, 80%), white powder (mp 134−135 °C), elution system for automatic column chromatography: CHA–EtOAc, 7:3.					
2.7c	*2-(Benzo[d]thiazol-2-yl)-2-(1-cyclopropylpyrrolidin-2-ylidene)acetonitrile*	Neat film 2182 (C≡N), 1548 (C=N, C=C).	$CDCl_3$: ratio *E:Z* = 9:1 (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.95−1.03 (м, NCHC$\underline{H_2}$), 1.08−1.18 (м, 2H, NCHC$\underline{H_2}$), 2.04 (quint, *J* = 7.6, 2H, 4-CH_2), 3.08−3.21 (м, 1H, NCH), 3.51 (t, *J* = 7.8, 2H, 3-CH_2), 3.60 (t, *J* = 7.3, 2H, 5-CH_2), 7.26 (ddd,	(75 MHz, $CDCl_3$), δ, ppm: 10.6 (CH_2), 20.6 (CH_2), 30.1 (CH), 36.4 (CH_2), 54.3 (CH_2), 71.8 (C), 120.9 (C), 121.0 (CH), 121.2 (CH), 123.4 (CH), 125.7 (CH), 134.0 (C), 154.4 (C), 167.1 (C), 167.5 (C).	**HRMS** (ESI) Calculated for $C_{16}H_{16}N_3S$ (M + H^+): 282.1065, Found: 282.1071.

			*J* = 8.3, 7.4, 1.3, 1H, H-6), 7.39 (ddd, *J*= 8.5, 7.7, 1.3, 1H, H-5), 7.79 (d d, *J* = 5.6, 0.8, 1H, H-7), 7.82 (d d, *J* = 5.6, 0.9, 1H, H-4).		
Yield 832 mg (2.96 mmol, 74%), white powder (mp144 °C).					
2.13a	*2-(1H-Benzo[d]imidazol-2-yl)-2-(1-methylpyrrolidin-2-ylidene)acetonitrile* 	KBr 3297 (NH), 2184 (C≡N), 1575, 1528 (C=N, C=C).	DMSO-d_6: ratio *E:Z* = 5:1 (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): *E* isomer: 1.93 (quint, 7.6, 2H, 4-CH_2), 3.33 (t, *J* = 7.6, 2H, 3-CH_2), 3.37 (s, 3H, CH_3), 3.62 (t, *J* = 7.2, 2H, 5-CH_2), 7.32−7.46 (м, 2H, H Ar), 7.00−7.08 (м, 2H, H Ar), 11.75 (s, 1H, NH); *Z* isomer: 2.01 (quint, 7.6, 2H, 4-CH_2), 2.78 (s, 3H, CH_3), 3.00 (t, *J* = 7.8, 2H, 3-CH_2), 3.65 (t, *J* = 7.2, 2H, 5-CH_2), 7.08−7.16 (м, 2H, H Ar), 7.32−7.46 (м, 1H, H Ar), 7.51 (d, *J* = 8.4, 1H, H-4), 12.25 (s, 1H, NH).	(101 MHz, DMSO-d_6), δ, ppm: *E* isomer: 20.3 (CH_2), 36.0 (CH_3), 36.3 (CH_2), 57.8 (CH_2), 62.3 (C), 111.0 (CH), 117.5 (CH), 121.1 (CH), 121.2 (CH), 122.7 (C), 134.7 (C), 144.5 (C), 151.6 (C), 167.0 (C); *Z* isomer:20.5 (CH_2), 36.3 (CH_3), 37.3 (CH_2), 59.0 (CH_2), 62.3 (C), 111.2 (CH), 118.3 (CH), 121.2 (C), 121.5 (CH), 122.0 (CH), 134.6 (C), 144.0 (C), 147.8 (C), 164.9 (C).	**HRMS** (ESI) Calculated for $C_{14}H_{15}N_4$ (M + H^+): 239.1297, Found: 239.1299.
Yield 760 mg (3.2 mmol, 80%), white powder (mp 262 °C).					
2.13b	*2-(1H-Benzo[d]imidazol-2-yl)-2-(1-benzylpyrrolidin-2-ylidene)acetonitrile* 	KBr 3289 (NH), 2188 (C≡N), 1588, 1576, 1524 (C=N, C=C)	DMSO-d_6: ratio *E:Z* = 5:1 (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): *E* isomer: 1.97 (quint, *J* = 7.4, 2H, 4-CH_2), 3.43 (t, *J* = 7.7, 2H, 3-CH_2), 3.58 (t, *J* = 7.2, 2H, 5-CH_2), 5.11 (s, 2H, $N_{Bn}CH_2$), 7.00−7.55 (м, 9H, H Ar), 11.83 (s, 1H, NH). *Z* isomer: 2.03 (quint, *J* = 7.4, 2H, 4-CH_2), 3.09 (t, *J* = 7.7, 2H, 3-CH_2), 3.65 (t, *J* = 7.1, 2H, 5-CH_2), 4.92 (s, 2H, NCH_2), 6.87−6.93 (м, 2H, H Ar), 7.02−7.52 (м, 7H, H Ar), 12.14 (s, 1H, NH).	(101 MHz, DMSO-d_6), δ, ppm: *E* isomer: 20.4 (CH_2), 36.6 (CH_2), 50.7 (CH_2), 55.8 (CH_2), 62.8 (C), 111.1 (CH), 117.6 (CH), 120.5 (C), 121.3 (CH), 121.4 (CH), 127.5 (CH), 127.9 (CH), 129.2 (CH), 134.7 (C), 136.7 (C), 144.4 (C), 151.2 (C), 166.5 (C); *Z* isomer: 20.7 (CH_2), 37.4 (CH_2), 51.8 (CH_2), 57.6 (CH_2), 63.8 (C), 111.3 (CH), 118.2 (CH), 121.5 (CH), 122.2 (CH), 122.6 (C), 127.55 (2CH), 127.63 (CH), 128.8 (2CH), 134.6 (C), 136.6 (C), 143.8 (C), 147.5 (C), 163.6	**HRMS** (ESI) розраховано for $C_{20}H_{19}N_4$ (M + H^+): 315.1610, Found: 315.1608.

				(C).	
Yield 970 mg (3.08 mmol, 77%), white powder (mp 264−265 °C).					
2.13c	*2-(1H-Benzo[d]imidazol-2-yl)-2-(1-cyclopropylpyrrolidin-2-ylidene)acetonitrile* 	Neat film 3296 (NH), 2184 (C≡N), 1559, 1515 (C=N, C=C).	$CDCl_3$: E isomer 100%		**HRMS** (ESI) Calculated for $C_{16}H_{17}N_4$ (M + H^+): 265.1453, Found: 265.1459.
			(300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.96–1.04 (м, 2H, NCHC$\underline{H_2}$), 1.05–1.15 (м, 2H, NCHC$\underline{H_2}$), 2.02 (quint, *J* = 7.6, 2H, 4-CH_2), 3.05–3.16 (м, 1H, CH), 3.55 (t, *J* = 7.6, 2H, 3-CH_2), 3.57 (t, *J* = 7.1, 2H, 5-CH_2) 7.12–7.26 (м, 2H, H Ar), 7.35–7.68 (s, 2H, H Ar), 9.22 (s, 1H, NH)	(101MHz, DMSO-d_6), δ, ppm: 10.7 (CH_2), 20.7 (CH_2), 29.8 (CH), 36.0 (CH_2), 54.2 (CH_2), 65.4 (C), 121.1 (2CH), 121.7 (2CH), 122.2 (C), 150.7 (C), 167.5 (C).	
Yield 634 mg (2.4 mmol, 60 %), white powder (mp 259 °C).					
2.14b	*2-(1-Benzylpyrrolidin-2-ylidene)-2-(quinolin-2-yl)-acetonitrile* 	Neat film 2179 (C≡N), 1561, 1533, 1498 (C=N, C=C).	DMSO-d_6: ratio *E:Z* = 1:3.3. *Z* isomer		**HRMS** (ESI) Calculated for $C_{22}H_{20}N_3$ (M + H^+): 326.1657, Found: 326.1663.
			(300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): *Z* isomer: 1.96 (quint, *J* = 7.5, 2H, 4-CH_2), 3.47 (t, J = 7.7, 2H, 3-CH_2), 3.56 (t, *J* = 7.1, 2H, 5-CH_2), 5.15 (s, 2H, $N_{Bn}CH_2$), 7.29−7.47 (м, 5H, H Ph), 7.46 (ddd, *J* = 8.5, 7.0, 1.4, 1H, H-6), 7.55 (d, *J* = 8.8, 1H, H-3), 7.68 (ddd, *J* = 8.5, 7.0, 1.4, 1H, H-7), 7.83 (d, *J* = 6.7, 1H, H-8), 7.86 (d, *J* = 6.8, 1H, H-5), 8.21 (d, *J* = 8.7, 1H, H-4). *E* isomer: 2.08 (quint, *J* = 7.5, 2H, 4-CH_2), 3.15 (t, *J* = 7.8, 2H, 3-CH_2), 3.70 (t, *J* = 7.1, 2H, 5-CH_2), 4.78 (s, 2H, NCH_2), 6.79−6.93 (м, 2H, H_{Ph}-2,6), 7.11−7.24 (м, 3H, H_{Ph}-3,4,5), 7.29 (d, *J* = 8.6, 1H, H-3), 7.29−7.47 (м, 1H, H-6), 7.60−7.64 (м, 2H, H-7), 7.80−7.88 (м, 1H, H-8), 8.10 (d, *J* = 8.6, 1H, H-4).	(101 MHz, DMSO-d_6), δ, ppm: *Z* isomer: 20.85 (CH_2), 36.5 (CH_2), 51.2 (CH_2), 55.2 (CH_2), 72.5 (C), 120.0 (CH), 122.1 (C), 125.3 (C), 125.4 (CH), 127.6 (2CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 129.2 (2CH), 130.0 (CH), 136.5 (CH), 136.9 (C), 147.5 (C), 156.7 (C), 167.4 (C). *E* isomer: 20.81 (CH_2), 37.9 (CH_2), 53.2 (CH_2), 57.9 (CH_2), 74.6 (C), 121.4 (CH), 122.1(C), 124.2(C), 125.9 (CH), 127.2 (2CH), 127.5 (CH), 128.0 (CH), 128.1 (CH), 128.7 (2CH), 130.1 (CH), 136.4 (CH), 136.6 (C), 147.1 (C), 154.5 (C), 163.9 (C).	

Yield 872 mg (2.68 mmol, 67%), white powder (mp 141 °C), elution system for column chromatography: first column: CH_2Cl_2 (100%), second: CHA–EtOAc 5:1.					
2.15a	*2-(1-Methylpyrrolidin-2-ylidene)-2-(4-oxo-3,4-dihydroquinazolin-2-yl)acetonitrile* 	Neat film 3200, 3143 (NH), 2187 (C≡N), 1661 (C=O), 1561 (C=N, C=C).	*E* isomer 100%, *Z* isomer traces		**HRMS** (ESI) Calculated for $C_{15}H_{15}N_4O$ (M + H^+): 267.1246, Found: 267.1252.
			(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.10 (quint, *J* = 7.4, 2H, 4-CH_2), 3.48 (s, 3H, CH_3), 3.58 (t, *J* = 7.9, 2H, 3-CH_2), 3.69 (t, *J* = 7.3 Hz, 2H, 5-CH_2), 7.34 (t, *J* = 7.5, 1H, H-6), 7.51 (d, *J* = 8.1, 1H, H-8), 7.67 (t, *J* = 7.3, 1H, H-7), 8.22 (d, *J* = 7.8, 1H, H-5), 9.10 (s, 1H, NH).	(101MHz, $CDCl_3$), δ, ppm: 20.3 (CH_2), 36.7 (CH_3), 36.9 (CH_2), 57.9 (CH_2), 66.6 (C), 119.4 (C), 119.8 (C), 125.0 (CH), 126.4 (CH), 126.5 (CH), 134.5 (CH), 149.4 (C), 150.4 (C), 161.9 (C), 170.2 (C).	
Yield 800 mg (3.2 mmol, 75%), light brown powder (mp 203−204 °C).					
2.16b	*2-(1-Benzylpyrrolidin-2-ylidene)-2-(4-methylthiazol-2-yl)acetonitrile* 	Neat film 2185 (C≡N), 1560, 1525 (C=N, C=C).	$CDCl_3$: ratio *E:Z* = 3:1		**HRMS** (ESI) Calculated for $C_{17}H_{18}N_3S$ (M + H^+): 296.1221, Found: 296.1223.
			(300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): *E* isomer: 1.99 (quint, *J* = 7.5, 2H, 4-CH_2), 2.40 (d, *J* = 1.0, 3H, CH_3), 3.42 (t, *J* = 7.8, 2H, 3-CH_2), 3.49 (t, *J* = 7.2, 2H, 5-CH_2), 6.66 (q, *J* = 1.0, 1H, H-5), 5.09 (s, 2H, NCH_2Ph), 7.23–7.43 (м, 5H, Ar H); *Z* isomer: 2.09 (quint, *J* = 7.4, 2H, 4-CH_2), 2.36 (d, *J* = 1.0, 3H, CH_3), 3.17 (t, *J* = 7.8, 2H, 3-CH_2), 3.65 (t, *J* = 7.1, 2H, 5-CH_2), 4.74 (s, 2H, NCH_2Ph), 6.69 (q, *J* = 1, 1H, H-5), 7.00–6.94 (м, 1H, H-4), 7.43–7.23 (м, 4H, Ar H).	(75 MHz, $CDCl_3$), δ, ppm: *E* isomer: 17.4 (CH_2), 20.5 (CH_2), 36.3 (CH_2), 51.5 (CH_2), 54.8 (CH_3), 69.4 (C), 110.2 (CH), 120.8 (C), 127.8 (CH), 127.9 (CH), 128.9 (CH), 135.6 (C), 152.2 (C), 164.3 (C); *Z* isomer: 17.2 (CH_3), 20.6 (CH_2), 37.2 (CH_2), 57.3 (CH_2), 52.9 (CH_2), 69.5 (C), 112.9 (CH), 122.9 (C), 127.2 (CH), 127.5 (CH), 128.6 (CH), 135.7 (C), 151.8 (C), 166.0 (C).	
Elution system for column chromatography: hexane–EtOAc, 5:1. The second purification: recrystallization from ethanol in the presence of activated charcoal. Yield 850 mg (2.88 mmol, 72 %), white powder (mp 120–121 °C).					
2.17a	*2-(1-Methyl-1H-*	Neat film	DMSO-d_6: ratio *E:Z* = 1.5:1.		**HRMS** (ESI)

	benzo[d]imidazol-2-yl)-2-(1-methylpyrrolidin-2-ylidene)acetonitrile 	2179 (C≡N), 1591 (C=N, C=C).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): *E* isomer: 2.01 (quint, *J* = 7.4, 2H, 4-CH_2), 2.42 (s, 3H, NCH_3), 3.03 (t, *J* = 7.8, 2H, 3-CH_2), 3.60 (t, *J* = 6.8, 2H, 5-CH_2), 3.73 (s, 3H, $N_{Het}CH_3$), 7.14–7.28 (м, 2H, H-5,6), 7.45–7.63 (м, 2H, H-4,7-H). *Z* isomer: 1.84 (quint, *J* = 7.5, 2H, 4-CH_2), 2.80 (t, *J* = 7.8, 2H, 3-CH_2), 3.39 (s, 3H, NCH_3), 3.62 (t, *J* = 6.7, 2H, 5-CH_2), 3.76 (s, 3H, $N_{Het}CH_3$), 7.14–7.28 (м, 2H, H-5,6), 7.45–7.63 (м, 2H, H-4,7).	(101 MHz, DMSO-d_6), δ, ppm: *E* isomer: 20.5 (CH_2), 30.9 (CH_3), 35.7 (CH_2),35.8 (CH_3), 58.6 (CH_2), 59.3 (C), 110.7 (CH), 119.1 (CH), 122.0 (C), 122.1 (CH), 122.5 (CH), 135.7 (C), 142.7 (C), 148.1 (C), 165.9 (C). *Z* isomer: 20.1 (CH_2), 31.2 (CH_3), 35.1 (CH_2), 35.5 (CH_3), 58.0 (CH_2), 58.1 (C), 110.4 (CH), 118.7 (CH), 120.8 (C), 121.9 (CH), 122.1 (CH), 135.9 (C), 142.9 (C), 150.8 (C), 167.1 (C).	Calculated for $C_{15}H_{17}N_4$ (M + H^+): 253.1453, Found: 253.1458.
Elution system for column chromatography: gradient CHA–EtOAc, 3:7 to CHA–EtOAc–CH_2Cl_2, 3:14:3. The 2-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)acetonitrile was partly isolated from the column. 5-Metoxy-1-methyl-3,4-dihydro-2*H*-pyrrolinium hexafluorophosphate was used for the reaction **2.19a**. Yield 575 mg (2.28 mmol, 57 %), yellow viscous liquid					
2.18a	*2-(Benzo[d]oxazol-2-yl)-2-(1-methylpyrrolidin-2-ylidene)acetonitrile* 	Neat film 2193 (C≡N), 1580, 1547 (C=N, C=C), 1042 (C–O).	$CDCl_3$: *E* isomer 100% (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.11 (quint, *J* = 7.6, 2H, 4-CH_2), 3.50 (t, *J* = 8.3, 2H, 3-CH_2), 3.52 (s, 3H, CH_3), 3.69 (t, *J* = 7.2, 2H, 5-CH_2), 7.20 (t, *J* = 7.4, 1H, H-6), 7.26 (t, *J* = 7.0, 1H, H-5), 7.47 (d, *J* = 7.8, 1H, H-7), 7.57 (d, *J* = 7.6, 1H, H-4).	(101 MHz, $CDCl_3$), δ, ppm: 20.0 (CH_2), 36.2 (CH_3), 36.5 (CH_2), 58.4 (CH_2), 63.1 (C), 109.9 (CH), 118.1 (CH), 119.0 (C), 123.11 (CH), 123.9 (CH), 142.6 (C), 149.7 (C), 163.0 (C), 167.9 (C).	**HRMS** (ESI) Calculated for $C_{14}H_{14}N_3O$ (M + H^+): 240.1137, Found: 240.1140.
Yield 760 mg (3.16 mmol, 79 %), white powder (mp 223 °C).					
2.18b	*2-(Benzo[d]oxazol-2-yl)-2-(1-benzylpyrrolidin-2-ylidene)acetonitrile* 	Neat film 2198 (C≡N), 1564, 1537 (C=N, C=C), 1060 (C–O).	$CDCl_3$: *E* isomer 100% (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.06 (quint, *J* = 7.6, 2H, 4-CH_2), 3.59 (t, *J* = 7.0, 4H, 3,5-CH_2), 5.18 (s, 3H, $N_{Bn}CH_2$), 7.15–7.27 (м, 2H, H-5,6), 7.42–7.28 (м, 5H, H_{Ph}), 7.46 (d, *J* = 7.7, 1H, H-7), 7.56 (d, *J* = 7.6, 1H, H-4).	(101 MHz, $CDCl_3$), δ, ppm: 20.0 (CH_2), 37.0 (CH_2), 51.7 (CH_2), 55.6 (CH_2), 63.6 (C), 110.0 (CH), 118.2 (CH), 118.5 (C), 123.3 (CH), 124.0 (CH), 127.8 (CH), 128.1 (CH), 129.0 (CH), 135.1 (C), 142. 5 (C), 149.7 (C), 163.1 (C), 167.3 (C).	**HRMS** (ESI) Calculated for $C_{20}H_{18}N_3O$ (M + H^+): 316.1450, Found: 316.1451

Yield 1.11 г (3.52 mmol, 88 %), white powder (mp 189–190 °C).					
2.21	*2-(Cyano(1-methylpyrrolidin-2-ylidene)methyl)-3-methylbenzo[d]oxazol-3-ium hexafluorophosphate* 	Neat film 2206 (C≡N), 1551, 1413 (C=C, C=N), 833 (P–F).	(400 MHz, CD_3CN), δ, ppm (*J*, Hz): 2.15–2.25 (м, 2H, 4-CH_2), 3.30–3.43 (м, 2H, 3-CH_2), 3.50 (s, 3H, NCH_3), 3.98 (t, *J* = 7.4, 2H, 5-CH_2), 4.02 (s, 3H, $N_{Het}CH_3$), 7.57 (t. d, *J* = 7.8, 1.6, 1H, Ar H), 7.62 (td, *J* = 7.7, 1.3, 1H, Ar H), 7.65–7.68 (м, 1H, Ar H), 7.73 (d d, *J* = 7.6, 1.0, 1H, Ar H). **^{19}F NMR** (376 MHz, CD_3CN), δ, ppm (*J*, Hz): -72.97 (d, $^1J_{F\text{-}P}$ = 706.5). **^{31}P NMR** (162 MHz, CD_3CN), δ, ppm (*J*, Hz): -144.64 (sept, $^1J_{P\text{-}F}$ = 706.5).	(101 MHz, CD_3CN), δ, ppm (*J*, Hz): 19.1 (CH_2), 33.5 (CH_3), 37.6 (CH_2), 37.7 (CH_3), 58.0 (C), 60.8 (CH_2), 111.5 (CH), 112.3 (CH), 115.2 (CN), 126.8 (CH), 127.0 (CH), 131.7 (C), 146.5 (C), 163.4 (C), 173.9 (C).	**HRMS** (ESI) Calculated for: $C_{15}H_{16}N_3O^+$ 254.1293, Found: 254.1296; Calculated for PF_6^- : 144.9642, Found 144.9645.
Yield (over two steps) 0.18 g (0.45 mmol, 30 %), white powder (mp 169–170 °C).					
2.22	*2-(Cyano(1-methylpyrrolidin-2-ylidene)methyl)-3-methylbenzo[d]thiazol-3-ium hexafluorophosphate* 	Neat film 2193 (C≡N), 1503, 1495, 1456 (C=C, C=N), 839 (P–F).	(300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.07 (quint, *J* = 7.7, 2H, 4-CH_2), 3.21 (t, *J* = 7.7, 2H, 3-CH_2), 3.27 (s, 3H, NCH_3), 3.91 (t, *J* = 7.3, 2H, 5-CH_2), 4.03 (c, 3H, $N_{Het}CH_3$), 7.69 (t, *J* = 7.5, 1H, H-6), 7.80 (ddd, *J* = 8.3, 7.7, 1.2, 1H, H-5), 8.06 (d, *J* = 8.4, 1H, H-4), 8.26 (d, *J* = 8.0, 1H, H-7). **^{31}P NMR** (162 MHz, Acetone-d_6), δ, ppm (*J*, Hz): -144.28 (sept, *J* = 707.6).	(75 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 20.1 (CH_2), 37.3 (CH_2), 38.2 (CH_3), 38.7 (CH_3), 60.4 (CH_2), 61.8 (C), 116.8 (CH), 117.8 (C), 124.0 (CH), 127.8 (CH), 128.2 (C), 129.4 (CH), 142.0 (C), 170.7 (C), 171.9 (C).	**HRMS** (ESI) Calculated for $C_{15}H_{16}N_3S^+$: 270.1065, Found: 270.1070; Calculated for PF_6^-: 144.9642, Found: 144.9645.
Yield (over two steps) 0.4 g (0.96 mmol, 64 %), white powder (mp 188–189 °C).					

General method of 2-hetaryl-2-(5-R-3-oxoindolin-2-ylidene)acetonitriles synthesis (2.23a-c, 2.25, 2.26).

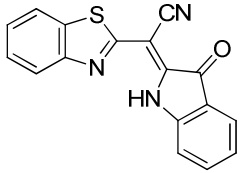
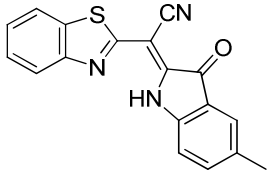
Phosphorus pentachloride (1.3 mmol) was added to the strongly stirred suspension/solution of 5-R-isatine (1 mmol) in hot benzene (10 ml – 15ml) and the resulting mixture was refluxed over 1 hour. At this point, solution of hetarylacetonitrile in benzene was added portionwise (the characteristic changing of color observed in each case) and the mixture was allowed to cool to room temperature upon stirring. The precipitate was then filtrated and washed with ethanol, water and again with ethanol. Dry precipitate was purified by filtration through the plug of silica gel (eluent: CH_2Cl_2)

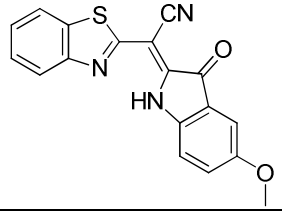
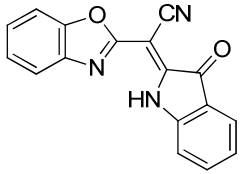
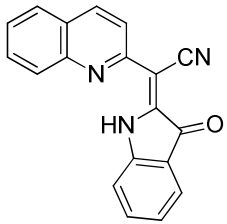
2-(3-methylbenzo[d]thiazol-2(3H)-ylidene)-2-(3-oxo-3H-indol-2-yl)acetonitrile ***(2.27a)*** have been synthesiszed according to the procedure described for the synthesis of 2-hetaryl-2-(5-R-3-oxoindolin-2-ylidene)acetonitriles (**2.23a-c**, **2.25**, **2.26**).

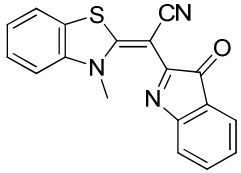
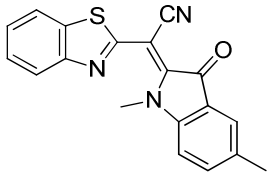
2-(Benzo[*d*]thiazol-2-yl)-2-(1,5-dimethyl-3-oxoindolin-2-ylidene)acetonitrile (2.28b).

The mixture of 2-benzo[*d*]thiazol-2-yl-2-(5-R-3-oxoindolin-2-ylidene)acetonitrile **2.23b** (159 mg, 0.5 mmol) and K_2CO_3 (83 mg, 0.75 mmol) in a minimal quantity of dry DMF was strirred at room temperature over 10 min. In the presence of K_2CO_3 the color of solution changes from initial purple to dark-blue. CH_3I (47 µl, d = 2.28 g/cm^3, 0.75 mmol) was added to reaction mixture and stirring was continued over 1h. The precipitate was filtrated off and purified by automatic column chromatography (elution system: CHA–CH_2Cl_2, 1:1). Yield 141 mg (0.43 mmol, 85%), dark violet powder.

Table 6.2. Physico-chemical characteristics of 2-azahetaryl-2-(5-R-3-oxoindolin-2-ylidene)acetonitriles **2.23, 2.25, 2.26-2.28**

Compound	**IUPAC name**	**IR, ν, cm^{-1}**	**^{1}H NMR**	**^{13}C NMR**	**HRMS/MS, elemental analysis**
2.24a	*(Z)-2-(Benzo[d]thiazol-2-yl)-2-(3-oxoindolin-2-ylidene)acetonitrile* 	KBr 3408 (NH), 2205 (C≡N), 1712(C=O), 1589 (C=C, C=N).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.16 (td, *J* = 7.5, 0.8, 1H, H_{Is}-5), 7.50–7.56 (m, 2H, H_{Bt}-5, H_{Is}-7), 7.66 (ddd, *J* = 8.2, 7.8, 1.1, 1H, H_{Bt}-6), 7.66–7.71 (m, 1H, H_{Is}-6), 7.73 (d, *J* = 7.6, 1H, 4-H_{Is}), 8.20 (d, *J* = 8.1, 1.0, 0.6, 1H, H-7), 8.21 (d, *J* = 8.0, 1.3, 0.6, 1H, H-4), 11.55 (s, 1H, NH).	(101 MHz, DMSO-d_6), δ, ppm: 80.2 (C), 114.5 (CH), 116.9 (C), 119.9 (C), 123.0 (CH), 123.2 (CH), 123.6 (CH), 125.7 (CH), 126.4 (CH), 127.6 (CH), 134.3 (C), 138.2 (CH), 143.7 (C), 151.9 (C), 154.0 (C), 163.4 (C), 185.1 (C).	**HRMS** (ESI) Calculated for $C_{17}H_{10}N_3OS$ (M + H$^+$): 304.0545, Found: 304.0545.
Yield 236 mg (0.78 mmol, 78%), dark red powder (mp > 300 °C).					
2.24b	*(Z)-2-(Benzo[d]thiazol-2-yl)-2-(5-methyl-3-oxoindolin-2-ylidene)acetonitrile* 	KBr 3433 (NH), 2204 (C≡N), 1718 (C=O). 1596 (C=C, C=N).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.33 (s, 3H, CH_3), 7.40 (d, *J* = 8.2, 1H, H_{Is}-7), 7.47–7.53 (m, 2H, H_{Is}-6,, H_{Bt}-5), 7.54 (s, 1H, H_{Is}-4), 7.65 (ddd, *J* = 8.2, 7.6, 1.1, 1H, H_{Bt}-6), 8.18 (d, *J* = 7.8, 1H, H_{Bt}-4), 8.20 (d, *J* = 7.7, 1H, H_{Bt}-7), 11.48 (s, 1H, NH).	(101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 20.6 (CH_3), 79.7 (C), 114.3 (CH), 116.9 (C), 120.0 (C), 122.9 (CH), 123.1 (CH), 125.6 (CH), 126.3 (CH), 127.6 (CH), 133.1 (C), 134.3(C), 138.8 (CH), 143.9 (C), 150.0 (C), 154.0 (C), 163.5 (C), 185.1 (C).	**HRMS** (ESI) Calculated for $C_{18}H_{12}N_3OS$ (M + H$^+$): 318.0701, Found: 318.0704.
Yield 222 mg (0.7 mmol, 70%), dark red powder (mp 300–301 °C).					
2.24c	*(Z)-2-(Benzo[d]thiazol-2-yl)-2-(5-methoxy-3-oxoindolin-2-ylidene)acetonitrile*	KBr 3428 (NH), 2201 (C≡N), 1702 (C=O), 1591 (C=C, C=N), 1213 (C–O).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.81 (s, 1H, OCH3), 7.25 (d, *J* = 2.2, 1H, H_{Is}-4), 7.28 (d d, *J* = 8.6, 2.5, 1H, H_{Is}-6), 7.44 (d, *J* = 8.6, 1H, H_{Is}-7), 7.52 (t, *J* = 7.5, 1H, H_{Bt}-6), 7.65 (t, *J* = 7.7, 1H, H_{Bt}-5), 8.20 (d, *J* = 8.0, 1H, H_{Bt}-4), 8.18 (d, *J* = 8.2, 1H, H_{Bt}-7),	(101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 56.3 (CH_3), 79.6 (C), 108.9 (CH), 115.5 (C), 117.0 (C), 120.4 (C), 122.9 (CH), 123.1 (CH), 125.2 (CH), 126.2 (CH), 127.6 (CH), 134.2 (CH), 144.1 (C), 146.2 (C), 154.1 (C), 156.2 (C), 163.5 (C), 185.1 (C).	**HRMS** (ESI) Calculated for $C_{18}H_{12}N_3O_2S$ (M + H$^+$): 334.0650, Found: 334.0647.

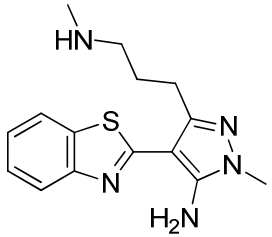
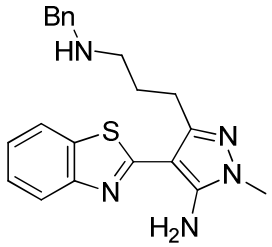
			11.42 (s, 1H, NH).		
Yield 290 mg (0.87 mmol, 87%), dark violet powder (mp 297–298 °C).					
2.25a	*(Z)-2-(Benzo[d]oxazol-2-yl)-2-(3-oxoindolin-2-ylidene)acetonitrile* 	KBr 3435 (NH), 2214 (C≡N), 1719 (C=O). 1596 (C=C, C=N).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.16 (td, *J* = 7.4, 0.8, 1H, H_{Is}-5), 7.47–7.51 (m, 2H, H_{Bzo}-5,6), 7.52–7.55 (m, 1H), 7.67 (td, *J* = 7.8, 1.3, 1H, H_{Is}-6), 7.72 (d, *J* = 7.5, 1H, H_{Is}-4), 7.83–7.90 (m, 2H, H_{Bzo}-4,7), 11.37 (s, 1H, NH).	(101 MHz, DMSO-d_6), δ, ppm: 74.0 (C), 111.6 (CH), 114.5 (C), 114.6 (CH), 119.97 (C), 120.01 (CH), 123.8 (CH), 125.7 (CH), 126.0 (CH), 126.6 (CH), 138.3 (CH), 141.7 (C), 145.9 (C), 149.9 (C), 151.7 (C), 159.5 (C), 184.6 (C).	**HRMS** (ESI) Calculated for $C_{17}H_{10}N_3O_2$ (M + H^+): 288.0773, Found: 288.0773.
Yield 221 mg (0.77 mmol, 77%), dark red powder (mp > 300 °C).					
2.26a	*(E)-2-(3-Oxoindolin-2-ylidene)-2-(quinolin-2-yl)acetonitrile* 	KBr 3423 (NH), 2203 (C≡N), 1712 (C=O), 1586 (C=C, C=N).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.14 (td, *J* = 7.4, 0.7, 1H, H_{Is}-5), 7.57 (d, *J* = 8.0 Hz, 1H, H_Q-8), 7.66 – 7.72 (m, 2H, H_{Is}-6-, H_Q-7), 7.73 (d, *J* = 7.5, 1H, 4-H_{Is}), 7.90 (ddd, *J* = 8.3, 6.9, 1.4, 1H, H_Q-6), 7.96 (d, *J* = 8.7, 1H, H_Q-3), 8.04 (d, *J* = 8.3, 1H, H_{Is}-7), 8.56 (d, *J* = 8.8, 1H, H_Q-3), 8.59 (d, *J* = 8.5, 1H, H_Q-5), 11.98 (s, 1H, NH).	(101 MHz, DMSO-d_6), δ, ppm: 85.2 (C), 114.3 (CH), 117.3 (C), 119.7 (C), 120.3 (CH), 123.1 (CH), 125.5 (CH), 126.6 (C), 127.9 (CH), 128.3 (CH), 129.5 (CH), 130.9 (CH), 138.0 (CH), 138.4 (CH), 144.5 (C), 147.4 (C), 152.0 (C), 153.2 (C), 185.6 (C).	**HRMS** (ESI) Calculated for $C_{19}H_{12}N_3O$ (M + H^+): 298.0980, Found: 298.0984.
Yield 250 mg (0.84 mmol, 84%), bright red powder (mp > 300 °C).					
2.27a	*2-(3-methylbenzo[d]thiazol-2(3H)-ylidene)-2-(3-oxo-3H-indol-2-yl)acetonitrile*	Neat film 2197 (C≡N), 1725 (C=O), 1511, 1478 (C=C, C=N).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 4.26 (s, 3H, CH_3), 7.07–7.14 (m, 1H, H_{Is}-5), 7.23 (d, *J* = 7.7 Hz, 1H, H_{Is}-7), 7.44–7.49 (m, 1H, H_{Is}-6), 7.49– 7.52 (m, 1H, H_{Is}-4), 7.55 (td, *J* = 7.5, 1.2,		**HRMS** (ESI) Calculated for $C_{18}H_{12}N_3OS$ (M + H^+): 318.0701, Found:

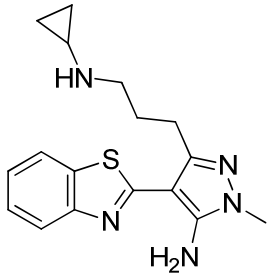
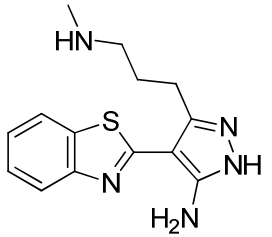
			1H, H_{Bt}-5), 7.64 (ddd, *J* = 8.5, 7.5, 1.2, 1H, H_{Bt}-6), 7.83 (d, *J* = 8.4, 1H, H_{Bt}-7), 8.14 (d d, J = 8.0, 0.6, 1H, H_{Bt}-4).		318.0699.
Yield 225 mg (0.84 mmol, 71%), dark violet powder (mp 270–271 °C).					
2.28b	*2-(Benzo[d]thiazol-2-yl)-2-(1,5-dimethyl-3-oxoindolin-2-ylidene)acetonitrile* 	Neat film 2204 (C≡N), 1713 (C=O), 1574 (C=C, C=N).	(400 MHz, CD_2Cl_2), δ, ppm (*J*, Hz): 2.42 (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 7.01 (d, *J* = 8.2, 1H, H_{Is}-7), 7.47–7.53 (m, 1H, H_{Is}-6, H_{Bt}-6), 7.56–7.62 (m, 1H, H_{Is}-7,), 8.01 (ddd, *J* = 8.0, 1.2, 0.6, 1H, H_{Bt}-7), 8.11 (ddd, *J* = 8.2, 1.2, 0.6, 1H, H_{Bt}-4).	(101 MHz, CD_2Cl_2), δ, ppm: 20.3 (CH_3), 35.3 (CH_3), 82.0 (C), 110.4 (CH), 117.6 (C), 119.9 (C), 121.7 (CH), 123.4 (CH), 125.5 (CH), 126.0 (CH), 126.7 (CH), 133.5 (C), 136.0 (C), 138.2 (CH), 146.1 (C), 151.9 (C), 153.4 (C), 160.8 (C), 184.4 (C).	**HRMS** (ESI) Calculated for $C_{19}H_{14}N_3OS$ (M + H^+): 332.0858, Found: 332.0858.
Elution system for column chromatography: CHA–CH_2Cl_2, 1:1. Yield 141 mg (0.43 mmol, 85%), dark violet powder.					

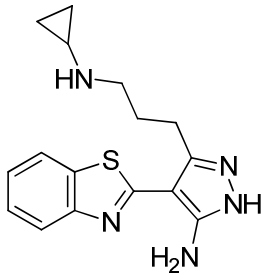
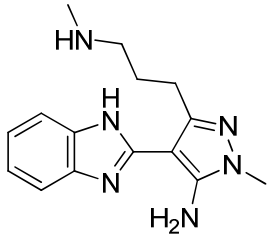
General procedure for the synthesis of 3-(*ω*-aminopropyl)-4-hetaryl-5-aminopyrazole (or isoxazole) 3.1-3.7.

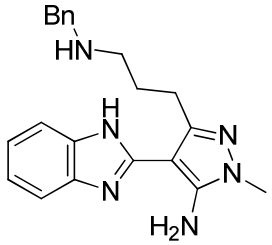
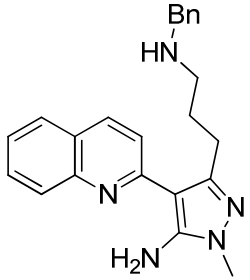
10-20 equiv of binucleophile ($NH_2NH_2 \cdot H_2O$ or NH_2OH (50% water solution) or NH_2NHMe) were added to a strongly stirred solution of 2-hetaryl-(*N*-R-pyrrolidin-2-ylidene)acetonitrile (1 mmol) in dioxane (10 ml). The reaction mixture was then heated to reflux for 3−8 h (TLC control, elution system: $CHCl_3$−CH_3OH, 20:1 unless otherwise noted), cooled down, and concentrated under reduced pressure. Purification by column chromatography (for **3.4b, 3.5b**) or by trituration with a minimal quantity of acetone (for **3.1a, 3.1b, 3.2a, 3.7a**) or acetonitrile (for **3.1c, 3.2c**) or water–acetone (for **3.6a**) yielded the desired product.

