KAUNAS UNIVERSITY OF TECHNOLOGY

VAIDA MILIŠIŪNAITĖ

SYNTHESIS OF NOVEL CONDENSED PYRAZOLE RING CONTAINING HETEROCYCLIC SYSTEMS AND INVESTIGATION OF THEIR PROPERTIES

Doctoral dissertation
Physical Sciences, Chemistry (03P)

2018, Kaunas

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VAIDA MILIŠIŪNAITĖ

NAUJŲ KONDENSUOTŲJŲ HETEROCIKLINIŲ SISTEMŲ, TURINČIŲ PIRAZOLO ŽIEDĄ, SINTEZĖ IR JŲ SAVYBIŲ TYRIMAS

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CONTENTS

List of Abbreviations and Physical Units

[DABCO-H][AcO] – 1,4-diazobicyclo[2.2.2]octane (DABCO) based ionic liquids
A-549 – adenocarcinomic human alveolar basal epithelial cells
AChE – acetylcholinesterase
APT – attached proton test
BChE – butyrylcholinesterase
CB1R – cannabinoid type 1 receptor
CCR1 – C-C motif chemokine receptor 1
CCRF – human acute lymphoblastic leukemia cells
CV-B3 – coxsackie B4 virus
DCC – *N*,*N*'-Dicyclohexylcarbodiimide
DIEA – *N*,*N*-Diisopropylethylamine
EV-A71 – the enterovirus A (sero)type enterovirus A71
G2 – gap 2 phase, which is the second subphase of interphase in the cell cycle directly preceding mitosis
GI50 – concentration of drug to cause 50% reduction in the proliferation of cancer cells
*h*CAs IX and XII – carbonic anhydrase isoforms
h-e5`NT – human ecto-5'-nucleotidase
HeLA – immortal cell line
Hep G2 – human liver cancer cell line
HMBC – heteronuclear multiple bond coherence
HRMS – high resolution mass spectrometry
HSQC – heteronuclear single quantum coherence
Huh-7 – human liver cell line
IC50 – half maximal inhibitory concentration
K-562 – myelogenous leukemia cell line
LC – liquid chromatography
M – mitosis
MCF-7 – breast cancer cell line
MeOH – methanol
MS – mass spectrometry
MTBPS – mycobacterium tuberculosis pantothenate synthetase
MTT – colorimetric assay for assessing cell metabolic activity
NBS – *N*-bromosuccinimide
NH_2NHTs – *p*-toluenesulfonyl hydrazide
NHC – *N*-heterocyclic carbene complex
NMR – nuclear magnetic resonance
NOESY – nuclear overhauser effect spectroscopy
OTf – trifluoromethanesulfonate
Panc-1 – human pancreatic cancer cell line isolated from a pancreatic carcinoma of ductal cell origin
ppm – parts per million
ROESY – rotating-frame overhauser effect spectroscopy

rt – room temperature
SAR – structure–activity relationship
SIRT1 – NAD-dependent deacetylase sirtuin-1
SIRT2 – NAD-dependent deacetylase sirtuin 2
SKNSH – human neuroblastoma cell line
*t*Bu – *tert*-butylate
TLC – thin layer chromatography
TMS – trimethylsilane
TMS – trimethylsilyl
TOCSY – total correlation spectroscopy
δ – chemical shift

1. INTRODUCTION

Pyrazoles and their derivatives represent a class of important nitrogen-containing heterocyclic compounds that are covering a broad range of synthetic as well as natural products that display innumerable chemical, biological, agrochemical, and pharmacological properties.

Fused compounds that are containing pyrazole moiety possess a broad spectrum of biological activities. It is known that derivatives containing pyrazolopyrimidine scaffold show pharmacological properties such as cyclin-dependent kinase (CDK) inhibitory, antiproliferative, anticancer, antituberculosis, sedative, antibacterial, antifungal, antileishmanial, and act like antiviral agents, antidepressants[1]. Furopyrazole based molecules demonstrate antimicrobial and antitumor activities[2], while benzopyranopyrazole derivatives have anxiolytic, hypnotic, and anticonvulsant activity to the nervous system; moreover, they can be used as antihypertensive, antibacterial, diuretic, uricosuric, and vasodilative agents[3]. Pyrazole-benzimidazole hybrids show potential anti-proliferative activity against lung (A-549), breast (MCF-7), and cervical (HeLa) carcinoma cell lines.[4] Several drugs have been developed from pyrazole derivatives for the past two decades. For instance, Allopurinol (pyrazolo[3,4-*d*]pyrimidin-4-one) decreases high blood uric acid level, Sildenafil (pyrazolo[4,3-*d*]pyrimidine) is used to treat erectile dysfunction and pulmonary arterial hypertension, Zaleplon (pyrazolo[1,5-*a*]pyrimidine) is effective in reducing latency to sleep without evidence of undesired effects in elderly patients with insomnia, and Zolazepam (pyrazolo[3,4-*e*]diazepine) is used as an anesthetic for a wide range of animals in veterinary medicine (Figure 1.1). There is a growing body of evidence that pyrazole and its derivatives provide a viable and valuable area for drug discovery. In view of the diverse pharmacological profile of condensed pyrazoles, design and synthesis of new biologically active condensed pyrazole derivatives have been a subject of many research studies for medicinal chemists.

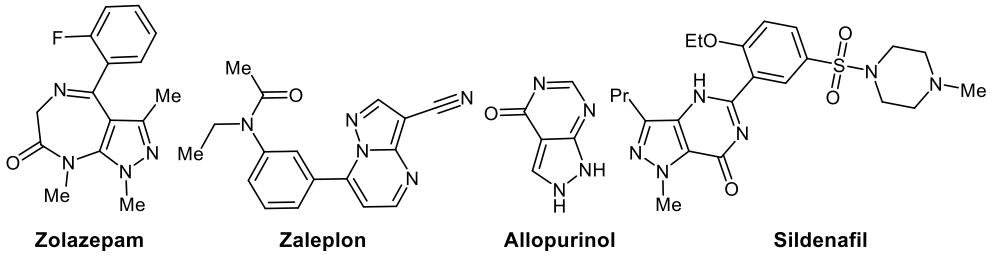


Figure 1.1 Pyrazole nucleus containing pharmaceutical drugs

Because pyrazolo[3,4-*b*]pyridine skeleton is a donor-*π*-acceptor system, some research[1b] concerning the fluorescent properties of its derivatives has been disclosed as well. In addition, the fused heterocyclic systems such as dipyrazolo[3,4-*b*:3',4'-*d*]pyridines exhibit strong fluorescence and have been applied in the preparation of blue light-emitting diodes[1b]. Furthermore, pyrazoles are pluripotent ligands in coordination chemistry, optical brighteners and UV stabilizers, photoinduced electron transfer systems, and units in supramolecular entities[1b]. Among those, pyrazole compounds

have attracted much attention in recent years owing to its wide application in chemistry and material science as well.

The majority of annulated pyrazoles can be achieved by multi-component reactions. Zhang et al. reported synthesis of trifluoromethylated *trans*-4,5-dihydrofuro[2,3-*c*]pyrazoles *via* the high stereoselective reaction of arsonium bromides and the electron-deficient alkenes in the presence of K_2CO_3 as a base[5]. A literature survey suggested that 2*H*-pyrazolo[4,3-*c*]pyridines are usually accomplished by the treatment of 4-chloro or 4-iodopyridines possessing a carbonyl moiety at 3-position with various hydrazines or heating mixtures of (*E*)-1-(4-azidopyridin-3-yl)-*N*-phenylmethanimines in toluene[6]. Turki et al. obtained benzopyrano[2,3-*c*]pyrazoles by treating 3-cyano iminocoumarins with hydrazines or hydrazides under the acidic catalyst conditions[3].

As annulated pyrazole systems are of interest to medicinal chemists and materials scientists, and their synthesis is a worthwhile task; therefore, it has been decided to explore new synthetic approaches of various condensed pyrazoles systems and investigate the biological and optical activities of the obtained compounds.

The main aim of this dissertation:

Design, synthesis, and investigation of novel polycyclic heterocyclic systems by employing ring-closure reactions of *vic*-bifunctionalized pyrazoles.

The tasks proposed for the achievement of the above stated aim were as follows:

1. Synthesize 4-alkynyl-1-phenyl-1*H*-pyrazol-3-ols and investigate their transformation to 2*H*-furo[2,3-*c*]pyrazoles.

2. Synthesize 3-alkynylpyrazole-4-carbaldehydes and the corresponding alkanones and examine their transformation to 2*H*-pyrazolo[4,3-*c*]pyridines.

3. Synthesize novel 4-aroylpyrazol-3-ols and investigate their transformation to benzopyrano[2,3-*c*]pyrazol-4(2*H*)-ones.

4. Synthesize 3- and 5-alkynylpyrazole-4-carbaldehydes and examine their condensation with (het)aryl diamines.

5. Investigate the structure of novel heterocyclic compounds by advanced methods of NMR spectroscopy.

6. Investigate functional properties of novel heterocyclic compounds.

Scientific novelty: Bicyclic 2*H*-furo[2,3-*c*]pyrazoles were synthesized from commercially available 3-hydroxypyrazole *via* three strep synthetic approach by preparing 4-alkynyl- and 4-(arylethynyl)pyrazol-3-ols which participated in silver (I) or gold (I) mediated 5-*endo*-*dig* cyclization. Pyrazole-4-carbaldehydes that are carrying an alkynyl function group adjacent to the formyl moiety are valuable starting materials for the construction of condensed pyrazole systems. The prepared precursors were tested in various cyclisation reactions with dry ammonia or (het)aryl 1,2-diamines. A series of novel pyrazolo[4,3-*c*]pyridines were tested in structure–activity relationship (SAR) research for cytotoxicity against K-562 and MCF-7 cancer cell lines. The obtained 2*H*- and 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles, 3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*']dipyridines, and 13,13a-dihydro-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]perimidines showed good optical properties. Moreover, the transformation

of commercially available 3-hydroxypyrazole to pyrazole esters underwent Fries rearrangement reaction to provide 4-aroylpyrazol-3-ols that were excellent building blocks for benzopyrano[2,3-*c*]pyrazol-4(2*H*)-ones.

Main statements for the defense:

1. 4-Alkynyl- and 4-(arylethynyl)pyrazol-3-ols undergo 5-*endo*-*dig* cyclization mediated by a silver (I) or gold (I) catalyst to form 2*H*-furo[2,3-*c*]pyrazole ring system.

2. Treating 3-alkynyl-1*H*-pyrazole-4-carbaldehydes, 4-ethanones and 4-propanones with dry ammonia affords a versatile library of 2*H*-pyrazolo[4,3-*c*]pyridines.

3. 4-Aroylpyrazol-3-ols, bearing halogen atom at 2nd position of aryl substituent, are convenient synthons for the synthesis of benzopyrano[2,3-*c*]pyrazol-4(2*H*)-ones.

4. *Vic*-alkynylpyrazole-4-carbaldehydes are suitable precursors for tandem cyclisations with (het)aryl diamines.

The results of the doctoral dissertation were presented at 7 scientific conferences, and 2 articles were published in reviewed scientific journals.

2. LITERATURE REVIEW

The aim of this literature review is to provide an overview concerning synthesis and application of various condensed pyrazole systems.

2.1. Synthesis of bicyclic pyrazole derivatives

Recently, much attention has been paid to the development of newer approaches to obtain bicyclic pyrazole systems[7]. For example, Lilly has presented a bicyclic pyrazolidinone LY 186826 exhibiting antibiotic activity better than that of several penicillins and cephalosporins[8]. Moreover, new promising herbicides[9] and potent drug molecules for treatment of cognitive dysfunctions such as Alzheimer disease were introduced (Figure 2.1)[10].

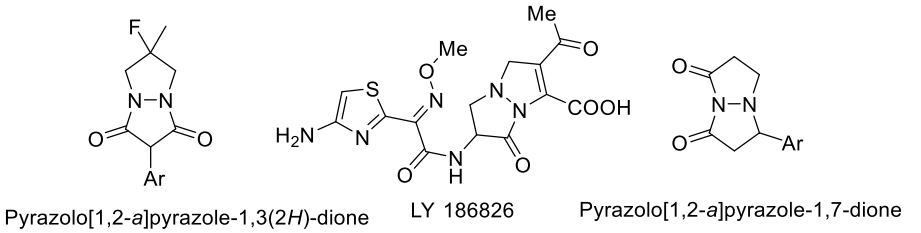


Figure 2.1 Biologically active bicyclic pyrazolidinone and pyrazolo[1,2-*a*]pyrazoles

It is known that pyrazolo[1,5-*b*]pyrazoles are used as hair dyes[11,12], and 3-oxo-3*H*-pyrazolo[1,2-*a*]pyrazol-4-ium-1-olates can be used with fertilizers as nitrification inhibitors (Figure 2.2)[13]. It is essential to mention that pyrazolo[3,4-*c*]pyrazoles are useful for the treatment of esophageal, gastrointestinal mucosa injury[14], and brain injury[14]; moreover, they are known as immunostimulatory,[14] antianginal,[15] and antitumor [16] agents.

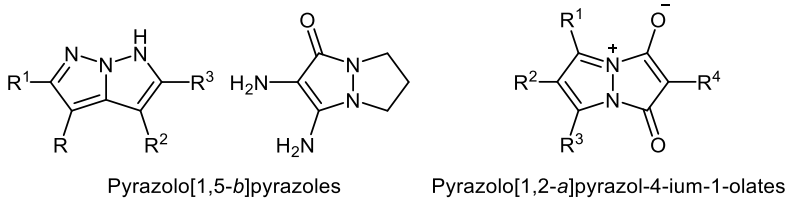


Figure 2.2 Bicyclic fused pyrazole compounds used as hair dyes and nitrification inhibitors

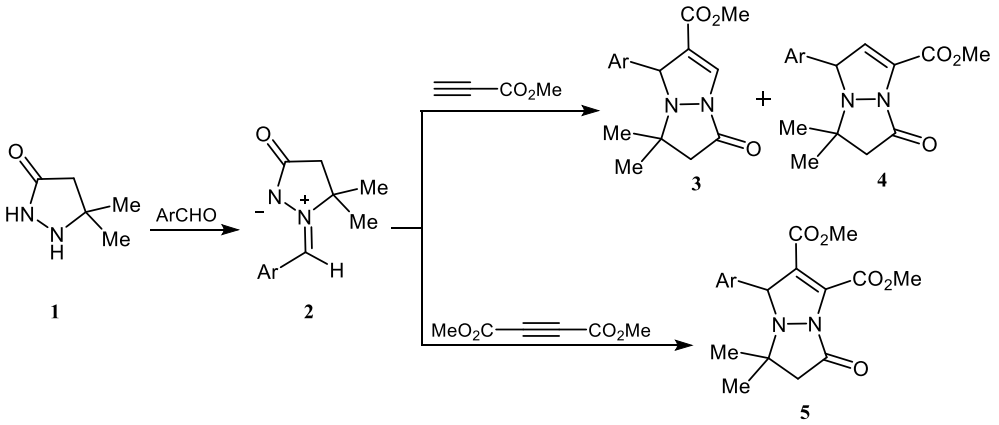
2.1.1. Pyrazolo[1,2-*a*]pyrazoles

There are three general approaches to synthesize pyrazolo[1,2-*a*]pyrazoles:

- 1,3-dipolar cycloaddition of various acetylenes to azomethinimines,
- cycloaddition of azines to dipolarphiles,
- reaction of pyrazoles with ketene, 1,3-dicarbonyl, or dinitrile compounds[10].

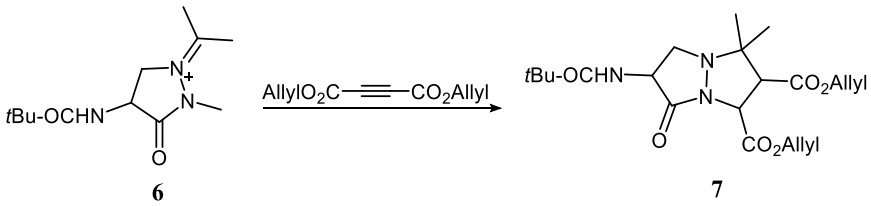
For example, 1,3-dipolar cycloaddition of methyl propiolate with [(*Z*)-arylmethylene]dimethylpyrazolidinone azomethine imine **2**, which was formed through

the condensation of dimethylpyrazolidinone **1** with aromatic aldehydes, gave a mixture of the regioisomeric pyrazolo[1,2-*a*]pyrazoles **3** and **4**[10], whereas pyrazolo[1,2-*a*]pyrazoles **5** were synthesized by using 1,3-dipolar cycloaddition of azomethine imines to dimethyl acetylenedicarboxylate (DMAD) (Scheme 2.1)[10].



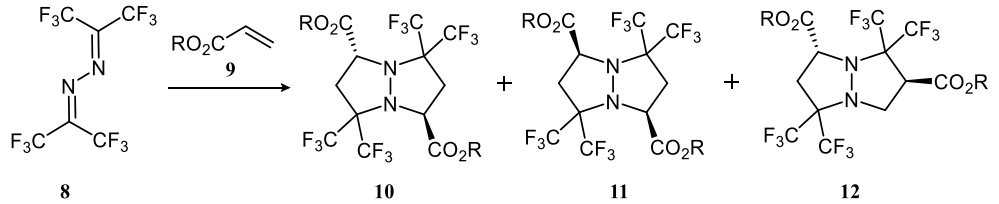
Scheme 2.1 1,3-Dipolar cycloaddition of [(*Z*)-arylmethylene]dimethylpyrazolidinone azomethine imine **2**

Bicyclic pyrazolidinone **7** can be obtained as well by cycloaddition of the ylide **6** and diallyl acetylenedicarboxylate (Scheme 2.2)[17].



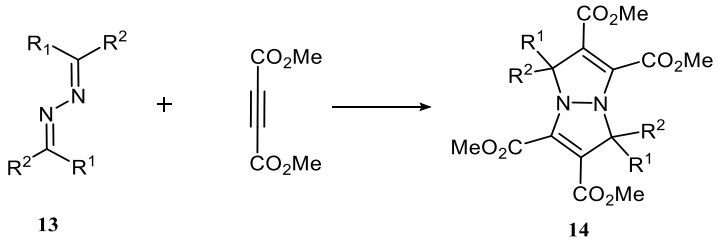
Scheme 2.2 Cycloaddition of the ylide **6**

Another method to synthesize pyrazolpyrazoles is to perform a cycloaddition of azines to dipolarophiles. For instance, pyrazolopyrazoles **10–12** were obtained by a "crisscross" cycloaddition reaction of 1,2-bis(perfluoropropan-2-ylidene)hydrazine **8** with olefins **9**; the desired products formed in approximately 65% yields (Scheme 2.3)[18].



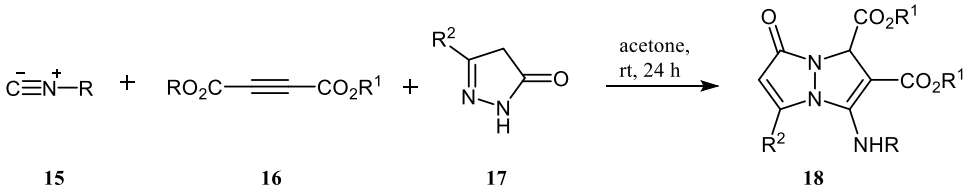
Scheme 2.3 Cycloaddition between the azines **8** and dipolarophiles **9**

El-Alali and Al-Kamali reported a [2+3] cycloaddition reaction of aldazines or ketazines **13** with DMAD to afford pyrazolopyrazoles **14** (Scheme 2.4)[19].



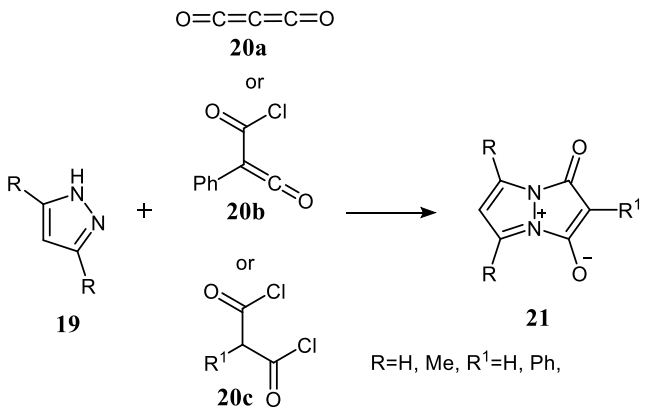
Scheme 2.4 [2+3] Cycloaddition of aldazines or ketazines **13**

In 2005, Adib et al.[20] presented a novel synthesis strategy of functionalized 7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazoles. 2,4-dihidro-3*H*-pyrazol-3-ones **17** were treated with isocyanides **15** and dialkyl acetylenedicarboxylates **16** in a smooth 1:1:1 addition reaction to obtain highly functionalized desired pyrazole derivatives **18** in 69–81% yields (Scheme 2.5)[20].



Scheme 2.5 Synthesis of 7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazoles **18**

An efficient method for pyrazolpyrazoles synthesis is to perform a reaction between pyrazoles and ketene, 1,3-dicarbonyl, or dinitrile compounds. For example, pyrazoles **19** were treated with propa-1,2-diene-1,3-dione or 3-oxo-2-phenylacryloyl chlorides **20** in order to get cross-conjugated pyrazolium hydroxides **21** (Scheme 2.6)[21].



Scheme 2.6 Reaction between pyrazoles **19** and compounds **20**

2.1.2. Pyrrolo[3,4-*c*]pyrazoles

It is well known that pyrrolopyrazole has been exploited as a hinge binder for a number of protein kinase targets[22]. Steeghs et al. reported that an Aurora kinase inhibitor PHA-739358 (Figure 2.3) has advanced into the phase II clinical trials for the treatment of cancer because of very good pharmacokinetic properties and general safety profiles in phase I clinical study[23]. Brasca et al. presented a potent cyclin dependent kinases (CDK) inhibitor PHA-793887 which inhibits the tumor growth in preclinical xenograft tumor models. For this reason, it was further chosen as an anticancer agent for clinical evaluation[24]. In 2010, Shi et al.[22] reported a synthesis of novel 1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazoles as Aurora-A kinase inhibitors. It is worth pointing out that two of these compounds have ideal anti-proliferative activities *in vitro*[22c].

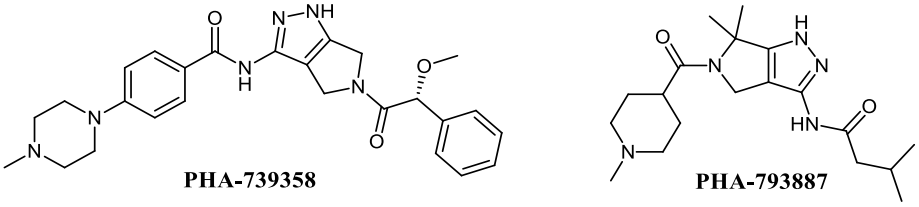
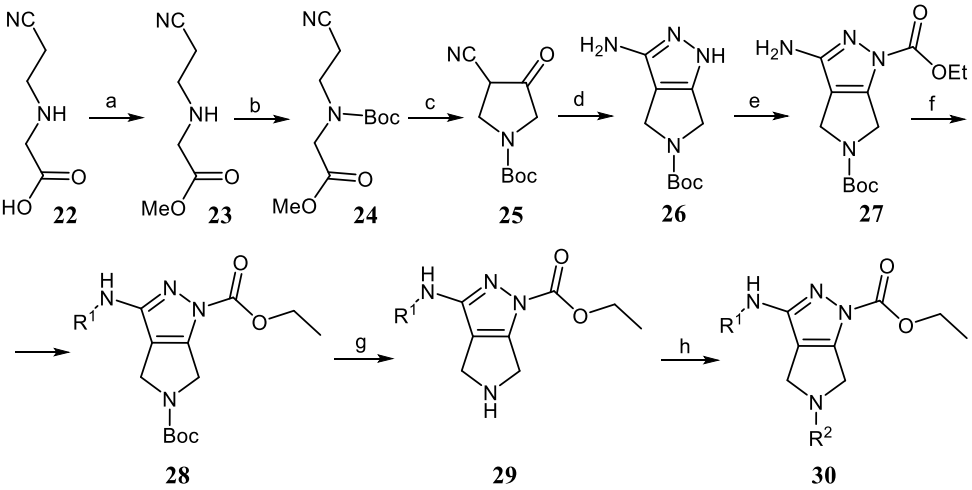


Figure 2.3 Aurora kinase inhibitors

The desired compounds were obtained according to the methods described in literature[22c] with minor revision by Shi et al. Firstly, 2-(2-cyanoethylamino)acetic acid **22** was treated with sulfuric acid and methanol to afford methyl ester **23** (Scheme 2.7). The amino group of compound **23** was further protected in order to get compound **24**, which was treated with sodium methoxide.



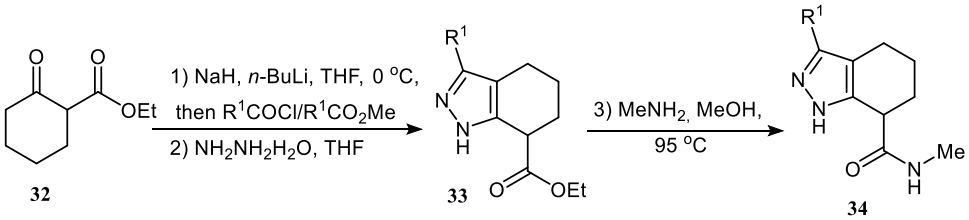
Reagents and conditions: (a) MeOH, H_2SO_4, 7 h, reflux; (b) di-*tert*-butyl dicarbonate, DCM/aq $NaHCO_3$ (1:1), 24 h, 22 °C; (c) MeOH, toluene, 3 h, 80 °C, then 2 N HCl; (d) hydrazine hydrochloride, EtOH, 3 h, 60 °C, then $NaHCO_3$, EtCOOCl, THF, 20 h, 0–5 °C; (f) R^1COCl, DIEA, THF, 12 h, 22 °C; (g) TFA/DCM (1:1) 10 equiv, 1 h, 22 °C; (h) R^2COCl, DIEA, THF, 6 h, 22 °C.

Scheme 2.7 Preparation of pyrrolo[3,4-*c*]pyrazole **30**

The obtained 4-oxo-pyrrolidine-3-carbonitrile **25** was cyclised to tetrahydropyrrolopyrazole **26** using hydrazine. Intermediate compound **26** was treated with ethyl chlorocarbonate in order to get compound **27**. Later, after acylation, the compound **27** was transformed to derivative **28**. After the amino group deprotection reaction of the latter compound, the obtained pyrazoles **29** were employed in the reaction with acyl chloride to afford pyrazole systems **30**.

2.1.3. Construction of bicyclic pyrazole carboxamides

Therrien et al.[25] presented synthesis and biological evaluation of an unprecedented series of bicyclic pyrazole derivatives as SIRT1 and SIRT2 inhibitors. Firstly, commercially available ethyl 2-oxocyclohexanecarboxylate **32** was acylated with either acyl chloride or methyl carboxylate to afford 1,3-diketone intermediates that were reacted with hydrazine hydrate in THF to obtain tetrahydroindazoles **33**. They were further converted to carboxamides **34** in the presence of a 7N solution of ammonia in methanol upon heating in a sealed tube or treating ester **33** with methylamine in methanol (Scheme 2.8)[25].



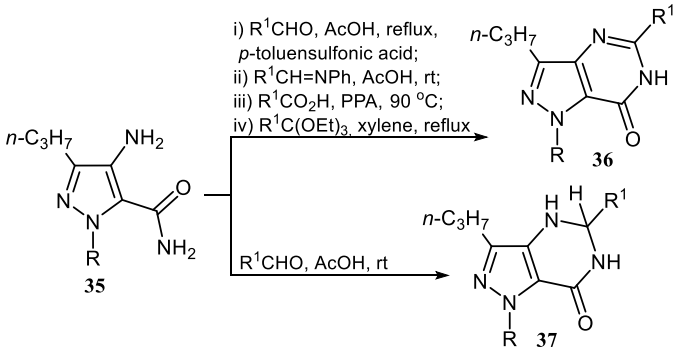
Scheme 2.8 Synthesis of bicyclic pyrazole carboxamides **34**

2.1.4. Construction of pyrazolopyrimidines

2.1.4.1. Pyrazolo[4,3-*d*]pyrimidines

The synthesis of pyrazolo[4,3-*d*]pyrimidines was firstly reported in 1956. A study of biological activity of numerous compounds which were synthesized by using different synthetic pathways was represented[1a]. In 1956, Robins et al. presented the synthesis of pyrazolo[4,3-*d*]pyrimidines as potential purine antagonists[26]. Pyrazolo[4,3-*d*]pyrimidines received attention from medicinal chemists due to the broad spectrum of pharmacological activities such as adenosine receptor antagonists[27], cytokinin antagonists[28], corticotrophin releasing factor receptor antagonists[29], anti-leishmanial[30], phosphodiesterase 5 (PDE5) inhibitors[31], anti-viral and anti-fungal[32], antiinflammatory[33], agents in male and female sexual dysfunctions[34] etc.

In 2005, Reddy et al. [1c] reported that pyrazolo[4,3-*d*]pyrimidin-7-ones **36** were synthesized by treating starting metarials **35** with appropriate aldehydes in acetic acid in the presence of catalytic amount of *p*-toluensulfonic acid (Scheme 2.9).

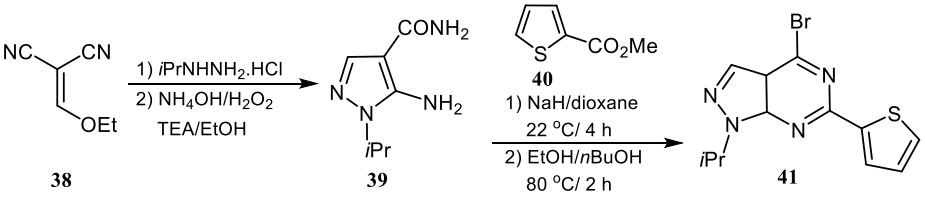


Scheme 2.9 Synthesis of pyrazolo[4,3-*d*]pyrimidines **36** and **37**

In addition, tetrahydropyrazolo[4,3-*d*]pyrimidin-7-ones **37** were obtained in the reaction of starting material **35** with 4-*N*,*N*-dimethylamino benzaldehydes, where acetic acid is used as a solvent. It is important to mention that arylideneaniline may as well be used for these reactions in order to get corresponding pyrazolo[4,3-*d*]pyrimidines **36**. In this case, the excess of 2 equivalents of arylideneaniline was used, because performing an equimolar reaction provided product **37**. Moreover, pyrazolo[4,3-*d*]pyrimidines **36** were as well synthesized by heating starting material **35** with aromatic carboxylic acids in polyphosphoric acid (PPA) (Scheme 2.9)[1c]. Reddy with coworkers demonstrated that triethyl orthoesters were used to afford the directly desired pyrazolopyrimidines by refluxing them with pyrazolo carboxamides in xylene (Scheme 2.9)[1c].

2.1.4.2. Pyrazolo[4,5-*d*]pyrimidines

Xing et al.[35] have reported the synthesis and investigation of novel pyrazolo[4,5-*d*]pyrimidines **41**. The authors have achieved target compounds by using general synthetic route where 2-(ethoxyvinylidene)-malononitrile **38** was treated with isopropylhydrazine; later, the reaction was proceeded in the presence of basic hydrogen peroxide to obtain aminoamide **39**. Pyrazole **39** was condensated with methyl thiophene-2-carboxylate **40** to get the desired 1*H*-pyrazolo[4,5-*d*]pyrimidinol **41** (Scheme 2.10)[35]. The activities against replication of poliovirus-1, EV-A71, and CV-B3 enteroviruses of the synthesized compounds **41** were tested.



Scheme 2.10 Synthesis of 1*H*-pyrazolo[4,5-*d*]pyrimidinol **41**

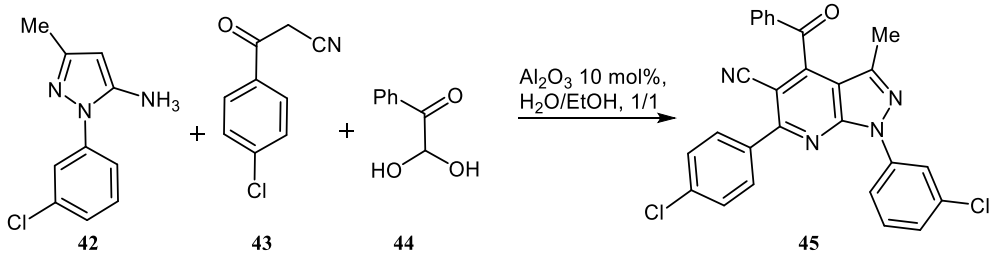
Later, the synthesized compounds were functionalized to provide 1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carboxamides which were evaluated in the primary biological screen, and 22 of these derivatives were confirmed to be active against the

used enterovirus strain (CVB3-H3)[35]. Xing et al. reported that inhibitors with the highest selectivity indicators at 50% inhibition of viral replication (SI_{50}) were those with the isopropyl group at the N1 position and thiophenyl-2-yl unit at C6 position. Moreover, the promising improvement could be influenced by C4 position because many different *N*-aryl groups showed better antiviral activities and compatibilities than the lead compound. Finally, the authors have noticed that some compounds showed good antienteroviral activity, which was important for the antienteroviral drug design[35].

2.1.5. Construction of pyrazolopyridines

Evidently, the nitrogen-based heterocyclic compounds incorporating the pyridine moiety is an essential scaffold known for a wide range of biological activities. El-Gohary and Shaabanb have reported that pyridines were found to have DNA binding affinity, and notable, they highlighted the significance of compounds containing pyridine nucleus as antimicrobial and antitumor agents[36]. In 2017, Pelit noted that pyrazolopyridines exhibit numerous biological properties such as anti-viral agent, HIV inhibitors, CCR1 antagonists, protein kinase inhibitors, and they as well exhibit parasiticidal properties and antimalarial activities[37]. In 2013, Ganesh et al. reported that pyrazolo[4,3-*c*]pyridine derivatives such as 3-phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridines act as MTB PS inhibitors[38]. Furthemore, El-Gohary, and Shaabanb have marked that pyrazolopyridine nucleus are structurally similar to purine scaffold; for this reason, pyrazolopyridines might compete with purines and prohibit the synthesis of nucleic acids[36]. It is important to mention that several 4-aryl-5-substitued pyrazolo[3,4-*b*]pyridines were reported to be efficient antitumor agents[36]. Due to the aforementioned facts, the molecular hybridization involving the combining of two heterocycles could reinforce biological acitivity.

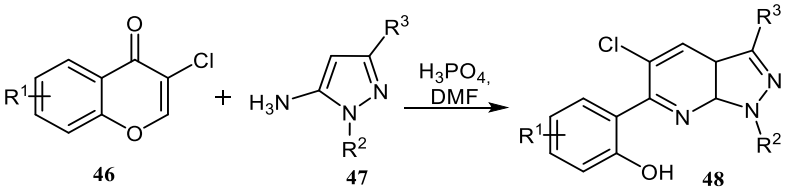
Arlan et al.[39] have published a one-pot three-component synthetic approach to obtain a group of new 4-aroyl-1,6-diaryl-3-methyl-1*H*-pyrazlo[3,4-*b*]pyridine-5-carbonitriles (Scheme 2.11). The authors have chosen 1-(3-chlorophenyl)-3-methyl-1*H*-pyrazol-5-amine **42**, 3-(4-chlorophenyl)-3-oxopropanenitrile **43**, and phenylglyoxal hydrate **44** as starting compounds to explore this reaction; unfortunately, the formation of the desired product **45** was not observed even after 24 h of stirring without a catalyst at room temperature. Later, scientists proceeded the reaction under the refluxing conditions in the presence of different catalysts and different solvent systems, and finally, product **45** was obtained with an isolated 89% yield[39].



Scheme 2.11 Synthesis of bicyclic 3-methyl-1*H*-pyrazlo[3,4-*b*]pyridine-5-carbonitriles

Arlan et al. as well have tested the effect of the amount of catalyst performing reaction with different amounts of nano-Al_2O_3; however, the increasing amount of catalyst did not improve the yield. Scientists have claimed that the above mentioned pyrazolopyridines could serve as intermediates for new planar polycyclic heterocycles[39].

In 2018, Miliutina et al.[40] presented a study concerning the novel domino reaction between 3-chlorochromones **46** and electron-rich aminoheterocycles, providing various new pyrazolo[3,4-*b*]pyridines **48** (Scheme 2.12).



Scheme 2.12 Synthesis of pyrazolo[3,4-*b*]pyridines **48**

As chlorine could behave as an activating group for the regioselective formation of products and an applicable leaving group in intramolecular cyclization reaction, scientists have chosen 3-chlorochromones **46** as starting materials. The best results were obtained when reactions were proceeded under acidic conditions in the presence of phosphoric acid, using DMF as a solvent. It has been noticed as well that the temperature made a huge influence (it should not be too high), and additional activation was indispensable, in spite of the fact that chromone reactivity was not sufficient (Scheme 2.12)[40].

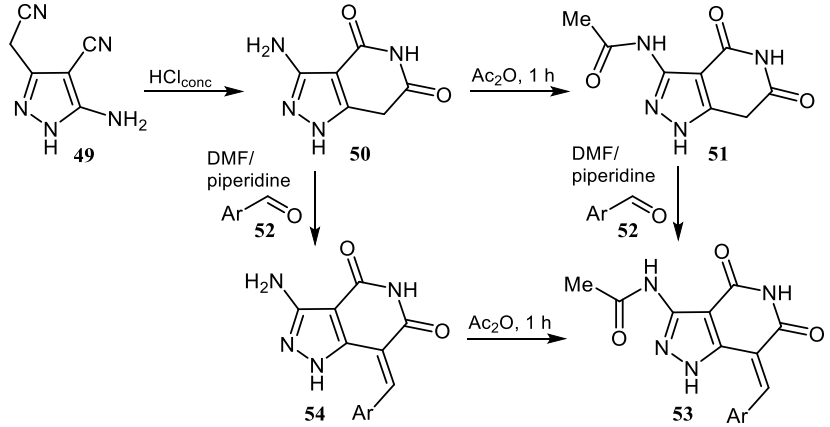
The obtained pyrazolo[3,4-*b*]pyridines **48** were further examined as promising inhibitors against ecto-5′-nucleotidases (e5′NT).[44] The scientists analyzed compounds **48** towards both human (*h*-) and rat (*r*-) isozymes and discovered that the majority of them inhibited *h*-e5′NT at very low concentrations[40].

Miliutina et al. examined the synthesized pyrazolo[3,4-*b*]pyridines **48** for cytotoxic activity on cervical cancer cell lines (HeLa) in the presence of carboplatin as a standard drug. Interestingly, all compounds were significant inhibitors towards cancer cell lines because they showed more than 80% inhibition against cervical cancer (HeLa)[40].

Metwally and Deeb reported[41] that compounds **54** could be synthesized by refluxing aminopyrazolo[4,3-*c*]pyridine **50** with aromatic aldehydes **52** in DMF (Scheme 2.13). The acetylation of compounds **54** with acetic anhydride provided products which were completely identical in all aspects (melting point, mixed melting point, and IR) with compounds **53** (Scheme 2.13)[41].

Some of the newly synthesized pyrazolo[4,3-*c*]pyridine derivatives[41] were investigated for anticancer activity. The results of the cytotoxic activity revealed that compound **54** (Ar=4-MeO-C_6H_4) was the most active compound against the breast and liver carcinoma cell lines with IC_{50} values of 1.937 and 3.695 μg/mL compared to a reference drug (doxorubicin) with IC_{50} values of 2.527 and 4.749 μg/ml, respectively. Moreover, compound **54 (**Ar=4-Cl-C_6H_4) was a potent compound against the

colon carcinoma cell line with IC_{50} = 2.914 μg/ml compared to the doxorubicin with IC_{50} value of 3.641 μg/ml.[41]

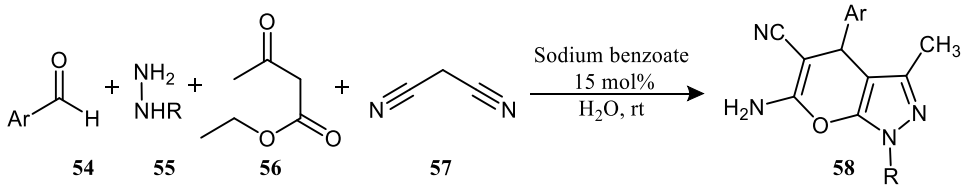


Scheme 2.13 Synthesis of 4*H*-pyrazolo[4,3-*c*]pyridine-4,6-(5*H*)-dione

2.1.6. Dihydropyrano[2,3-*c*]pyrazoles

Dihydropyrano[2,3-*c*]pyrazoles are an important part of numerous biologically active compounds and are attractive templates for medicinal chemistry. Pyrano[2,3-*c*]pyrazoles have several biological activities such as molluscicidal[42], insecticidal[43], antiinflammatory[44], analgesic[48], and anticancer[45]. In 1973, Junek and Aigner were the first who obtained pyranopyrazoles; the reaction was done by treating 3-methyl-1-phenylpyrazolin-5-one with tetracyanoethylene[46].

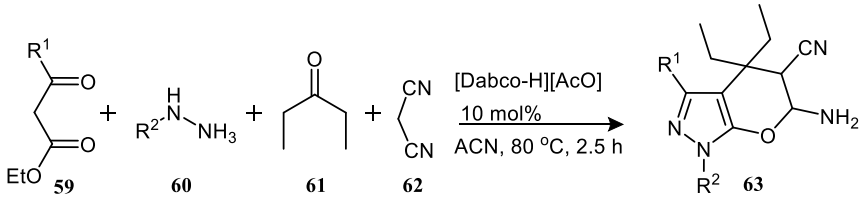
Kiyani et al.[47] reported the synthesis of pyranopyrazoles **58** by treating aryl aldehydes **54** with hydrazines **55**, ethyl acetoacetate **56** and malonitrile **57** in the presence of sodium benzoate as the mild basic catalyst (Scheme 2.14).



Scheme 2.14 Synthesis of pyranopyrazoles **58**

The authors demonstrated an efficient method to obtain pyranopyrazoles *via* four-component reaction, to get the desired products **58** without column purification by using environmentally friendly reaction conditions[47].

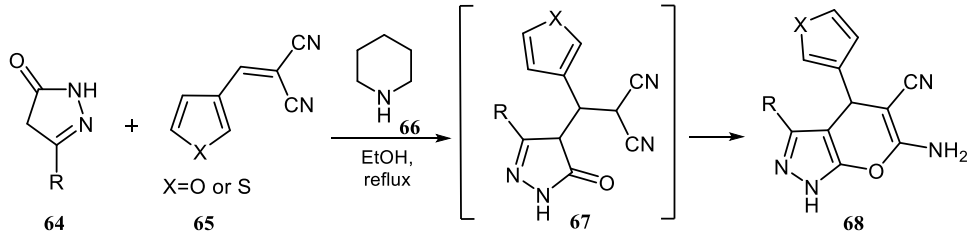
Liu and coauthors[48] demonstrated the synthesis of pyranopyrazoles **63** by using ketones **61** instead of aldehydes (Scheme 2.15). The reaction of ethyl acetoacetates **59**, hydrazines **60**, malononitrile **61**, and 3-pentanone **61** in the presence of [Dabco-H][AcO] as a catalyst gave ketone-derived dihydropyrano[2,3-*c*]pyrazoles **63** in good yields[48].



59 60 61 62 63

Scheme 2.15 Synthesis of dihydropyranopyrazoles **63**

Abdelrazek et al.[42] published another synthetic route to afford pyrano[2,3-*c*]pyrazole derivatives **68** (Scheme 2.16). In this case, pyrazol-5-ones **64** underwent a cyclization reaction with 3-furfurylidene or 3-thienylidene malononitriles **65**.



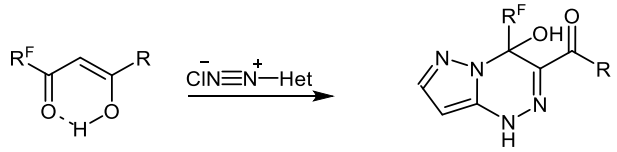
64 65 67 68

Scheme 2.16 Cyclisation of pyrazol-5-ones **64** with 3-furfurylidene/3-thienylidene malononitriles **65**

2.1.7. Synthesis of pyrazolotriazines

It is well known that pyrazolotriazines are interesting heterocyclic structures due to their broad spectrum of biological activities such as anticancer[49], cyclin-dependent protein kinase 7 (CDK7) inhibitory[50], antifungal[51], and antioxidant[52].

Nasr et al. published synthesis of a novel group of pyrazolo[3,4-*d*][1,2,3]triazines and investigated their anticancer activity *in vitro* against three different cell lines, namely, Huh-7, Panc-1, and CCRF[53]. Shchegol'kov et al.[52] reported the synthesis of novel 7-hydroxy-7-polyfluoroalkyl-4,7-dihydroazolo[5,1-*c*][1,2,4]triazines and tested them as AChE, BChE, and CaE inhibitors. Shchegol'kov have previously published a method to obtain 7-polyfluoroalkyl-4,7-dihydroazolo[5,1-*c*][1,2,4]triazines by one-pot reaction, treating azocoupled polyfluoroalkyl-containing 1,3-dicarbonyl reagents with hetaryldiazonium salts (Scheme 2.17)[52].



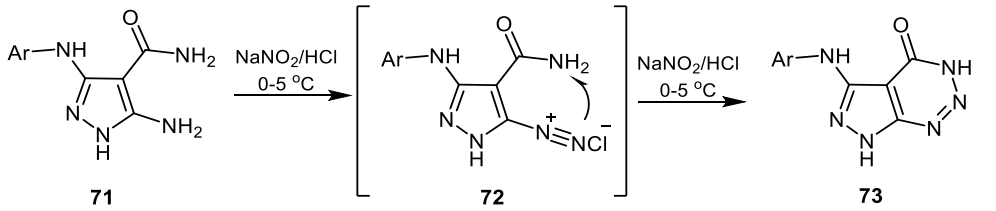
69 70

Scheme 2.17 Synthesis of dihydropyrazolo[5,1-*c*][1,2,4]triazine-3-carboxylate **70**

Scientists used this developed methodology to synthesize a novel series of dihydroazolotriazines by treating polyfluoroalkyl-1,3-dicarbonyl compounds **69** with pyrazolyldiazonium chlorides to afford ethyl-4-hydroxy-7-methyl(phenyl)-4-polyfluoroalkyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine-3-carboxylates **70** (Scheme 2.17).

In order to understand the influence of compounds **70** substituents on AChE, BChE, and CaE inhibition, Shchegol'kov et al.[52] synthesized dialkyl-4-hydroxy-4-polyfluoroalkyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine-3,8-dicarboxylates (Scheme 2.17) and investigated inhibitory activity against AChE, BChE, and CaE of all the synthesized compounds. The authors have noticed that derivatives **70** did not act as AChE and BChE inhibitors; however, they acted as selective CaE inhibitors[52].

Hassan et al.[54] published an investigation of 3*H*-pyrazolo[3,4-*d*][1,2,3]triazin-4(7*H*)-ones **73** anticancer activity *in vitro*. The authors synthesized the novel compounds from diazotized 5-aminopyrazoles **71** (Scheme 2.18)[54].