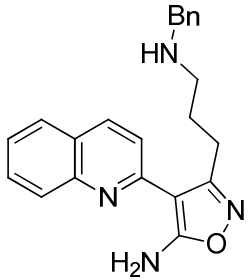
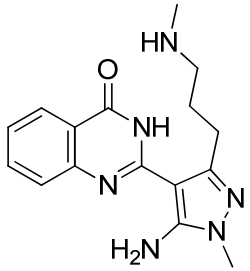
Table 6.3. Physico-chemical characteristics of 3-(ω-aminopropyl)-4-hetaryl-5-aminopyrazole (or isoxazole) **3.1-3.7.**

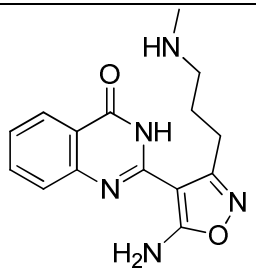
Compound	**IUPAC name**	**IR, ν, cm^{-1}**	**^{1}H NMR**	**^{13}C NMR**	**HRMS/MS, elemental analysis**
3.1a	*4-(Benzo[d]thiazol-2-yl) - 1-methyl -3-(3-(methylamino)propyl)-1H-pyrazol-5-amine* 	Neat film 3376, 3292 (NH, NH_2ν), 1623 (NH_2δ), 1564, 1536 (C=C, C=N).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.98 (quint, *J* = 7.4 Hz, 2H, 2-CH_2), 2.48 (s, 3H, NHC<u>H</u>$_3$), 2.76 (t, *J* = 7.1 Hz, 2H, 1-CH_2), 2.85−2.97 (m, 2H, 3-CH_2), 3.66 (s, 3H, NCH_3), 5.77 (s, 2H, NH_2), 7.28 (dd, *J* = 7.1, 1.3, 1H, H-6), 7.43 (dd, *J* = 7.2, 1.3, H-5), 7.84 (d, *J* = 7.7, 1H, H-7), 7.88 (d, *J* = 8.0, 1H, H-4).	(101 MHz, $CDCl_3$), δ, ppm: 26.2 (CH_2), 28.8 (CH_2), 33.8 (CH_3), 36.5 (CH_3), 51.9 (CH_2), 97.9 (C), 121.08 (CH), 121.09 (CH), 123.5 (CH), 125.9 (CH), 132.4 (C), 147.1 (C), 149.5 (C), 152.7 (C), 162.2 (C).	**HRMS** (ESI) Calculated for $C_{15}H_{20}N_5S$ (M + H^+): 302.1451, Found: 302.1446.
Yield 187 mg (0.62 mmol, 62%), white powder (mp 158−159 °C). The reaction was directly scaled up to 12.61 g of starting material affording 10.3 g (85% yield) of the desired product.					
3.1b	*4-(Benzo[d]thiazol-2-yl)-3-(3-(benzylamino)propyl)-1-methyl-1H-pyrazol-5-amine* 	Neat film 3391, 3298 (NH, NH_2ν), 1622 (NH_2δ), 1539 (C=C, C=N).	(300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.05 (quint, 7.4, 2H, 2-CH_2), 2.82 (t, *J* = 7.4, 2H, 1-CH_2), 2.95 (t, 7.8, 2H, 3-CH_2), 3.58 (s, 3H, CH_3), 4.04 (s, 2H, NCH_2), 6.86 (s, 2H, NH_2), 7.31 (ddd, *J* = 8.4, 7.5, 0.9, 1H, Ar H), 7.52−7.35 (m, 6H, Ar H), 7. 89 (d, *J* = 7.9, 1H, H-7), 8.00 (d, *J* = 7.5, 1H, H-4).	(75 MHz, CD_3OD), δ, ppm: 25.4 (CH_2), 26.1 (CH_2), 33.9 (CH_3), 47.9 (CH_2), 52.1 (CH_2), 97.8 (C), 121.9 (2CH), 124.6 (CH), 127.0 (CH), 130.0 (2CH), 130.3 (CH), 130.6 (2CH), 132.7 (C), 133.2 (C), 148.7 (C), 149.6 (C), 153.8 (C), 162.6 (C).	**HRMS** (ESI) Calculated for $C_{21}H_{24}N_5S$ (M + H^+): 378.1752, Found: 378.1747.
Yield 264 mg (0.70 mmol, 70%), white powder (mp 192−193 °C).					
3.1c	*4-(Benzo[d]thiazol-*	Neat film	(300 MHz, $CDCl_3$), δ, ppm (*J*, Hz):	(101 MHz, $CDCl_3$), δ, ppm: 6.3	**HRMS** (ESI)

	2-yl)-3-(3-(cyclopropylamino)-propyl)-1-methyl-1H-pyrazol-5-amine 	3396, 3376, 3292 (NH, NH_2ν), 1623 (NH_2δ), 1563, 1540 (C=C, C=N).	0.33−0.41 (m, 2H, NCHC<u>H</u>$_2$), 0.41−0.48 (m, 2H, NCHC<u>H</u>$_2$), 1.99 (quint, *J* = 7.6, 2H, 2-CH_2), 2.13−2.23 (m, 1H, NC<u>H</u>CH_2), 2.87 (t, *J* = 7.2, 2H, 1-CH_2), 2.91 (t, *J* = 7.7, 2H, 3-CH_2), 3.68 (s, 3H, CH_3), 5.76 (s, 2H, NH_2), 7.29 (ddd, *J* = 8.2, 7.6, 1.2, 1H, H-6), 7.44 (ddd, *J* = 8.2, 7.3, 1.3, 1H, H-5), 7.85 (dd, J = 8.0, 1.3, 1H, H-7), 7.89 (dd, *J* = 8.2, 1.2, 1H, H-4)	(2CH_2), 26.2 (CH_2), 28.9 (CH_2), 30.2 (CH_3), 33.8 (CH), 49.3 (CH_2), 97.9 (C), 121.07 (CH), 121.10 (CH), 123.5 (CH), 125.9 (CH), 132.4 (C), 147.1 (C), 149.5 (C), 152.7 (C), 162.2 (C).	Calculated for $C_{17}H_{22}N_5S$ (M + H^+): 328.1596, Found: 328.1592.
Yield 203 mg (0.62 mmol, 62%), white powder (mp 171 °C).					
3.2a	*4-(Benzo[d]thiazol-2-yl)-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine* 	Neat film 3311 (NH, NH_2ν), 1624 (NH_2δ), 1580, 1543 (C=C, C=N).	(300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.74−1.91 (m, 2H, 2-CH_2), 2.29 (s, 3H, NCH_3), 2.57 (t, *J* = 6.9, 2H, 1-CH_2), 2.76−2.91 (m, 2H, 3-CH_2), 6.23 (s, 2H, NH_2), 7.30 (ddd, *J* = 7.6, 7.3, 1.1, 1H, H-6), 7.44 (ddd, *J* = 8.0, 7.7, 1.3, 1H, H-5), 7.87 (d, *J* = 8.0, 1H, H-7), 8.01 (d, *J* = 7.8, 1H, H-4).	(75 MHz, DMSO-d_6) δ 25.2 (CH_2), 28.5 (CH_2), 36.6 (CH_3), 51.7 (CH_2), 97.4 (C), 121.3 (CH), 122.0 (CH), 124.0 (CH), 126.6 (CH), 132.4 (C), 146.4 (C), 153.0 (2C), 162.6 (C).	**HRMS** (ESI) Calculated for $C_{14}H_{18}N_5S$ (M + H^+): 288.1283, Found: 288.1281.
Yield 161 mg (0.56 mmol, 56%), light orange powder (mp 205 °C).					
3.2c	*4-(Benzo[d]thiazol-2-yl)-3-(3-(cyclopropylamino)-propyl)-1H-pyrazol-5-amine*	Neat film 3411, 3291, 3197 (NH, NH_2ν), 1602 (NH_2δ), 1539, 1540, 1496 (C=C, C=N).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.20−0.32 (m, 2H, NCHC<u>H</u>$_2$), 0.34−0.47 (m, 2H, NCHC<u>H</u>$_2$), 1.85 (quint, *J* = 7.3, 2H, 2-CH_2), 2.08−2.18 (m, 1H, NC<u>H</u>CH_2), 2.72 (t, *J* = 7.0, 2H, 1-CH_2), 2.83 (t, *J* = 7.4, 2H, 3-CH_2), 6.25 (s, 2H, NH_2), 7.31 (t, *J* = 7.5, 1H, H-6), 7.45 (t, *J* = 7.6, 1H, H-5), 7.87 (d, *J* = 8.0, 1H, H-7), 8.02 (d,	(101 MHz, DMSO-d_6), δ, ppm: 6.1 (2CH_2), 25.2 (CH_2), 28.2 (CH), 30.5 (CH_2), 49.0 (CH_2), 97.8 (C), 121.2 (CH), 122.0 (CH), 124.0 (CH), 126.6 (CH), 132.3 (C), 146.9 (C), 152.9 (2C), 162.3 (C).	**HRMS** (ESI) Calculated for $C_{16}H_{20}N_5S$ (M + H^+): 314.1439, Found: 314.1438.

			J = 7.8, 1H, H-4).		
Yield 134 mg (0.43 mmol, 43%), whitish powder (mp 121−123 °C).					
3.3a	*4-(1H-Benzo[d]imidazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine* 	Neat film 3306, 3206 (NH, NH_2ν), 1622 (NH_2δ), 1580 (C=C, C=N).	(300 MHz, DMSO-d_6), δ, ppm (J, Hz): 1.95 (quint, J = 6.9, 1H, 2-CH_2), 2.45 (s, 3H, NHC$\underline{H}_3$), 2.79 (t, J = 6.7, 2H, 1-CH_2), 2.92 (t, J = 7.2, 2H, 3-CH_2), 3.58 (s, 3H, NCH_3), 6.54 (s, 2H, NH_2), 7.04−7.16 (m, 2H, Ar H), 7.46−7.57 (m, 2H, Ar H).	(75 MHz, DMSO-d_6), δ, ppm (J, Hz): 25.0 (CH_2), 26.2 (CH_2), 33.8 (CH_3), 34.5 (CH_3), 48.7 (CH_2), 92.4 (C), 114.5 (2CH), 121.3 (2CH), 146.5 (2C), 148.6 (2C), 149.3 (C).	**HRMS** (ESI) Calculated for $C_{15}H_{21}N_6$ (M + H^+): 285.1828, Found: 285.1825.
Elution system for column chromatography (and TLC): $CHCl_3$−CH_3OH, 10:3. Further trituration of the obtained yellowish oil with acetone induces its consolidation. Yield 186 mg (0.65 mmol, 65%), whitish powder (mp 181−183 °C).					
3.3b	*4-(1H-Benzo[d]imidazol-2-yl)-3-(3-(benzylamino)-propyl)-1-methyl-1H-pyrazol-5-amine*	Neat film 3301 (NH, NH_2ν), 1623 (NH_2δ), 1579 (C=C, C=N).	(400 MHz, DMSO-d_6), δ, ppm (J, Hz): 1.84 (quint, J = 6.7, 2H, 2-CH_2), 2.55 (t, J = 6.4, 2H, 1-CH_2), 2.84 (t, J = 7.0, 2H, 3-CH_2), 3.56 (s, 3H, CH_3), 3.74 (s, 2H, NCH_2), 6.49 (s, 2H, NH_2), 7.01−7.08 (m, 2H, Ar H), 7.22−7.29 (m, 1H, Ar H), 7.29−7.40 (m, 6H, Ar H).	(101 MHz, DMSO-d_6), δ, ppm: 24.8 (CH_2), 28.8 (CH_2), 34.4 (CH_3), 46.8 (CH_2), 52.7 (CH_2), 92.6 (C), 121.2 (2CH), 127.2 (CH), 128.7 (6CH), 140.3 (3C), 147.2 (C), 148.6 (C), 149.7 (C).	**HRMS** (ESI) Calculated for $C_{21}H_{25}N_6$ (M + H^+): 361.2141, Found: 361.2140.

					
Elution system for column chromatography (and TLC): $CHCl_3$−CH_3OH, 10:3. Further trituration of the obtained oil with acetone induces its consolidation. Yield 234 mg (0.65 mmol, 65%), whitish powder (mp 135 °C).					
3.4b	*3-(3-(Benzylamino)propyl)-1-methyl-4-(quinolin-2-yl)-1H-pyrazol-5-amine* 	Neat film 3261 (NHν, NH_2ν), 1619 (NH_2δ), 1599, 1547, 1518 (C=C, C=N).	(300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.01 (quint, *J* = 7.0, 2H, 2-CH_2), 2.82 (t, *J* = 6.8, 2H, 1-CH_2), 2.98 (t, *J* = 7.5, 2H, 3-CH_2), 3.57 (s, 3H, CH_3), 3.84 (s, 2H, NC$\underline{H_2}$Ph), 6.04 (s, 2H, NH_2), 7.23−7.38 (m, 5H, H Ph), 7.41 (ddd, *J* = 8.1, 7.0, 1.2, 1H, H-6), 7.56 (d, *J* = 8.8, 1H, H-3), 7.64 (ddd, *J* = 8.4, 6.9, 1.5, 1H, H-7), 7.71 (dd, *J* = 8.1, 1.2, 1H, H-8), 7.91 (d, *J* = 8.4, 1H, H-5), 8.01 (d, *J* = 8.8, 1H, H-4).	(101 MHz, $CDCl_3$), δ, ppm: 27.5 (CH_2), 28.1 (CH_2), 33.6 (CH_3), 48.8 (CH_2), 53.4 (CH_2), 100.8 (C), 118.9 (CH), 124.8 (CH), 125.3 (C), 127.2 (CH), 127.4 (CH), 127.8 (CH), 128.3 (2CH), 128.4 (2CH), 129.5 (CH), 136.1 (CH), 139.2 (C), 147.4 (C), 147.8 (C), 148.9 (C), 154.8 (C).	**HRMS** (ESI) Calculated for $C_{23}H_{26}N_5$ (M + H^+): 372.2188, Found: 372.2181.
Elution system for column chromatography: $CHCl_3$−CH_3OH, 20:1. Further trituration of the obtained oil with acetone induces its consolidation. Yield 204 mg (0.55 mmol, 55%), yellow powder (mp 170–171°C).					
3.5b	*3-(3-(Benzylamino)propyl)-4-(quinolin-2-yl)isoxazol-5-amine*	Neat film 3327 (NHν, NH2ν), 1631 (NH2δ), 1598, 1541 (C=C, C=N), 1294 (C−O).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.06 (quint, *J* = 7.0, 2H, 2-CH_2), 2.85 (t, *J* = 6.9 Hz, 2H, 1-CH_2), 3.06 (t, *J* = 7.5, 2H, 3-CH_2), 3.86 (s, 2H, , NC$\underline{H_2}$Ph), 7.03 (s, 2H, NH_2), 7.24−7.31 (m, 1H, H_{Ph}-4), 7.32−7.42 (m, 4H, H Ph), 7.46 (ddd, *J* = 8.1, 7.0, 1.1, 1H, H-6), 7.55 (d, *J* = 8.8, 1H, H-3), 7.68 (ddd, *J* = 8.4, 6.9, 1.5, 1H, H-7), 7.75 (dd, *J* = 8.2, 1.0, 1H, H-8),	(75 MHz, $CDCl_3$), δ, ppm: 25.4 (CH_2), 27.0 (CH_2), 48.4 (CH_2), 53.6 (CH_2), 91.7 (C), 117.9 (CH), 125.2 (CH), 125.5 (C), 127.2 (CH), 127.5 (CH), 127.8 (CH), 128.3 (2CH), 128.5 (2CH), 129.8 (CH), 136.5 (CH), 139.4 (C), 147.3 (C), 152.5 (C), 161.3 (C), 169.2 (C).	**HRMS** (ESI) Calculated for $C_{22}H_{23}N_4O$ (M + H^+): 359.1872, Found: 359.1862.

			7.93 (d, *J* = 8.4, 1H, H-5), 8.08 (d, *J* = 8.7, 1H, H-4).		
Elution system for column chromatography: $CHCl_3$−CH_3OH, 20:1. Yield 204 mg (0.5 mmol, 50%), light orange powder (mp 125–126°C).					
3.6a	*2-(5-Amino-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-4-yl)quinazolin-4(3H)-one* 	Neat film 3358, 3284 (NHν, NH_2ν), 1668 (C=O), 1575, 1557, (NH_2δ, C=C, C=N).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.93 (quint, *J* = 6.8, 2H, 2-CH_2), 2.38 (s, 3H, NHC$\underline{H_3}$), 2.55 (t, *J* = 5.7, 2H, 1-CH_2), 2.83 (t, *J* = 6.3, 2H, 3-CH_2), 3.55 (s, 3H, NCH_3), 6.65 (s, 2H, NH_2), 7.22 (dd, *J* = 8.3, 7.4, 1H, H-6), 7.48 (d, *J* = 8.0, 1H, H-8),7.59 (ddd, *J* = 8.4, 7.6, 1.4, 1H, 7-H), 7.99 (dd, 1.2, 1H, 5-H), 9.53 (br. s, 1H, NH).	(101 MHz, DMSO-d_6), δ, ppm: 23.4 (CH_2), 27.6 (CH_2), 33.4 (CH_3), 34.4 (CH_3), 46.9 (CH_2), 98.5 (C), 120.5 (C), 123.5 (CH), 125.8 (CH), 126.0 (CH), 133.1 (CH), 146.9 (C), 149.0 (C), 150.7 (C), 156.2 (C), 167.2 (C).	**HRMS** (ESI) Calculated for $C_{15}H_{21}N_6$ (M + H^+): 313.1777, Found: 313.1772.
Yield 194 mg (0.62 mmol, 62%), white powder (mp 173 °C).					
3.7a	*2-(5-Amino-3-(3-(methylamino)propyl)isoxazol-4-yl)quinazolin-4(3H)-one*	Neat film 3347, 3284 (NHν, NH_2ν), 1633 (C=O), 1607, 1571 (NH_2δ, C=C, C=N), 1243 (C−O).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.92−2.07 (m, 2H, 2-CH_2), 2.51 (s, 3H, CH_3), 2.75−2.83 (m, 2H, 1-CH_2), 2.92−3.03 (m, 2H, 3-CH_2), 7.18 (t, *J* = 7.2, 1H, H-6), 7.51 (d, *J* = 7.6, 1H, H-8), 7.54 (t, *J* = 7.2, 1H, H-7), 7.96 (d, *J* = 7.0, 1H, H-5), 8.04 (s, 2H, NH_2).	(101 MHz, DMSO-d_6), δ, ppm: 21.7 (CH_2), 26.6 (CH_2), 33.0 (CH_3), 47.0 (CH_2), 90.3 (C), 120.8 (C), 123.2 (CH), 125.7 (CH), 126.0 (CH), 132.4 (CH), 151.1 (C), 157.0 (C), 160.8 (C), 169.5 (C), 170.5 (C).	**HRMS** (ESI) Calculated for $C_{15}H_{18}N_5O_2$ (M + H^+): 300.1460, Found: 300.1462.

					
Yield 224 mg (0.75 mmol, 75%), light orange powder (mp 171–172 °C).					

3-(5-Amino-4-(benzo[d]thiazol-2-yl)-1-methyl-1*H*-pyrazol-3-yl)-*N*,*N*,*N*-trimethylpropan-1-aminium iodide (3.8).

MeI (0.137 ml, *d* = 2.28 g/ml, 2.2 mmol) was added dropwise to a stirred solution of 4-(benzo[*d*]thiazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1*H*-pyrazol-5-amine **3.1a** (301 mg, 1 mmol) and MeONa (54 mg, 1 mmol) in MeOH (6 ml). Stirring was pursued for 3 h. The resulting white precipitate (mp 249−250 °C) was filtered off and analyzed without additional purification steps. We observed complete conversion of the starting material to the desired product but we suspected the presence of NaI.

***tert*-Butyl (3-(4-(benzo[d]thiazol-2-yl)-5-(benzylamino)-1-methyl-1H-pyrazol-3-yl)propyl)(methyl)carbamate (3.10).**

Di-*tert*-butyl dicarbonate (120 mg, 0.55 mmol) was added to a stirred solution of 4-(benzo[*d*]thiazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine **3.1a** (151 mg, 0.5 mmol) in trifluoroethanol (TFE) (3 ml) at rt. The reaction was completed in 10 min. After evaporation of volatiles under reduced pressure, the crude product was purified by automated flash chromatography (elution system: gradient of CH_2Cl_2−acetone, 9:1 to CH_2Cl_2−acetone, 2:3) to yield 187 mg (0.47 mmol, 93%) of white solid (mp 129−130 °C).

A suspension of tert-butyl (3-(5-amino-4-(benzo[*d*]thiazol-2-yl)-1-methyl-1H-pyrazol-3-yl)propyl)(methyl)carbamate (187 mg, 0.47 mmol), AcOH (0.05 ml, 0.94 mmol), benzaldehyde (0.06 ml, 0.56 mmol), and activated molecular sieves in toluene (5 ml) was stirred in a sealed vessel overnight at 120 °C. At this point, two spots were detected by TLC (CH_2Cl_2−acetone, 9:1) corresponding to the reactant (R_f = 0.27) and the desired imine (R_f = 0.67 (bright yellow spot)). The reaction was broken off at that point, filtrated through a plug of celite, and the liquid was concentrated under reduced pressure. The obtained solid was redissolved in dry ethanol (5 ml) and 3 equiv of $NaBH_4$ (53 mg, 1.4 mmol) was subsequently added. The reaction was stirred for 30 min at rt (during this time, the color of the reaction mixture changed from yellow to white due to reduction of the imine to amine) under

Ar. Dilution of the reaction mixture with ethanol, filtration through a plug of Celite, and concentration under reduced pressure gave a mixture of **3.1a** and **3.10** in 100% yield. After compound separation by automated flash chromatography (elution system:gradient of CH_2Cl_2–acetone, 19:1 to CH_2Cl_2–acetone, 9:1), secondary amine **3.10** was obtained as a colorless oil (108 mg, 0.22 mmol, 47%).

_N_-(3-(3,5-Dimethyl-3_H_-benzo[4,5]imidazo[1,2-_c_]-pyrazolo[4,3-_e_]pyrimidin-1-yl)propyl)-_N_-methylacetamide (3.11).

A solution of 4-(1*H*-benzo[*d*]imidazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1*H*-pyrazol-5-amine **3.3a** (142 mg, 0.5 mmol) in 1,1,1-triethoxyethane (10 ml) was refluxed for 20 min, and Ac_2O (0.47 ml, d= 1.087 g/ml, 5 mmol) was added to the reaction mixture at this point. After another 5 min of stirring, the reaction ceased (TLC elution system: $CHCl_3$–acetone, 2:1) and the mixture was concentrated under reduced pressure. The crude product was purified by automated flash chromatography (elution system: gradient of $CHCl_3$–acetone, 2:1) to yield 152 mg (0.43 mmol, 87%) of white solid (mp 97–98 °C).

_N_-Methyl-_N_-(3-(3-methyl-3_H_-benzo[4,5]imidazo-[1,2-_c_]pyrazolo[4,3-_e_][1,2,3]triazin-1-yl)propyl)nitrous amide (3.12)

t-BuONO (0.12 ml, *d* = 0.867 g/ml, 1 mmol) was added dropwise to a strongly stirred solution of 4-(1*H*-benzo[*d*]-imidazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine **3.3a** (142 mg, 0.5 mmol) in DMF (5 ml, 65 °C), and the gas evolution was observed by bubble counter. After 10 min of stirring, TLC control (CH_2Cl_2−acetone, 9:1) indicated the presence of two spots corresponding to the starting material and new product. The pH of the reaction mixture was slightly basic. Another portion of *t*-BuONO (0.24 ml, 2 mmol) was added dropwise, and the pH of the reaction mixture turned to acidic (pH ~ 3). After 10 min of stirring, another TLC control was made to ensure the conversion of starting material and formation of one main product. The reaction mixture was allowed to

cool to rt, and pH was brought to neutral−slightly basic by addition of saturated aq. $NaHCO_3$. This aqueous phase was extracted with EtOAc (three times), and collected organic extracts were washed with brine and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by automated flash chromatography (elution system: CH_2Cl_2−acetone, 19:1) to yield 137 mg (0.42 mmol, 85%) of **3.12** as a bright yellow solid (mp 163−164 °C).

Note: 1) the aliquot for TLC was taken from the reaction mixture followed by addition of saturated aq. $NaHCO_3$ to make pH neutral−slightly basic and extraction with EtOAc. 2) The solution of *t*-BuONO is acidic when purchased from commercial sources. Its acidity is enough to generate the nitrosonium ion and bring the reaction to completion.

_N_-(3-(4-(Benzo[_d_]thiazol-2-yl)-5-iodo-1-methyl-1_H_-pyrazol-3-yl)propyl)-_N_-methylnitrous amide (3.13).

t-BuONO (0.6 ml, d = 0.876 g/ml, 5 mmol) was added dropwise to a stirring suspension of **3.1a** (301 mg, 1 mmol) and I_2 (1.1 g, 4.3 mmol) in acetonitrile (10 ml) at 65 °C. After stirring for 20 min, the mixture was cooled to room temperature, and saturated aq. $Na_2S_2O_3$ was added. The mixture was extracted three times with ethyl acetate, and the combined organic extracts were washed with saturated aq. NaCl and dried over $MgSO_4$. Evaporation of volatiles under reduced pressure and further purification by automated flash chromatography (elution system: CH_2Cl_2−acetone, 19:1) yielded 168 mg of **3.13** (0.38 mmol, 38%) as a light orange solid (mp 104−105 °C). The reaction was directly scaled up to 1.8 g (6 mmol) of starting material, affording 0.83 g (32% yield) of the desired product.

3-(4-(Benzo[_d_]thiazol-2-yl)-5-iodo-1-methyl-1_H_-pyrazol-3-yl)-_N_-methylpropan-1-amine (3.14a).

p-TsOH monohydrate (1.52 g, 8 mmol) was added portionwise to a strongly stirred solution of 4-(benzo[*d*]thiazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1*H*-

pyrazol-5-amine **3.1a** (0.602 g, 2 mmol) in MeCN 10 (ml), and the reaction mixture was stirred over a 5 min period. The flask was then cooled to 0 °C in an ice-water bath and KI (0.83 g, 5 mmol), CuI (1 mg, 0.005 mmol), and *t*-BuONO (0.302 ml, d = 1.368 g/ml, 4 mmol) were added subsequently to the reaction mixture. The solution was stirred at 0 °C for 20 min then allowed to warm to rt, and stirring was continued for a further 2 h. Then, the reaction mixture was quenched with water (30 ml), 5% aq. $Na_2S_2O_3$ solution (30 ml), and saturated aq. $NaHCO_3$ solution to reach pH 8−9. This mixture was transferred to a separatory funnel, and the aqueous phase was extracted with EtOAc (3 × 50 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and then concentrated under reduced pressure. The crude mixture was purified by automated flash chromatography (elution system: gradient of $CHCl_3$−Et_3N,10:1 to $CHCl_3$−Et_3N−CH_3OH, 10:1:0.2) to give 0.247 g (0.6 mmol, 30%) of **3.14a** as a white solid (mp 189 °C) after trituration of the residues with MeCN. The reaction was directly scaled up to 1.8 g (6 mmol) of starting material, affording 0.74 g (30% yield) of the desired product.

tert-Butyl (3-(4-(Benzo[*d*]thiazol-2-yl)-5-iodo-1-methyl-1*H*-pyrazol-3-yl)propyl)(methyl)carbamate (3.15).

Ditert-butyl dicarbonate (120 mg, 0.55 mmol) was added to a stirred solution of 22 (206 mg, 0.5 mmol) in TFE (3 ml) at rt followed by the addition of NaOMe (30 mg, 0.55 mmol). The reaction was completed in 30 min. After evaporation of volatiles under reduced pressure, the crude product was purified by automated flash chromatography (elution system: gradient of CH_2Cl_2−acetone, 19:1 to CH_2Cl_2−acetone, 9:1) to yield 179 mg (0.35 mmol, 70%) of **3.15** as a white solid (mp 122 °C).

General Procedure for the Synthesis of R-(3-(4-(Benzo[*d*]thiazol-2-yl)-5-aryl/hetaryl/styryl-1-methyl-1Hpyrazol-3-yl))propyl-1-amine (3.16−3.20).

N-(3-(4-(Benzo[*d*]-thiazol-2-yl)-5-iodo-1-methyl-1H-pyrazol-3-yl)propyl)-*N*-methylpropan-1-amine **3.14a**/ *N*-methylnitrous amide **3.13**/ *tert*-butyl-

(methyl)carbamate **3.15** (0.15 mmol), boronic acid (**3.16a-c**, **3.17**)/ its diethanolamine ester (**3.18**, **3.19**)/ trifluoroborate salt (**3.20**) (0.17 mmol), Cs_2CO_3 (64 mg, 0.18 mmol), and $Pd(PPh_3)_4$ (9 mg, 0.0075 mmol) were placed in a two-necked flask fitted with a water condenser and rubber septum. The system was evacuated and back-filled with argon. This sequence was repeated three times. Dioxane−H_2O, 5:1 mixture (8 ml) was degassed beforehand by the Freeze−Pump−Thaw method and transferred to the reaction vessel under a positive pressure of argon. The resulting mixture was stirred under argon at 110 °C overnight. After cooling to room temperature, the reaction mixture was diluted with H2O, transferred to the separatory funnel, and extracted three times with EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by automated flash chromatography. Reaction conditions for **3.20**: teflon reactor, 140 °C, 24 h. Note: indole was implemented into the reaction in the form of trifluoroboronate salt with nitrogen protected with *tert*-butyloxycarbonyl.

_N_-(3-(4-(Benzo[_d_]thiazol-2-yl)-1-methyl-1_H_-pyrazol-3-yl)propyl)-_N_-methylnitrous Amide (3.21).

t-BuONO (0.24 ml, *d* = 0.867 g/ml, 2 mmol) was added dropwise to a strongly stirred solution of 4-(benzo[*d*]thiazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1*H*-pyrazol-5-amine **3.1a** (0.301 g, 1 mmol) in DMF (5 ml, 65 °C), and the gas evolution was observed by bubble counter. After 10 min of stirring, the TLC control (CH_2Cl_2−acetone, 9:1) indicated the presence of two spots corresponding to the starting material and new product. The pH of the reaction mixture was slightly basic. Another portion of *t*-BuONO (0.48 ml, 4 mmol) was added dropwise, and the pH of the reaction mixture turned to acidic (pH ∼ 3). After 10 min of stirring, another TLC control was made to ensure the conversion of starting material and formation of one main product. The reaction mixture was allowed to cool to rt, and pH was brought to neutral−slightly basic by addition of saturated aq. $NaHCO_3$. This aqueous phase was extracted with EtOAc (three times), and collected organic extracts were washed with

brine and dried over $MgSO_4$. The solution was concentrated under reduced pressure, and the residue was purified by automated flash chromatography (system: gradient of EtOAc−CHA, 7:3 to EtOAc, 100%) to yield 290 mg (0.92 mmol, 92%) of white solid (mp 72−73 °C).

3-(4-(Benzo[*d*]thiazol-2-yl)-1-methyl-1*H*-pyrazol-3-yl)-*N*-methylpropan-1-aminium chloride (3.22).

HCl gas (generated by dropwise addition of H_2SO_4 on solid NaCl) was bubbled vigorously through an ice-cold solution of *N*-(3-(4-(benzo[*d*]thiazol-2-yl)-1-methyl-1*H*-pyrazol-3-yl)propyl)-*N*-methylnitrous amide **3.21** (158 mg, 0.5 mmol) in dry methanol (8 ml) for 20 min. The resultant precipitate was filtered off and washed with ether to yield 157 mg (0.485 mmol, 97%) of white solid (mp 152−153 °C).

***N*-(3-(4-(Benzo[*d*]thiazol-2-yl)-5-(4-methoxyphenyl)-1-methyl-1*H*-pyrazol-3-yl)propyl)-*N*-methylnitrous Amide (3.16c).**

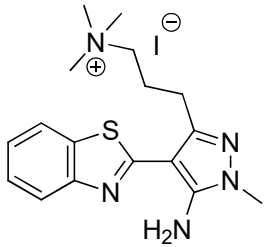
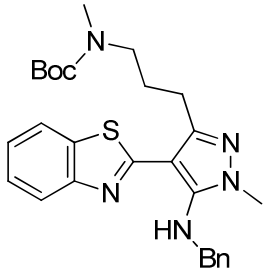
N-(3-(4-(Benzo[*d*]thiazol-2-yl)-1-methyl-1*H*-pyrazol-3-yl)propyl)-*N*-methylnitrous amide **3.21** (95 mg, 0.3 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and Bu_4NOAc (181 mg, 0.6 mmol) were placed in a flame-dried two-necked flask fitted with a water condenser and rubber septum. The system was evacuated and back-filled with argon. This sequence was repeated three times. DMA (3 ml) and 4-bromoanisole (0.06 ml, d = 1.494 g/ml, 0.45 mmol) were sequentially added under a stream of argon at room temperature. The resulting mixture was stirred at 70 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc, filtered through a plug of Celite, and eluted with additional EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified using automated flash chromatography (system: gradient of CH_2Cl_2−acetone, 19:1 to CH_2Cl_2−acetone, 9:1) to yield 126 mg (0.3 mmol, 100%) of **3.16c** as a light orange solid (mp 140 °C).

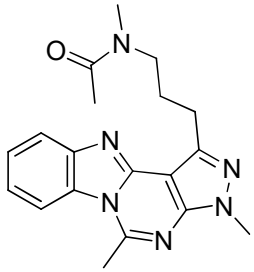
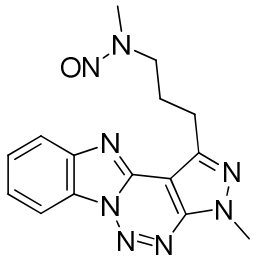
Pyrazoles **3.23-3.28, 3.30** and amide **3.31a** were obtained according to the general procedure described for 3-(ω-aminopropyl)-4-hetaryl-5-aminopyrazoles (isoxazoles) **3.1-3.7.** *Note:* for pyrazoles **3.27**, **3.28**, **3.30** that were synthesized from pyrrolidinacetonitriles substituted with quaternized azaheterocycles the solvent for reaction is EtOH. The reaction continues during 2-3 h.

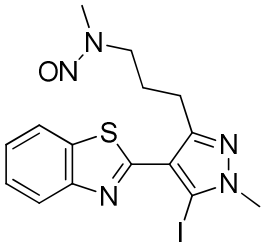
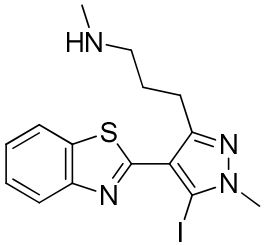
General procedure for the synthesis of 5-(2-amino-1-(1,3-dimethyl-1*H*-benzo[*d*]imidazol-2(3*H*)-ylidene)-2-oxoethyl)-1-methyl-3,4-dihydro-2*H*-pyrrol-1-ium iodide chloride (3.31b).

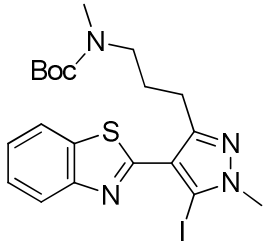
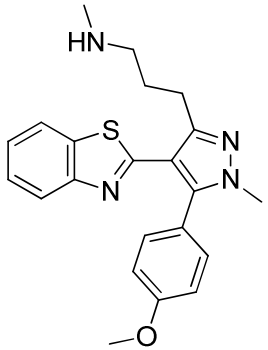
The strongly stirred mixture of 2-(cyano(1-methylpyrrolidin-2-ylidene)methyl)-1,3-dimethyl-1*H*-benzo[*d*]imidazol-3-ium iodide **2.8** (0.3 mmol, 118 mg) and 20 equiv of 2.5 M NaOH in ethanol (3 ml) was refluxed over 3 h period. At this point the reaction was cooled down and treated with 1M HCl to slightly acidic pH (pH around 6). The reaction mixture was concentrated under reduced pressure and the solid precipitate was triturated with dry ethanol. The precipitate was filtered off and the mother liquid was collected, concentrated under reduced presure and triturated with minimal quantity of ethanol. After another filtration–mother liquid collection–concentration **3.31b** was obtained as a beige solid (71 mg, 0.22 mmol,73%).

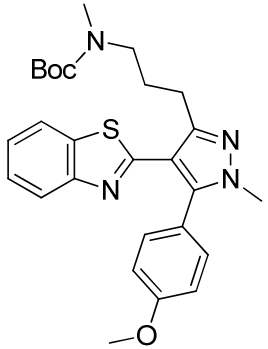
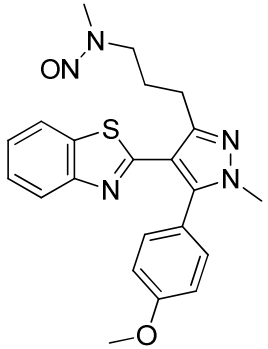
Table 6.4. Physico-chemical characteristics of 3-(ω-aminopropyl)-4-hetaryl-5-aminopyrazole derivatives **3.8-3.30** and amide **3.31**.

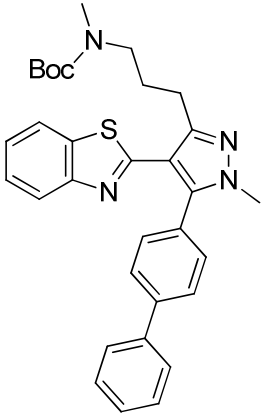
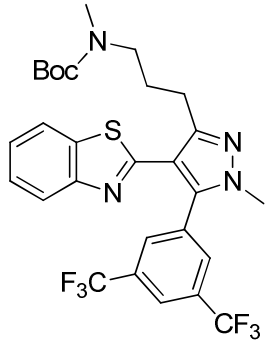
Compound	IUPAC name	IR, ν, cm^{-1}	^{1}H NMR	^{13}C NMR	HRMS/MS, elemental analysis
3.8	*3-(5-Amino-4-(benzo[d]thiazol-2-yl)-1-methyl-1Hpyrazol-3-yl)-N,N,N-trimethylpropan-1-aminium iodide* 	Neat film 3393 (NH_2ν), 1614 (NH_2δ), 1563, 1535 (C=C, C=N).	(400 MHz, methanol-d_4), δ, ppm (*J*, Hz): 2.21−2.36 (m, 2H, 2-CH_2), 2.96 (t, *J* = 7.3, 2H, 3-CH_2), 3.17 (s, 9H, 3-CH_3), 3.48−3.59 (m, 2H, 1-CH_2), 3.65 (s, 3H, NCH_3), 7.30 (ddd, *J* = 8.2, 7.6, 1.2, 1H, H-6), 7.45 (ddd, *J* = 8.2, 7.3, 1.3, 1H, H-5), 7.86−7.93 (m, 2H, H-4,7).	(101 MHz, methahol-d_4), δ, ppm (*J*, Hz): 21.3 (CH_2), 24.3 (CH_2), 32.8 (CH_3), 52.2 (t, $^{1}J_{C\text{-}N}$ = 4.0, 3CH_3), 65.9 (t, $^{1}J_{C\text{-}N}$ = 3.0, 2-CH_2), 96.7 (C), 120.79 (CH), 120.84 (CH), 123.5 (CH), 125.9 (CH), 132.0 (C), 147.0 (C), 148.5 (C), 152.8 (C), 161.4 (C).	**HRM**S (ESI) Calculated for $C_{17}H_{24}N_5S$ (M + H^+): 330.1752, Found: 330.1758.
Yield 100%, white powder (mp 249−250 °C).					
3.10	*tert-Butyl (3-(4-(benzo[d]thiazol-2-yl)-5-(benzylamino)-1-methyl-1H-pyrazol-3-yl)propyl)(methyl)carbamate* 	Neat film 3271 (NH), 1690 (C=O), 1560 (C=C, C=N), 1249 (C−O), 1164 (C−N).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.47 (s, 9H, 3CH_3), 1.95−2.07 (m, 2H, 2-CH_2), 2.82−2.94 (m, 5H, 3-CH_2, NBocC$\underline{H_3}$), 3.28−3.50 (m, 2H, 1-CH_2), 3.81 (s, 3H, $N_{Pyr}CH_3$), 4.55 (s, 2H, NC$\underline{H_2}$Ph), 7.28−7.38 (m, 4H, H_{Ph}-2,4,6, H_{Bt}-6), 7.39−7.47 (m, 3H, H_{Bt}-5), 7.80−7.88 (m, 2H, H_{Bt}-4,7), 7.79 (br. s, NH).	(101 MHz, $CDCl_3$), δ, ppm: 25.8 (CH_2), 27.1 (CH_2), 28.5 (3CH_3), 34.3 (CH_3), 36.8 (CH_3), 48.9 (CH_2), 50.3 (CH_2), 79.2 (C), 100.6 (C), 121.0 (CH), 121.2 (CH), 123.7 (CH), 126.0 (CH), 127.1 (2CH), 127.5 (CH), 128.7 (2CH), 132.5 (C), 138.9 (C), 149.3 (C), 149.5 (C), 152.5 (C), 155.8 (C), 162.0 (C).	**HRMS** (ESI) Calculated for $C_{27}H_{34}N_5O_2S$ (M + H^+): 492.2433, Found: 492.2433.

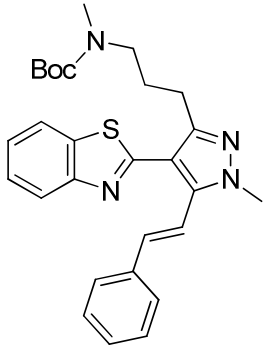
Yield 108 mg (0.22 mmol, 47%). Colorless oil.					
3.11	*N-(3-(3,5-Dimethyl-3H-benzo[4,5]imidazo[1,2-c]-pyrazolo[4,3-e]pyrimidin-1-yl)propyl)-N-methylacetamide* 	Neat film 1656 (C=O), 1623, 1601, 1544, 1525 (C=C, C=N).	(300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): (mixture of rotamers) 2.09 (s, 1.2H, $CO(CH_3)$), 2.14 (s, 1.8H, $CO(CH_3)$), 2.22−2.39 (m, 2H, 2-CH_2), 2.98 (s, 1.8H, NAc$C\underline{H}_3$), 3.07 (s, 1.2H, NAc$C\underline{H}_3$), 3.18−3.29 (m, 5H, 3-CH_2, $C(CH_3)$), 3.45−3.53 (m, 1.2H, 1-CH_2), 3.55−3.63 (m, 0.8H, 1-CH_2), 4.10 (s, 1.2H, $N_{Pyr}CH_3$), 4.11 (s, 1.8H, $N_{Pyr}CH_3$), 7.37−7.47 (m, 1H, H-6), 7.51−7.60 (m, 1H, H-5), 7.92−8.00 (m, 1H, H-4), 8.00−8.08 (m, 1H, H-7).	(101 MHz, $CDCl_3$), δ, ppm: (mixture of rotamers) 21.2 (CH_3), 22.0 (CH_3), 24.4 (CH_3), 24.5 (CH_3), 25.7 (CH_2), 25.9 (CH_2), 26.0 (CH_2), 26.9 (CH_2), 33.3 (CH_3), 34.1 (CH_3), 34.2 (CH_3), 36.2 (CH_3), 47.1 (CH_2), 50.5 (CH_2), 99.3 (C), 113.9 (CH), 114.0 (CH), 119.8 (CH), 122.1 (CH), 122.2 (CH), 125.5 (CH), 125.7 (CH), 128.8 (C), 145.2 (C), 145.2 (C), 145.7 (C), 145.8 (C), 146.5 (C), 146.9 (C), 147.0 (C), 149.8 (C), 150.0 (C), 170.5 (C), 170.6 (C).	**HRMS** (ESI) Calculated for $C_{19}H_{22}N_6O$ (M + H^+): 351.1929, Found: 351.1928.
Yield 87% (152 mg, 0.43 mmol), white powder (mp 97−98 °C).					
3.12	*N-Methyl-N-(3-(3-methyl-3H-benzo[4,5]imidazo-[1,2-c]pyrazolo[4,3-e][1,2,3]triazin-1-yl)propyl)nitrous amide* 	Neat film 1652, 1527, 1447 (C=N, C=C, N=O), 1280 (N=O), 1333 (N-=O), 1038 (N−N), 1129 (C−N).	(300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): (mixture of rotamers) 2.22−2.35 (m, 0.4H, 2-CH_2), 2.45−2.63 (m, 1.6H, 2-CH_2), 3.14 (s, 2.4H, $NNO(CH_3)$), 3.20−3.26 (m, 0.4H, 3-CH_2), 3.28−3.38 (m, 1.6H, 3-CH_2), 3.75−3.83 (m, 0.4H, 1-CH_2), 3.85 (s, 0.6H, $NNO(CH_3)$), 4.32−4.41 (m, 1.6H, 1-CH_2), 4.38 (s, 3H, $N_{Pyr}CH_3$), 7.52−7.60 (m, 1H, H-6), 7.60−7.69 (m, 1H, H-5), 7.94−8.00 (m, 1H, H-4), 8.33−8.40 (m, 1H, H-7).	(75 MHz, $CDCl_3$), δ, ppm: (mixture of rotamers) 24.2 (CH_2), 25.3 (CH_2), 25.8 (CH_2), 26.5 (CH_2), 31.4 (CH_3), 35.5 (CH_3), 38.9 (CH_3), 44.0 (CH_2), 53.1 (CH_2), 101.2 (C), 111.9 (CH), 120.0 (CH), 123.7 (CH), 127.2 (CH), 128.8 (C), 136.7 (C), 142.6 (C), 144.2 (C), 145.1 (C),145.3 (C).	**HRMS** (ESI) Calculated for $C_{15}H_{17}N_8O$ (M + H^+): 325.1525, Found: 325.1529
Yield 137 mg (0.42 mmol, 85%), bright yellow powder (mp 163−164 °C).					
3.13	*N-(3-(4-(Benzo[d]thiazol-2-*	Neat film 1538 (C=N,	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): (mixture of rotamers) 1.93−2.04 (m,	(101 MHz, $CDCl_3$), δ, ppm: (mixture of rotamers) 24.8 (CH_2), 25.3 (CH_2),	**MS** (ESI) m/z: $[M+ H]^+$ Found

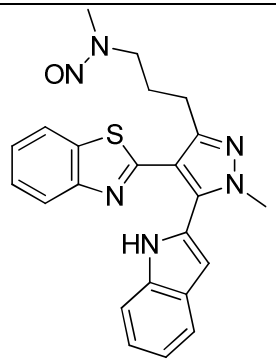
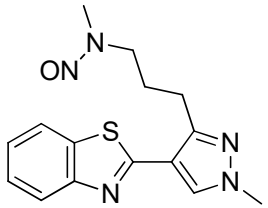
	yl)-5-iodo-1-methyl-1Hpyrazol-3-yl)propyl)-N-methylnitrous amide 	C=C), 1450, 1435 (N=O),1332 (N=O), 1040 (N−N), 1144 (C−N).	0.4H, 2-CH_2), 2.15−2.28 (m, 1.6H, 2-CH_2), 3.01−3.06 (m, 0.4H, 3-CH_2), 3.08 (s, 2.4H, NNO(CH_3)), 3.11−3.17 (m, 1.6H, 3-CH_2), 3.70−3.76 (m, 0.4H, 1-CH_2), 3.78 (s, 0.6H, NNO(CH_3)), 4.00 (s, 0.6H, $N_{Pyr}CH_3$), 4.01 (s, 2.4H, $N_{Pyr}CH_3$), 4.25−4.31 (m, 1.6H, 1-CH_2), 7.41 (ddd, J = 8.3, 7.3, 1.2, 1H, H-6), 7.51 (ddd, *J* = 8.3, 7.2, 1.3, 1H, H-5), 7.93 (ddd, *J* = 7.9, 1.1, 0.6, 1H, H-7), 8.04 (ddd, *J* = 8.2, 1.1, 0.6 Hz, 0.8H, H-4), 8.08 (ddd, J = 8.2, 1.1, 0.6, 0.2H,H-4).	25.7 (CH_2), 27.2 (CH_2), 31.4 (CH_3), 39.1 (CH_3), 40.51 (CH_3), 40.53 (CH_3), 44.5 (CH_2), 53.5 (CH_2), 86.7 (C), 120.2 (C), 121.3 (CH), 122.8 (CH), 125.0 (CH), 126.2 (CH), 134.3 (C), 152.3 (C), 153.0 (C), 159.0 (C).	for $C_{15}H_{17}IN_5OS$: 442.55. **Found, %**: C 40.95; H 3.29; N 15.87. $C_{15}H_{16}IN_5OS$. **Calculated, %**: C 40.83; H 3.65; N 15.87.
Yield 168 mg (0.38 mmol, 38%), light orange powder (mp 104−105 °C).					
3.14a	*3-(4-(Benzo[d]thiazol-2-yl)-5-iodo-1-methyl-1H-pyrazol-3-yl)-N-methylpropan-1-amine* 	Neat film 3394 (NHν), 1537 (C=C, C=N).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.95 (quint, *J* = 7.3, 2H, 2-CH_2), 2.44 (s, 3H, NHC$\underline{H_3}$), 2.69 (t, *J* = 6.9, 2H, 1-CH_2), 3.11 (t, *J* = 7.5, 2H, 3-CH_2), 4.01 (s, 3H, $N_{Pyr}CH_3$), 7.35−7.46 (m, 1H, H-6), 7.48−7.55 (m, 1H, H-5), 7.93 (d, *J* = 7.9, 1H, H-7), 8.07 (d, *J* = 8.0, 1H, H-4)	(101 MHz, $CDCl_3$), δ, ppm: 25.4 (CH_2), 28.8 (CH_2), 36.1 (CH_3), 40.5 (CH_3), 51.2 (CH_2), 86.5 (C, C-I), 120.1 (C), 121.3 (CH), 122.8 (CH), 124.9 (CH), 126.1 (CH), 134.5 (C), 153.0 (C), 153.3 (C), 159.5 (C).	**HRMS** (ESI) Calculated for $C_{15}H_{18}N_4SI$ (M + H^+): 413.0297, Found: 413.0297.
Yield 247 mg (0.6 mmol, 30%), white powder (mp 104−105 °C).					
3.15	*tert-Butyl (3-(4-(Benzo[d]thiazol-2-yl)-5-iodo-1-methyl-1H-pyrazol-3-yl)propyl)(methyl)ca*	Neat film 1690 (C=O), 1519 (C=C, C=N), 1030, 1250 (C−O).	1H NMR (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.42 (s, 9H, 3CH_3), 1.86−2.04 (m, 2H, 2-CH_2), 2.86 (s, 3H, $N_{Pr}CH_3$), 2.98−3.11 (m, 2H, 3-CH_2), 3.23−3.41 (m, 2H, 1-CH_2), 4.01 (s, 3H, $N_{Pyr}CH_3$), 7.40 (t, *J* = 7.5, 1H, H-6),	(101 MHz, $CDCl_3$), δ, ppm: 25.5 (CH_2), 27.2 (CH_2), 28.4 (3CH_3), 34.1 (CH_3), 40.4 (CH_3), 48.7 (CH_2), 79.1 (C), 86.6 (C), 120.0 (C), 121.2 (CH), 122.9 (CH), 124.9 (CH), 126.1 (CH), 134.5 (C), 153.0 (C), 153.4 (C), 155.8	**HRMS** (ESI) Calculated for $C_{20}H_{26}IN_4O_2S$ (M + H^+): 513.0821, Found:

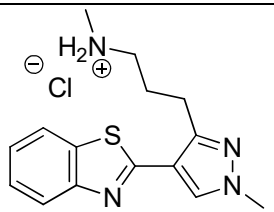
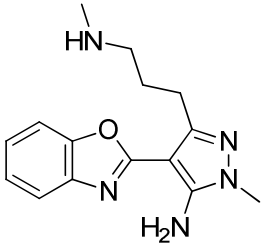
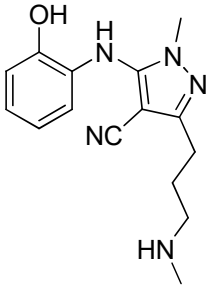
	rbamate 		7.51(t, *J* = 7.6, 1H, H-5), 7.93 (d, *J* = 7.9, 1H, H-7), 8.08 (d, *J* = 8.1, 1H, H-4).	(C), 159.3 (C).	513.0817.
Yield 179 mg (0.35 mmol, 70%), white powder (mp 122 °C).					
3.16a	*3-(4-(Benzo[d]thiazol-2-yl)-5-(4-methoxyphenyl)-1-methyl-1H-pyrazol-3-yl)-N-methylpropan-1-amine* 	Neat film 3303 (NHν), 1519 (C=C, C=N), 1249 (C−O)	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.81 (s, 1H, NH), 2.01 (quint, *J* = 7.0, 2H, 2-CH_2), 2.44 (s, 3H, $N_{Pr}CH_3$), 2.73 (t, *J* = 6.9, 2H, 1-CH_2), 3.11−3.26 (m, 2H, 3-CH_2), 3.69 (s, 3H, $N_{Pyr}CH_3$), 3.90 (s, 3H, OCH_3), 7.01−7.08 (m, 2H, H_{Ar}-3,5), 7.24 (ddd, *J* = 8.3, 7.3, 1.1, 1H, H-6), 7.29−7.35 (m, 2H, H_{Ar}-2,6), 7.39 (ddd, *J* = 8.3, 7.2, 1.2, 1H, H-5), 7.66 (ddd, *J* = 7.9, 1.1, 0.6, 1H, H-7), 7.92−7.98 (m, 1H, ddd, *J* = 8.0, 1.1, 0.6, 1H, H-4).	(101 MHz, $CDCl_3$), δ, ppm: 25.5 (CH_2), 29.1 (CH_2), 36.3 (CH_3), 36.8 (CH_3), 51.6 (CH_2), 55.4 (CH_3), 113.7 (C), 114.6 (CH), 121.0 (CH), 121.1 (C), 122.3 (CH), 124.2 (CH), 125.7 (CH), 131.9 (2CH), 134.4 (C), 143.8 (C), 151.4 (C), 153.2 (C), 160.9 (C), 161.1 (C).	**HRMS** (ESI) Calculated for $C_{22}H_{25}N_4OS$ (M + H^+): 393.1749, Found: 393.1743.
Elution system for column chromatography: CH_2Cl_2−CH_3OH–Et_3N, 8:1:1. Yield 41 mg (0.11 mmol, 70%), yellowish powder (mp 96−97 °C).					
3.16b	*tert-Butyl (3-(4-(Benzo[d]thiazol-2-yl)-5-(4-methoxyphenyl)-1-methyl-1H-pyrazol-3-yl)propyl)(methyl)-*	Neat film 1691 (C=O), 1519 (C=C, C=N), 1251 (C−O).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.45 (s, 9H, 3CH_3), 1.95−2.13 (m, 2H, 2-CH_2), 2.92 (s, 3H, $N_{Pr}CH_3$), 3.09−3.21 (m, 2H, 3-CH_2), 3.34−3.47 (m, 2H, 1-CH_2), 3.70 (s, 3H, $N_{Pyr}CH_3$), 3.93 (s, 3H, OCH_3), 7.04−7.10 (m, 2H, H_{Ar}-3,5), 7.27 (ddd,	(101 MHz, $CDCl_3$), δ, ppm: 25.5 (CH_2), 27.4 (CH_2), 28.5 (3CH_3), 34.0 (CH_3), 36.8 (CH_3), 48.9 (CH_2), 55.4 (CH_3), 79.0 (C), 113.5 (C), 114.6 (2CH), 120.96 (CH), 121.04 (C), 122.5 (CH), 124.3 (CH), 125.7 (CH), 131.9 (2CH), 134.4 (C), 143.9 (C),	**HRMS** (ESI) Calculated for $C_{27}H_{33}N_4O_3S$ (M + H^+): 493.2273, Found: 493.2273.

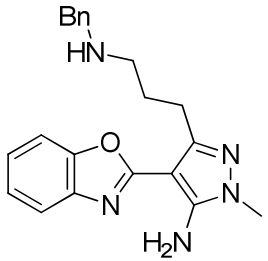
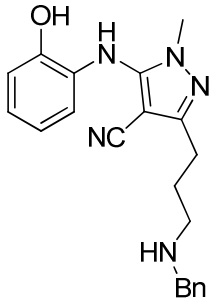
	carbamate 		*J* = 8.3, 7.2, 1.2, 1H, H-6), 7.31−7.36 (m, 2H, H_{Ar}-2,6), 7.41 (ddd, *J* = 8.3, 7.2, 1.2, 1H, H-5), 7.69 (ddd, *J* = 8.0, 1.2, 0.6, 1H, H-7), 7.97 (d, *J* = 8.0, 1H, H-4).	151.3 (C), 153.2 (C), 155.9 (C), 160.9 (C), 161.0 (C).	
Elution system for column chromatography: CHA−EtOAc, 6:4. Yield 72 mg (0.15 mmol, 98%), yellowish powder (mp 116 °C).					
3.16c	*N-(3-(4-(Benzo[d]thiazol-2-yl)-5-(4-methoxyphenyl)-1-methyl-1H-pyrazol-3-yl)propyl)-N-methylnitrous amide* 	Neat film 1519 (C=N, C=C), 1451 (N=O), 1333(N=O), 1029, 1249 (C−O), 1175 (C−N).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): (mixture of rotamers) 2.03−2.13 (m, 0.4H, 2-CH_2), 2.24−2.35 (m,1.6H, 2-CH_2), 3.09−3.17 (m, 0.4H, 3-CH_2), 3.13 (s, 2.4H, $N_{Pr}CH_3$), 3.19−3.30 (m,1.6H, 3-CH_2), 3.69 (s, 0.6H, $N_{Pyr}CH_3$), 3.70 (s, 2.4H, $N_{Pyr}CH_3$), 3.78−3.86 (m, 0.4H, 1-CH_2), 3.83 (s, 0.6H, $N_{Pr}CH_3$), 3.93 (s, 0.6H, OCH_3), 3.94 (s, 2.4H, OCH_3), 4.36 (t, *J* = 7.2, 1.6H, 1-CH_2), 7.06−7.11 (m, 2H, H_{Ar}-3,5), 7.27 (ddd, *J* = 8.0, 7.6, 1.1, 1H, H-6), 7.31−7.37 (m, 2H, H_{Ar}-2,6), 7.42 (ddd, *J* = 8.3, 7.3, 1.2, 1H, H-5), 7.68 (ddd, *J* = 8.0, 1.4, 0.6, 1H, H-7), 7.95 (ddd, *J* = 8.2, 1.3, 0.6, 0.8H, H-4), 7.98 (ddd, *J* = 8.2, 1.3, 0.6, 0.2H, H-4).	(101 MHz, $CDCl_3$), δ, ppm: (the signals of dominating rotamer are only mentioned) 25.3 (CH_2), 27.4 (CH_2), 31.4 (CH_3), 36.8 (CH_3), 53.8 (CH_3), 55.4 (CH_2), 113.7 (C), 114.7 (2CH), 120.8 (C), 121.0 (CH), 122.4 (CH), 124.4 (CH), 125.8 (CH), 131.9 (2CH), 134.3 (C), 144.1 (C), 150.2 (C), 153.1 (C), 160.9 (C), 161.0 (C).	**HRMS** (ESI) Calculated for $C_{22}H_{24}N_5O_2S$ (M + H^+): 422.1651, Found: 422.1652.
Elution system for column chromatography: gradient CH_2Cl_2−acetone, 19:1 to CH_2Cl_2−acetone, 9:1. Yield 62 mg (0.15 mmol, 98%), light orange powder (mp 140 °C).					
3.17	*tert-Butyl (3-(5-([1,1´-Biphenyl]-4-yl)-4-(benzo[d]-*	Neat film 1688 (C=O), 1522 (C=C,	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.46 (s, 9H, 3CH_3), 2.00−2.12 (m, 2H, 2-CH_2), 2.93 (s, 3H, $N_{Pr}CH_3$),	(101 MHz, $CDCl_3$), δ, ppm: 25.4 (CH_2), 27.4 (CH_2), 28.5 (3CH_3), 34.0 (CH_3), 37.0 (CH_3), 48.9 (CH_2), 79.0	**HRMS** (ESI) Calculated for $C_{32}H_{35}N_4O_2S$ (M

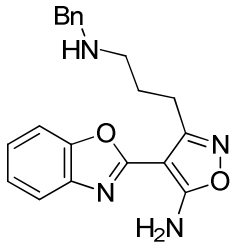
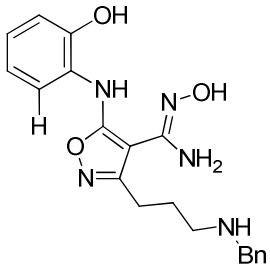
	thiazol-2-yl)-1-methyl-1H-pyrazol-3-yl)propyl)(methyl)-carbamate 	C=N), 1245 (C−O).	3.07−3.23 (m, 2H, 3-CH_2), 3.34−3.50 (m, 2H, 2-CH_2), 3.77 (s, 3H, $N_{Pyr}CH_3$), 7.27 (ddd, *J* = 8.0, 7.6, 1.1, 1H, H_{Het}-6), 7.39 – 7.47 (m, 1H, H_{Ar}-4´), 7.42 (ddd, *J* = 8.3, 7.2, 1.2, 1H, H_{Het}-5), 7.47–7.55 (m, 4H, H_{Ar}-2´,3´,5´,6´), 7.69 (ddd, *J* = 8.0, 1.3, 0.6, 1H, H_{Het}-7), 7.68–7.76 (m, 2H, H_{Ar}-3,5), 7.75–7.82 (m, 2H, H_{Ar}-2,6), 8.00 (d, *J* = 8.1, 1H, H_{Het}-4).	(C), 113.6 (C), 121.0 (CH), 122.6 (CH), 124.4 (CH), 125.8 (CH), 127.1 (2CH), 127.7 (2CH), 127.9 (C), 128.0 (CH), 129.0 (2CH), 130.9 (2CH), 134.5 (C), 140.0 (C), 142.7 (C), 143.7 (C), 151.4 (C), 153.2 (C), 155.9 (C), 160.7 (C).	+ H^+): 539.2481, Found: 539.2485.
Elution system for column chromatography: gradient CH_2Cl_2−acetone, 19:1 to CH_2Cl_2−acetone, 23:2. Yield 78 mg (0.15 mmol, 97%), yellowish powder (mp 124−125 °C).					
3.18	*tert-Butyl (3-(4-(Benzo[d]thiazol-2-yl)-5-(3,5-bis-(trifluoromethyl)phenyl)-1-methyl-1H-pyrazol-3-yl)propyl)-(methyl)carbamate* 	Neat film 1689 (C=O), 1522 (C=C, C=N), 1248 (C−O).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.46 (s, 9H, 3CH_3), 1.97−2.12 (m, 2H, 2-CH_2), 2.91 (s, 3H, $N_{Pr}CH_3$), 3.01−3.16 (m, 2H, 3-CH_2), 3.34−3.49 (m, 2H, 3-CH_2), 3.78 (s, 3H, $N_{Pyr}CH_3$), 7.33 (ddd, *J* = 8.3, 7.3, 1.2, 1H, H_{Het}-6), 7.45 (ddd, *J* = 8.3, 7.3, 1.2, 1H, H_{Het}-5), 7.77 (ddd, *J* = 8.1, 1.2, 0.6, 1H, H_{Het}-7), 7.93 (ddd, *J* = 8.2, 1.3, 0.5, 1H, H_{Het}-4), 8.01 (s, 2H, H_{Ar}-2,6), 8.06 (s, 1H, H_{Ar}-4). **^{19}F NMR** (376 MHz, $CDCl_3$)), δ, ppm: −62.88.	(101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 25.3 (CH_2), 27.3 (CH_2), 28.5 (3CH_3), 34.1 (CH_3), 37.3 (CH_3), 48.8 (CH_2), 79.1 (C), 114.3 (C), 122.9 (q, *J* = 272.8, 2CF_3), 121.1 (CH), 122.8 (CH), 123.5 (CH), 124.9 (CH), 126.2 (CH), 127.0 (C), 131.1 (2CH), 131.5 (C), 132.2 (q, *J* = 33.7, 2<u>C</u>CF_3), 134.3 (C), 140.3 (C), 151.5 (C), 153.0 (C), 155.8 (C), 159.0 (C).	**MS** (ESI) m/z: [M + H^+] Found for $C_{28}H_{29}F_6N_4O_2S$: 599.13. **Found, %:** C 56.12; H 4.35; N 9.19. $C_{28}H_{28}F_6N_4O_2S$. **Calculated, %:** C 56.18; H 4.71; N 9.36.
Elution system for column chromatography: gradient CH_2Cl_2−acetone, 19:1 to CH_2Cl_2−acetone, 23:2.Yield 81 mg (0.14 mmol, 90%), white powder					

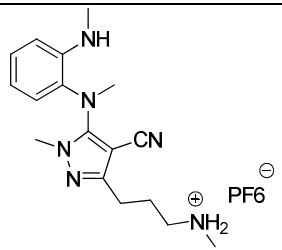
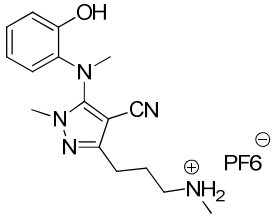
(mp 126 °C).					
3.19	*(E)-tert-Butyl (3-(4-(Benzo[d]thiazol-2-yl)-1-methyl-5-styryl-1H-pyrazol-3-yl)propyl)(methyl)carbamate* 	Neat film 1684 (C=O), 1542 (C=C, C=N), 1244 (C−O).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.44 (s, 9H, 3-CH_3), 1.88−2.07 (m, 2H, 2-CH_2), 2.88 (s, 3H, $N_{Pr}CH_3$), 2.97−3.13 (m, 2H, 3-CH_2), 3.30−3.44 (m, 2H, 1-CH_2), 4.01 (s, 3H, $N_{Pyr}CH_3$), 7.04 (d, *J* = 16.7, 1H, CH-1), 7.34 (d, *J* = 16.6, 1H, CH-2), 7.33−7.40 (m, 2H, H_{Het}-6, H_{Ar} –4), 7.40−7.46 (m, 2H, H_{Ar}-3,5), 7.49 (ddd, J = 8.3, 7.2, 1.2, 1H, H_{Het}-5), 7.53−7.57 (m, 2H, H_{Ar}-2,6), 7.87 (ddd, *J* = 7.9, 1.3, 0.7, 1H, H_{Het}-7), 7.98−8.11 (m, 1H, H_{Het}-4).	^{13}C (101 MHz, $CDCl_3$), δ, ppm: 25.1 (CH_2), 27.0 (CH_2), 28.5 (3CH_3), 34.1 (CH_3), 37.9 (CH_3), 48.8 (CH_2), 79.1 (C), 113.2 (C), 115.2 (CH), 121.2 (CH), 122.8 (CH), 124.6 (CH), 126.0 (CH), 126.9 (2CH), 128.9 (2CH), 134.7 (C), 136.2 (C), 137.0 (CH), 140.5 (C), 150.9 (C), 153.4 (C), 155.8 (C), 160.5 (C).	**HRMS** (ESI) Calculated for $C_{28}H_{33}N_4O_2S$ (M + H^+): 489.2324, Found: 489.2322.
Elution system for column chromatography: gradient CH_2Cl_2−acetone, 19:1 to CH_2Cl_2−acetone, 23:2. Yield 53 mg (0.11 mmol, 72%), orange powder (mp 105−106 °C).					
3.20	*N-(3-(4-(Benzo[d]thiazol-2-yl)-5-(1H-indol-2-yl)-1-methyl-1H-pyrazol-3-yl)propyl)-N-methylnitrous amide*	Neat film 3185 (NHν), 1532 (C=N, C=C), 1454, 1427 (N=O, C−H), 1333 (N=O).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): (mixture of rotamers) 2.05 (quint, *J* = 7.6, 0.4H, 2-CH_2), 2.28 (quint, *J* = 7.3, 1.6H, 2-CH_2), 2.99−3.05 (m, 0.4H, 3-CH_2), 3.09 (s, 2.4H, $N_{Pr}CH_3$), 3.10−3.15 (m, 1.6H, 3-CH_2), 3.74−3.79 (m, 0.4H, 1-CH_2), 3.80 (s, 0.6H, $N_{Pr}CH_3$), 4.10 (s, 2.4H, $N_{Pyr}CH_3$), 4.11 (s, 0.6H, $N_{Pyr}CH_3$), 4.32 (t, *J* = 7.1, 1.6H, 1-CH_2), 6.81 – 6.86 (m, 1H, H_{Ind}-3), 7.19 (ddd, *J* = 7.8, 7.5, 0.9, 1H, H_{Ind}-7), 7.30 (ddd, *J* = 8.1, 7.6, 1.0, 1H, H_{Ind}-5), 7.40 (ddd, *J* = 8.2, 7.6, 1.0, 1H, H_{Het}-6), 7.53 (ddd, *J* = 8.2, 7.6, 1.1, 1H, H_{Het}-5),	(101 MHz, $CDCl_3$), δ, ppm: (the signals of dominating rotamer are only mentioned) 25.0 (CH_2), 27.2 (CH_2), 31.5 (CH_3), 39.0 (CH_3), 53.5 (CH_2), 104.9 (CH), 111.7 (CH), 113.0 (C), 120.4 (CH), 120.9 (CH), 121.4 (CH), 122.2 (CH), 123.3 (CH), 125.2 (CH), 125.6 (C), 126.5 (CH), 128.0 (C), 134.6 (C), 136.2 (C), 136.3 (C), 149.6 (C), 152.2 (C), 161.0 (C).	**HRMS** (ESI) Calculated for $C_{23}H_{23}N_6OS$ (M + H^+): 431.1648, Found: 431.1650.

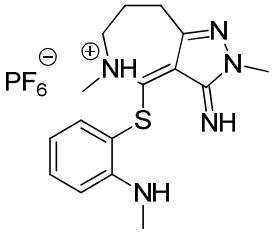
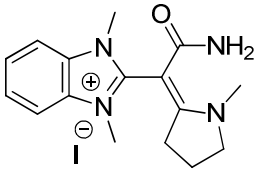
			7.55 (d, 8.3, 1H, H_{Ind}-4), 7.72 (d, *J* = 7.8, 1H, H_{Ind}-7), 7.85 (d, *J* = 7.8, 1H, H_{Het}-7), 8.10 (d, *J* = 8.0, 1H, H_{Het}-4), 11.67 (s, 0.8H, NH), 11.84 (s, 0.2H, NH).		
Yield 15 mg (0.4 mmol, 24%), light yellow powder (mp 178 °C). Elution system for column chromatography: gradient CH_2Cl_2, 100% to CH_2Cl_2−acetone, 93:7.					
3.21	*N-(3-(4-(Benzo[d]thiazol-2-yl)-1-methyl-1H-pyrazol-3-yl)propyl)-N-methylnitrous amide* 	Neat film 1566, 1556 (O=N, C=C, C=N), 1425 (N=O), 1331 (N=O), 1038 (N−N), 1140 (C−N).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): (mixture of rotamers) 2.03 (quint, *J* = 7.6, 0.4H, 2-CH_2), 2.25 (quint, *J* = 7.5, 1.6 H, 2-CH_2), 3.03 (t, *J* = 7.5, 0.4 H, 3-CH_2), 3.11 (s, 2.4 H, $N_{Pr}CH_3$), 3.13 (t, *J* = 7.5, 1.6 H, 3-CH_2), 3.76 (t, *J* = 7.4, 0.4 H, 1-CH_2), 3.79 (s, 0.6 H, $N_{Pr}CH_3$), 3.90 (s, 0.6 H, $N_{Pyr}CH_3$), 3.91 (s, 2.4 H, $N_{Pyr}CH_3$), 4.31 (t, *J* = 7.2, 1.6 H, 1-CH_2), 7.31−7.37 (m, 1H, H-6), 7.43−7.50 (m, 1H, H-5), 7.84 (d, *J* = 8.0, 1H, H-7), 7.88 (s, 1H, H_{Pyr}-5), 7.93−8.00 (m, 1H, H-4).	(101 MHz, $CDCl_3$), δ, ppm: (mixture of rotamers) 24.88 (CH_2), 24.92 (CH_2), 25.4 (CH_2), 27.3 (CH_2), 30.3 (CH_3), 31.5 (CH_3), 39.1 (CH_3), 44.5 (CH_2), 53.6 (CH_2), 115.1 (C), 121.3 (CH), 121.48 (CH), 121.5 (CH), 124.64 (CH), 124.67 (CH), 126.2 (CH), 131.64 (CH), 131.71 (CH), 134.01 (C), 134.06 (C), 150.25 (C), 150.32 (C), 153.79 (C), 153.82 (C), 160.04 (C), 160.08 (C).	**HRMS** (ESI) Calculated for $C_{15}H_{18}N_5OS$ (M + H^+): 316.1232, Found: 316.1231.
Yield 290 mg (0.92 mmol, 92%), white powder (mp 72−73 °C).					
3.22	*3-(4-(Benzo[d]thiazol-2-yl)-1-methyl-1H-pyrazol-3-yl)-N-methylpropan-1-aminium chloride*	Neat film 3431 (NH_2ν), 1603, 1559, 1529 (C=C, C=N, NH_2δ).	(400 MHz, CD_3OD), δ, ppm (*J*, Hz): 2.23 (quint, *J* = 7.3, 2H, 2-CH_2), 2.73 (s, 3H, $N_{Pr}CH_3$), 3.10−3.21 (m, 4H, 1,3-CH_2), 3.98 (s, 3H, $N_{Pyr}CH_3$), 7.52 (t, *J* = 7.7, 1H, Het H), 7.62 (t, J = 7.7, 1H, Het H), 8.00 (d, *J* = 8.2, 1H, Het H), 8.07 (d, *J* = 8.1, 1H, Het H), 8.44 (s, 1H, H_{Pyr}-5).	(101 MHz, CD_3OD), δ, ppm: 24.0 (CH_2), 24.4 (CH_2), 32.2 (CH_3), 38.1 (CH_3), 48.4 (CH_2), 112.3 (C), 119.8 (CH), 122.1 (CH), 125.8 (CH), 127.4 (CH), 132.0 (C), 133.5 (CH), 148.5 (C), 150.1 (C), 162.8 (C).	**HRMS** (ESI) Calculated for $C_{15}H_{19}N_4S$ (M + H^+): 287.1330, Found: 287.1337.

					
Yield 157 mg (0.485 mmol, 97%), white powder (mp 152−153 °C).					
3.23a	*4-(Benzo[d]oxazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine* 	Neat film 3310 (NHν, NH_2ν), 1625 (NH_2δ), 1580 (NHδ, C=C, C=N), 1065 (C-O).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.90 (quint, *J* = 7.2, 2H, 2-CH_2), 2.40 (s, 3H, $N_{Pr}CH_3$), 2.74 (t, *J* = 7.4, 1-CH_2), 2.86 (t, *J* = 7.5, 2H, 3-CH_2), 3.59 (s, 3H, $N_{Pyr}CH_3$), 6.55 (s, 2H, NH_2), 7.26 (dd, *J* = 7.7, 1.4, 1H, Het H), 7.30 (dd, *J* = 7.6, 1.4, 1H, Het H), 7.61 (dd, *J* = 7.6, 1.4, 1H, Het H), 7.64 (dd, *J* = 7.6, 1.4, 1H, Het H).	(101 MHz, DMSO-d_6), δ, ppm: 22.2 (CH_2), 25.9 (CH_2), 26.6 (CH_3), 34.6 (CH_3), 50.1 (CH_2), 88.9 (C), 110.5 (CH), 118.2 (CH), 123.5 (CH), 124.7 (CH), 141.8 (C), 148.9 (C), 149.0 (C), 149.7 (C), 160.9 (C).	**HRMS** (ESI) Calculated for $C_{15}H_{20}N_5O$ (M + H^+) 286.1668, Found 286.1661.
Isomers **3.23a** and **3.24a** were separated by column chromatography (elution system: $CHCl_3$–CH_3OH–Et_3N (20:2:1), R_f **2.23a** = 0.43, R_f **2.24a** = 0.29). Yield 80 mg (0.28 mmol, 28%), white powder (mp 143–144 °C).					
3.24a	*5-((2-Hydroxyphenyl)amino)-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazole-4-carbonitrile* 	Neat film 3352 (NHν, OHν), 2218 (C≡N), 1564 (NHδ, C=C, C=N), 1280 (C–O).	(300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.90 (quint, *J* = 7.5, 2H, 2-CH_2), 2.44 (s, 3H, $N_{Pr}CH_3$), 2.57 (t, *J* = 7.6, 2H, 1-CH_2), 2.79 (t, *J* = 7.6, 2H, 3-CH_2), 3.62 (s, 3H, $N_{Pyr}CH_3$), 6.70 (ddd, *J* = 7.0, 7.3, 2.0, 1H, H-5), 6.79 (d, *J* = 7.9, 1H, H-6), 6.84 (ddd, *J* = 6.8, 6.8, 1.4, 1H, H-4), 6.89 (dd, *J* = 7.8, 1.7, 1H, H-3), 8.09 (s, 1H, NH).	(101 MHz, DMSO-d_6), δ, ppm: 24.8 (CH_2), 25.5 (CH_2), 33.7 (CH_3), 35.8 (CH_3), 49.0 (CH_2), 79.2 (C), 114.4 (C), 116.1 (CH), 119.6 (CH), 120.4 (CH), 123.8 (CH), 129.3 (C), 148.2 (C), 149.1 (C), 152.6 (C).	**HRMS** (ESI) Calculated for $C_{15}H_{20}N_5O$ (M + H^+) 286.1668, Found 286.1667.

Yield 57 mg (0.20 mmol, 20 %), white powder (mp 140-141 °C).					
3.23b	*4-(benzo[d]oxazol-2-yl)-3-(3-(benzylamino)propyl)-1-methyl-1H-pyrazol-5-amine* 	Neat film 3300 (NHν, NH_2ν), 1623 (NH_2δ), 1578 (C=C, C=N), 1064 (C–O).	(300 MHz,$CDCl_3$), δ, ppm (*J*, Hz): 2.03 (quint, *J* = 7.2, 2H, 2-CH_2), 2.83 (t, *J* = 7.0, 2H, 1-CH_2), 3.03 (t, *J* = 7.5, 2H, 3-CH_2), 3.64 (s, 3H, NCH_3), 3.85 (s, 2H, $N_{Bn}CH_2$), 5.42 (s, 2H, NH_2), 7.19–7.25 (m, 1H, H-6), 7.25–7.36 (m, 6H, Ph H, H-5), 7.43 (d, *J* = 7.5, 1H, H-7), 7.60 (d, *J* = 7.9, 1H, H-4).	**^{13}C** (75 MHz, $CDCl_3$), δ, ppm: 26.0 (CH_2), 28.8 (CH_2), 33.9 (CH_2), 48.9 (CH_2), 53.6 (CH_2), 91.0 (C), 109.9 (CH), 118.1 (CH), 123.1 (CH), 124.1 (CH), 126.9 (CH), 128.2 (2CH), 128.4 (2CH), 140.1 (C), 141.6 (C), 148.2 (C), 149.2 (C), 150.2 (C), 160.6 (C).	**HRMS** (ESI) Calculated for $C_{21}H_{24}N_5O$ (M + H^+) 362.1981, Found: 362.1974.
Isomers **3.23b** and **3.24b** were separated by column chromatography (elution system: gradient acetone–$CHCl_3$, 5:1) to acetone 100%, R_f **3.23b** = 0.3, R_f **3.24b** = 0.2. Further trituration of the obtained oil with minimal quantity of acetone induces its consolidation. Yield 127 mg (0.35 mmol, 35 %), white powder (mp 129–131 °C).					
3.24b	*3-(3-(Benzylamino)propyl)-5-((2-hydroxyphenyl)amino)-1-methyl-1H-pyrazole-4-carbonitrile* 	Neat film 3286 (NHν, OHν), 2216 (C≡N), 1559 (NHδ, C=C, C=N), 1255, 1279 (C-O).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.76 (quint, *J* = 7.1, 2H, 2-CH_2), 2.53 (t, *J* = 7.1, 2H,1-CH_2), 2.55 (t, *J* = 7.5, 2H, 3-CH_2), 3.59 (s, 3H, $N_{Pyr}CH_3$), 3.68 (s, 2H, $N_{Bn}CH_2$), 6.67–6.76 (m, 2H, H-3,4), 6.81–6.88 (m, 2H, H-5,6), 7.18–7.24 (m, 1H, H_{Bn}-4), 7.26-7.36 (m, 4H, H_{Bn}-2,3,5,6), 7.89 (s, 1H, NH), 9.66 (s, 1H, OH). Signals of δ_H 7.89 and 9.66 ppm disappear upon D_2O addition.	(101 MHz, DMSO-d_6), δ, ppm: 25.5 (CH_2), 28.6 (CH_2), 35.7 (CH_3), 48.5 (CH_2), 53.3 (CH_2), 79.7 (C), 114.6 (C), 115.9 (CH), 119.7 (CH), 119.8 (CH), 123.5 (CH), 126.9 (CH), 128.3 (2CH), 128.5 (2CH), 129.5 (C), 141.4 (C), 147.9 (C), 148.7 (C), 153.6 (C).	**HRMS** (ESI) Calculated for $C_{21}H_{24}N_5O$ (M + H^+) 362.1981, Found: 362.1973.
Yield 116 mg (0.32 mmol, 32 %), white powder (mp 131–132 °C).					
3.25b	*4-(benzo[d]oxazol-2-yl)-3-(3-*	Neat film 3388, 3289	1H NMR (400 MHz,$CDCl_3$), δ, ppm (*J*, Hz): 2.07 (quint, *J* = 7.2, 2H, 2-	101 MHz, $CDCl_3$), δ, ppm: 24.1 (CH_2), 27.4 (CH_2), 48.5 (CH_2), 53.7	**HRMS** (ESI) Calculated for

	(benzylamino)propyl)isoxazol-5-amine 	(NHν, NH_2ν), 1623 (NH_2δ) 1582 (NHδ, C=C, C=N), 1063, 1041 (C-O).	CH_2), 2.84 (t, *J* = 7.1, 2H, 2-CH_2), 3.06 (t, *J* = 7.5, 2H, 2-CH_2), 3.86 (s, 2H, $N_{Bn}CH_2$), 6.48 (s, 2H, NH_2), 7.23–7.38 (m, 7H, Ar H), 7.45 (d, *J* = 7.8, 1H, H-7), 7.61 (d, *J* = 7.9, 1H, H-4).	(CH_2), 83.3 (C), 110.1 (CH), 118.5 (CH), 123.7 (CH), 124.5 (CH), 127.0 (CH), 128.2 (2CH), 128.4 (2CH), 139.8 (C), 141.2 (C), 149.3 (C), 158.4 (C), 161.8 (C), 169.6 (C).	$C_{20}H_{21}N_4O_2$ (M + H^+) 349.1665, Found: 349.1655.
The mixture of products **3.25b** and **3.26b** were separated by column chromatography (elution system: gradient acetone–$CHCl_3$, 5:2 to acetone 100%). After complete coming out of **3.25b** from the column the polarity of elution system was increased (elution system: acetone–Et_3N–MeOH 20:1:0.2). Yield 94 mg (0.27 mmol, 27 %), white powder (mp 97–99 °C).					
3.26b	*(Z)-3-(3-(benzylamino)propyl)-N'-hydroxy-5-((2-hydroxyphenyl)amino)isoxazole-4-carboximidamide* 	Neat film 3282 (OH, NHν, NH_2 ν), 1638 (NH_2δ), 1536 (NHδ, C=C, C=N), 1250 (C–O).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.80 (quint, *J* = 7.4, 2H, 2-CH_2), 2.55 (m, 2.40–2.60, 2H, 1-CH_2), 2.83 (t, *J* = 7.5, 2H, 3-CH_2), 3.69 (s, 2H, $N_{Bn}CH_2$), 5.75 (s, 2H, NH_2), 6.82 (td, *J* = 7.4, 1.4, 1H, H-5), 6.86 (td, *J* = 7.4, 1.4, 1H, H-4), 7.56 (dd, *J* = 7.9, 1.7, 1H, H-6), 6.91 (dd, *J* = 7.8, 1.5, 1H, H-3), 7.21 (t, *J* = 6.7, 1H, H_{Bn}-4), 7.26–7.37 (m, 4H, H_{Bn}-2,3,5,6), 9.34 (s, 1H), 9.52 (s, 1H), 10.10 (br.s, 1H). Note: the integral intensity of signals at δ_H 5.75, 9.34, 9.52 and 10.10 ppm diminish upon addition of D_2O.	(101 MHz, DMSO-d_6), δ, ppm: 23.5 (CH_2), 27.2 (CH_2), 47.9 (CH_2), 52.9 (CH_2), 88.1 (C), 115.2 (CH), 116.8 (CH), 120.0 (CH), 123.1 (CH), 127.2 (CH), 127.3 (C), 128.6 (2CH), 128.6 (2CH), 140.1 (C), 145.9 (C), 147.7 (C), 161.4 (C), 163.6 (C).	**HRMS** (ESI) Calculated for $C_{20}H_{24}N_5O_3$ (M + H^+) 382.1879, Found: 382.1873.
Yield 88 mg (0.23 mmol, 23 %), white powder (mp 90 °C).					
3.27	*4-cyano-N-methyl-N-(2-(methylamino)phenyl)-3-(3-(methylamino)propyl)-1H-pyrazol-5-aminium iodide*	Neat film 3362, 3166 (NHν, NH_2ν), 2214 (CN), 1591(NH_2δ), 1513 (NHδ, C=C, C=N).	(400 MHz, CD_3CN), δ, ppm (*J*, Hz): 2.07 (quint, *J* = 7.2, 2H, 2-CH_2), 2.62 (s, 3H, $NH_2^+CH_3$), 2.74 (t, *J* = 7.2, 2H, 3-CH_2), 2.81 (s, 3H, NHC$\underline{H_3}$), 3.03 (t, *J* = 7.1, 2H, 1-CH_2), 3.22 (s, 3H, $N_{Ph}CH_3$), 4.74 (s, 1H, NH), 6.66 (ddd, *J* = 7.5, 1.3, 1H, H-5), 6.72 (dd, *J* =	(101 MHz, CD_3CN), δ, ppm: 24.6 (CH_2), 24.5 (CH_2), 30.2 (CH_3), 33.7 (CH_3), 39.7 (CH_3), 49.5 (CH_2), 76.2 (C), 111.6 (CH), 115.1 (C), 117.2 (CH), 128.2 (CH), 130.0 (CH), 131.7 (C), 147.5 (C), 153.1 (C), 156.6 (C).	**HRMS** (ESI) Calculated for $C_{16}H_{23}IN_6^+$ 299.1984, Found: 299.1987.