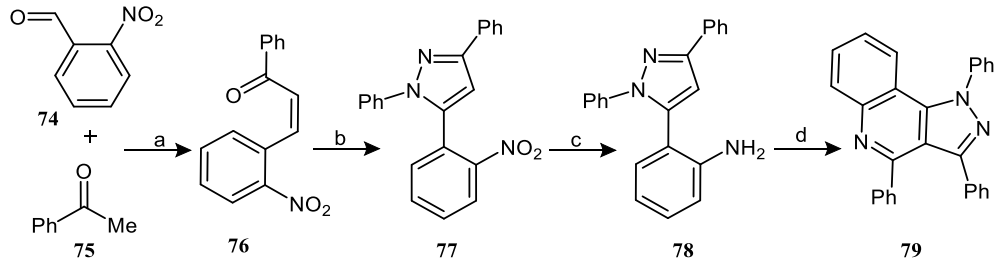


Scheme 2.18 Construction of 3*H*-pyrazolo[3,4-*d*][1,2,3]triazin-4(7*H*)-ones **73**

2.2. Synthesis of tricyclic condensed pyrazole derivatives

2.2.1. Pyrazolo-quinoline derivatives

Kasaboina et al.[55] presented an efficient approach to synthesize pyrazolo-quinoline derivatives and the investigation of the anti-profilerative activity against different cancer lines. The intermediate aniline **78** was obtained in three-step synthesis. First, 2-nitrobenzaldehyde **74** was transformed to acetophenone **75** by using 40% aqueous NaOH solution and ethanol as a solvent to give compound **76** (Scheme 2.19). The latter compound was cyclised with phenyl hydrazine in the presence of iodine in acetic acid to give pyrazole **77**. In the next reaction, nitro group was reducted to amine with iron powder, concentrated HCl performing reaction in a methanol.



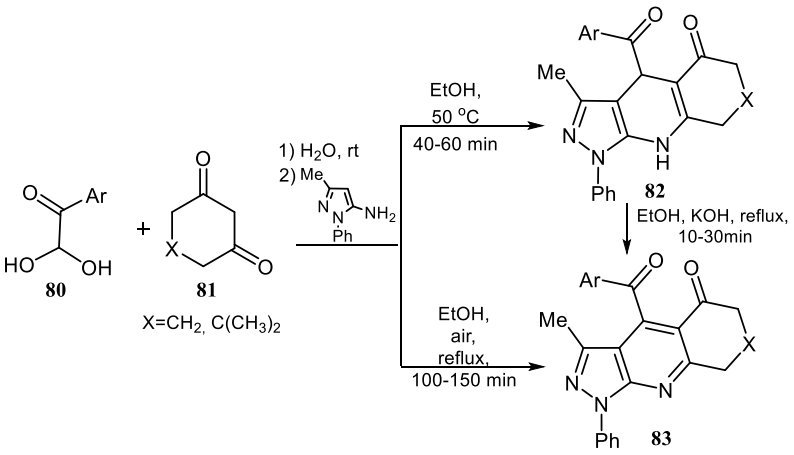
Reagents and conditions: (a) 40% NaOH, EtOH, rt, 30 min; (b) $PhNHNH_2$, I_2, AcOH, reflux, 3 h; (c) Fe powder, HCl_{conc}, MeOH, reflux, 3 h; (d) benzaldehyde, I_2, DMSO, reflux, 3 h.

Scheme 2.19 Construction of 1*H*-pyrazolo[4,3-*c*]quinolones **79**

Finally, the desired products **79** were obtained by treating 2-(1,3-diphenyl-1*H*-pyrazol-5-yl)aniline **78** with different aldehydes in the presence of molecular iodine and DMSO as a solvent (Scheme 2.19)[55].

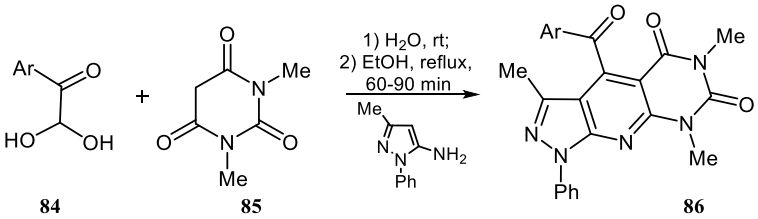
These synthesized novel compounds were tested *in vitro* for anti-proliferative activity against different cancer cell lines such as A-549, HeLa, SKNSH, HepG2, and MCF-7. The authors have noticed that 3-(4-bromophenyl)-4-(2,4-dichlorophenyl)-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinolones **79** exhibited potent activity against MCF-7 compared with standard Daxorubicin. These results may lead to the discovery of new potent antitumor agents[55].

In 2017, Ezzati et al.[56] in Tetrahedron published a synthetic study of new series of pyrazolo[3,4-*b*]quinolin-5-ones **82** and pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidin-5,7-diones **83**. The authors found out that pyrazolo[3,4-*b*]quinolones **82–83** could be obtained in a one-pot three-component reaction, treating arylglyoxals **82** with 1,3-diketones **81** (cyclohexane-1,3-dione or dimedone) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine in H_2O/EtOH (Scheme 2.20).



Scheme 2.20 Construction of pyrazolo[3,4-*b*]quinolin-5-ones **82** and pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidin-5,7-diones **83**

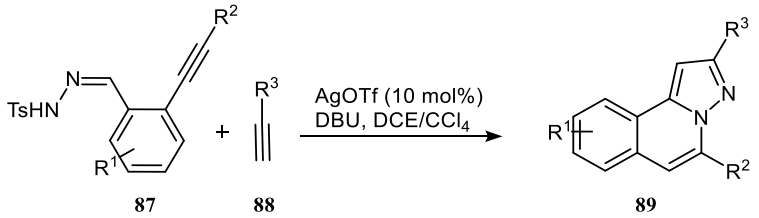
Depending on the reaction temperature, a selective formation of **82** or **83** could be achieved[56] (Scheme 2.20).



Scheme 2.21 Construction of pyrazolopyrido[2,3-*d*]pyridimine-5,7(6*H*,8*H*)-diones **86**

Ezzati and coworkers reported that pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridimine-5,7(6*H*,8*H*)-diones **86** could be obtained by the reaction of arylglyoxals **84** with 1,3-dimethylbarbituric acid **85** and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine in H_2O/EtOH system under reflux in very good yields (73–96%) (Scheme 2.21)[56].

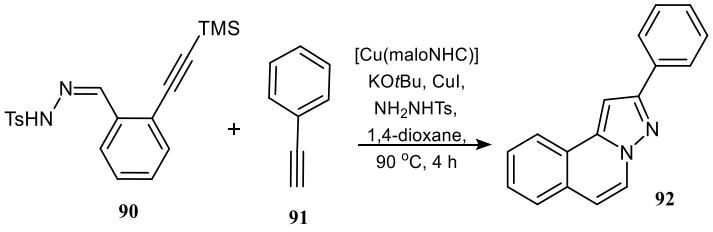
Pyrazolo[5,1-*a*]isoquinolines, which incorporate both isoquinoline and pyrazole scaffolds, represent one of the most attractive structures of the fused *N*-heterocyclic compounds, which may show promising biological activity[57]. In 2009, Chen et al.[57] presented an investigation of AgOTf catalyzed tandem cyclization between *N*'-(2-alkynylbenzylidene)-hydrazides **87** and various alkynes **88** to obtain 1,2-dihydroisoquinolines **89** in very good yields (Scheme 2.22).



87 **88** **89**

Scheme 2.22 Reaction between *N*'-(2-alkynylbenzylidene)-hydrazides **87** and various alkynes **88**

In 2007, Liu et al.[58] reported an efficient synthetic strategy for 2-arylpyrazolo[5,1-*a*]isoquinolines **92** catalyzed by [Cu(maloNHC)] catalyst. In this synthesis approach, *N*'-(2-((trimethylsilyl)ethynyl)-benzylidene)hydrazides **90** were annulated with terminal aromatic alkynes **91** in the presence of [Cu(maloNHC)] catalyst, CuI, KO*t*Bu, and NH_2NHTs in 1,4-dioxane (Scheme 2.23).



90 **91** **92**

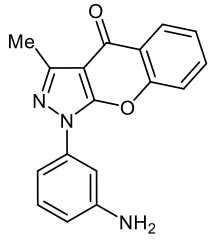
Scheme 2.23 Synthesis of 2-substituted pyrazolo[1,5-*a*]isoquinolines **92**

This study extends the implementation of Cu/NHC as a catalyst in *N*-heterocyclic compounds synthesis, where alkyne is reactant; however, it as well expands the library of 2-substituted pyrazolo[1,5-*a*]isoquinolines[58].

2.2.2. Synthesis of chromenopyrazole compounds

Chromeno derivatives are interesting to scientists due to their wide range of biological activities. For instance, chromeno compounds are used as anticonvulsant, antimicrobial, antiinflammatory, TNF-α inhibition, antimalarial, and anticancer agents[59]. Thus, compounds that are containing chromeno and pyrazole scaffolds are much more attractive because pyrazole nucleus is significantly known due to the diversified applications in different areas. For example, compound **93** is known as A_2-subtype selective adenosine receptor antagonist (Figure 2.4)[60].

It is known that chromenopyrazoles are non-psychoactive CB1R agonists with peripheral antinociceptive properties[61]. For these reasons, the synthesis of novel compounds that are containing both chromeno and pyrazole rings have always been attractive[61].

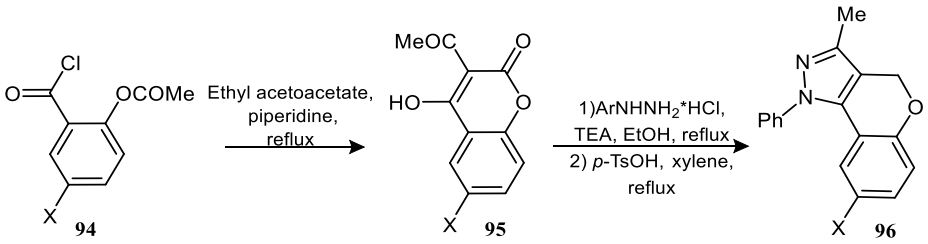


93

Figure 2.4 A_2-subtype selective adenosine receptor antagonist

2.2.2.1. Chromeno[4,3-*c*]pyrazol-4-ones

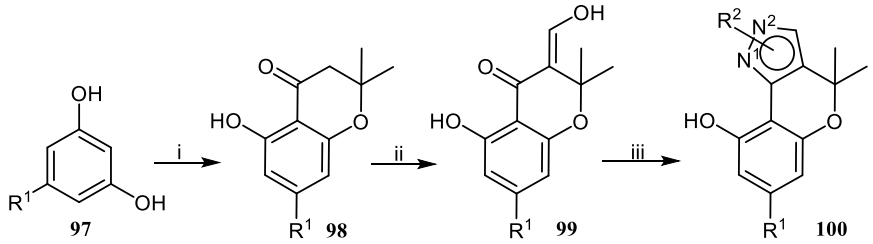
In 2018, Bonardi et al.[62] reported the synthesis of new class inhibitors of tumor-associated carbonic anhydrases hCAs IX and XII: the chromeno[4,3-*c*]pyrazol-4-ones and pyrano[4,3-*c*]pyrazol-4-ones. Chromeno[4,3-*c*]pyrazol-4-ones **96** were synthesised from 5-substituted 2-hydroxybenzaldehydes by Knoevenagel condensation with ethyl acetoacetate in the presence of piperidine under microwave irradation following the reaction with suitable arylhydrazines in boiling ethanol and cyclization in refluxing xylene in the presence of *para*-toluensulfonic acid (Scheme 2.24)[62].



Scheme 2.24 Synthesis of chromeno[4,3-*c*]pyrazol-4-ones **96**

Morales et al.[61] have synthesized various novel chromenopyrazoles **100** (Scheme 2.25) and screened them for biological activities. The desired products **100** were synthesized from the corresponding resorcinols **97** (Scheme 2.25). Firstly, the starting materials **97** were obtained by demethylation of 5-(1',1'-dimethyl-*n*-hepthyl)-1,3-dimethoxybenzene. Later, the corresponding resorcinols **97** were treated with 3,3-dimethylacrylic acid in methansulfonic acid by using phosphorus pentoxide to get 7-alkyl-5-hydroxy-2,2-dimethylchroman-4-ones **98**. This reaction was performed under the microwave irradiation, applying the reaction conditions that were reported by Lim et al[63]. (*Z*)-7-alkyl-5-hydroxy-3-(hydroxymethylen)-2,2-dimethylchroman-4-ones **99** were obtained by applying α-formation synthetic approach proposed by Press et al.[64]. Finally, β-ketoaldehydes of intermediate compounds **99** underwent condensation with appropriate hydrazines to yield 7-alkyl-1(2),4-dihydro-4,4-dimethylchromeno[4,3-

c]pyrazol-9-oles **100** (Scheme 2.25). It has been noticed that *β*-reactions of ketoaldehydes with methyl- and ethylhydrazines yielded the formation of two isomers (N^1- and N^2-substituted pyrazoles); however, the analogous reaction with arylhydrazines resulted in the formation of only one isomer. The scientists explained that for *N*'-arylhydrazines, *N*'-hydrazine was much more nucleophilic than *N*-hydrazine, and for this reason, only one isomer was obtained in the reaction[65].



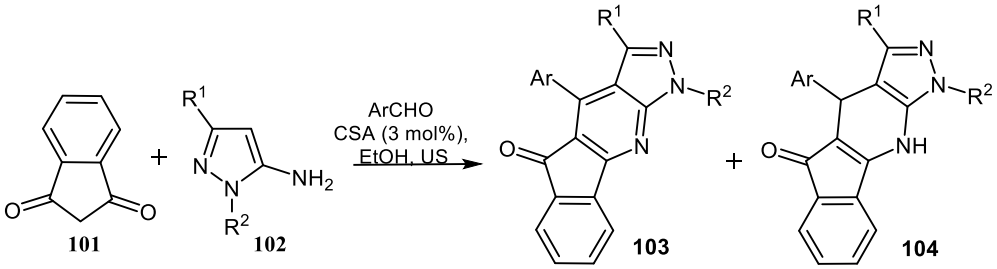
Reaction conditions: (i) 3,3-dimethylacrylic acid, methanesulfonic acid, P_2O_5, 8 h, 70 ºC, 81%, (ii) NaH, THF, MW, 25 min, 45 ºC, (iii) 1) ethyl formate, MW, 25 min, 45 ºC, 76%, 2) corresponding hydrazine, EtOH, 1–4 h, 40 ºC, 36–50%)

Scheme 2.25 Novel chromenopyrazoles **100** synthesized by Morales et al.

2.3. Synthesis of tetracyclic condensed pyrazole derivatives

2.3.1. Construction of fused polycyclic pyrazolo[4,3-*e*]pyridines

In 2017, Pelit et al.[37] published her study of one-pot three-component synthetic approach to provide novel fused polycyclic pyrazolopyridines **103** and **104** with excellent yields. Under this protocol, the reaction between 1,3-dimethyl-1*H*-pyrazol-5-amine or 3-phenyl-1*H*-pyrazol-5-amine **102**, indan-1,3-dione **101,** and various aromatic aldehydes was proceeded in ethanol in the presence of organocatalyst, for instance, camphor-10-sulfonic acid (Scheme 2.26)[37].

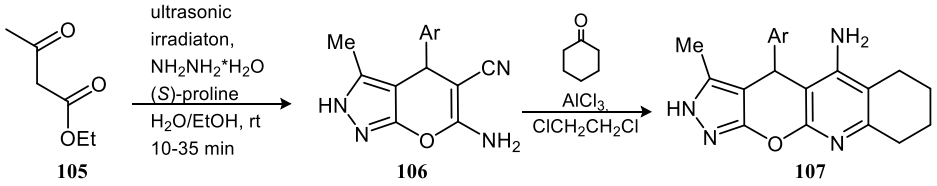


Scheme 2.26 Construction of fused polycyclic pyrazolo[4,3-*e*]pyridines

Pelit et al. as well investigated the antioxidant activity of synthesized novel fused polycyclic pyrazolo[4,3-*e*]pyridines **103**. When product bearing substituent Ar=4-cyanophenyl, it exhibited excellent antioxidant activity better than that of BHT, resorcinol, and ascorbic acid[37].

2.3.2. Tetracyclic tacrine analogs containing pyrano[2,3-*c*]pyrazole

In 2014, Khoobi et al.[66] reported a novel two-step synthetic approach for tacrine-based acetylcholinesterase (AChE) inhibitors, replacing the benzene ring of tacrine with aryl-dihydropyrano[2,3-*c*]pyrazoles. Firstly, the authors investigated one-pot four-component reaction of ethylacetoacetate **105**, hydrazine hydrate, malonitrile, and aromatic aldehydes, varying different catalysts ((*S*)-proline, piperidine, pyridine, NaOH, K_2CO_3) and environmentally benign solvents such as water, EtOH, polyethylene glycol. Khoobi and coworkers found out that the best results were achieved by using (*S*)-proline as a catalyst and water-ethanol medium (1:1) (Scheme 2.27). It was observed that ultrasonic irradiation accelerated the reaction (shortened it to 20 minutes) and improved the yield (the yield increased from 81% to 92%). In the next step – Friedländer reaction – obtained pyrano[2,3-*c*]pyrazoles **106** were treated with cyclohexanone in the presence of $AlCl_3$ to obtain the target compounds **107**. Intermediate and target compounds were isolated as a mixture of enantiomers with no detectable optical activity.



Scheme 2.27 Novel tetracyclic tacrine analogs containing pyrano[2,3-*c*]pyrazole **107**

Novel compounds **107** were tested for anti-AChE activity, and it has been noticed that the majority of them showed potent and selective anti-AChE activity in submicromolar range. In particular, the most potent compound (where Ar = 3,4-dimethoxyphenyl group) was more active than the reference drug tacrine: this derivative could protect neurons against oxidative stress[66].

2.4. Conclusions

The synthesis of fused heterocycles that are containing pyrazole unit have been systematically reviewed and discussed. It could be concluded that the synthesis of annulated pyrazole derivatives is significantly important among the medicinal and materials chemistry scientists, and it is a worthwhile and challenging task from the point of view of organic chemistry.

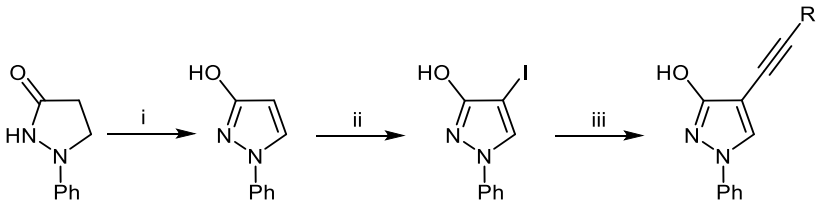
3. RESULTS AND DISCUSSION

3.1. Synthesis of 2*H*-furo[2,3-*c*]pyrazoles

Pyrazole nuclei is widely found in a lot of pharmaceutically active compounds. It is reported that pyrazole compounds possess anticancer, antibacterial analgesic, antiinflammatory, antimicrobial, and antipriliferative activities[67]. Moreover, the compounds containing furan ring are significantly attractive because of their biological and pharmalogical properties, and they are widely found in numerous natural products[5]. For instance, Bandock et al.[67] reported that *Nitrofurantoin* and *Furazolidone* are potent nitrofuran drugs, which possess various antimicrobial properties, including activity against trypanosomes. Nevertheless, the access to 2*H*-furo[2,3-*c*]pyrazoles, where both fused pyrazole and furan moieties are aromatic, is still quite limited, and their chemistry and functional properties remain largely unexplored. Due to the mentioned facts, it has been decided to synthesize a group of various novel 2*H*-furo[2,3-*c*]pyrazoles.

3.1.1. Synthesis of 4-alkynyl-1-phenyl-1*H*-pyrazol-3-ols

As a starting material for the synthesis of 4-alkinyl-3-hydroxy-1-phenyl-1*H*-pyrazole derivatives **4-14**, 1-phenyl-1*H*-pyrazol-3-ol (**1**), which was readily accessible from the oxidation of 1-phenyl-3-pyrazolidinone[68], was used. 1-Phenylpyrazolidin-3-one (**1**) was treated with excess of aqueous acidic $FeCl_3$ solution in refluxing EtOH to give pyrazole **2** in 70% yield. The iodination of compound **2** with iodine in the presence of KOH in DMF afforded 4-iodo-1*H*-pyrazol-3-ol **3** (Scheme 3.1)[69]. It has been shown previously that the Sonogashira-type coupling of the aforementioned iodinated compound with phenylacetylene under the standard reaction conditions ($Pd(PPh_3)_2Cl_2$, CuI, and TEA) gives 4-(phenylethynyl)-substituted pyrazolol **4** (Scheme 3.1)[69].



1 **2** **3** **4-14**

Reagents and conditions: (i) $FeCl_3$, EtOH, 100 °C, 1 h; (ii) I_2, KOH, DMF, rt, 2 h, 80%; (iii) RC≡CH, $PdCl_2(PPh_3)_2$, CuI, TEA, DMF, 60 °C, 1–12 h, 64–85%.

Scheme 3.1 Synthesis of 4-alkynyl-3-hydroxy-1-phenyl-1*H*-pyrazoles **4**–**14**

When various het(aryl)- and alkyl acetylenes were used in the coupling with **3** under the same reaction conditions, the compounds **4–13** were obtained in 64–85% yield (Scheme 3.1, Table 3.1). Compound **14** was detected by LC-MS analysis; however, it was not obtained because of a very low reaction yield (Table 3.1). It was found that the temperature for 'Sonogashira' cross coupling reaction could not be higher than 60 °C.

Table 3.1 Synthesized various 4-alkynyl-3-hydroxy-1-phenyl-1*H*-pyrazoles **4**–**14**

Compound	R	Yield, %	Compound	R	Yield, %
4	Ph	76	**10**	*n*-Bu	85
5	4-MePh	75	**11**	*n*-Pent	78
6	4-EtPh	78	**12**	cyclopropyl	64
7	4-FPh	73	**13**	TMS	50
8	4-EtOPh	79	**14**	C_2H_4OH	traces
9	3-Thienyl	75			

It was noticed that at higher than 60 °C temperature, compound **3** was deiodinated, and cross-coupling reaction did not work, or products were formed in very low yields.

Figure 3.1 shows ^{13}C NMR spectrum of compound **13**. The full and unambiguous assignments of ^{13}C NMR resonances were achieved by using combined applications of standard NMR spectroscopic techniques such as APT, COSY, TOCSY, NOESY, gs-HSQC, and gs-HMBC.The presence of signals of carbons of *C*≡CTMS and C≡*C*TMS at 93.9 and 92.3 ppm proves the formation of the desired product. In the 'aliphatic' part, there is a signal of TMS group carbons at 0.17 ppm. In the 'aromatic' part, there are signals of phenyl ring carbons (119.1 (Ph C-2,6), 129.9 (Ph C-4), 131.7 (Ph C-3,5), and 139.1 (Ph C-1)) and signals of pyrazole ring carbons (98.2 (C-4), 126.8 (C-5), and 163.8 (C-3).

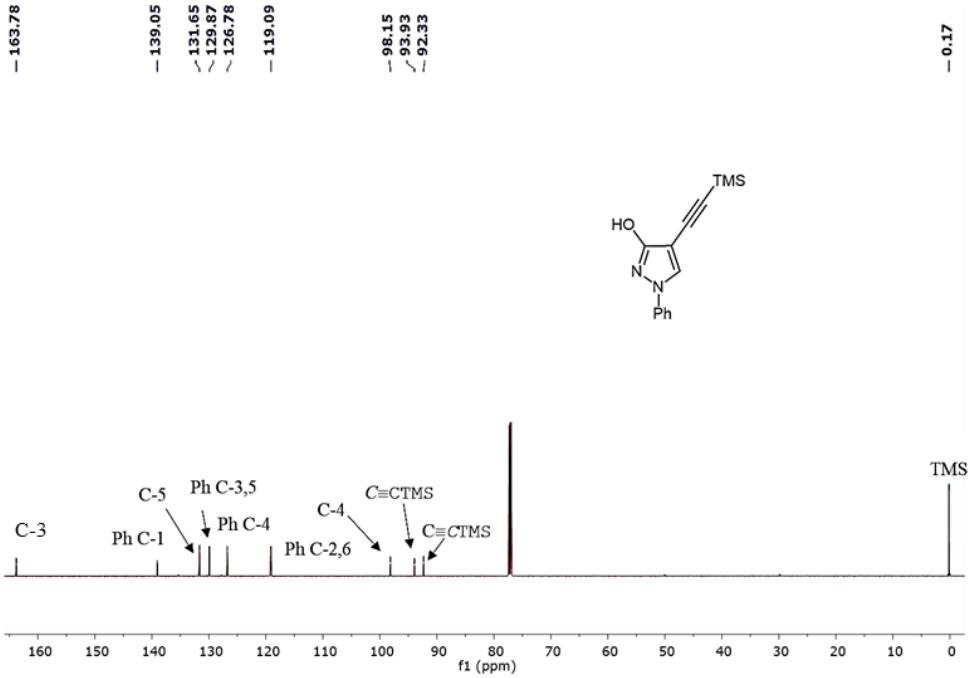


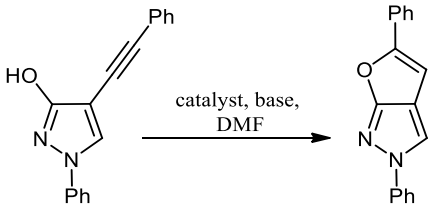
Figure 3.1 ^{13}C NMR spectrum of compound **13**

3.1.2. Cyclisation of the 2*H*-furo[2,3-*c*]pyrazoles from corresponding 4-alkynyl-pyrazol-3-ols

It is known that the compounds bearing alkynyl and hydroxy groups in adjacent positions can undergo cyclisation reaction[70]. The most recent approaches have focused on the synthesis of benzofurans from 2-alkynyl phenols. In most published literature, benzo[*b*]furans were obtained *via* tandem Sonogashira coupling/5-*endo*-dig cyclisation by applying palladium catalyst or copper salts[70c]. Demera et al.[70c] presented a novel base-promoted synthesis of benzo[*b*]furans with good yields; this synthetic approach is palladium/copper free and avoids applying expensive and air sensitive reagents[70c].

Having prepared a series of hydroxy-ethynyl substrates **4**–**13**, the optimal conditions for the subsequent cyclization reaction were investigated by using pyrazole **4** as the model compound (Table 3.2).

Table 3.2 Optimization of reaction conditions for construction of furopyrazole **15**



4 **15**

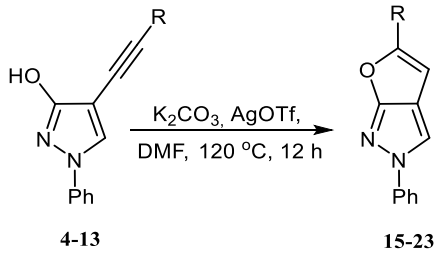
Entry	Base	Catalyst	Temperature, °C	Time, h	Yield, %
1	Cs_2CO_3	-	60	24	no product
2	Cs_2CO_3	-	120	96	traces
3	K_2CO_3	-	120	96	47%
4	K_2CO_3	[(Ph_3P)Au]Cl (10	120	14	69%
5	K_2CO_3	AgOTf (10 mol%)	120	14	92%
6	K_2CO_3	AgOTf (10 mol%)	80	96	15%
7	-	AgOTf (1 eq.)	120	96	traces
8	Cs_2CO_3	AgOTf (10 mol%)	120	96	69%

First, the desired cyclization of pyrazole **4** to 2*H*-furo[2,3-*c*]pyrazole **15** was attempted by using the synthetic protocol, involving Cs_2CO_3 in dry DMF at 60 °C, which was previously successfully used for the preparation of benzo[*b*]furans by the cyclisation of *o*-alkynylphenols[74c]. Unfortunately, no addition of the hydroxy group across the carbon-carbon triple bond was observed even after heating the reaction mixture in the analogues reaction conditions for 24 hours (Table 3.2, Entry 1). The low reactivity of the pyrazole hydroxy functionality in comparison with that of *o*-alkynylphenols may be explained by the structural specificity of pyrazol-3-ols, whereas they could exist in two tautomeric forms, namely the OH-form and the NH-form[71]. The formation *via* the 5-*endo*-*dig* cyclization of some amount of compound **15** was detected by LC/MS measurements only when the reaction mixture contained

Cs_2CO_3 as a base and was heated at 120 °C for 4 days (Table 3.2, Entry 2). Surprisingly, when K_2CO_3 was used instead of Cs_2CO_3, the desired 2-phenyl-2*H*-furo[2,3-*c*]pyrazole was obtained in a significantly higher yield (47%, Table 3.2, Entry 3). Some of the most effective catalysts for the electrophilic activation of alkynes under homogeneous conditions are gold(I) [72] and silver(I) [73] salts or complexes, and a broad range of versatile synthetic methods have been developed for the construction of carbon-heteroatom bonds by using these types of catalysts. For example, the gold (I) catalyst $[(Ph_3PAu)_3O]BF_4$ was applied in the regioselective intramolecular cyclization of alkynols to construct bicyclic ethers[74], while the silver(I) catalyst AgOTf efficiently catalyzed the intramolecular cyclization of phenoxyethynyl diols into 2,3-unsaturated lactones[75]. In this case, adding 10 mol% of chloro(triphenylphosphine)gold(I) improved the yield of product **15** to 69% (Table 3.2, Entry 4). Even better results were obtained when AgOTf was used as a catalyst. In this case, the target product **15** was obtained with an excellent 92% yield (Table 3.2, Entry 5).

It is important to note that the reaction temperature had a significant effect on the yield of the product, and when the temperature was lowered to 80 °C, the yield of the product did not exceed 15% (Table 3.2, Entry 6). The presence of the base plays a crucial role in the cyclization described herein, and the transformation of pyrazole **4** to pyrazole **15** did not occur in the presence of only the catalyst and no base (Table 3.2, Entry 7).

Finally, the reaction optimization experiments showed that the Cs_2CO_3/AgOTf system does not offer any advantages for this cyclization compared to the K_2CO_3/AgOTf system (Table 3.2, Entry 8).



4-13 **15-23**

Scheme 3.2 Cyclization of hydroxy-alkynyl substrates to 2,5-disubstituted 2*H*-furo[2,3-*c*]pyrazoles

With the identified optimized conditions for the 5-*endo-dig* cyclization reaction, the scope of this transformation for the preparation of several 2,5-disubstituted 2*H*-furo[2,3-*c*]pyrazoles was explored (Scheme 3.2). For substrates **4–13**, the reactions were complete after 14 hours at 120 °C, and the products **15–23** were generated in fair to excellent yields (Table 3.3).

Table 3.3 Synthesized various 2-phenyl-2*H*-furo[2,3-*c*]pyrazole derivatives

	15	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
R	Ph	4'-MePh	4'-EtPh	4'-FPh	4'-OEtPh	3-Thienyl	*n*-Bu	*n*-Pent	cyclopropyl
Yield, %	92	87	92	86	81	62	94	82	90

However, the cyclization was not accomplished when pyrazole **13** (R=TMS) was used as a precursor; the decomposition of compound **13** was observed.

The structure assignment of compounds **15–23** was determined by multinuclear NMR and IR spectroscopy and high-resolution mass spectrometry (HRMS) data.

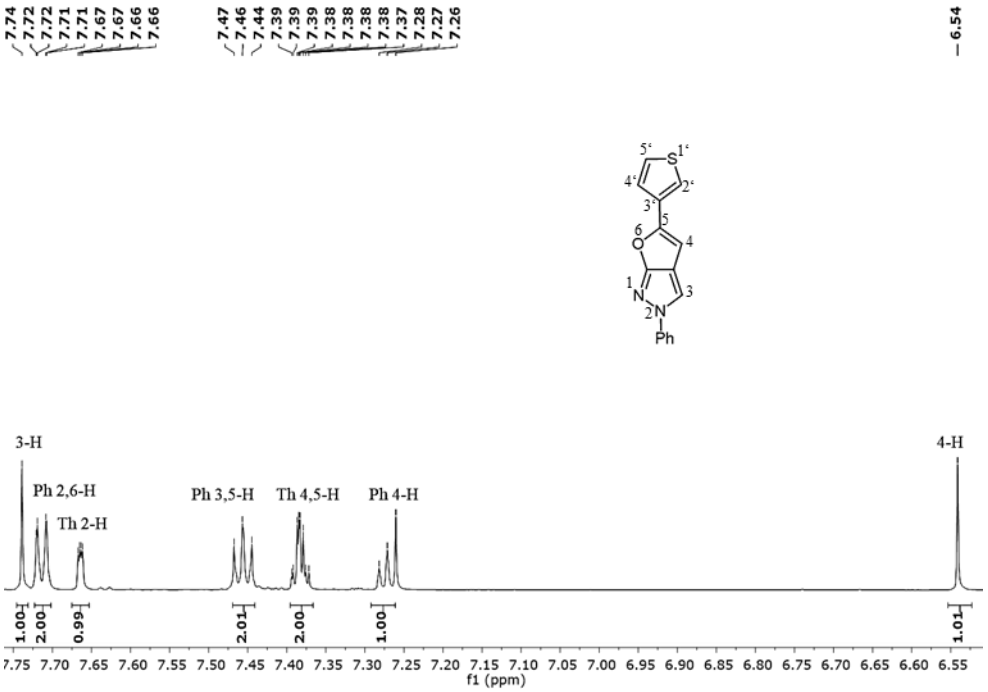


Figure 3.2 ^{1}H NMR spectrum of compound **20**

Figure 3.2 shows ^{1}H NMR spectrum of compound **20**. The presence of a singlet signal of 4-H proton at 6.54 ppm proves the formation of desired furopyrazole product. In the 'aromatic' part, there are signals of phenyl ring protons (multiplets of Ph 4-H, Ph 3,5-H, and Ph 2,6-H at 7.26–7.28, 7.44–7.47, and 7.71–7.72 ppm, respectively), thienyl ring protons (7.37–7.39 (Th 4,5-H) and 7.66–7.67 (Th 2-H) ppm), and a pyrazole ring proton (7.74 (3-H) ppm).

To sum up, it has been demonstrated a new, four-step synthetic route to 2*H*-furo[2,3-*c*]pyrazoles, starting from commercially available 1-phenyl-3-pyrazolidinone. The oxidation of the latter compound with an aqueous acidic $FeCl_3$ solution and iodination of the intermediate compound with iodine in DMF smoothly afforded 1-phenyl-4-iodopyrazol-3-ol, which underwent a Pd-catalyzed coupling with terminal alkynes to give the corresponding 4-alkynyl-3-hydroxy-1-phenyl-1*H*-pyrazoles. The desired 5-*endo-dig* cyclization leading to the formation of the 2*H*-furo[2,3-*c*]pyrazole ring system can be easily achieved by the heating of the aforementioned hydroxy-alkynyl substrates with base in DMF in the presence of a gold(I) or silver(I) catalyst.

3.2. Synthesis of substituted 2*H*-pyrazolo[4,3-*c*]pyridines

Metwally and Deeb[41] have recently reported that pyridine nucleaus containing compounds are significantly attractive to scientists due to their employment in drug discovery. Considering high therapeutic characterization of the pyridine-incorporated drugs, medicinal chemists have a worthwhile task to synthesize novel chemotherapeutic agents. Among numerous biologically active annelated pyrazole derivatives, synthetically demanding 2*H*-pyrazolo[4,3-*c*]pyridines are relatively understudied[6].

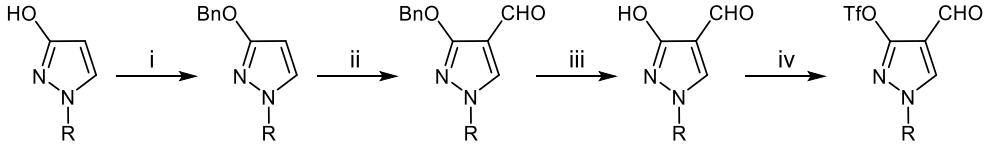
In recent research, it has been demonstrated that 2*H*-pyrazolo[4,3-*c*]pyridines can as well be easily accessed from 3-hydroxy-1-phenyl-1*H*-pyrazole-4-carbaldehyde and the corresponding ethanone *via* intermediate triflates, making use of a Sonogashira cross-coupling and dry ammonia induced cyclization reactions[6,77]. Therefore, in this study, it was further examined the applicability of this synthetic approach and prepared a library of various 2*H*-pyrazolo[4,3-*c*]pyridines, primarily varying by the substituents at the 2-, 4-, and 6-positions in order to assess their biological activity and formulate a possible structure-activity relationships[6].

3.2.1. Synthesis of starting materials

In a series of recent publications, it has been demonstrated that pyrazole-4-carbaldehydes, carrying an alkynyl function adjacent to the formyl moiety, are valuable starting materials for the construction of condensed pyrazole systems such as dipyrazolo[1,5-*a*:4,3-*c*]pyridines[76a], 2*H*- and 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles, 3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*']dipyridines, 13,13a-dihydro-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]pyrimidi-nes[76b], and 2,6-diphenyl-2*H*-pyrazolo[4,3-*c*]pyridines[6,76c,d].

In this study[16], there was further elaborated the synthetic potential of 1-substituted-1*H*-pyrazoles that are carrying an alkynyl function adjacent to the carbonyl moiety. The synthesis of starting triflates **30**, **31**, **36**, and **37** for the Sonogashira cross-coupling reaction is presented in Schemes 3.3 and 3.4. Commercially available, but otherwise undescribed 3-hydroxy-1-methyl-1*H*-pyrazole-4-carbaldehyde **23,** which was obtained by refluxing methylhydrazine with 2,3-dichlorpropionate in EtOH overnight, the precursor for the preparation of the triflate **31**, was synthesized following an analogous approach, which has been previously described for its analog 3-hydroxy-1-phenyl-1*H*-pyrazole-4-carbaldehyde **2**[77] (Scheme 3.3). In short, the Vilsmeier-Haack reaction conditions were applied for the synthesis of 4-benzyloxy-1-methyl-1*H*-pyrazole **25**, which was obtained by benzylation of the readily available starting compound **23**[76c] under the standard conditions with benzyl chloride, similarly to the described procedure[78]. Upon heating compound **25** with DMF/$POCl_3$ at 70 °C for half an hour, the target carbaldehyde **27** was formed in 60% yield (Scheme 3.3). Alternatively, the preparation of carbaldehyde **27** can as well be achieved by the oxidation of (3-(benzyloxy)-1-methyl-1*H*-pyrazol-4-yl)methanol with manganese dioxide[78c]. The debenzylation of compound **27** was accomplished by the treatment with TFA in toluene, conditions that are typically used for the selective deprotection of *o*-benzylsalicylaldehydes[78d], furnishing the target carbaldehyde **29** in 90% yield. Having

precursor **29** in hand, the author of this dissertation further treated it with triflic anhydride in the presence of TEA in DCM[78e] to obtain the corresponding triflate **31** in 85% yield. The same synthetic pathway was applied to obtain 3-triflyloxy-1-phenyl-1*H*-pyrazole-4-carbaldehyde **30** from 3-hydroxy-1-phenyl-1*H*-pyrazole **2**, as it has been described previously[81] (Scheme 3.3)[6].



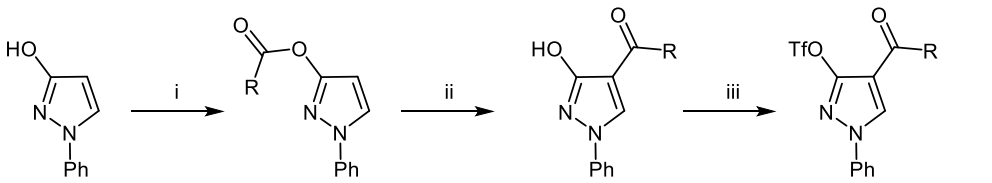
2, R = Ph; **23**, R = Me
24, R = Ph [77]; **25**, R = Me
26, R = Ph [77]; **27**, R = Me
28, R = Ph [77]; **29**, R = Me
30, R = Ph [77]; **31**, R= Me

Reagents and conditions: (i) BnCl, NaH, DMF, argon atmosphere, 0–60 °C, 1 h, 90% (for **3**), 85% (for **4**); (ii) $POCl_3$, DMF, 0–60 °C, 0.5 h, 85% (for **5**), 81% (for **6**); (iii) TFA, toluene, rt, 15 h, 90% (for **7**), 85% (for **8**); (iv) Tf_2O, TEA, DCM, rt, 1 h, 85% (for **9**), 83% (for **10**).

Scheme 3.3 Synthesis of pyrazolecarbaldehydes **30** and **31**

Triflates **36** and **37** were synthesized similarly to the previously described approach[77] (Scheme 3.4). Fries rearrangement conditions ($AlCl_3$, SC_2) were applied to 1-phenyl-1*H*-pyrazol-3-yl acetate **32**[79a] and the corresponding pivalate **33**, which were obtained from the readily available 3-hydroxy-1-phenyl-1*H*-pyrazole **2**[79b] and acetic anhydride or isobutylchloride, respectively. Triflation of 1-phenyl-1*H*-pyrazol-3-ols **34**[71] and **35** afforded 1-phenyl-1*H*-pyrazol-3-yl trifluoromethanesulfonates **36** and **37** in 85% and 96% yield, respectively[6].

Firstly, pyrazole **2** was acylated refluxing in acetic anhydride for half an hour to get compound **32** with 79% yield, whereas to obtain compound **33** with isolated 90% yield, 3-hydroxypyrazole **2** was reacted with isobutylchloride in DCM in the presence of pyridine. The latter compounds were used in Fries rearrangement reactions with $AlCl_3$ in CS_2 to isolate compounds **34** and **35** with 74% and 89% yields, respectively. Last, pyrazoles **34** and **35** participated in the reactions with triflate anhydride to get pseudohalogenides **36** and **37** with isolated yields 85% and 96%, respectively (Scheme 3.4)[6,77].



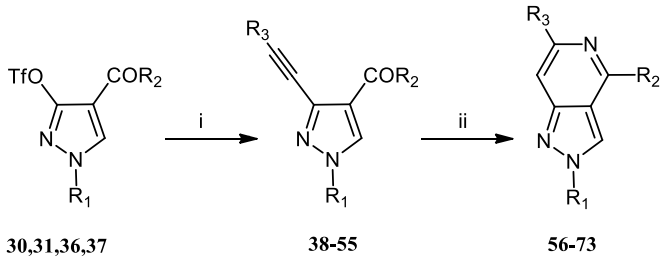
2
32, R = Me, 79% [77]; **33**, R = *i*-Pr, 90%
34, R = Me, 74%[77]; **35**, R = *i*-Pr, 89%
36, R = Me, 85% [77]; **37**, R = *i*-Pr, 96%

Reagents and conditions: (i) Ac_2O, 100 °C, 0.5 h or isobutylchloride, pyridine, DCM, rt, 1 h (ii) $AlCl_3$, CS_2, reflux, 3 h; (iii) Tf_2O, TEA, DCM, rt, 1 h.

Scheme 3.4 Synthesis of ethenone **36** and propanone **37**

3.2.2. Construction of 2*H*-pyrazolo[4,3-*c*]pyridines from corresponding 3-alkynylpyrazoles

The construction of the target pyrazolopyridines from 3-alkynylpyrazole-4-carbaldehydes, ethanones, and propanones is represented in Scheme 3.5. The prepared triflates **30**, **31**, **36,** and **37** were successfully coupled with various alkyl and aryl acetylenes under the standard Sonogashira cross-coupling reaction conditions ($Pd(PPh_3)_2Cl_2$, CuI, TEA, DMF) to give the corresponding 3-alkynyl-1-phenyl-1*H*-pyrazoles **38–55** in good to very good yields, in most cases (Scheme 3.5, Table 3.4). The couplings of 4-acetyl-1-phenyl-1*H*-pyrazol-3-yl trifluoromethanesulfonate (**36**) with phenyl-, 3-thienyl-, and *n*-pentylacetylenes gave the corresponding products in fair yields of less than 70%. Notably, 1-phenyl-3-trifluoromethylsulfoxy-1*H*-pyrazole-4-carbaldehydes resulted in better yields of the Sonogashira cross-coupling reaction in comparison with the corresponding 4-ethanones. Finally, compounds **38–55**, bearing the alkynyl group moiety adjacent to the carbonyl group, were treated with dry ammonia under the elevated temperature and pressure, allowing the direct formation of pyrazolo[4,3-*c*]pyridines **56–73** generally in very good to excellent yields (Scheme 3.5, Table 3.4)[6,77].



Reagents and conditions: (i) R_3-C≡CH, $Pd(PPh_3)_2Cl_2$, TEA, CuI, DMF, 60 °C, 1–38 h; (ii) NH_3, MeOH, 120 °C, 15 h.

Scheme 3.5 Synthesis of pyrazolepyridine systems **56–73**

It is noteworthy that this methodology proved to be applicable to the synthesis of 2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine **63** and its 4-methyl and 4-isopropyl derivatives, **70** and **73**, respectively (Scheme 3.5, Table 3.4)[6].

The synthesis of the aforementioned **63** has been accomplished before employing inconvenient highly toxic and unstable reactants, i.e., by cycloaddition of 3-pyridine, which is accessible by lead tetraacetate oxidation of 1-aminotriazolo[4,5-*c*]pyridine to *N*-phenylsydnone[80]. In contrast, the synthetic approach makes use of the convenient TMS-protected, commercially available, trimethylsilylacetylene, which efficiently undergoes Sonogashira cross-coupling with corresponding triflates **30**, **36**, and **37**, furnishing **42**, **52**, and **55** in 78–87% yield. The latter, due to the convenient lability of the TMS protecting group, upon the treatment with dry ammonia under the elevated temperature and pressure, directly gives rise to the target TMS-deprotected 2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridines **63**, **70**, and **73** in 88–95% yield (Scheme 3.5, Table 3.4)[6].