			8.1, 1.3, 1H, H-3), 7.08 (dd, *J* = 7.5, 1.5, 1H, H-6), 7.23 (ddd, *J* = 8.1, 7.5, 1.5, 1H, H-4).		
Product was purified by recrystallization from acetonitrile. Yield 362 mg (0.85 mmol, 85%), light brown powder (mp 187–188 °C).					
3.28	*3-(4-cyano-5-((2-hydroxyphenyl)(methyl)amino)-1-methyl-1H-pyrazol-3-yl)-N-methylpropan-1-amonium hexafluorophosphate* 	Neat film 3632, 3259 (OH, NH_2), 2220 (CN), 1596(NH_2^+δ), 1553, 1511 (NHδ, C=C, C=N), 1281 (C–O), 839 (P–F).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.88–1.97 (m, 2H, 2-CH_2), 2.58 (s, 3H, $NH_2^+CH_3$), 2.60–2.65 (m, 2H, 3-CH_2), 2.92 – 3.01 (m, 2H, 1-CH_2), 3.24 (s, 3H, $N_{Pyr}CH_3$), 3.31 (s, 3H, $N_{Ph}CH_3$), 6.82 (ddd, *J* = 8.2, 7.6, 1.4, 1H, H-5), 6.88 (dd, *J* = 8.1, 1.4, 1H, H-3), 6.97 (dd, *J* = 7.9, 1.6, 1H, H-6), 7.03 (ddd, *J* = 8.0, 7.3, 1.6, 1H, H-4), 8.31 (s, 2H, NH_2^+), 9.71 (s, 1H, OH). **^{31}P NMR** (162 MHz, DMSO-d_6), δ, ppm (*J*, Hz): δ -144.20 (sept, *J* = 711.2). **^{19}F NMR** (376 MHz, DMSO-d_6), δ, ppm (*J*, Hz): -70.15 (d, *J* = 711.2).	(101 MHz, DMSO-d_6), δ, ppm: 24.4 (CH_2), 24.5 (CH_2), 33.0 (CH_3), 36.4 (CH_3), 41.2 (CH_3), 48.3 (CH_2), 80.7 (C), 115.1 (C), 117.0 (CH), 120.2 (CH), 124.4 (CH), 126.7 (CH), 133.6 (C), 151.6 (C), 152.1 (C), 152.9 (C).	**HRMS** (ESI) Calculated for $C_{16}H_{22}N_5O^+$ 300.1824, Found: 300.1826; Calculated for PF_6^-144.9642, Found: 144.9646.
Products were purified by automatic column chromatography (elution system: gradient $CH_3OH–CH_2Cl_2$, 1:19 to $CH_3OH–CH_2Cl_2$, 1:9). Yield 392 mg (0.88 mmol, 88%), white powder (mp 165–166 °C).					

3.30	*3-imino-2,5-dimethyl-4-((2-(methylamino)phenyl)thio)-2,3,5,6,7,8-hexahydropyrazolo[4,3-c]azepin-5-ium hexafluorophosphat* 	Neat film 3424, 3374, 3154 (NHν), 1654, 1610, 1592 (C=N, C=C, NHδ), 832 (P–F).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.09–2.19 (m, 2H, 7-CH_2), 2.74 (d, *J* = 5.0, 3H, $N_{Ph}CH_3$), 2.75–2.80 (m, 2H, 8-CH_2), 3.26 (s, 3H, $N_{Azepine}CH_3$), 3.31–3.38 (m, 2H, 6-CH_2), 3.76 (s, 3H, $N_{Pyr}CH_3$), 5.31 (q, *J* = 5.1, 1H, $N_{Ph}H$), 6.60 (ddd, *J* = 8.1, 7.5, 1.2, 1H, H-4), 6.65 (dd, *J* = 8.2, 1.1, 1H, H-6), 7.15 (dd, *J* = 7.7, 1.5, 1H, H-3), 7.24 (ddd, 1H, *J* = 8.5, 7.8, 1.5, 1H, H-5), 8.80 (s, 1H, NH), 9.00 (s, 1H, NH). **^{31}P NMR** (162 MHz, DMSO-d_6), δ, ppm (*J*, Hz): -144.20 (sept, *J* = 711.2). **^{19}F NMR** (376 MHz, DMSO-d_6), δ, ppm (*J*, Hz): -70.16 (d, *J* = 711.4).	(101 MHz, DMSO-d_6), δ, ppm: 22.2 (CH_2), 27.6 (CH_2), 30.6 (CH_3), 37.5 (CH_3), 38.2 (CH_3), 52.6 (CH_2), 111.2 (CH), 113.3 (C), 114.2 (C), 117.4 (CH), 131.2 (CH), 134.2 (CH), 135.5 (C), 149.5 (C), 151.5 (C), 159.1 (C).	**HRMS** (ESI) Calculated for $C_{16}H_{22}N_5S^+$ 316.1596, Found: 316.1591; Calculated for PF_6^-144.9642, Found: 144.9649.
Products were purified by automatic column chromatography (elution system: gradient $CH_3CN–CH_2Cl_2$, 19:1 to $CH_3CN–CH_2Cl_2$, 22:3). Yield 360 mg (0.78 mmol, 78%), white powder (mp 177–178 °C).					
3.31a	*5-(2-amino-1-(1,3-dimethyl-1H-benzo[d]imidazol-2(3H)-ylidene)-2-oxoethyl)-1-methyl-3,4-dihydro-2H-pyrrol-1-ium iodide* 	Neat film 3432 (NH_2ν), 1639 (C=O) 1599, 1560 (NH_2δ, C=C)	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): (mixture of rotamers, the signals of dominating rotamer are only mentioned) δ 1.90–2.08 (m, 2H, 4-CH_2), 2.20 (s, 3H, NCH_3), 3.28 (t, *J* = 7.3, 2H, 3-CH_2), 3.59 (t, *J* = 7.0, 2H, 5-CH_2), 3.77 (s, 6H, 2NCH_3), 6.67 (s, 2H, NH_2), 7.60–7.71 (m, 2H, H-5,6), 7.91–8.02 (m, 2H, H-4,7).	(75 MHz, DMSO-d_6), δ, ppm: 20.6 (CH_2), 32.0 (2CH_3), 35.0 (CH_2), 35.3 (CH_3), 56.4 (CH_2), 76.4 (C), 112.9 (2CH), 125.7 (2CH), 131.7 (2C), 151.0 (C), 167.0 (C), 169.0 (C, <u>C</u>O).	**HRMS** (ESI) Calculated for $C_{16}H_{21}N_4O$ (M + H^+) 285.1715, Found: 285.1718.
Product was purified by recrystalliaztion from propan-2-ol. Yield 312 mg (0.8 mmol, 79%), light brown powder.					

General procedure for the synthesis of (*Z*)-2-(benzo[*d*]thiazol-2-yl)-2-((*E*)-3-((dimethylamino)methylen)pyrrolidin-2-yledene)acetonitrile (4.2a).

DMF DMA (1.07 ml, d = 0.897 g/cm^3, 8 mmol) was added to a solution of 2-benzo[*d*]thiazol-2-yl-2-(pyrrolidin-2-ylidene)acetonitrile **2.1b** (0.965 g, 4 mmol) in anhydrouys toluene (15 ml) and the resultant mixture was left to reflux over 3 h (TLC control, $CHCl_3$-CH_3OH, 95:5). At this point another portion of DMF DMA (1.07 ml, 8 mmol) was added to the reaction mixture. Reaction was left to reflux until complete convertion of starting material. If necessary another portion of DMF DMA should be added. After the reaction was completed the precipitate was filtered off and purified by recrystallization from ethanol-dioxane mixture. Yield 0.84 g (2.84 mmol, 71%), yllow-green powder (mp 194–195 °C).

1-Methyl-2,3-dihydro-1*H*-benzo[4,5]imidazo[1,2-*a*]pyrrolo [2,3-*d*]pyridine-11-carbonitrile (4.4)

DMF DMA (0.16 ml, 0.6 mmol) was added to a solution of 2-benzo[*d*]imidazol-2-yl-2-(1-methylpyrrolidin-2-ylidene)acetonitrile **2.13a** (119 mg, 0.5 mmol) in anhydrouys toluene (8 ml) and the resultant mixture was left to reflux until complete convertion of starting material, approimately 30 min (TLC control, $CHCl_3$-CH_3OH, 9:1). Product was purified by tritutation with hot propan-2-ol. Yield 111 mg (0.45 mmol, 90%), white powder (mp > 300 °C).

General procedure for the synthesis of 2-(benzo[*d*]thiazol-2-yl)-2-((*E*)-3-((R-amino)methylene)purrolidin-2-ylidene)acetonitrile 4.6-4.8

1-R-amine (1.5 mmol) was added to a solution of (*Z*)-2-(benzo[*d*]thiazol-2-yl)-2-((*E*)-3-((dimethylamino)methylene)pyrrolidin-2-ylidene)acetonitrile **4.2a** (592 mg, 2 mmol) in dioxane-ethanol mixture (16 ml, 1:1) and the resultant mixture was left to reflux over 3 h. At this point another portion of 1-R-amine (1.5 mmol) was added and the refluxing was continued until complete convertion of starting material (TLC control, $CHCl_3$-CH_3OH, 19:1). The raction mixture was cooled down; the precipitate was filtered off and recrystallized from ethanol.

7-(Benzo[*d*]thiazol-2-yl)-5-benzyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-6(5*H*)-imine (4.9).

NaOEt (75 mg, 1.1 mmol) was added to a solution of (*Z*)-2-(benzo[d]thiazol-2-yl)-2-((*E*)-3-((benzylamino)methylene)pyrrolidin-2-ylidene)acetonitrile **4.6** (358 mg, 1 mmol) in dioxane-ethanol mixture (10 ml, 4:1) and the resultant mixture was left to reflux over 15 min. The blue fluorescence appears and the bright yellow precipitate forms. The reaction mixture was cooled down; the precipitate was filtered off and recrystallized from ethanol. Yield 323 mg (0.9 mmol, 90%), yellow powder, (mp 225 °C).

6-Amino-7-(benzo[*d*]thiazol-2-yl)-5-benzyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-5-ium hydrogensulafate (4.10a).

Pyrrolo[3,2-*c*]pyridin-6-imine **4.9** (179 mg, 0.5 mmol) was stirred upon reflux in 30% H_2SO_4 water-dioxane mixture over 36 h. During this time the hydrolysis of imino group did not occur (TLC control). When the mixture was cooling down the precipitate of the salt **4.10a** was formed. Yield is 228 mg (0.49 mmol, 98%).

6-Amino-7-(benzo[*d*]thiazol-2-yl)-5-benzyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-5-ium chloride (4.10b).

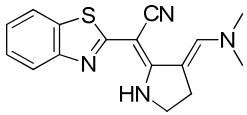
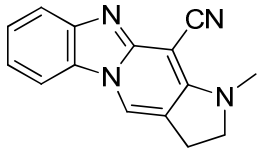
HCl gas was bubbled vigorously through an ice-cold solution of pyrrolo[3,2-*c*]pyridin-6-imine **4.9** (179 mg, 0.5 mmol) in anhydrous dioxane for 30 min. The resultant precipitate was filtered off and washed with ether to yield 198 mg (0.49 mmol, 98%), white powder.

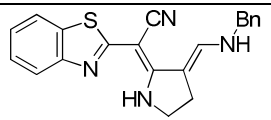
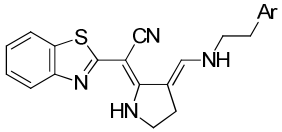
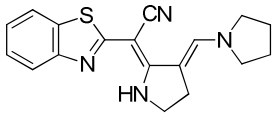
7-(Benzo[*d*]thiazol-2-yl)-5-benzyl-6-(dimethylamino)-1-methyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-5-ium iodide (4.11).

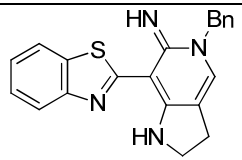
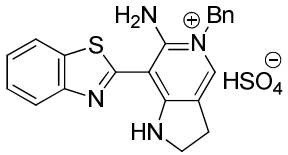
The mixture of pyrrolo[3,2-*c*]pyridin-6-imine **4.9** (107mg, 0.3 mmol) in CH_3CN-DMF (10 ml, 5:1) and K_2CO_3 (207 mg, 1.5 mmol) was stirred at 80 °C over 5 min. At this point MeI (0.1 ml, d = 2.279 g/cm^3, 1.5 mmol) was added to reaction mixture and the stirring was pursued for another 30 min. After the reaction was

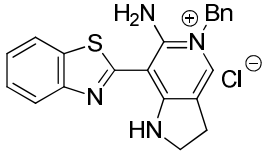
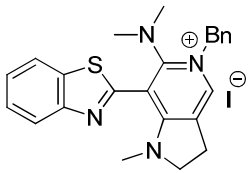
ceased (TLC control, CH_2Cl_2–CH_3OH–Et_3N, 9:1:0.1) the realultant precipitate was filtrated off; filtrate was condensed under reduced pressure and the residue was triturated with CH_2Cl_2. Yield 80%, (118 mg, 0.22 mmol), yellowish powder.

Table 6.5. Physico-chemical characteristics of 2-azahetaryl-2-(pyrrolidin-2-ylidene)acetonitrile derivatives functionalized at C-3 centre of pyrrolidine fragment **4.2a**, **4.4**, **4.6-4.11**

Compound	**IUPAC name**	**IR, ν, cm^{-1}**	**^{1}H NMR**	**^{13}C NMR**	**HRMS/MS, elemental analysis**
4.2a	***(****Z)-2-(benzo[d]thiazol-2-yl)-2-((E)-3-((dimethylamino)methylen)pyrrolidin-2-yledene)acetonitrile* 	Neat film 3201 (NH), 2172 (C≡N), 1636, 1553 (C=C, C=N).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.02–3.11 (m, 2H, 2CH$_3$, 4-CH$_2$), 3.67 (t, *J* = 7.9, 2H, 5-CH$_2$), 7.16–7.22 (m, 1H, H-6), 7.33–7.39 (m, 1H, H-5), 7.68 (d, *J* = 7.8, 1H, Ar H), 7.76 (s, 1H, C<u>H</u>N(CH$_3$)$_2$), 7.85–7.90 (m, 1H, Ar H), 10.24 (s, 1H, NH).	(101 MHz, DMSO-d_6), δ, ppm: 26.8 (CH$_2$), 42.6 (2CH$_3$), 46.3 (CH$_2$), 61.8 (C), 99.0 (C), 119.8 (CH), 121.7 (CH), 123.1 (CH), 123.7 (C), 126.4 (CH), 131.7 (C), 144.5 (CH), 154.0 (C), 164.7 (C), 168.8 (C).	**HRMS** (ESI) Calculated for $C_{16}H_{17}N_4S$ (M + H$^+$): 297.1174, Found: 297.1173.
Yield 840 mg (2.84 mmol, 71%), yellow-green powder (mp 194–195 °C).					
4.4	*1-Methyl-2,3-dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrrolo[2,3-d]pyridine-11-carbonitrile* 	KBr 2198 (C≡N), 1674, 1590, 1514 (C=C, C=N).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.03 (t, *J* = 7.9, 2H, 3-CH$_2$), 3.32 (s, 3H, CH$_3$), 3.80 (t, *J* = 7.8, 2H, 2-CH$_2$), 7.18 (t, *J* = 7.3, 1H, Ar H), 7.30 (t, *J* = 7.7, 1H, Ar H), 7.58 (d, *J* = 7.9, 1H, H-7), 7.89 (d, *J* = 7.6, 1H, H-4).	(101 MHz, DMSO-d_6), δ, ppm: 23.2 (CH$_2$), 34.2 (CH$_3$), 56.4 (CH$_2$), 67.1 (C), 110.8 (CH), 116.8 (C), 117.6 (CH), 120.9 (CH), 121.5 (C), 123.1 (CH), 124.8 (CH), 130.1 (C), 143.5 (C), 149.3 (C), 156.1 (C).	**Calculated, %:** C, 72.56; H, 4.87; N, 22.57. $C_{15}H_{12}N_4$. **Found, %**: C, 72.58; H, 4.43; N, 21.60.
Yield 111 mg (0.45 mmol, 90%), white powder (mp > 300 °C).					
4.6	*(Z)-2-(benzo[d]thiazol-2-yl)-2-((E)-3-((benzylamino)methylene)pyrrolidin-2-ylidene)acetonitrile*	KBr 3289, 3258 (NH), 2186 (C≡N), 1645, 1557 (C=C, C=N).	(400 MHz, DMSO-d_6-CCl$_4$), δ, ppm (*J*, Hz): 2.75 (t, *J* = 7.4, 2H, 4-CH$_2$), 3.78 (t, *J* = 7.7, 2H, 5-CH$_2$), 4.38 (d, *J* = 5.5, 2H, CHNHC<u>H$_2$</u>), 7.04 (d.t, *J* = 12.3, 5.6, 2H, CHN<u>H</u>CH$_2$), 7.14 (t, *J* = 7.1, 1H, H-6), 7.24–7.40 (m, 6H, Ph H, H-5), 7.61 (d, *J* = 8.0, 1H, Ar H), 7.76 (d, *J* = 7.8, 1H, Ar H), 7.95 (d, *J*	(101 MHz, DMSO-d_6), δ, ppm: 26.0 (CH$_2$), 45.8 (CH$_2$), 51.8 (CH$_2$), 61.9 (C), 101.2 (C), 120.0 (CH), 121.8 (CH), 123.2 (CH), 123.4 (C), 126.5 (CH), 127.7 (2CH), 127.8 (CH), 129.1 (2CH), 131.8 (C), 140.3 (C), 142.4 (CH), 154.1 (C), 162.5 (C), 168.6 (C).	**Calculated, %:** C, 70.36; H, 5.06; N, 15.63. $C_{21}H_{18}N_4S$. **Found, %**: C, 70.40; H, 5.26; N, 15.87.

			= 12.9, 1H, C<u>H</u>NHCH$_2$), 10.22 (s, 1H, NH).		
Yield 660 mg (1.84 mmol, 92%), yellow powder (mp 190 °C).					
4.7	*(Z)-2-(benzo[d]thiazol-2-yl)-2-((E)-3-(((3,4-dimethoxyphenethyl) amino)methylene)pyrrolidin-2-ylidene)acetonitrile* 	KBr 3319 (NH), 2176 (C≡N), 1654, 1648, 1561 (C=C, C=N).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.58–2.67 (m, 2H, CH$_2$), 2.76 (t, *J* = 7.1, 2H, CH$_2$), 3.27–3.43 (m, 2H, CH$_2$), 3.65–3.80 (m, 8H, 2CH$_3$, CH$_2$), 6.69–6.80 (m, 1H, H-6$_{3,4\text{-(OMe)2Ar}}$, CHN<u>H</u>CH$_2$), 6.84 (d, *J* = 1.9, 1H, H-2$_{3,4\text{-(OMe)2Ar}}$), 6.87 (d, *J* = 8.2, 1H, H-5$_{3,4\text{-(OMe)2Ar}}$), 7.15–7.22 (m, 1H, H-6), 7.32–7.40 (m, 1H, H-5), 7.64–7.69 (m, 1H, Ar H), 7.80 (dt, *J* = 13.2, 1.6, 1H, C<u>H</u>NHCH$_2$), 7.84–7.89 (m, 1H, Ar H), 10.08 (s, 1H, NH).	(101 MHz, DMSO-d_6), δ, ppm: 26.0 (CH$_2$), 37.0 (CH$_2$), 45.6 (CH$_2$), 50.1 (CH$_2$), 55.8 (CH$_3$), 56.0 (CH$_3$), 61.7, 100.1 (C), 112.5 (CH), 113.1 (CH), 119.8 (CH), 121.1 (CH), 121.7 (CH), 123.1 (CH), 123.3 (C), 126.3 (CH), 131.6 (C), 131.7 (C), 142.3 (C), 147.8 (C), 149.1 (C), 154.0 (C), 162.4 (C), 168.6 (C).	**Calculated, %:** C, 66.64; H, 5.29; N, 12.95. $C_{24}H_{24}N_4O_2S$. **Found, %**: C, 64.76; H, 5.20; N, 12.61.
Yield 744 mg (1.72 mmol, 86%), yellow powder (mp 170 °C).					
4.8	*(Z)-2-(benzo[d]thiazol-2-yl)-2-((E)-3-(pyrrolidin-1-ylmethylene)pyrrolidin-2-ylidene)acetonitrile* 	Neat film 3206 (NH), 2171 (C≡N), 1629, 1555 (C=N, C=C).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.83–1.89 (m, 4H, CHN(CH$_2$)$_2$(C<u>H$_2$</u>)$_2$), 3.10 (t, *J* = 7.7, 2H, 4-CH$_2$), 3.49–3.60 (m, 4H, CHN(C<u>H$_2$</u>)$_2$(CH$_2$)$_2$), 3.66 (t, *J* = 7.9, 2H, 5-CH$_2$), 7.19 (t, *J* = 7.6, 1H, H-6), 7.36 (t, *J* = 7.8, 1H, H-5), 7.68 (d, *J* = 7.9, 1H, H-7), 7.87 (d, *J* = 7.8, 1H, H-4), 8.01 (s, 1H, C<u>H</u>N(CH$_2$)$_2$(CH$_2$)$_2$), 10.25 (s, 1H, NH).	(101 MHz, DMSO-d_6), δ, ppm: 25.4 (2CH$_2$), 26.6 (CH$_2$), 46.1 (CH$_2$), 51.1 (2CH$_2$), 61.7 (C), 99.8 (C), 119.8 (CH), 121.7 (CH), 123.1 (CH), 123.7 (C), 126.4 (CH), 131.7 (C), 140.9 (CH), 154.0 (C), 164.0 (C), 168.8 (C).	**HRMS** (ESI) Calculated for $C_{18}H_{19}N_4S$ (M + H$^+$) 323.1330, Found 323.1331.
Yield 548 mg (1.7 mmol, 85%), yellow powder (mp 221–222 °C).					
4.9	*7-(Benzo[d]thiazol-2-yl)-5-benzyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-6(5H)-imine*	KBr 3315 (NH), 1678, 1579, 1563 (C=C, C=N).	(400 MHz, **CDCl$_3$**), δ, ppm (*J*, Hz): 2.98 (td, *J* = 7.8, 1.6, 2H, 3-CH$_2$), 3.96 (t, *J* = 7.9, 2H, 2-CH$_2$), 4.93 (s, 2H, CHNC<u>H$_2$</u>), 6.83 (t, *J* = 1.6, 1H, C<u>H</u>NCH$_2$), 7.24–7.34 (m, 6H, H-6, H$_{Ph}$-2,4,6), 7.35 – 7.39 (m, 2H, H$_{Ph}$-	(101 MHz, CDCl$_3$), δ, ppm (*J*, Hz): 24.7 (CH$_2$), 47.5 (CH$_2$), 54.3 (CH$_2$), 94.4 (C), 112.6 (C), 120.3 (CH), 121.1 (CH), 122.8 (CH), 125.2 (CH), 126.6 (2CH), 127.9 (CH), 129.1 (2CH), 130.9 (CH), 134.2 (C), 135.7 (C),	**Calculated, %:** C, 70.36; H, 5.06; N, 15.63. $C_{24}H_{24}N_4O_2S$. **Found, %**: C, 70.56; H, 5.11;

			3,5), 7.42 (ddd, *J* = 8.4, 7.3, 1.2, 1H, H-5), 7.87–7.89 (m, 1H, H-4), 7.89–7.91 (m, 1H, H-7). DMSO-d_6 : ratio imine:enamine 1.6:1. (400 MHz, **DMSO-d_6**), δ, ppm (*J*, Hz): Imine: 2.95 (t, *J* = 7.2, 2H, 3-CH_2), 3.87 (t, *J* = 7.2, 2H, 2-CH_2), 5.03 (s, 2H, CHNC$\underline{H}_2$), 6.32 (s, 1H, N$\underline{H}$CNBn), 7.12–7.54 (m, 8H), 7.86 (d, *J* = 8.3, 1H, Ar H), 7.90 (d, *J* = 7.7, 1H, Ar H), 9.28 (s, 1H, NH). Enamine: 2.74 (t, *J* = 7.1, 2H, 3-CH_2), 3.99 (t, 6.9, 2H, 2-CH_2), 5.07 (s, 2H, CHNC$\underline{H}_2$), 6.83 (s, 1H, C$\underline{H}$NCH_2), 7.12–7.54 (m, 7H), 7.75 (d, *J* = 7.8, 1H, Ar H), 7.94 (d, *J* = 8.0, 1H, Ar H), 9.13 (br.s, 2H, NH_2). The signals of NH proton disappear upon D_2O addition; the signal of CH proton broadening.	151.6 (C), 154.5 (C), 157.1 (C), 165.3 (C).	N, 15.46.
Yield 323 mg (0.9 mmol, 90%), yellow powder (mp 225 °C).					
4.10a	*6-Amino-7-(benzo[d]thiazol-2-yl)-5-benzyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-5-ium hydrogensulafate* 		(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.13 (t, *J* = 7.9, 2H, 3-CH_2), 3.89 (t, *J* = 8.2, 2H, 2-CH_2), 5.42 (s, 2H, CHNC$\underline{H}_2$), 7.32–7.37 (m, 2H, H_{Ph}-2,6), 7.38–7.41 (m, 1H, H_{Ph}-4), 7.43–7.48 (m, 2H, H_{Ph}-3,5), 7.55 (t, *J* = 7.6, 1H, H-6), 7.63 (t, *J* = 7.6, 1H, H-5), 7.82 (s, 1H, C$\underline{H}$NCH_2), 8.13 (d, *J* = 8.0, 1H, H-4), 8.21 (d, *J* = 7.7, 1H, H-7), 8.57 (s, 1H, NH), 8.68 (s, 2H, NH_2). The signals of NH proton disappear upon D_2O addition.	(101 MHz, DMSO-d_6), δ, ppm: 24.3 (CH_2), 48.3 (CH_2), 54.8 (CH_2), 91.7 (C), 120.8 (C), 122.4 (CH), 122.9 (CH), 126.2 (CH), 127.2 (CH), 127.4 (2CH), 128.5 (CH), 129.3 (2CH), 133.3 (C), 134.1 (CH), 135.0 (C), 151.6 (C), 152.2 (C), 158.7 (C), 161.4 (C).	
Yield 228 mg (0.49 mmol, 98%), white powder.					

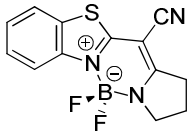
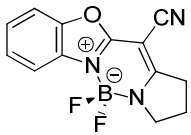
4.10b	*6-Amino-7-(benzo[d]thiazol-2-yl)-5-benzyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-5-ium chloride* 	KBr 3400, 3283 (NH), 1677, 1655, 1617, 1596, 1578 (C=C, C=N).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.07–3.13 (m, 2H, 3-CH_2), 3.85 (t, *J* = 8.3, 2H, 2-CH_2), 5.45 (s, 2H, CHNC$\underline{H}_2$), 7.30–7.34 (m, 2H, H_{Ph}-2,6), 7.34–7.38 (m, 1H, H_{Ph}-4), 7.39–7.45 (m, 2H, H_{Ph}-3,5), 7.52 (ddd, *J* = 8.2, 7.6, 1.2, 1H, H-6), 7.60 (ddd, *J* = 8.3, 7.8, 1.3, 1H, H-5), 7.83 (br.s, 1H, C$\underline{H}$NCH_2), 8.08 – 8.13 (m, 1H, H-4), 8.18–8.21 (m, 1H, H-7), 8.61 (s, 1H, NH), 8.76 (c, 2H, NH_2). The integral intensity of the signals corresponds to NH protons dimish upon D_2O addition.	(101 MHz, DMSO-d_6), δ, ppm: 24.3 (CH_2), 48.3 (CH_2), 54.8 (CH_2), 91.6 (C), 120.8 (C), 122.4 (CH), 122.9 (CH), 126.2 (CH), 127.2 (CH), 127.5 (2CH), 128.5 (CH), 129.3 (2CH), 133.4 (C), 134.1 (CH), 135.2 (C), 151.6 (C), 152.2 (C), 158.8 (C), 161.4 (C).	**HRMS** (ESI) Calculated for $C_{21}H_{19}N_4S^+$ 359.1329, Found 359.1328.
Yield 198 mg (0.49 mmol, 98%), white powder.					
4.11	*7-(Benzo[d]thiazol-2-yl)-5-benzyl-6-(dimethylamino)-1-methyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-5-ium iodide* 	Neat film 1660, 1576, 1527 (C=C, C=N).	(400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.34 (c, 6H, NCH), 3.01–3.10 (m, 2H, 3-CH_2), 3.91 (t, *J* = 8.8, 2H, 2-CH_2), 5.27 (s, 2H, CHNC$\underline{H}_2$), 7.22–7.26 (m, 2H, H_{Ph}-2,6), 7.32–7.37 (m, 1H, H_{Ph}-4), 7.39–7.44 (m, 2H, H_{Ph}-3,5), 7.57 (td, *J* = 7.6, 1.4, 1H, H-6), 7.62 (td, *J* = 7.7, 1.5, 1H, H-5), 8.00–8.07 (m, 1H, C$\underline{H}$NCH_2), 8.1 –8.15 (m, 1H, H-4), 8.22–8.26 (m, 1H, H-7).	(101 MHz, DMSO-d_6), δ, ppm: 23.5 (CH_2), 35.4 (CH_3), 42.4 (CH_3), 57.4 (CH_2), 57.6 (CH_2), 104.8 (C), 123.2 (CH), 123.9 (CH), 126.9 (CH), 127.1 (C), 127.2 (2CH), 127.4 (CH), 128.6 (CH), 129.4 (2CH), 135.9 (CH), 136.4 (C), 136.6 (C), 152.5 (C), 158.1 (C), 159.1 (C), 159.6 (C).	**HRMS** (ESI) Calculated for $C_{25}H_{25}N_4S^+$ 401.1800, Found 401.1800. Calculated for I^- 126.9045, Found 126.9047.
Yield 118 mg (0.22 mmol, 80%), yellowish powder.					

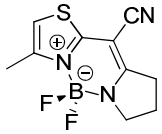
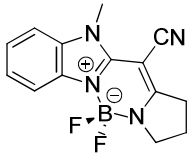
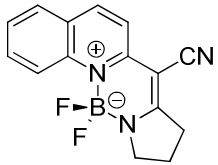
General procedure for the synthesis of BF_2-rigidified complexes 5.1a-h.

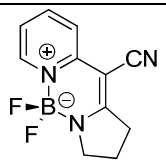
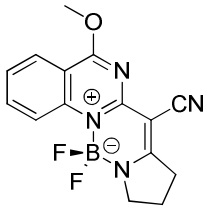
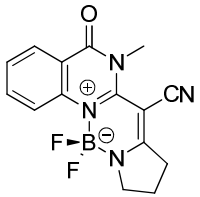
(*Z*)-2-hetaryl-2-(pyrrolidin-2-ylidene)acetonitriles **2.1a-d, g, i, 2.9, 2.10** (0.5 mmol) and *N*,*N*-diisopropylethylamine (0.25 ml, *d* = 0.782 g/ml, 1.5 mmol) were heated to reflux in dichloromethane (8 ml) for 15 min. BF_3•OEt_2 (0.5 ml, *d* = 1.130 g/ml, 4 mmol) was added and the mixture was refluxed another 30 min. After the reaction was cooled down, it was diluted with additional amount of dichloromethane and washed with water 3 times and brine 1 time. The organic fraction was dried over Na_2SO_4, filtrated off and evaporated under reduced pressure. The crude products were purified by automated flash chromatography.

Preparation of the samples of Films of polymeric composites (FPC).

The samples for the investigation were prepared with a free FPC surface, (glass substrate)/ITO/FPC, where ITO is an electroconducting layer of SnO_2: In_2O_3. To prepare the samples filtered solutions of CuL_2, NiL_2, CoL_2 complexes, and SOM in methylene chloride were deposited on a glass substrate with a layer of ITO and dried at room temperature for 24 h and then in a drying cabinet at 80 °C for 48 h. The content of HL and metal complexes in the SOM amounted to between 1 and 50 wt.%. Increase of the concentration of the additives in the SOM to more than 50 wt.% leads to nonuniformity in the morphology of the films, which cannot be permitted for use in photoelectric converters. The thickness of the FPC was ~1.5 µm

Table 6.6. Physico-chemical characteristics of BF_2-complexes **5.1a-h**					
Compound	**IUPAC name**	**IR, ν, cm^{-1}**	**^{1}H NMR**	**^{13}C NMR**	**HRMS/MS, elemental analysis**
5.1a	*BF_2-rigidified (Z)-2-(benzo[d]thiazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile* 	Neat film 2204 (C≡N), 1598, 1584 (C=N, C=C).	(300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.24–2.36 (m, 2H, 4-CH_2), 3.19 (t, *J* = 8.0, 2H, 3-CH_2), 4.04–4.10 (m, 2H, 5-CH_2), 7.41 (ddd, *J* = 8.4, 7.4, 1.1, 1H, H-6), 7.54 (ddd, *J* = 8.4, 7.4, 1.3, 1H, H-5), 7.75 (ddd, *J* = 8.0, 1.2, 0.5, 1H, H-7), 8.02 – 8.07 (m, 1H, H-4). **^{19}F NMR** (282 MHz, $CDCl_3$), δ, ppm (*J*, Hz): -139.07 (q, *J* = 29.0). **^{11}B NMR** (96 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.48 (t, *J* = 29.3).	(75 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 21.3 (CH_2), 34.3 (CH_2), 51.6 (CH_2), 70.3 (C), 116.6 (C), 118.1 (t, $^{2}J_{CN}$ = 3.2, 4-CH), 121.9 (CH), 125.4 (CH), 127.4 (C), 127.8 (CH), 142.9 (C), 166.9 (C), 170.1 (C).	**HRMS** (DCI-CH_4) Calculated for $C_{13}H_{11}BF_2N_3S$ (M + H$^+$) 290.0735, Found 290.0741.
Elution system for column chromatography: CH_2Cl_2–CHA, 7:3. Yield 133 mg (0.46 mmol, 92%), white powder (mp 233 °C)					
5.1b	*BF_2-rigidified (Z)-2-(benzo[d]oxazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile* 	Neat film 2214 (C≡N), 1636, 1616, 1532 (C=N, C=C).	(300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.24–2.39 (m, 2H, 4-CH_2), 3.22 (t, *J* = 8.0, 2H, 3-CH_2), 4.03–4.10 (m, 2H, 5-CH_2), 7.40 (ddd, *J* = 7.9, 7.6, 1.6, 1H, Het H), 7.46 (ddd, *J* = 7.9, 7.7, 1.5, 1H, Het H), 7.53–7.61 (m, 1H, 7-H, Het H), 7.67–7.75 (m, 1H, 5-H). **^{19}F NMR** (282 MHz, $CDCl_3$), δ, ppm (*J*, Hz): -140.41 (q, *J* = 26.0). **^{11}B NMR** (96 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.17 (t, *J* = 26.2).	(75 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 21.4 (CH_2), 34.8 (CH_2), 51.7 (CH_2), 61.2 (C), 111.2 (CH), 114.2 (C), 114.9 (CH), 125.6 (CH), 126.4 (CH), 130.9 (C), 148.1 (C), 162.7 (C), 173.1 (C).	**HRMS** (DCI-CH_4) Calculated for $C_{13}H_{11}BF_2N_3O$ (M + H$^+$) 274.0963, Found: 274.0969.
Elution system for column chromatography: CH_2Cl_2–CHA, 7:3. Yield 123 mg (0.45 mmol, 89%), white powder (mp 226–227 °C).					
5.1c	*BF_2-rigidified (Z)-2-(4-methylthiazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile*	Neat film 2202 (C≡N), 1592, 1567 (C=N, C=C).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.20–2.29 (m, 2H, 4-CH_2), 2.51 (td, $^{3}J_{HN}$ = 1.6, $^{3}J_{HH}$ = 1.2, 3H, CH_3), 3.12 (t, *J* = 8.0, 2H, 3-CH_2), 3.95–4.01 (m, 2H, 5-CH_2), 6.60 (d, *J* = 1.2, 1H, H-5). **^{19}F NMR** (282 MHz, $CDCl_3$), δ, ppm	(101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 14.63 (t, $^{2}J_{CN}$ = 4.0, CH_3), 21.7 (CH_2), 34.0 (CH_2), 51.2 (CH_2), 69.2 (C), 107.9 (CH), 117.2 (C), 145.1 (C), 167.1 (C), 168.5 (C).	**HRMS** (DCI-CH_4) Calculated for: $C_{10}H_{11}BF_2N_3S$ (M + H$^+$) 254.0735,

			(*J*, Hz): -133.57 (q, *J* = 29.5). **^{11}B NMR** (96 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.15 (t, *J* = 29.8).		Found: 290.0732.
Elution system for column chromatography: CH_2Cl_2–CHA, 3:2. Yield 118 mg (0.47 mmol, 93%), white powder (mp 156–157 °C).					
5.1d	*BF_2-rigidified (Z)-2-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile* 	Neat film 2206 (C≡N), 1584, 1542 (C=N, C=C).	(300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.20–2.31 (m, 2H, 4-CH_2), 3.18 (t, *J* = 8.0, 2H, 3-CH_2), 3.99–4.06 (m, 2H, 5-CH_2), 4.07 (s, 3H, NCH_3), 7.30–7.43 (m, 3H, Het H), 7.77–7.86 (m, 1H, H-4). **^{19}F NMR** (282 MHz, $CDCl_3$), δ, ppm (*J*, Hz): -143.18 (q, *J* = 27.7). **^{11}B NMR** (96 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.15 (t, *J* = 28.0).	(101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 21.5 (CH_2), 30.8 (CH_3), 34.9 (CH_2), 51.2 (CH_2), 59.3 (C), 109.2 (CH), 114.9 (CH), 118.2 (C), 124.1 (CH), 124.4 (CH), 131.9 (C), 133.5 (C), 147.8 (C), 172.1 (C).	**HRMS** (DCI-CH_4) Calculated for $C_{14}H_{14}BF_2N_4$ (M + H^+) 287.1280, Found: 287.1278.
Elution system for column chromatography: CH_2Cl_2–CHA, 7:3. Yield 106 mg (0.37 mmol, 73%), white powder (mp 280 °C).					
5.1e	*BF_2-rigidified (E)-2-(pyrrolidin-2-ylidene)-2-(quinolin-2-yl)acetonitrile* 	Neat film 2201 (C≡N), 1632, 1596, 1553 (C=N, C=C).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.22–2.33 (m, 2H, 4-CH_2), 3.22 (t, *J* = 8.0, 2H, 3-CH_2), 4.06–4.13 (m, 2H, 5-CH_2), 7.50 (t, *J* = 7.4, 1H, H-6), 7.58 (d, *J* = 9.1, 1H, H-3), 7.72 (d, *J* = 8.2, 1H, H-5) 7.74 (ddd, *J* = 8.5, 8.1, 1.5, 1H, H-7), 8.07 (d, *J* = 9.1, 1H, H-4), 8.61 (d.t, $^2J_{HH}$ = 8.4 Hz, $^3J_{HN}$ = 2.5, 1H, H-8). **^{19}F NMR** (376 MHz, $CDCl_3$), δ, ppm (*J*, Hz): -131.79 (q, *J* = 32.9). **^{11}B NMR** (128 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.33 (t, *J* = 33.0).	(101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 21.1 (CH_2), 34.9 (CH_2), 52.0 (CH_2), 72.75 (t, $^2J_{CN}$ = 2.5, Het<u>C</u>CN), 118.5 (C), 118.6 (CH), 122.45 (t, $^2J_{CN}$ = 8.6, 8-<u>C</u>H), 125.3 (C), 125.9 (CH), 128.6 (CH), 131.9 (CH), 139.58 (t, $^1J_{CN}$ = 2.8 Hz, $(CH)_4$<u>C</u>N), 140.4 (CH), 152.7 (C), 169.7 (C).	**HRMS** (DCI-CH_4) Calculated for $C_{15}H_{13}BF_2N_3$ (M + H^+) 284.1171, Found: 284.1165.
Elution system for column chromatography: CH_2Cl_2–CHA, 3:2. Yield 118 mg (0.45 mmol, 89%), bright yellow powder (mp 224 °C).					
5.1f	*BF_2-rigidified (E)-2-(pyridin-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile*	Neat film 2202 (C≡N), 1631, 1596 (C=N, C=C).	(400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.17–2.27 (m, 2H, 4-CH_2), 3.17 (t, *J* = 8.0 Hz, 2H, 3-CH_2), 3.95–4.00 (m, 2H, 5-CH_2), 7.13 (ddd, *J* = 7.6, 6.1, 1.3, 1H, H-5), 7.55 (d, *J* = 8.6, 1H, H-3), 7.85 (ddd, *J* = 8.7, 7.1, 1.6, 1H, H-4),	(101 MHz, $CDCl_3$), δ, ppm: 21.4 (CH_2), 34.6 (CH_2), 51.4 (CH_2), 70.4 (C), 117.5 (CH), 118.2 (C), 119.8 (CH), 139.5 (CH), 140.2 (CH), 150.9 (C), 169.4 (C).	**HRMS** (DCI-CH_4) Calculated for $C_{11}H_{11}BF_2N_3$ (M + H^+) 234.1014, Found:

			8.31 (d, J = 6.2, 1H, H-6). **^{19}F NMR** (376 MHz, $CDCl_3$), δ, ppm (J, Hz): -137.84 (q, J = 29.3). **^{11}B NMR** (128 MHz, $CDCl_3$), δ, ppm (J, Hz): 1.24 (t, J = 29.7).		234.1012.
Elution system for column chromatography: CH_2Cl_2–CHA, 3:2. Yield 105 mg (0.45 mmol, 90%), yellowish powder (mp 158–159 °C).					
5.1g	*BF_2-rigidified (Z)-2-(4-methoxyquinazolin-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile* 	Neat film 2209 (C≡N), 1626, 1594 (C=N, C=C), 1212 (C–O).	(400 MHz, $CDCl_3$), δ, ppm (J, Hz): 2.18–2.33 (m, 2H, 4-CH_2), 3.21 (t, J = 8.0, 2H, 3-CH_2), 4.02–4.07 (m, 2H, 5-CH_2), 4.31 (s, 3H, CH_3, OCH_3) 7.49 (ddd, J = 8.3, 7.1, 0.8, 1H, H-6), 7.83 (ddd, J = 8.8, 7.1, 1.6, 1H, H-7), 8.10 (dd, J = 8.1, 1.4, 1H, H-5), 8.38 (d.t, $^2J_{HH}$ = 8.9, $^3J_{HN}$ = 2.6, 1H, H-8). **^{19}F NMR** (376 MHz, $CDCl_3$), δ, ppm (J, Hz): -134.37 (q, J = 32.1). **^{11}B NMR** (128 MHz, $CDCl_3$), δ, ppm (J, Hz): 2.21 (t, J = 32.6).	(101 MHz, $CDCl_3$), δ, ppm (J, Hz): 21.0 (CH_2), 34.8 (CH_2), 51.8 (CH_2), 55.7 (CH_3), 73.7 (C), 113.4 (C), 117.9 (C), 121.5 (t, $^2J_{CN}$ = 7.6, 8-<u>C</u>H), 124.4 (CH), 126.0 (CH), 135.4 (CH), 143.0 (t, $^1J_{CN}$ = 2.7, $(CH)_4$<u>C</u>N), 158.4 (C), 166.7 (C), 171.4 (C).	**HRMS** (DCI-CH_4) Calculated for $C_{15}H_{14}BF_2N_4O$ (M + H^+) 315.1229, Found: 315.1236.
Elution system for column chromatography: CH_2Cl_2–CHA, 7:3. Yield 127 mg (0.41 mmol, 81%), greenish powder (mp 232–233 °C).					
5.1h	*BF_2-rigidified (Z)-2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile* . 	Neat film 2204 (C≡N), 1685 (C=O), 1623 (C=N, C=C).	(400 MHz, $CDCl_3$), δ, ppm (J, Hz): 2.22–2.34 (m, 2H, 4-CH_2), 3.26 (t, J = 8.0, 1H, 3-CH_2), 3.98 (s, 3H, NCH_3), 4.07–4.13 (m, 2H, 5-CH_2), 7.42–7.48 (m, 1H, H-6), 7.76 (ddd, J = 8.9, 7.2, 1.8, 1H, H-7), 8.27 (dd, J = 7.9, 1.7, 1H, H-5), 8.28 (dt, $^2J_{HH}$ = 8.9, $^2J_{HN}$ = 3.0, 1H, 8-H). **^{19}F NMR** (376 MHz, $CDCl_3$), δ, ppm (J, Hz): -134.82 (q, J = 30.8). **^{11}B NMR** (128 MHz, $CDCl_3$), δ, ppm (J, Hz): 1.60 (t, J = 31.4).	(101 MHz, $CDCl_3$), δ, ppm (J, Hz): 20.4 (CH_2), 36.38 (CH_2), 36.44 (CH_3), 52.7 (CH_2), 66.3 (C), 117.7 (C), 118.0 (C), 121.8 (t, $^2J_{CN}$ = 9.3, 8-<u>C</u>H), 126.4 (CH), 127.7 (CH), 135.4 (CH), 139.8 (t, $^1J_{CN}$ = 2.4, $(CH)_4$<u>C</u>N), 154.7 (C), 160.1 (C), 173.5 (C).	**HRMS** (DCI-CH_4) Calculated for $C_{15}H_{14}BF_2N_4O$ (M + H^+) 315.1229, Found: 315.1224.
Elution system for column chromatography: CH_2Cl_2–CHA, 7:3. Yield 118 mg (0.38 mmol, 75%), white powder (mp degradate when heating).					