Table 3.4 Synthesized Sonogashira type precursors **38–55** and pyrazolo[4,3-*c*]pyridines **56–73**

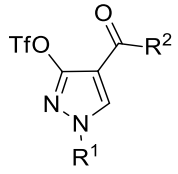
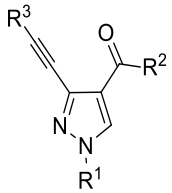
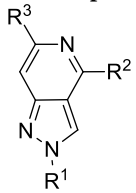
Entry	Substrate 	'Sonogashira' product 	Yield, %	Cyclisation product 	Yield, %
1.	**31**: R^1=Me, R^2=H	**38**: R^1=Me, R^2=H, R^3=Ph	75	**56:** R^1=Me, R^2=H, R^3=Ph	79
2.	**30**: R^1=Ph, R^2=H	**39**: R^1=Ph, R^2=H, R^3=Ph	81	**57**: R^1=Ph, R^2=H, R^3=Ph	89
3.	**30**: R^1=Ph, R^2=H	**40**: R^1=Ph, R^2=H, R^3=3-Thienyl	75	**58**: R^1=Ph, R^2=H, R^3=3-Thienyl	94
7.	**30**: R^1=Ph, R^2=H	**41**: R^1=Ph, R^2=H, R^3=cyclopropyl	86	**59**: R^1=Ph, R^2=H, R^3=cyclopropyl	98
8.	**30**: R^1=Ph, R^2=H	**42**: R^1=Ph, R^2=H, R^3=*n*-Bu	90	**60**: R^1=Ph, R^2=H, R^3=*n*-Bu	84
9.	**30**: R^1=Ph, R^2=H	**43**: R^1=Ph, R^2=H, R^3=*n*-Pent	92	**61**: R^1=Ph, R^2=H, R^3=*n*-Pent	89
10.	**30**: R^1=Ph, R^2=H	**44**: R^1=Ph, R^2=H, R^3=C_2H_4OH	90	**62**: R^1=Ph, R^2=H, R^3= C_2H_4OH	86
11.	**30**: R^1=Ph, R^2=H	**45**: R^1=Ph, R^2=H, R^3=TMS	78	**63**: R^1=Ph, R^2=H, R^3= H	95
12.	**30**: R^1=Ph, R^2=CH_3	**46**: R^1=Ph, R^2= CH_3, R^3=Ph	65	**64**: R^1=Ph, R^2= CH_3, R^3=Ph	91
13.	**30**: R^1=Ph, R^2= CH_3	**47**: R^1=Ph, R^2= CH_3, R^3=3-Thienyl	66	**65**: R^1=Ph, R^2= CH_3, R^3=3-Thienyl	81
15.	**30**: R^1=Ph, R^2= CH_3	**48**: R^1=Ph, R^2= CH_3, R^3=cyclopropyl	80	**66**: R^1=Ph, R^2= CH_3, R^3=cyclopropyl	80
16.	**30**: R^1=Ph, R^2= CH_3	**49**: R^1=Ph, R^2= CH_3, R^3=*n*-Bu	75	**67**: R^1=Ph, R^2=CH_3, R^3=*n*-Bu	88
17.	**30**: R^1=Ph, R^2= CH_3	**50**: R^1=Ph, R^2= CH_3, R^3=*n*-Pent	65	**68**: R^1=Ph, R^2= CH_3, R^3=*n*-Pent	88
18.	**30**: R^1=Ph, R^2= CH_3	**51**: R^1=Ph, R^2= CH_3, R^3=C_2H_4OH	86	**69**: R^1=Ph, R^2= CH_3, R^3= C_2H_4OH	86
19.	**30**: R^1=Ph, R^2= CH_3	**52**: R^1=Ph, R^2= CH_3, R^3=TMS	83	**70**: R^1=Ph, R^2= CH_3, R^3= H	88
20.	**37**: R^1=Ph, R^2=*i*Pr	**53**: R^1=Ph, R^2= *i*Pr, R^3=Ph	90	**71**: R^1=Ph, R^2= *i*Pr $_3$, R^3=Ph	92
21.	**37**: R^1=Ph, R^2=*i*Pr	**54**: R^1=Ph, R^2= *i*Pr, R^3=*n*-Bu	81	**72**: R^1=Ph, R^2= *i*Pr $_3$, R^3= *n*-Bu	84
22.	**37**: R^1=Ph, R^2=*i*Pr	**55**: R^1=Ph, R^2= *i*Pr, R^3=TMS	87	**73**: R^1=Ph, R^2= *i*Pr $_3$, R^3=H	92

Figure 3.3 shows ^{1}H NMR spectra of compounds **52** and **70**. It is important to mention that during the cyclization process, the trimethylsilyl group was eliminated. The presence of 7-H proton (multiplet) and 6-H proton (doublet) signals at 7.46–7.48,

and 8.20 ppm in the spectrum of compound **70** proves the formation of the desired pyrazolopyridine **70**. In the 'aliphatic' part of compound **52** spectrum, there are signals of trimethylsiliyl group protons at 0.30 ppm, which is absence in the spectrum of compound **70** and methyl group protons at 2.66 ppm (in the spectrum of compound **70,** the signal of methyl group protons is observed at 2.85 ppm). In the 'aromathic' part of compound **52** spectrum, there are signals of phenyl ring protons (multiplets of 4-H, 3,5-H, and 2,6-H) at 7.36–7.38, 7.46–7.48, and 7.70–7.71 ppm, respectively; moreover, there is a signal of pyrazole proton at 5-position at 8.40 ppm. Meanwhile, in the 'aromathic' part of compound **70** spectrum, there are signals of phenyl ring protons (multiplets of 4-H, 3,5-H, and 2,6-H at 7.46–7.48, 7.55–7.58, and 7.91–7.93 ppm, respectively), and there is a singlet signal of pyrazole proton at 3-position at 8.58 ppm. The complete and unambiguous assignments of the ^{1}H resonances were achieved by using standard Bruker software in conjunction with standard NMR spectroscopic techniques, such as DEPT, COSY, TOCSY, NOESY, gs-HSQC, and gs-HMBC.

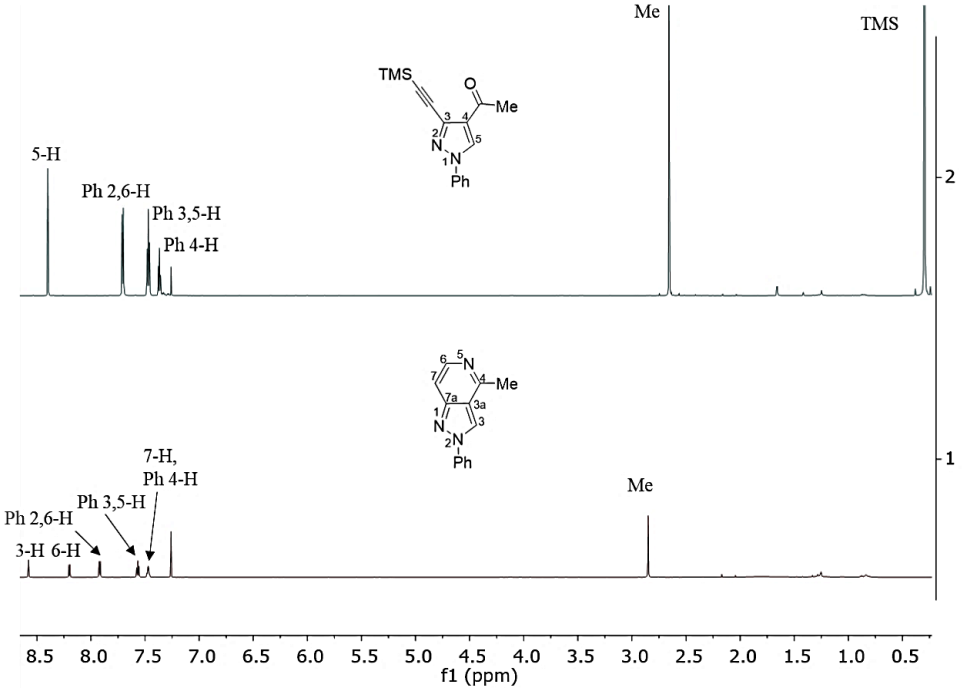


Figure 3.3 ^{1}H NMR spectra of compounds **52** and **70**

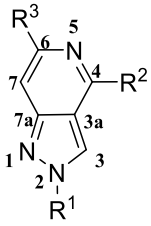
3.2.3. Evaluation of biological activity of synthesized pyrazolo[4,3-*c*]pyridines

All synthesized 2*H*-pyrazolo[4,3-*c*]pyridines were sent to the Palacký University in Olomouc, the Czech Republic, for screening for anticancer activity against two cell lines, i.e., K-562 and MCF-7.

3.2.3.1. Anticancer activity *in vitro*

The above mentioned synthesized pyrazole compounds **56–74** were evaluated for their cytotoxicity against two human cancer cell lines, i.e., K-562 (chronic myeloid leukemia cells) and MCF-7 (breast cancer cells). In most cases, it was noticed that the majority of pyrazolopyridines has exhibited moderate cytotoxicity with GI_{50} values in the micromolar range (Table 3.5). Notably, the most effective compounds contained phenyl group at the 2-position with no substituent at the 4-position and either an aryl or alkyl at the 6-position (compounds **57**, **58**, **60**, **61**). It is noteworthy that the replacing of phenyl substituent at 2-position (compound **57**) with a methyl group resulted in a complete loss of the activity (compound **56**). The increasing of bulkiness of the substituents at the 4-position reduced the cytotoxicity of derivatives, i.e., the introducing of methyl (compounds **64**, **68**) and isopropyl (compound **71**) substituents resulted in a gradual decrease in potency of the compounds compared to the unsubstituted derivatives (compounds **57**, **61**). The replacement of the substituents at the 6-position enabled the fine-tuning of cytotoxicity of the compounds. Surprisingly, lack of the substituent at this position or introduction of a polar ethylhydroxy group resulted in completely inactive derivatives (compounds **62**, **63**, **69**, **70**), while various other substituents were relatively well tolerated. The most effective substituents at 6-position were alkyl chains and aromatic rings. The derivatives, bearing a phenyl ring at the 7-position, exhibited good cytotoxic values with GI_{50} values for compound **57,** reaching 3.4 μM for K-562 and 4.8 μM for MCF-7 cells (Table 3.5).

Table 3.5 Synthesized Sonogashira type precursors **38–55** and pyrazolo[4,3-*c*]pyridines **56–73**

Structure	Compound no	R^1	R^2	R^3	GI_{50} (μM)*	
					K-562	MCF-7
	**56**	Me	H	Ph	>100	>100
	57	Ph	H	Ph	3.4	4.8
	58	Ph	H	3-thienyl	8.3	9.8
	59	Ph	H	cyclopropyl	60.5	69.3
	60	Ph	H	*n*-Bu	6.7	13.3
	61	Ph	H	*n*-Pent	2.1	11.8
	62	Ph	H	ethylhydroxy	>100	>100
	63	Ph	H	H	>100	>100
	64	Ph	CH_3	Ph	6.3	11.0
	65	Ph	CH_3	3-thienyl	10.0	22.2
	66	Ph	CH_3	cyclopropyl	25.9	63.5
	67	Ph	CH_3	*n*-Bu	8.5	11.1
	68	Ph	CH_3	*n*-Pent	6.9	17.0
	69	Ph	CH_3	ethylhydroxy	>100	>100
	70	Ph	CH_3	H	>100	>100
	71	Ph	*i*Pr	Ph	36.8	91.0
	72	Ph	*i*Pr	*n*-Bu	12.9	33.3
	73	Ph	*i*Pr	H	>100	98.8

* Data are means of at least two independent measurements.

Unfortunately, the attempts to replace the phenyl ring with a slightly less aromatic thiophene or aliphatic cyclopropyl rings resulted in less active derivatives; phenyl derivatives **57** and **64** were twofold more potent than analogous thiophen-3-yl derivatives **58** and **65**[6] (Table 3.5).

Interestingly, the replacing of the cyclopropyl ring with linear aliphatic substituents resulted in the increased cytotoxicity of the compounds. Thus, among the prepared derivatives, compound **61**, bearing a pentyl substituent at the 6-position, a phenyl ring at the 2-position, and lacking a substituent at the 4-position, proved to be the most cytotoxic, reaching 2.1 μM GI_{50} value for K-562 cells (Table 3.5)[6].

3.2.3.2. Effect on the cell cycle and apoptosis

All compounds displaying a GI_{50} lower than 80 μM in at least one cell line underwent cell-cycle investigation in K-562 and MCF-7 cell lines to gain preliminary information about their mechanism of action (Table 3.6). The cells were treated with tested compounds for 24 h at 10 μM concentrations. Tubuline-interfering agent nocodazole and cyclin-dependent kinase 4 inhibitor palbociclib were used as positive controls, causing dominant mitotic and G1 arrest, respectively.

Table 3.6 Cell cycle analysis in K-562 and MCF-7 cells treated with active 2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridines at a single dose of 10 μM

Compound	K-562 cell cycle phases (%)				MCF-7 cell cycle phases (%)			
	subG1	G1	S	G2/M	subG1	G1	S	G2/M
Untreated	15.0	34.6	50.3	15.0	7.1	60.7	34.1	5.3
57	43.0	19.8	5.5	74.7	14.3	56.8	26.2	17.0
58	34.2	21.7	37.3	41.1	24.2	39.5	29.1	31.4
59	19.6	32.3	52.2	15.5	7.5	64.7	29.4	5.9
60	37.7	24.8	12.8	62.3	31.1	36.0	30.3	33.7
61	35.4	14.8	3.3	82.0	50.3	18.1	26.3	55.6
63	46.2	13.7	36.1	50.2	11.9	65.5	20.5	14.1
64	45.7	26.2	29.2	44.6	22.7	37.2	31.2	31.6
65	15.3	34.7	45.8	19.6	9.0	63.6	30.2	6.3
66	40.8	28.2	30.5	41.4	19.3	48.5	24.0	27.5
67	28.3	21.8	28.3	49.9	31.1	50.2	18.1	31.7
70	21.3	35.1	46.6	18.3	6.7	62.6	30.6	6.9
71	47.1	26.7	44.2	29.0	7.8	66.1	24.5	9.4
nocodazole (25	49.4	3.6	26.8	69.7	32.1	14.4	49.9	35.7
palbociclib	35.0	54.0	30.1	15.9	7.5	90.0	5.5	4.6

The majority of compounds exhibited a clear effect on the cell cycle in both cell lines; the increased cell populations in G2/M phases and corresponding decreases in G1 and S phase populations were observed (Table 3.6). The highest percentages of a G2/M population were found in cultures treated with compounds **57**, **60**, **61**, **64,** and **68**, all of which displayed the strongest cytotoxicities as well (Table 3.6). In addition, a substantial increase of sub-G1 populations was observed in cultures treated with the most potent compounds **57**, **58**, **60**, **61**, **64**, **65**, **67,** and **72**, indicating ongoing apop-

tosis. Sub-G1 populations have been usually higher in K-562 cells, probably as a consequence of their higher sensitivity to novel compounds, which was observed in the cytotoxicity assays (Table 3.6)[6].

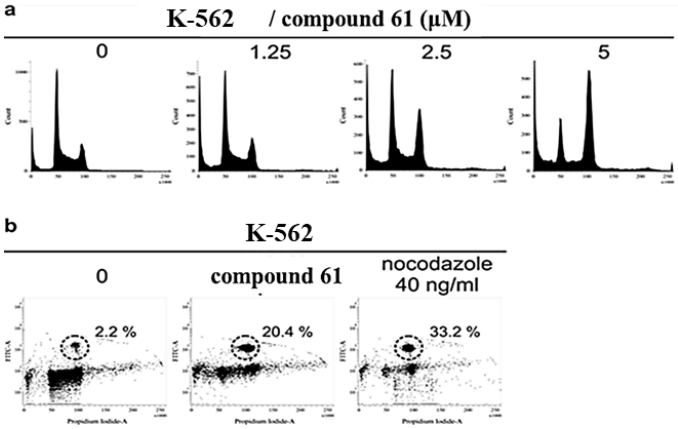


Figure 3.4 Cell cycle arrest in K-562 cells treated with compound **61** for 24 h. (a) DNA histograms of cells treated with different doses of the compound **61**. (b) Phosphorylation of histone H3 at serine-10 in cells treated with 5 μM dose of compound **61**. Nocodazole was used as a positive control.[10] Due to the strong cytotoxicity of **61** in the K-562 cell line, it was sought to identify the type of cell death that occurred.

Compound **61** with the strongest effect on the cell cycle was further assayed at several concentrations (Figure 3.4). DNA histograms revealed a clear dose-dependent arrest in G2/M phases. In order to discriminate between arrest in G2 and M, there was quantified the phosphorylation of histone H3 at serine-10, a common mitotic marker. Flow cytometric analysis revealed a strong accumulation of cells with phosphorylated histone, confirming the arrest in mitosis (Figure 3.4)[6].

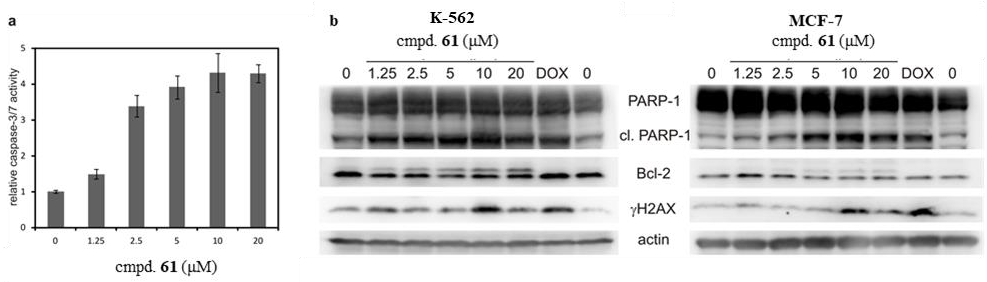


Figure 3.5 Induction of apoptosis in cells treated with different doses of compound **61** for 24 h. (a) Caspase-3/7 activity was measured in lysates prepared from treated K-562 cells by using the fluorogenic substrate Ac-DEVD-AMC and normalized against untreated control cell lysates. (b) Immunoblotting analysis of apoptosis-related proteins in treated K-562 and MCF-7 cells. Doxorubucin (DOX, 1 μM) was used as a control. Actin levels were detected to verify equal loading[6].

The caspase activation in treated cells was measured by an enzymatic assay, using fluorescently labeled peptide substrate Ac-DEVD-AMC of caspases 3/7 (Figure 3.5) that revealed clear dose-dependent responses in the micromolar range. In parallel,

the lysates of treated K-562 and MCF-7 cells were subjected to immunoblotting. The analysis revealed a dose-dependent increase in the 89 kDa fragment of PARP-1, a known caspase substrate (Figure 3.5)[6]. The author as well detected phosphorylation of histone H2AX at Ser-139 (γH2AX), a modification required for DNA fragmentation during apoptosis[81].

There has been observed the appearance of a slowly migrating, phosphorylated form of Bcl-2 connected with the G2/M arrest of the cell cycle and apoptosis. In summary, the analyses confirmed that compound **61** can activate apoptotic machinery in a dose-dependent manner[6].

In order to describe the mechanism of antimitotic action of the prepared compounds, there was explored the CDK1/cyclin B, a well-known mitotic regulator, as a possible target, especially due to the structural similarity to 2,3,4,6-substituted pyrazolo[4,3-*c*]pyridines which have been identified as kinase inhibitors[82]. The synthesized compounds **56–74** were screened for their inhibitory activity against CDK1, but the assay did not reveal any inhibition (data not shown). The further profiling of compound **61** against other mitotic kinases, including DAPK3, CDK1, CHK1, NIM1, AURKA, NDR1, NEK2/4/6, PIM2, PLK2/3, TTK, and WEE1, did not point to any of these kinases as a target of compound **61** (data not shown). This finding was expected, given that these compounds lack an H-bond donor-acceptor motif which is common in most kinase inhibitors, including the previously mentioned pyrazolo[4,3-*c*]pyridines[6,77].

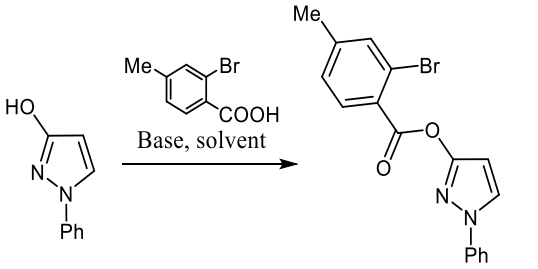
To sum up, there was developed an efficient synthetic approach to obtain variously substituted 2*H*-pyrazolo[4,3-*c*]pyridines, employing Sonogashira cross-coupling and a subsequent substituent-tolerant annulation reaction in the presence of ammonia. Consequently, a group of substituted 2*H*-pyrazolo[4,3-*c*]pyridines was evaluated for the cytotoxicity against K-562 and MCF-7 cancer cell lines; they exhibited anticancer activity *in vitro* through the arresting cell cycle in mitosis and induction of apoptosis; however, the mechanism of cellular action remains unclear.

3.3. Synthesis of substituted benzopyrano[2,3-*c*]pyrazol-4(2*H*)-ones

It is known that benzopyrano and pyrazole compounds have a broad spectrum of biological activities[42-44]. Particularly, the heterocyclic compounds, containing pyrazole and benzofuran nuclei, are significantly attractive to scientists for numerous applications and evaluations of biological activities[59-62]. Due to this reason, it was decided to synthesize a series of novel benzopyrano[2,3-*c*]pyrazol-4(2*H*)-ones and screen their biological activities. 2-hydroxy aromatic ketones are applicable synthons to synthesize oxygen-containing heterocyle systems such as benzofuranone, chromanone, benzoxazole, and dibenzooxazepine; moreover, these heterocycles can be employed as building blocks for drugs such as celiprolol, acebutolol, and propafenone[83]. Holzer et al. reported a simple and straightforward synthesis of fluoro-substituted 3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-4(1*H*)-one from the corresponding 4-aroylpyrazol-5-ols, using NaH/DMF or K_2CO_3/MeCN system[84]. The author of this dissertation has decided to examine this methodology and to synthesize the substituted chromeno[2,3-*c*]pyrazol-4(2*H*)-ones (Scheme 3.6).

First of all, as starting materials were chosen 3-hydroxy-1-phenyl-1*H*-pyrazole **2** and 3-hydroxy-1-methyl-1*H*-pyrazole (**23)**. These synthons were transformed to acylated pyrazoles **75–89** by using aroyl chlorides or aroyl acids. *O*-acylation with aroyl chlorides was performed in the presence of TEA in chloroform at room temperature to obtain the desired products[85]. Meanwhile, the treating of pyrazoles **2** or **23** with aroyl acids was more complicated (Table 3.7). 3-hydroxypyrazole **2** and 2-bromo-4-methylbenzoic acid were chosen as a model system to determine optimal reaction conditions. Firstly, the author tried to perform this acylation under the above mentioned reaction conditions, using TEA as a base and chloroform as a solvent; however, no desired product was detected (Table 3.7, Entry 1)[85]. Later, the esterification was tested in the presence of pyridine: chloroform was used as a solvent; unfortunately, the reaction did not work (Table 3.7, Entry 2)[86]. Phakhodee et al. published an investigation on aryl esterification mediated by the Ph_3P-I_2/Et_3N system; the author decided to examine this methodology, but the desired product was not obtained (Table 3.7, Entry 4)[87].

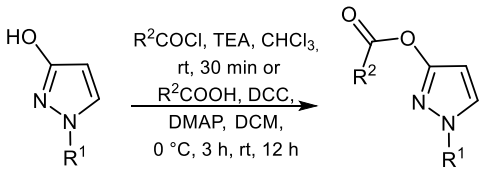
Table 3.7 Study of reaction conditions for *O*-acylation by using aroyl acids



2 **76**, 80%

Entry	Base	Solvent	Additives	Temperature	Yield, %
1	TEA	Chloroform	-	rt	No
2	pyridine	Toluene	-	110 °C	No
3	K_2CO_3[88]	DMF	Cu	rt - > 120 °C	No
4	TEA	DCM	I_2, PPh_3	Rt	No
5	DMAP	DCM	DCC	0 °C - > rt	80

In 2012, Kwon et al. reported a synthetic route, involving DCC coupling in order to transform benzoic acids to esters[89]. This DCC coupling was examined under Kwon proposed reaction condition by treating 3-hydroxypyrazole with 2-bromo-4-methylbenzoic acid. The desired product was obtained with 80% yield (Table 3.7, Entry 5). Under this protocol, firstly, DCC was added to the solution of benzoic acid in DCM, and the mixture was stirred for 1 hour at 0 °C temperature in order to make acid active for the esterifiction. After that, 3-hydroxyprazole and DMAP was added to the reaction mixture, and it was stirred at 0 °C temperature for 2 hours. Later, the stirring was continued for 24 hours at room temperature. Under these conditions, the compounds **76**,**78**, **80**, **81**, **85,** and **87** were obtained with isolated 71–81% yield (Scheme 3.6, Table 3.9).



2, R^1=Ph
23, R^1=Me

75-83, R^1 = Ph, 71-89%
84-89, R^1 = Me, 70-85%

Scheme 3.6 *O*-acylation of pyrazoles **2** and **23** with aroyl acids or chlorides

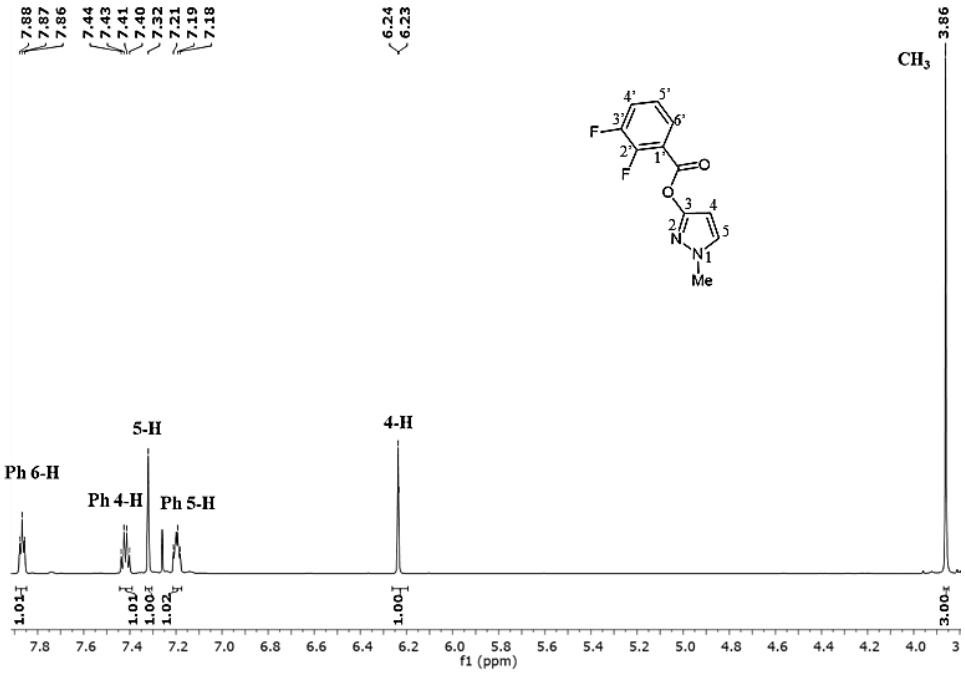
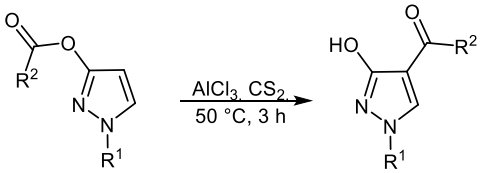


Figure 3.6 ^{1}H NMR spectra of compound **78**

Figure 3.6 shows ^{1}H NMR spectrum of compound **78**. In the 'aliphatic' part, there is a singlet signal of methyl group protons at 3.86 ppm. In the 'aromatic' part, there are signals of phenyl ring protons (multiplets of Ph 4-H, 5-H, and 6-H at 7.40–7.44, 7.18–7.21, and 7.86–7.88 ppm, respectively) and signals of pyrazole ring protons (singlet of 5-H at 7.32 ppm and doublet of 4-H ar 6.23–6.24 ppm).



75-83, R^1 = Ph, 71-89%
84-89, R^1 = Me, 70-85%

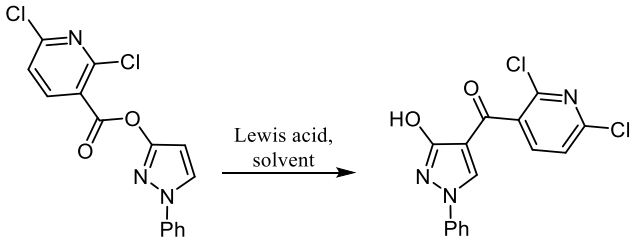
90-95, R^1 = Ph, 75-90%
96-100, R^1 = Me, 69-85%

Scheme 3.7 Fries rearrangement reaction of pyrazoles **75–89**

The next step in this synthetic approach was to prepare suitable compounds for the cyclizations of benzopyrano[2,3-*c*]pyrazol-4(2*H*)-ones (Scheme 3.7). Pyrazole esters were treated with excess of $AlCl_3$ in carbon disulfide at 50 °C temperature for 3–12 hours (Scheme 3.7). Using Fries rearrangement reaction conditions, the compounds **90–100** were synthesized in fair to very good yields (15–84%) (Scheme 3.7, Table 3.9).

It is worth pointing out that 4-aroylpyrazol-3-ols, which contained other hetaroyl substituent than phenyl ring, did not accomplish Fries rearrangement reaction to afford the desired products, and the decomposition of 4-aroylpyrazol-3-ols to 3-hydroxypyrazole was observed (Table 3.8, Entry 1). Nevertheless, it was decided to test other reaction conditions in order to get the desired compounds and avoid decomposition. 4-aroylpyrazol-3-ol **81** was chosen as a model compound for this investigation (Table 3.8, Entry 2–5).

Table 3.8 Study of reaction conditions for Fries rearrangement by using 4-hetaroylpyrazol-3-ol



81 **81'**

Entry	Base	Solvent	Temperature	Yield, %
1	$AlCl_3$	CS_2	50 °C	Decomposition
2	BF_3*Et_2O	-	130 °C	Decomposition
3	BF_3*Et_2O	Toluene	130 °C	Decomposition
4	Zn powder	DMF	120 °C	Decomposition
5	TfOH	ACN	rt	Decomposition

In 2000, Jessica et al. published a one-step synthesis of monomethyl- and monoethyl- derivatives of acetylhydroquinones from boron trifluoride ethyl or methyl etherate complexes and hydroquinone diesters[90]. However, upon treatment with BF_3 etherate, the expected 4-aroylpyrazol-3-ol was not isolated; the starting material decomposed to 3-hydroxypyrazole (Table 3.8, Entry 2). BF_3 etherate suitability to obtain the desired compound was as well tested by using solvent free conditions (Table 3.8, Entry 3). In 2004, Paul and Gupta reported that zinc powder by using DMF as a solvent significantly catalyzed the selective Fries rearrangement of acetylated phenols under the microwave/conventional heating, and the selective migration of the acyl group was observed with good yields (64–80%) (Table 3.8)[91]. These proposed reaction conditions were tested (Table 3.8, Entry 4); unfortunately, the starting compound **81** decomposed to 3-hydroxypyrazole. Further, the synthetic route published by Murashige et al. was tried, but the desired product was not detected: the starting material **81** decomposed to 3-hydroxypyrazole **1** (Table 3.8, Entry 5)[92].

Fries rearrangement was not accomplished with compounds **81–83** and **89**. It has been noticed that during Fries rearrangement, the phenyl group at 1-position of the pyrazole ring influenced better results.

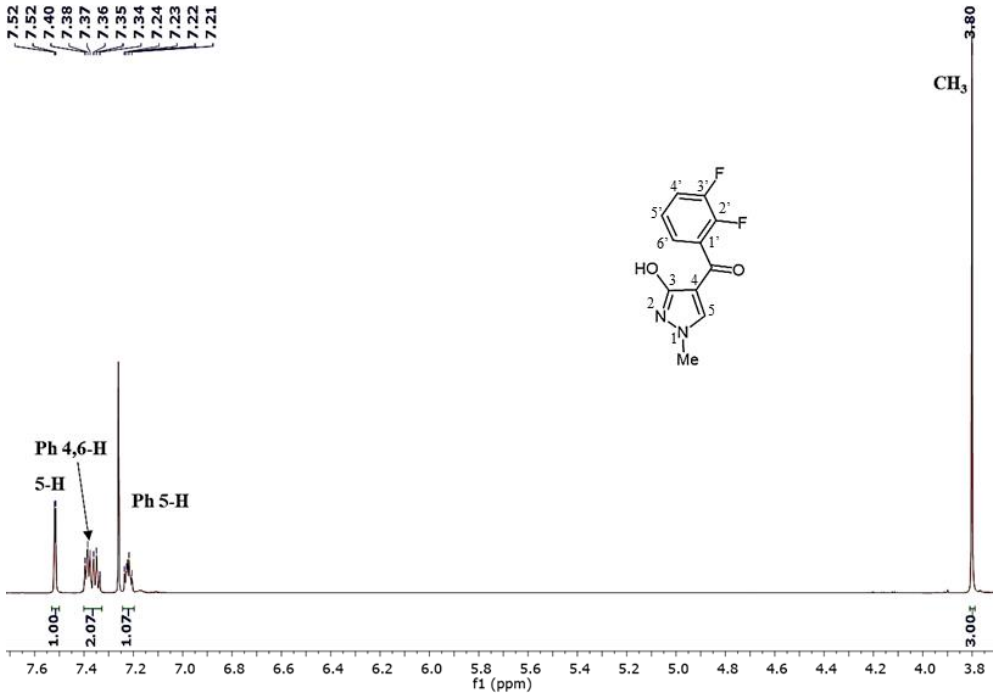
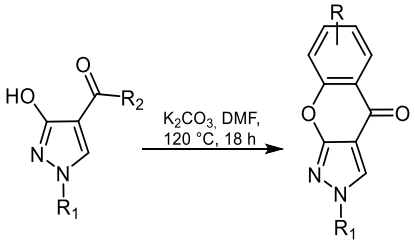


Figure 3.7 ^{1}H NMR spectra of compound **99**

Figure 3.7 shows ^{1}H NMR spectrum of compound **99**. The absence of pyrazole 4-H proton signal at 6.23–6.24 ppm, which was in the above showed Figure 3.6 of compound **87**, proves the ester transformation to 4-aroylpyrazol-3-ol **99**. In the 'aliphatic' part, there is the same signal of methyl group protons at 3.80 ppm. In the 'aromatic' part, there are signals of phenyl ring protons (multiplets of 5-H and 4,6-H at 7.34–7.40 ppm and 7.21–7.24 ppm, respectively) and a signal of pyrazole ring proton, doublet of 5-H, at 7.52 ppm.



90-95, R_1 = Ph, 75-90%
96-100, R_1 = Me, 69-85%

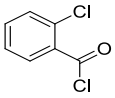
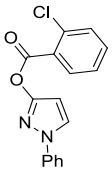
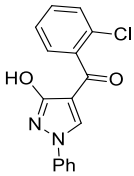
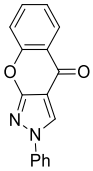
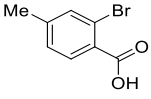
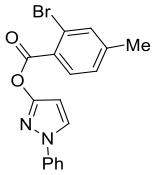
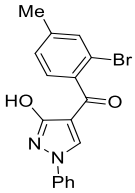
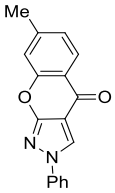
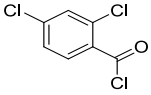
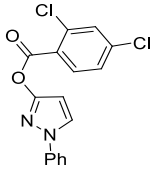
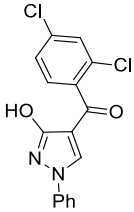
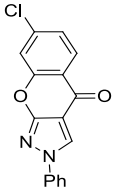
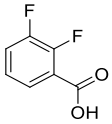
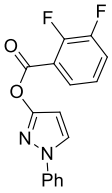
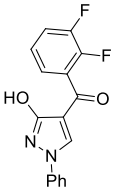
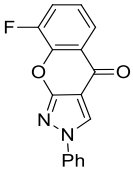
101-105, R_1 = Ph, 75-91%
106-110, R_1 = Me, 71-90%

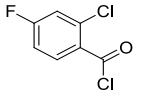
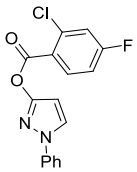
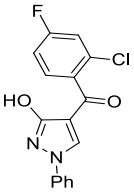
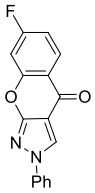
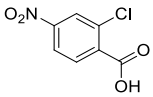
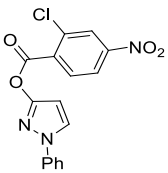
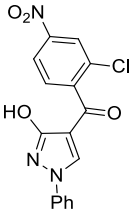
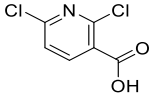
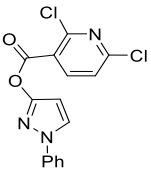
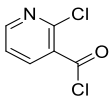
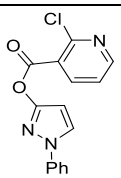
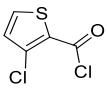
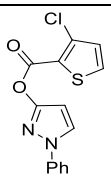
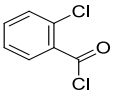
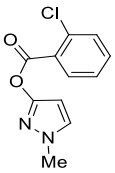
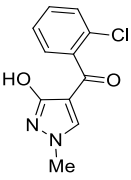
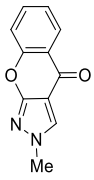
Scheme 3.8 Construction of benzopyrano[2,3-*c*]pyrazol-4(2*H*)-ones **101**–**110**

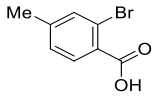
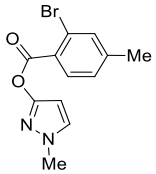
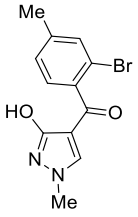
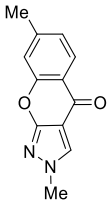
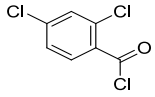
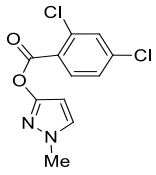
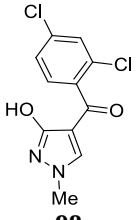
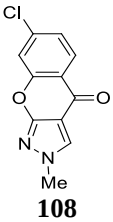
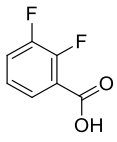
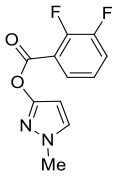
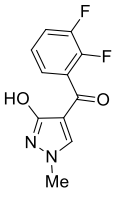
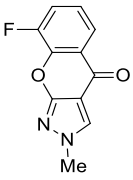
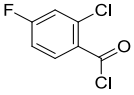
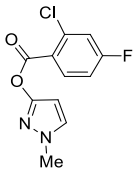
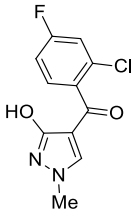
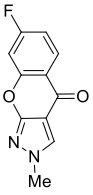
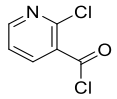
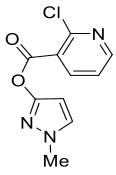
Having successfully prepared 4-aroylpyrazol-3-ols **90-100**, their ability to participate in cyclization reaction to form benzopyrano[2,3-*c*]pyrazol-4(2*H*)-ones was

examined (Scheme 3.8)[84]. This was briefly demonstrated by treating compounds **90–100**, bearing keto- and a hydroxy group at adjacent positions with K_2CO_3, where DMF was used as a solvent, for 18 hours at 120 °C temperature (Scheme 3.8)[84b]. In order to increase the yield of this reaction, NaH was employed as a base instead of K_2CO_3, and DMF changed to ACN; however[84b], the desired result was not achieved: the product **101** was isolated with 35% yield. The direct formation of benzopyrano[2,3-*c*]pyrazol-4(2*H*)-ones **101–110** was observed in very good yields (71–91%, Scheme 3.8, Table 3.9).

Table 3.9 Structures and isolated yields of benzopyrano[2,3-*c*]pyrazol-4(2*H*)-ones and their precursors

Entry	RCOCl/ RCOOH	Acylation product	Yield, %	Product after Fries rearrangement reaction	Yield, %	Cyclisation product	Yield, %
1		 **75**	86	 **90**	81	 **101**	90
2		 **76**	82	 **91**	75	 **102**	75
3		 **77**	81	 **92**	77	 **103**	91
4		 **78**	88	 **93**	84	 **104**	88

Entry	RCOCl/ RCOOH	Acylation product	Yield, %	Product after Fries rearrangement reaction	Yield, %	Cyclisation product	Yield, %
5		 **79**	80	 **94**	83	 **105**	89
6		 **80**	84	 **95**	80	decomposition	-
7		 **81**	71	decomposition		-	
8		 **82**	82	decomposition			
9		 **83**	89	decomposition			
10		 **84**	85	 **96**	25	 **106**	80

Entry	RCOCl/ RCOOH	Acylation product	Yield, %	Product after Fries rearrangement reaction	Yield, %	Cyclisation product	Yield, %
11		 **85**	83	 **97**	69	 **107**	93
12		 **86**	80	 **98**	80	 **108**	90
13		 **87**	85	 **99**	65	 **109**	76
14		 **88**	85	 **100**	74	 **110**	71
15		 **89**	80	decomposition		-	

Presumably, due to the nitro group at 4-position in the benzoic acid, the cyclisation was not accomplished with compound **95** (Table 3.9).

Figure 3.8 shows $^{1}H,^{15}N$ HMBC spectra of compound **110**. There are two signals of N-1 and N-2 at -109.9 and -185.0 ppm, respectively. $^{1}H,^{15}N$ HMBC spectra shows correlation between CH_3 protons and N-2 nitrogen atom and correlation between 3-H

proton and N-2 nitrogen atom. Moreover, in this spectra, there is a correlation between CH_3 protons and N-1 nitrogen atom.

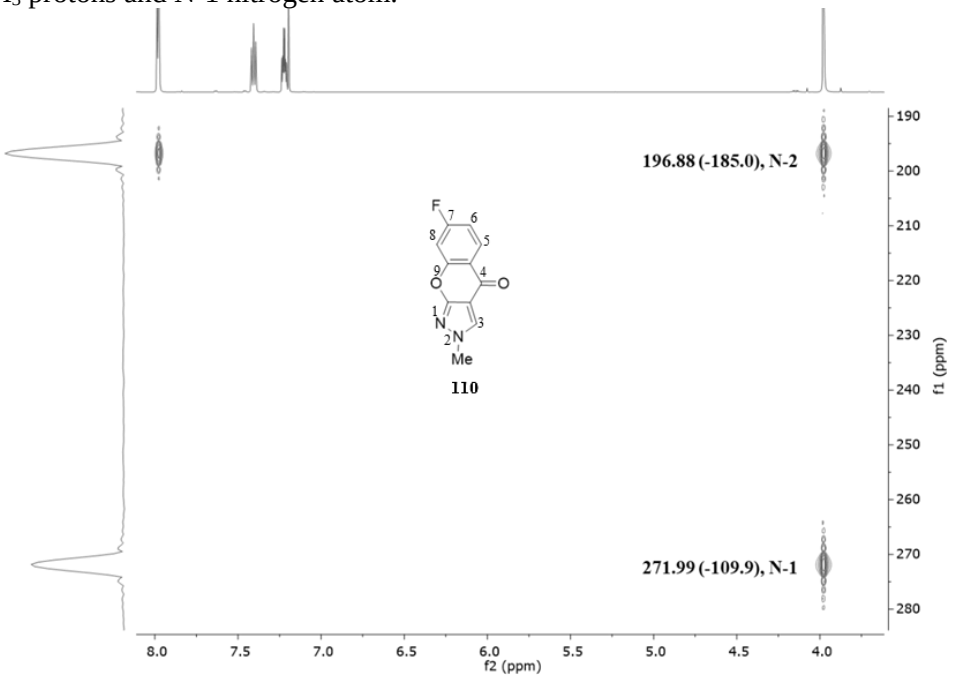


Figure 3.8 ^{15}N, ^{1}H HMBC spectra of compound **110**

To sum up, as a result of this research, there was demonstrated a new three-step synthetic approach to chromeno[2,3-*c*]pyrazol-4(2*H*)-ones, starting from commercially available 1-phenylpyrazolidin-3-one. The desired cyclization product can be easily achieved by the heating of corresponding hydroxy-aroyl substrates with base in DMF.

3.4. Synthesis of pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles and related new ring systems by tandem cyclisation of *vic*-alkynylpyrazole-4-carbaldehydes with (het)aryl-1,2-diamines

Benzimidazole derivatives are associated with various types of pharmacokinetic and pharmacodynamic properties. For instance, the most prominent benzimidazole compound in nature is *N*-riosyldimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12[93]. Ramesh Babu et al. reported that numerous pyrido[1,2-*a*]benzimidazoles have interesting biological properties like antiimflammatory, analgesic, antimicrobial, antiviral, and antineoplastic activities. Moreover, some of these compounds as well possess the fluorescent properties and were found to be useful in synthetic fibres[94]. It is known that compounds that are bearing ethynyl- and aldehyde groups in adjacent positions are important starting materials to synthesize the condensed heterocyclic compounds[95]. In addition, *o*-phenylendiamines are significant reagents to get fused *N*-heterocyclic building blocks, which are ubiquitous in

natural products and play a significant role in the pharmaceutical and agrochemical industries[76b].

In the continuation of this program, which is devoted to exploiting the synthetic potential of these building blocks, the author presents a simple method for the synthesis of 2*H*- and 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole, 3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*']dipyridines, and 13,13a-dihydro-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]perimi-dine derivatives. These compounds represent previously unknown tetracyclic and pentacyclic *N*-containing heterocyclic systems[76b].

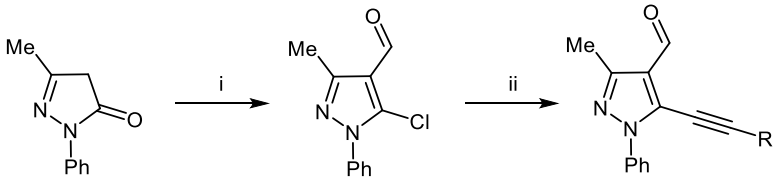
3.4.1. Construction of the 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles

The synthesis strategy for the construction of the 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole ring system was based on the tandem cyclisation of *vic*-alkynylpyrazole-4-carbaldehydes with benzene-1,2-diamines, as outlined in Scheme 1. Recently, either the addition of 2-arylbenzimidazoles to alkynyl bromides followed by Pd-catalyzed intramolecular C-H vinylation or Rh-catalyzed intramolecular oxidative cross-coupling of 1-styrylbenzimidazoles has been employed for the construction of the benzimidazo[2,1-*a*]isoquinoline ring system, which is the benzo analogue of the aforementioned ring system[96]. However, since the commonly used method for obtaining benzimidazo[2,1-*a*]isoquinoline derivatives consists of reacting 2-alkynylbenzaldehydes with 1,2-phenylenediamines under different reaction conditions, several variants such as microwave-accelerated tandem processes, silver(I) catalyzed tandem reactions in water, and iodocyclisations have been applied[76b].

The synthesis strategy for the construction of the 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole ring system was based on the tandem cyclisation of *vic*-alkynylpyrazole-4-carbaldehydes with benzene-1,2-diamines.

3.4.1.1. The synthesis of the starting 5-alkynylpyrazole-4-carbaldehydes

The synthesis of the starting 5-alkynylpyrazole-4-carbaldehydes **113–114** was accomplished *via* Sonogashira coupling of the corresponding 5-chloropyrazole-4-carbaldehyde **112** and phenylacetylene or 1-hexine (Scheme 3.9). The intermediate compound 5-chloropyrazole-4-carbaldehyde **112** was obtained from pyrazole **111** by Vilsmeier–Haack reaction by using DMF and $POCl_3$ (Scheme 3.9)[76d].



111 **112** **113, R=Ph, 64%** **114, R=*n*Bu, 56%**

Reagents and conditions: (i) $POCl_3$, DMF, -10 – 65 °C, 1 h; (ii) R-C≡CH, $Pd(PPh_3)_2Cl_2$, TEA, CuI, DMF, 75 °C, 1–12 h;

Scheme 3.9 Synthesis of starting materials **113** and **114**

The figure 3.9 shows ^{13}C NMR spectrum of compound **114** (R=*n*Bu). The presence of signals of *C*≡C*n*Bu and C≡*Cn*Bu carbons at 70.4 and 97.2 ppm, respectively, proves the formation of the desired product. In the 'aliphatic' part, there are signals of *n*Bu group carbons at 13.7, 19.3, 22.2, 30.4 ppm, respectively. In the 'aromatic' part, there are signals of phenyl ring carbons (119.9 (Ph C-2,6), 128.3 (Ph C-4), 129.8 (Ph C-3,5), and 138.9 (Ph C-1)) and signals of pyrazole ring carbons (125.7 (C-4), 128.3 (C-5), 139.3 (C-3)) and 184.8 (C=O).