SUPPLEMENTARY INFORMATION

*(Z)-2-(Benzo[d]thiazol-2-yl)-2-(pyrrolidin-2-ylidene)acetonitrile (**2.1b**).*

okuG0097.1.fid
1
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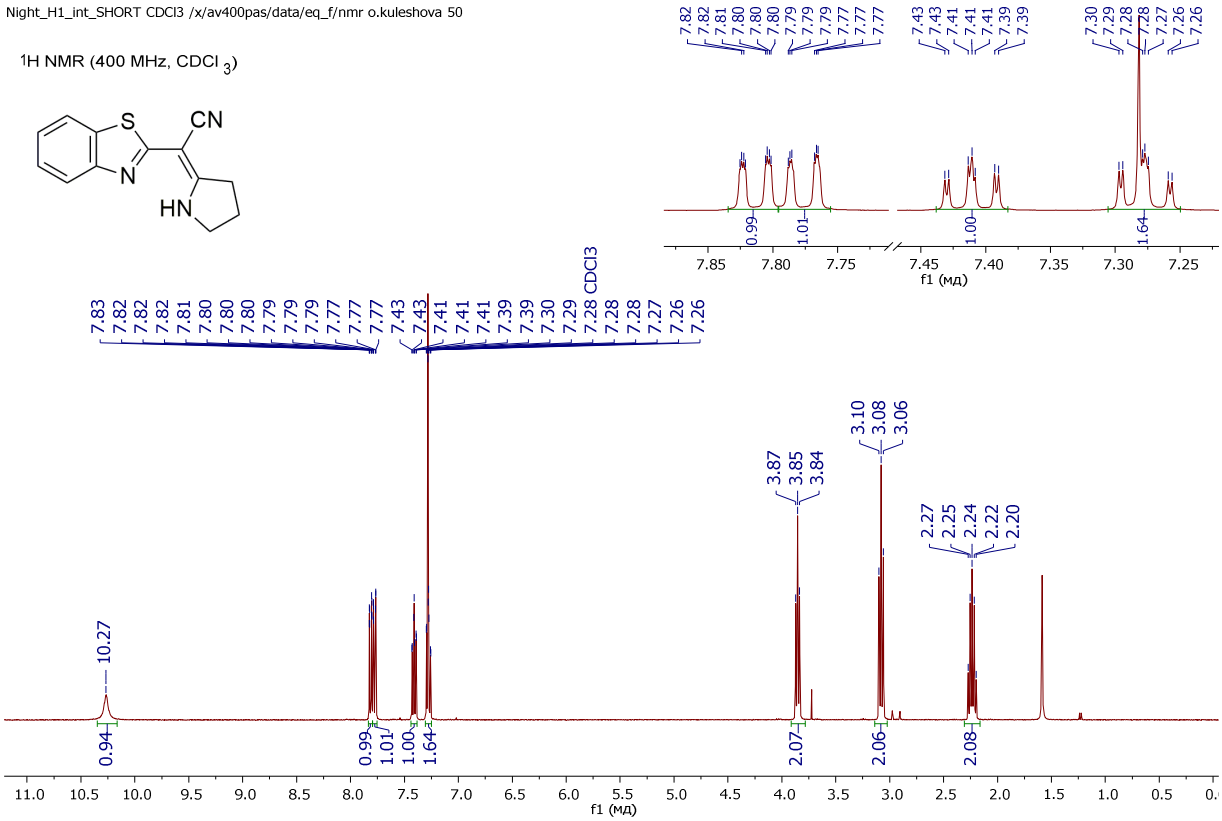
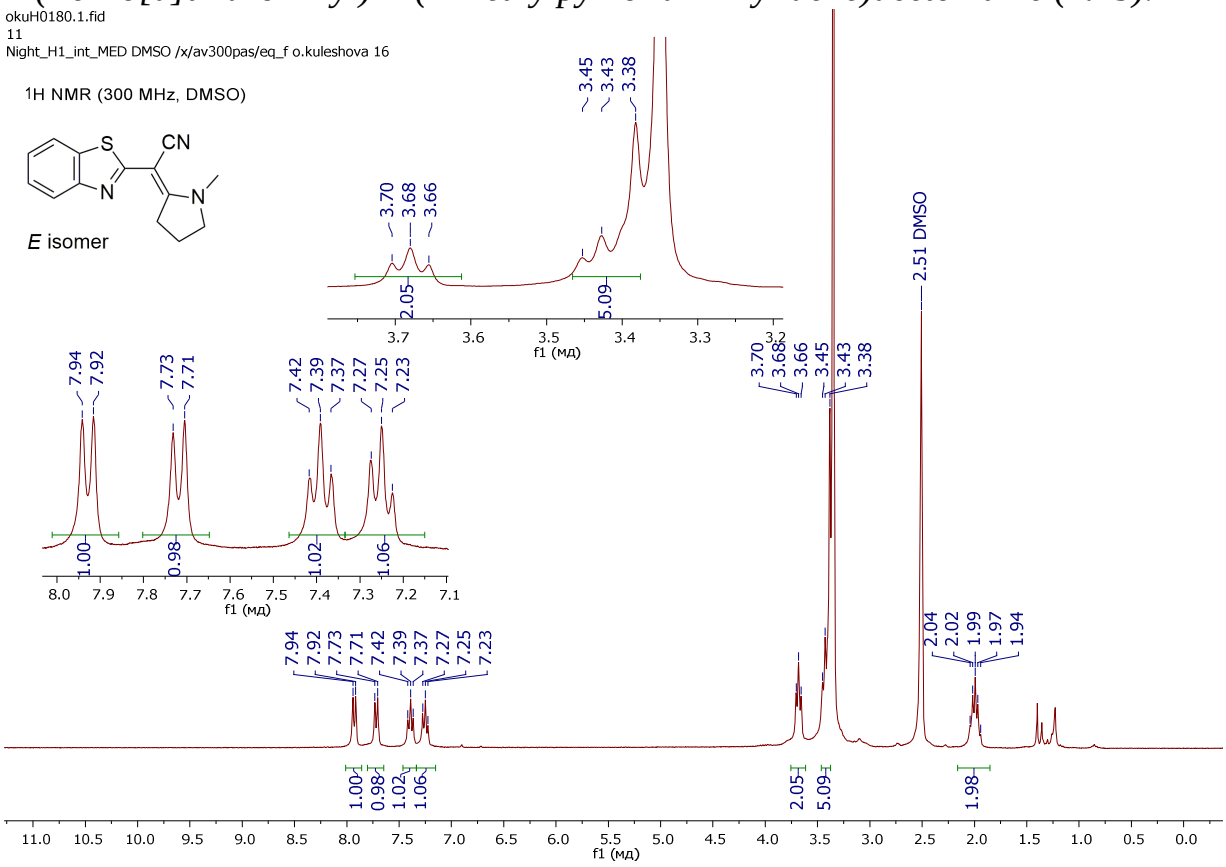


*2-(Benzo[d]thiazol-2-yl)-2-(1-methylpyrrolidin-2-ylidene)acetonitrile (**2.7b**).*

okuH0180.1.fid
11
Night_H1_int_MED DMSO /x/av300pas/eq_f o.kuleshova 16



*2-(Cyano(1-methylpyrrolidin-2-ylidene)methyl)-3-methylbenzo[d]oxazol-3-ium hexafluorophosphate (**2.21**).*

okuG0580.1.fid
BzoNMeNMePF6
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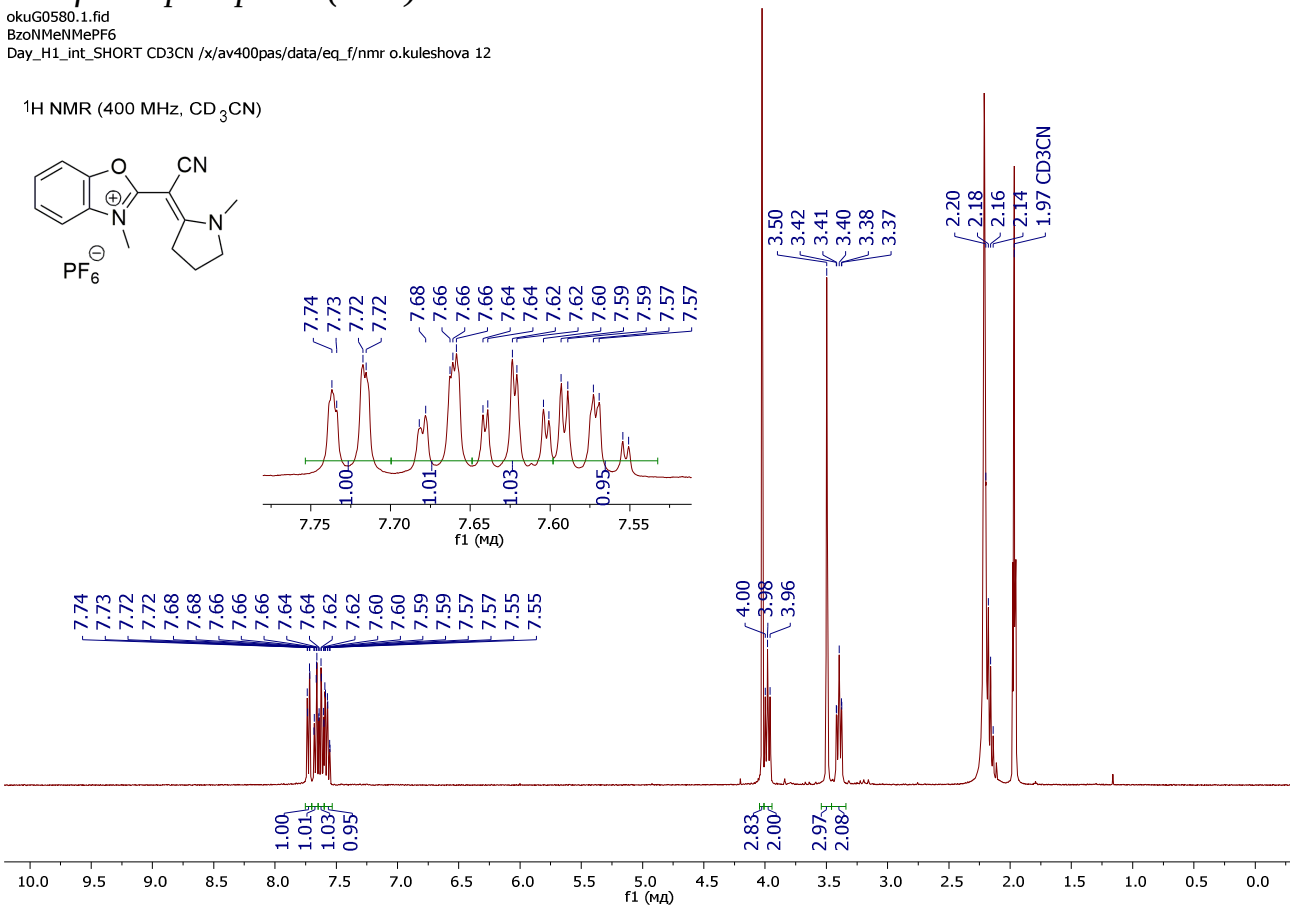

*(Z)-2-(benzo[d]thiazol-2-yl)-2-(5-methyl-3-oxoindolin-2-ylidene)acetonitrile (**2.23b**).*

okuG0602.1.fid
BtIsMe 0.0032g
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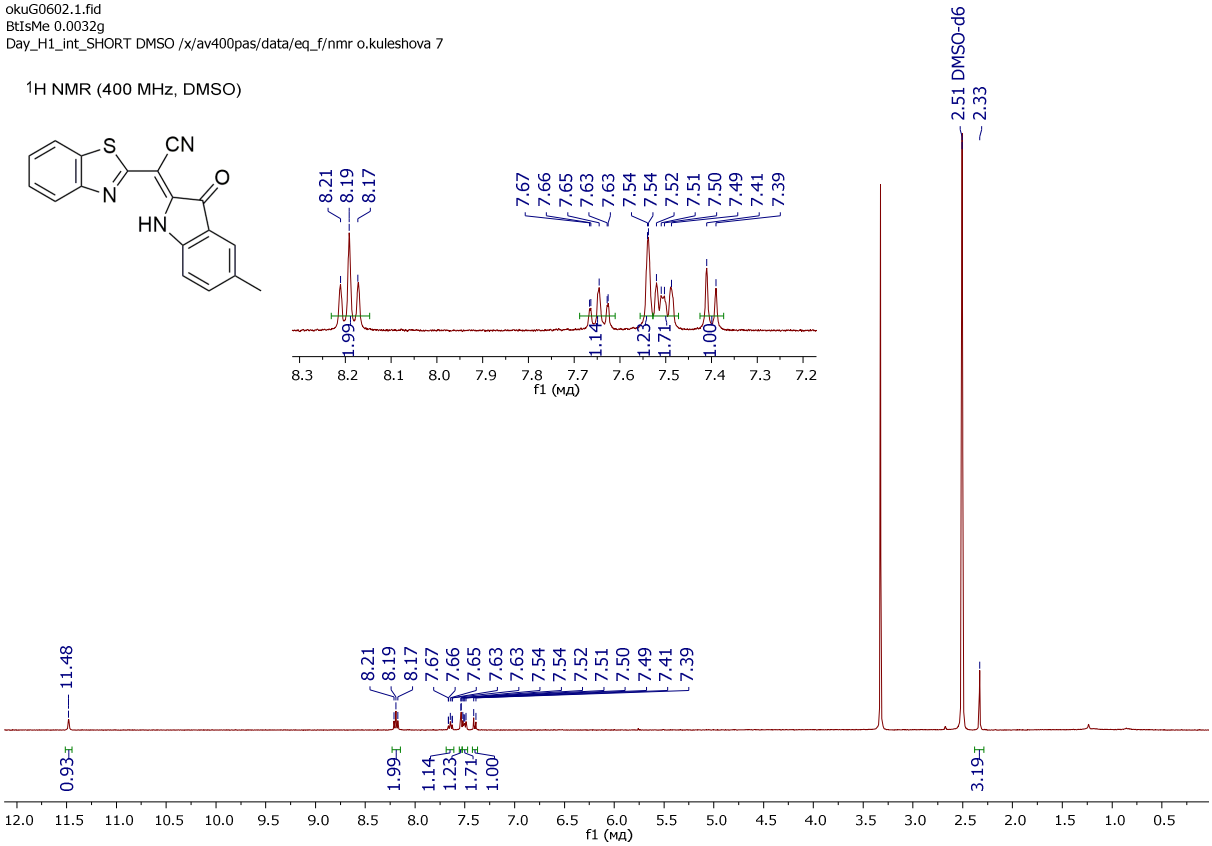
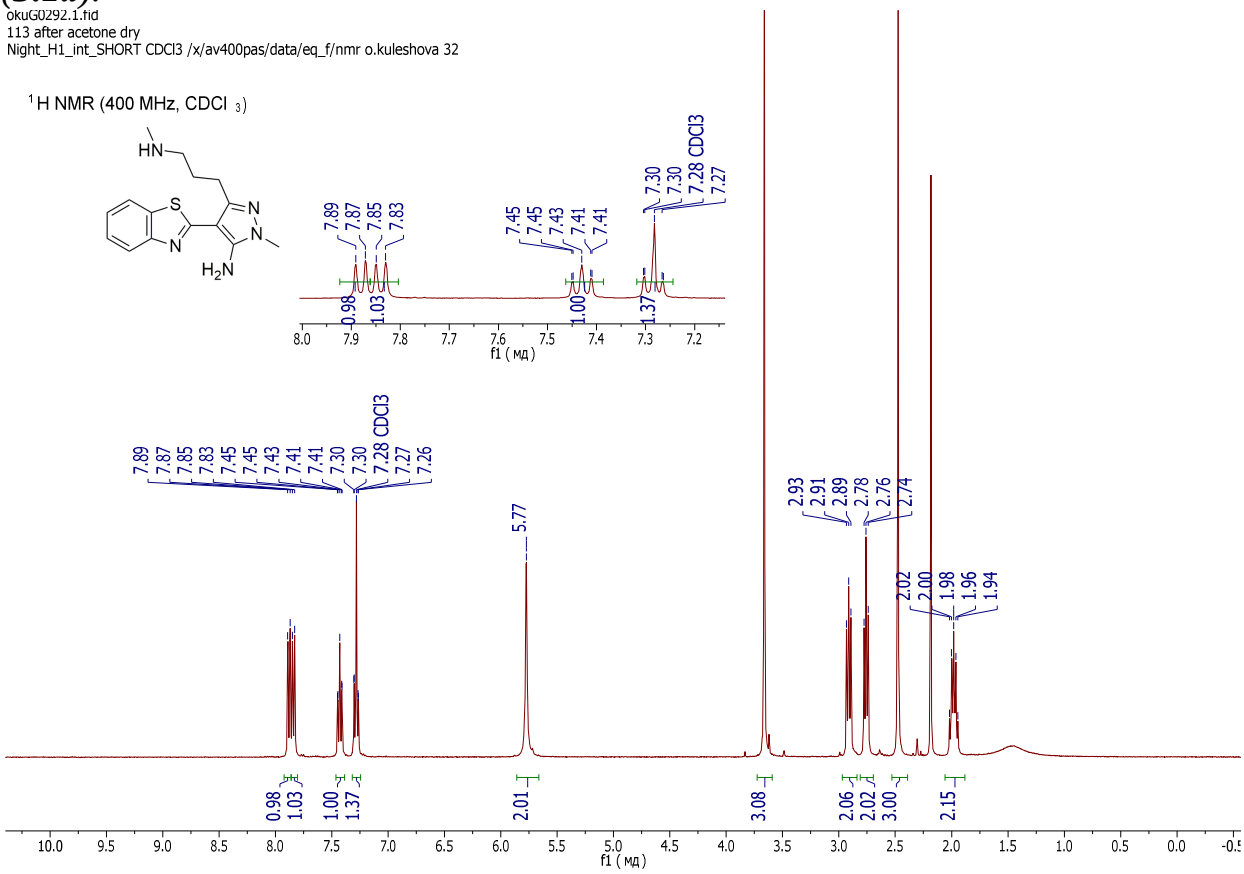


*4-(Benzo[d]thiazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine (**3.1a**).*

okuG0292.1.fid
113 after acetone dry
Night_H1_int_SHORT CDCl3 /x/av400pas/data/eq_f/nmr o.kuleshova 32

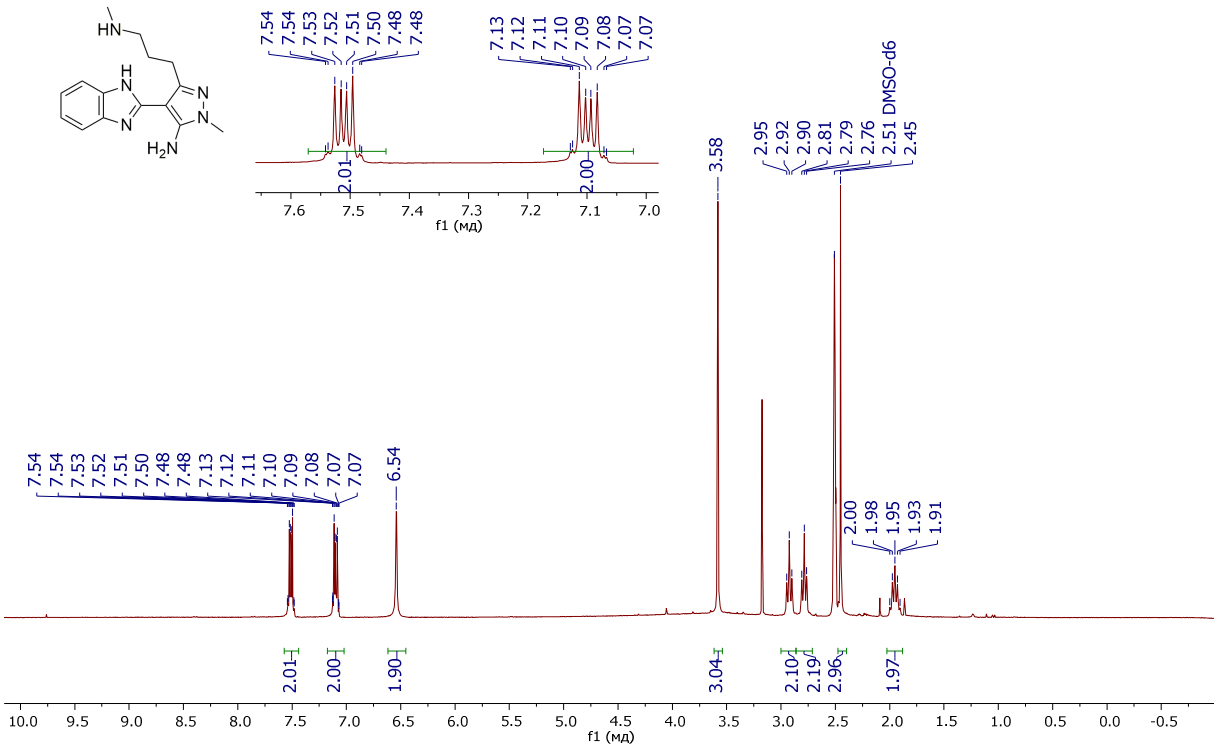
^{1}H NMR (400 MHz, CDCl$_3$)



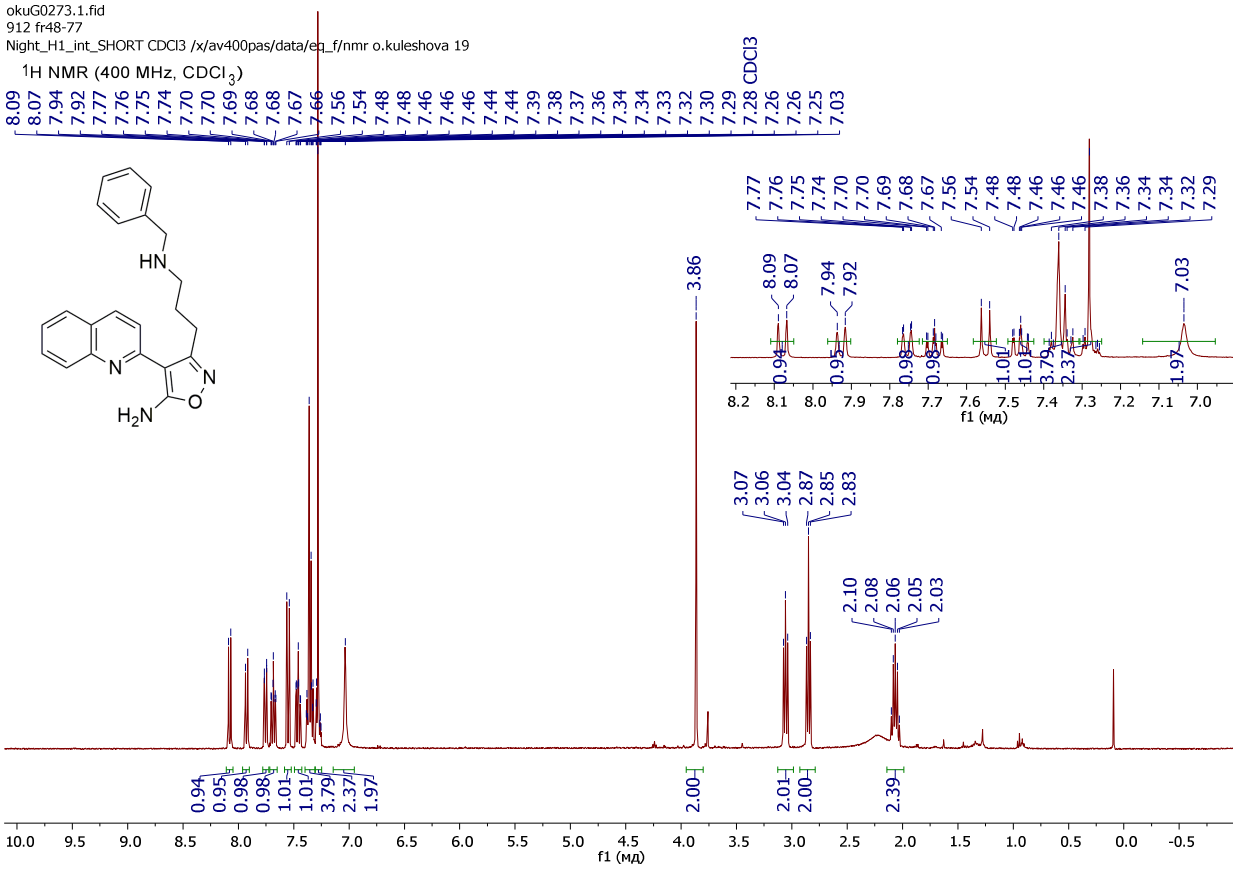
*4-(1H-Benzo[d]imidazol-2-yl)-1-methyl-3-(3-(methylamino)propyl)-1H-pyrazol-5-amine (**3.3a**).*

okuH0351.1.fid
212 11mg
Night_H1_int_SHORT DMSO /x/av300pas/eq_f o.kuleshova 1

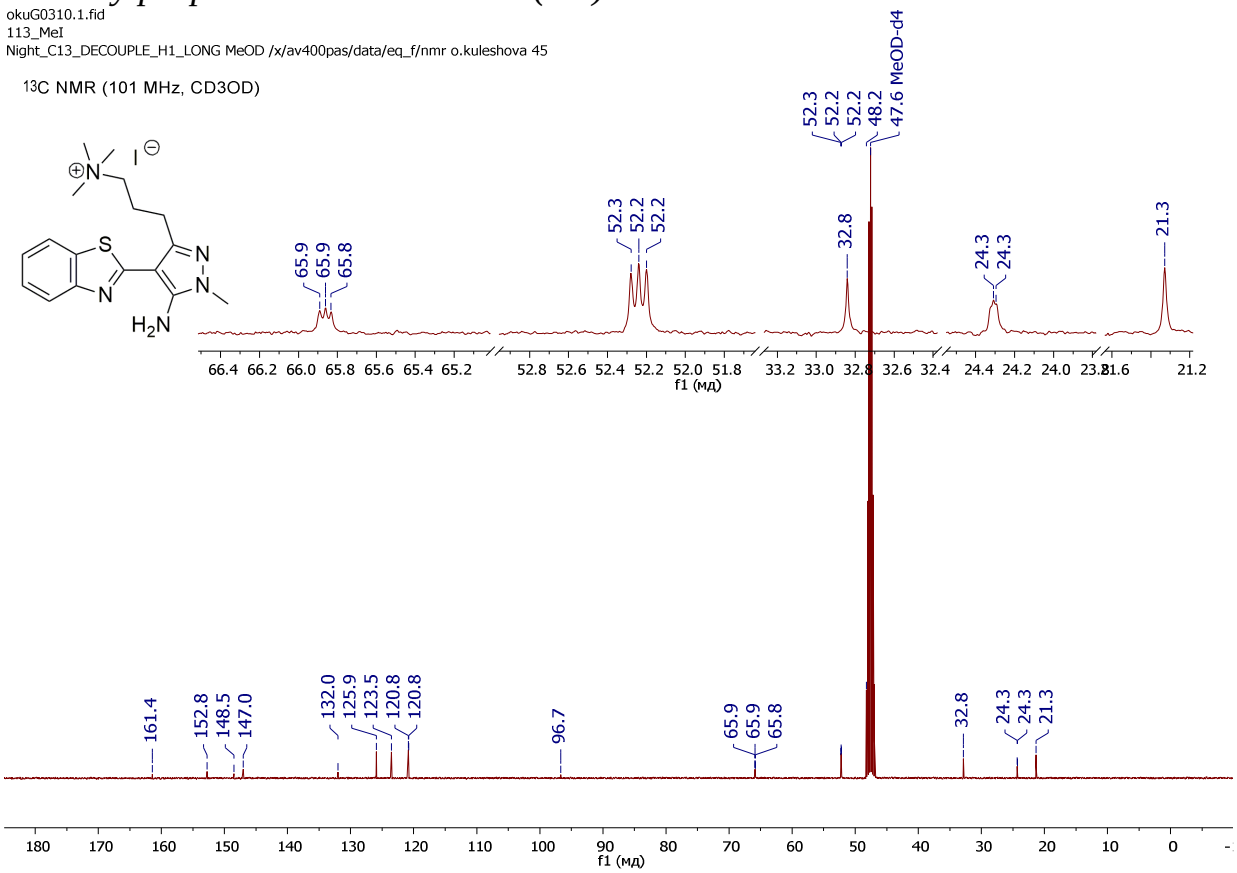
^{1}H NMR (300 MHz, DMSO)



*3-(3-(Benzylamino)propyl)-4-(quinolin-2-yl)isoxazol-5-amine (**3.5b**).*



*3-(5-Amino-4-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrazol-3-yl)-N,N,N-trimethylpropan-1-aminium iodide (**3.8**).*



*Tert-butyl (3-(4-(benzo[d]thiazol-2-yl)-5-(benzylamino)-1-methyl-1H-pyrazol-3-yl)propyl)(methyl)carbamate (**3.10**).*

okuG0746.1.fid
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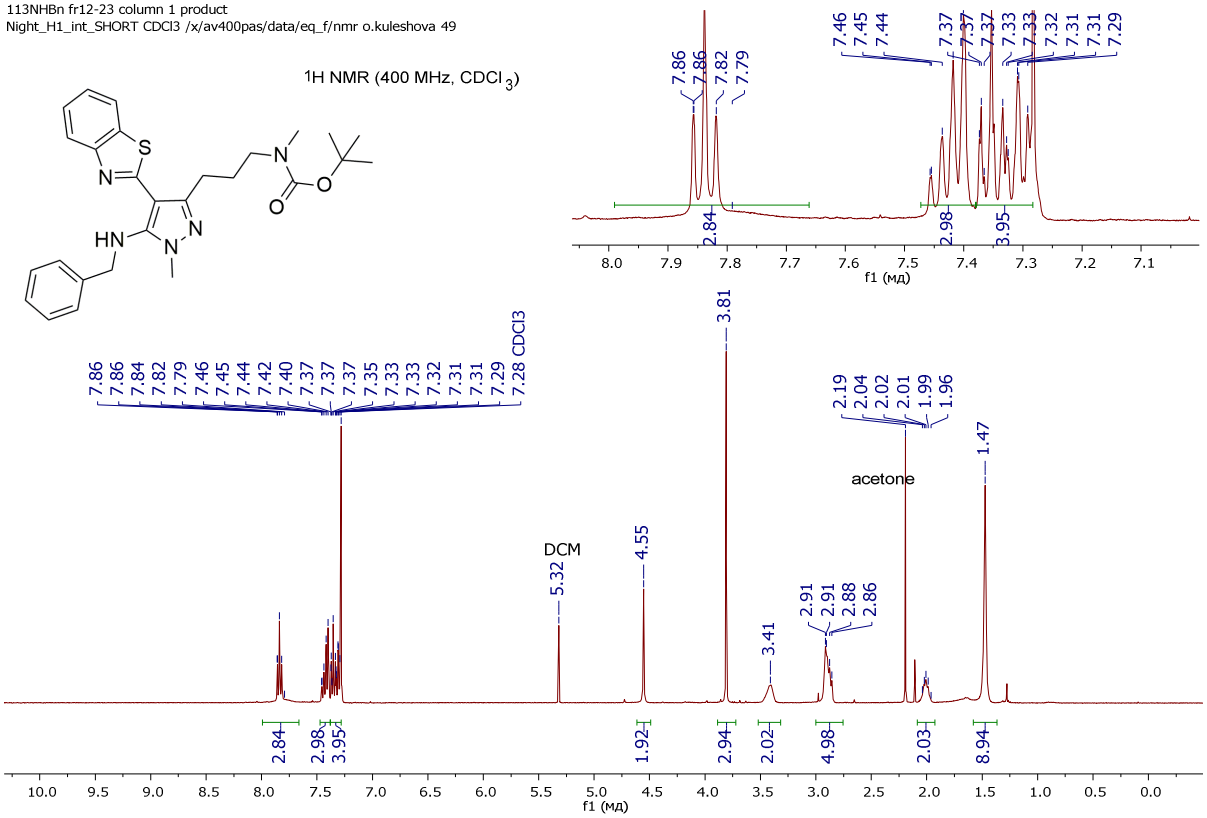
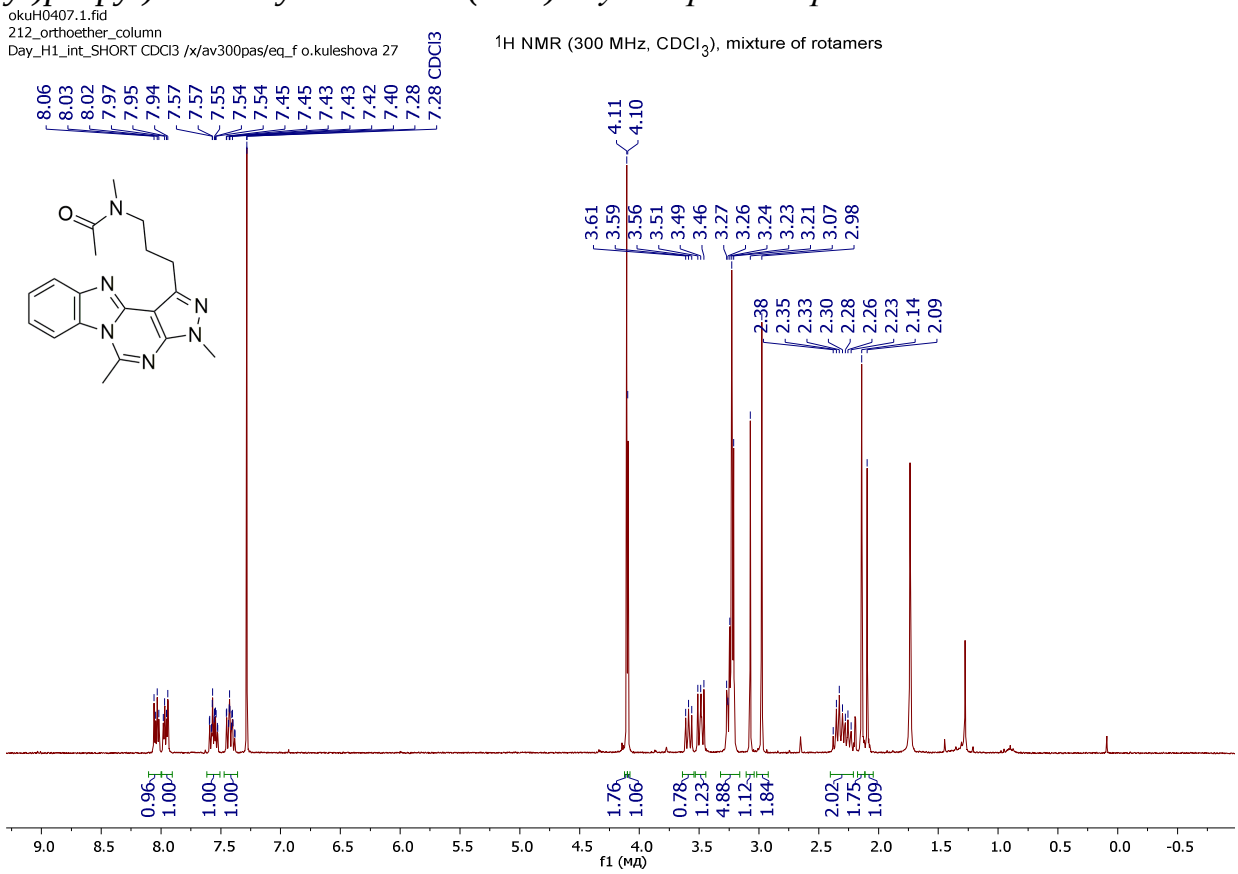
Night_H1_int_SHORT CDCl3 /x/av400pas/data/eq_f/nmr o.kuleshova 49



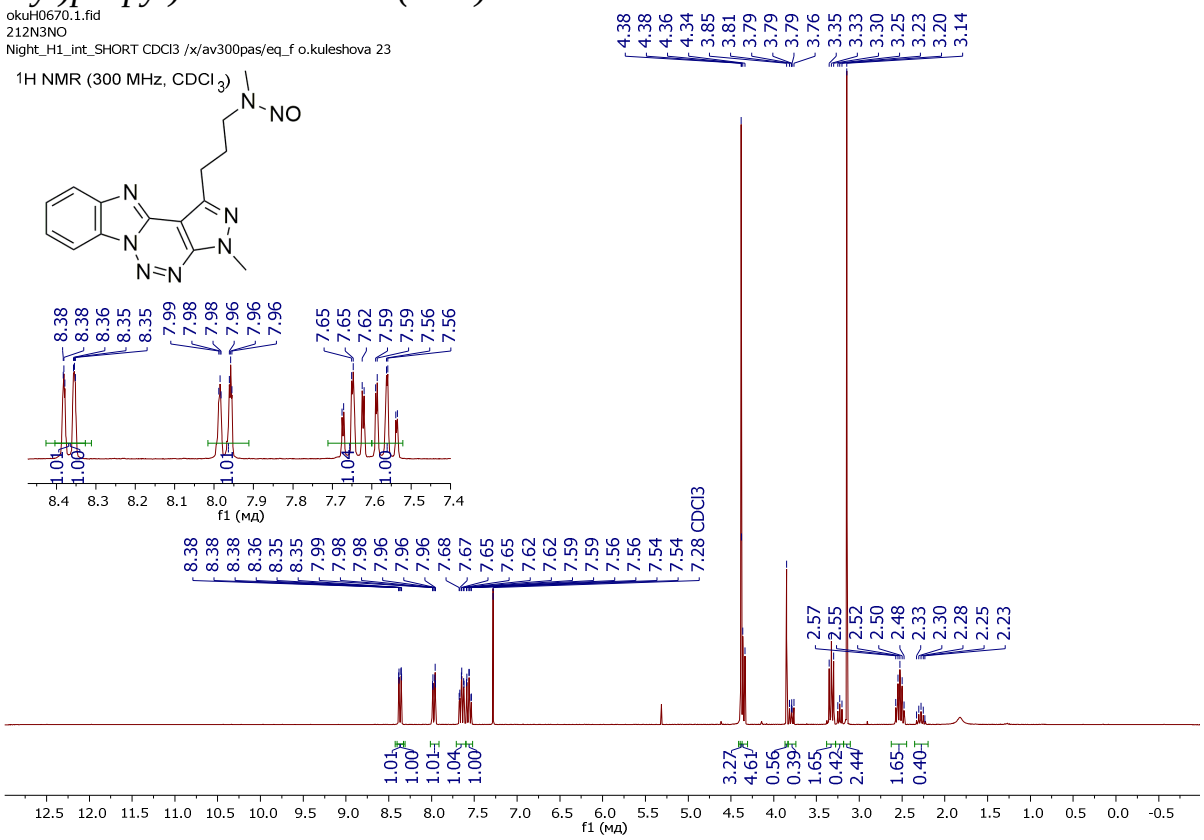
*N-(3-(3,5-dimethyl-3H-benzo[4,5]imidazo[1,2-c]pyrazolo[4,3-e]pyrimidin-1-yl)propyl)-N-methylacetamide (**3.11**). Суміш ротамерів.*

okuH0407.1.fid
212_orthoether_column
Day_H1_int_SHORT CDCl3 /x/av300pas/eq_f o.kuleshova 27



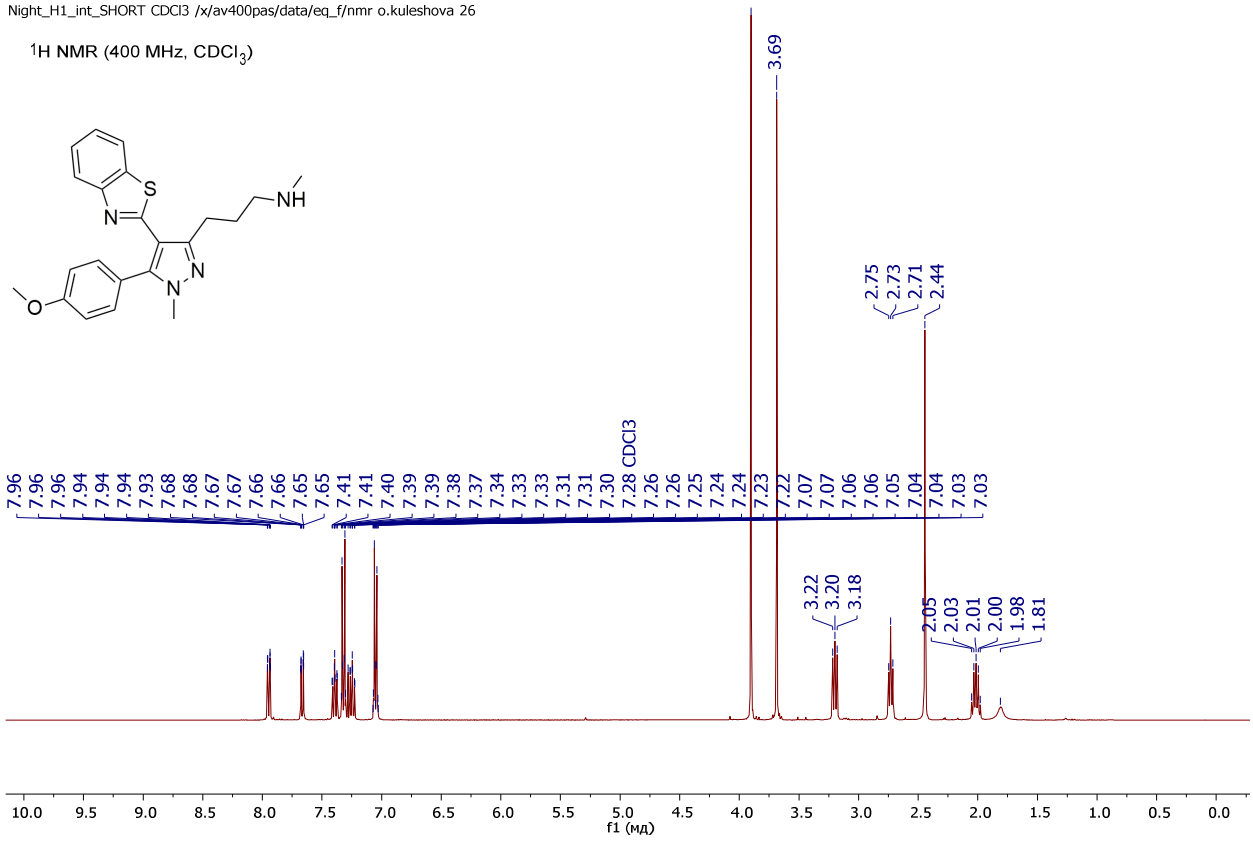
*N-methyl-N-(3-(3-methyl-3H-benzo[4,5]imidazo[1,2-c]pyrazolo[4,3-e][1,2,3]triazin-1-yl)propyl)nitrous amide (**3.12**).*

okuH0670.1.fid
212N3NO
Night_H1_int_SHORT CDCl3 /x/av300pas/eq_f o.kuleshova 23



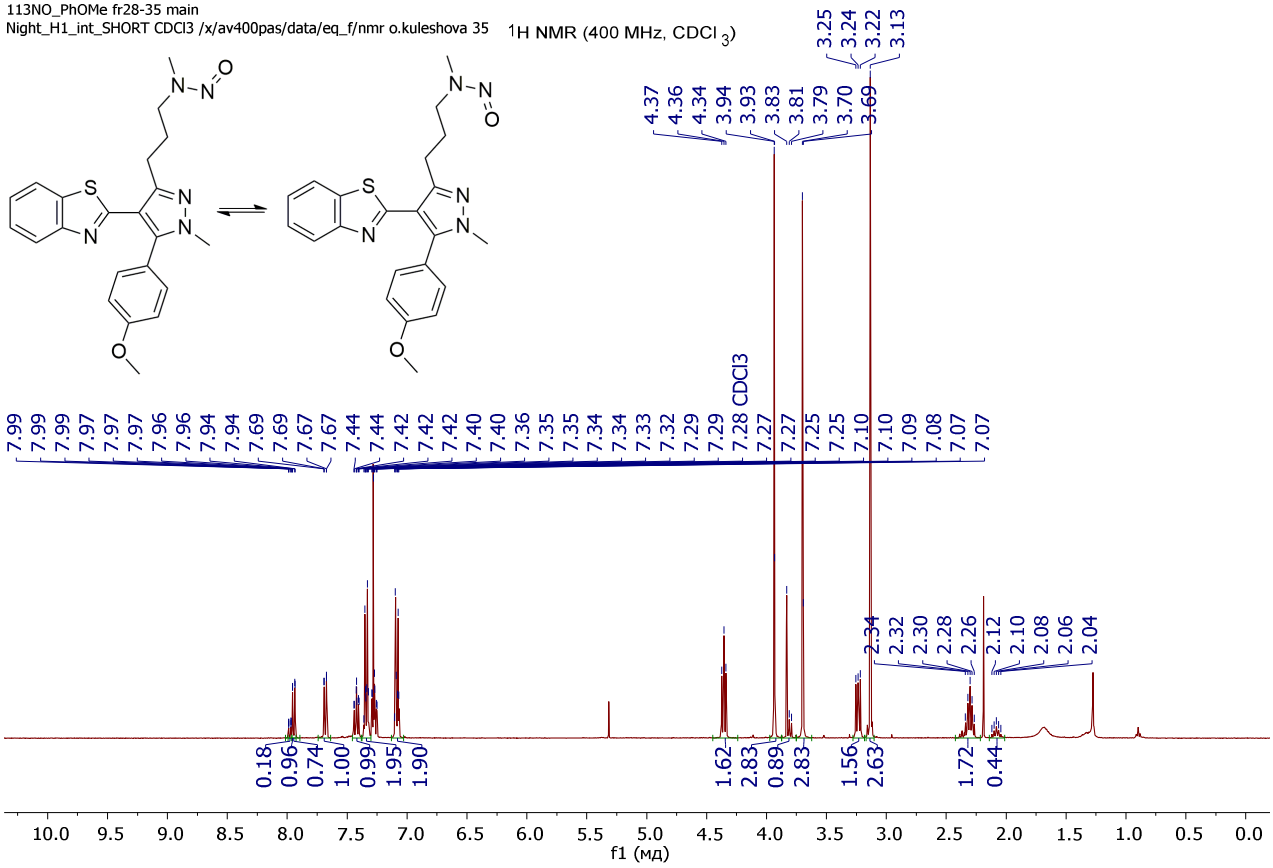
*3-(4-(benzo[d]thiazol-2-yl)-5-(4-methoxyphenyl)-1-methyl-1H-pyrazol-3-yl)-N-methylpropan-1-amine (**3.16a**).*

okuG0507.1.fid
113 Ph OMe after MeOH NH3
Night_H1_int_SHORT CDCl3 /x/av400pas/data/eq_f/nmr o.kuleshova 26



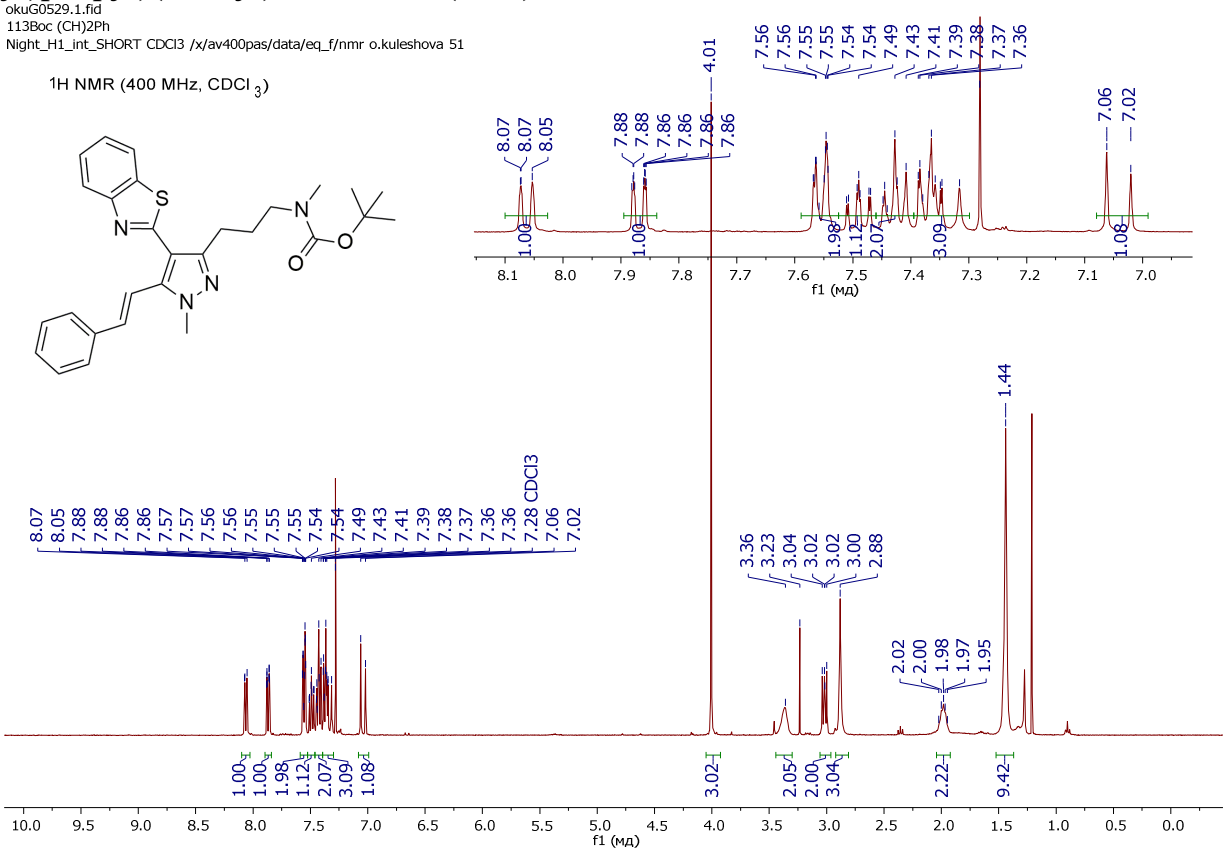
*N-(3-(4-(benzo[d]thiazol-2-yl)-5-(4-methoxyphenyl)-1-methyl-1H-pyrazol-3-yl)propyl)-N-methylnitrous amide (**3.16c**).*

okuG0619.1.fid
113NO_PhOMe fr28-35 main
Night_H1_int_SHORT CDCl3 /x/av400pas/data/eq_f/nmr o.kuleshova 35



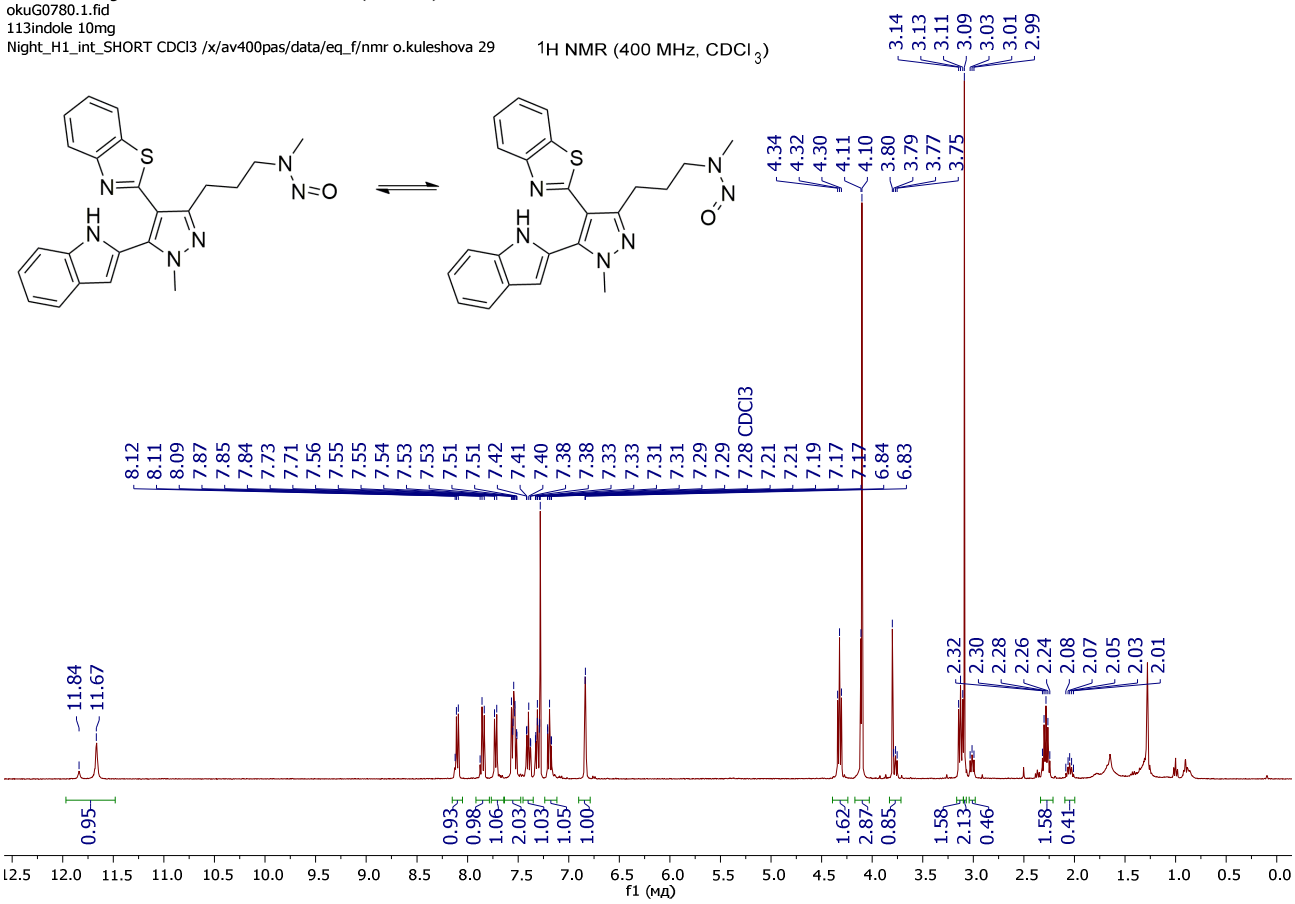
*(E)-Tert-butyl (3-(4-(benzo[d]thiazol-2-yl)-1-methyl-5-styryl-1H-pyrazol-3-yl)propyl)(methyl)carbamate (**3.19**).*

okuG0529.1.fid
113Boc (CH)2Ph
Night_H1_int_SHORT CDCl3 /x/av400pas/data/eq_f/nmr o.kuleshova 51



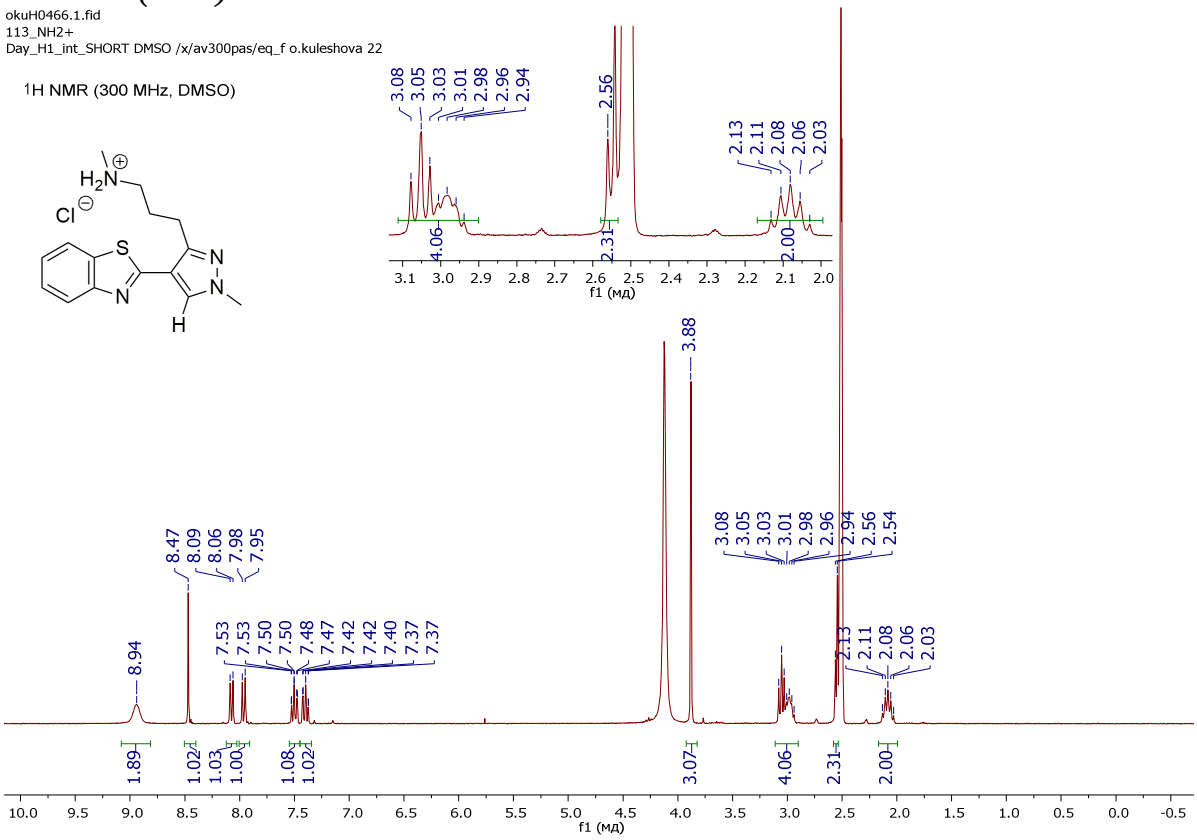
*N-(3-(4-(benzo[d]thiazol-2-yl)-5-(1H-indol-2-yl)-1-methyl-1H-pyrazol-3-yl)propyl)-N-methylnitrous amide (**3.20**).*

okuG0780.1.fid
113indole 10mg
Night_H1_int_SHORT CDCl3 /x/av400pas/data/eq_f/nmr o.kuleshova 29

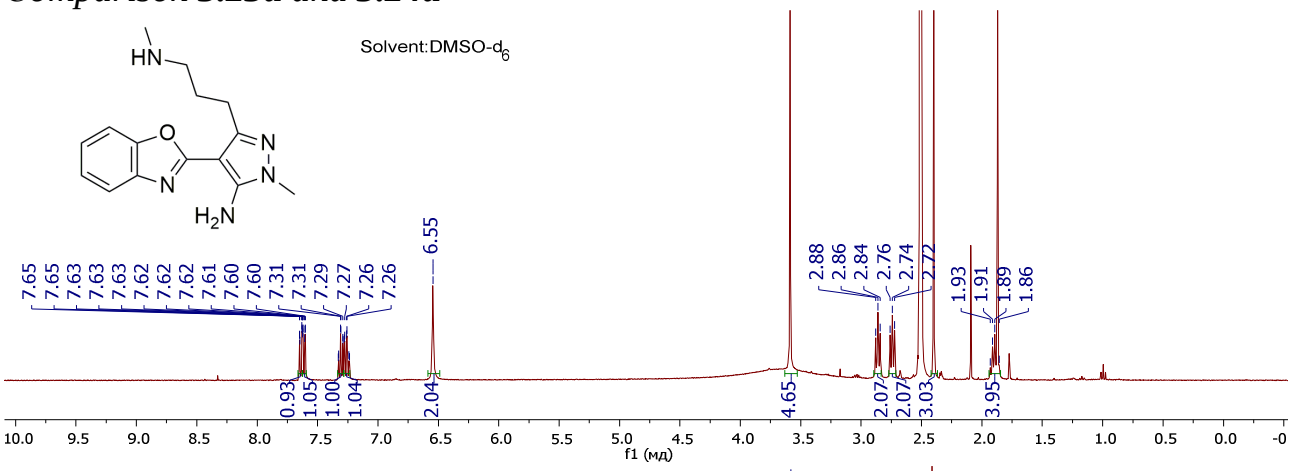


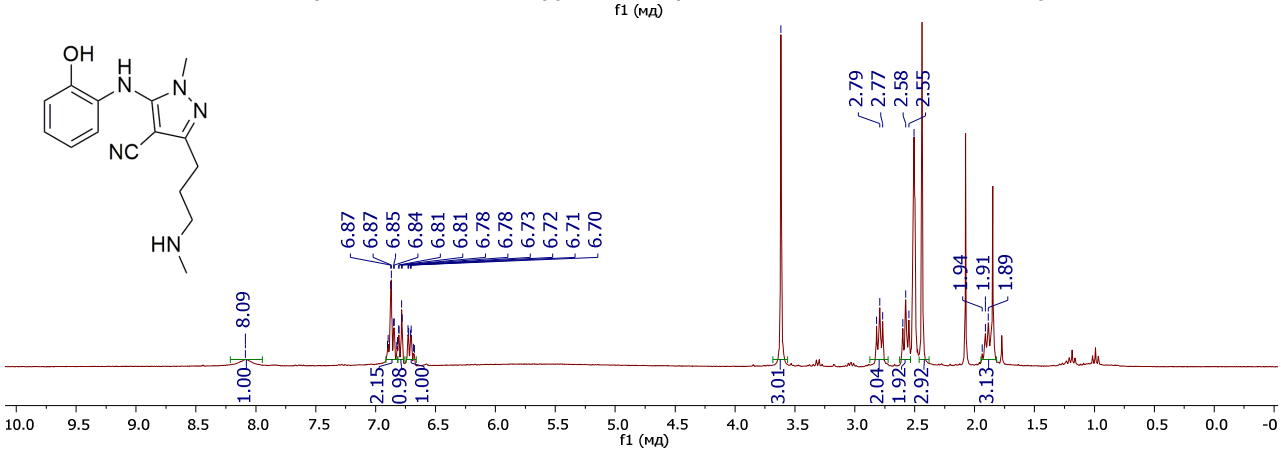
*3-(4-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrazol-3-yl)-N-methylpropan-1-aminium chloride (**3.22**).*

okuH0466.1.fid
113_NH2+
Day_H1_int_SHORT DMSO /x/av300pas/eq_f o.kuleshova 22

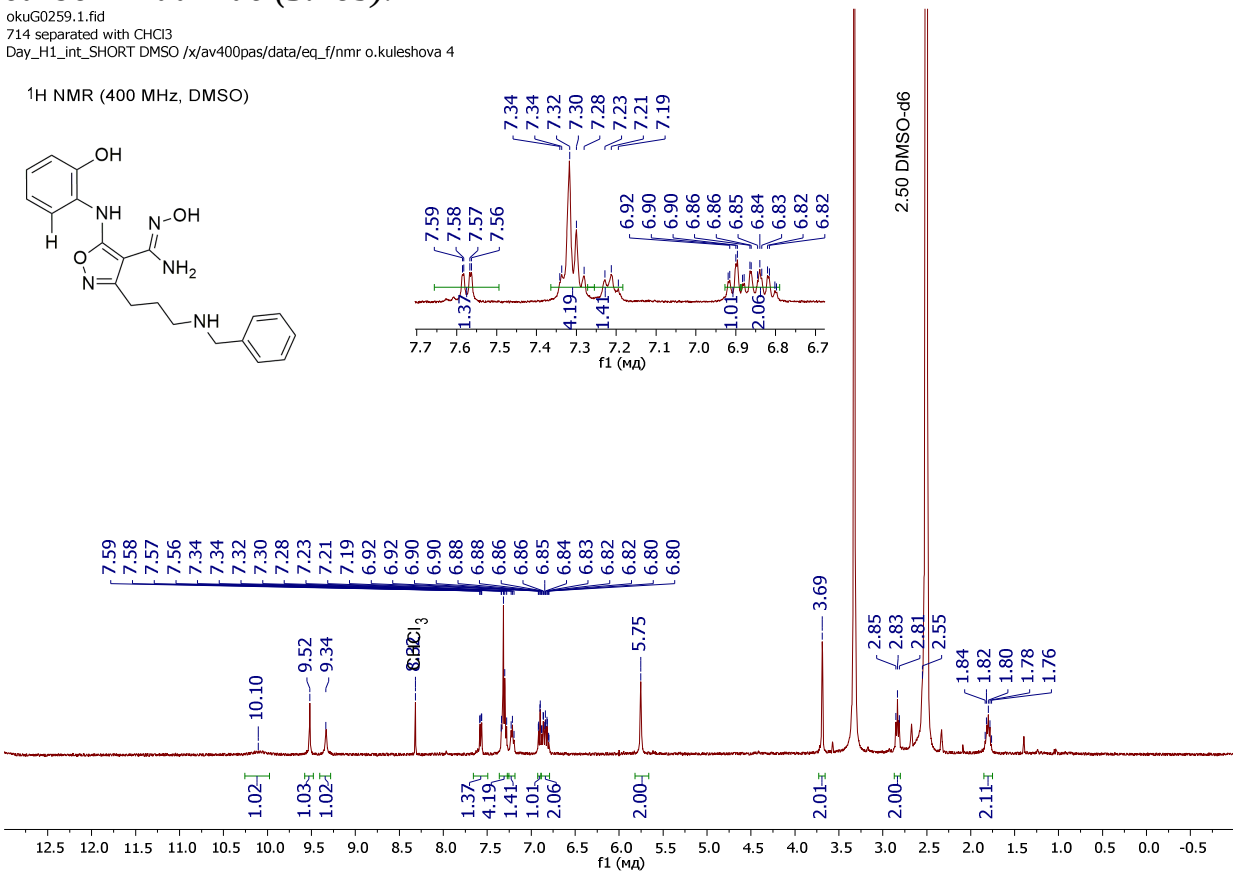


*Comparison **3.23a** and **3.24a***





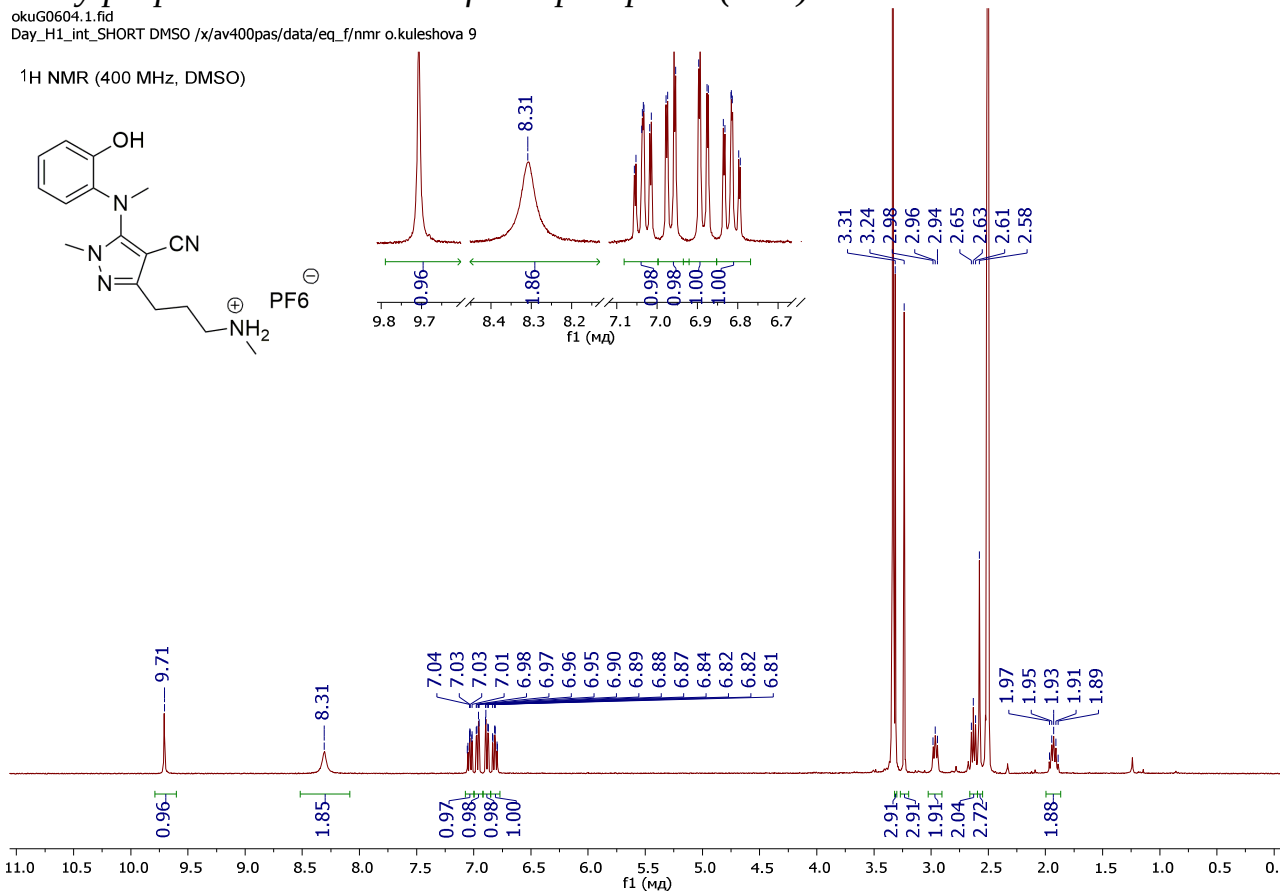
*(Z)-3-(3-(benzylamino)propyl)-N'-hydroxy-5-((2-hydroxyphenyl)amino)isoxazole-4-carboximidamide (**3.26b**).*



*3-(4-cyano-5-((2-hydroxyphenyl)(methyl)amino)-1-methyl-1H-pyrazol-3-yl)-N-methylpropan-1-aminium hexafluorophosphate (**3.28**).*

okuG0604.1.fid
Day_H1_int_SHORT DMSO /x/av400pas/data/eq_f/nmr o.kuleshova 9

^{1}H NMR (400 MHz, DMSO)



*3-Imino-2,5-dimethyl-4-((2-(methylamino)phenyl)thio)-2,3,5,6,7,8-hexahydropyrazolo[4,3-c]azepin-1-ium hexafluorophosphate (**3.30**).*

okuK0058.1.fid
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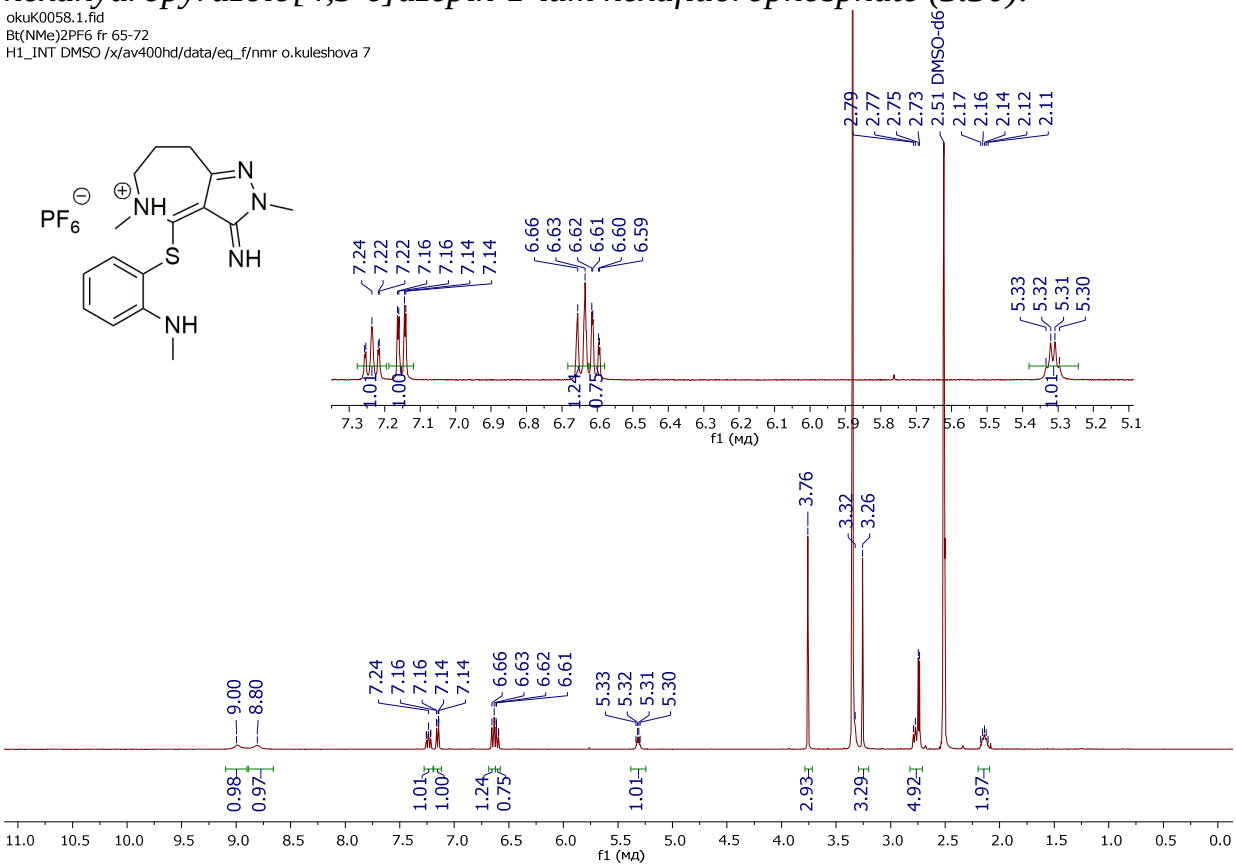
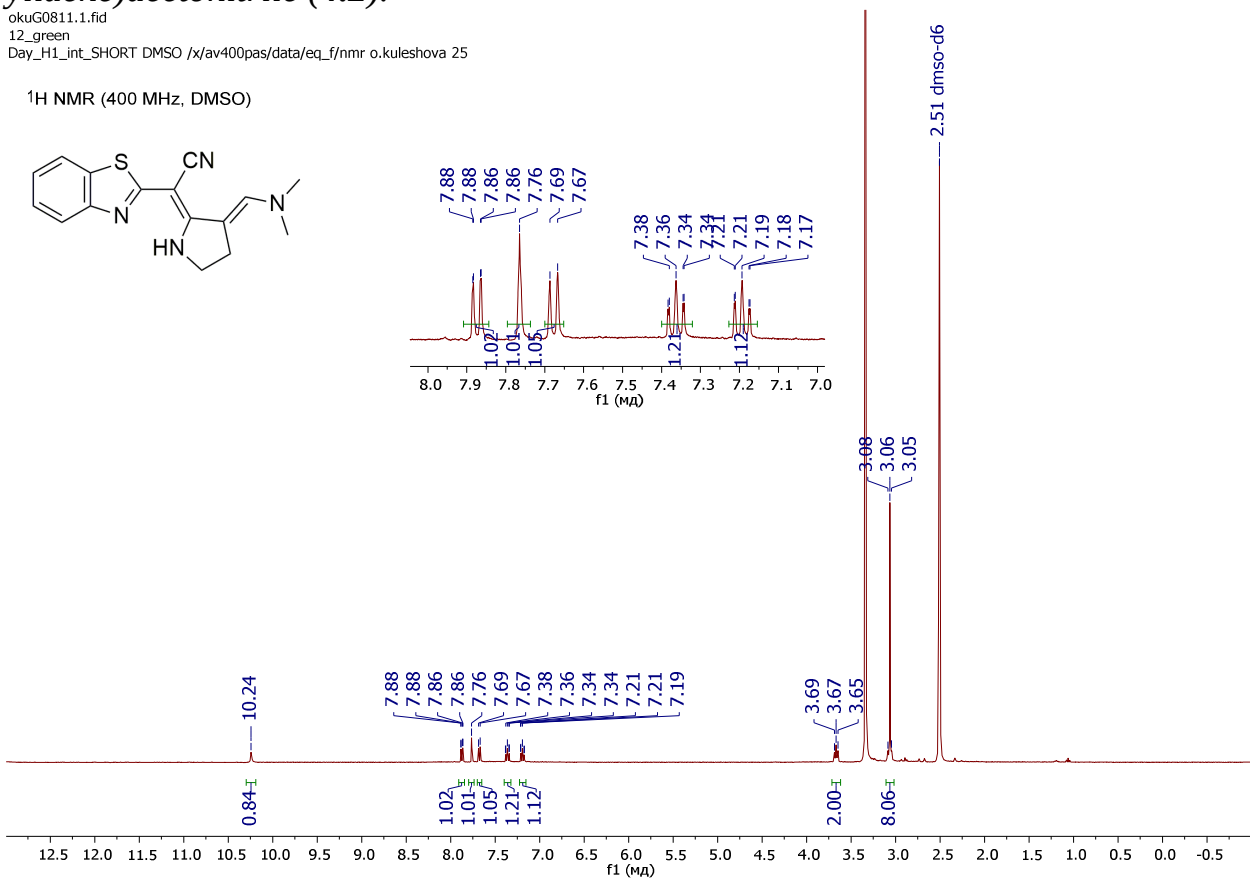
H1_INT DMSO /x/av400hd/data/eq_f/nmr o.kuleshova 7



*(Z)-2-(benzo[d]thiazol-2-yl)-2-3-((dimethylamino)methylene)pyrrolidin-2-ylidene)acetonitrile (**4.2**).*

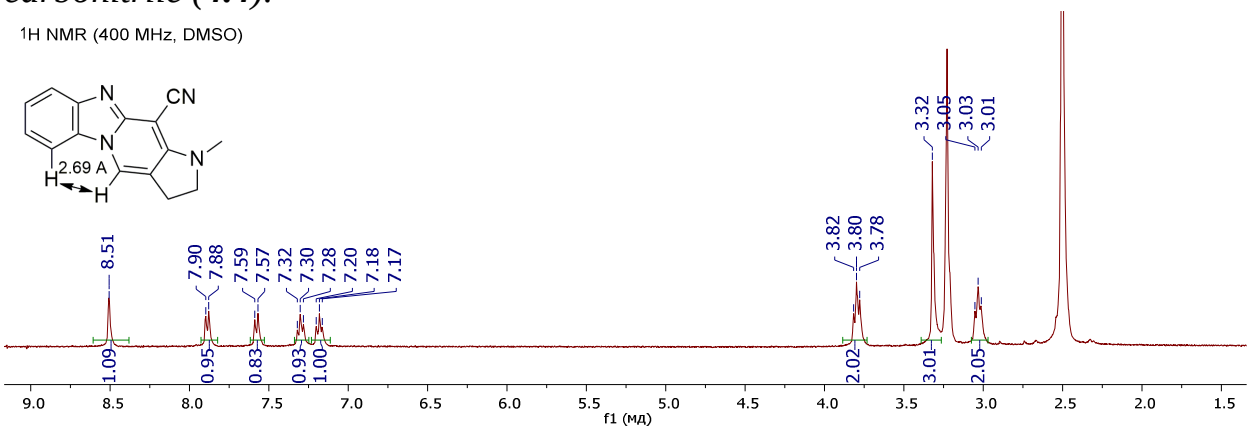
okuG0811.1.fid
12_green
Day_H1_int_SHORT DMSO /x/av400pas/data/eq_f/nmr o.kuleshova 25

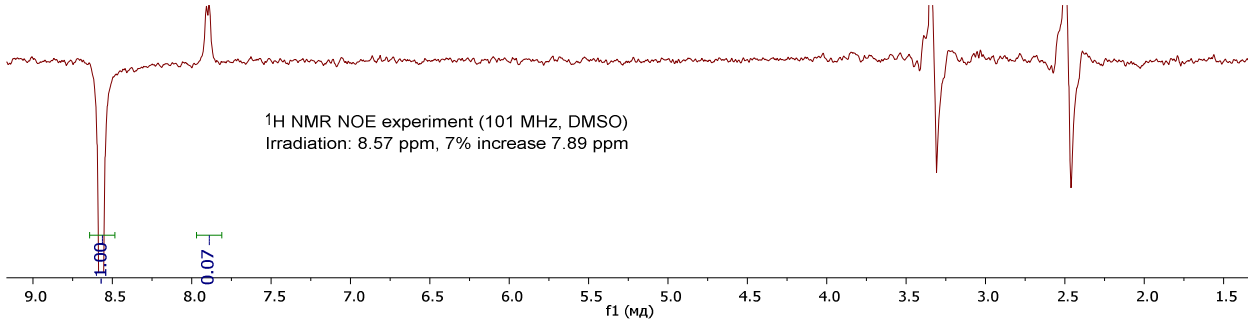
^{1}H NMR (400 MHz, DMSO)



*1-methyl-2,3-dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrrolo[2,3-d]pyridine-11-carbonitrile (**4.4**).*

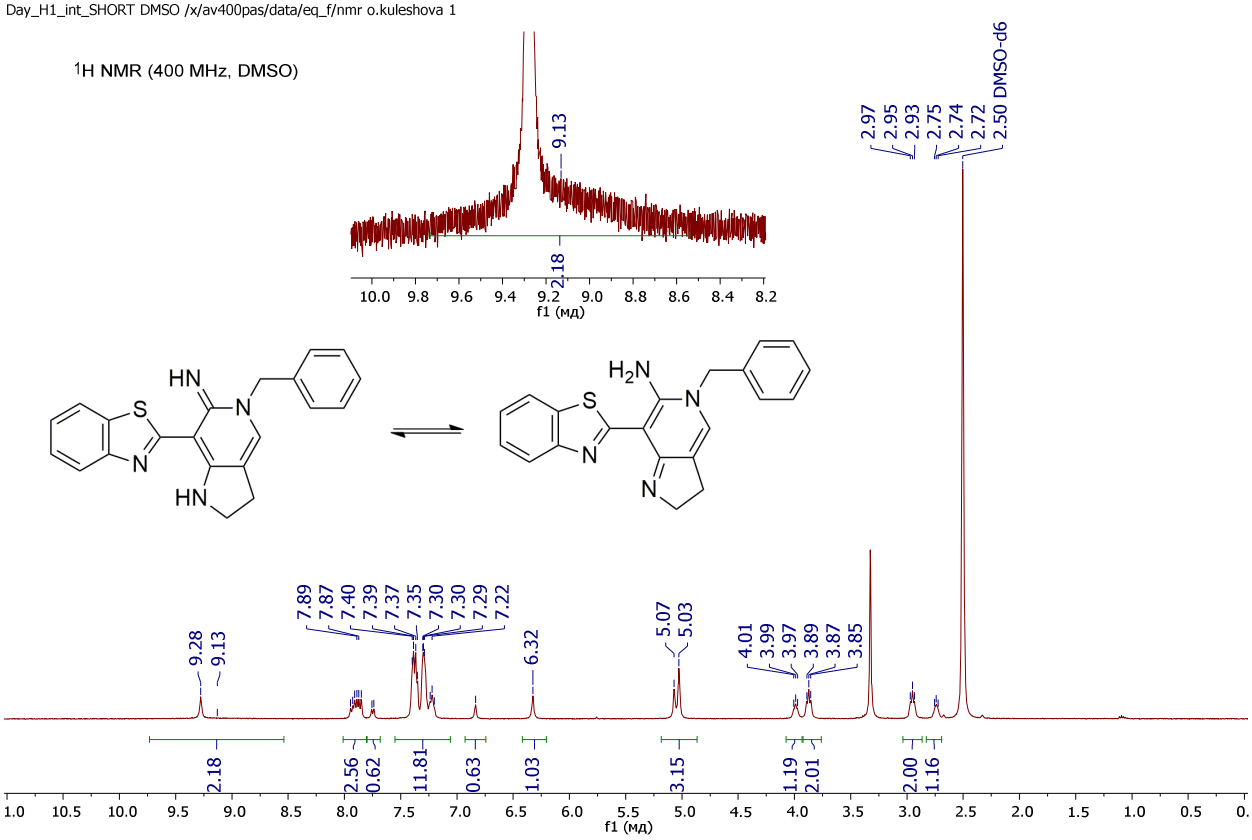
^{1}H NMR (400 MHz, DMSO)