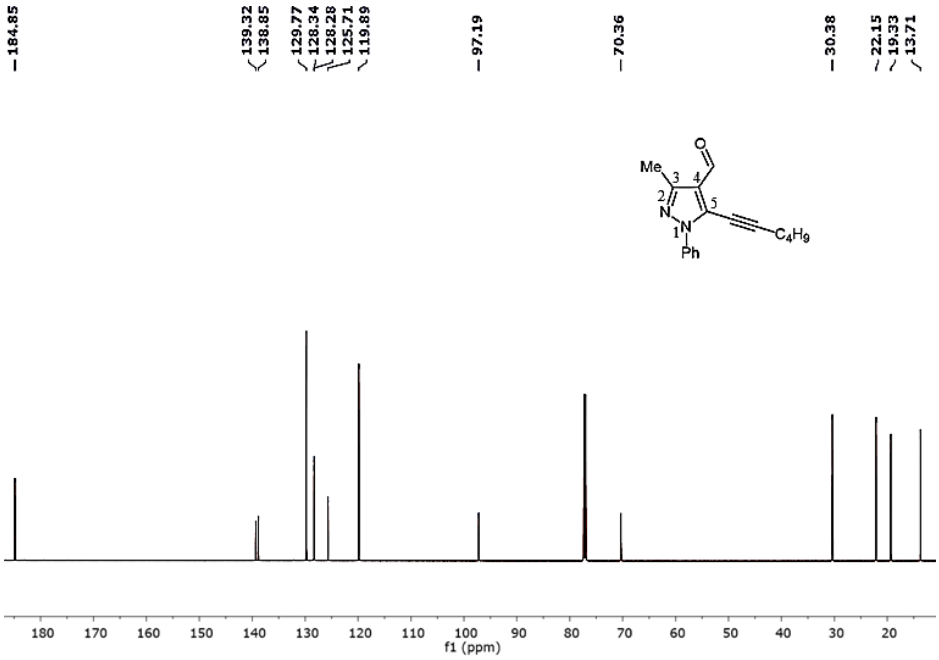
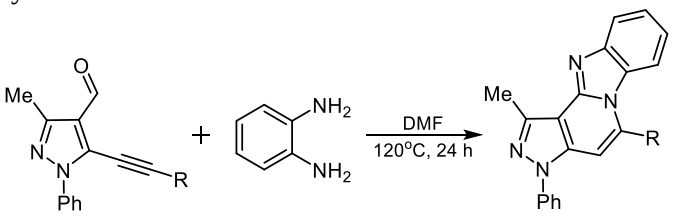


Figure 3.9 ^{13}C NMR spectra of compound **114**

3.4.1.2. Tandem cyclisations of the 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles from the corresponding 5-alkynylpyrazole-4-carbaldehydes

The synthesis strategy for the construction of the 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole ring system was started from the investigation of optimal conditions for the cyclisation, where starting material **113** was chosen as a model compound. In order to find the optimal conditions for the tandem cyclisation, the starting material **113** was first reacted with benzene-1,2-diamine in DMSO under metal-free conditions or in the presence of a CuI catalyst with either conventional heating or microwave irradiation (Table 3.9, Entry 1,2)[97]. However, in all cases, the reaction gave a complex mixture of products, containing only the traces of desired cyclisation product **115**. In contrast, the changing of reaction solvent to DMF dramatically enhanced the yield of compound **115** to 90% without any need for the CuI catalyst (Table 3.9, Entry 3, Scheme 3.10). The reaction of **114** with benzene-1,2-diamine under analogous conditions afforded the compound **116** in 79% yield (Scheme 3.10). DMSO may have been an inadequate solvent under the applied reaction conditions due to its

oxidizing properties[98a], whereas one of the starting materials, namely, benzene-1,2-diamine, is very sensitive to the oxidation[103b,76b].



113, R=Ph,
114, R=*n*-Bu

115, R=Ph, 90%
116, R=*n*-Bu, 79%

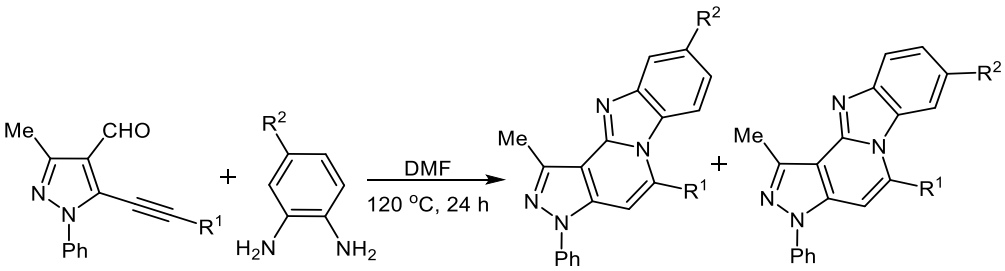
Scheme 3.10 Construction of pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles **115–116**

Table 3.9 Optimization of tandem cyclisation conditions

Entry	Solvent	Additives	Temperature	Yield, %
1	DMSO	-	120 °C*	Traces
2	DMSO	CuI	120 °C*	Traces
3	DMF	-	120 °C	90%

*The reaction was employed by microwave irradiation

With the optimal conditions at hand, the scope of the reaction was assessed by reacting pyrazole-4-carbaldehydes **113–114** with 4-methyl-, 4-chloro-, and 4-nitro-benzene-1,2-diamines (Scheme 3.11). In principle, the use of 'asymmetric' benzene-1,2-diamines can lead to the regioisomeric reaction products (**117a-f** and **118a-f**, respectively, Scheme 3.11). The results obtained with precursor **113** demonstrated that the use of benzene-1,2-diamines with either electron-donating or electron-withdrawing groups in most cases gave good to acceptable yields of the target tetracycles **117a-c**, whereas the isomeric compounds **118a–c** were not isolated by using this method (Scheme 3.11).



113, R=Ph
114, R=*n*-Bu

117 a-f

118a-f

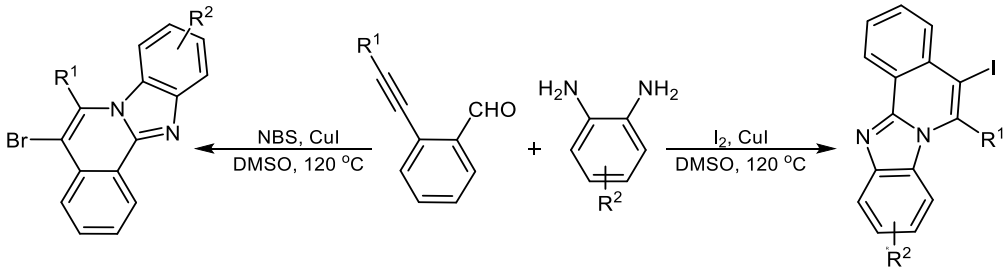
R^1 / R^2	Me	Cl	NO_2
Ph	**117a**, 75%	**117b**, 77%	**117c**, 48%
n-Bu	**117d**:**118d**, 1:0,55, 70%	**117e**, 60%	**118f**, 65%

Scheme 3.11 Construction of pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole derivatives **117–118**

However, the reaction of compound **114** with 4-methylbenzene-1,2-diamine provided regioisomers **117d** and **118d** (ratio 1:0.55) as an inseparable mixture of 70% of total yield (Scheme 3.11)[76b]. Surprisingly, in the case of the reaction of 4-chlorobenzene-1,2-diamine with pyrazole **114**, the corresponding 9-chloro derivative **117e** was obtained only in 60% yield, whereas the employment of 4-nitrobenzene-1,2-diamine gave the 8-nitro derivative **118f** as the sole isolated product in 65% yield. Only trace amounts of the other regioisomers (**118e** and **117f**, respectively) could be detected in the reaction mixture (Scheme 3.11)[76b].

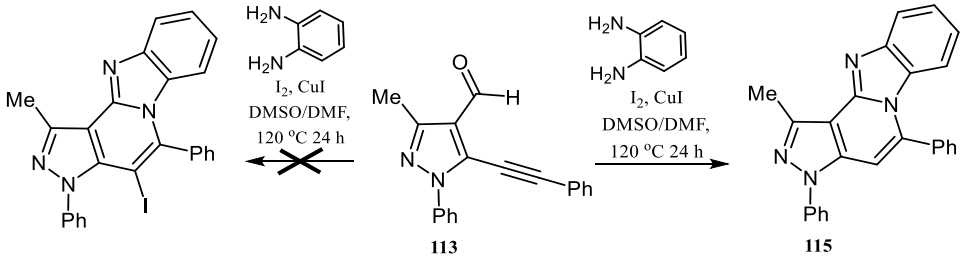
3.4.1.3. Iodocyclisation of the 5-alkynylpyrazole-4-carbaldehyde

The study of Ouyang et al. presented that the cyclisation and halogenation could be achieved by one-pot reaction using *o*-phenylendiamines and benzenaldehydes, bearing alkinyl group in the 2[nd] position (Scheme 3.12)[95a].



Scheme 3.12. Iodocyclisation of the 5-alkynylpyrazole-4-carbaldehyde **113** in one pot reaction

The authors claimed that the iodocyclisation technology is an efficient method to perform copper-promoted electrophilic tandem cyclisation to form fused benzimidazoles with the halo group which are important substrates for drug discovery (Scheme 3.12).



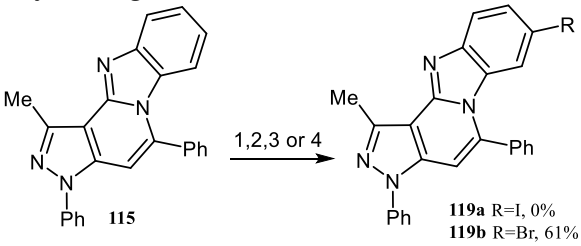
Scheme 3.13 Study of compound **113** iodocyclisation

The synthetic route, proposed by Ouyang et al., was performed with precursor **113** (Scheme 3.13) in DMF in the presence of copper iodide and iodine; however, the desired product was not obtained. Later, it was decided to change the solvent from DMF to DMSO, but the reaction did not work. In order to develop iodocyclisation with starting material **113**, the amount of copper iodide was increased from 5mol% to 20mol%; unfortunately, the desired halogenated product was not achieved (Scheme 3.13).

3.4.2. Functionalization of 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles

The author as well explored the further functionalization of tetracycle **115** (Table 3.10). In the research of Ouyang et al., they demonstrated the functionalization of cyclized benzimidazole[94a] by transforming it to halogenated product, which could be suitable for Pd cross-coupling reactions (Table 3.10).

Table 3.10 Study of halogenation reaction conditions



Entry	Solvent	Additives	Time, h	Temperature,	Yield, %	Product
1	DMF	I_2, CuI,	48	120		
2	DMF	I_2, KOH	24	rt	0	**119a**
3	DMF	NIS	48	rt		
4	DMF	NBS	48	rt	66	**119b**

It was decided to examine this protocol to the benzimidazole systems. Firstly, precursor **115** was examined in iodination reaction by varying different reagents and temperatures; unfortunately, no successful result was achieved (Table 3.10, Entry 1–3). Later, the treatment of pyrazole **115** with NBS in DMF at room temperature gave the bromo derivative **119b** (Table 3.10, Entry 4)[76b].

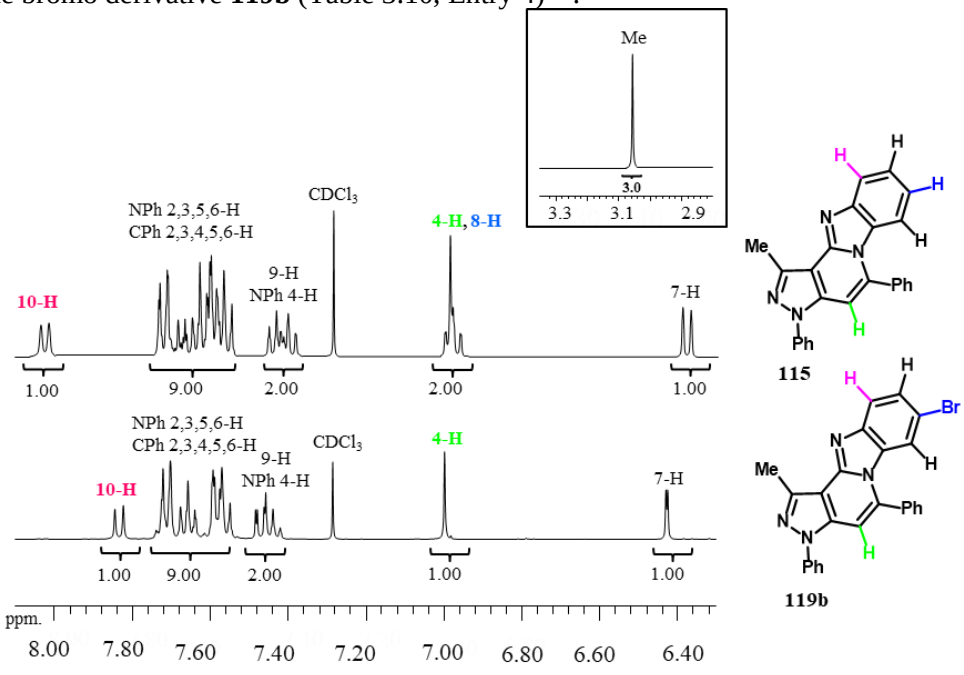
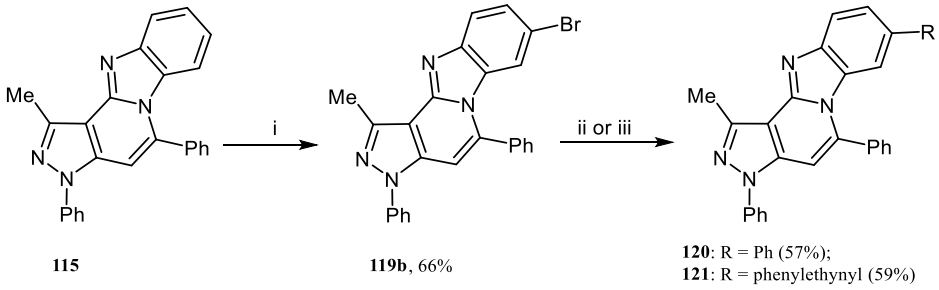


Figure 3.10 ^{1}H NMR spectra of compounds **115** and 1**19b**

The formation of halogenated compound was confirmed by MS where two peaks (M^+ and $[M+2]^+$) were observed. The attachment of the bromine atom at position 8 was fully shown by the careful NMR spectroscopic analysis (Figure 3.10).

Figure 3.10 shows ^1H NMR spectra of starting compound **115** and brominated product **119b**. The absence of 8-H proton signal at 6.94 ppm in the spectrum of compound **119b**, which was in the above shown spectra of compound **115**, proves that hydrogen atom was replaced by the bromine. There are signals of CH_3 group protons in both compounds spectra at 3.06 ppm (compound **115**) and 3.04 ppm (compound **119b**). There are signals of 7-H and 4-H protons at 6.36 ppm and 6.93 ppm (compound **115**) and 6.41 ppm and 6.95 ppm (compound **119b**), respectively. In the 'aromatic' part, there are signals of 9-H proton and protons of monosubstituted phenyl rings linked to pyrazolo and C-5 atom at 7.40–7.70 ppm. Moreover, there is a signal of 10-H proton at 7.96 ppm (compound **115**) and 7.78 ppm (compound **119b**).

The ability of the bromine atom in **119b** to participate in palladium-catalyzed cross-coupling reactions was proven by the Suzuki-type reaction of **119b** with phenylboronic acid, which afforded compound **120** in 57% yield. This coupling was carried out at 100 °C under microwave irradiation in EtOH by using $Pd(PPh_3)_4$ as the catalyst and aq Cs_2CO_3 as a base (Scheme 3.14). Microwave-assisted Sonogashira reaction conditions ($Pd(PPh_3)_2Cl_2$, CuI, and triethylamine at 130 °C and 100W for 10 min) were applied to the cross-coupling of **119b** with phenylacetylene. The reaction proceeded smoothly to afford compound **121** in 59% yield (Scheme 3.14)[76b].



115 **119b**, 66% **120**: R = Ph (57%); **121**: R = phenylethynyl (59%)

Reagents and conditions: (i) NBS, DMF, rt 24 h; (ii) 'Suzuki' $PhB(OH)_2$, Cs_2CO_3, $Pd(PPh_3)_4$, EtOH, MW, 100 °C, 50 W, 10 min (for **120**); (iii) 'Sonogashira' phenylacetylene, $Pd(PPh_3)_2Cl_2$, TEA, CuI, DMF, MW, 130 °C, 100 W, 10 min (for **121**).

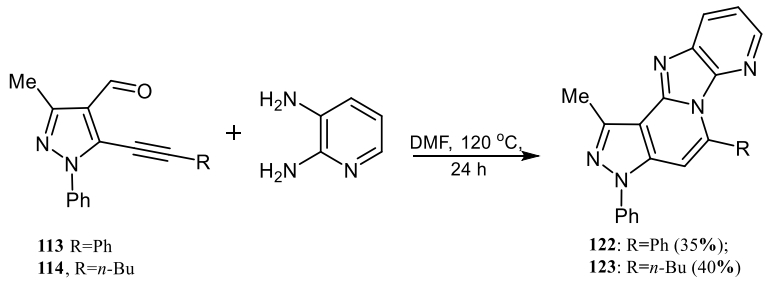
Scheme 3.14 Synthesis and cross-coupling reactions of compound **119b**

To sum up, the ability to functionalize pyrazolo pyrido benzimidazoles by employing halogenation and various cross coupling reactions was investigated.

3.4.3. Construction of the 3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*']dipyridines

In continuation of this study, it was decided to evaluate 2,3-diaminopyridine activity for tandem cyclisation reaction with pyrazole-4-carbdehydes **113–114**. When 2,3-diaminopyridine was used as the diamine component in the reaction with precursors **113–114,** the reaction provided the 3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b'*]dipyridine derivatives **122–123** (Scheme 3.15)[76b].

In principle, the formation of two isomeric structures occurred in this reaction due to the different position of the pyridine nitrogen in the ring system plane. However, only regioisomers **122–123** were isolated from the complex reaction mixture with low yields of 35% and 40%, respectively (Scheme 3.15)[76b]. In order to increase the yield of this reaction, copper iodide was employed as a catalyst; however, the desired result was not achieved.



113 R=Ph
114, R=*n*-Bu

122: R=Ph (35%);
123: R=*n*-Bu (40%)

Scheme 3.15 Construction of the 3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*']dipyridine ring system

3.4.4. Construction of the 13,13a-dihydro-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]perimidine ring system

It is known that pyrido[1,2-*a*]pyrimidines play a significant role in medicinal chemistry due to their numerous pharmacological activities such as antidepressant, gastrointestinal protective, neurotropic, anticancer activities, and stress protecting. This scaffold is found in some of marketed drugs, for instance: pemirolast, pirenperone, and barmastine (Figure 3.11)[99]. Due to the above mentioned reasons, it was decided to synthesize 13,13a-dihydro-3*H*-pyrazo-lo[4',3':3,4]pyrido[1,2-*a*]perimidine ring system by using naphtalendiamine.

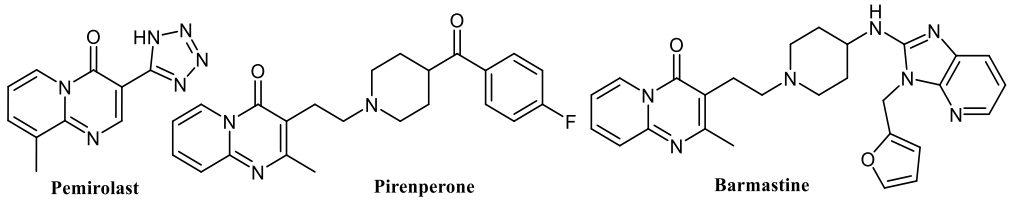
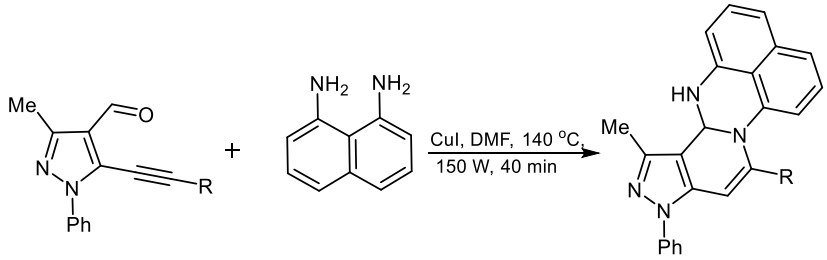


Figure 3.11 Pyrido[1,2-*a*]pyrimidine scaffold containing drugs

The reaction of **113–114** with 1,8-naphthalenediamine under the same reaction conditions as described above (heating in DMF) yielded no product of **124–125** type. A similar phenomenon has been observed by Nagarayan and coworkers[100] when they explored the tandem cyclisation of 2-(alkynyl)carbazole-3-carbaldehydes with different diamines. Thus, the author of this dissertation tried to adapt the copper-catalyzed annulation reaction conditions that were recently demonstrated by Tokimizu et al. [101] in the synthesis of highly fused perimidines. Nevertheless, the heating of pyrazole **113** with 1.8 equiv of 1,8-naphthalenediamine in DMF at 120 °C in the presence of 10 mol % of CuI under conventional conditions gave a complex reaction mixture with no obvious formation of the desired product **124**. The author of this dissertation was

pleased to find that microwave-assisted heating (140 °C, 150 W, 40 min) provided the pyrazolo[4',3':3,4]pyrido[1,2-*a*]perimidine compound **124** in 45% yield (Scheme 3.16).



113, R=Ph
114, R=*n*-Bu

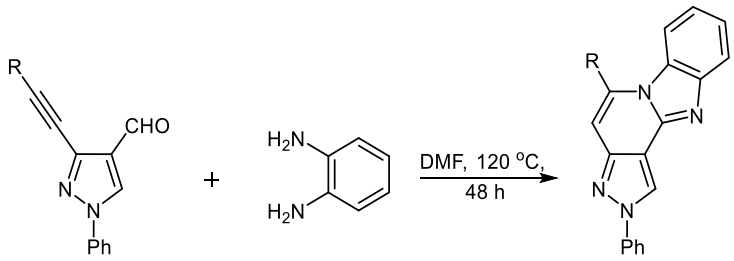
124: R = Ph (45%);
125: R = *n*-Bu (44%)

Scheme 3.16 Construction of the 13,13a-dihydro-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]perimidines

When the same reaction conditions were applied with precursor **114**, the accordant congener **125** was formed in 44% isolated yield (Scheme 3.16). Next, it was chosen to employ copper-catalyzed annulation proposed by Tokimizu et al.[101], though pyrazole **113** was conventionally heated in DMF with 1,8-naphtalendiamine in the presence of 10 mol% of copper iodide; nevertheless, no desired result was achieved. Later, it was presumed that microwave-assisted heating could accomplish this reaction[76b] (Scheme 3.16).

3.4.5. Construction of the 2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles

Considering the aforementioned results, the reaction between carbaldehydes **39**, **42,** and benzene-1,2-diamines was as well explored (Scheme 3.17). Again, the reaction of both precursors **39**, **42** with benzene-1,2-diamine provided the corresponding 2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*] compounds **126–127** in acceptable yields (Scheme 3.17)[76b].

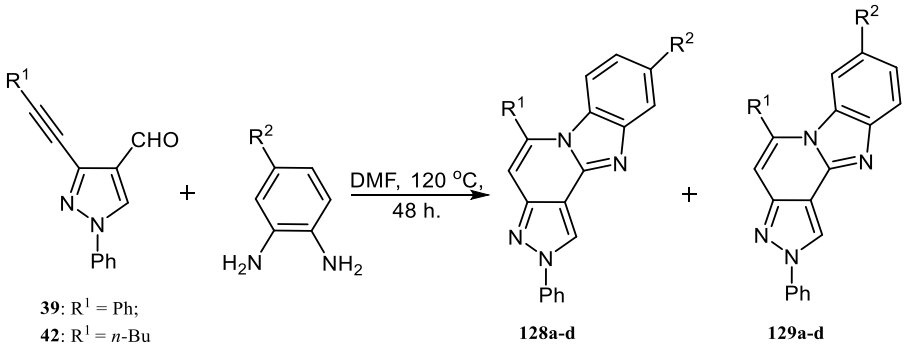


39: R = Ph;
42: R = *n*-Bu

126, R = Ph, 50%;
127, R = *n*-Bu, 84%

Scheme 3.17 Construction of the 2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*] compounds **126–127**

When precursors **39**, **42** reacted with 4-methylbenzene-1,2-diamine, the reaction gave regioisomers (**128a**, **129a** from **39** and **128c**, **129c** from **42**) as inseparable mixtures (Scheme 3.18). Compounds **128a** and **129a** were formed in the ratio of 1:0.62, whereas their congeners **128c** and **129c** were formed in the ratio of 1:0.25 (Scheme 3.18). Additionally, the formation of regioisomeric products was observed in the course of the reaction between pyrazole **39** and 4-chlorobenzene-1,2-diamine (Scheme 3.18). In this case, the author of the dissertation was lucky to separate and fully characterize each of the isomers. 9-Chloro-2,5-diphenyl-2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (**128b**) was obtained in 40% yield, whereas its 8-substituted analogue **129b** was formed in 30% yield (Scheme 3.18)[76b]. In the case of the reaction of pyrazole **42** with 4-chlorobenzene-1,2-diamine, the regioisomer **128d** was isolated as a sole product in 57% yield (Scheme 3.18). Notably, the 3-alkynylpyrazoles **39**, **42** required longer heating in DMF (48 h) than the 5-alkynylpyrazoles **113–114** in the tandem cyclisation reaction with benzene-1,2-diamines[76b].



39: R^1 = Ph;
42: R^1 = *n*-Bu

128a-d **129a-d**

R^1/ R^2	Me	Cl
Ph	**128a**:**129a**, 1:0.62, 60%	**129b**, 40%, **129b**, 30%
***n*-Bu**	**128c**:**129c**, 1:0.25, 60%	**128d**, 57%

Scheme 3.18 Construction of the 2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*] compounds **128–129**

In conclusion, there has been developed a synthetic approach for tandem cyclisation *via* pyrazole compounds, bearing alkynyl and aldehyde groups in neighboring positions. It was demonstrated that the heating of 5-alkynyl- or 3-alkynylpyrazole-4- carbaldehydes with the appropriate *o*-phenylendiamines without any catalyst in DMF provided 2*H*- and 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles. It should be noted that 3-alkynylpyrazoles **39** and **42** cyclisation was performed for longer period (48 h) than 5-alkynylpyrazoles **113–114** cyclisation (24h) with benzene-1,2-diamines. Further, the treating of 5-alkynylpyrazole-4-carbaldehyde with pyridine-2,3-diamine led to obtain 1-methyl-3-phenyl-3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*']dipyridines, though the conducting of reaction with naphthalene-1,8-diamine provided 13,13a-dihydro-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]perimidines. Notwithstanding, promoted by copper iodide under microwave heating, the latter cyclisation proceeded[76b].

3.4.6. Single-crystal X-ray diffraction analysis

Suitable crystals of **118f** and **127** for X-ray diffraction analysis were obtained from acetonitrile; the molecular structure and crystallographic numbering is shown in Figure 3.12. The selected geometric parameters are given in the Tables 3.11 and 3.12[76b].

Molecule **118f** consists of almost planar 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole moiety with attached phenyl ring, which is turned to the plane of the heterocyclic unit for c.a. 20° (Figure 3.12, Table 3.11). The side chain butyl carbons C(17), C(18), and C(19) are in the plane of the heterocyclic unit, and only C(20) is out of this plane[76b].

Table 3.11 Selected geometric parameters of **118f** (Å, °)

N1–C12	1.322 (27)	N7–N8	1.379 (23)
N1–C2	1.380 (28)	N8–C9	1.323 (28)
N4-C12	1.407 (25)	N7–C11	1.364(26)
N4–C3	1.407 (27)	N7–C21	1.426 (28)
N1–C12–N4	113.80 (18)	C9–N8–N7	106.63(16)
C3–N4–C12–N1	0.44 (22)	C9–C10–C11–C6	-179.02(19)
C18–C17–C5–C6	-2.69 (29)	C11–N7–C21–C22	-21.27(0.33)

The bond lengths and bond angles within the imidazole ring of **118f** are similar to those of pyrido[1,2-*a*]benzimidazole derivatives, while bond lengths and bond angles in the pyrazole ring are comparable with the values found by the analysis of 1-phenylpyrazole derivatives (Table 3.11)[76b].

The 2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole unit of **127** is planar and is as well almost co-planar with the phenyl ring (Table 3.12).

Table 3.12 Selected geometric parameters of **127** (Å, °)

N1–C12	1.316 (17)	N7–N8	1.371 (16)
N1–C2	1.386 (19)	N7–C11	1.336 (19)
N4-C12	1.406 (18)	N8–C9	1.357 (18)
N4–C3	1.408 (18)	N8–C21	1.428 (19)
N1–C12–N4	113.84 (13)	C9–N8–N7	112.90 (12)
C3–N4–C12–C10	-179.61 (12)	N7–C11–C10–C12	-179.98 (13)
C6–C5–C17–C18	2.33 (20)	C9–N8–C21–C22	176.98 (14)

Moreover, all carbon atoms of the side butyl chain are located in the same plane as the phenyl ring and heterocyclic ring system atoms. The bond lengths within the planar molecule of **127** are similar to those of **127** (Figure 3.12, Table 3.12)[76b].

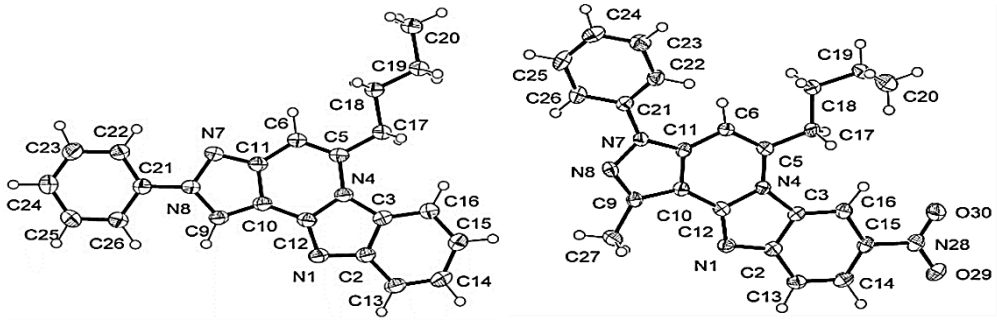


Figure 3.12 ORTEP drawing of 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole **118f** and ORTEP drawing of 2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole **127**

3.4.7. Optical investigations

The electronic absorption spectra of the selected 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles (**115–116**, **117a–c**, **119b**, and **120–121**), 3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*']dipyridines (**122–123**), 2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles (**126–127** and **128b, d**), and 13,13a-dihydro-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]perimidine (**124**) were recorded in THF (Table 3.13).

Table 3.13 Absorption (λ_{abs} and ε) and fluorescence (λ_{em} and quantum yield, Φ_f) parameters for compounds **115–116**, **117a–c**, **119b**, **120–124**, **126–127**, and **128b, d** in THF*

Entry	Compound	λ_{abs} (nm)	$\varepsilon\times10^3$, ($dm^3mol^{-1}cm^{-1}$)	λ_{em*} (nm)	Stokes shift (nm)	Φ_f (%)
1	**115**	209 283	31.21 43.63	458	175	45
2	**116**	208 273 281	28.86 57.23 61.30	397	116	13
3	**117a**	208 285	24.03 34,84	464	179	49
4	**117b**	208 286	27.81 38.08	446	160	27
5	**117c**	209 283 337	31.48 42.19 13.41	488	151	0.1
6	**119b**	208 278 286	14.59 15.62 16.33	456	170	10
7	**120**	200 209 295	27.50 52.17 72.97	478	183	28
8	**121**	209 302	47.19 59.22	473	171	28

Entry	Compound	λ_{abs} (nm)	$\varepsilon \times 10^3$, ($dm^3mol^{-1}cm^{-1}$)	λ_{em*} (nm)	Stokes shift (nm)	Φ_f (%)
9	**122**	209 287	32.04 43.46	438	151	27
10	**123**	209 284 311	20.01 42.30 11.05	380	96	25
11	**124**	209 380	57.52 19.51	456	76	0.1
12	**126**	200 242 339	28.62 36.37 20.43	389	50	38
13	**127**	241 281 339	41.59 35.78 23.27	386	47	58
14	**128b**	245 289 336	30.65 32.20 18.26	385	49	45
15	**128d**	244 284 337	45.80 41.02 27.40	382	45	51

* λ_{ex}=310 nm.

No significant differences were observed between the main absorption bands of 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles (Table 3.13, Entries 1–6 and 9–11)[76b]. The 3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b'*]dipyridines (Table 3.13), except the nitro-compound **117c**, showed similar results. Pyrazole **117c** exhibited a significant bathochromic shift of the near ultraviolet band compared to the rest compounds and showed an absorption maximum at 337 nm[76b].

The electronic spectra of the 2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles (Table 3.13, Entries 14–17) possessed a near ultraviolet band with an absorption maximum at approximately 340 nm in all cases, whereas the substituents attached at various positions of the heterocyclic ring system had a negligible influence on the position of the absorption bands. The fluorescence emission profile of the aforementioned fused heterocycles was obtained in THF (Table 3.13) and revealed a strong influence of molecular structure on the character of the fluorescence emission. The solutions of those 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles, which possessed 5-phenyl substitutent, exhibited a strong fluorescence with an emission maximum (λ_{em}) in the range from 446 (**117b**, Entry 4) to 488 nm (**117c**, Entry 5) and large Stokes shifts of c.a. 170 nm. However, 5-butyl substituted compound **116** showed a significant hypsochromic shift (c.a. 60 nm) to compare with 5-phenyl one **115** (Entries 2 and 3, respectively). A similar feature was found in the case of the 3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*']dipyridines **122** (R = Ph) and **123** (R = *n*Bu), which spectra contained the emission maximum (λ_{em}) at 438 and 380 nm, respectively. The spectrum of the brominated compound **119b** revealed λ_{em} at 456 nm (Entry 8), similar to that of the starting substrate **115** (Entry 1), but the

further substitution of bromine by a phenyl ring (compound **120**) or a 2-phenylethenyl moiety (compound **121**) initiated a significant bathochromic shift to λ_{em} at 478 and 473 nm, respectively[76b].

For all the 2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles (**126–127**, **128b, d**), the fluorescence spectra displayed the emission maximum (λ_{em}) ranging from 382 to 385 nm and Stokes shifts of c.a. 50 nm. By contrast, the electronic and spatial properties of the substituents had only a limited influence on the character of the fluorescence spectra. The solution that contain the 13,13a-dihydro-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]perimidine **124** exhibited λ_{em} at 456 nm[76b].

The fluorescence quantum yield (Φf) of the solutions was estimated by the integrating sphere method. It appeared that the fluorescence quantum yield was sensitive to the structure of the compounds. For the 5-phenyl-benzimidazole **115**, the observed Φ_f value was c.a. 45%, whereas for its 5-butyl analogue **116**, Φ_f was fixed slightly above 13%. It is known that the direct attachment of halogens, especially heavy ones, or a nitro group to the core of an aromatic compound can significantly reduce the fluorescence quantum yield (Φ_f)[96]. Indeed, in the case of the 8-bromo-benzimidazole **119b**, Φ_f fell to 9.7%, whereas for the 8-nitro compound **117c**, Φ_f dropped to a negligible value of 0.1%. The 13,13a-dihydro-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]perimidine (**133**) emitted only negligible fluorescence (Φf = 0.1%). The values of Φ_f for the 5-phenyl- and 5-butyl-2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazoles (**126**-**127**) were 38% and 58%, respectively. The attachment of a chlorine atom at the 9-position of the heterocyclic core did not significantly change the fluorescence quantum yield (Φ_f), which remained at high values of 49% and 45% for compounds **128b** and **128d**, respectively[76b].

In conclusion, it was demonstrated that the 2*H*- and 3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole ring systems could be obtained without any catalyst by heating 5-alkynyl- or 3-alkynylpyrazole-4-carbaldehydes with the appropriate benzene-1,2-diamines in DMF. The reaction of 5-alkynylpyrazole-4-carbaldehydes with pyridine-2,3-diamine leads to the production of 1-methyl-3-phenyl-3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*']dipyridines, whereas the use of naphthalene-1,8-diamine leads to 13,13a-dihydro-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]perimidines. However, in the latter case, CuI catalysis and microwave heating is necessary. The pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole fluorophores were characterized by their good quantum yields and large Stokes shifts. Therefore, the derivatives of these heterocycles can be considered for use as attractive, tailor-made emitters in the applications as energetic substances and markers[76b].

4. EXPERIMENTAL PART

4.1. Chemistry

4.1.1. Instrumentation

The melting points were determined on a Reichert–Kofler hot-stage microscope or in capillary tubes on capillary melting point apparatus Electrothermal MEL-TEMP® and are uncorrected. Mass spectra were obtained on a Shimadzu LCMS 2020 Single Quadrupole Liquid Chromatograph Mass Spectrometer. IR spectra in KBr pellets were recorded on a Bruker Tensor 27 spectrometer and are reported in the frequency of absorption (cm^{-1}) or on a Bruker Vertex v70 FTIR spectrometer equipped with a diamond ATR accessory. HRMS spectra were recorded with a Bruker micrO-TOF-QIII spectrometer. ^{1}H NMR, ^{13}C NMR, and ^{15}N NMR spectra were recorded from $CDCl_3$ solutions at 25 °C on either a Bruker Avance III 400 instrument (400 MHz for ^{1}H, 100 MHz for ^{13}C, 40 MHz for ^{15}N) by using a directly detecting BBFO probe or on a Bruker Avance III 700 instrument (700 MHz for ^{1}H, 176 MHz for ^{13}C) equipped with a 5 mm TCI ^{1}H-^{13}C/^{15}N/D z-gradient cryoprobe. The solvent (residual) signals were used as internal standards and were related to TMS with δ 7.26 ppm (^{1}H) and δ 77.00 ppm (^{13}C). ^{15}N NMR spectra were referenced against neat, external nitromethane. The full and unambiguous assignments of ^{1}H, ^{13}C, and ^{15}N NMR resonances were achieved by using combined applications of standard NMR spectroscopic techniques such as APT, COSY, TOCSY, NOESY, gs-HSQC, and gs-HMBC. Diffraction data were collected on Bruker-Nonius KappaCCD diffractometer at room temperature and as well at 100 °C. The crystal structures were solved by using known programs. The UV/vis spectra were recorded on a Perkin Elmer Lambda 35 UV/vis spectrometer. The fluorescence spectra were recorded on an FL920 fluorescence spectrometer from Edinburgh Instruments. The PL quantum yields were measured from dilute THF solutions by an absolute method by using the Edinburgh Instruments integrating sphere that was excited with a Xe lamp. Optical densities of the sample solutions were ensured to be below 0.1 to avoid reabsorption effects. All the optical measurements were performed at rt under ambient conditions. For chromatographic separations, silica gel 60 (230–400 mesh, Merck) was used.

4.1.2. Materials

All chemicals were purchased from Sigma-Aldrich and Fluorochem, and used as received without further purification. Organic solvents were purified and dried by the standard methods[102].

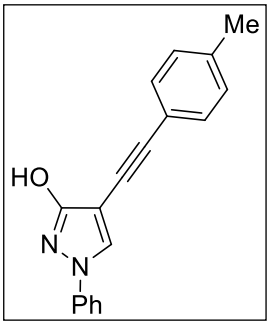
4.1.2.1. General procedure for the preparation of 4-alkynyl-3-hydroxy-1-phenyl-1*H*-pyrazoles 4–13 by the Sonogashira-type cross-coupling reaction.

In to the solution of 4-iodo-1-phenyl-1*H*-pyrazol-3-ol (**4**) (1 mmol) in dry DMF (2 mL) under an argon atmosphere were added TEA (0.7 mL, 5 mmol), the appropriate ethyne (1.5 mmol), $Pd(PPh_3)_2Cl_2$ (70 mg, 0.1 mmol), and CuI (36 mg, 0.2 mmol). The mixture was stirred under an argon atmosphere at 58 °C temperature for the given

time, and then it was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by flash chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:6, v/v) to yield compounds **5–13**.

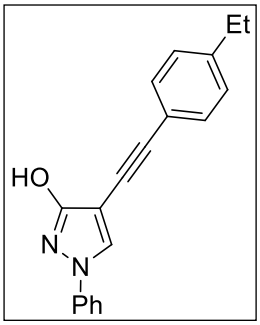
4.1.2.1.1. 4-[(4-Methylphenyl)ethynyl]-1-phenyl-1*H*-pyrazol-3-ol (5)

The reaction mixture was stirred for 12 hours. White solid, yield 206 mg, 75%, mp 168–169 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3125, 3069, 3029 (OH, CH_{arom}), 2923 (CH_{aliph}), 2217 (C≡C), 1597, 1532, 1504, 1314, 1208 (C=C, C–N, C–O), 815, 755, 688 (CH=CH of mono- and disubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 2.36 (CH_3), 7.14–7.15 (m, 2H, CPh 3,5-H), 7.29–7.31 (m, 1H, NPh 4-H), 7.42–7.43 (m, 2H, CPh 2,6-H), 7.48–7.50 (m, 2H, NPh 3,5-H), 7.53–7.54 (m, 2H, NPh 2,6-H), 7.87 (s, 1H, 5-H), 11.74 (br s, 1H, OH). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 21.6 (CH_3), 77.8 (*C*H≡CPh), 92.6 (C-4), 92.8 (C≡*C*Ph), 119.2 (NPh C-2,6), 120.4 (CPh C-1), 126.8 (NPh C-4), 129.2 (CPh C-3,5), 130.0 (NPh C-3,5), 131.1 (C-5), 131.6 (CPh C-2,6), 138.3 (CPh C-4), 139.1 (NPh C-1), 163.8 (C-3). MS m/z (%): 275 ([M+H]$^+$,100). HRMS (ESI) for $C_{18}H_{14}N_2ONa$ ([M+Na]$^+$) calcd 297.0998, found 297.0998.



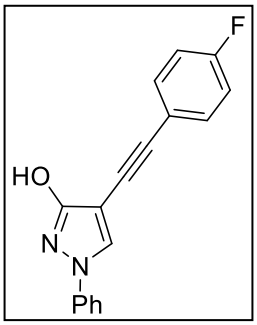
4.1.2.1.2. 4-[(4-Ethylphenyl)ethynyl]-1-phenyl-1*H*-pyrazol-3-ol (6)

The reaction mixture was stirred for 3 hours. Yellowish solid, yield 225 mg, 78%, mp 164–165 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3060, 3029 (OH, CH_{arom}), 2964, 2928 (CH_{aliph}), 2220 (C≡C), 1597, 1540, 1503, 1414, 1208 (C=C, C–N, C–O), 830, 751, 678 (CH=CH of mono- and disubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 1.25 (t, ^3J=7.7 Hz, 3H, CH_3), 2.66 (q, ^3J=7.7 Hz, 2H, CH_2), 7.18–7.18 (m, 2H, CPh 3,5-H), 7.29–7.31 (m, 1H, NPh 4-H), 7.45–7.50 (m, 4H, CPh 2,6-H, NPh 3,5-H), 7.53–7.54 (m, 2H, NPh 2,6-H), 7.87 (s, 1H, 5-H), 11.91 (br s, 1H, OH). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 15.5 (CH_3), 28.9 (CH_2), 77.8 (*C*≡CPh), 92.6 (C-4), 92.8 (C≡*C*Ph), 119.2 (NPh C-2,6), 120.7 (CPh C-1), 126.8 (NPh C-4), 128.0 (CPh C-3,5), 130.0 (NPh C-3,5), 131.2 (C-5), 131.6 (CPh C-2,6), 139.0 (CPh C-4), 144.6 (NPh C-1), 163.9 (C-3). MS m/z (%): 289 ([M+H]$^+$,100). HRMS (ESI) for $C_{19}H_{16}N_2ONa$ ([M+Na]$^+$) calcd 311.1155, found 311.1155.



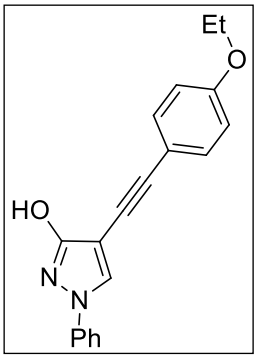
4.1.2.1.3. 4-[(4-Fluorophenyl)ethynyl]-1-phenyl-1*H*-pyrazol-3-ol (7)

The reaction mixture was stirred for 12 hours. White solid, yield 203 mg, 73%, mp 197–198 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3067, 3052 (OH, CH_{arom}), 2218 (C≡C), 1597, 1536, 1501, 1212 (C=C, C–N, C–O), 831, 754, 679 (CH=CH of mono- and disubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 7.03 (t, ^3J(4FPh 3,5-H,



2,6-H)= 8.5 Hz, 2H, 4FPh 3,5-H), 7.30–7.32 (m, 1H, NPh 4-H), 7.48–7.52 (m, 4H, NPh 3,5-H, 4FPh 2,6-H), 7.53–7.54 (m, 2H, NPh 2,6-H), 7.88 (s, 1H, 5-H), 11.11 (br s, 1H, OH). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 79.2 (*C*≡C4FPh), 91.6 (C≡*C*4FPh), 92.2 (C-4), 115.7 (^2J=22.1 Hz, 4FPh C-3,5), 119.2 (NPh C-2,6), 119.6 (^4J=3.8 Hz, 4FPh C-1), 126.6 (NPh C-4), 130.0 (NPh C-3,5), 131.1 (C-5), 133.5 (^3J=8.9 Hz, 4FPh C-2,6), 139.1 (NPh C-1), 162.6 (^1J=248.5 Hz, 4FPh C-4), 163.6 (C-3). MS m/z (%): 279 ([M+H]$^+$,00). HRMS (ESI) for $C_{17}H_{11}FN_2ONa$ ([M+Na]$^+$) calcd 301.0748, found 301.0748.

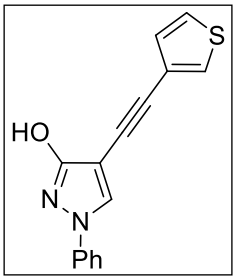
4.1.2.1.4. 4-[(4-Etoxyphenyl)ethynyl]-1-phenyl-1*H*-pyrazol-3-ol (8)



The reaction mixture was stirred for 12 hours. White solid, yield 240 mg, 79%, mp 194–195 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3056 (OH, CH_{arom}), 2977, 2923 (CH_{aliph}), 2134 (C≡C), 1597, 1502, 1473, 1245, 1173, 1043 (C=C, C–N, C–O), 824, 754, 678 (CH=CH of mono- and disubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 1.42 (t, $^3J(CH_3,CH_2)$=7.0 Hz, 3H, CH_3), 4.05 (q, $^3J(CH_2,CH_3)$=7.0 Hz, 2H, CH_2), 6.85–6.86 (m, 2H, CPh 3,5-H), 7.28–7.30 (m, 1H, NPh 4-H), 7.45–7.46 (m, 2H, CPh 2,6-H), 7.47–7.49 (m, 2H, NPh 3,5-H), 7.53–7.55 (m, 2H, NPh 2,6-H), 7.86 (s, 1H, 5-H), 10.74 (br s, 1H, OH). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 14.9 (CH_3), 63.6 (CH_2), 76.8 (*C*≡CPh), 92.6 (C-4), 92.7 (C≡*C*Ph), 114.6 (CPh C-3,5), 115.4 (CPh C-1), 119.0 (NPh C-2,6), 126.7 (NPh C-4), 129.9 (NPh C-3,5), 130.7 (C-5), 133.2 (CPh C-2,6), 139.2 (NPh C-1), 159.1 (CPh C-4), 163.5 (C-3). MS m/z (%): 305 ([M+H]$^+$,100). HRMS (ESI) for $C_{19}H_{16}N_2O_2Na$ ([M+Na]$^+$) calcd 327.1104, found 327.1105.