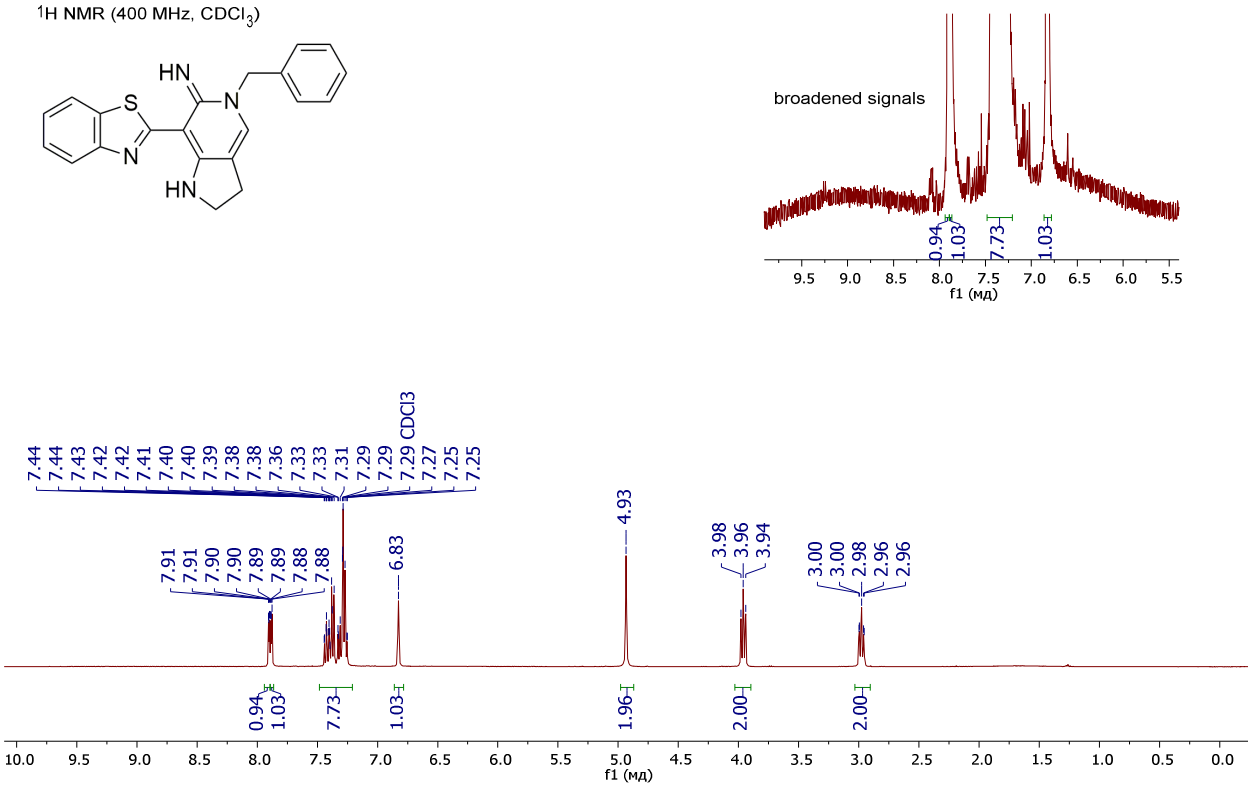


7-(benzo[d]thiazol-2-yl)-5-benzyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-6(5H)-imine ***(4.9)***.

okuG0655.1.fid
121_1 ampula dmso
Day_H1_int_SHORT DMSO /x/av400pas/data/eq_f/nmr o.kuleshova 1

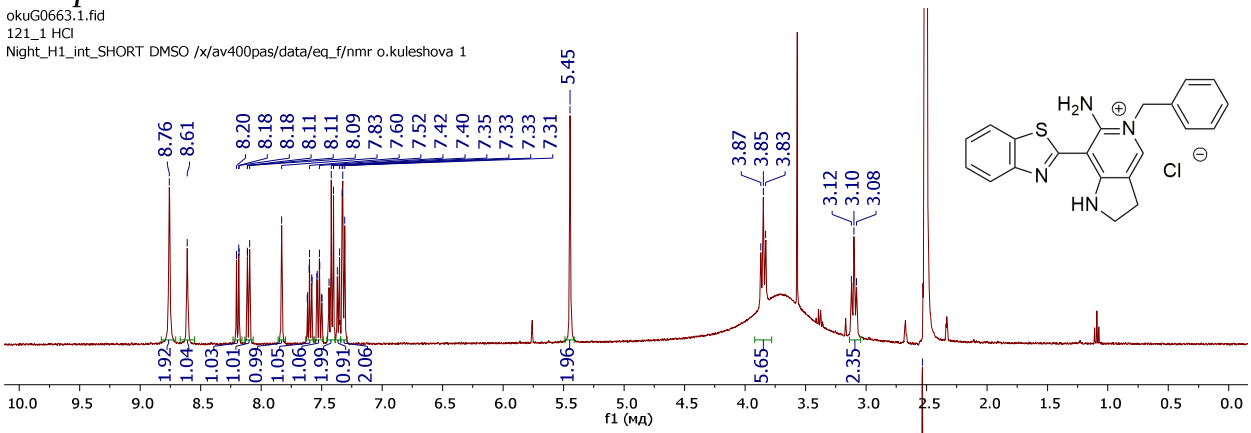


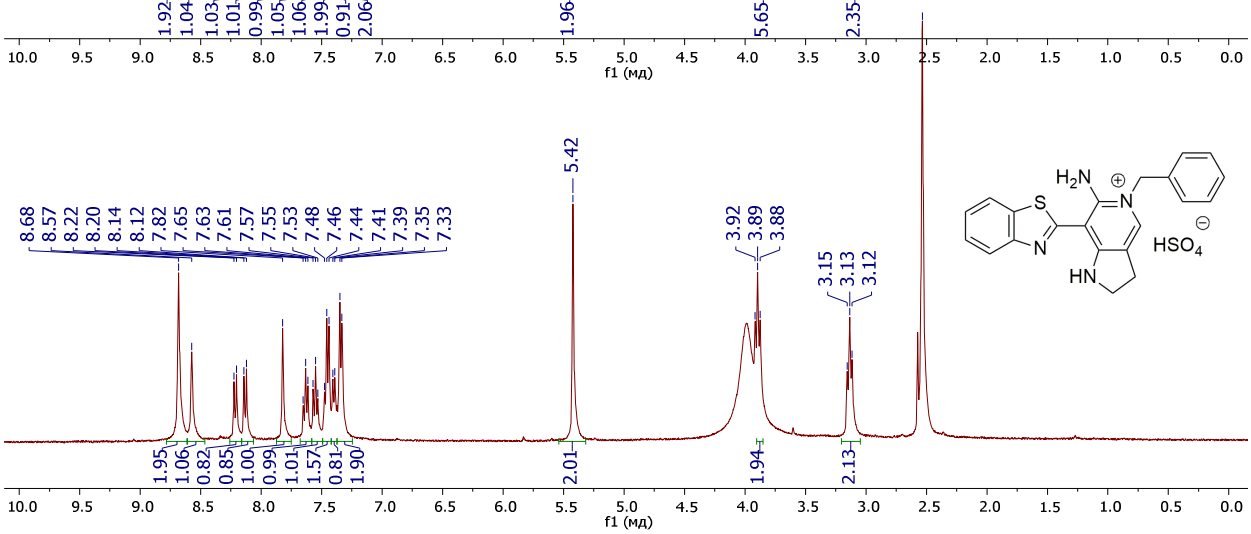
okuK0065.1.fid
121_1
H1_INT CDCl3 /x/av400hd/data/eq_f/nmr o.kuleshova 8



*Comparison **4.10a** and **4.10b**.*

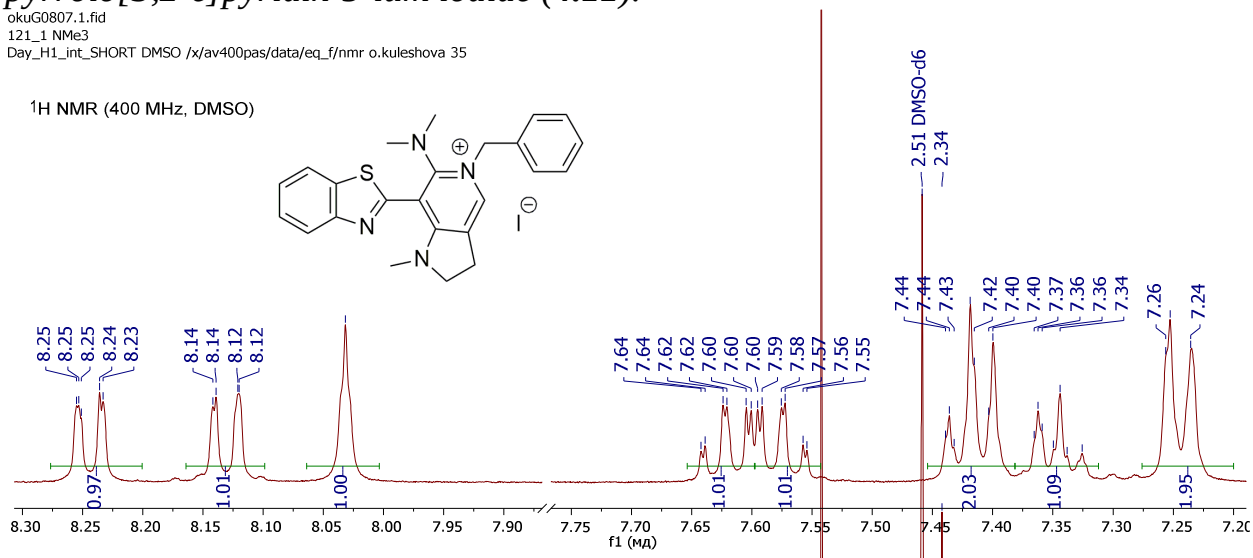
okuG0663.1.fid
121_1 HCl
Night_H1_int_SHORT DMSO /x/av400pas/data/eq_f/nmr o.kuleshova 1

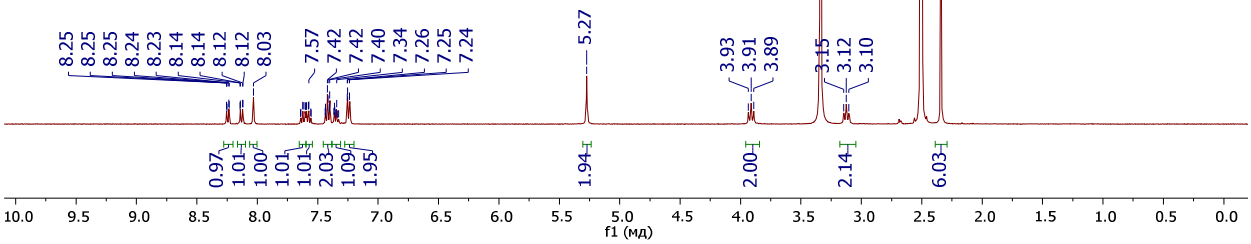




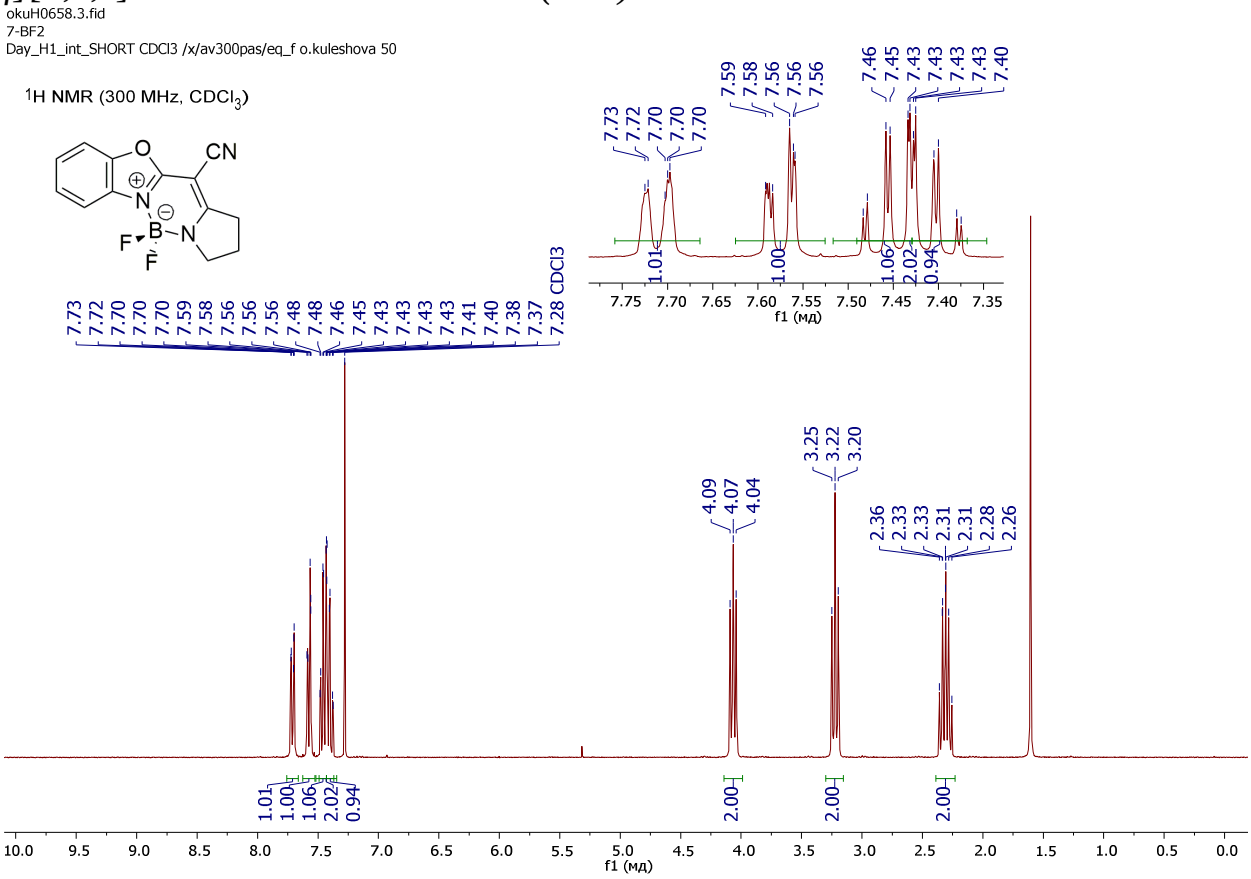
*7-(Benzo[d]thiazol-2-yl)-5-benzyl-6-(dimethylamino)-1-methyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-5-ium iodide (**4.11**).*

okuG0807.1.fid
121_1 NMe3
Day_H1_int_SHORT DMSO /x/av400pas/data/eq_f/nmr o.kuleshova 35





*12-Cyano-5,5-difluoro-1,2,3,5-tetrahydrobenzo[4,5]oxazolo[3,2-c]pyrrolo[2,1-f][1,3,2]diazaborinin-6-ium-5-uide (**5.1b**).*



PUBLICATION LIST

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3. Amirkhanov, V.M.; Volovenko, Yu.M.; Davidenko, N.A.; **Kuleshova, E.A.**; Litsis, O.O.; Mokrinskaya, E.V.; Sliva, T.Yu.; Khilya, O.V.; Chuprina, N.G. Photovoltaic properties of polymeric film composites with Ni(II), Co(II) and Cu(II) complexes, *Theor. Exp. Chem.*, **2017**, *53* (3), 187-193.
4. **Kuleshova, O.**; Khilya, O.; Volovenko, Yu.; Mallet-Ladeira, S.; Dyakonenko, V.; Gras, E. Expedited route to fully substituted amino-pyrazole building blocks and their further transformations. *ACS Omega*, **2017**, *2*, 8911-8927.
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1. Kuleshova, O.; Khilya, O.; Volovenko, Y.; Gras E. Functionalized azaheterocycles: straightforward approaches to new bimodal imaging probes. *8th International conference in chemistry Toulouse-Kiev*, Materials of reports and performances, Toulouse, France, 1-3^{d} June **2015**; p. 193.
2. Kuleshova, O.; Khilya, O.; Volovenko, Y.; Gras, E. Azahetarylacetonitrile chemistry: prospects seeing with fresh eyes. *Jornées de chimie organique September*, Programme and Book of Abstracts, Palaiseau, France 7-9 September **2016**; p. 367.

3. Scherban, V.V.; Kuleshova, O.O.; Keda T.E.; Khilya, O.V.; Zaporozhets, O.A.; Volovenko, Yu.M. New heterocyclic derivatives of benzothiazole as promising spectroscopic reagents. *Modern trends 2016,* Book of abstracts of Kyiv conference on analytical chemistry, Kyiv, Ukraine, 18-22 October **2016**; p.22.

4. Kuleshova, O.; Khilya, O.; Volovenko, Y.; Gras E. Toward the synthesis of fully substituted 4-hetarylazoles. *9th International conference in chemistry Kyiv-Toulouse,* Materials of reports and performances, Kyiv, Ukraine, 4-9th June **2017**; p. 89.

5. Scherban, V.V.; Kuleshova, O.O.; Novodvorskyi, E.M.; Keda, T.Ie.; Khilya, O.V.; Zaporozhets O.A., Volovenko Yu.M. Benzothiazole and benzoxazole derivatives as novel optical probes for Zinc determination. *9th International conference in chemistry Kyiv-Toulouse,* Materials of reports and performances, Kyiv, Ukraine, 4-9th June **2017**; p. 256.

6. Kuleshova, O.; Khilya, O.; Volovenko, Y.; Gras E. Synthesis of 1,2-azoles via a cascade of addition-ring closure-ring opening. *Modern chemistry problems,* Book of abstracts of 18th International conference for Students and PhD students, Kyiv, Ukraine, 17-19th May, **2017**; p. 98

7. Scherban V.V., Kuleshova O.O., Novodvorskyi E.M., Keda T.Y., Khilya O.V., Zaporozhets O.A., Volovenko Yu.M. Benzothiazole and benzoxazole derivatives as novel optical probes for Zinc determination. *Modern trends 2017,* Book of abstracts of Kyiv conference on analytical chemistry, Kyiv, Ukraine, 18-21 October **2017**; p.32.

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9. Kuleshova, O.O.; Khilya, O.V.; Volovenko, Yu.M.; Gras, E. Nouvelles approaches de 4-hetarylpyrazoles totalement sabstitués. *Langues, sciences et pratiques,* Actes du 1er Colloque international francophone en Ukraine, Kiev, Ukraine, 19-20 Octobre **2017**; p. 84-85.

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Thesis summary

The research carried out in the course of this PhD work is centered on cyclic 2-azahetaryl-3-enaminonitrile derivatives which represent an attractive scaffold due to its high number of potential reactive sites. Regioselective functionalization of each site may give access to various structurally different Nitrogen-containing moieties featuring an azaheterocycle substituent.

One first application in heterocyclic synthesis of 2-azahetaryl-2-(1-R-pyrrolidin-2-ylidene)acetonitriles, readily accessed from available and cheap starting materials, is their involvement in Knorr-type synthesis of pyrazoles (isoxazoles) where they play the role of the 1,3-dielectrophiles. Thus 4-azahetaryl-3-(ω-aminopropyl)-1*H*-pyrazole(isoxazole)-5-amines are formed with complete regioselectivity in good yields 50-85%. This establishes an efficient and easily reproducible two-step approach to heterocycle-substituted amino-pyrazoles from heterocyclic acetonitriles.

Unprecedented subsequent transformations were carried out providing an access to regioselectively derivatized polyamino azoles, tetracyclic compounds in up to 45% overall yield and arylated pyrazoles in up to 71% yield through diazotization, followed by arylation through Suzuki−Miyaura cross-coupling or C−H activation. We illustrated the unprecedented but efficient nitrogen protection as a nitrosamine during the Pd-catalyzed cross-coupling. Also the possibility of pyrazoles C–H activation in order to get densely substituted pyrazoles was shown for the first time.

We also performed the quaternarization of the nitrogen of the heterocycle to investigate the effect of a cationic moiety on the regioselectivity of the reaction of such azahetaryl-3-enaminonitrile derivatives with 1,2-binucleophiles. The increased electron demand on the heterocycle induced a reaction path shift that produced the azole ring-opened product. Derivatives of benzoxazole and benzimidazole form second way products straight away, while the one of benzothiazole undergoes the “classical” transformation pathway and subsequent nucleophilic substitution at C-2 center of benzothiazole leading to azepine cycle formation. In the case of

benzoxazolyl substituted enaminonitriles under the same conditions both regioisomers are formed.

Formylation reaction of 2-(benzo[*d*]thiazol-2-yl)-2-(pyrrolidin-2-ylidene) acetonitrile with *N*,*N*-dimethylformamide dimethyl acetal (DMF DMA), followed by further reamination and cyclization under basic conditions gave rise to pyrrolo[3,2-*c*]pyridine-6-imine, a compound that exhibits a high fluorescent quantum yield (Φ = 61%) and proved to be very sensitive to protonation. Both characteristics are expected to be useful to develop an unprecedented water detection test for aprotic solvents. We have demonstrated that such a fluorometric method for determining water content in DMSO presents a limit of detection of 0.068%. From other enaminonitriles reactions with DMF DMA provided either a mixture of methylated and formylated products, or only methylated products (few adducts also shown non reactivity). These observations prompted us to assume that the presence of easily accessible NH group is essential in formylation of the C-3 center of pyrrolidine allowing to propose a mechanism for this uncommon reaction.

2-Azahetaryl-2-(pyrrolidin-2-ylidene)acetonitriles and their 3-oxo-benzo-analogues were also used to create: a) visible spectrophotometric probes for Zn(II) b) water stable BF_2-rigidified complexes that overcome the limitations of BODIPY-dyes and have Stokes shifts up to 9000 cm^{-1}, emission at violet-blue range, fluorescence both in solution (Φ up to 90%) and crystalline state; c) films of polymeric composites exhibiting photovoltaic effect.

Résumé de thése

Les recherches effectuées au cours de ce travail de thèse sont centrées sur les dérivés cycliques de type 2-azahetaryl-3-énaminonitrile qui représentent une structure d'intérêt du fait de son nombre élevé de sites réactifs potentiels. La fonctionnalisation régiosélective de chaque site donne en effet accès à des une grande diversité structurelle de composés azoté et substitué par un azahétérocycle.

Un atout majeur des 2-azahetaryl-2-(1-R-pyrrolidin-2-ylidene)acétonitriles est leur grande accessibilité à partir de matières premières simples et bon marché. Nous avons pu étudier leur emploi dans la synthèse des pyrazoles (isoxazoles). Ils jouent alors le rôle de diélectrophiles 1,3. L'action d'hydrazine (hydroxylamine) conduit à des 5-amino-4-azahetaryl-3-(ω-aminopropyl)-1*H*-pyrazole (isoxazole) formés avec une régiosélectivité complète et de bons rendements 50-85%. Ceci établit une approche en deux étapes efficace et facilement reproductible à des amino-pyrazoles substitués par des hétérocycles à partir d'acétonitriles hétérocycliques.

Des transformations subséquentes ont été réalisées donnant accès à des polyamino-azoles dérivatisés régiosélectivement, à des composés tétracycliques jusqu'à un rendement global de 45% et à des pyrazoles arylés jusqu'à 71% de rendement par diazotation suivie d'une arylation par couplage croisé Suzuki-Miyaura ou C–H activation. Nous avons illustré une protection de l'azote efficace sous forme de nitrosamine pendant le couplage croisé catalysé par Pd.

Nous avons également effectué la quaternarisation de l'azote de l'hétérocycle pour étudier l'effet d'une moitié cationique sur la régiosélectivité de la réaction de tels dérivés 2-azahetaryl-3-énaminonitrile avec des 1,2-binucléophiles. L'augmentation de la demande en électrons sur l'hétérocycle a induit un changement de chemin réactionnel qui a conduit à un produit issu de l'ouverture du cycle azole. Une différence de réactivité entre les dérivés du benzoxazole et du benzimidazole d'une part et du benzothiazole d'autre part a été observée. Alors que les premiers suivent la voie d'ouverture de cycle, le second suit une transformation «classique» puis une substitution nucléophile au centre C-2 du benzothiazole conduisant à la formation du

cycle de l'azépine. Dans le cas des énaminonitriles substitués par un benzoxazolyle dans les mêmes conditions, les deux régioisomères sont formés.

La réaction de formylation du 2-(benzo[*d*]thiazol-2-yl)-2-(pyrrolidin-2-ylidène) acétonitrile avec le *N*,*N*-diméthylformamide diméthylacétal (DMF DMA), suivie d'une amination et d'une cyclisation dans des conditions basiques a engendré à la pyrrolo[3,2-*c*]pyridine-6-imine, un composé qui présente un rendement quantique fluorescent élevé (Φ = 61%) et s'est révélé très sensible à la protonation. Les deux caractéristiques devraient être utiles pour développer un test de détection d'eau originaux pour les solvants aprotiques. Nous avons démontré qu'une telle méthode fluorométrique pour déterminer la teneur en eau dans le DMSO présente une limite de détection de 0,068%. A partir d'autres réactions d'énaminonitriles avec du DMF DMA un mélange de produits méthylés et formylés est obtenu, soit seulement des produits méthylés (peu d'adduits ont également montré une non-réactivité). Ces observations nous ont amenés à supposer que la présence de groupe NH facilement accessible est essentielle dans la formylation du centre C-3 de la pyrrolidine permettant de proposer un mécanisme pour cette réaction peu commune.

Les 2-azahetaryl-2-(pyrrolidin-2-ylidène)acétonitriles et leurs 3-oxo-benzo-analogues ont également été utilisés pour créer: a) des sondes spectrophotométriques pour Zn(II); b) des complexes BF_2-rigidifiés stables à l'eau qui dépassent les limitations des BODIPY et ont des décalages de Stokes jusqu'à 9000 cm^{-1}, émission en bleu violet, fluorescence à la fois en solution (Φ jusqu'à 90%) et à l'état cristallin; c) des films de composites polymériques présentant un effet photovoltaïque.

CONTENU PRINCIPAL (en français)

Dans **l'introduction** le cadre général et les objectifs de l'étude de 2-azahetaryl-3-énaminonitriles **A** (*Figure 1*) sont présentés.

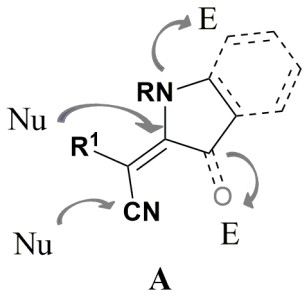


Figure 1. *Structure générale des 2-azahéaryl-3-énaminonitriles cycliques étudiés dans cette thèse.*

Dans un **premier chapitre**, une étude générale de la littérature concernant les 2-(1-R-pyrrolidin-2-ylidène)acétonitriles et leurs analogues benzo-fusionnés **A** est presenté. Des détails sont fournis sur les différentes approches de synthèse de ces composés. Leurs différentes réactivités en fonction de leur nature cyclique ou

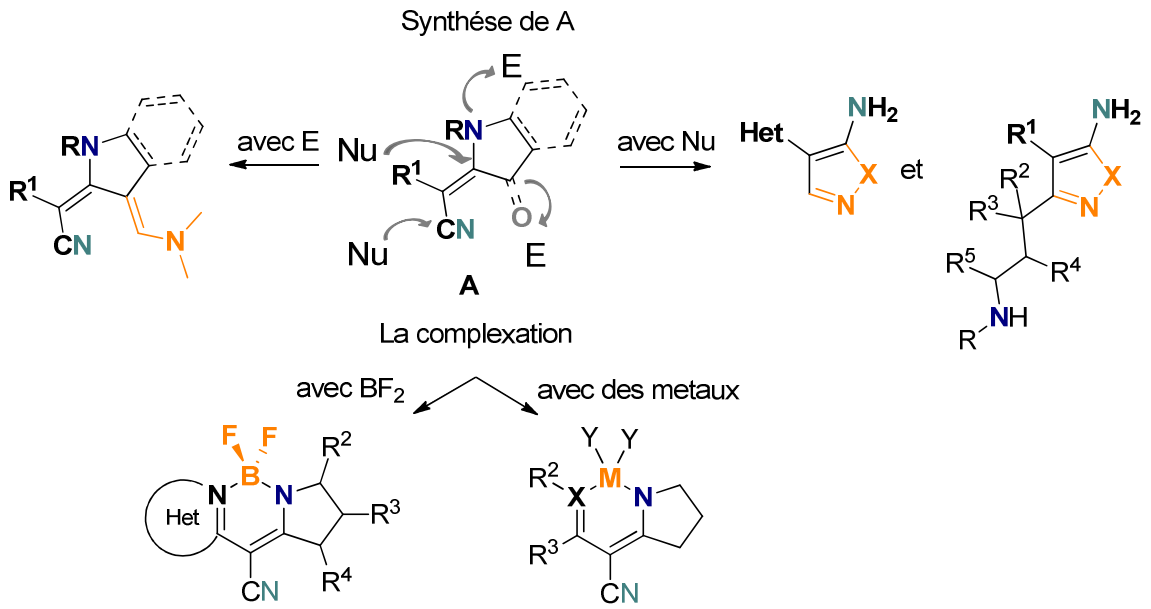


Figure 2. *Représentation graphique de la revue de littérature.*

acyclique et de leurs substitutions sont alors recouvertes d'une gamme de nucléophiles et d'acétals de diméthylformamide. Une dernière partie de ce chapitre

décrit la complexation du bore et des métaux par le 2-(pyrrolidin-2-ylidène)acétonitrile et les applications des complexes isolés sont caractérisées (*Figure 2*).

Un **deuxième chapitre** décrit en détail la synthèse et la caractérisation des 2-azahétaryl-2-(1-R-pyrrolidin-2-ylidène)acétonitrile et du 2-azahétaryl-2-(3-oxoindolin-2-ylidène)acétonitrile **A** (R^1 = Het) obtenu au cours de nos études. Une étude approfondie de la configuration par différentes méthodes analytiques, telles que la diffraction des rayons X, la RMN incluant des expériences à température variable ainsi que le calcul, est ensuite décrite.

2-Azahétaryl-2-(pyrrolidin-2-ylidène)acétonitriles

On peut accéder au 2-azahétaryl-2-(1-R-pyrrolidin-2-ylidène)acétonitriles par deux voies représentées sur le *Schéma 1*.

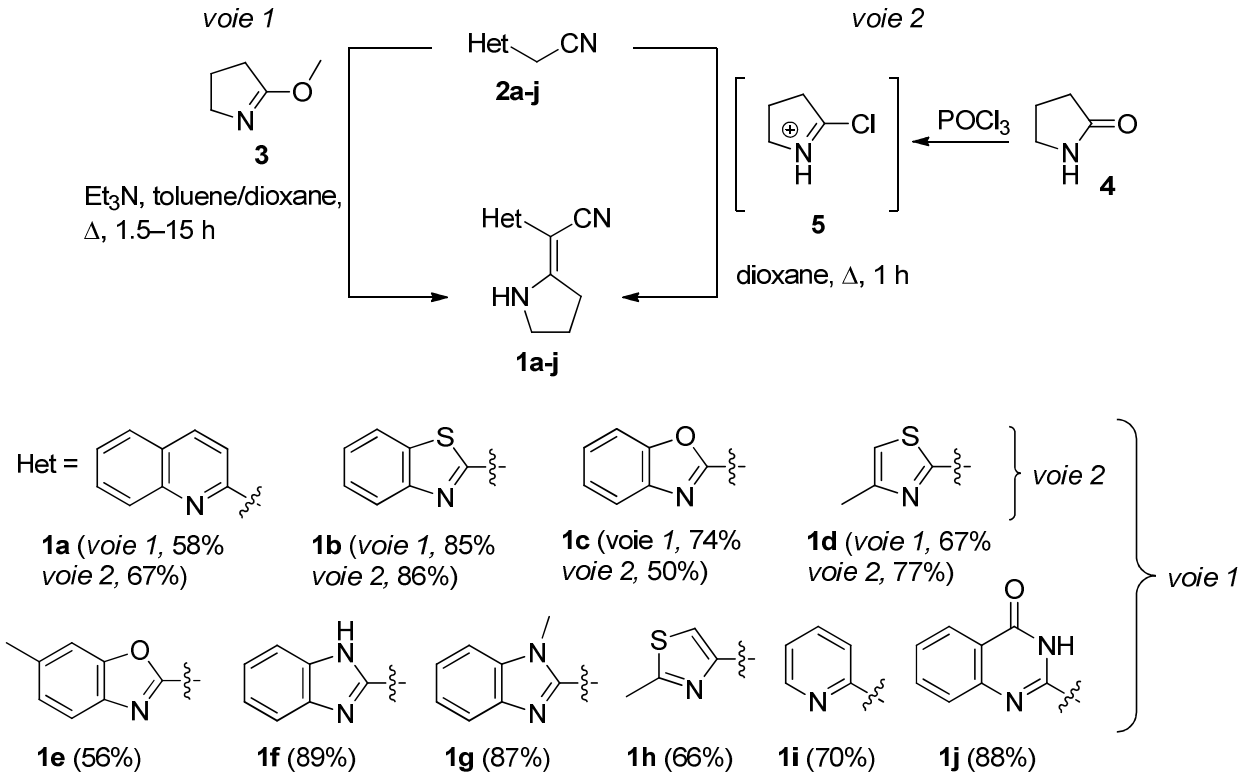


Schéma 1. *Voies d'accès à la synthèse des 2-azahétaryl-2-(pyrrolidin-2-ylidène) acétonitriles* ***1****.*

La première voie comprend la synthèse d'éther lactimique **3** qui se condense après avec l'hétarylacétonitrile **2**. L'ajustement de ce schéma de synthèse nous a

permis d'augmenter le nombre de substituants hétérocycliques dans les 2-(pyrrolidin-2-ylidène)acétonitriles et d'obtenir 8 nouveaux composés **1b-h, j**.

Nous avons également mis au point une nouvelle méthode pour la synthèse des énaminonitriles **1** en utilisant une condensation à trois composants impliquant l'hétarylacétonitrile **2**, l'oxychlorure de phosphore et la pyrrolidin-2-one **4**. Contrairement à la méthode décrite précédemment (*Schéma 1, voie 1*) qui nécessite la préparation initiale de 5-méthoxy-3,4-dihydro-2*H*-pyrroles **3** la méthode proposée est simplifiée permettant la génération *in situ* de cation 5-chloro-3,4-dihydro-2H-pyrrolinium **5** et préparation du 2-hétaryl-2-(pyrrolidin-2-ylidène)acétonitrile souhaité en 1 heure (*Schéma 1, voie 2*).

Étant donné la structure de **1**, on peut supposer qu'il peut exister sous forme de mélange d'isomères *Z* et *E* (isomérisation autour de la liaison énamine C=C). Cependant, un seul jeu de signaux dans les spectres RMN, dans lesquels le proton NH déplacé vers le champ faible (8,7-11,3 ppm), ainsi que des données XRD, indiquent que seule la forme *Z* est observée. Selon les calculs de chimie quantique, la quantité théorique d'isomère *E* ne dépasse pas 0,1%.

2-Azahétaryl-2-(1-alkylpyrrolidin-2-ylidène)acétonitriles

Nous avons montré que le schéma de synthèse permettant d'accéder aux 2-azahetaryl-2-(1-alkylpyrrolidin-2-ylidène)acétonitriles par alkylation de leurs analogues non substitués en N ne fonctionne pas correctement. Ainsi, nous avons développé une stratégie alternative pour leur synthèse, représentée sur le *Schéma 2, voie 1*. La condensation entre les 2-azahetarylacétonitriles anion **2** (obtenu par déprotonation par NaH) et 5-méthoxy-1-R-3,4-dihydro-2*H*-pyrrol-1-ium **14** ou **15** se déroule à température ambiante en donnant 57-91% de énamine désiré **6-12**. Le procédé alternatif pour la synthèse est illustré dans le *Schéma 2, la voie 2* est analogue à la méthode qui a été développée pour la synthèse d'énaminonitriles **1** non substitués (*Schéma 1, voie 2*).

Compte tenu de la structure des énaminonitriles N substitués **6-12**, on pourrait également supposer qu'ils existent sous la forme d'un mélange d'isomères *Z* et *E*.

Cependant, les données d'analyse DRX ont révélé quà l'état solide le diastéréoisomère présentant un encombrement stérique inférieure (N-alkyle et CN en position cis) est isolé préférentiellement.

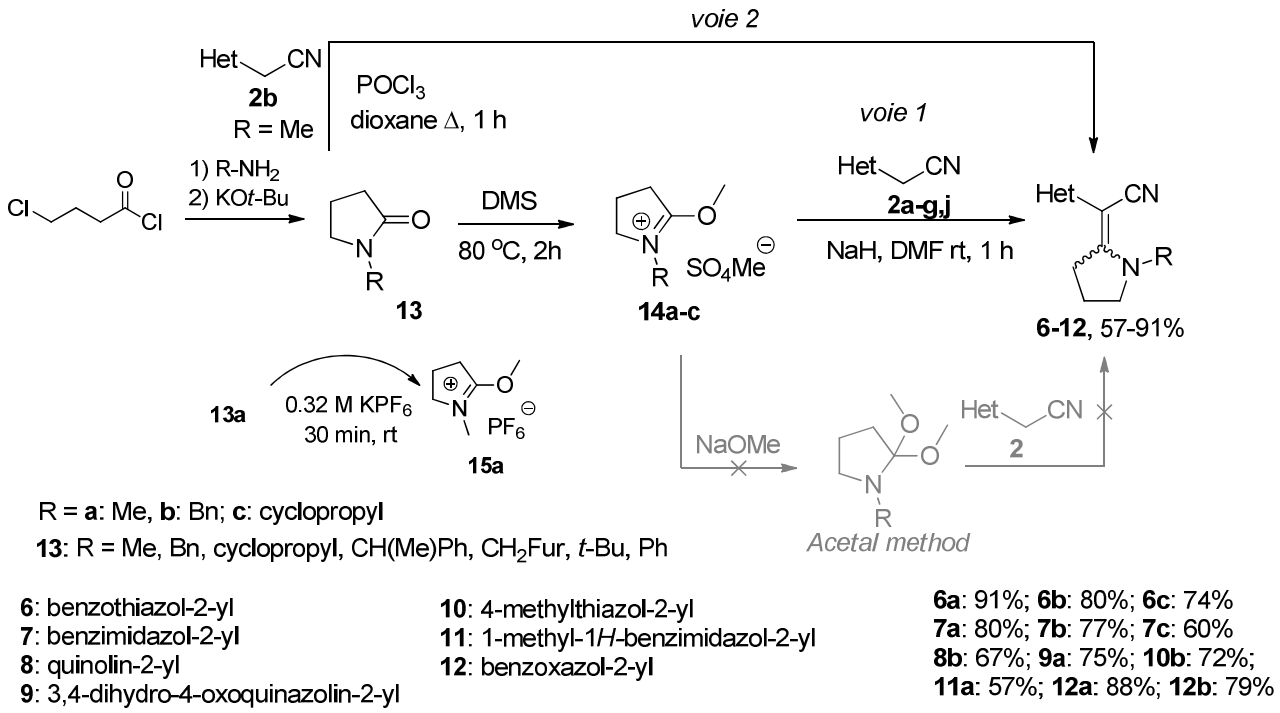


Schéma 2. *Synthèse de 2-azahétaryl-2-(1-alkylpyrrolidin-2-ylidène)acétonitriles* ***6-12****.*

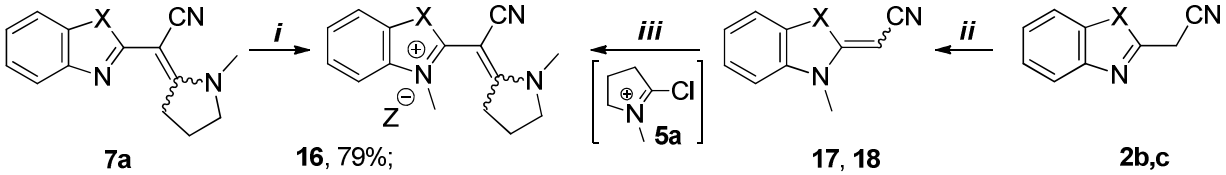
L'état cristallin a révélé une conformation presque plane du cycle pyrrolidine (déviation du plan à 0,16 Å), qui est quasi-coplanaire avec le substituant hétérocyclique (angle dièdre inférieur à 9 °).

Néanmoins l'étude RMN démontre que la solution contient un mélange de diastéréoisomères. Deux singulets larges de 3-CH_2 et N-CH_3 adjacents à la liaison C=C sont divisés en quatre pics indépendants lors du refroidissement. Sur la base des données spectrales, l'énergie d'activation libre ($\Delta G^{\neq}$) pour l'échange entre les espèces diastéréoisomères **7a** E et **7a** Z a été calculée. Les valeurs de $\Delta G^{\neq}$ trouvées $\Delta G^{\neq}$ E → Z = 14,4 kcal/mol, $\Delta G^{\neq}$ Z → E = 13,3 kcal/mol sont en accord avec les précédentes indiquées pour ces énamines conjuguées et caractérisent le procédé d'isomérisation comme étant à basse énergie.

2-(Pyrrolidin-2-ylidène)acétonitriles substitués par des benzazoles quaternisés

La position C-2 du fragment énaminonitrile a été activée par quaternisation de l'azote du benzazole, ce qui a favorisé la séparation des charges dans la molécule.

La quaternisation a été réalisée par alkylation directe du pyrrolidinacétonitrile **7a**, substitué par un benzimidazolyle, ou de l'hétérolacétonitrile dans le cas des dérivés benzoxazolyl **2b** et benzothiazolyl **2c**; les précurseurs accédés **17** et **18** réagissent encore avec le chlorure d'imidoyl **5a** généré *in situ* (*Schéma 3*).



i: 5 equiv. MeI, K_2CO_3, DMF, Δ, 2 h; ***ii:*** a) DMS, 70 °C, 1 h; b) NaOH; ***iii:*** a) 1-methylpyrrolidin-2-one, $POCl_3$, diovane, Δ, 15 min; b) KPF_6. **7a:** X = NH; **16**: X = NMe, Z = I; **2c, 17, 19**: X = O, Z = PF_6; **2b, 18, 20**: X = S, Z = PF_6

Schéma 3. *2-(Pyrrolidin-2-ylidène)acétonitriles substitués par des benzazoles quaternisés* ***16, 19, 20.***

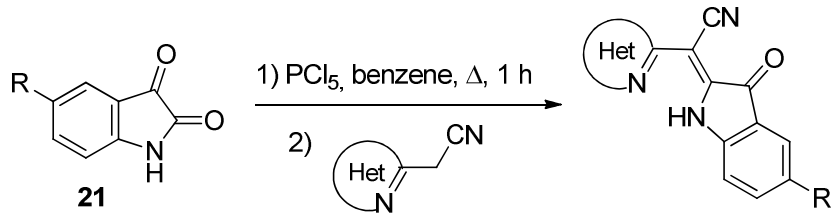
Le composé **16** existe sous forme de mélange de diastéréoisomères à la fois en solution (selon les données RMN dans $CDCl_3$, il y a 58% d'isomère) et à l'état solide (liaison C=C torsadée selon DRX, angle dièdre égal à 53°).

Dans les spectres RMN ^{13}C de **16**, **19** et **20**, le pic de l'atome C-2 du fragment d'énaminonitrile déplacé vers le champ faible (δ = 170,7–173,9 ppm) par rapport aux analogues neutres (δ = 167,0–168,1 ppm). Ceci indique le <u>déblindage</u> supplémentaire lié au déplacement de la densité électronique vers l'azote déficient en electrons.

2-Azahétaryl-2-(5-R-3-oxoindolin-2-ylidène)acétonitriles

L'indolin-2,3-dione **21** a été choisie comme matière de départ appropriée pour la synthèse de 2-azahétaryl-2-(5-R-3-oxoindolin-2-ylidène)acétonitriles **22-24**. On sait que sa fonctionnalisation par nucléophiles est possible en position 2 via la formation d'imidochlorure intermédiaire. Habituellement, ce dernier est isolé et dissous dans un solvant plus polaire pour effectuer une réaction de condensation.

En raison de la faible stabilité de l'imidochlorure, le rendement de la réaction est toujours faible. Nous avons ainsi développé une nouvelle approche en un *pot* qui comprend la formation in situ d'imidochlorure (~ 1 h, ébullition dans le benzène) et sa condensation ultérieure avec l'hététylacétonitrile (*Schéma 4*). La durée totale de réaction est d'environ 1 heure, l'étape limitante étant la formation d'imidochlorure. Les produits sont formés avec des rendements élevés; il existe des composés de couleurs vives variant du rouge au violet et exibit une longue bande d'absorption de longueur d'onde dans la gamme 515-550 nm. Selon la RMN et la DRX, les composés de données **22-24** existent sous forme de *Z* à la fois en solution et à l'état solide. Cette configuration est probablement stabilisée par une liaison hydrogène intramoléculaire (N···H–N).



R = **a**: H, **b**: Me, **c**: OMe

22: benzothiazol-2-yl; **23**: benzoxazol-2-yl; **24**: quinol-2-yl

22a-c, **23a**, **24a**, 70-87%

22a: 78%; **22b**: 70%; **22c**: 87%; **23a**: 77%; **24a**: 84%

Schéma 4. *Synthesis of 2-azahétaryl-2-(5-R-3-oxoindolin-2-ylidène)acétonitriles* ***22-24***.

La particularité des 3-oxindoles functionalizé **22-24** est leur comportement lors du changement de l'acidité du milieu. Tout en augmentant la basicité du milieu, le déplacement batochrome d'absorption λ_{max} se produit, 150 nm pour **22b** (λ_{abs}^{max} = 680 nm) et 130 nm pour **23a** (λ_{abs}^{max} = 665 nm). Visuellement, c'est le passage du violet au bleu. Les constantes de dissociation conditionnelles (pKa) ont été calculées pour **22b** et **23a** sur la base des données obtenues: $pKa_{\mathbf{22b}}$ = 10,09 ± 0,05; $pKa_{\mathbf{23a}}$ = 10,96 ± 0,25.

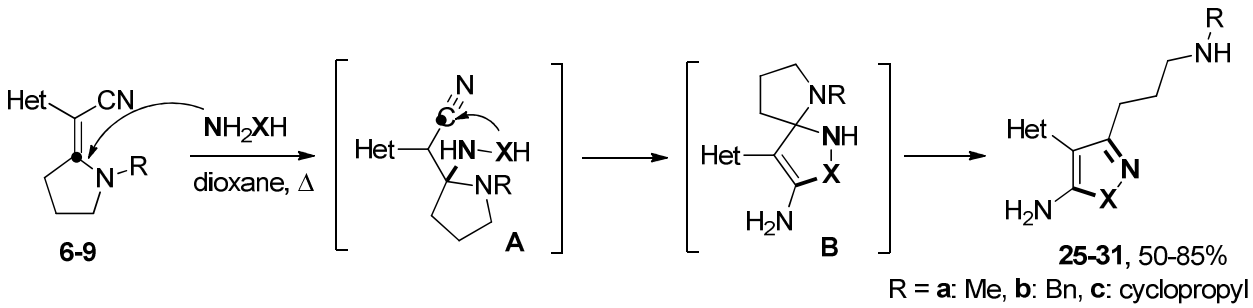
Dans le **troisième chapitre**, nous décrivons la réactivité du 2-azahétaryl-2-(1-R-pyrrolidin-2-ylidène)acétonitrile en tant que 1,3-diélectrophiles envers les composés binucléophiles et la synthèse de pyrazoles et d'isoxazoles substitués

différemment. Les transformations en aval sur les pyrazoles sont décrites en détail et ont montré une excellente région et chimiosélectivité.

Réactions de 2-azahétaryl-2-(1-R-pyrrolidin-2-ylidène)acétonitriles avec des 1,2-binucléophiles faisant intervenir l'atome C-2 de pyrrolidine et le carbone du groupe nitrile

La délocalisation de la densité d'électrons d'un fragment d'énamine dans le 2-azahéaryl-2-(pyrrolidin-2-ylidène)acétonitriles 1, 6-12 (selon les données RMN et DRX) favorise un déplacement de l'équilibre énamine-imminium, augmentant le caractère électrophile de l'atome C-2 du fragment d'énaminonitrile et diminuant simultanément celui du groupe nitrile. Ces observations suggèrent que les 1,3-diélectrophiles peuvent réagir avec les binucléophiles de manière régiosélective.

La réaction se déroule en douceur avec des pyrrolidinacétonitriles à substitution N-alkyle dans le dioxane au reflux avec un excès de 10-20 équivalents du réactif binucléophile et fournit les pyrazoles et les isoxazoles avec des rendements modérés à bons (50-85%) (*Schéma 5*). Une conversion de cycle de pyrrolidine en pyrazole (ou isoxazole) devrait se produire par attaque nucléophile sur le carbone insaturé de la pyrrolidine, donnant **A**; les intermédiaires spiro **B** se formeraient alors par attaque du deuxième atome du binucléophile sur le groupe nitrile en une forme favorisée de 5 exo-dig. Enfin, l'ouverture du cycle pyrrolidine est favorisé par l'aromatisation du cycle azole et fournit la chaîne aliphatique substituée par l'azote **25-31**. Cette ouverture du cycle conclut le mécanisme d'addition nucléophile- annulation spirannique et ouverture de cycle (ANSARO) qui explique le déroulement de cette transformation (*Schéma 5*).



25: benzothiazol-2-yl, X = NMe; **26**: benzothizol-2-yl X = NH; **27**: benzimidazol-2-yl, X = NMe; **28**: quinolin-2-yl, X = NMe; **29**: quinolin-2-yl, X = O; **30**: 3,4-dihydro-4-oxoquinazolin-2-yl, X = NMe; **31**: 3,4-dihydro-4-oxoquinazolin-2-yl, X = O. **25a**, 85%; **25b**, 70%; **25c**, 62%; **26a**, 56%; **26c**, 43%; **27a**, 65%; **27b**, 65%; **28b**, 50%; **29b**, 55%; **30a**, 62%; **31a**, 75%

Schéma 5. *Réactions de 2-azahétaryl-2-(1-R-pyrrolidin-2-ylidène)acétonitriles avec des 1,2-binucléophiles.*

La nature des substituants alkyl et hétaryl s'est avérée n'affecter que modérément l'efficacité de la réaction, bien que la substitution benzothiazole fournisse systématiquement de meilleurs rendements. L'implication du groupe nitrile est mise en évidence par la disparition de ses signaux caractéristiques de l'étirement des vibrations dans l'intervalle 2198−2178 cm^{-1} des spectres IR. Les spectres de RMN ^1H révèlent la présence du groupe NH_2 à 6,25-6,94 ppm pour les pyrazoles et de 8,04 à 8,20 ppm pour les isoxazoles. La structure des composés a également été confirmée par DRX.

Fonctionnalisation régiosélective de 3-(*ω*-aminopropyl)-4-azahetaryl-5-aminopyrazoles

L'alkylamine secondaire est significativement plus nucléophile que l'aromatique primaire et la réaction d'alkylation du rendement en **25a** est le sel d'ammonium **32**. Lors de la protection d'une amine secondaire avec un groupe *tert*-butyloxycarbonyle, l'alkylation réductive régiosélective du groupe amino primaire est soumise à un composé **33** (*Schéma 6*).

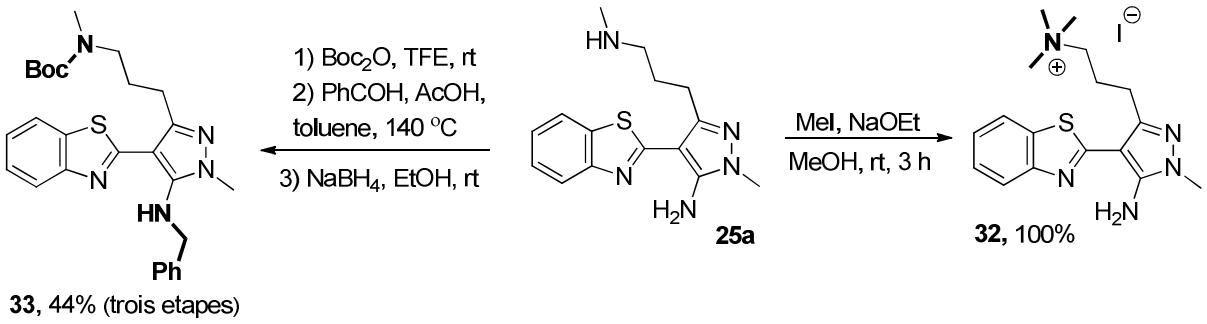


Schéma 6. *Alkylation régiosélective des groupes amino de* ***25a****.*

Le groupe aminé pendant du pyrazole et à proximité de NH du benzimidazole permet la condensation de **27a** avec des électrophiles tels que des orthoesters (*Schéma 7 , voie 1*). Cette approche pourrait délivrer des échafaudages de pyrazolopyrimidine intéressants à des fins de chimie médicinale, comme cela a été illustré dans le développement d'inhibiteurs de la glycogène synthase kinase 3, une enzyme impliquée dans de nombreuses maladies telles que le diabète de type II, la maladie d'Alzheimer, le cancer, le trouble bipolaire et l'inflammation. On a également eu accès à un composé aromatique tétracyclique en quelque sorte similaire par un simple traitement de **27a** avec un excès de nitrite de *tert*-butyle dans le DMF (*Schéma 7, voie 2*).

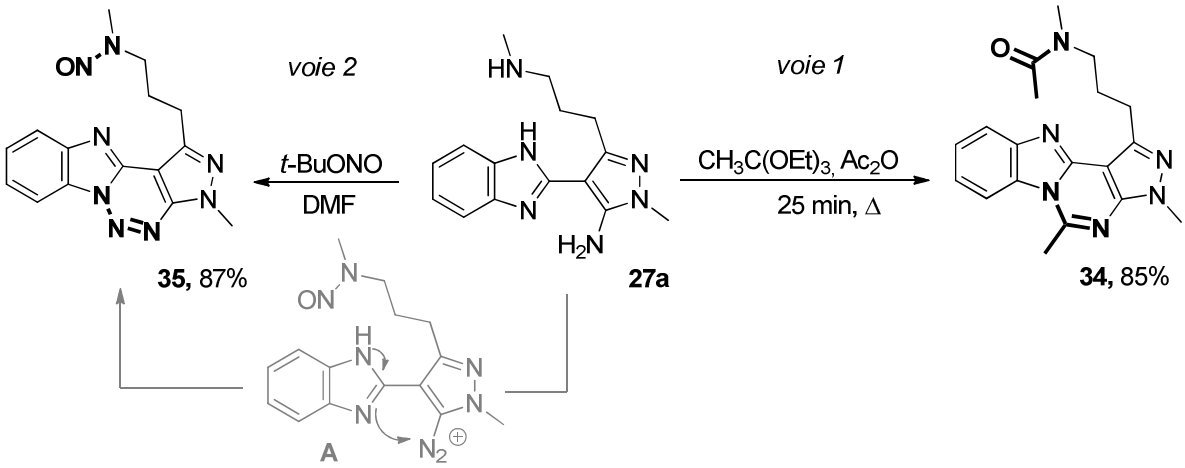


Schéma 7. *Accès direct aux structures tétracycliques fusionnées* ***34****,* ***35****.*

Dans ces conditions, l'intermédiaire diazonium pourrait en effet être piégé par l'azote de l'imidazole pour générer le triazène **35** correspondant, avec une

protection concomitante de l'amine secondaire en tant que nitrosamine. Il présente une structure tétracyclique unique qui n'a jamais été décrite auparavant et, en tant que telle, élargit l'espace chimique de la chimie hétérocyclique.

Le groupe amino a également été utilisé pour introduire les substituants aromatiques, stéryliques ou hétéroaromatiques à la 5ème position du pyrazole (*Schéma 8*). La première étape d'halogénation est soumise à la procédure classique de Sandmeyer ou à une méthode modifiée impliquant l'utilisation de nitrite de *tert*-butyl et d'iode cristallin. Le 5-iodopyrazole **36** est le produit de réaction majoritaire. Dans le second cas, nous introduisons un halogène et une protection sur le groupe amino secondaire par un procédé en un *one pot*. La réaction de couplage croisé de Suzuki-Miyaura subit un rendement quantitatif pour les substitutions aromatiques et stéryliques et un rendement modéré de 24% pour l'indolyl.

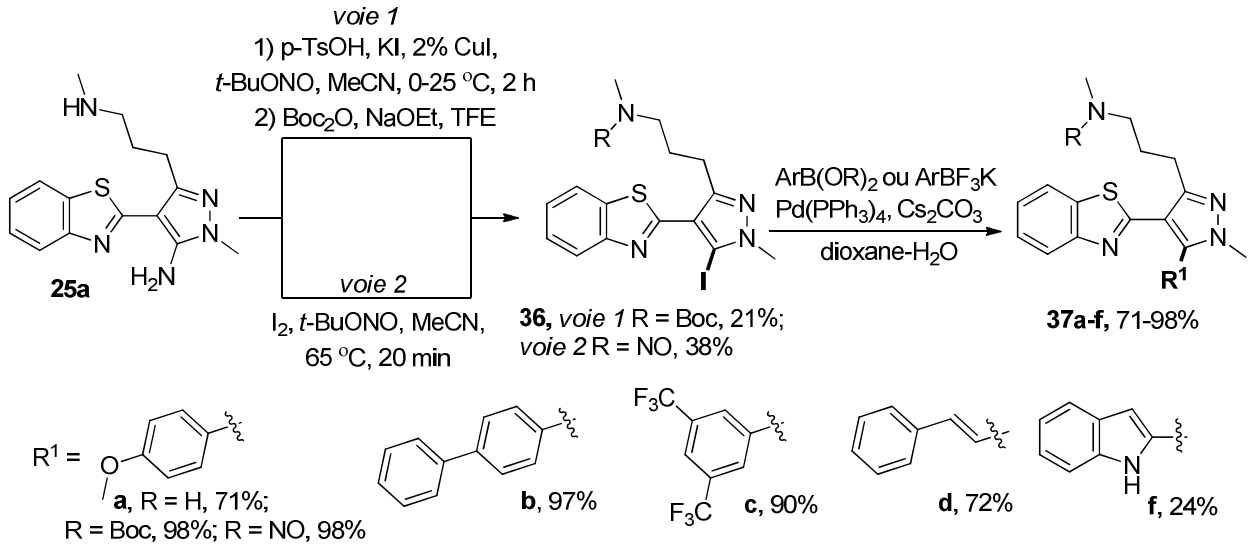


Schéma 8. *La réaction de l'iodation du 5-aminopyrazole* ***25a*** *par Zandmeier. Couplage croisé de Suzuki-Miyaura pour 5-iodopyrazole* ***36****.*

Une approche différente pour introduire le substituant aryle à la 5ème position du pyrazole est la désamination réductrice par la formation de pyrazole **38** suivie d'une étape d'activation C–H. Les conditions opératoires de la première étape sont similaires à celles appliquées pour l'introduction de l'halogène mais le

donneur de radicaux hydrogène est le DMF. La réaction de couplage suivante conduit à **37a** avec un rendement quantitatif (*Schéma 9*).

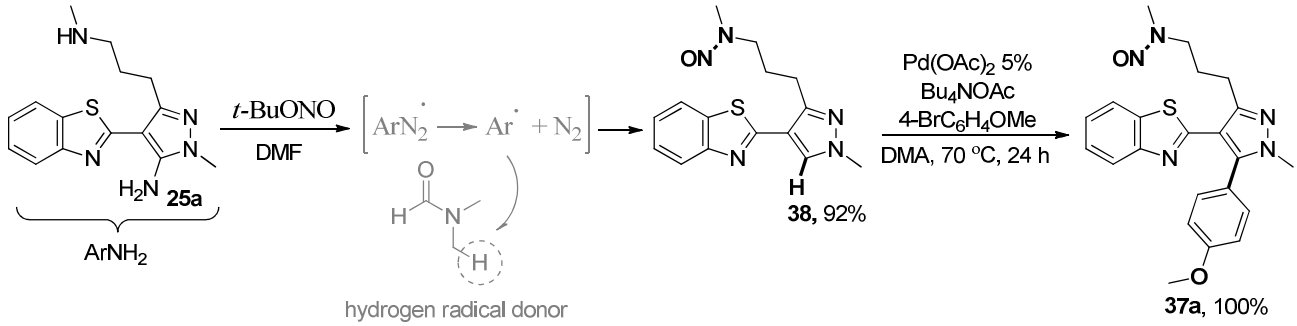


Schéma 9. *Reductive deamination and futher C–H functionalization of pyrazole* ***25a****.*

Ainsi, en optimisant la technique, nous avons pu augmenter le rendement en 5-arylpyrazoles de 21% à 92%.

Réactions de 2-azahétaryl-2-(1-R-pyrrolidin-2-ylidène)acétonitriles avec des 1,2-binucléophiles impliquant l'atome C-2 de pyrrolidine et l'atome C-2 d'azahétérocycle

En procédant à la réaction de 2-benzoxazol-2-yl-2-(1-R-pyrrolidin-2-ylidène)acétonitriles avec de la méthylhydrazine, on a pu récupérer deux composés **38** et **39** après la séparation du mélange réactionnel. Une caractéristique du produit cyclique d'isoxazole ouvert **39** est le déplacement des protons aromatiques vers le champ fort dans le spectre RMN ^{1}H et la présence d'une vibration caractéristique du groupe nitrile dans les spectres IR (2216-2218 cm^{-1}).

Le mécanisme comprend l’attaque NH à l’atome C-2 du noyau pyrrolidine menant à l’intermédiaire A dans lequel YH se situe identiquement à proximité du groupe nitrile et de l’atome C-2 du benzoxazole et attaque l’une ou l’autre avec une probabilité qui dépend directement de leur électrophilie (*Schéma 10*).

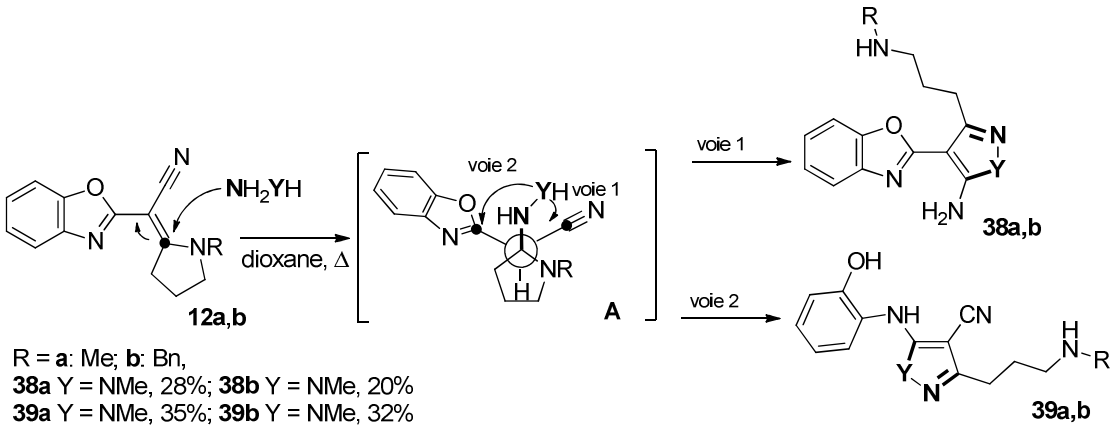


Schéma 10. *La réaction des 2-benzoxazol-2-yl-2-(1-R-pyrrolidin-2-ylidène)acétonitriles* ***12*** *avec de la méthylhydrazine.*

En introduisant les énaminonitriles cycliques substitués par des azoles quaternisés **16**, **19** dans la réaction avec les 1,2-binucléophiles, on observe la formation de produits à cycle ouvert **40**, **41** (*Schéma 11*). Lorsque le dérivé de benzothiazole **20** réagit avec la méthylhydrazine, la transformation subit selon la 1ère voie; l'ouverture du cycle thiazole procède à la deuxième étape avec formation simultanée d'azépine **42** (*Schéma 11*). Les structures des produits ont été confirmées par RMN 2D et DRX.

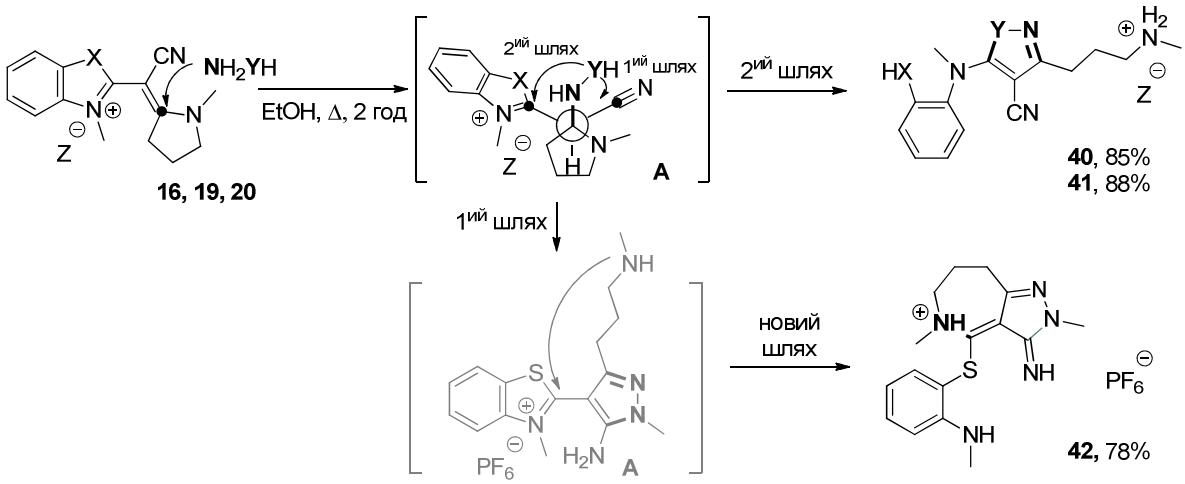


Schéma 11. *Réaction des énaminonitriles cycliques substitués par des azoles quaternisés avec des hydrazines.*

Après avoir développé le caractère électrophile du 2-azahétaryl-2-(1-R-pyrrolidin-2-ylidène)acétonitriles, nous démontrons au **chapitre 4** que ces adduits peuvent également se comporter comme nucléophiles en présence d'électrophiles tels que les acétals de diméthylformamide.

Les données expérimentales ainsi que les précédents de la littérature nous ont amenés à supposer que la présence du groupe NH facilement accessible est essentielle à la formylation du centre C-3 de la pyrrolidine, ce qui permet de proposer un mécanisme pour cette réaction peu commune (*Schéma 12*).

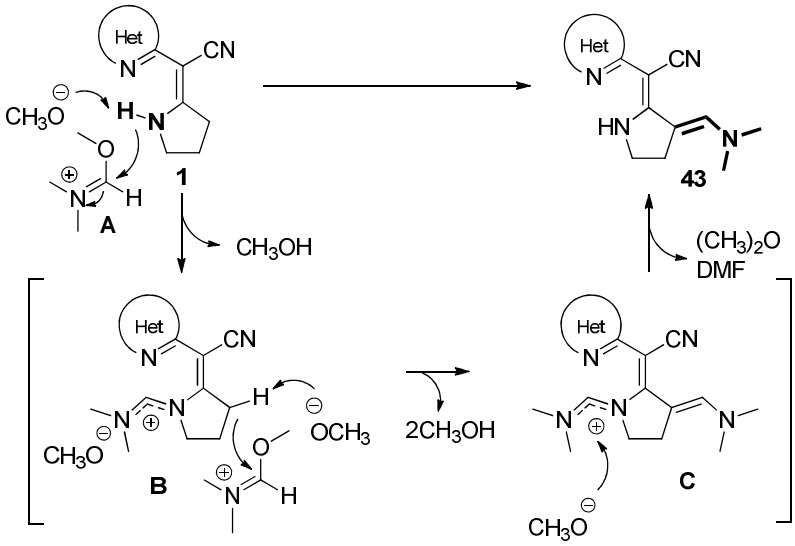


Schéma 12. *Mécanisme proposé pour la réaction de 2-azahétaryl-2-(1-R-pyrrolidin-2-ylidène)acétonitriles **1** avec DMF DMA.*

L'incorporation de la fraction diméthylméthylidène se fait de manière réversible par attaque nucléophile de l'ion aza-oxo-stabilisé **A** par l'azote de la pyrrolidine, ce qui donne l'intermédiaire intermédiaire **B**; la position C-3 de la pyrrolidine dans **B** activée par effet inductif (-I) du groupe amidine et amélioration de la stabilité mésomérique de l'anion par la fraction acrylonitrile. En conséquence, une déprotonation par un anion méthoxy et une réaction avec une autre molécule de DMF DMA peuvent se produire, produisant **C**; celle-ci se transforme en 2-azahéaryl-2-(3- (diméthylamino)méthylène)pyrrolidin-2-ylidène)acétonitrile **43** par inversion de la première étape (*Schéma 12)*.

Synthèse de pyrrolo [3,2-*c*]pyridin-6-imine, étude physico-chimique et perspectives d'utilisation

Un modèle de produit de formylation **43a** été incorporé à une réaction de transamination avec de la benzylamine, suivie d'une cyclisation en pyrrolo[3,2-c]pyridine-6-imine **45** en présence d'une base (*Schéma 13)*.

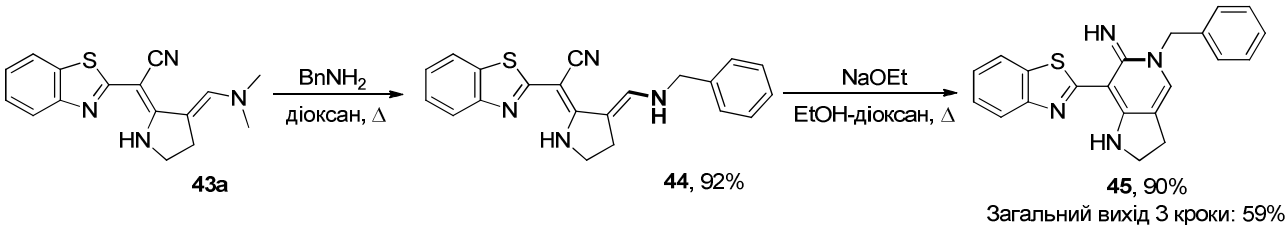


Schéma 13**. Synthèse de pyrrolo[3,2-c]pyridine-6-imine **45.

Le pyrrolo[3,2-*c*]pyridin-6-imine **45** existe sous la forme d'un mélange d'équilibre d'énamine et d'imine en solution et d'énamine à l'état solide. En raison du fragment de vinamidine, le composé est très sensible à la présence de donneurs de protons. Il y a une large bande dans les spectres d'absorption en solvant aprotique (toluène, dioxane, acétonitrile, DMSO) dans la région de 320-340 nm, qui devient étroite entre 320-370 nm en présence de donneurs de protons, à savoir HCl, H_2O, MeOH, EtOH.

Une telle sensibilité de la pyrrolo[3,2-c]pyridin-6-imine **45** à la protonation avec un rendement quantique de fluorescence élevé (Φ = 61 %, standard – sulfate de quinine) a été utilisée pour développer un test fluorométrique de l'eau sans précédent pour les solvants aprotiques. Nous avons montré qu'une telle méthode fluorimétrique pour déterminer la teneur en eau du DMSO présentait une limite de détection de 0,068%.

Le cinquième chapitre est consacré à la formation de (i) complexes de bore et de difluorure de 2-azahétaryl-2-(1*H*-pyrrolidin-2-ylidène)acétonitrile et propriétés photophysiques d'une gamme d'adduits isolés; (ii) les complexes d-métal (Cu, Zn, Co, Ni), leur isolement et leur caractérisation complète ainsi que leur mise en œuvre dans des dispositifs permettant d'étudier leurs puissantes applications dans les cellules solaires et de détecter le Zn et Cu dans les fluides biologiques.

Complexes rigidifiés par le BF_2 sur la base du 2-azahétaryl-2-(pyrrolidin-2-ylidène)acétonitriles

Les complexes BF_2 du 2-azéhetaryl-2-(pyrrolidin-2-ylidène)acétonitrile **46** ont des analogues structuraux avec les colorants BODIPY, à savoir le boroazacycle. Les colorants BODIPY présentent des propriétés uniques, à savoir les rendements quantiques élevés, une bonne stabilité dans les conditions physiologiques, les bandes d'absorption et d'émission étroites. Malgré la fluorescence intense des colorants BODIPY en solution, ils ont un faible décalage de Stokes qui interrompt l'analyse du signal des objets biologiques et ils ne sont presque pas fluorescents à l'état solide. La désymétrisation du ligand bidente dans le complexe de bore est l'une des solutions pour vaincre les colorants BODIPY. Nous avons procédé à la désymétrisation en introduisant des hétérocyles ayant des propriétés fondamentalement différentes. Les huit complexes **46a-h** ont été obtenus par la procédure illustrée dans le *schéma 14*.

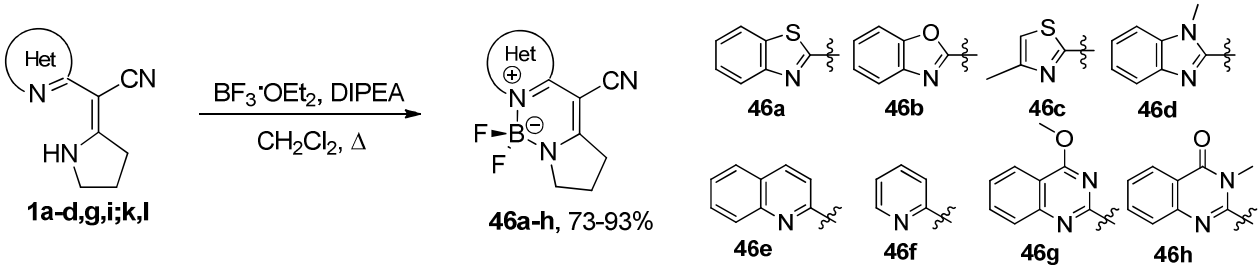


Schéma 14. *Synthèse de BF_2 complexes* ***46****.*

Tous les complexes sont stables à l'eau, ont des décalages de Stokes allant jusqu'à 9000 cm^{-1}, une émission dans la gamme bleu-violet, une fluorescence à la fois en solution (Φ jusqu'à 90%) et à l'état cristallin. Une caractéristique importante de la biovizualisation est la neutralité de telles sondes permettant de traverser la membrane cellulaire. La brillance de ces colorants est suffisante pour les études *in vitro*, mais leur émission (400 - 460 nm) est hors de la fenêtre optique (650 - 900 nm) nécessaire aux études *in vivo*. Néanmoins, la présence du groupe BF_2 pourrait être utilisée pour incorporer le marqueur radioactif [^{18}F] et donnerait à ces sondes le caractère bimodal.

Complexes de 2-azahetaryl-2-(pyrrolidin/5-R-3-oxoindolin-2-ylidène) acétonitriles avec des métaux 3d: synthèse, structure et perspectives d'utilisation

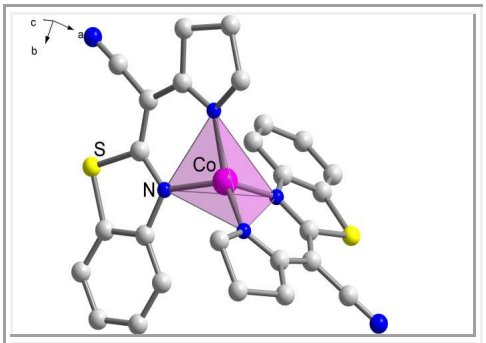


Figure 3. *Structure moléculaire du composé* ***47b*** *avec Co (II).*

Le metal 3d central dans le complexe **47** comportant les ligands enaminonitrile **1** prend une géométrie tétraédrique avec une coordination par quatre atomes d'azote (*Figure 3*). Les propriétés photovoltaïques et photoconductrices des composites de film d'un copolymère de styrène avec le méthacrylate d'octyle (COM) et les additions des complexes de **47** avec Co (II), Cu (II), Ni (II) ont été étudiées. Le plus grand effet photovoltaïque comporte des films contenant du CoL_2. La valeur du potentiel électrique de la surface (V_{PH}^{max}) augmente dans une rangée de CuL_2 (80 mV), NiL_2 (120 mV), CoL_2 (180mV).

Compte tenu de la position λ_{max} dans le domaine visible du spectre, ainsi que de la tendance des composés à former des complexes chélatés, nous avons étudié les propriétés photophysiques du 2-azahetaryl-2-(5-R-3-oxoindolin-2-ylidène)acétonitriles **22-24** en présence d'ions métalliques (3d). La formation de complexe à partir du composé modèle **2.24b** avec Cu(II) et Zn(II) est caractérisée par un décalage bathochrome significatif des maxima d'absorption ($\Delta\lambda \geq 70$ nm); changement de la couleur du violet (λ_{max} = 530 nm) au bleu (λ_{max} = 600 nm). En appliquant la méthode logarithmique limitée à la recherche de complexes, nous avons trouvé que des complexes de stabilité moyenne se sont formés. Les réactifs sont sensibles et indiquent la détection de la limite des ions (LD) calculée selon le critère 3S en dessous de 1 µmol/l. La formation complexe se produit lentement avec d'autres métaux 3d dans des conditions d'interaction avec Zn(II) et Cu(II), comme dans le cas de Co(II) ou ne se produit pas dans le cas de Ni(II). Pour la détermination sélective de Zn(II), les ions Cu(II) peuvent être masqués par les ions thiosulfate.

La sixième chapitre de la thèse est une partie expérimentale, qui décrit les méthodes de synthèse des composés décrits dans le travail, et une description de leurs caractéristiques spectrales et physiques.

Conclusions général

Les travaux menés dans le cadre de cette thèse ont permis de mettre au point des méthodes de préparation des 2-azahétaryl-2-(1-R-pyrrolidine-2-ylidène)acétonitriles comportant des substituants azahétéro-cycliques de nature neutre et cationique et du 2-azahétaryl-2-(5-R-3-oxoindolin-2-ylidène)acétonitriles. La méthode pour accéder aux 2-azahétaryl-2-(1*H*-pyrrolidine-2-ylidène)acétonitriles a été optimisée, permettant un élargissement significatif de la portée de la réaction à de nombreux substituants azahétérocycliques (jusqu'à 12, à partir de 2).

Nous avons établi que les 2-azahétqryl-2-(1*H*-pyrrolidine-2-ylidène)acétonitriles existent à la fois dans la solution et à l'état solide en tant qu'isomères *Z*, contrairement au 2-azahétaryl-2-(1-alkylpyrrolidine 2-ylidène) les acétonitriles qui existent sous forme d'isomères *Z* à l'état solide et sous forme d'un mélange de diastéréoisomères *Z*/*E* dans la solution. L'énergie d'activation libre de rotation à la double liaison C=C a été calculée: $\Delta G^{\neq}$ *E*→*Z* = 14,4 kcal/mol, $\Delta G^{\neq}$ *Z*→*E* = 13,3 kcal/mol, valeur caractéristique des processus à basse énergie.

Dans notre étude sur la réaction des 2-azahétaryl-2-(1-R-pyrrolidine-2-ylidène) acétonitriles avec des fragments binucléophiles, tels que les hydrazines et l'hydroxylamine, nous avons observé une régiosélectivité complète. En effet, il a été établi que la première attaque nucléophile est dirigée contre un atome de C-2 de pyrrolidine. L'orientation de l'attaque suivante est déterminée par la nature du substituant azahétérocylique:

- dans le cas de substituants azahétérocycliques neutres (à côté du benzoxazole), l'attaque est dirigée contre le carbone du groupe nitrile conduisant aux 3-(ω-aminopropyl)-4-azahétaryl-5-aminopyrazoles;

- dans le cas des dérivés du benzoxazole, l'attaque se produit à la fois sur le groupe nitrile et avec la même probabilité sur l'atome C-2 de l'azahétérocycle conduisant aux isomères structuraux: le 4-benzo[*d*]oxazol-2-yl-3-aminopropyl)-1*H*-azol-5-amines et 5-((2-hydroxyphényl)amino)-3-(3-(R-amino)propyl)-1*H*-pyrazol-4-carbonitriles (4-carboxydiimide dans le cas de hydroxylamine);
- dans le cas du benzoxazole et du benzimidazole quaternisés, l'attaque est dirigée contre l'atome C 2 de l'azahétérocycle conduisant au 3-(4-cyano-5-((2-R-phényl)méthylamino)-1-R^1-1*H*-pyrazol-3-yl)-N-méthylpropan-1-amines.

Avec le benzothiazole quaternisé, la première attaque est dirigée contre le carbone du groupe nitrile suivi de l'attaque suivante de la chaîne *ω*-aminopropyle par l'atome C-2 du *N*-méthylbenzothiazole conduisant à un dérivé azépine original.

En partant de 3-(ω-aminopropyl)-4-azahetaryl-5-aminopyrazoles, nous avons étudié des méthodes de fonctionnalisation régiosélective de leurs groupes amino, la condensation dans des composés tétracycliques, à savoir le benzo[4,5]imidazo[1,2-c]pyrazolo[4,3-*e*]*pyrimidine* et *[1,2,3]triazine* avec un rendement global allant jusqu'à 87%; et la désamination via une étape de diazotation suivie par une arylation de Suzuki-Miyaura et une activation de C–H conduisant à des pyrazoles substitués par 5-aryl(styryl, indol-2-yl) avec un rendement global allant jusqu'à 92%.

Nous avons également exploré les propriétés du 2-azahétaryl-2-(1-R-pyrrolidine-2-ylidène) acétonitriles en réaction avec le DMF DMA. Il a été établi que la présence de groupes NH facilement accessibles est essentielle dans la «formylation» du centre C-3 de la pyrrolidine. La méthode de synthèse de pyrrolo[3,2-*c*]pyridine-6-imine (PP) avec 59% en 3 étapes a été développée. L'utilisation envisagée de PP pour la détermination de la teneur en eau dans des solvants organiques aprotiques par dosage fluorométrique a été développée pour le DMSO présentant une limite de détection de 0,068%.

Enfin, nous avons étudié la structure et les propriétés photophysiques de complexes de 2-azahétaryl-2-(pyrrolidine/3-oxoindolin-2-ylidène) acétonitriles avec des métaux 3d et du bore.

Cela nous a permis d'établir leur utilité puisque:

- Les principales caractéristiques des complexes BF_2 à base de 2-azahétaryl-2 (pyrrolidin-2-ylidène)acétonitriles sont les grands déplacements de Stokes (jusqu'à 9000 cm^{-1}), haute luminosité (jusqu'à 86400 $l \cdot mol^{-1} \cdot cm^{-1}$), solvatofluorochromie positive, fluorescence à l'état solide et stabilité de l'eau.
- Les films de composites polymériques avec ajouts de complexes métalliques de 2-azahétaryl-2-(pyrrolidin-2-ylidène)acétonitriles avec du Co(II), du Cu(II), du Ni(II) (ML_2) ont un effet photovoltaïque. Le potentiel électrique de la surface atteint la plus grande valeur de 180 mV dans le cas de CoL_2.
- Le 2-azahétaryl-2-(5-R-3-oxoindolin-2-ylidène)acétonitriles a démontré une grande visibilité lors de la chélation du Zn(II) et du Cu(II): $\Delta\lambda \geq 70$ nm, λ_{ligand}^{max} = 515-530 nm (rouge-violet), $\lambda_{complex}$max = 590–605 nm (bleu), au pH des fluides biologiques. La limite de détection des ions est de 0,4 à 1,0 µmol/l.

Ce travail illustre donc les grands développements potentiels pouvant être réalisés sur la base d'une approche synthétique efficace des hétérocycles polyfonctionnels. Nous avons montré que les efforts de synthèse permettent non seulement de nouveaux accès à des composés densément fonctionnalisés, mais fournissent également des outils moléculaires simples pour les études photophysiques permettant de nouveaux développements dans un large éventail de domaines. À ce titre, ces travaux contribuent à faire de la molécule le centre de tout développement scientifique en sciences chimiques.