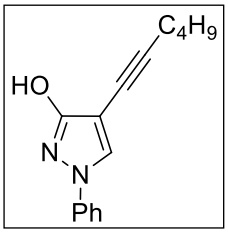
4.1.2.1.5. 1-Phenyl-4-[(thiophen-3-yl)ethynyl]-1*H*-pyrazol-3-ol (9)

The reaction mixture was stirred for 2 hours. Brown solid, yield 197 mg, 74%, mp 204.5–205.5 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3127, 3109, 3069, 3059, 3046, 3004 (OH, CH_{arom}), 2220 (C≡C), 1595, 1533, 1503, 1397, 1305, 1254, 1206, 1060 (C=C, C–N, C–O), 751, 681 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, DMSO-d_6): δ_H ppm 7.21 (dd, ^3J(4-H,5-H)=5.0 Hz, ^4J(4-H,2-H)=1.2 Hz, 1H, Th 4-H), 7.23–7.25 (m, 1H, Ph 4-H), 7.44–7.47 (m, 1H, Ph 3,5-H), 7.62 (dd, ^3J(5-H,4-H)=4.9 Hz, ^4J(5-H,2-H)=2.9 Hz, 1H, Th 5-H), 7.71–7.72 (m, 2H, Ph 2,6-H), 7.79 (dd, ^4J(2-H,5-H)=3.0 Hz, ^4J(2-H,4-H)=1.2 Hz, 1H, Th 2-H), 8.62 (s, 1H, 5-H), 11.07 (s, 1H, OH). ^{13}C NMR (176 MHz, DMSO-d_6): δ_C ppm 79.6 (*C*≡CTh), 87.0 (C≡*C*Th), 91.3 (C-4), 117.2 (Ph C-2,6), 121.8 (Th C-3), 125.8 (Ph C-4), 126.8 (Th C-5), 128.9 (Th C-2), 129.5 (Ph C-3,5, Th C-4), 130.7 (C-5),



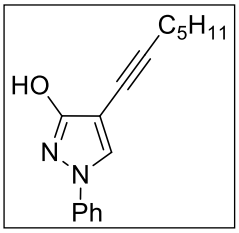
139.1 (Ph C-1), 162.7 (C-3). MS m/z (%): 267 ([M+H]$^+$, 100). HRMS (ESI) for $C_{15}H_{11}N_2OS$ ([M+H]$^+$) calcd 267.0587, found 267.0584.

4.1.2.1.6. 4-(Hex-1-yn-1-yl)-1-phenyl-1*H*-pyrazol-3-ol (10)



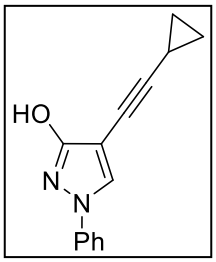
The reaction mixture was stirred for 24 hours. Yellow solid, yield 204 mg, 85%, mp 140–141.5 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3120, 3070, 3049, 2958, 2931 (OH, CH_{arom}, CH_{aliph}), 1597, 1587 1526, 1504, 1415, 1307, 1234, 1210, 1062 (C=C, C–N, C-O), 756, 678 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.94 (t, ^3J=7.4 Hz, 3H, $C_3H_6CH_3$), 1.47 (sext, ^3J=7.4 Hz, 2H, $C_2H_4CH_2CH_3$), 1.59 (quin, ^3J=7.4 Hz, 2H, $CH_2CH_2C_2H_5$), 2.42 (t, ^3J=7.2 Hz, 2H, $CH_2C_3H_7$), 7.26–7.28 (m, 1H, Ph 4-H), 7.44–7.46 (m, 2H, Ph 3,5-H), 7.48–7.50 (m, 2H, Ph 2,6-H), 7.74 (s, 1H, 5-H), 11.65 (s, 1H, OH). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 13.8 ($C_3H_6CH_3$), 19.5 ($CH_2C_3H_7$), 22.2 ($C_2H_4CH_2CH_3$), 31.0 ($CH_2CH_2C_2H_5$), 69.1 ($C{\equiv}CC_4H_9$), 92.9 (C-4), 93.8 ($C{\equiv}CC_4H_9$), 119.0 (Ph C-2,6), 126.5 (Ph C-1), 129.9 (Ph C-3,5), 130.9 (C-5), 139.2 (Ph C-4), 163.9 (C-3). MS m/z (%): 241 ([M+H]$^+$, 100). HRMS (ESI) for $C_{15}H_{17}N_2O$ ([M+H]$^+$) calcd 241.1335, found 241.1332.

4.1.2.1.7. 4-(Hept-1-yn-1-yl)-1-phenyl-1*H*-pyrazol-3-ol (11)



The reaction mixture was stirred for 12 hours. Brown solid, yield 198 mg, 78%, mp 110–111 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3131, 3057 (OH, CH_{arom}), 2947, 2922 (CH_{aliph}), 2163 (C≡C), 1595, 1529, 1499 (C=C, C–N, C–O), 761, 691 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.91 (t, ^3J=7.3 Hz, 3H, $C_4H_8CH_3$), 1.35 (sext, ^3J=7.0 Hz, 2H, $C_3H_6CH_2CH_3$), 1.42 (quin, ^3J=7.0 Hz, 2H, $C_2H_4CH_2C_2H_5$), 1.61 (quin, ^3J=7.3 Hz, 2H, $CH_2CH_2C_3H_7$), 2.42 (t, ^3J=7.2 Hz, 2H, $CH_2C_4H_9$), 7.26–7.28 (m, 1H, Ph 4-H), 7.44–7.46 (m, 2H, Ph 3,5-H), 7.49–7.50 (m, 2H, Ph 2,6-H), 7.74 (s, 1H, 5-H), 11.41 (br s, 1H, OH). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 14.2 ($C_4H_8CH_3$), 19.8 ($CH_2C_4H_9$), 22.4 ($C_3H_6CH_2CH_3$), 28.6 ($CH_2CH_2C_3H_7$), 31.3 ($C_2H_4CH_2C_2H_5$), 69.1 ($C{\equiv}CC_5H_{11}$), 92.8 (C-4), 93.9 ($C{\equiv}CC_5H_{11}$), 119.0 (Ph C-2,6), 126.5 (Ph C-4), 129.9 (Ph C-3,5), 130.9 (C-5), 139.2 (Ph C-4), 163.8 (C-3). MS m/z (%): 255 ([M+H]$^+$, 100). HRMS (ESI) for $C_{16}H_{18}N_2ONa$ ([M+Na]$^+$) calcd 277.1311, found 277.1310.

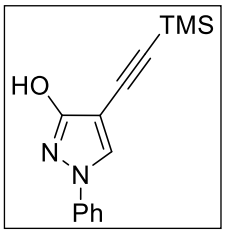
4.1.2.1.8. 4-(Cyclopropylethynyl)-1-phenyl-1*H*-pyrazol-3-ol (12)



The reaction mixture was stirred for 2 hours.White solid, yield 143 mg, 64%, mp 185.5–187 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3122, 3074, 3051 (OH, CH_{arom}) 2999, 2954, 2920 (CH_{aliph}), 1596, 1526, 1504, 1420, 1308, 1242, 1210, 1063(C=C, C–N, C-O), 758, 678 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.79–0.81 (m, 2H, CH_2), 0.82–0.86 (m, 2H, CH_2), 1.45–1.49 (m, 1H, $CH(CH_2)_2$), 7.26–7.28 (m, 1H, Ph 4-H), 7.44–7.48 (m, 4H, Ph 2,3,5,6-H), 7.72 (s, 1H, 5-H), 11.45 (s, 1H,

OH). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 0.6 ($CH(CH_2)_2$), 8.8 ($CH(CH_2)_2$), 63.8 ($C\equiv CC_3H_5$), 92.2 (C-4), 96.2 ($C\equiv CC_3H_5$), 118.5 (Ph C-2,6), 126.0 (Ph C-4), 129.4 (Ph C-3,5), 130.5 (C-5), 138.6 (Ph C-1), 163.4 (C-3). MS m/z (%): 225 ([M+H]$^+$, 100). HRMS (ESI) for $C_{14}H_{13}N_2O$ ([M+H]$^+$) calcd 225.1022, found 225.1021.

4.1.2.1.9. 1-Phenyl-4-((trimethylsilyl)ethynyl)-1*H*-pyrazol-3-ol (13)

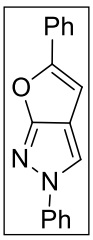


The reaction mixture was stirred for 24 hours. White solid, 64 mg, yield 50%, mp 175–176 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3073, 3059 (OH, CH_{arom}), 2956, 2926 (CH_{aliph}), 2155 (C≡C), 1600, 1586, 1530, 1507, 1247, 1208, 1201, 1064 (CH_3–Si, C=C, C–N, C–O), 868, 841, 812, 758, 692 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.24 (s, 9H, TMS), 7.26–7.30 (m, 1H, Ph 4-H), 7.44–7.47 (m, 2H, Ph 3,5-H), 7.49–7.51 (m, 2H, Ph 2,6-H), 7.83 (s, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 0.4 (TMS) 92.5, 94.1 ($C\equiv$CTMS, C-4), 98.3 (C≡CTMS), 119.3 (Ph C-2,6), 127.0 (Ph C-4), 130.1 (Ph C-3,5), 131.8 (C-5), 139.2 (Ph C-1), 164.0 (C-3). MS m/z (%): 257 ([M+H]$^+$, 100). HRMS (ESI) for $C_{14}H_{16}N_2OSiNa$ ([M+Na]$^+$) calcd 279.0951, found 279.0951.

4.1.2.2. General procedure for the cyclization of 4-alkynyl-3-hydroxy-1-phenyl-1*H*-pyrazoles 4-13.

AgOTf (13 mg, 0.05 mmol) and K_2CO_3 (110 mg, 1 mmol) were added into the solution of appropriate pyrazoles **4–13** (0.5 mmol) in absolute DMF (1 ml). The mixture was stirred at 120 °C temperature for 14 hours, diluted with water, and the extraction was done with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4; the solvent was evaporated. The residue was purified by flash chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:6, v/v) to yield compounds **15–23**.

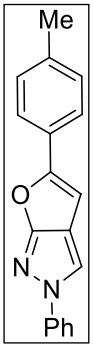
4.1.2.2.1. 2,5-Diphenyl-2*H*-furo[2,3-*c*]pyrazole (15)



Yellowish solid, yield 112 mg, 86%, mp 193.5–194.3°C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3139, 3062, 3045 (CH_{arom}), 1622, 1596, 1587, 1511, 1481, 1454, 1434, 1388, 1315, 1271, 1198, 1154, 1073, 1035, 1004 (C=C, C–N, C–O–C), 748, 722, 685 (CH=CH of monosubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 6.67 (s, 1H, 4-H), 7.19–7.22 (m, 1H, NPh 4-H), 7.25–7.28 (m, 1H, CPh 4-H), 7.35–7.37 (m, 2H, CPh 3,5-H), 7.38–7.40 (m, 2H, NPh 3,5-H), 7.65–7.66 (m, 2H, NPh 2,6-H), 7.69 (s, 1H, 3-H), 7.71–7.72 (m, 2H, CPh 2,6-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 96.5 (C-4), 113.8 (C-3a), 116.3 (C-3), 119.2 (NPh C-2,6), 124.6 (CPh C-2,6), 126.3 (NPh C-4), 128.6 (CPh C-4), 128.9 (CPh C-3,5), 129.6 (NPh C-3,5), 130.7 (CPh C-1), 141.1 (NPh C-1), 159.3 (C-5), 167.0 (C-6a). MS m/z (%): 261 ([M+H]$^+$, 100). HRMS (ESI) for $C_{17}H_{12}N_2NaO$ ([M+Na]$^+$) calcd 283.0842, found 283.0842.

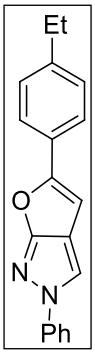
4.1.2.2.2. 5-(4-Methylphenyl)-2-phenyl-2*H*-furo[2,3-*c*]pyrazole (16)

White solid, yield 119 mg, 87%, mp 211–212°C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3045, 3020 (CH_{arom}), 2956, 2917 (CH_{aliph}), 1694, 1597, 1500, 1441, 1388 (C=C, C–N, C–O–C), 796, 746, 684 (CH=CH of mono- and disubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 2.39 (CH_3), 6.68 (s, 1H, 4-H), 7.23–7.25 (m, 2H, 5-Ph 3,5-H), 7.26–7.28 (m, 1H, NPh 4-H), 7.45–7.47 (m, 2H, NPh 3,5-H), 7.67–7.69 (m, 2H, 5-Ph 2,6-H), 7.71–7.73 (m, 2H, NPh 2,6-H), 7.74 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 21.5 (CH_3), 95.6 (C-4), 113.8 (C-3a), 116.1 (C-3), 119.1 (NPh C-2,6), 124.6 (5-Ph C-2,6), 126.2 (NPh C-4), 128.0 (5-Ph C-1), 129.6 (NPh C-3,5), 129.6 (5-Ph C-3,5), 138.7 (5-Ph C-4), 141.1 (NPh C-1), 159.6 (C-5), 168.9 (C-6a). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −169.9 (N-2), −127.9 (N-1). MS m/z (%): 275 ([M+H]$^+$, 100). HRMS (ESI) for $C_{18}H_{14}N_2NaO$ ([M+Na]$^+$) calcd 297.0998, found 297.0999.



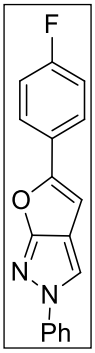
4.1.2.2.3. 5-(4-Ethylphenyl)-2-phenyl-2*H*-furo[2,3-*c*]pyrazole (17)

White solid, yield 133 mg, 92%, mp 180–181 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3060 (CH_{arom}), 2965, 2921 (CH_{aliph}), 1618, 1597, 1501, 1480, 1447, 1386 (C=C, C–N, C–O–C), 834, 753, 687 (CH=CH of mono- and disubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 1.25 (t, ^3J=7.6 Hz, 3H, CH_3), 2.67 (q, ^3J=7.6 Hz, 2H, CH_2), 6.66 (s, 1H, 4-H), 7.24–7.26 (m, 3H, 5-Ph 3,5-H, NPh 4-H), 7.43–7.45 (m, 2H, NPh 3,5-H), 7.68–7.71 (m, 4H, 5-Ph 2,6-H, NPh 2,6-H), 7.72 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 15.6 (CH_3), 28.9 (CH_2), 95.6 (C-4), 113.8 (C-3a), 116.1 (C-3), 119.1 (NPh C-2,6), 124.7 (5-Ph C-2,6), 126.2 (NPh C-4), 128.2 (5-Ph C-1), 128.4 (5-Ph C-3,5), 129.6 (NPh C-3,5), 141.1 (NPh C-1), 145.1 (5-Ph C-4), 159.6 (C-5), 168.9 (C-6a). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −170.0 (N-2), −128.0 (N-1). MS m/z (%): 289 ([M+H]$^+$, 100). HRMS (ESI) for $C_{19}H_{16}N_2ONa$ ([M+Na]$^+$) calcd 311.1155, found 311.1156.

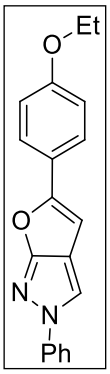


4.1.2.2.4. 5-(4-Fluorophenyl)-2-phenyl-2*H*-furo[2,3-*c*]pyrazole (18)

White solid, yield 120 mg, 86%, mp 220-221 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3066, 3047 (CH_{arom}), 1596, 1498, 1447, 1385, 1223 (C=C, C–N, C–O–C), 843, 750, 687 (CH=CH of mono- and disubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 6.67 (s, 1H, 4-H), 7.13 (t, ^3J(4FPh 3,5-H, 2,6-H)=8.5 Hz, 2H, 4FPh 3,5-H), 7.27–7.29 (m, 1H, NPh 4-H), 7.45–7.48 (m, 2H, NPh 3,5-H), 7.71–7.73 (m, 2H, NPh 2,6-H), 7.75–7.77 (m, 3H, 4FPh 2,6-H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 96.2 (C-4), 113.7 (C-3a), 116.1 (C-3), 116.2 (4FPh C-3,5, ^2J 61.1 Hz), 119.2 (NPh C-2,6), 126.4 (NPh C-4), 126.5 (4FPh C-2,6, ^3J=8.1 Hz), 127.0 (4FPh C-1, ^4J=2.7 Hz), 129.6 (NPh C-3,5), 141.1 (NPh C-1), 158.3 (C-5), 162.9 (4FPh C-4, ^1J=248.6 Hz), 168.9 (C-6a). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −169.4 (N-2), −127.5 (N-1). MS m/z (%): 279 ([M+H]$^+$, 100). HRMS (ESI) for $C_{17}H_{11}FN_2ONa$ ([M+Na]$^+$) calcd 301.0748, found 301.0749.

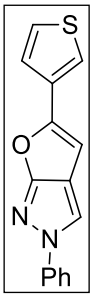


4.1.2.2.5. 5-(4-Ethoxyphenyl)-2-phenyl-2*H*-furo[2,3-*c*]pyrazole (19)



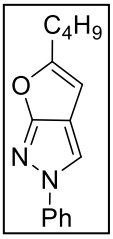
White solid, yield 123 mg, 81%, mp 190–191 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3063, 3046 (CH_{arom}), 2978, 2924 (CH_{aliph}), 1597, 1501, 1387, 1249, 1239 (C=C, C–N, C–O–C). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 1.44 (t, ^3J=7.0 Hz, 3H, CH_3), 4.08 (q, ^3J=7.0 Hz, 2H, CH_2), 6.58 (s, 1H, 4-H), 6.94–6.96 (m, 2H, 5-Ph 3,5-H), 7.25–7.27 (m, 1H, NPh 4-H), 7.44–7.47 (m, 2H, NPh 3,5-H), 7.69–7.72 (m, 4H, NPh 2,6-H, 5-Ph 2,6-H), 7.72 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 14.9 (CH_3), 63.7 (CH_2), 94.5 (C-4), 113.9 (C-3a), 114.9 (5-Ph C-3,5), 115.8 (C-3), 119.1 (NPh C-2,6), 123.4 (5-Ph C-1), 126.09 (NPh C-4), 126.13 (5-Ph C-2,6), 129.6 (NPh C-3,5), 141.2 (NPh C-1), 159.46 (5-Ph C-4), 159.54 (C-5), 168.9 (C-6a). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −170.6 (N-2), −128.2 (N-1). MS m/z (%): 304 ($[M+H]^+$, 100). HRMS (ESI) for $C_{19}H_{16}N_2O_2Na$ ($[M+Na]^+$) calcd 327.1104, found 327.1104.

4.1.2.2.6. 2-Phenyl-5-(thiophen-3-yl)-2*H*-furo[2,3-*c*]pyrazole (20)



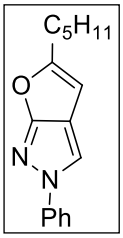
Yellowish solid, yield 83 mg, 62%, mp 191–193 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3139, 3128, 3110, 3097, 3065, 3045(CH_{arom}), 1594, 1587, 1510, 1497, 1480, 1463, 1441, 1386, 1328, 1239, 1218, 1177, 1075, 1036, 1026 (C=C, C–N, C–O–C), 777, 684 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 6.54 (s, 1H, 4-H), 7.26–7.28 (m, 1H, Ph 4-H), 7.37–7.39 (m, 2H, Th H), 7.44–7.47 (m, 2H, Ph 3,5-H), 7.66 (dd, ^4J(2-H,5-H) = 2.8 Hz, ^4J(2-H,4-H) = 1.4 Hz, 1H, Th 2-H), 7.71–7.72 (m, 2H, Ph 2,6-H), 7.74 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 96.1 (C-4), 113.6 (C-3a), 116.3 (C-3), 119.1 (Ph C-2,6), 121.3 (Th C-2), 124.7 (Th C), 126.2 (Ph C-4), 126.7 (Th C), 129.6 (Ph C-3,5), 132.3 (Th C-3), 141.1 (Ph C-1), 156.1 (C-5), 168.7 (C-6a). MS m/z (%): 267 ($[M+H]^+$, 100). HRMS (ESI) for $C_{15}H_{11}N_2OS$ ($[M+H]^+$) calcd 267.0587, found 267.0589.

4.1.2.2.7. 5-Butyl-2-phenyl-2*H*-furo[2,3-*c*]pyrazole (21)



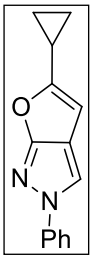
Brown solid, yield 54 mg, 93%, mp 88.5–90 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3141, 3126, 3074, 3050 (CH_{arom}), 2968, 2954, 2928, 2857 (CH_{aliph}), 1595, 1577, 1506, 1460, 1447, 1438, 1382, 1320, 1231, 1202, 1120, 1073, 1035 (C=C, C–N, C–O–C), 753, 691 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.95 (t, ^3J=7.4 Hz, 3H, $C_3H_6CH_3$), 1.42 (sext, ^3J=7.4 Hz, 2H, $C_2H_4CH_2CH_3$), 1.70 (quin, ^3J=7.6 Hz, 2H, $CH_2CH_2C_2H_5$), 2.69 (t, ^3J=7.5 Hz, 2H, $CH_2C_3H_7$), 6.06 (s, 1H, 4-H), 7.22–7.25 (m, 1H, Ph 4-H), 7.41–7.43 (m, 2H, Ph 3,5-H), 7.61 (s, 1H, 3-H), 7.67–7.68 (m, 2H, Ph 2,4-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 13.8 ($C_3H_6CH_3$), 22.2 ($C_2H_4CH_2CH_3$), 28.7 ($CH_2C_3H_7$), 29.5 ($CH_2CH_2C_2H_5$), 96.7 (C-4), 113.0 (C-3a), 115.1 (C-3), 118.9 (Ph C-2,6), 125.8 (Ph C-4), 129.4 (Ph C-3,5), 141.2 (Ph C-1), 163.1 (C-5), 168.1 (C-6a). MS m/z (%): 263 ($[M+Na]^+$, 100). HRMS (ESI) for $C_{15}H_{16}N_2NaO$ ($[M+Na]^+$) calcd 263.1155, found 263.1152.

4.1.2.2.8. 5-Pentyl-2-phenyl-2*H*-furo[2,3-*c*]pyrazole (22)



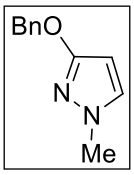
White solid, yield 104 mg, 82%, mp 77–78 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3068, 3048 (CH_{arom}), 2952, 2926 (CH_{aliph}), 1599, 1580, 1508, 1448, 1388 (C=C, C–N, C–O), 727, 686 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.94 (t, ^3J=7.1 Hz, 3H, $C_4H_8CH_3$), 1.37–1.42 (m, 4H, $C_2H_4C_2H_4CH_3$), 1.75 (quin, ^3J=7.4 Hz, 2H, $CH_2CH_2C_3H_7$), 2.71 (t, ^3J=7.4 Hz, 2H, $CH_2C_4H_9$), 6.09 (s, 1H, 4-H), 7.25–7.28 (m, 1H, Ph 4-H), 7.44–7.46 (m, 2H, Ph 3,5-H), 7.65 (s, 1H, 3-H), 7.70–7.71 (m, 2H, Ph 2,4-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 14.1 ($C_4H_9CH_3$), 22.5 ($C_3H_6CH_2CH_3$), 27.3 ($CH_2CH_2C_3H_7$), 29.1 ($CH_2C_4H_9$), 31.4 ($C_2H_4CH_2C_2H_5$), 96.8 (C-4), 113.1 (C-3a), 115.2 (C-3), 119.0 (Ph C-2,6), 125.9 (Ph C-4), 129.5 (Ph C-3,5), 141.3 (Ph C-1), 163.2 (C-5), 168.9 (C-6a). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −172.0 (N-2), −128.3 (N-1). MS m/z (%): 255 ([M+H]$^+$, 100). HRMS (ESI) for $C_{16}H_{18}N_2ONa$ ([M+Na]$^+$) calcd 277.1311, found 277.1311.

4.1.2.2.9. 5-Cyclopropyl-2-phenyl-2*H*-furo[2,3-*c*]pyrazole (23)



Brown solid, yield 101 mg, 90%, mp 98.5–100 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3149, 3135, 3089, 3027, 3007 (CH_{arom}), 2955, 2917, 2850 (CH_{aliph}), 1595, 1585, 1507, 1460, 1443, 1390, 1374, 1296, 1230, 1213, 1122, 1045, 1035, (C=C, C–N, C–O–C), 757, 689 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.94–0.97 (m, 4H, $CH(CH_2)_2$), 1.92–1.96 (m, 1H, $CH(CH_2)_2$), 6.06 (s, 1H, 4-H), 7.21–7.25 (m, 1H, Ph 4-H), 7.40–7.43 (m, 2H, Ph 3,5-H), 7.59 (s, 1H, 3-H), 7.65–7.66 (m, 2H, Ph 2,6-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 6.9 ($CH(CH_2)_2$), 9.9 ($CH(CH_2)_2$), 95.4 (C-4), 113.1 (C-3a), 114.9 (C-3), 118.8 (Ph C-2,6), 125.7 (Ph C-4), 129.4 (Ph C-3,5), 141.1 (Ph C-1), 163.7 (C-5), 168.3 (C-6a). MS m/z (%): 225 ([M+H]$^+$, 100). HRMS (ESI) for $C_{14}H_{13}N_2O$ ([M+H]$^+$) calcd 225.1022, found 225.1022.

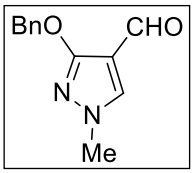
4.1.2.3. 3-(Benzyloxy)-1-methyl-1*H*-pyrazole (25)[103].



A solution of 3-hydroxy-1-methyl-1*H*-pyrazole (**23)** (710 mg, 7.2 mmol) in dry DMF (20 mL) was cooled to 0 ºC temperature under inert atmosphere, and NaH (60% dispersion in mineral oil, 290 mg, 7.2 mmol) was added portion wise. After stirring mixture for 15 min, benzyl chloride (0.82 mL, 7.2 mmol) was added drop wise. The mixture was stirred at 60 ºC temperature for 1 hour, then poured into water and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtrated, and the solvent was evaporated. The residue was purified by column chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:7, v/v) to give pure compound **25** as a brown liquid, yield 1205 mg, 90%. IR (ν_{max}, cm^{-1}): 3118, 3089, 3064, 3032, 3008 (CH_{arom}), 2931 (CH_{aliph}), 1537, 1491, 1429, 1360, 1223, 1052, 1018 (C=C, C–N, C–O–C), 731, 696, 658, 457 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 3.75 (s, 3H, CH_3), 5.20 (s, 2H, CH_2Ph), 5.66 (d, ^3J(4-H,5-H)=2.4 Hz, 1H, 4-H), 7.13 (d, ^3J(5-H,4-H)=2.4 Hz, 1H, 5-H), 7.30–7.33 (m, 1H, Ph 4-H), 7.36–7.39 (m, 2H, Ph 3,5-H), 7.45–7.48 (m, 2H, Ph 2,6-H). ^{13}C NMR

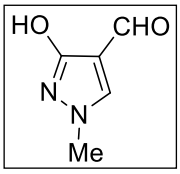
(176 MHz, $CDCl_3$): δ_C ppm 39.0 (CH_3), 70.9 (CH_2Ph), 90.5 (C-4), 127.8 (Ph C-2,6), 128.0 (Ph C-4), 128.5 (Ph C-3.5), 131.4 (C-5), 137.3 (Ph C-1), 163.3 (C-3). MS m/z (%): 189 ($[M+H]^+$, 100). HRMS (ESI) for $C_{11}H_{12}N_2ONa$ ($[M+Na]^+$) calcd 211.0842, found 211.0842.

4.1.2.4. 3-(Benzyloxy)-1-methyl-1*H*-pyrazole-4-carbaldehyde (27). Phosphorus oxychloride (1.59 mL, 17 mmol) was added dropwise to DMF (1.32 mL, 17 mmol) at –10 °C temperature. Then, pyrazole **25** (800 mg, 4.25 mmol) was added to the Vilsmeier-Haack complex, and the reaction mixture was heated at 70 °C temperature for 12 hours. After the neutralization with 10% aq $NaHCO_3$ solution, the precipitate was filtered off and recrystallized from DCM to give pure compound **27** as a white solid, yield 775 mg, 85%, mp 54–56 °C (ethyl acetate).



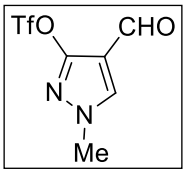
IR (ν_{max}, cm^{-1}): 3121, 3099, 3045 (CH_{arom}), 2992, 2947 (CH_{aliph}), 1666 (C=O), 1588, 1577, 1541, 1510, 1315, 1181 (C=C, C–N, C–O–C), 894, 883, 706 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 3.77 (s, 3H, CH_3), 5.32 (s, 2H, CH_2Ph), 7.32–7.36 (m, 1H, Ph 4-H), 7.36–7.40 (m, 2H, Ph 3,5-H), 7.46–7.47 (m, 2H, Ph 2,6-H), 7.69 (s, 1H, 5-H), 9.76 (s, 1H, CHO). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 39.8 (CH_3), 71.0 (CH_2Ph), 109.6 (C-4), 128.0 (Ph C-2,6), 128.3 (Ph C-4), 128.6 (Ph C-3.5), 133.4 (C-5), 136.4 (Ph C-1), 163.3 (C-3), 183.1 (CHO). MS m/z (%): 217 ($[M+H]^+$, 100). HRMS (ESI) for $C_{11}H_{12}N_2ONa$ ($[M+Na]^+$) calcd 239.0791, found 239.0791.

4.1.2.5. 3-(Benzyloxy)-1-methyl-1*H*-pyrazole-4-carbaldehyde (29).



Into the solution of pyrazole **27** (570 mg, 2.6 mmol) in toluene (10 mL), TFA (10 mL) was added. The mixture was stirred at room temperature for 48 hours. Toluene and TFA were evaporated. The residue was purified by column chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:1, v/v) to give pure compound **29** as a colorless solid, yield 295 mg, 90%, mp 201–202 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3291 (OH), 3099 (CH_{arom}), 2992, 2947 (CH_{aliph}), 1666 (C=O), 1541, 1510, 1315, 1181 (C=C, C–N). ^{1}H NMR (700 MHz, DMSO-d_6): δ_H ppm 3.67 (s, 3H, CH_3), 8.04 (s, 1H, 5-H), 9.60 (s, 1H, CHO), 10.90 (s, 1H, OH). ^{13}C NMR (176 MHz, DMSO-d_6): δ_C ppm 38.9 (CH_3), 108.4 (C-4), 134.0 (C-5), 161.9 (C-3), 182.6 (CHO). MS m/z (%): 127 ($[M+H]^+$, 100). HRMS (ESI) for $C_5H_6N_2O_2Na$ ($[M+Na]^+$) calcd 149.0322, found 149.0321.

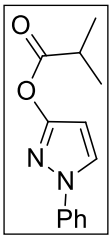
4.1.2.6. 4-Formyl-1-methyl-1*H*-pyrazol-3-yl trifluoromethanesulfonate (31). Pyrazole **29** (250 mg, 2 mmol), trifluormethansulfonic anhydride (1 mL, 6 mmol), and TEA (1 mL, 7.2 mmol) were dissolved in DCM (20 mL), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4; the solvent was evaporated. The residue was purified by column chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:4, v/v) to give pyrazole **31** as a brown solid, yield 435 mg, 85%, mp 54–55 °C (ethyl acetate).



IR (ν_{max}, cm^{-1}): 3091, 3043, 3017 (CH_{arom}), 2958, 2918 (CH_{aliph}), 1675 (C=O),

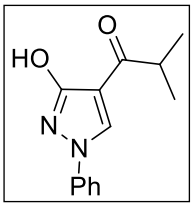
1552, 1429, 1205, 1135, 884, 875, 794, 744, 601, 511 (C–C, C–N, C–F). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 3.93 (s, 3H, CH_3), 7.87 (s, 1H, 5-H), 9.80 (s, 1H, CHO). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 40.7 (CH_3), 113.6 (C-4), 116.0, 117.8, 119.6, 121.5 (CF_3 ^{1}J=321.2 Hz), 134.7 (C-5), 151.2 (C-3), 181.0 (CHO). MS m/z (%): 259 ([M+H]$^+$, 100). HRMS (ESI) for $C_6H_5F_3N_2O_4SNa$ ([M+Na]$^+$) calcd 280.9814, found 280.9814.

4.1.2.7. 1-Phenyl-1*H*-pyrazol-3-yl 2-methylpropanoate (33).



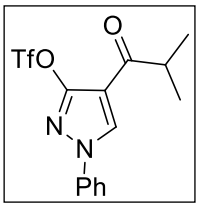
Into the solution of 3-hydroxy-1-phenyl-1*H*-pyrazole (**2**)[75] (470 mg, 2.9 mmol) in DCM (10 mL), pyridine (2.3 mL) and isobutyrylchloride (0.33 mL, 3.2 mmol) were added. The mixture was stirred at room temperature for 30 min, poured into water, and extracted with DCM. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtrated, and the solvent was evaporated. The residue was purified by column chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:4, v/v) to give pure compound **33** as a brown liquid, yield 601 mg, 90%. IR (ν_{max}, cm^{-1}): 3134, 3064, 3050 (CH_{arom}), 2977, 2938, 2912 (CH_{aliph}), 1761 (C=O), 1599, 1532, 1453, 1391, 1124, 1113, 1092 (C=C, C–N, C–O–C), 752, 688 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 1.36 (d, ^{3}J(CH(CH_3)$_2$,CH(CH$_3$)$_2$)=7.1 Hz, 6H, CH(CH_3)$_2$), 2.85–2.90 (m, 1H, CH(CH$_3$)$_2$), 6.41 (d, ^{3}J(4-H,5-H)=2.6 Hz, 1H, 4-H), 7.28–7.30 (m, 1H, Ph 4-H), 7.44–7.46 (m, 2H, Ph 3,5-H), 7.64–7.66 (m, 2H, Ph 2,6-H), 7.86 (d, ^{3}J(5-H,4-H)=2.6 Hz, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 18.8 (CH(*C*H$_3$)$_2$), 34.1 (*C*H(CH$_3$)$_2$), 98.8 (C-4), 118.7 (Ph C-2,6), 126.5 (C-5), 127.7 (Ph C-4), 129.4 (Ph C-3,5), 139.7 (Ph C-1), 156.8 (C-3), 174.2 (O-C=O). MS m/z (%): 231 ([M+H]$^+$, 100). HRMS (ESI) for $C_{13}H_{14}N_2O_2Na$ ([M+Na]$^+$) calcd 253.0947, found 253.0947.

4.1.2.8. 1-(3-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)-2-methylpropan-1-one



(35). Into the solution of $AlCl_3$ (2.453 g, 18.4 mmol) in CS_2 (8 mL), a solution of pyrazole **33** (350 mg, 1.5 mmol) in CS_2 (28 mL) was added drop wise at 0 °C temperature. The mixture was stirred at 55 °C temperature for 3 hours. After the neutralization with ice-cold water (33 mL) and 6N HCl (15 mL), the precipitate was filtered off and purified by column chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:4, v/v) to give pure compound **35** as a white solid, yield 310 mg, 89%, mp 97–98 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3309 (OH), 3122, 3068, 3052 (CH_{arom}), 2965, 2932 (CH_{aliph}), 1656 (C=O), 1559, 1530, 1508, 1459, 1319, 1233, 1217 (C=C, C–N), 747, 685, 671 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 1.07 (d, ^{3}J=6.9 Hz, 6H, CH(CH_3)$_2$), 3.33–3.36 (m, 1H, CH(CH$_3$)$_2$), 7.29–7.31 (m, 1H, Ph 4-H), 7.47–7.49 (m, 2H, Ph 3,5-H), 7.80–7.81 (m, 2H, Ph 2,6-H), 8.87 (s, 1H, 5-H), 11.12 (s, 1H, OH). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 18.7 (CH(*C*H$_3$)$_2$), 36.9 (*C*H(CH$_3$)$_2$), 109.4 (C-4), 118.1 (Ph C-2,6), 126.5 (Ph C-4), 129.6 (Ph C-3,5), 131.4 (C-5), 138.9 (Ph C-1), 161.4 (C-3), 198.6 (C=O). MS m/z (%): 231 ([M+H]$^+$, 100). HRMS (ESI) for $C_{13}H_{14}N_2O_2Na$ ([M+Na]$^+$) calcd 253.0947, found 253.0947.

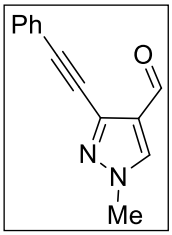
4.1.2.9. 4-(2-Methylpropanoyl)-1-phenyl-1*H*-pyrazol-3-yl trifluoromethanesulfonate (37). This compound was synthesized in analogy to compound **29** from pyrazole **35** (252 mg, 2 mmol). Pyrazole **37** was obtained as a white solid, yield 495 mg, 96%, mp 96–97 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3094, 3061 (CH_{arom}), 2980, 2937, 2918 (CH_{aliph}), 1555, 1452, 1427, 1231, 1213, 1201, 1138 (C=C, C–N, C–F), 973, 881, 760, 740, 607, 599, 505 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 1.23–1.24 (m, 6H, $CH(CH_3)_2$), 3.15–3.18 (m, 1H, $CH(CH_3)_2$), 7.39–7.41 (m, 1H, Ph 4-H), 7.49–7.51 (m, 2H, Ph 3,5-H), 7.66–7.67 (m, 2H, Ph 2,6-H), 8.35 (s, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 18.7 ($CH(CH_3)_2$), 38.8 ($CH(CH_3)_2$), 113.6 (C-4), 116.0, 117.8, 119.5 (Ph C-2,6), 119.6, 121.5 (CF_3 ^1J=322.1 Hz), 128.5 (Ph C-4), 129.9 (Ph C-3,5), 130.8 (C-5), 138.5 (Ph C-1), 151.9 (C-3), 196.6 (C=O). MS m/z (%): 363 ($[M+H]^+$, 100). HRMS (ESI) for $C_6H_5F_3N_2O_4SNa$ ($[M+Na]^+$) calcd 385.0440, found 385.0440.



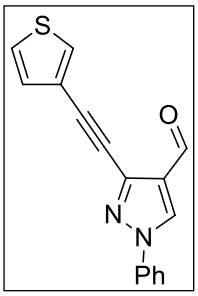
4.1.2.10. General procedure for the preparation of 4-alkynyl-1-phenyl-1*H*-pyrazole-4-carbaldehydes, ethanones, and propanones by Sonogashira cross-coupling reaction.

Into the solution of appropriate pyrazoles **30**, **31**, **36**, or **37** (0.5 mmol) in dry DMF (1 mL) under the argon atmosphere TEA (4.0 mL, 2.5 mmol), appropriate acetylene (0.75 mmol), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol), and CuI (18 mg, 0.1 mmol) were added. The mixture was stirred for the given time under argon atmosphere at 70 °C temperature, diluted with water, and the extraction was done with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by column chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:8, v/v) to yield compounds **38–55**.

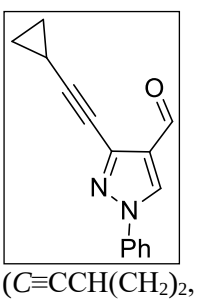
4.1.2.10.1. 1-Methyl-3-(phenylethynyl)-1*H*-pyrazole-4-carbaldehyde (38). The reaction mixture was stirred for 8 hours. Brown amorphous solid, 105 mg, yield 75%, mp 123–124 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3100, 3057, 3042 (CH_{arom}), 2954, 2925 (CH_{aliph}), 2221 (C≡C), 1681 (CHO), 1598, 1560, 1533, 1497, 1441, 1181 (C=C, C–N), 909, 880, 775, 755, 690 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 3.85 (s, 3H, CH_3), 7.24–7.27(m, 3H, Ph 3,4,5-H), 7.46–7.47 (m, 2H, Ph 2,6-H), 7.90 (s, 1H, 5-H), 9.88 (s, 1H, CHO). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 40.1 (CH_3), 79.0 (*C*≡CPh), 94.1 (C≡*C*Ph), 113.6 (C-3), 122.0 (Ph C-1), 125.0 (C-4), 128.6 (Ph C-2,6), 134.8 (C-5), 184.3 (CHO). MS m/z (%): 211 ($[M+H]^+$, 100). HRMS (ESI) for $C_{16}H_{10}N_2OSNa$ ($[M+Na]^+$) calcd 233.0685, found 233.0685.



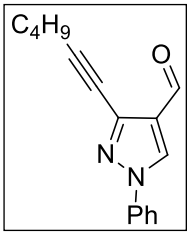
4.1.2.10.2. 1-Phenyl-3-[(thiophen-3-yl)ethynyl]-1*H*-pyrazole-4-carbaldehyde (40). The reaction mixture was stirred for 8 hours. White solid, yield 105 mg, 75%, mp 123–124 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3126, 3036 (CH_{arom}), 2229 (C≡C), 1676 (C=O), 1596, 1561, 1462, 1409, 1297, 1125 (C=C, C–N), 909, 873, 815, 621, 598, 512 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 7.28 (d, ^3J(4-H,5-H)=4.9 Hz, 1H, Th 4-H), 7.34 (dd, ^3J(5-H,4-H)=4.9 Hz, ^4J(5-H,2-H)=2.9 Hz, 1H, Th 5-H), 7.40–7.42 (m, 1H, Ph 4-H), 7.68 (d, ^4J(2-H,5-H)=2.9 Hz, 1H, Th 2-H), 7.50–7.52 (m, 2H, Ph 3,5-H), 7.74–7.76 (m, 2H, Ph 2,6-H), 8.44 (s, 1H, 5-H), 10.09 (s, 1H, CHO). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 78.6 (*C*≡CTh), 90.3 (C≡*C*Th), 120.0 (Ph C-2,6), 120.9 (Th C-3), 125.91 (C-4), 125.95 (Th C-5), 128.5 (Ph C-4), 128.7 (C-5), 129.9 (Ph C-3,5), 130.0 (Th C-4), 130.8 (Th C-2), 138.7 (C-3), 138.9 (Ph C-1), 182.7 (CHO). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −158.2 (N-1), −72.0 (N-2). MS m/z (%): 279 ($[M+H]^+$, 100). HRMS (ESI) for $C_{16}H_{10}N_2OSNa$ ($[M+Na]^+$) calcd 301.0406, found 301.0406.



4.1.2.10.3. 3-(Cyclopropylethynyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (41). The reaction mixture was stirred for 1 hour. White solid, yield 103 mg, 86%, mp 90–91 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3121, 3065, 3014 (CH_{arom}), 2881, 2782 (CH_{aliph}), 2232 (C≡C), 1677 (C=O), 1599, 1530, 1504, 1361, 1226 (C=C, C–N), 865, 849, 801, 757, 704, 685, 506 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.92–0.98 (m, 4H, CH(CH_2)$_2$), 1.52–1.57 (m, 1H, C*H*(CH_2)$_2$), 7.37–7.41 (m, 1H, Ph 4-H), 7.47–7.52 (m, 2H, Ph 3,5-H), 7.70–7.73 (m, 2H, Ph 2,6-H), 8.37 (s, 1H, 5-H), 9.97 (s, 1H, C*H*O). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 0.4 (CH(*C*H_2)$_2$), 9.1 (*C*H(CH_2)$_2$), 65.5 (*C*≡CCH(CH_2)$_2$, 100.2 (C≡*C*CH(CH_2)$_2$), 119.9 (Ph C-2,6), 125.9 (C-4), 128.3 (Ph C-4), 128.4 (C-5), 129.8 (Ph C-3,5), 138.9 (C-3), 139.3 (Ph C-1), 184.8 (*C*HO). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −157.6 (N-1), N-2 was not found. MS m/z (%): 237 ($[M+H]^+$, 100). HRMS (ESI) for $C_{15}H_{12}N_2ONa$ ($[M+Na]^+$) calcd 259.0842, found 259.0844.

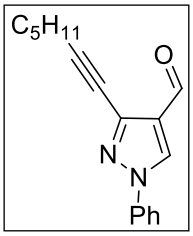


4.1.2.10.4. 3-(1-Hexyn-1-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (42). The reaction mixture was stirred for 2 hours. Brown liquid, yield 113 mg, 90%. IR (ν_{max}, cm^{-}): 3046 (CH_{arom}), 2961, 2935 (CH_{aliph}), 1678, 1529, 1507, 1228 (CHO, C=C, C–N), 758, 685 (CH=CH of monosubstituted benzene) cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.98 (t, ^3J=7.4 Hz, 3H, $C_3H_6CH_3$), 1.48–1.53 (m, 2H, $C_2H_4CH_2CH_3$), 1.63–1.69 (m, 2H, $CH_2CH_2C_2H_5$), 2.53 (t, ^3J=7.1 Hz, 2H, $CH_2C_3H_7$, 7.37–7.39 (m, 1H, Ph 4-H), 7.47–7.49 (m, 2H, Ph 3,5-H), 7.70–7.72 (m, 2H, Ph 2,6-H), 8.40 (s, 1H, 5-H), 10.01 (s, 1H, CHO). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 13.7 ($C_3H_6CH_3$), 19.3 ($CH_2C_3H_7$), 22.2 ($C_2H_4CH_2CH_3$), 30.4 ($CH_2CH_2C_2H_5$), 70.4 (*C*≡CC_4H_9), 97.2 (C≡*C*C_4H_9), 119.9 (Ph C-2,6), 125.7 (C-4), 128.28 (C-5), 128.34 (Ph C-4), 129.8 (Ph C-3,5), 138.8 (Ph C-1), 139.3 (C-3), 184.9 (CHO). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm –159.1 (N-1),



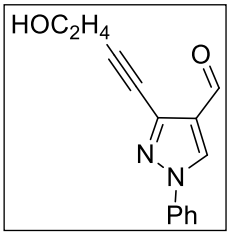
–71.8 (N-2). MS m/z (%): 253 ([M+H]$^+$, 100). HRMS (ESI) for $C_{16}H_{17}N_2O$ ([M+H]$^+$) calcd 253.1335, found 235.1337.

4.1.2.10.5. 3-(Hept-1-yn-1-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (43).



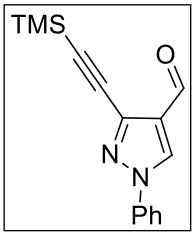
The reaction mixture was stirred for 4 hours. Brown liquid, yield 128 mg, 92%. IR (ν_{max}, cm^{-1}): 3124, 3053 (CH_{arom}), 2956, 2931, 2860 (CH_{aliph}), 2243 (C≡C), 1684 (C=O), 1599, 1531, 1504, 1464, 1398, 1296 (C=C, C–N), 956, 757, 689, 509 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.89-0.93 (m, 3H, $C_4H_8CH_3$), 1.34–1.39 (m, 2H, $C_3H_6CH_2CH_3$), 1.44–1.48 (m, 2H, $C_2H_4CH_2C_2H_5$), 1.65–1.69 (m, 2H, $CH_2CH_2C_3H_7$), 2.48–2.51 (m, 2H, $CH_2C_4H_9$), 7.36–7.39 (m, 1H, Ph 4-H), 7.46–7.49 (m, 2H, Ph 3,5-H), 7.69–7.72 (m, 2H, Ph 2,6-H), 8.38 (s, 1H, 5-H), 9.99 (s, 1H, CHO). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 14.0 ($C_4H_8CH_3$), 19.5 ($CH_2C_4H_9$), 22.2 ($C_3H_6CH_2CH_3$), 28.0 ($CH_2CH_2C_3H_7$), 31.1 ($C_2H_4CH_2C_2H_5$), 70.3 ($C{\equiv}CC_5H_{11}$), 97.2 ($C{\equiv}CC_5H_{11}$), 119.8 (Ph C-2,6), 125.7 (C-4), 128.2 (Ph C-4), 128.3 (C-5), 129.7 (Ph C-3,5), 138.8 (Ph C-1), 139.3 (C-3), 184.8 (CHO). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm –158.6 (N-1), –72.4 (N-2). MS m/z (%): 267 ([M+H]$^+$, 100). HRMS (ESI) for $C_{17}H_{18}N_2ONa$ ([M+Na]$^+$) calcd 289.1306, found 289.1311.

4.1.2.10.6. 3-(4-Hydroxybut-1-yn-1-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (44). The reaction mixture was stirred for 4 hours. White solid, 108 mg, yield



90%, mp 111–112 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3454 (OH), 3126, 3065 (CH_{arom}), 2929 (CH_{aliph}), 2240 (C≡C), 1679 (C=O), 1598, 1531, 1504, 1462, 1402, 1362, 1315, 1226, 1051 (C=C, C–N), 866, 812, 796, 755, 685 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 2.74–2.76 (m, 2H, CH_2CH_2OH), 3.87–3.88 (m, 2H, CH_2CH_2OH), 7.35–7.37 (m, 1H, Ph 4-H), 7.44–7.47 (m, 2H, Ph 3,5-H), 7.66–7.68 (m, 2H, Ph 2,6-H), 8.37 (s, 1H, 5-H), 9.95 (CHO). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 24.1(CH_2CH_2OH), 60.8 (CH_2CH_2OH), 72.4 ($C{\equiv}CC_2H_4OH$), 94.0 ($C{\equiv}CC_2H_4OH$), 119.8 (NPh C-2,6), 125.8 (C-4), 128.4 (Ph C-4), 129.5 (Ph C-3,5), 129.8 (C-5), 138.1 (C-3), 138.7 (Ph C-1), 184.8 (CHO). MS m/z (%): 241 ([M+H]$^+$, 100), 263 ([M+Na]$^+$, 30). HRMS (ESI) for $C_{14}H_{12}N_2ONa$ ([M+Na]$^+$) calcd 263.0792, found 263.0791.

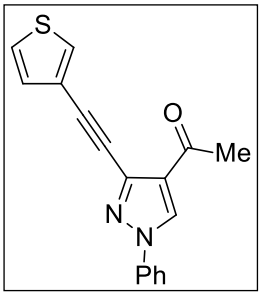
4.1.2.10.7. 1-Phenyl-3-[(trimethylsilyl)ethynyl]-1*H*-pyrazole-4-carbaldehyde (45). The reaction mixture was stirred for 10 hours. White solid, yield 105 mg,



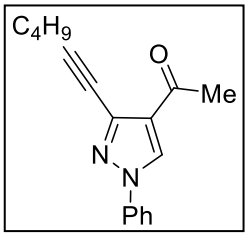
78%, mp 97–98 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3128, 3067 (CH_{arom}), 2960, 2854 (CH_{aliph}), 2167 (C≡C), 1678 (C=O), 1598, 1531, 1503, 1363, 1251, 1223 (C=C, C–N), 956, 838, 751, 726, 683 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.30 (s, 9H, TMS), 7.37–7.41 (m, 1H, Ph 4-H), 7.47–7.51 (m, 2H, Ph 3,5-H), 7.70–7.72 (m, 2H, Ph 2,6-H), 8.39 (s, 1H, 5-H), 10.01 (s, 1H, CHO). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 0.2 (TMS), 93.6 (C≡CTMS), 102.0 ($C{\equiv}$CTMS), 120.1 (Ph C-

2,6), 126.2 (C-4), 128.3 (C-5), 128.5 (Ph C-4), 129.9 (Ph C-3,5), 138.7 (C-3), 138.8 (Ph C-1), 184.7 (CHO). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm –157 (N-1), N-2 was not found. MS m/z (%): 269 ($[M+H]^+$, 100). HRMS (ESI) for $C_{15}H_{16}N_2OSiNa$ ($[M+Na]^+$) calcd 291.0924, found 291.0928.

4.1.2.10.8. 1-{1-Phenyl-3-[(thiophen-3-yl)ethynyl]-1*H*-pyrazol-4-yl}ethan-1-one (47). The reaction mixture was stirred for 8 hours. White solid, yield 97 mg, 66%, mp 116–117 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3117, 3054, 3022 (CH_{arom}), 2996, 2955, 2917 (CH_{aliph}), 2232 (C≡C), 1655 (C=O), 1597, 1514, 1508, 1351, 1264, 1232, 1058 (C=C, C–N), 872, 774, 761, 708, 691, 680, 620, 503 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 2.73 (s, 3H, CH_3), 7.28 (d, ^3J(4-H,5-H)=5.2 Hz, 1H, Th 4-H), 7.35–7.37 (m, 1H, Th 5-H), 7.39–7.42 (m, 1H, Ph 4-H), 7.50–7.52 (m, 2H, Ph 3,5-H), 7.68 (d, ^4J(2-H,5-H)=2.9 Hz, 1H, Th 2-H), 7.75–7.77 (m, 2H, Ph 2,6-H), 8.47 (s, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 29.1 (CH_3), 80.8 (*C*≡CTh), 90.1 (C≡*C*Th), 119.7 (Ph C-2,6), 121.1 (Th C-3), 125.8 (Th C-5), 126.9 (C-4), 128.1 (Ph C-4), 129.7 (Th C-4), 129.7 (Ph C-3,5), 129.9 (C-5), 130.2 (Th C-2), 136.2 (C-3), 138.8 (Ph C-1), 192.2 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −160.4 (N-1), −72.5 (N-2). MS m/z (%): 293 ($[M+H]^+$, 100). HRMS (ESI) for $C_{17}H_{12}N_2OSiNa$ ($[M+Na]^+$) calcd 315.0563, found 315.0561.



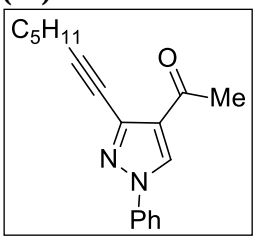
4.1.2.10.9. 1-[3-(Cyclopropylethynyl)-1-phenyl-1*H*-pyrazol-4-yl]ethan-1-one (48). The reaction mixture was stirred for 1 hour. White solid, yield 100 mg, 80%, mp 127–128 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3129, 3078 (CH_{arom}), 2993, 2956, 2923 (CH_{aliph}), 2233 (C≡C), 1670 (C=O), 1599, 1521, 1448, 1362, 1260, 1241, 1221 (C=C, C–N), 977, 940, 863, 751, 705, 683 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.90–0.96 (m, 4H, $CH(CH_2)_2$), 1.53–1.57 (m, 1H, $CH(CH_2)_2$), 2.62 (s, 3H, CH_3), 7.34–7.36 (m, 1H, Ph 4-H), 7.45–7.47 (m, 2H, Ph 3,5-H), 7.69 (m, 2H, Ph 2,6-H), 8.38 (s, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 0.4 ($CH(CH_2)_2$), 8.8 ($CH(CH_2)_2$), 29.1 (CH_3), 67.8 (*C*≡C$CH(CH_2)_2$), 99.9 (C≡*C*$CH(CH_2)_2$), 119.8 (Ph C-2,6), 126.9 (C-4), 128.0 (Ph C-4), 129.7 (C-5), 129.8 (Ph C-3,5), 136.7 (C-3), 139.0 (Ph C-1), 192.6 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm –160.2 (N-1), N-2 was not found. MS m/z (%): 251 ($[M+H]^+$, 100). HRMS (ESI) for $C_{16}H_{14}N_2ONa$ ($[M+Na]^+$) calcd 273.0998, found 273.0998.



4.1.2.10.10. 1-[3-(Hex-1-yn-1-yl)-1-phenyl-1*H*-pyrazol-4-yl]ethan-1-one (49). The reaction mixture was stirred for 1 hour. White solid, yield 100 mg, 80%, mp 127–128 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3129, 3078 (CH_{arom}), 2993, 2956, 2923 (CH_{aliph}), 2233 (C≡C), 1670 (C=O), 1599, 1521, 1448, 1362, 1260, 1241, 1221 (C=C, C–N), 977, 940, 863, 751, 705, 683 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.94 (t,

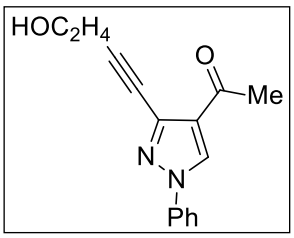
^3J=7.4 Hz, 3H, $C_3H_6CH_3$), 1.48–1.51 (m, 2H, $C_2H_4CH_2CH_3$), 1.62–1.66 (m, 2H, $CH_2CH_2C_2H_5$), 2.49–2.51 (m, 2H, $CH_2C_3H_7$), 2.51 (s, 1H, CH_3), 7.32–7.34 (m, 1H, Ph 4-H), 7.43–7.46 (m, 2H, Ph 3,5-H), 7.69–7.70 (m, 2H, Ph 2,6-H), 8.38 (s, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 13.7 ($C_3H_6CH_3$), 19.4 ($CH_2C_3H_7$), 22.2 ($C_2H_4CH_2CH_3$), 29.0 (CH_3), 30.3 ($CH_2CH_2C_2H_5$), 72.7 (C≡CC_4H_9), 96.9 (C≡CC_4H_9), 119.7 (Ph C-2,6), 126.7 (C-4), 128.0 (Ph C-4), 129.7 (C-5), 129.8 (Ph C-3,5), 136.7 (C-3), 138.9 (Ph C-1), 192.5 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm –160.1 (N-1), –70.8 (N-2). MS m/z (%): 267 ([M+H]$^+$, 100). HRMS (ESI) for $C_{17}H_{18}N_2ONa$ ([M+Na]$^+$) calcd 289.1311, found 289.1312.

4.1.2.10.11. 1-[3-(Hept-1-yn-1-yl)-1-phenyl-1*H*-pyrazol-4-yl]ethan-1-one (50). The reaction mixture was stirred for 4 hours. Brown liquid, yield 91 mg, 65%.



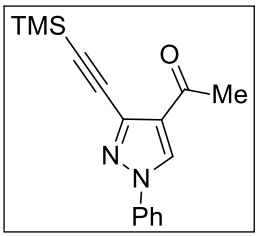
IR (ν_{max}, cm^{-1}): 3130, 3064 (CH_{arom}), 2957, 2928, 2860 (CH_{aliph}), 2240 (C≡C), 1666 (C=O), 1522, 1457, 1362, 1262, 1245, 1217 (C=C, C–N), 751, 706, 685 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.91 (t, ^3J=7.3 Hz, 3H, $C_4H_8CH_3$), 1.33–1.38 (m, 2H, $C_3H_6CH_2CH_3$), 1.43–1.47 (m, 2H, $C_2H_4CH_2C_2H_5$), 1.64–1.69 (m, 2H, $CH_2CH_2C_3H_7$), 2.50 (t, ^3J=7.2 Hz, 2H, $CH_2C_4H_9$), 2.63 (CH_3), 7.31–7.36 (m, 1H, Ph 4-H), 7.44–7.46 (m, 2H, Ph 3,5-H), 7.69–7.70 (m, 2H, Ph 2,6-H), 8.39 (s, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 14.0 ($C_4H_8CH_3$), 19.7 ($CH_2C_4H_9$), 22.3 ($C_3H_6CH_2CH_3$), 28.0 ($CH_2CH_2C_3H_7$), 29.0 (CH_3), 31.3 ($C_2H_4CH_2C_2H_5$), 72.7 (C≡CC_5H_{11}), 97.0 (C≡CC_5H_{11}), 119.7 (Ph C-2,6), 126.7 (C-4), 128.0 (Ph C-4), 128.6 (C-5), 129.7 (Ph C-3,5), 136.7 (C-3), 138.9 (Ph C-1), 192.5 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm –161.8 (N-1), N-2 was not found. MS m/z (%): 281 ([M+H]$^+$, 100). HRMS (ESI) for $C_{18}H_{20}N_2ONa$ ([M+Na]$^+$) calcd 303.1468, found 303.1468.

4.1.2.10.12. 1-[3-(4-Hydroxybut-1-yn-1-yl)-1-phenyl-1*H*-pyrazol-4-yl]ethan-1-one (51). The reaction mixture was stirred for 4 hours. White solid, yield

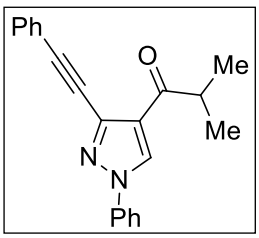


109 mg, 86%, mp 121-122 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3130, 3068, 3026 (CH_{arom}), 2995, 2961, 2945 (CH_{aliph}), 2240 (C≡C), 1666 (C=O), 1521, 1460, 1350, 1262, 1249, 1217 (C=C, C–N), 755, 731, 685, 577, 468 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 2.59 (CH_3), 2.75–2.77 (m, 2H, CH_2CH_2OH), 3.89–3.91 (m, 2H, CH_2CH_2OH), 7.36–7.38 (m, 1H, Ph 4-H), 7.47–7.49 (m, 2H, Ph 3,5-H), 7.69–7.71 (m, 2H, Ph 2,6-H), 8.36 (s, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 24.3(CH_2CH_2OH), 28.8(CH_3), 60.8 (CH_2CH_2OH), 74.7 (C≡CC_2H_4OH), 93.7 (C≡CC_2H_4OH), 119.7 (NPh C-2,6), 126.4 (C-4), 128.2 (Ph C-4), 129.8 (Ph C-3,5), 130.1 (C-5), 136.3 (C-3), 138.9 (Ph C-1), 192.0 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm –160.4 (N-1), –70.5 (N-2). MS m/z (%): 255 ([M+H]$^+$, 100). HRMS (ESI) for $C_{15}H_{14}N_2ONa$ ([M+Na]$^+$) calcd 277.0947, found 277.0947.

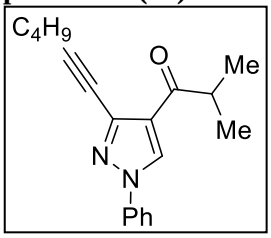
4.1.2.10.13. 1-{1-Phenyl-3-[(trimethylsilyl)ethynyl]-1*H*-pyrazol-4-yl}ethan-1-one (52). The reaction mixture was stirred for 12 hours. White solid, yield 117 mg, 83%, mp 89-90 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3129, 3065 (CH_{arom}), 2959, 2899 (CH_{aliph}), 2167 (C≡C), 1666 (C=O), 1523, 1507, 1442, 1363, 1261, 1206 (C=C, C–N), 858, 847, 755, 690 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.30 (s, 9H, TMS), 2.66 (s, 3H, CH_3), 7.36–7.38 (m, 1H, Ph 4-H), 7.46–7.48 (m, 2H, Ph 3,5-H), 7.70–7.71 (m, 2H, Ph 2,6-H), 8.40 (s, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 0.3 (TMS), 29.1 (CH_3), 96.3 (*C*≡CTMS), 101.9 (C≡*C*TMS), 119.9 (Ph C-2,6), 127.5 (C-4), 128.2 (C-5), 129.8 (Ph C-4), 129.9 (Ph C-3,5), 135.9 (C-3), 138.9 (Ph C-1), 192.5 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm –158.7 (N-1), N-2 was not found. MS m/z (%): 283 ([M+H]$^+$, 100). HRMS (ESI) for $C_{16}H_{18}N_2OSiNa$ ([M+Na]$^+$) calcd 305.1081, found 305.1081.



4.1.2.10.14. 2-Methyl-1-[1-phenyl-3-(phenylethynyl)-1*H*-pyrazol-4-yl]propan-1-one (53). The reaction mixture was stirred for 1 hour. White solid, yield 141 mg, 90%, mp 105–106 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3121, 3061 (CH_{arom}), 2968, 2869 (CH_{aliph}), 2265 (C≡C), 1664 (C=O), 1521, 1443, 1350, 1227 (C=C, C–N), 989, 875, 751, 685 (CH=CH of monosubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 1.29 (d, ^3J=6.9 Hz, 6H, $CH(CH_3)_2$), 3.72–3.76 (m, 1H, $CH(CH_3)_2$), 7.37–7.40 (m, 4H, NPh 4-H, CPh 3,4,5-H), 7.48–7.50 (m, 2H, NPh 3,5-H), 7.61–7.62 (m, 2H, CPh 2,6-H), 7.75–7.76 (m, 2H, NPh 2,6-H), 8.47 (s, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 18.9 ($CH(CH_3)_2$), 38.0 ($CH(CH_3)_2$), 81.3 (*C*≡CPh), 94.0 (C≡*C*Ph), 119.9 (NPh C-2,6), 122.2 (CPh C-1), 125.8 (C-4), 128.1 (NPh C-4), 128.6 (CPh C-3,5), 129.3 (CPh C-4), 129.8 (NPh C-3,5), 130.6 (C-5), 131.9 (CPh C-2,6), 135.7 (C-3), 139.0 (NPh C-1), 198.9 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm –158.6 (N-1), N-2 was not found. MS m/z (%): 315 ([M+H]$^+$, 100). HRMS (ESI) for $C_{21}H_{18}N_2ONa$ ([M+Na]$^+$) calcd 337.1311, found 337.1311.

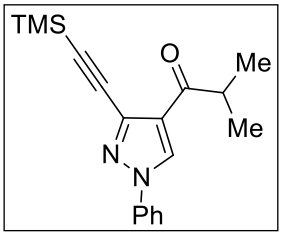


4.1.2.10.15. 1-[3-(Hex-1-yn-1-yl)-1-phenyl-1*H*-pyrazol-4-yl]-2-methylpropan-1-one (54). The reaction mixture was stirred for 1 hour. Colorless liquid, yield 119 mg, 81%. IR (ν_{max}, cm^{-1}): 3122, 3056 (CH_{arom}), 2961, 2929, 2871, 2855 (CH_{aliph}), 2237 (C≡C), 1665 (C=O), 1519, 1436, 1352, 1228 (C=C, C–N), 959, 879, 857, 756, 686 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.93–0.95 (m, 3H, $C_3H_6CH_3$), 1.22 (d, ^3J=7.0 Hz, 6H, $CH(CH_3)_2$), 1.47–1.52 (m, 2H, $C_2H_4CH_2CH_3$), 1.62–1.66 (m, 2H, $CH_2CH_2C_2H_5$), 2.49–2.51 (m, 2H, $CH_2C_3H_7$), 3.64–3.70 (m, 1H, $CH(CH_3)_2$), 7.31–7.36 (m, 1H, NPh 4-H), 7.44–7.48 (m, 2H, NPh 3,5-H), 7.68–7.72 (m, 2H, NPh 2,6-H), 8.41 (s, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 13.7 ($C_3H_6CH_3$), 18.8 ($CH(CH_3)_2$), 19.4 ($CH_2C_3H_7$) 22.2 ($C_2H_4CH_2CH_3$), 30.4 ($CH_2CH_2C_2H_5$), 37.6 ($CH(CH_3)_2$), 72.6 (*C*≡CC_4H_9), 96.0



(C≡*C*C_4H_9), 119.7 (NPh C-2,6), 125.3 (C-4), 127.9 (NPh C-4), 129.6 (NPh C-3,5), 130.3 (C-5), 136.1 (C-3), 139.0 (NPh C-1), 199.2 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm –160.5 (N-1), –72.2 (N-2). MS m/z (%): 295 ([M+H]$^+$, 100). HRMS (ESI) for $C_{19}H_{24}N_2O_2Na$ ([M+Na+H_2O]$^+$) calcd 335.1730, found 335.1723.

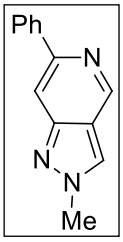
4.1.2.10.16. 2-Methyl-1-{1-phenyl-3-[(trimethylsilyl)ethynyl]-1*H*-pyrazol-4-yl}propan-1-one (55). The reaction mixture was stirred for 12 hours. White solid, yield 135 mg, 87%, mp 91–92 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3124, 3060 (CH_{arom}), 2987, 2971, 2933, 2903 (CH_{aliph}), 2166 (C≡C), 1665 (C=O), 1518, 1435, 1354, 1247, 1226 (C=C, C–N), 873, 848, 757, 705 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.30 (s, 9H, TMS), 1.20–1.26 (m, 6H, CH(CH_3)$_2$), 3.72–3.76 (m, 1H, C*H*(CH_3)$_2$), 7.36–7.39 (m, 1H, Ph 4-H), 7.45–7.49 (m, 2H, Ph 3,5-H), 7.71–7.72 (m, 2H, Ph 2,6-H), 8.42 (s, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 0.3 (TMS), 18.7 (CH(*C*H_3)$_2$), 37.7 (*C*H(CH_3)$_2$), 96.1 (*C*≡CC_4H_9), 100.9 (C≡*C*C_4H_9), 119.9 (Ph C-2,6), 126.2 (C-4), 128.2 (Ph C-4), 129.7 (Ph C-3,5), 130.5 (C-5), 135.3 (C-3), 139.0 (Ph C-1), 199.2 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm –158.9 (N-1), N-2 was not found. MS m/z (%): 311 ([M+H]$^+$, 100). HRMS (ESI) for $C_{18}H_{22}N_2ONa$ ([M+Na]$^+$) calcd 333.1394, found 333.1394.4.



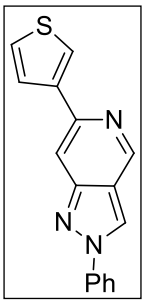
4.1.2.11. General procedure for the cyclization of 3-ethynyl-1-phenyl-1*H*-pyrazole-4-carbaldehydes (38–45), ethanones (46–52), and propanones (53–55).

A solution of compound **38–55** (0.5 mmol) in dry ammonia and methanol (NH_3/MeOH 2 M, 8 mL) was heated at 120 °C temperature for 15 hours in a steel reactor. The solvent was evaporated, and the crude was purified by column chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:4, v/v) to yield compounds **56–73**.

4.1.2.11.1. 2-Methyl-6-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (56). White solid, yield 83 mg, 79%, mp 159–160 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3106, 3062, 3030 (CH_{arom}), 2997, 2943 (CH_{aliph}), 1615, 1471, 1367, 1240, 1153 (C=C, C–N), 926, 858, 831, 755, 688, 677 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 4.27 (s, 3H, CH_3), 7.38–7.40 (m, 1H, Ph 4-H), 7.47–7.50 (m, 2H, Ph 3,5-H), 7.93 (s, 1H, 7-H), 8.05–8.09 (m, 2H, Ph 2,6-H), 8.08 (s, 1H, 3-H), 9.28 (s, 1H, 4-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 40.9 (CH_3), 107.0 (C-7), 119.4 (C-3a), 125.1 (C-3), 127.2 (Ph C-2,6), 128.4 (Ph C-4), 128.8 (Ph C-3,5), 140.3 (Ph C-1), 146.3 (C-4), 151.1 (C-6), 151.6 (C-7a). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm –160.6 (N-2), –97.6 (N-1), –87.7 (N-5). MS m/z (%): 210 ([M+H]$^+$, 100). HRMS (ESI) for $C_{13}H_{12}N_3$ ([M+H]$^+$) calcd 210.1027, found 210.1026.

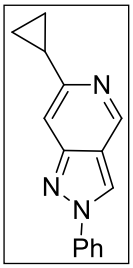


4.1.2.11.2. 2-Phenyl-6-(thiophen-3-yl)-2*H*-pyrazolo[4,3-*c*]pyridine (58).



White solid, yield 130 mg, 94%, mp 129–130 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3132, 3113, 3064, 3041 (CH_{arom}), 1506, 1362, 1254, 1202, 1039 (C=C, C–N), 862, 803, 760, 750, 687 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 7.42–7.43 (m, 1H, Th 4-H), 7.47–7.49 (m, 1H, Ph 4-H), 7.56–7.59 (m, 2H, Ph 3,5-H), 7.70–7.71 m, 1H, Th 5-H), 7.91 (s, 1H, 7-H), 7.92–7.94 (m, 2H, Ph 2,6-H), 8.00–8.01 (m, 1H, Th 2-H), 8.58 (d, ^4J(3-H,4-H)=0.8 Hz, 1H, 3-H), 9.28 (d, ^4J(4-H,3-H)=1.2 Hz 1H, 4-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 106.4 (C-7), 119.8 (C-3a), 121.4 (Ph C-2,6), 122.1 (C-3), 123.3 (Th C-2), 126.2 (Th C-5), 126.4 (Th C-4), 129.0 (Ph C-4), 130.0 (Ph C-3,5), 140.1 (Ph C-1), 142.7 (Th C-3), 147.4 (C-4), 147.6 (C-6), 151.7 (C-7a). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −145.1 (N-2), −99.7 (N-1). MS m/z (%): 278 ($[M+H]^+$, 100). HRMS (ESI) for $C_{16}H_{12}N_3S$ ($[M+H]^+$) calcd 278.0746, found 278.0747.

4.1.2.11.3. 6-Cyclopropyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (59). White solid, yield 115 mg, 98%, mp 143–144 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3116, 3090, 3036, 3006 (CH_{arom}), 2923, 2850 (CH_{aliph}), 1597, 1497, 1377, 1318, 1201, 1053, 1038 (C=C, C–N), 769, 761, 691 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.99–1.01 (m, 2H, $CH_2CHC\mathit{H}_2$), 1.05–1.07 (m, 2H, $C\mathit{H}_2CHCH_2$), 2.14–2.18 (m, 2H, $CH_2C\mathit{H}CH_2$), 7.40 (s, 1H, 7-H), 7.42–7.45 (m, 1H, Ph 4-H), 7.52–7.54 (m, 2H, Ph 3,5-H), 7.87–7.89 (m, 2H, Ph 2,6-H), 8.52 (s, 1H, 3-H), 9.12 (s, 1H, 4-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 8.9 ($\mathit{C}H_2CH\mathit{C}H_2$), 17.5 ($CH_2\mathit{C}HCH_2$), 106.6 (C-7), 119.3 (C-3a), 121.4 (Ph C-2,6), 122.0 (C-3), 128.8 (Ph C-4), 129.8 (Ph C-3,5), 140.1 (Ph C-1), 146.9 (C-4), 151.6 (C-7a), 155.7 (C-6). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −145.3 (N-2), −91.0 (N-5), N-1 was not found. MS m/z (%): 236 ($[M+H]^+$, 100). HRMS (ESI) for $C_{15}H_{14}N_3$ ($[M+H]^+$) calcd 236.1182, found 236.1184.



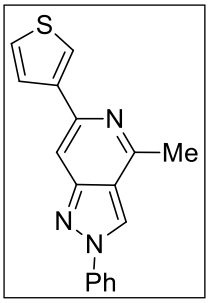
4.1.2.11.4. 6-Butyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (60). Brown amorphous solid, yield 105 mg, 84%. IR (ν_{max}, cm^{-1}): 3138, 3013 (CH_{arom}), 2949, 2930, 2867 (CH_{aliph}), 1507, 1468, 1372, 1320, 1208, 1053, 1037 (C=C, C–N), 763, 751, 689 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.95–0.97 (m, 3H, $C_3H_6C\mathit{H}_3$), 1.40–1.45 (m, 2H, $C_2H_4C\mathit{H}_2CH_3$), 1.76–1.80 (m, 2H, $CH_2C\mathit{H}_2C_2H_5$), 2.88–2.90 (m, 2H, $C\mathit{H}_2C_3H_7$), 7.40 (s, 1H, 7-H), 7.43–7.45 (m, 1H, Ph 4-H), 7.53–7.55 (m, 2H, Ph 3,5-H), 7.88–7.89 (m, 2H, Ph 2,6-H), 8.52 (s, 1H, 3-H), 9.18 (s, 1H, 4-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 14.1 ($C_3H_6\mathit{C}H_3$), 22.6 ($C_2H_4\mathit{C}H_2CH_3$), 32.0 ($CH_2\mathit{C}H_2C_2H_5$), 38.3 ($\mathit{C}H_2C_3H_7$), 108.3 (C-7), 119.2 (C-3a), 121.4 (Ph C-2,6), 121.8 (C-3), 128.8 (Ph C-4), 129.9 (Ph C-3,5), 140.2 (Ph C-1), 147.0 (C-4), 151.7 (C-7a), 155.7 (C-6). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −145.5 (N-2), −78.9 (N-5), N-1 was not found. MS m/z (%): 252 ($[M+H]^+$, 100). HRMS (ESI) for $C_{16}H_{18}N_3$ ($[M+H]^+$) calcd 252.1495, found 252.1497.

4.1.2.11.5. 6-Pentyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (61). Brown amorphous solid, yield 118 mg, 89%. IR (ν_{max}, cm^{-1}): 3122, 3063, 3040 (CH_{arom}), 2949, 2925, 2856 (CH_{aliph}), 1466, 1324, 1206, 1037 (C=C, C–N), 862, 759, 750, 684 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.89–0.90 (m, 2H, $C_4H_8CH_3$), 1.37–1.39 (m, 4H, $C_2H_4(CH_2)_2CH_3$), 1.78–1.81 (m, 2H, $CH_2CH_2C_3H_7$), 2.86–2.89 (m, 2H, $CH_2C_4H_9$), 7.40 (s, 1H, 7-H), 7.43–7.44 (m, 1H, Ph 4-H), 7.52–7.55 (m, 2H, Ph 3,5-H), 7.88–7.89 (m, 2H, Ph 2,6-H), 8.52 (s, 1H, 3-H), 9.18 (s, 1H, 4-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 14.2 ($C_4H_8CH_3$), 22.7 ($C_3H_6CH_2CH_3$), 29.6 ($CH_2CH_2C_3H_7$), 31.7 ($C_2H_4CH_2C_2H_5$), 38.6 ($CH_2C_4H_{11}$), 108.3 (C-7), 119.1 (C-3a), 121.4 (Ph C-2,6), 121.8 (C-3), 128.8 (Ph C-4), 129.8 (Ph C-3,5), 140.2 (Ph C-1), 146.9 (C-6), 151.7 (C-4), 155.8 (C-7a). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −145.3 (N-2), −79.8 (N-5), N-1 was not found. MS m/z (%): 266 ($[M+H]^+$, 100). HRMS (ESI) for $C_{17}H_{20}N_3$ ($[M+H]^+$) calcd 266.1652, found 266.1652.

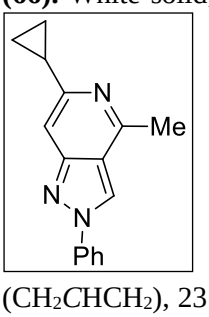
4.1.2.11.6. 2-(2-Phenyl-2*H*-pyrazolo[4,3-*c*]pyridin-6-yl)ethan-1-ol (62). Brown solid, yield 86%, 103 mg, mp 215–216 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3187 (OH), 3108, 3067, 3022 (CH_{arom}), 2961, 2935, 2916 (CH_{aliph}), 1503, 1325, 1227, 1213, 1056 (C=C, C–N), 765, 752, 677 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 3.11–3.12 (m, 2H, CH_2CH_2OH), 4.05–4.06 (m, 2H, CH_2CH_2OH), 7.45–7.48 (m, 2H, H-7, Ph 4-H), 7.55–7.58 (m, 2H, Ph 3,5-H), 7.89–7.90 (m, 2H, Ph 2,6-H), 8.58 (s, 1H, 3-H), 9.16 (s, 1H, 4-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 39.6 (CH_2CH_2OH), 62.7 (CH_2CH_2OH), 109.5 (C-7), 119.4 (C-3a), 121.5 (Ph C-2,6), 122.3 (C-3), 129.1 (Ph C-4), 129.9 (Ph C-3,5), 140.0 (Ph C-1), 151.3 (C-4), 153.6 (C-7a). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −144.3 (N-2), −100.5 (N-1), −88.3 (N-5). MS m/z (%): 240 ($[M+H]^+$, 100). HRMS (ESI) for $C_{14}H_{14}N_3O$ ($[M+H]^+$) calcd 240.1131, found 240.1131.

4.1.2.11.7. 2-Phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (63). White solid, yield 193 mg, 95%, mp 132 °C (ethyl acetate),(lit mp 132–133 °C[10]). IR (ν_{max}, cm^{-1}): 3129, 3094, 3064 (CH_{arom}), 1614, 1490, 1466, 1365, 1349, 1315, 1210, 1178 (C=C, C–N), 916, 827, 760, 750, 684, 587, 508, 431 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_N ppm 7.45–7.48 (m, 1H, Ph 4-H), 7.54–7.56 (m, 2H, Ph 3,5-H), 7.62–7.64 (m, 1H, 7-H), 7.90–7.91 (m, 2H, Ph 2,6-H), 8.31–8.32 (m, 1H, 6-H), 8.63 (s, 1H, 3-H), 9.27 (s, 1H, 4-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 111.8 (C-7), 120.5 (C-3a), 121.6 (Ph C-2,6), 122.4 (C-3), 129.1 (Ph C-4), 129.9 (Ph C-3,5), 140.0 (Ph C-1), 142.1 (C-6), 147.5 (C-4), 150.4 (C-7a). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −147.4 (N-2), –99.6 (N-1), –89.8 (N-5). MS m/z (%): 196 ($[M+H]^+$, 100). HRMS (ESI) for $C_{12}H_{10}N_3$ ($[M+H]^+$) calcd 196.0869, found 196.0869.

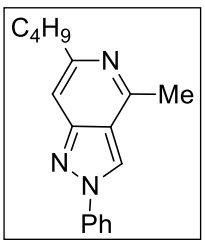
4.1.2.11.8. 4-Methyl-2-phenyl-6-(thiophen-3-yl)-2*H*-pyrazolo[4,3-*c*]pyridine (65). White solid, yield 118 mg, 81%, mp 92–93 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3129, 3104, 3072 (CH_{arom}), 2982, 2948, 2911 (CH_{aliph}), 1546, 1507, 1374, 1202, 1045 (C=C, C–N), 849, 796, 763, 744, 690 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 2.86 (s, 3H, CH_3), 7.39–7.40 (m, 1H, Th 4-H), 7.43–7.45 (m, 1H, Ph 4-H), 7.53–7.55 (m, 2H, Ph 3,5-H), 7.67–7.68 (m, 1H, Th 5-H), 7.72 (s, 1H, 7-H), 7.90–7.91 (m, 2H, Ph 2,6-H), 8.01–8.02 (m, 1H, Th 2-H), 8.49 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 23.3 (CH_3), 104.3 (C-7), 119.7 (C-3a), 121.2 (Ph C-2,6), 121.9 (C-3), 123.2 (Th C-2), 126.2 (Th C-4,5), 128.7 (Ph C-4), 129.8 (Ph C-3,5), 140.1 (Ph C-1), 142.8 (Th C-3), 147.3 (C-4), 152.0 (C-7a), 156.2 (C-6). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −147.4 (N-2), –99.6 (N-1), –89.8 (N-5). MS m/z (%): 292 ($[M+H]^+$, 100). HRMS (ESI) for $C_{17}H_{14}N_3S$ ($[M+H]^+$) calcd 292.0903, found 292.0903.



4.1.2.11.9. 6-Cyclopropyl-4-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (66). White solid, yield 99 mg, 80%, mp 85–86 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3129, 3078, 3044 (CH_{arom}), 2996, 2911, 2850 (CH_{aliph}), 1500, 1401, 1300, 1202, 1071, 1041 (C=C, C–N), 821, 760, 750, 685, 538 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.95–0.98 (m, 2H, CH_2CHCH_2), 0.99–1.01 (m, 2H, CH_2CHCH_2), 2.14–2.16 (m, 2H, CH_2CHCH_2), 2.75 (s, 3H, CH_3), 7.16 (s, 1H, 7-H), 7.40–7.42 (m, 1H, Ph 4-H), 7.50–7.53 (m, 2H, Ph 3,5-H), 7.86–7.87 (m, 2H, Ph 2,6-H), 8.44 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 8.7 (CH_2CHCH_2), 17.6 (CH_2CHCH_2), 23.0 (CH_3), 103.6 (C-7), 119.4 (C-3a), 121.2 (Ph C-2,6), 121.7 (C-3), 128.5 (Ph C-4), 129.8 (Ph C-3,5), 140.2 (Ph C-1), 152.0 (C-7a), 155.6 (C-4), 155.9 (C-6). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −147.9 (N-2), −90.4 (N-5), N-1 was not found. MS m/z (%): 250 ($[M+H]^+$, 100). HRMS (ESI) for $C_{16}H_{16}N_3$ ($[M+H]^+$) calcd 250.1339, found 250.1337.

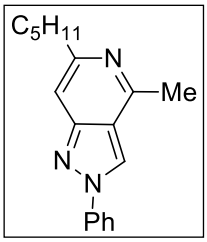


4.1.2.11.10. 6-Butyl-4-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (67). Brown liquid, yield 116 mg, 88%. IR (ν_{max}, cm^{-1}): 3070 (CH_{arom}), 2955, 2928, 2870 (CH_{aliph}), 1618, 1597, 1544, 1510, 1374, 1165, 1043 (C=C, C–N), 758, 688 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.94–0.97 (m, 3H, $C_3H_6CH_3$), 1.40–1.45 (m, 2H, $C_2H_4CH_2CH_3$), 1.71–1.79 (m, 2H, $CH_2CH_2C_2H_5$), 2.81 (s, 3H, CH_3), 2.81–2.86 (m, 2H, $CH_2C_3H_7$), 7.24 (s, 1H, 7-H), 7.42–7.44 (m, 1H, H-4), 7.52–7.54 (m, 2H, Ph 3,5-H), 7.88–7.89 (m, 2H, Ph 2,6-H), 8.49 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 14.2 ($C_3H_6CH_3$), 22.6 ($C_2H_4CH_2CH_3$), 23.1 (CH_3), 32.1 ($CH_2CH_2C_2H_5$), 38.3 ($CH_2C_3H_7$), 106.0 (C-7), 119.2 (C-3a), 121.3 (Ph C-2,6), 121.8 (C-3), 128.6 (Ph C-4), 129.8 (Ph C-3,5), 140.2 (Ph C-1), 152.0 (C-7a), 155.5 (C-4), 155.6 (C-6). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −147.6 (N-2), −85.2 (N-5), N-1 was



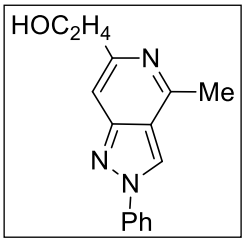
not found. MS m/z (%): 266 ([M+H]$^+$, 100). HRMS (ESI) for $C_{17}H_{20}N_3$ ([M+H]$^+$) calcd 266.1652, found 266.1654.

4.1.2.11.11. 4-Methyl-6-pentyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (68).

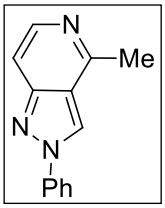


Brown liquid, yield 123 mg, 88%. IR (ν_{max}, cm^{-1}): 3100, 3071 (CH_{arom}), 2954, 2928, 2870, 2857 (CH_{aliph}), 1619, 1597, 1544, 1510, 1374, 1309, 1043 (C=C, C–N), 758, 688 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.82–0.91 (m, 2H, $C_4H_{11}CH_3$), 1.35–1.41 (m, 4H, $C_2H_4C_2H_4CH_3$), 1.76–1.80 (m, 2H, $CH_2CH_2C_3H_7$), 2.82 (CH_3), 2.84–2.86 (m, 2H, $CH_2C_4H_9$), 7.24 (s, 1H, H-7), 7.42–7.45 (m, 1H, Ph 4-H), 7.53–7.55 (m, 2H, Ph 3,5-H), 7.88–7.89 (m, 2H, Ph 2,6-H), 8.50 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 14.2 ($C_4H_8CH_3$), 22.8 ($C_3H_6CH_2CH_3$), 23.0 (CH_3), 29.6 ($CH_2CH_2C_3H_7$), 31.7 ($C_2H_4CH_2C_2H_5$), 38.4 ($CH_2C_4H_{11}$), 106.1 (C-7), 119.2 (C-3a), 121.3 (Ph C-2,6), 121.9 (C-3), 128.7 (Ph C-4), 129.8 (Ph C-3,5), 140.2 (Ph C-1), 152.0 (C-7a), 155.4 (C-4), 155.6 (C-6). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −148.9 (N-2), −85.0 (N-5), N-1 was not found. MS m/z (%): 280 ([M+H]$^+$, 100). HRMS (ESI) for $C_{18}H_{22}N_3$ ([M+H]$^+$) calcd 280.1808, found 280.1808.

4.1.2.11.12. 2-(4-Methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridin-6-yl)ethan-1-ol (69). White solid, yield 109 mg, 86%, mp 126–127 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3227 (OH), 3149, 3072, 3018 (CH_{arom}), 2945, 2919, 2870 (CH_{aliph}), 1622, 1501, 1389, 1374, 1306, 1212, 1164, 1053 (C=C, C–N), 844, 756, 741, 682, 571 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 2.74 (s, 3H, CH_3), 3.03 (t, ^3J=5.5 Hz, 2H, CH_2CH_2OH), 4.00–4.02 (m, 2H, CH_2CH_2OH), 7.22 (s, 1H, 7-H), 7.40–7.42 (m, 2H, H-7, Ph 4-H), 7.49–7.51 (m, 2H, Ph 3,5-H), 7.84–7.85 (m, 2H, Ph 2,6-H), 8.48 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 23.0 (CH_3), 39.4 (CH_2CH_2OH) 62.7 (CH_2CH_2OH), 107.0 (C-7), 119.2 (C-3a), 121.2 (Ph C-2,6), 122.0 (C-3), 128.7 (Ph C-4), 129.8 (Ph C-3,5), 140.0 (Ph C-1), 151.5 (C-7a), 153.4 (C-6), 155.7 (C-4). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −146.8 (N-2), −92.3 (N-5), N-1 was not found. MS m/z (%): 254 ([M+H]$^+$, 100). HRMS (ESI) for $C_{15}H_{16}N_3O$ ([M+H]$^+$) calcd 254.1288, found 254.1287.

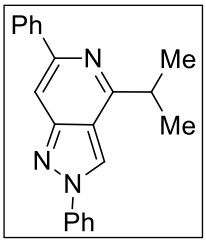


4.1.2.11.13. 4-Methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (70). Brown amorphous solid, yield 92 mg, 88%. IR (ν_{max}, cm^{-1}): 3066 (CH_{arom}), 2995 (CH_{aliph}), 1596, 1498, 1416, 1370, 1345, 1237, 1190, 1031 (C=C, C–N), 807, 756, 746, 687, 638, 529 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 2.85 (s, 3H, CH_3), 7.46–7.48 (m, 2H, 7-H, Ph 4-H), 7.55–7.58 (m, 2H, Ph 3,5-H), 7.91–7.93 (m, 2H, Ph 2,6-H), 8.20 (d, ^3J(6-H,7-H)=6.4 Hz, 1H, 6-H), 8.58 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 23.0 (CH_3), 109.5 (C-7), 120.6 (C-3a), 121.5 (Ph C-2,6), 122.0 (C-3), 128.9 (Ph C-4), 129.9 (Ph C-3,5), 140.1 (Ph C-1), 142.1 (C-6), 150.9 (C-4), 156.4 (C-7a). ^{15}N NMR (71 MHz, $CDCl_3$):



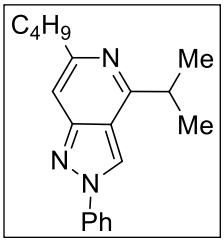
δ_N ppm −146.9 (N-2), −98.48 (N-1), −91.0 (N-5). MS m/z (%): 210 ([M+H]$^+$, 100). HRMS (ESI) for $C_{12}H_{13}N_3$ ([M+H]$^+$) calcd 210.1026, found 210.1026.

4.1.2.11.14. 2,6-Diphenyl-4-(propan-2-yl)-2*H*-pyrazolo[4,3-*c*]pyridine (71).



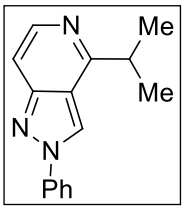
White solid, yield 143 mg, 92%, mp 97–98 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3126, 3064, 3023 (CH_{arom}), 2960, 2924, 2898 (CH_{aliph}), 1600, 1510, 1466, 1399, 1314, 1277, 1203, 1046 (C=C, C–N), 767, 760, 756, 696, 684, 635 (CH=CH of monosubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 1.54 (d, ^3J=7.0 Hz, 6H, CH(CH_3)$_2$), 3.52–3.56 (m, 1H, CH(CH$_3$)$_2$), 7.38–7.40 (m, 1H, CPh 4-H), 7.44–7.47 (m, 1H, NPh 4-H), 7.48–7.52 (m, 2H, CPh 3,5-H), 7.55–7.58 (m, 2H, NPh 3,5-H), 7.89 (s, 1H, 7-H), 7.93–7.96 (m, 2H, NPh 2,6-H), 8.18–8.19 (m, 2H, CPh 2,6-H), 8.57 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 21.9 (CH(*C*H$_3$)$_2$), 35.8 (*C*H(CH$_3$)$_2$), 104.5 (C-7), 118.0 (C-3), 121.2 (NPh C-2,6), 127.0 (CPh C-2,6), 128.2 (CPh C-4), 128.56 (CPh C-3,5), 128.62 (NPh C-4), 129.7 (NPh C-3,5), 140.1 (CPh C-1), 140.4 (NPh C-1), 150.5 (C-6), 152.8 (C-7a), 164.1 (C-4). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −148.9 (N-2), −86.5 (N-1), −90.8 (N-5). MS m/z (%): 314 ([M+H]$^+$, 100). HRMS (ESI) for $C_{21}H_{20}N_3$ ([M+H]$^+$) calcd 314.1652, found 314.1652.

4.1.2.11.15. 6-Butyl-2-phenyl-4-(propan-2-yl)-2*H*-pyrazolo[4,3-*c*]pyridine (72). Brown liquid, yield 123 mg, 84%. IR (ν_{max}, cm^{-1}): 3111, 3065, 3047 (CH_{arom}),



2959, 2929 (CH_{aliph}), 1615, 1598, 1541, 1510, 1467, 1376, 1306, 1275, 1211, 1196, 1161, 1044 (C=C, C–N), 848, 757, 688 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 0.95–0.97 (m, 3H, $C_3H_6CH_3$), 1.40–1.44 (m, 2H, $C_2H_4CH_2CH_3$), 1.44–1.47 (m, 6H, CH(CH_3)$_2$), 1.75–1.80 (m, 2H, $CH_2CH_2C_2H_5$), 2.85–2.90 (m, 2H, $CH_2C_3H_7$), 3.41–3.45 (s, 1H, CH(CH$_3$)$_2$), 7.23 (s, 1H, 7-H), 7.42–7.46 (m, 1H, H-7), 7.53–7.54 (m, 2H, Ph 3,5-H), 7.89–7.90 (m, 2H, Ph 2,6-H), 8.53 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 14.2 ($C_3H_6CH_3$), 22.1 (CH(*C*H$_3$)$_2$), 22.6 ($C_2H_4CH_2CH_3$), 31.8 ($CH_2CH_2C_2H_5$), 36.3 (*C*H(CH$_3$)$_2$), 38.3 ($CH_2C_3H_7$), 105.8 (C-7), 116.9 (C-3a), 121.3 (C-3), 121.4 (Ph C-2,6), 128.5 (Ph C-4), 129.8 (Ph C-3,5), 140.3 (Ph C-1), 152.8 (C-7a), 155.4 (C-6), 164.1 (C-4). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −147.4 (N-2), −99.6 (N-1), −90.8 (N-5). MS m/z (%): 294 ([M+H]$^+$, 100). HRMS (ESI) for $C_{19}H_{24}N_3$ ([M+H]$^+$) calcd 294.1965, found 294.1965.

4.1.2.11.16. 2-Diphenyl-4-(propan-2-yl)-2*H*-pyrazolo[4,3-*c*]pyridine (73).

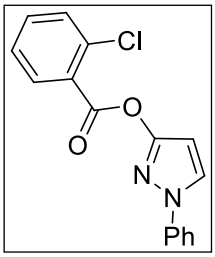


Brown liquid, yield 109 mg, 92%. IR (ν_{max}, cm^{-1}): 3061 (CH_{arom}), 2966, 2927, 2869 (CH_{aliph}), 1609, 1510, 1498, 1369, 1276, 1238, 1193, 1026 (C=C, C–N), 806, 757, 688 (CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 1.47 (d, ^3J=7.1 Hz, 6H, CH(CH_3)$_2$), 3.46–3.50 (m, 1H, CH(CH$_3$)$_2$), 7.44–7.47 (m, 2H, 7-H, Ph 4-H,), 7.54–7.56 (m, 2H, Ph 3,5-H), 7.90–7.92 (m, 2H, Ph 2,6-H), 8.25 (d, ^3J(6-H,7-H)=6.4 Hz, 1H, 6-H), 8.60 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 21.8 (CH(*C*H$_3$)$_2$), 35.4 (*C*H(CH$_3$)$_2$), 109.4 (C-

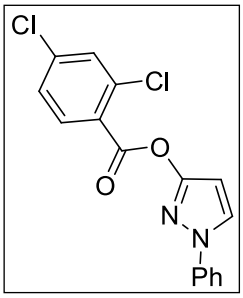
7), 118.7 (C-3a), 121.4 (Ph C-2,6), 121.5 (C-3), 128.7 (Ph C-4), 129.7 (Ph C-3,5), 140.0 (C-6), 142.1 (Ph C-1), 151.2 (C-7a), 165.0 (C-4). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −147.4 (N-2), −100.6 (N-1), −95.3 (N-5). MS m/z (%): 238 ([M+H]$^+$, 100). HRMS (ESI) for $C_{15}H_{16}N_3$ ([M+H]$^+$) calcd 238.1339, found 238.1339.

4.1.2.12. General procedure for the preparation of *o*-acylated-1-phenyl-1*H*-pyrazoles by using aroyl chlorides.

Into the solution of corresponding 3-hydroxy-1*H*-pyrazole **1** or **23** (0.5 mmol) in chloroform (5 mL), appropriate aroyl chloride (0,5 mmol), triethylamine (1 mmol) were added. The mixture was stirred for 30 min at room temperature; later, it was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by column chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:7, v/v) to provide compounds **75**, **77**, **79**, **81**, **84**–**85**.



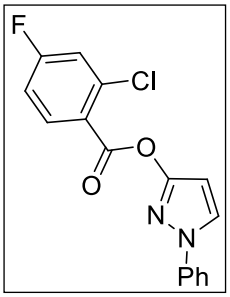
4.1.2.12.1. 1-Phenyl-1*H*-pyrazol-3-yl 2-chlorobenzoate (75). White solid, yield 129 mg, 86%, mp 52–53 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3153, 3132 (CH_{arom}), 1756 (C=O), 1599, 1535, 1457, 1389 1236, 1168 (C–O–C, C=C, C=N), 756, 746, 703, 680 (C–Cl, CH=CH mono-, and disubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 6.56 (d, ^3J(4-H,5-H)=2.3 Hz, 1H, 4-H), 7.28–7.30 (m, 1H, NPh 4-H), 7.39–7.42 (m, 1H, CPh 3-H), 7.44–7.46 (m, 2H, NPh 3,5-H), 7.50–7.54 (m, 2H, CPh 4,5-H), 7.66–7.67 (m, 2H, NPh 2,6-H), 7.91 (d, ^3J(5-H,4-H)=2.3 Hz, 1H, 5-H), 8.16 (d, ^3J(CPh 6-H, 5-H)=7.8 Hz, 1H, CPh 6-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 99.2 (C-4), 119.0 (NPh C-2,6), 126.7, 126.8 (CPh C-5, NPh C-4), 128.0 (C-5), 129.6 (NPh C-3,5), 131.6 (CPh C-3), 132.5 (CPh C-4), 133.7 (CPh C-6), 135.1 (CPh C-2), 139.9 (NPh C-1), 156.2 (C-3), 162.2 (C=O). MS m/z (%): 299 ([M+H]$^+$, 100). HRMS (ESI) for $C_{16}H_{11}N_2ClO_2Na$ ([M+Na]$^+$) calcd 321.0401, found 321.0402



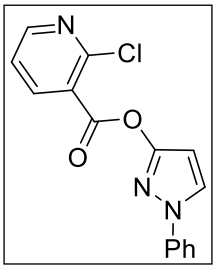
4.1.2.12.2. 1-Phenyl-1*H*-pyrazol-3-yl 2,4-dichlorobenzoate (77). White solid, yield 135 mg, 81%, mp 85–86 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3177, 3135, 3095, 3067, 3029 (CH_{arom}), 1752 (C=O), 1601, 1585, 1538, 1474, 1456, 1389, 1278, 1264, 1233, 1096, 1057, 1046, 1005 (C–O–C, C=C, C–N), 865, 818, 760, 747, 683, 672, 476 (C–Cl, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 6.53 (d, ^3J(4-H,5-H)=2.5 Hz, 1H, 4-H), 7.27–7.29 (m, 1H, NPh 4-H), 7.37 (d, ^3J(CPh 5-H,6-H)=9.1 Hz, 1H, CPh 5-H), 7.43–7.45 (m, 2H, NPh 3,5-H), 7.54 (s, 1H, CPh 3-H), 7.64–7.66 (m, 2H, NPh 2,6-H), 7.90 (d, ^3J(5-H,4-H)=2.5 Hz, 1H, 5-H), 8.12 (d, ^3J(CPh 6-H,5-H)=8.5Hz, 1H, CPh 6-H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 99.1 (C-4), 118.9 (NPh C-2,6), 126.4 (CPh C-1), 126.7 (NPh C-4), 127.3 (CPh C-5), 128.0 (C-5), 131.5 (CPh C-3), 133.5 (CPh C-6), 136.3 (CPh C-2), 139.6 (CPh C-4), 139.7 (NPh C-1), 156.3 (C-3), 161.3 (C=O). ^{15}N

NMR (71 MHz, $CDCl_3$): δ_N ppm −178.6 (N-2), −103.9 (N-1). MS m/z (%): 332 ($[M]^+$, 100), 334 ($[M+2]^+$, 60). HRMS (ESI) for $C_{16}H_{10}C_{l2}N_2O_2$ ($[M+Na]^+$) calcd 355,0012, found 355,0011.

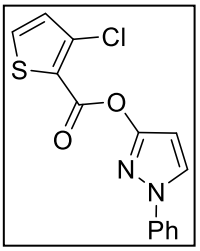
4.1.2.12.3. 1-Phenyl-1*H*-pyrazol-3-yl 2-chloro-4-fluorobenzoate (79). White solid, yield 126 mg, 80%, mp 83–84 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3069, 3044 (CH_{arom}), 1750 (C=O), 1600, 1577, 1489, 1456, 1387, 1298, 1232, 1004 (C–O–C, C=C, C–N, C–F), 913, 877, 765, 752, 685, 600 (C–Cl, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 6.54 (d, ^3J(4-H,5-H)=2.5 Hz, 1H, 4-H), 7.10–7.13 (m, 1H, CPh 5-H), 7.26–7.31 (m, 2H, NPh 4-H, CPh, 3-H), 7.44–7.46 (m, 2H, NPh 3,5-H), 7.65–7.67 (m, 2H, NPh 2,6-H), 7.90 (d, ^3J(5-H,4-H)=2.5 Hz, 1H, 5-H), 8.24 (dd, ^3J(CPh 6-H,5-H)=8.8 Hz, ^4J(CPh 6-H,3-H)=6.1 Hz, 1H, CPh 6-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 99.2 (C-4), 114.39, 114.51 (^2J=21.5 Hz, CPh C-5), 119.0 (NPh C-2,6), 119.19, 119.33 (^2J=25.1 Hz, CPh C-3), 124.28, 124.30 (^4J=3.3 Hz, CPh C-1), 126.8 (NPh C-4), 128.0 (C-5), 129.6 (NPh C-3,5), 134.69, 134.74 (^3J=10.0 Hz, CPh C-6), 137.31, 137.38 (^3J=10.9 Hz, CPh C-2), 139.8 (NPh C-1), 156.4 (C-3), 161.23 (C=O), 164.15, 165.62 (^1J=258.7 Hz, CPh C-4). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −178.3 (N-2), −104.0 (N-1). MS m/z (%): 317 ($[M+H]^+$, 100). HRMS (ESI) for $C_{16}H_{10}ClFN_2O_2Na$ ($[M+Na]^+$) calcd 339.0307, found 339.0307.



4.1.2.12.4. 1-Phenyl-1*H*-pyrazol-3-yl 2-chloropyridine-3-carboxylate (82). Yellow solid, yield 123 mg, 82%, mp 105–106 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3059 (CH_{arom}), 1764 (C=O), 1596, 1587, 1537, 1464, 1410, 1276, 1249, 1219, 1079, 1074, 1133, 1001(C=C, C–N, C–O–C), 782, 766, 757, 724, 618, 523, 489, 421 (C–Cl, CH=CH of monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 6.49 (d, ^3J(4-H,5-H)=2.7 Hz, 1H, 4-H), 7.21–7.24 (m, 1H, Ph 4-H), 7.34 (dd, ^3J(Pyr 5-H,4-H)=7.8 Hz, ^3J(Pyr 5-H,6-H)=4.8 Hz, 1H, Pyr 5-H), 7.37–7.39 (m, 2H, Ph 3,5-H), 7.59–7.60 (m, 2H, Ph 2,6-H), 7.87 (d, ^3J(5-H,4-H)=2.7 Hz, 1H, 5-H), 8.40 (^3J(Pyr 6-H,5-H)=7.7 Hz, ^4J(Pyr 6-H,4-H)=2.0 Hz, 1H, Pyr 6-H), 8.52 (^3J(Pyr 4-H,5-H)=4.8 Hz, ^4J(Pyr 4-H,6-H)=4.8 Hz, 1H, Pyr 4-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 98.9 (C-4), 118.6 (Ph C-2,6), 122.2 (Pyr C-5), 124.9 (Pyr C-1), 126.6 (Ph C-4), 128.0 (C-5), 129.4 (Ph C-3,5), 139.5 (Ph C-1), 141.1 (Pyr C-6), 150.9 (Pyr C-2), 152.7 (Pyr C-4), 155.9 (C-3), 160.9 (C=O). MS m/z (%): 300 ($[M+H]^+$, 100). HRMS (ESI) for $C_{15}H_{10}ClN_3O_2Na$ ($[M+Na]^+$) calcd 322.0354, found 322.0353.

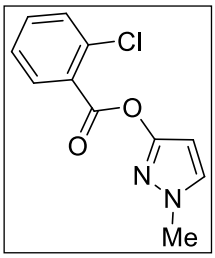


4.1.2.12.5. 1-Phenyl-1*H*-pyrazol-3-yl 3-chlorothiophene-2-carboxylate (83). White solid, yield 136 mg, 89%, mp 132–133 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3078 (CH_{arom}), 1739 (C=O), 1513, 1458, 1414, 1393, 1361, 1264, 1248, 1066 (C=C, C–N, C–O–C), 913, 759, 750, 683, 639, 609, 501 (C–Cl, CH=CH of monosubstituted

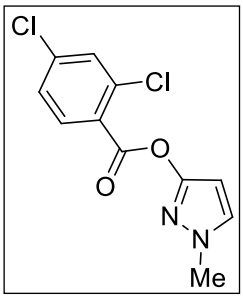


benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 6.51 (d, ^{3}J(4-H,5-H)=2.6 Hz, 1H, 4-H), 7.10 (d, ^{3}J(Th 4-H,5-H)=5.3 Hz, 1H, Th 4-H), 7.28-7.30 (m, 1H, NPh 4-H), 7.44–7.7.46 (m, 2H, NPh 3,5-H), 7.61 (d, ^{3}J(5-H,4-H)=5.3 Hz, 1H, Th 5-H), 7.65–7.67 (m, 2H, NPh 2,6-H), 7.89 (d, ^{3}J(5-H,4-H)=2.6 Hz, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 99.2 (C-4), 119.0 (NPh C-2,6), 123.9 (Th C-1), 126.7 (Ph C-4), 128.0 (C-5), 129.6 (Ph C-3,5), 130.7 (Th C-3), 132.2 (Th C-4), 134.2 (Th C-2), 156.1 (C-3), 157.6 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −178.6 (N-2), −103.6 (N-1). MS m/z (%): 304 ([M]$^+$, 100), 306 ([M+2]$^+$, 30). HRMS (ESI) for $C_{14}H_9ClN_2O_2SNa$ ([M+Na]$^+$) 326.9965, found 326.9966.

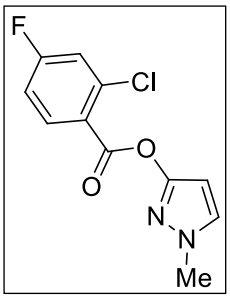
4.1.2.12.6. 1-Methyl-1*H*-pyrazol-3-yl 2-chlorobenzoate (84). Brown liquid, yield 100 mg, 85%. IR (ν_{max}, cm^{-1}): 3126 (CH_{arom}), 2944 (CH_{aliph}), 1758 (C=O), 1591, 1528, 1479, 1463, 1432, 1406, 1282, 1243, 1101, 1033 (C–O–C, C=C, C–N), 865, 745, 714, 657, 615, 475 (C–Cl, CH=CH of mono- and disubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 3.83 (s, 3H, CH_3), 6.23 (d, ^{3}J(4-H, 5-H)=2.5 Hz, 1H, 4-H), 7.30 (d, ^{3}J(5-H, 4-H)=2.4 Hz, 1H, 5-H), 7.33–7.36 (m, 1H, Ph 3-H), 7.45–7.49 (m, 2H, Ph 4,5-H), 8.07 (dd, ^{3}J(6-H, 5-H)=7.8 Hz, ^{3}J(6-H, 4-H)=1.7 Hz, 1H, Ph 6-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 39.4 (CH_3), 96.6 (C-4), 126.8 (Ph C-3), 128.4 (Ph C-1), 131.4 (C-5), 131.5 (Ph C-4), 133.5 (Ph C-6), 132.3 (Ph C-5), 134.8 (Ph C-2), 154.6 (C-3), 162.4 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −196.6 (N-2), −98.7 (N-1). MS m/z (%): 237 ([M+H]$^+$, 100). HRMS (ESI) for $C_{11}H_{19}ClN_2O_2Na$ ([M+Na]$^+$) calcd 259.0245, found 259.0245.



4.1.2.12.7. 1-Methyl-1*H*-pyrazol-3-yl 2,4-dichlorobenzoate (86). Brown solid, yield 98 mg, 72%, mp 72–73 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3120, 3099, 3089 (CH_{arom}), 2984, 2949 (CH_{aliph}), 1759 (C=O), 1650, 1585, 1525, 1477, 1465, 1436, 1408, 1374, 1289, 1276, 1236, 1214, 1156, 1093, 1030 (C–O–C, C=C, C–N), 869, 837, 762, 741, 677, 654, 537, 488, 468 (C–Cl, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 3.85 (s, CH_3), 6.24 (d, ^{3}J(4-H,5-H)=2.3 Hz, 1H, 4-H), 7.31 (d, ^{3}J(5-H,4-H)=2.2 Hz, 1H, 5-H), 7.35 (dd, ^{3}J(5-H,6-H)=8.5 Hz, ^{4}J(5-H,3-H)=1.9 Hz, 1H, Ph 5-H), 7.52 (d, ^{4}J(3-H,5-H)=1.9 Hz, 1H, 3-H), 8.06 (d, ^{3}J(6-H,5-H)=8.5 Hz, 1H, 6-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 39.5 (CH_3), 96.6 (C-4), 126.7 (Ph C-1), 127.3 (Ph C-5), 131.4 (C-5), 131.5 (Ph C-3), 133.4 (Ph C-6), 136.1 (Ph C-2), 139.5 (Ph C-4), 154.5 (C-3), 161.6 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −196.3 (N-2), −98.8 (N-1). MS m/z (%): 271 ([M+H]$^+$, 100). HRMS (ESI) for $C_{11}H_{19}Cl_2N_2O_2$ ([M+H]$^+$) calcd 271.0036, found 271.0035.

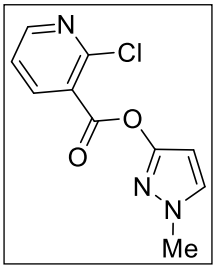


4.1.2.12.8. 1-Methyl-1*H*-pyrazol-3-yl 2-chloro-4-fluorobenzoate (88).



Brown solid, yield 107 mg, 84%, mp 87–88 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3062, 3038, 3002 (CH_{arom}), 2983, 2956 (CH_{aliph}), 1745 (C=O), 1599, 1577, 1524, 1491, 1468, 1432, 1391, 1298, 1234, 1208, 1094, 1032 (C–O–C, C=C, C–N, C–F), 901, 832, 772, 760, 683, 597, 484 (C–Cl, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 3.84 (s, 3H, CH_3), 6.22–6.23 (m, 1H, 4-H), 7.06–7.09 (m, 1H, Ph 3-H), 7.24 (dd, ^3J(5-H,6-H)=8.5 Hz, ^4J(5-H,3-H)=2.5 Hz, 1H, Ph 5-H), 7.31 (d, ^3J(5-H,4-H)=2.2 Hz, 1H, 5-H), 8.14–8.17 (m, 1H, 6-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 39.4 (CH_3), 96.6 (C-4), 114.3, 114.4 (^2J=21.5 Hz, Ph C-5), 119.0, 119.2 (^2J=24.8 Hz, Ph C-3), 124.49, 124.51 (^4J=3.5 Hz, Ph C-1), 131.4 (C-5), 134.5, 134.6 (^3J=9.7 Hz, Ph C-6), 137.05, 137.11 (^3J=10.9 Hz, Ph C-2), 154.5 (C-3), 161.5 (C=O), 164.0, 165.5 (^1J=257.6 Hz, Ph C-4). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −196.3 (N-2), −98.6 (N-1). MS m/z (%): 255 ($[M+H]^+$, 100). HRMS (ESI) for $C_{11}H_{19}ClFN_2O_2$ ($[M+H]^+$) calcd 255.0331, found 255.0330.

4.1.2.12.9. 1-Methyl-1*H*-pyrazol-3-yl 2-chloropyridine-3-carboxylate (89).



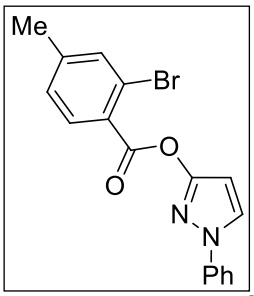
Brown solid, yield 95 mg, 80%, mp 78–79 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3075, 3043 (CH_{arom}), 2930 (CH_{aliph}), 1755 (C=O), 1168, 1579, 1563, 1531, 1464, 1433, 1406, 1272, 1242, 1228, 1219, 1130, 1071, 1039 (C=C, C–N, C–O–C), 782, 766, 757, 724, 618, 523, 489, 421 (C–Cl). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 3.86 (s, 3H, CH_3), 6.49 (d, ^3J(4-H,5-H)=2.7 Hz, 1H, 4-H), 7.21–7.24 (m, 1H, Ph 4-H), 7.34 (dd, ^3J(Pyr 5-H,4-H)=7.8 Hz, ^3J(Pyr 5-H,6-H)=4.8 Hz, 1H, Pyr 5-H), 7.37–7.39 (m, 2H, Ph 3,5-H), 7.59–7.60 (m, 2H, Ph 2,6-H), 7.87 (d, ^3J(5-H,4-H)=2.7 Hz, 1H, 5-H), 8.40 (^3J(Pyr 6-H,5-H)=7.7 Hz, ^4J(Pyr 6-H,4-H)=2.0 Hz, 1H, Pyr 6-H), 8.52 (^3J(Pyr 4-H,5-H)=4.8 Hz, ^4J(Pyr 4-H,6-H)=4.8 Hz, 1H, CPh 4-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 39.4 (CH_3), 96.4 (C-4), 122.3 (Ph C-5), 125.4 (Ph C-1), 131.5 (C-5), 141.1 (Ph C-6), 150.9 (Ph C-2), 152.7 (Ph C-4), 154.3 (C-3), 161.4 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −195.7 (N-2), −99.1 (N-1), −70.7 (Pyr N-2). MS m/z (%): 238 ($[M+H]^+$, 100). HRMS (ESI) for $C_{10}H_9ClN_3O_2$ ($[M+H]^+$) calcd 238.0378, found 238.0377.

4.1.2.13. General procedure for the preparation of *o*-acylated-1-phenyl-1*H*-pyrazoles by using aroyl acids.

Into the solution of corresponding aroyl acid (0.5 mmol) in dichlormethane (5 mL), DCC (0,53 mmol) was added at 0 °C temperature, and the reaction mixture was stirred for 1 hour. Later, 3-hydroxypyrazole (0,05 mmol) and DMAP were added, and the reaction was stirred for 2 hours at 0 °C temperature. After 2 hours of stirring, the reaction mixture was stirred for 12 hours at room temperature. After completion of the reaction as indicated by TLC, the mixture was quenched with water (10 mL) and extracted with dichormethane (3 × 10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The

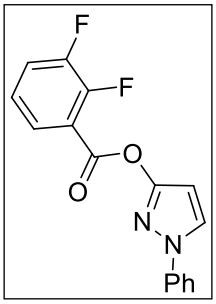
obtained residue was purified by column chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:6, v/v) to provide the desired products **76**, **78**, **80**, **81**, **85**, **87**.

4.1.2.13.1. 1-Phenyl-1*H*-pyrazol-3-yl 2-bromo-4-methylbenzoate (76).



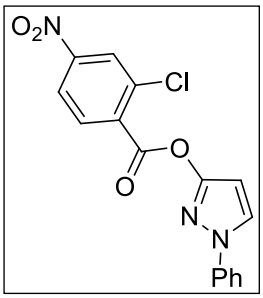
White solid, yield 146 mg, 82%, mp 64–65 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3073, 3062, 3038 (CH_{arom}), 2961, 2919 (CH_{aliph}), 1748 (C=O), 1599, 1535, 1503, 1450, 1388, 1278, 1240, 1208, 1102, 1055 (C–O–C, C=C, C–N), 757, 743, 682 (C–Br, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 2.41 (s, 3H, CH_3), 6.55 (d, ^3J(4-H,5-H)=2.5 Hz, 1H, 4-H), 7.24 (d, ^3J(5-H,6-H)=8.0 Hz, 1H, CPh 5-H), 7.28–7.30 (m, 1H, NPh 4-H), 7.44–7.46 (m, 2H, NPh 3,5-H), 7.58 (s, 1H, CPh 3-H), 7.66–7.67 (m, 2H, NPh 2,6-H), 7.90 (d, ^3J(5-H,4-H)=2.5 Hz, 1H, 5-H), 8.08 (d, ^3J(6-H,5-H)=8.0 Hz, 1H, CPh 6-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 21.4 (CH_3), 99.2 (C-4), 118.9 (NPh C-2,6), 123.3 (CPh C-2), 126.7 (NPh C-4), 126.8 (CPh C-1), 127.9 (C-5), 128.3 (CPh C-5), 129.6 (NPh C-3,5), 132.7 (CPh C-6), 135.7 (CPh C-3), 139.9 (NPh C-1), 145.1 (CPh C-4), 156.6 (C-3), 162.5 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −178.9 (N-2), −105.0 (N-1). MS m/z (%): 356 ($[M]^+$, 100), 358 ($[M+2]^+$, 100). HRMS (ESI) for $C_{17}H_{13}BrN_2O_2Na$ ($[M+Na]^+$) calcd 379.0053, found 379.0053.

4.1.2.13.2. 1-Phenyl-1*H*-pyrazol-3-yl 2,3-difluorobenzoate (78).

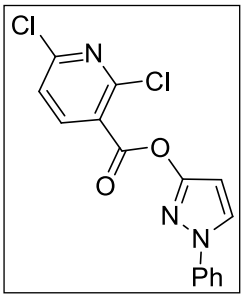


White solid, yield 132 mg, 88%, mp 75–76 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3095, 3110 (CH_{arom}), 1747 (C=O), 1604, 1539, 1492, 1457, 1398, 1236, 1140, 1172, 1139, 1075 (C–O–C, C=C, C=N, C–F), 840, 749, 719, 689 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 6.53 (d, ^3J(4-H,5-H)=2.6 Hz, 1H, 4-H), 7.20–7.24 (m, 1H, CPh 5-H), 7.30–7.32 (m, 1H, NPh 4-H), 7.44–7.48 (m, 3H, NPh 3,5-H, CPh 4-H), 7.65–7.68 (m, 2H, NPh 2,6-H), 7.91 (d, ^3J(5-H,4-H)=2.5 Hz, 1H, 5-H), 7.92–7.94 (m, 1H, CPh 6-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 99.2 (C-4), 119.0 (NPh C-2,6), 119.53, 119.58 ($^{2,3}J$=6.2 Hz, CPh C-1), 122.52, 122.54, 122.69, 122.71 (^2J=17.5 Hz, ^3J=1.5 Hz, CPh C-4), 124.08, 124.13, 124.14, 124.19 (^3J=6.6 Hz, ^4J=1.8 Hz, CPh C-5), 126.8 (NPh C-4), 127.33, 127.37 ($^{4,5}J$=3.8 Hz, CPh C-6), 128.1 (C-5), 139.8 (NPh C-1), 150.22, 150.30, 150.54, 150.61, 151.72, 151.80, 151.96, 152.03 ^1J=250 Hz, ^2J=12.7 Hz, CPh C-2,3), 156.23 (C-3), 160.35, 160.39, 160,39, 160.43 ($^{3,4}J$=3.6 Hz, C=O). MS m/z (%): 301 ($[M+H]^+$, 100). HRMS (ESI) for $C_{16}H_{10}F_2N_2NaO_2$ ($[M+Na]^+$) calcd 323.0603, found 323.0602.

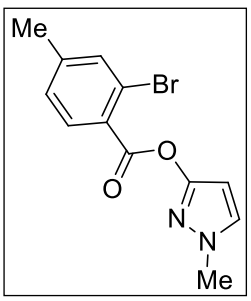
4.1.2.13.3. 1-Phenyl-1*H*-pyrazol-3-yl 2-chloro-4-nitrobenzoate (80). Brown solid, yield 144 mg, 84%, mp 117–118 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3093 (CH_{arom}), 1756 (C=O), 1598, 1526, 1502, 1450, 1396, 1347, 1262, 1236 (C–O–C, C=C, C=N, C–NO_2), 851, 776, 758, 731, 688 (C–Cl, CH=CH mono-, and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 6.56 (d, ^3J(4-H,5-H)=2.6 Hz, 1H, 4-H), 7.30–7.32 (m, 1H, NPh 4-H), 7.45–7.47 (m, 2H, NPh 3,5-H), 7.65–7.66 (m, 2H, NPh 2,6-H), 7.92 (d, ^3J(5-H,4-H)=2.6 Hz, 1H, 5-H), 8.22 (dd, ^3J(CPh 5-H,6-H)=8.6 Hz, ^4J(CPh 5-H,3-H)=2.2 Hz, 1H, CPh 5-H), 8.28 (d, ^3J(CPh 6-H,5-H)=8.6 Hz, 1H, CPh 6-H), 8.38 (d, ^4J(CPh 3-H,5-H)=2.2 Hz, 1H, CPh 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 98.9 (C-4), 119.0 (NPh C-2,6), 121.7 (CPh C-5), 126.5 (CPh C-3), 127.0 (NPh C-4), 128.2 (C-5), 129.7 (NPh C-3,5), 133.1 (CPh C-6), 133.9 (CPh C-1), 136.1 (CPh C-2), 139.7 (NPh C-1), 150.1 (CPh C-4), 155.9 (C-3), 160.8 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −177.7(N-2), −103.6 (N-1), −17.7 (NO_2). MS m/z (%): 344 ($[M+H]^+$, 100). HRMS (ESI) for $C_{16}H_{10}Cl\,N_3O_4Na$ ($[M+Na]^+$) calcd 366.0252, found 366.0251.



4.1.2.13.4. 1-Phenyl-1*H*-pyrazol-3-yl 2,6-dichloropyridine-3-carboxylate (81). White solid, yield 119 mg, 71%, mp 131–132 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3174, 3078 (CH_{arom}), 1751 (C=O), 1598, 1526, 1502, 1450, 1396, 1340, 1267, 1259, 1246, 1145, 1135, 1061 (C=C, C=N, C–O–C), 995, 871, 773, 755, 686, 667, 616, 562, 504 (C–Cl, CH=CH monosubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 6.55 (d, ^3J(4-H,5-H)=2.6 Hz, 1H, 4-H), 7.30–7.32 (m, 1H, Ph 4-H), 7.43–7.48 (m, 3H, Ph 3,5-H, Pyr 5-H), 7.64–7.67 (m, 2H, Ph 2,6-H), 7.91 (d, ^3J(5-H,4-H)=2.6 Hz, 1H, 5-H), 8.46 (d, ^3J(4-H,5-H)=2.6 Hz, 1H, Pyr 6-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 99.0 (C-4), 119.0 (Ph C-2,6), 123.1 (Pyr C-5), 127.7 (Pyr C-1), 127.0 (Ph C-4), 128.2 (C-5), 129.7 (Ph C-3,5), 139.7 (Ph C-1), 143.3 (Pyr C-6), 151.1 (Pyr C-2), 154.2 (Pyr C-4), 156.0 (C-3), 160.4 (C=O). MS m/z (%): 333 ($[M+H]^+$, 100). HRMS (ESI) for $C_{15}H_9ClN_3O_2Na$ ($[M+Na]^+$) calcd 355.9964, found 355.9965.

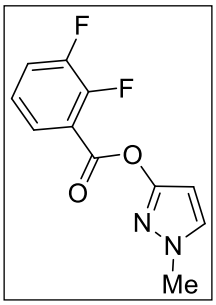


4.1.2.13.5. 1-Methyl-1*H*-pyrazol-3-yl 2-bromo-4-methylbenzoate (85). White solid, yield 123 mg, 83%, mp 57–58 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3039, 3025 (CH_{arom}), 2922 (CH_{aliph}), 1748 (C=O), 1602, 1529, 1488, 1458, 1432, 1409, 1270, 1230, 1209, 1156, 1098, 1082, 1053, 1032 (C=C, C–N), 876, 870, 829, 762, 752, 680, 665, 456 (C–Br, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 2.39 (s, 3H, PhCH_3), 3.86 (s, 3H, CH_3), 6.27 (d, ^3J(4-H,5-H)=2.3 Hz, C-4), 7.20–7.22 (m, 1H, Ph 5-H), 7.32 (d, ^3J(5-H,4-H)=2.1 Hz, 1H, 5-H), 7.55 (s, 1H, Ph 3-H), 8.01–8.02 (m, 1H, Ph 6-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 21.3 (PhCH_3), 39.4 (NCH_3), 96.7 (C-4), 123.1 (Ph



C-2), 127.0 (Ph C-1), 128.2 (Ph C-5), 131.4 (C-5), 132.5 (Ph C-6), 135.6 (Ph C-3), 144.9 (Ph C-4), 154.7 (C-3), 162.7 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −197.1 (N-2), −100.5 (N-1). MS m/z (%): 294 ([M]$^+$, 100), 296 ([M+2]$^+$, 98). HRMS (ESI) for $C_{12}H_{11}BrN_2O_2Na$ ([M+Na]$^+$) calcd 316.9896, found 316.9896.

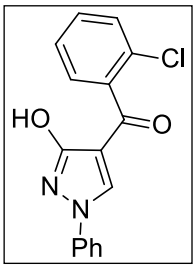
4.1.2.13.6. 1-Methyl-1*H*-pyrazol-3-yl 2,3-difluorobenzoate (87). Yellow solid, yield 93 mg, 78%, mp 67–68 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3087 (CH_{arom}), 2952 (CH_{aliph}), 1756, 1752 (C=O), 1592, 1528, 1488, 1473, 1467, 1407, 1282, 1274, 1271, 1248, 1237, 1214, 1122 (C–O–C, C=C, C=N, C–F), 950, 819, 753, 747, 608, 567, 479 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 3.86 (s, 3H, CH_3), 6.23–6.24 (m, 1H, 4-H), 7.18–7.22 (m, 1H, Ph 5-H), 7.32 (d, ^3J(5-H,4-H)=1.8 Hz, 1H, 5-H), 7.39–7.44 (m, 1H, CPh 4-H), 7.85–7.88 (m, 1H, Ph 6-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 39.5 (CH_3), 96.6 (C-4), 119.69, 119.72 ($^{2,3}J$=5.3 Hz, Ph C-1), 122.37, 122.47 ($^{2,3}J$=17.6 Hz, Ph C-4), 124.03, 124.06, 124.10 ($^{3,4}J$=7.0 Hz, Ph C-5), 127.25, 127.27 ($^{4,5}J$=3.5 Hz, Ph C-6), 131.4 (C-5), 150.19, 150.27, 150.57, 150.64, 151.69, 151.77, 151.99, 152.06 (^1J=250 Hz, ^2J=12.3 Hz, Ph C-3), 154.5 (C-3), 160.55, 160.57, 160.59 ($^{3,4}J$=3.7 Hz, C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −195.8 (N-2), −98.6 (N-1). MS m/z (%): 239 ([M+H]$^+$, 100). HRMS (ESI) for $C_{11}H_8F_2N_2NaO_2$ ([M+Na]$^+$) calcd 261.0446, found 261.0447.



4.1.2.14. General procedure for the preparation of 3-hydroxypyrazole ketones by using Fries rearrangement reaction.

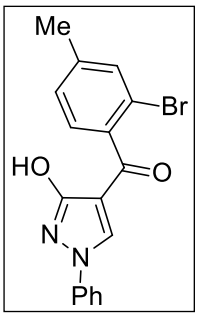
Into the solution of corresponding 3-hydroxy-1*H*-pyrazole **75–86** (0.5 mmol) in carbon disulfide (7 mL), the appropriate solution of $AlCl_3$ (6 mmol) in carbon disulfide (2 ml) was added. The mixture was stirred for 5 hours at 50 °C temperature; later, it was diluted with ice water (15 ml) and 6N HCl (7 ml). The obtained residue was purified by column chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:4, v/v) to provide to yield compounds **90–101**.

4.1.2.14.1. (2-Chlorophenyl)(3-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)methanone (90). White solid, yield 121 mg, 81%, mp 158–159 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3129 (OH), 3072 (CH_{arom}), 1629 (C=O), 1591, 1471, 1454, 1435, 1338, 1314, 1203, 1060 (C=C, C–N), 928, 752, 714, 690, 667, 651 (C–Cl, CH=CH of mono- and disubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 7.30–7.32 (m, 1H, NPh 4-H), 7.39–7.43 (m, 3H, CPh 5-H, NPh C-3,5), 7.45–7.48 (m, 1H, CPh 4-H), 7.49–7.51 (m, 2H, CPh C-3,6), 7.62–7.63 (m, 2H, NPh 2,6-H), 7.85 (s, 1H, 5-H), 9.16 (br s, 1H, OH). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 108.5 (C-4), 119.3 (NPh C-2,6), 127.1 (CPh C-5), 127.7 (NPh C-4), 129.0 (CPh C-6), 129.7 (NPh C-3,5), 130.1 (C-5), 130.8 (CPh C-3), 131.0 (CPh C-2), 132.0 (CPh C-4), 137.6 (CPh C-1), 138.9 (NPh C-1), 164.7 (C-3), 190.9 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −178.7 (N-2),



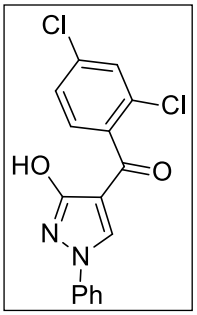
−117.6 (N-1). MS m/z (%): 299 ([M+H]$^+$, 100). HRMS (ESI) for $C_{16}H_{11}ClN_2NaO_2$ ([M+Na]$^+$) calcd 321.0401, found 321.0401

4.1.2.14.2. (2-Bromo-4-methylphenyl)(3-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)methanone (91). White solid, yield 134 mg, 75%, mp 139–140 °C (ethyl acetate).



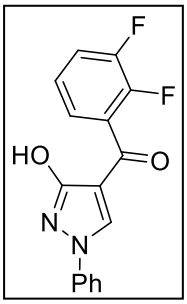
IR (ν_{max}, cm^{-1}): 3129, 3114 (OH), 3056 (CH_{arom}), 2956, 2924 (CH_{aliph}), 1762 (C=O), 1624, 1598, 1558, 1530, 1462, 1398, 1340, 1317, 1266, 1242, 1204, 1042 (C=C, C–N), 751, 688, 668, 603 (C–Br, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 2.42 (s, 3H, CH_3), 7.24–7.26 (m, 1H, CPh 5-H), 7.31–7.33 (m, 1H, NPh 4-H), 7.38–7.39 (m, 1H, CPh 6-H), 7.42–7.45 (m, 2H, NPh 3,5-H), 7.54 (s, 1H, CPh 3-H), 7.63–7.65 (m, 2H, NPh 2,6-H), 7.85 (s, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 21.3 (CH_3), 108.5 (C-7), 119.25 (CPh C-2), 119.33 (NPh C-2,6), 127.7 (NPh C-4), 128.3 (CPh C-5), 129.0 (CPh C-6), 129.7 (NPh C-3,5), 130.2 (C-5), 134.6 (CPh C-3), 136.8 (CPh C-1), 139.0 (Ph C-1), 143.0 (CPh C-4), 164.9 (C-3), 191.8 (C=O). MS m/z (%): 357 ([M]$^+$, 100), 359 ([M+2]$^+$, 100). HRMS (ESI) for $C_{17}H_{13}BrN_2O_2Na$ ([M+Na]$^+$) calcd 379.0053, found 379.0053.

4.1.2.14.3. (2,4-Dichlorophenyl)(3-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)methanone (92). White solid, yield 135 mg, 81%, mp 149–150 °C (ethyl acetate).



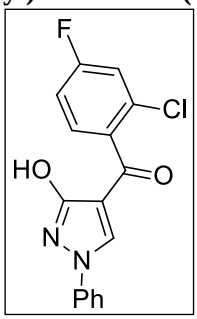
IR (ν_{max}, cm^{-1}): 3477 (OH), 3095, 3067, 3044, 3029 (CH_{arom}), 1752 (C=O), 1601, 1585, 1538, 1502, 1474, 1456, 1402, 1389, 1374, 1278, 1264, 1233, 1096, 1046, 1005 (C=C, C–N), 865, 818, 760, 747, 683, 672, 476, 406 (C–Cl, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 7.33–7.35 (m, 1H, NPh 4-H), 7.40 (d, ^3J(CPh 5-H,6-H)=8.2 Hz, ^4J(CPh 5-H,3-H)=1.9 Hz, 1H, CPh 5-H), 7.43–7.47 (m, 3H, NPh 3,5-H, CPh 6-H), 7.54 (d, ^4J(3-H,5-H)=1.8 Hz, 1H, CPh 3-H), 7.63–7.64 (m, 2H, NPh 2,6-H), 7.85 (s, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 108.5 (C-4), 119.4 (NPh C-2,6), 127.6 (CPh C-5), 127.9 (NPh C-4), 129.7 (CPh C-6, NPh C-3,5), 130.0 (C-5), 130.8 (CPh C-3), 132.2, 136.1, 137.6 (CPh C-1,2,4), 164.7 (C-3), 189.8 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −180.8 (N-2), −118.6 (N-1). MS m/z (%): 332 ([M]$^+$, 100), 334 ([M+2]$^+$, 70. HRMS (ESI) for $C_{16}H_{10}Cl_2N_2O_2Na$ ([M+Na]$^+$) calcd 355.0012, found 355.0011.

4.1.2.14.4. (2,3-Difluorophenyl)(3-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)methanone (93). White solid, yield 126 mg, 84%, mp 161–162 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3327 (OH), 3100, 3079, 3069, 3043 (CH_{arom}), 1628 (C=O), 1597, 1590, 1577, 1508, 1495, 1479, 1440, 1339, 1311, 1273, 1221, 1155, 1051, 1002 (C=C, C=N, C–F), 861, 852, 813, 771, 757, 752, 669, 621 (CH=CH mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 7.25–7.28 (m, 1H, CPh 5-H), 7.33–7.36 (m, 1H, NPh 4-H), 7.38–7.43 (m, 1H, CPh 4-H), 7.44–7.48 (m, 3H, NPh 3,5-H, CPh 6-H), 7.67–7.69 (m, 2H, NPh 2,6-H), 8.05–8.06 (m, 1H, 5-H). ^{13}C NMR (176



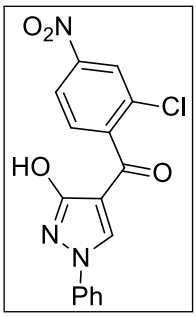
MHz, $CDCl_3$): δ_C ppm 108.4 (C-4), 119.5 (NPh C-2,6), 120.84, 120.94 ($^{2,3}J$=17.4 Hz, CPh C-4), 124.98, 125.00 ($^{4,5}J$=3.9 Hz, CPh C-6), 125.11, 125.14, 125.15, 125.17 (^{3}J=6.3 Hz, ^{4}J=4.6 Hz, CPh C-5), 127.9 (NPh C-4), 128.49, 128.55 ($^{2,3}J$=11.1 Hz, CPh C-1), 129.75, 129.80 (J=8.9 Hz, C-5), 129.80 (NPh C-3,5), 147.21, 147.29, 148.66, 148.74 (^{1}J=255.1 Hz, CPh C-2), 150.12, 150.19, 151.54, 151.62 (^{1}J=251.3 Hz, CPh C-3), 165.14 (C-3), 186.75, 186.76 ($^{2,3}J$=2.9 Hz, C=O). MS m/z (%): 301 ([M+H]$^+$, 100). HRMS (ESI) for $C_{16}H_{10}F_2N_2NaO_2$ ([M+Na]$^+$) calcd 323.0603, found 323.0602.

4.1.2.14.5. (2-Chloro-4-fluorophenyl)(3-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)methanone (94). White solid, yield 142 mg, 90%, mp 143–144 °C (ethyl acetate).



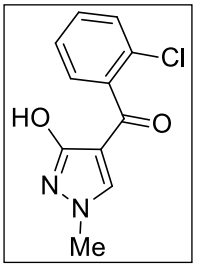
IR (ν_{max}, cm^{-1}): 3203 (OH), 3088, 3064 (CH_{arom}), 1625, 1599, 1582 (C=O), 1476, 1424, 1337, 1313, 1263, 1216, 1199, 1048 (C–F, C=C, C–N), 937, 887, 873, 824, 780, 759, 697, 687, 669, 618, 608, 491 (C–Cl, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 7.12–7.14 (m, 1H, CPh 5-H), 7.28–7.28 (m, 1H, CPh 3-H), 7.32–7.35 (m, 1H, NPh 4-H), 7.43–7.46 (m, 2H, NPh 3,5-H), 7.52–7.54 (m, 1H, CPh 6-H), 7.64–7.65 (m, 2H, NPh 2,6-H), 7.86 (s, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 108.5 (C-4), 114.54, 114.66 (^{2}J=21.5 Hz, CPh C-5), 118.43, 118.57 (^{2}J=24.8 Hz, CPh C-3), 119.4 (NPh C-2,6), 127.9 (NPh C-4), 129.7 (NPh C-3,5), 129.9 (C-5), 130.71, 130.76 (^{3}J=9.2 Hz, CPh C-6), 132.74, 132.80 (^{3}J=10.7 Hz, CPh C-2), 134.02, 134.04 (^{4}J=3.8 Hz, CPh C-1), 138.9 (NPh C-1), 162.98, 164.34 (^{1}J=255.1 Hz, CPh C-4), 164.8 (C-3), 190.0 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −178.5 (N-2), −116.8 (N-1). MS m/z (%): 317 ([M+H]$^+$, 100). HRMS (ESI) for $C_{16}H_{10}ClFN_2O_2Na$ ([M+Na]$^+$) calcd 339.0307, found 339.0307.

4.1.2.14.6. (2-Chloro-4-nitrophenyl)(3-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)methanone (95). Yellow solid, yield 137 mg, 80%, mp 208–209 °C (ethyl acetate).

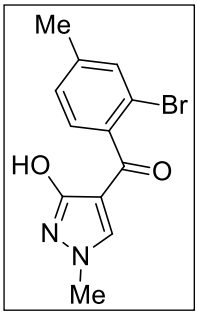


IR (ν_{max}, cm^{-1}): 3382 (OH), 3088, 3072, 3022 (CH_{arom}), 1636 (C=O), 1595, 1578, 1523, 1509, 1492, 1470, 1445, 1348, 1340, 1333, 1316, 1229, 1215, 1161, 1115, 1045 (C=C, C=N, C–NO_2), 934, 877, 758, 741, 668, 616 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, DMSO-d_6): δ_H ppm 7.31–7.35 (m, 1H, NPh 4-H), 7.49–7.51 (m, 2H, NPh 3,5-H), 7.77–7.82 (m, 3H, NPh 2,6-H, CPh 6-H), 8.28 (d, ^{3}J(5-H,6-H)=8.4 Hz, ^{4}J(5-H,3-H)=2.1 Hz, 1H, CPh 5-H), 8.40 (d, ^{4}J(3-H,5-H)=2.1 Hz, 1H, 3-H), 11.44 (br s, 1H, OH). ^{13}C NMR (176 MHz, DMSO-d_6): δ_C ppm 110.1 (C-4), 118.8 (NPh C-2,6), 123.0, 125.1, 127.4 (NPh C-4H), 130.0 (C-5, NPh C-3,5), 131.0, 133.4 (CPh C-1,2), 139.0 (NPh C-1), 145.9, 148.8, 162.1 (C-3), 185.5 (C=O). MS m/z (%): 344 ([M+H]$^+$, 100). HRMS (ESI) for $C_{16}H_{10}ClN_3NaO_4$ ([M+Na]$^+$) calcd 366.0251, found 366.0252.

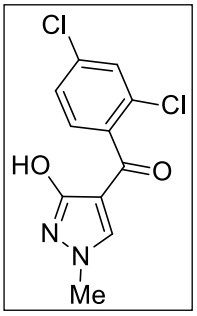
4.1.2.14.7. (2-Chlorophenyl)(3-hydroxy-1-methyl-1*H*-pyrazol-4-yl)methanone (96). Brown solid, 100 mg, yield 85%, mp 96–97 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3486 (OH), 3080, 3051, 3040, 3024 (CH_{arom}), 2955, 2924 (CH_{aliph}),1749 (C=O), 1598, 1567, 1531, 1502, 1451, 1417, 1393, 1379, 1339, 1265, 1257, 1243, 1133, 1059, 1025 (C=C, C–N), 869, 814, 772, 749, 710, 684, 668, 562, 504 (C–Cl, CH=CH of mono- and disubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 3.75 (s, 3H, CH_3), 7.31 (s, 1H, 5-H), 7.34–7.37 (m, 1H, Ph 4-H), 7.41–7.44 (m, 2H, Ph 3,5-H), 7.46–7.48 (m, 1H, Ph 6-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 39.8 (CH_3), 106.7 (C-4), 126.9 (Ph C-5), 128.9 (Ph C-6), 130.7 (Ph C-3), 130.9 (Ph C-2), 131.7 (Ph C-4), 134.0 (C-5), 137.8 (Ph C-1), 164.4 (C-3), 190.4 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −195.6 (N-2), −113.9 (N-1). MS m/z (%): 237 ($[M+H]^+$, 100). HRMS (ESI) for $C_{11}H_{19}ClN_2O_2Na$ ($[M+H]^+$) calcd 259.0245, found 259.0245.



4.1.2.14.8. (2-Bromo-4-methylphenyl)(3-hydroxy-1-methyl-1*H*-pyrazol-4-yl)methanone (97). White solid, 102 mg, yield 69%, mp 152–153 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3252 (OH, CH_{arom}), 2941 (CH_{aliph}), 1754 (C=O), 1644, 1618, 1600, 1565, 1536, 1492, 1477, 1413, 1341, 1175, 1152, 1078, 1045 (C=C, C–N), 846, 831, 797, 774, 721, 607, 464 (C–Br, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 2.34 (s, 3H, C*C*H_3), 3.70 (s, 3H, NCH_3), 7.14–7.16 (m, 1H, Ph 5-H), 7.26–7.27 (m, 1H, Ph 6-H), 7.30 (s, 1H, 5-H), 7.44 (d, ^3J(3-H,5-H)=1.6 Hz, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 21.1 (C*C*H_3), 39.6 (NCH_3), 106.4 (C-4), 119.0 (Ph C-2), 128.0 (Ph C-5), 128.7 (Ph C-6), 134.2 (C-5), 134.3 (Ph C-3), 136.8 (Ph C-1), 142.5 (Ph C-4), 164.2 (C-3), 191.0 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −196.3 (N-2), −113.5 (N-1), −95.3 (N-5). MS m/z (%): 294 ($[M]^+$, 100), 296 ($[M+2]^+$, 100). HRMS (ESI) for $C_{12}H_{11}BrN_3O_2Na$ ($[M+Na]^+$) calcd 316.9896, found 316.9897.

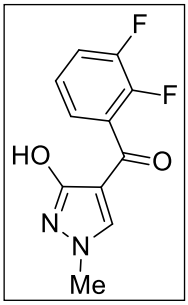


4.1.2.14.9. (2,4-Dichlorophenyl)(3-hydroxy-1-methyl-1*H*-pyrazol-4-yl)methanone (98). White solid, yield 108 mg, 80%, mp 184–185 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3262 (OH), 3071, 3025 (CH_{arom}), 1635 (C=O), 1565, 1536, 1503, 1462, 1429, 1415, 1340, 1291, 1172, 1159, 1103, 1077, 1054 (C=C, C–N), 926, 865, 827, 721, 669, 641, 567, 534, 453, 422 (C–Cl, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, DMSO-d_6): δ_H ppm 3.64 (s, 3H, CH_3), 7.41 (d, ^3J(6-H,5-H)=8.1 Hz, 1H, Ph 6-H), 7.48–7.49 (m, 1H, Ph 5-H), 7.68 (d, ^4J(3-H,5-H)=2.0 Hz, 1H, Ph 3-H), 7.88 (s, 1H, 5-H). ^{13}C NMR (176 MHz, DMSO-d_6): δ_C ppm 38.9 (CH_3), 107.2 (C-4), 127.5 (Ph C-5), 129.5 (Ph C-3), 129.8 (Ph C-6), 130.7 (Ph C-2), 134.6 (Ph C-1), 136.4 (C-5), 139.0 (Ph C-4) 161.1 (C-3), 185.4 (C=O). ^{15}N NMR



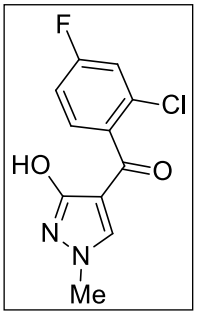
(71 MHz, DMSO-d_6): δ_N ppm −193.4 (N-2), −110.8 (N-1). MS m/z (%): 271 ([M+H]$^+$, 100). HRMS (ESI) for $C_{11}H_8Cl_2N_2O_2Na$ ([M+Na]$^+$) calcd 292.9855, found 292.9855.

4.1.2.14.10. (2,3-Difluorophenyl)(3-hydroxy-1-methyl-1*H*-pyrazol-4-yl)methanone (99). White solid, yield 101 mg, 85%, mp 164–165 °C (ethyl acetate). IR



(ν_{max}, cm^{-1}): 3279 (OH), 3037 (CH_{arom}), 2925 (CH_{aliph}), 1642 (C=O), 1564, 1543, 1512, 1472, 1428, 1348, 1266, 1201, 1169, 1077 (C–F, C=C, C–N), 993, 869, 856, 793, 773, 751, 721, 649, 615, 602, 548, 515, 457 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 3.80 (s, 3H, CH_3), 7.20–7.24 (m, 1H, Ph 5-H), 7.34–7.36 (m, 1H, Ph 4-H), 7.37–7.40 (m, 1H, Ph 6-H), 7.52 (d, J=3.1 Hz, 1H, 5-H), 9.39 (br s, 1H, OH). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 39.9 (CH_3), 106.6 (C-4), 120.51, 120.61 ($^{2,3}J$=17.2 Hz, Ph C-4), 124.87, 124.90 ($^{4,5}J$ =3.8 Hz, Ph C-6), 124.95, 124.98, 124.99, 125.02 (^3J =6.4 Hz, ^4J =4.6 Hz, Ph C-5), 128.71, 128.77 ($^{2,3}J$ =11.4 Hz, Ph C-1), 133.62, 133.67 (^5J =8.2 Hz, C-5), 147.09, 147.17, 148.54, 148.61 (^1J =254.5 Hz, ^2J =13.9 Hz, Ph C-2), 150.05, 150.12, 151.48, 151.55 (^1J =250.9 Hz, ^2J =13.0 Hz, Ph C-3), 164.8 (C-3), 186.13, 186.14 (J =^{3,4}1.8 Hz, C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −194.6 (N-2), −113.1 (N-1). MS m/z (%): 239 ([M+H]$^+$, 100). HRMS (ESI) for $C_{11}H_8F_2N_2O_2Na$ ([M+Na]$^+$) calcd 261.0446, found 261.0446.

4.1.2.14.11. (2-Chloro-4-fluorophenyl)(3-hydroxy-1-methyl-1*H*-pyrazol-4-yl)methanone (100). White solid, yield 94 mg, 74%, mp 169–170 °C (ethyl acetate).



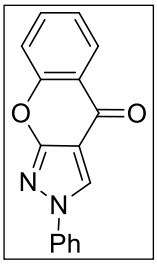
IR (ν_{max}, cm^{-1}): 3264 (OH), 3082, 3032 (CH_{arom}), 2956, 2927 (CH_{aliph}), 1635 (C=O), 1600, 1560, 1542, 1506, 1486, 1426, 1409, 1379, 1342, 1288, 1278, 1260, 1207, 1169, 1157, 1073, 1046 (C–F, C=C, C–N), 934, 888, 855, 817, 797, 769, 685, 646, 609, 599, 564, 429 (C–Cl, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, DMSO-d_6): δ_H ppm 3.65 (s, 3H, CH_3), 7.27–7.30 m 1H, Ph 5-H), 7.46–7.48 (m, 1H, Ph 6-H), 7.51–7.52 (m, 1H, Ph 3-H), 7.87 (s, 1H, 5-H), 10.62 (s, 1H, OH). ^{13}C NMR (176 MHz, DMSO-d_6): δ_C ppm 38.8 (CH_3), 107.2 (C-4), 114.28, 114.40 (^2J=21.4 Hz, Ph C-5), 116.88, 117.03 (^2J =25.2 Hz, Ph C-3), 130.14, 130.19 (^3J =9.3 Hz, Ph C-6), 130.71, 130.77 (^3J =10.8 Hz, Ph C-2), 136.3 (C-5), 136.67, 136.69 (^4J =3.5 Hz, Ph C-1), 161.0 (C-3), 161.36, 162.78 (^1J =249.9 Hz, Ph C-4), 185.4 (C=O). MS m/z (%): 255 ([M+H]$^+$, 100). HRMS (ESI) for $C_{11}H_8FClN_2O_2Na$ ([M+Na]$^+$) calcd 277.0151, found 277.0151.

4.1.2.15. General procedure for the preparation of benzopyrano[2,3-*c*]pyrazol-4(2*H*)-ones 101–110.

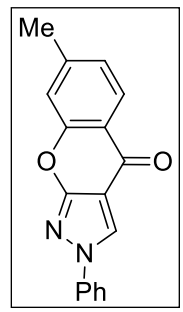
Into the solution of corresponding pyrazole **90–100** (0.5 mmol) in DMF (5 mL), potassium carbonate (1 mmol) was added. The mixture was stirred overnight at 120 °C temperature; later, it was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified

by column chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:8, v/v) to provide to yield compounds **101–110**.

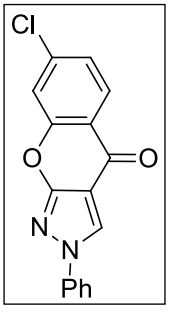
4.1.2.15.1. 2-Phenyl[1]benzopyrano[2,3-*c*]pyrazol-4(2*H*)-one (101). White solid, yield 118 mg, 90%, mp 204–205 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3096, 3069, 3044 (CH_{arom}), 1664 (C=O), 1600, 1585, 1572, 1492, 1467, 1452, 1432, 1318, 1293, 1217, 1161, 1101, 1052, 1024 (C–O–C, C=C, C–N), 955, 931, 905, 880, 764, 744, 708, 684, 664, 530, 503, 493, 471, 435 (CH=CH of mono- and disubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 7.38–7.42 (m, 2H, 6-H, Ph 4-H), 7.52–7.55 (m, 3H, 8-H, Ph 3,5-H), 7.70–7.72 (m, 1H, 7-H), 7.79–7.80 (m, 2H, Ph 2,6-H), 8.32 (dd, ^3J(5-H,6-H)=7.9 Hz, ^4J(5-H,7-H)=1.7 Hz, 1H, 5-H), 8.58 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 108.7 (C-3a), 118.8 (C-8), 119.9 (Ph C-2,6), 122.5 (C-4a), 124.3 (C-6), 125.4 (C-3), 127.0 (C-5), 134.7 (C-7), 156.0 (C-8a), 162.3 (C-9a), 174.8 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −170.5 (N-2), −116.6 (N-1). MS m/z (%): 263 ($[M+H]^+$, 100). HRMS (ESI) for $C_{16}H_{10}N_2NaO_2$ ($[M+Na]^+$) calcd 285.0634, found 285.0636.



4.1.2.15.2. 7-Methyl-2-phenyl[1]benzopyrano[2,3-*c*]pyrazol-4(2*H*)-one (102). White solid, yield 104 mg, 75%, mp 235–236 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3109, 3066 (CH_{arom}), 2996, 2922 (CH_{aliph}), 1648 (C=O), 1618, 1600, 1575, 1499, 1466, 1436, 1405, 1287, 1246, 1233, 1211, 1182, 1145, 1113 (C–O–C, C=C, C–N), 953, 905, 860, 771, 750, 710, 682, 663, 545, 481 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ 2.50 (s, 3H, CH_3), 7.18–7.20 (m, 1H, 6-H), 7.32 (s, 1H, 8-H), 7.39–7.41 (m, 1H, Ph 4-H), 7.51–7.53 (m, 2H, Ph 3,5-H), 7.77–7.80 (m, 2H, Ph 2,6-H), 8.19 (d, ^3J(5-H,6-H)=8.0 Hz, 1H, 5-H), 8.56 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 22.0 (CH_3), 108.8 (C-3a), 118.2 (C-8), 119.8 (Ph C-2,6), 120.2 (C-4a), 125.3 (C-3), 125.7 (C-6), 126.8 (C-5), 128.3 (Ph C-4), 129.9 (Ph C-3,5), 139.2 (Ph C-1), 146.3 (C-7), 156.2 (C-8a), 162.4 (C-9a), 174.8 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −170.8 (N-2), −116.8 (N-1). MS m/z (%): 277 ($[M+H]^+$, 100). HRMS (ESI) for $C_{17}H_{13}N_2O_2$ ($[M+H]^+$) calcd 277.0792, found 277.0791

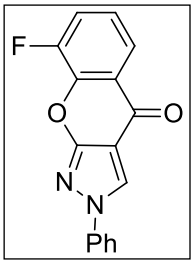


4.1.2.15.3. 7-Chloro-2-phenyl[1]benzopyrano[2,3-*c*]pyrazol-4(2*H*)-one (103). White solid, yield 135 mg, 91%, mp 209–210 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3110, 3069, 3055, 3043, 3030 (CH_{arom}), 1671 (C=O), 1601, 1583, 1561, 1509, 1467, 1441, 1411, 1282, 1214, 1203, 1079 (C–O–C, C=C, C–N), 962, 939, 919, 905, 869, 830, 767, 745, 726, 703, 682, 659, 619, 590, 541, 499, 476, 444 (C–Cl, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 7.36 (dd, ^3J(6-H,5-H)=8.5 Hz, ^4J(6-H,8-H)=1.9 Hz, 1H, 6-H), 7.41–7.44 (m, 1H, Ph 4-H), 7.52–7.56 (m, 3H, 8-H, Ph 3,5-H), 7.77–7.79 (m, 2H, Ph 2,6-H), 8.25 (d, ^3J(5-H,6-H)=8.5 Hz, 1H, 5-H), 8.56 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 108.6 (C-3a),

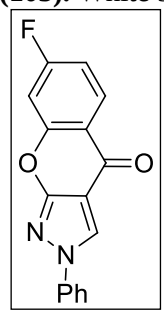


118.4 (C-8), 119.9 (Ph C-2,6), 121.2 (C-4a), 125.1 (C-6), 125.6 (C-3), 128.3 (C-5), 128.6 (Ph C-4), 130.0 (Ph C-3,5), 139.1 (Ph C-1), 140.7 (C-7), 156.2 (C-8a), 162.2 (C-9a), 173.9 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −169.9 (N-2), −115.6 (N-1). MS m/z (%): 297 ($[M+H]^+$, 100). HRMS (ESI) for $C_{16}H_9ClN_2O_2Na$ ($[M+Na]^+$) calcd 319.0245, found 319.0245.

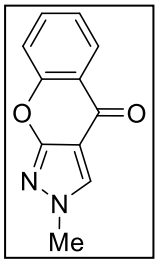
4.1.2.15.4. 8-Fluoro-2-phenyl[1]benzopyrano[2,3-*c*]pyrazol-4(2*H*)-one (104). Yellow solid, yield 123 mg, 88%, mp 255–256 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3104, 3022, 3003 (CH_{arom}), 1654 (C=O), 1617, 1600, 1510, 1483, 1441, 1434, 1300, 1286, 1264, 1213, 1183, 1157, 1065, 1052, 1021(C–O–C, C–F, C=C, C–N), 945, 911, 896, 866, 851, 818, 753, 699, 683, 659, 616, 600, 508, 498, 456 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 7.30–7.35 (m, 1H, 6-H), 7.41–7.45 (m, 1H, Ph 4-H), 7.49–7.57 (m, 3H, 7-H, Ph 3,5-H), 7.79–7.83 (m, 2H, Ph 2,6-H), 8.09 (d, ^3J(5-H,6-H)=7.9 Hz, 1H, 5-H), 8.59 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 108.6 (C-3a), 120.0 (Ph C-2,6), 120.8, 120.9 (^2J=17.6 Hz, C-7), 121.96, 121.98 (^4J=3.8 Hz, C-5), 123.75, 123.79 (^3J=6.5 Hz, C-6), 124.6 (C-4a), 125.6 (C-3), 128.6 (Ph C-4), 130.0 (Ph C-3,5), 139.1 (Ph C-1), 144.70, 144.76 (^2J=11.7 Hz, C-8a), 150.74, 152.18 (^1J=253.3 Hz, C-8), 161.8 (C-9a), 173.91, 173.93 (^4J=2.8 Hz, C=O). MS m/z (%): 281 ($[M+H]^+$, 100). HRMS (ESI) for $C_{16}H_9FN_2O_2Na$ ($[M+Na]^+$) calcd 303.0540, found 303.0540.



4.1.2.15.5. 7-Fluoro-2-phenyl[1]benzopyrano[2,3-*c*]pyrazol-4(2*H*)-one (105). White solid, yield 125 mg, 89%, mp 254–255 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3097, 3060 (CH_{arom}), 1662 (C=O), 1590, 1576, 1508, 1471, 1442, 1421, 1300, 1280, 1249, 1237, 1145, 1097, 1049 (C–F, C–O–C, C=C, C–N), 977, 961, 931, 913, 873, 824, 784, 769, 753, 717, 707, 685, 660, 619, 505, 490, 476, 452 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 7.10–7.13 (m, 1H, 6-H), 7.21–7.24 (m, 1H, 8-H), 7.41–7.44 (m, 1H, Ph 4-H), 7.52–7.55 (m, 2H, Ph 3,5-H), 7.77–7.79 (m, 2H, Ph 2,6-H), 8.32–8.35 (m, 1H, 5-H), 8.56 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 105.23, 105.40 (^2J=25.9 Hz, C-8), 108.6 (C-3a), 112.73, 112.86 (^2J=22.3 Hz, C-6), 119.40, 119.42 (^4J=2.6 Hz, C-4a), 119.9 (Ph C-2,6), 125.6 (C-3), 128.5 (Ph C-4), 129.42, 129.48 (^3J=10.8 Hz, C-5), 130.0 (Ph C-3,5), 139.1 (Ph C-1), 157.22, 157.29 (^3J=13.3 Hz, C-8a), 162.4 (C-9a), 165.64, 167.09 (^1J=255.2 Hz, C-7), 173.8 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −170.5 (N-2), −116.1 (N-1). MS m/z (%): 281 ($[M+H]^+$, 100). HRMS (ESI) for $C_{16}H_9FN_2O_2Na$ ($[M+Na]^+$) calcd 303.0540, found 303.0540.

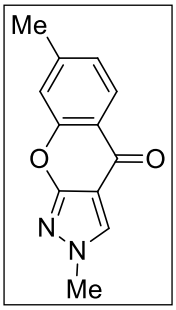


4.1.2.15.6. 2-Methyl[1]benzopyrano[2,3-*c*]pyrazol-4(2*H*)-one (106). White solid, yield 80 mg, 80%, mp 167–168 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3092, 3022 (CH_{arom}), 2998, 2941 (CH_{aliph}), 1656 (C=O), 1605, 1565, 1489, 1454, 1424, 1320, 1283, 1214, 1185, 1169, 1144, 1104, 1077 (C–O–C, C=C, C–N), 996, 983, 947, 878,



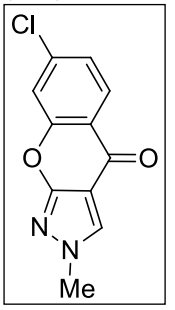
863, 760, 726, 710, 679, 656, 625, 610, 532, 478, 437 (CH=CH of mono- and disubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H pp 3.99 (s, 3H, CH_3), 7.30–7.33 (m, 1H, 6-H), 7.44–7.46 (m, 1H, 8-H), 7.62–7.64 (m, 1H, 7-H), 8.24 (dd, ^{3}J(5-H,6-H)=7.9 Hz, ^{4}J(5-H,7-H)=1.4 Hz, 1H, 5-H), 8.03 (s, 1H, 3-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 40.4 (CH_3), 107.0 (C-3a), 118.1 (C-8), 122.35 (C-4a), 123.9 (C-6), 126.7 (C-5), 129.1 (C-3), 134.3 (C-7), 155.7 (C-8a), 161.5 (C-9a), 174.4 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −170.4 (N-2), −115.8 (N-1). MS m/z (%): 201 ($[M+H]^+$, 100). HRMS (ESI) for $C_{11}H_8N_2O_2Na$ ($[M+Na]^+$) calcd 223.0478, found 223.0479.

4.1.2.15.7. 2,7-Dimethyl[1]benzopyrano[2,3-*c*]pyrazol-4(2*H*)-one (107).

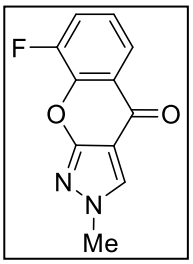


White solid, yield 100 mg, 93%, mp 210–211 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3096, 3002 (CH_{arom}), 2945, 2925, 2919 (CH_{aliph}), 1667, 1661 (C=O), 1626, 1577, 1567, 1499, 1470, 1438, 1414, 1317, 1245, 1173, 1112 (C–O–C, C=C, C–N), 866, 829, 772, 763, 723, 709, 580, 541, 473 (CH=CH of trisubstituted benzene). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 2.48 (s, 3H, C*C*H_3), 4.01 (s, 3H, NCH_3), 7.16 (d, ^{3}J(6-H,5-H)=8.0 Hz, ^{3}J(6-H,8-H)=1.5 Hz, 1H, 6-H), 7.28 (s, 1H, 8-H), 8.00 (s, 1H, 3-H), 8.14–8.15 (m, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 22.0 (C*C*H_3), 40.5 (NCH_3), 107.2 (C-3a), 118.1 (C-8), 120.2 (C-4a), 125.4 (C-6), 126.7 (C-5), 129.0 (C-3), 145.9 (C-7), 156.1 (C-8a), 161.7 (C-9a), 174.6 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −187.0 (N-2), −112.0 (N-1). MS m/z (%): 215 ($[M+H]^+$, 100). HRMS (ESI) for $C_{12}H_{10}N_2O_2Na$ ($[M+Na]^+$) calcd 237.0364, found 237.0364.

4.1.2.15.8. 7-Chloro-2-methyl[1]benzopyrano[2,3-*c*]pyrazol-4(2*H*)-one (108). White solid, yield 105 mg, 90%, mp 259–260 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3098, 3073, 3055, 3025 (CH_{arom}), 2955, 2925 (CH_{aliph}), 1662 (C=O), 1603, 1578, 1558, 1483, 1458, 1435, 1417, 1398, 1314, 1289, 1272, 1205, 1183, 1163, 1105, 1081 (C–O–C, C=C, C–N), 989, 970, 957, 914, 892, 862, 820, 764, 744, 707, 675, 633, 610, 588, 535, 449, 438 (C–Cl, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 4.02 (s, 3H, CH_3), 7.32 (dd, ^{3}J(6-H,5-H)=8.5 Hz, ^{4}J(6-H,8-H)=2.0 Hz, 1H, 6-H), 7.51 (d, ^{4}J(8-H, 6-H)=2.0 Hz 1H, 8-H), 8.01 (s, 1H, 3-H), 8.21 (d, ^{3}J(5-H,6-H)=8.5 Hz, 1H, 5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 40.7 (CH_3), 107.1 (C-3a), 118.3 (C-8), 121.2 (C-4a), 124.9 (C-6), 128.2 (C-5), 129.3 (C-3), 140.3 (C-7), 156.0 (C-8a), 161.5 (C-9a), 173.6 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −185.6 (N-2), −110.6 (N-1). MS m/z (%): 235 ($[M+H]^+$, 100). HRMS (ESI) for $C_{11}H_7ClO_2N_2Na$ ($[M+Na]^+$) calcd 257.0088, found 257.0089.

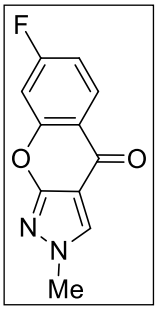


4.1.2.15.9. 8-Fluoro-2-methyl[1]benzopyrano[2,3-*c*]pyrazol-4(2*H*)-one (109). White solid, yield 83 mg, 76%, mp 235–236 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3087 (CH_{arom}), 2952, 2931 (CH_{aliph}), 1662 (C=O), 1623, 1617, 1587, 1568, 1486,



1445, 1431, 1312, 1269, 1262, 1218, 1180, 1161, 1128, 1067, 1020 (C–F, C–O–C, C=C, C–N), 973, 905, 879, 849, 751, 707, 688, 648, 614, 531, 424 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 4.04 (s, 3H, CH_3), 7.27–7.31 (m, 1H, 6-H), 7.46–7.49 (m, 1H, 7-H), 8.04–8.05 (m, 2H, 3,5-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 40.7 (CH_3), 107.1 (C-3a), 120.45, 120.55 (^2J=17.6 Hz, C-7), 121.84, 121.86 (^4J=3.5 Hz, C-5), 123.50, 123.53 (^3J=5.3 Hz, C-6), 124.6 (C-4a), 129.3 (C-3), 144.54, 144.61 (^2J=12.3 Hz, C-8a), 150.69, 152.12 (^1J=251.7 Hz, C-8), 161.1 (C-9a), 173.64, 173.66 (^4J=3.4 Hz, C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −196.9 (N-2), −109.9 (N-1). MS m/z (%): 219 ([M+H]$^+$, 100). HRMS (ESI) for $C_{11}H_{17}FO_2N_2Na$ ([M+Na]$^+$) calcd 241.0384, found 241.0383.

4.1.2.15.10. 7-Fluoro-2-methyl[1]benzopyrano[2,3-*c*]pyrazol-4(2*H*)-one (110). White solid, yield 78 mg, 71%, mp 239–240 °C (ethyl acetate). IR (ν_{max}, cm^{-1}):

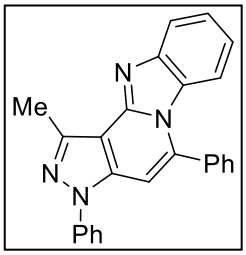


3099, 3067, 3044 (CH_{arom}), 2954, 2918 (CH_{aliph}), 1661 (C=O), 1622, 1602, 1569, 1495, 1472, 1438, 1410, 1315, 1254, 1222, 1163, 1146, 1100, 1080 (C–F, C–O–C, C=C, C–N), 995, 974, 947, 919, 880, 859, 819, 783, 763, 728, 707, 674, 636, 607, 483, 460, 416 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 4.02 (s, 3H, CH_3), 7.06–7.10 (m, 1H, 5-H,), 7.17–7.19 (m, 1H, 8-H), 8.01 (s, 1H, 3-H), 8.28–8.31 (m, 1H, 6-H). ^{13}C NMR (176 MHz, $CDCl_3$): δ_C ppm 40.6 (CH_3), 105.1, 105.2 (^2J=25.9 Hz, C-8), 107.0 (C-3a), 112.5, 112.6 (^2J=22.6 Hz, C-6), 119.40, 119.41 (^4J=2.5 Hz, C-4a), 129.2 (C-3), 129.27, 129.33 (^3J=10.6 Hz, C-5), 157.03, 157.11 (^3J=13.4 Hz, C-8a), 161.7 (C-9a), 165.4, 166.9 (^1J=255.0 Hz, C-7), 173.54 (C=O). ^{15}N NMR (71 MHz, $CDCl_3$): δ_N ppm −187.0 (N-2), −111.7 (N-1). MS m/z (%): 219 ([M+H]$^+$, 100). HRMS (ESI) for $C_{11}H_{17}FO_2N_2Na$ ([M+Na]$^+$) calcd 241.0384, found 241.0386.

4.1.2.16. Typical experimental procedure for the synthesis of tetracycles 115–118.

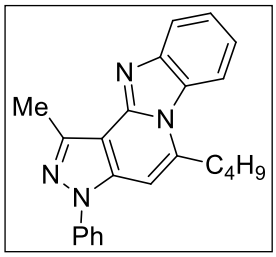
Corresponding alkyne **113** or **114** (0.5 mmol) and the appropriate *o*-aryldiamine (0.6 mmol) were dissolved in absolute DMF (2 mL), and the mixture was stirred at 120 °C temperature for 24 hours. After the completion of reaction as indicated by TLC, the mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by column chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:4, v/v) to provide the desired product.

4.1.2.16.1. 1-Methyl-3,5-diphenyl-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (115). White solid, yield 168 mg, 90%, mp 231 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3045 (CH_{arom}), 2923 (CH_{aliph}), 1653, 1596, 1509, 1495, 1450, 1371, 1267 (C=C, C–N), 761, 737, 710, 700 (CH=CH of mono- and disubstituted benzenes). ^{1}H NMR



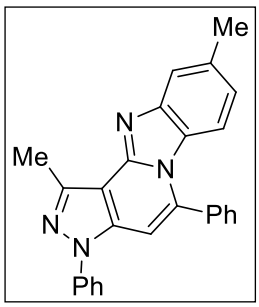
(400 MHz, $CDCl_3$): δ_H ppm 3.06 (s, 3H, CH3), 6.34–6.38 (m, 1H, 7-H), 6.91–6.97 (m, 1H, 8-H), 6.93 (s, 1H, 4-H), 7.34–7.39 (m, 1H, 9-H), 7.37–7.43 (m, 1H, NPh 4-H), 7.51–7.56 (m, 2H, NPh 3,5-H), 7.55–7.59 (m, 2H, CPh 2,6-H), 7.57–7.62 (m, 2H, CPh 3,5-H), 7.61–7.66 (m, 1H, CPh 4-H), 7.68–7.72 (m, 2H, NPh 2,6-H), 7.95–7.98 (m, 1H, 10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.8 (CH_3), 99.4 (C-4),109.7 (C-11b),113.9 (C-7),119.4 (C-10),120.6 (C-8), 123.3 (NPh C-2,6), 124.3 (C-9), 127.6 (NPh C-4), 129.1 (CPh C-3,5), 129.2 (CPh C-2,6), 129.6 (NPh C-3,5), 129.8 (C-6a), 130.2 (CPh C-4), 134.6 (CPh C-1), 138.7 (C-3a), 139.2 (NPh C-1), 140.2 (C-5), 145.0 (C-10a), 145.8 (C-11a), 146.6 (C-1). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −205.9 (N-6), −183.3 (N-3), −73.5 (N-2). MS m/z (%): 375 ([M+H]$^+$, 100). HRMS (ESI) for $C_{25}H_{19}N_4$ ([M+H]$^+$) calcd 375.1604, found 375.1604.

4.1.2.16.2. 5-Butyl-1-methyl-3-phenyl-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (116). White solid, yield 140 mg, 79%, mp 181 °C (ethyl acetate).



IR (ν_{max}, cm^{-1}): 3048 (CH_{arom}), 2968 (CH_{aliph}), 1656, 1596, 1506, 1454 (C=C, C–N), 763, 744, 695 (CH=CH of mono- and disubstituted benzenes). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 1.02 (t, *J*=7.3 Hz, 3H, $C_3H_6CH_3$), 1.52–1.63 (m, 2H, $C_2H_4CH_2CH_3$), 1.78–1.88 (m, 2H, $CH_2CH_2C_2H_5$), 2.99 (s, 3H, 1-CH_3), 3.24–3.29 (m, 2H, $CH_2C_3H_7$), 6.79 (s, 1H, 4-H), 7.28–7.34 (m, 1H, 8-H), 7.40–7.45 (m, 1H, NPh 4-H), 7.45–7.50 (m, 1H, 9-H), 7.54–7.60 (m, 2H, NPh 3,5-H), 7.67–7.70 (m, 2H, NPh 2,6-H), 7.89–7.93 (m, 1H, 7-H), 7.98–8.02 (m, 1H, 10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.8 (1-CH_3), 13.9 ($C_3H_6CH_3$), 22.3 ($C_2H_4CH_2CH_3$), 29.4 ($CH_2CH_2C_2H_5$), 33.8 ($CH_2C_2H_5$), 96.5 (C-4), 109.0 (C-11b), 114.0 (C-7), 119.6 (C-10), 121.0 (C-8), 123.2 (NPh C-2,6), 124.2 (C-9), 127.4 (NPh C-4), 129.6 (NPh C-3,5), 129.8 (C-6a), 138.7 (C-3a), 139.3 (NPh C-1), 142.2 (C-5), 145.3 (C-10a), 146.1 (C-11a), 146.4 (C-1). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −204.9 (N-6), −184.8 (N-3), −75.1 (N-2). MS m/z (%): 355 ([M+H]$^+$, 100). HRMS (ESI) for $C_{23}H_{23}N_4$ ([M+H]$^+$) calcd 355.1917, found 355.1917.

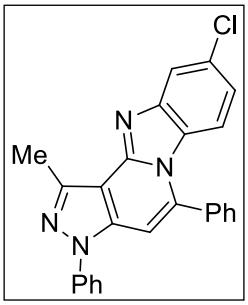
4.1.2.16.3. 1,9-Dimethyl-3,5-diphenyl-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (117a). White solid, yield 146 mg, 75%, mp 223 °C (ethyl acetate).



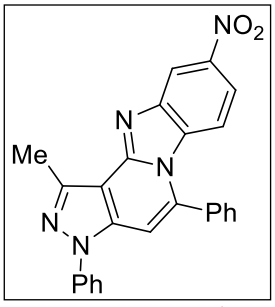
IR (ν_{max}, cm^{-1}): 3055 (CH_{arom}), 2922 (CH_{aliph}), 1655, 1597, 1507, 1372, 1275 (C=C, C–N), 760, 704 (C=C of mono- and trisubstituted benzenes). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 2.46 (s, 3H, 9-CH_3), 3.04 (s, 3H, 1-CH_3), 6.22 (d, ^3J(7-H,8-H)=8.5 Hz, 1H, 7-H), 6.76 (dd, ^3J(8-H,7-H)=8.5 Hz, ^4J(8-H,10-H)=1.3 Hz, 1H, 8-H), 6.91 (s, 1H, 4-H), 7.36–6.41 (m, 1H, NPh 4-H), 7.50–7.55 (m, 2H, NPh 3,5-H), 7.55–7.58 (m, 2H, CPh 2,6-H), 7.56–7.60 (m, 2H, CPh 3,5-H), 7.61–7.66 (m, 1H, CPh 4-H), 7.67–7.71 (m, 2H, NPh 2,6-H) 7.74 (d, ^4J(10-H,8-H)=1.3 Hz, 1H, 10-H). ^{13}C NMR (100 MHz,

$CDCl_3$): δ_C ppm 13.8 (1-CH_3), 21.5 (9-CH_3), 99.0 (C-4), 109.7 (C-11b), 113.3 (C-7), 119.1 (C-10), 122.1 (C-8), 123.3 (NPh C-2,6), 127.5 (NPh C-4), 127.8 (C-6a), 129.0 (CPh C-2,6), 129.2 (CPh C-3,5), 129.6 (NPh C-3,5), 130.1 (CPh C-4), 134.1 (C-9), 134.7 (CPh C-1), 138.6 (C-3a), 139.2 (NPh C-1), 140.1 (C-5), 145.4 (C-10a), 145.8 (C-11a), 146.5 (C-1). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −206.1 (N-6), −183.6 (N-3), −73.7 (N-2). MS m/z (%): 389 ($[M+H]^+$, 100). HRMS (ESI) for $C_{26}H_{21}N_4$ ($[M+H]^+$) calcd 389.1761, found 389.1760.

4.1.2.16.4. 9-Chloro-1-methyl-3,5-diphenyl-3*H*-pyrazolo[4',3':3,4]pyrido [1,2-*a*]benzimidazole (117b). White solid, yield 157 mg, 77%, mp 257 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3055 (CH_{arom}), 2923 (CH_{aliph}), 1652, 1595, 1507, 1431, 1372 (C=C, C–N), 810, 761, 731, 704 (C–Cl, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 3.03 (s, 3H, CH_3), 6.23 (d, ^3J(7-H,8-H)=8.9 Hz, 1H, 7-H), 6.88 (dd, ^3J(8-H,7-H)=8.9 Hz, 1H, 8-H), 6.97 (s, 1H, 4-H), 7.38–7.43 (m, 1H, NPh 4-H), 7.51–7.56 (m, 2H, NPh 3,5-H), 7.55–7.58 (m, 2H, CPh 2,6-H), 7.58–7.63 (m, 2H, CPh 3,5-H), 7.62–7.66 (m, 1H, CPh 4-H), 7.65–7.71 (m, 2H, NPh 2,6-H), 7.90–7.92 (m, 1H, 10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.8 (CH_3), 99.9 (C-4), 109.4 (C-11b), 114.5 (C-7), 118.6 (C-10), 121.0 (C-8), 123.4 (NPh C-2,6), 127.8 (NPh C-4), 128.3 (C-6a), 129.2 (CPh C-2,6), 129.3 (CPh C-3,5), 129.6 (NPh C-3,5), 130.0 (C-9), 130.4 (CPh C-4), 134.1 (CPh C-1), 138.8 (C-3a), 139.0 (NPh C-1), 139.9 (C-5), 145.4 (C-10a), 146.4 (C-11a), 146.7 (C-1). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −206.5 (N-6), −182.8 (N-3), −72.0 (N-2). MS m/z (%): 411 ($[M+2]^+$, 30), 409 (M^+, 100). HRMS (ESI) for $C_{25}H_{18}ClN_4$ ($[M+H]^+$) calcd 409.1215, found 409.1212.

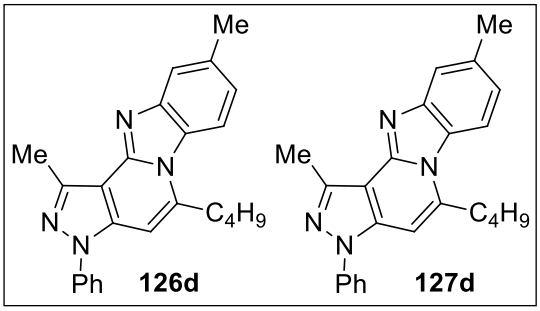


4.1.2.16.5. 1-Methyl-9-nitro-3,5-diphenyl-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (117c). Yellow solid, yield 100 mg, 48%, mp 296 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3058 (CH_{arom}), 2930 (CH_{aliph}), 1655, 1596, 1511, 1438, 1340 (C=C, C–N, C–NO_2), 817, 760, 720, 707, 696 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 3.02 (s, 3H, CH_3), 6.37 (d, ^3J(7-H,8-H)=9.2 Hz, 1H, 7-H), 7.03 (s, 1H, 4-H), 7.41–7.46 (m, 1H, NPh 4-H), 7.53–7.58 (m, 2H, NPh 3,5-H), 7.56–7.59 (m, 2H, CPh 2,6-H), 7.62–7.66 (m, 2H, CPh 3,5-H), 7.67–7.71 (m, 2H, NPh 2,6-H), 7.68–7.73 (m, 1H, CPh 4-H), 7.82 (dd, ^3J(8-H,7-H)=9.2 Hz, ^4J(8-H,10-H)=2.3 Hz, 1H, 8-H), 8.78 (d, ^4J(10-H,8-H)=2.3 Hz, 1H, 10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.7 (CH_3), 101.0 (C-4), 109.4 (C-11b), 113.7 (C-7), 115.2 (C-10), 115.7 (C-8), 123.5 (NPh C-2,6), 128.0 (NPh C-4), 129.2 (CPh C-2,6), 129.5 (CPh C-3,5), 129.7 (NPh C-3,5), 130.7 (CPh C-4), 133.7 (C-6a), 133.8 (CPh C-1), 138.7 (C-3a), 138.8 (NPh C-1), 139.9 (C-5), 144.6 (C-9), 144.8 (C-10a), 147.0 (C-1), 148.4 (C-11a). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −205.4 (N-6), −181.6 (N-3), −71.1 (N-2), −11.6



(NO_2). MS m/z (%): 420 ([M+1]$^+$, 100). HRMS (ESI) for $C_{25}H_{18}N_5O_2$ ([M+H]$^+$) calcd 420.1455, found 420.1458.

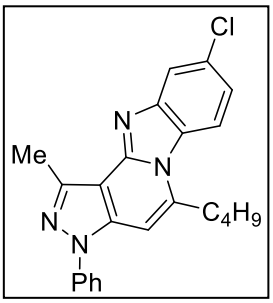
4.1.2.16.6. 5-Butyl-1,9-dimethyl-3-phenyl-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (117d) and 5-Butyl-1,8-dimethyl-3-phenyl-3*H*-pyrazolo[4',3':3,4]py-rido[1,2-*a*]benzimidazole (118d). White solids, yield 129 mg, 70%. Compounds were obtained as an inseparable mixture in ratio 1:0.55 (**117d**:**118d**).



4.1.2.16.6.1. 117d: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 1.01 (t, *J*=7.4 Hz, 3H, $C_3H_6CH_3$), 1.51–1.63 (m, 2H, $C_2H_4CH_2CH_3$), 1.77–1.87 (m, 2H, $CH_2CH_2C_2H_5$), 2.55 (s, 3H, 9-CH_3), 2.98 (s, 3H, 1-CH_3), 3.21–3.27 (m, 2H, $CH_2C_3H_7$), 6.77 (s, 1H, 4-H), 7.12 (d, ^3J(8-H,7-H)=8.3 Hz, 1H, 8-H), 7.39–7.44 (m, 1H, NPh 4-H), 7.53–7.60 (m, 2H, NPh 3,5-H), 7.66–7.70 (m, 2H, NPh 2,6-H), 7.76 (d, ^3J(7-H,8-H)=8.4 Hz, 1H, 7-H), 7.79 (s, 1H, 10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.8 (1-CH_3), 13.9 ($C_2H_6CH_3$), 21.5 (9-CH_3), 22.3 ($C_2H_4CH_2CH_3$), 29.4 ($CH_2CH_2C_2H_5$), 33.8 ($CH_2C_2H_7$), 96.1 (C-4), 109.1 (C-11b), 113.4 (C-7), 119.5 (C-10), 122.5 (C-8), 123.2 (NPh C-2,6), 127.3 (NPh C-4), 127.8 (C-6a), 129.6 (NPh C-3,5), 134.0 (C-9), 138.7 (C-3a), 139.3 (NPh C-1), 142.1 (C-5), 145.7 (C-10a), 146.2 (C-11a), 146.4 (C-1). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −205.2 (N-6), −185.0 (N-3), −75.4 (N-2).

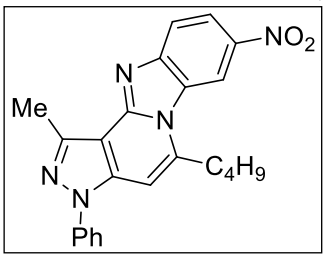
4.1.2.16.6.2. 118d: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 1.03 (t, *J*=7.4 Hz, 3H, $C_3H_6CH_3$), 1.52–1.64 (m, 2H, $C_2H_4CH_2CH_3$), 1.78–1.88 (m, 2H, $CH_2CH_2C_2H_5$), 2.57 (s, 3H, 9-CH_3), 2.98 (s, 3H, 1-CH_3), 3.26 (m, 2H, $CH_2CH_2C_2H_5$), 6.77 (s, 1H, 4-H), 7.30 (d, ^3J(9-H,10-H)=8.4 Hz, 1H, 9-H), 7.39–7.44 (m, 1H, NPh 4-H), 7.53–7.60 (m, 2H, NPh 3,5-H), 7.67–7.71 (m, 2H, NPh 2,6-H), 7.70 (s, 1H, 7-H), 7.88 (d, ^3J(10-H,9-H)= 8.3 Hz, 1H, 10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.8 (1-CH_3), 13.8 ($C_3H_6CH_3$), 22.2 (8-CH_3), 22.3 ($C_2H_4CH_2CH_3$), 29.5 ($CH_2CH_2C_2H_5$), 33.8 ($CH_2C_3H_7$), 96.4 (C-4), 109.1 (C-11b), 114.0 (C-7), 119.1 (C-10), 123.2 (NPh C-2,6), 125.6 (C-9), 127.4 (NPh C-4), 129.6 (NPh C-3,5), 130.0 (C-6a), 130.7 (C-8), 138.6 (C-3a), 139.3 (NPh C-1), 142.2 (C-5), 143.3 (C-10a), 145.9 (C-11a), 146.3 (C-1). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −205.2 (N-6), −185.0 (N-3), −75.4 (N-2). MS m/z (%): 369 ([M+H]$^+$, 100). Calcd. for $C_{24}H_{24}N_4$ (368.47): C, 78.23; H, 6.57; N, 15.21. Found: C, 77.84; H, 6.57; N, 15.17.

4.1.2.16.7. 5-Butyl-9-chloro-1-methyl-3-phenyl-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (117e). White solid, yield 117 mg, 60%, mp 166 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3064 (CH_{arom}), 2963 (CH_{aliph}), 1658, 1597, 1505, 1453, 1422, 1274 (C=C, C–N), 920, 804, 761, 696 (C–Cl, CH=CH of mono- and trisubstituted benzenes) ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 1.02 (t, *J*=7.3 Hz, 3H, $C_3H_6CH_3$), 1.51–1.62 (m, 2H, $C_2H_4CH_2CH_3$), 1.74–1.84 (m, 2H, $CH_2CH_2C_2H_5$), 2.94 (s, 3H, 1-CH3), 3.15–3.21 (m, 2H, $CH_2C_3H_7$), 6.80 (s, 1H, 4-H), 7.20 (dd, ^3J(8-H,7-H)=8.9 Hz,



^4J(8-H,10-H)=2.0 Hz, 1H, 8-H), 7.40–7.46 (m, 1H, NPh 4-H), 7.54–7.60 (m, 2H, NPh 3,5-H), 7.64–7.69 (m, 2H, NPh 2,6-H), 7.73 (d, ^3J(7-H,8-H)=8.9 Hz, 1H, 7-H), 7.90 (d, ^4J(10-H,8-H)=2.0 Hz, 1H, 10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.7 (1-CH_3), 13.9 ($C_3H_6CH_3$), 22.3 ($C_2H_4CH_2CH_3$), 29.2 ($CH_2CH_2C_2H_5$), 33.6 ($CH_2C_2H_7$), 96.8 (C-4), 108.9 (C-11b), 114.5 (C-7), 119.1 (C-10), 121.1 (C-8), 123.2 (NPh C-2,6), 127.5 (NPh C-4), 128.3 (C-6a), 129.6 (NPh C-3,5), 129.7 (C-9), 138.8 (C-3a), 139.1 (NPh C-1), 141.9 (C-5), 146.2 (C-10a), 146.4 (C-1), 147.0 (C-11a). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −205.5 (N-6), −184.4 (N-3), −74.0 (N-2). MS m/z (%): 391 ([M+2]$^+$, 39), 389 (M^+, 100). HRMS (ESI) for $C_{23}H_{22}ClN_4$ ([M+H]$^+$) calcd 389.1533, found 389.1536.

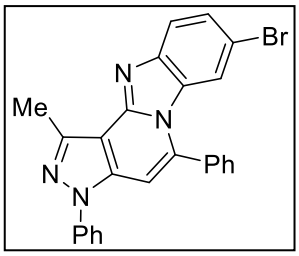
4.1.2.16.8. 5-Butyl-1-methyl-8-nitro-3-phenyl-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazo-le (118f). White solid, yield 130 mg, 65%, mp 237 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3073 (CH_{arom}), 2964 (CH_{aliph}), 1658, 1594, 1505, 1333, 1278 (C=C, C–N, NO_2), 763, 733, 696 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 1.06 (t, J=7.3 Hz, 3H, $C_3H_6CH_3$), 1.62–1.72 (m, 2H, $C_2H_4CH_2CH_3$), 1.84–1.93 (m, 2H, $CH_2CH_2C_2H_5$), 2.98 (s, 3H,1-CH_3), 3.33–3.39 (m, 2H, $CH_2C_3H_7$), 6.98 (s, 1H, 4-H), 7.44–7.50 (m, 1H, NPh 4-H), 7.57–7.63 (m, 2H, NPh 3,5-H), 7.66–7.70 (m, 2H, NPh 2,6-H), 7.95 (d, ^3J(10-H,9-H)=9.0 Hz, 1H, 10-H) 8.39 (dd, ^3J(9-H,10-H)=9.0 Hz, ^4J(9-H,7-H)=1.9 Hz, 1H, 9-H), 8.91 (d, ^4J(7-H,9-H)=1.9 Hz, 1H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.6 (1-CH_3), 13.8 ($C_3H_6CH_3$), 22.3 ($C_2H_4CH_2CH_3$), 29.1 ($CH_2CH_2C_2H_5$), 33.7 ($CH_2C_3H_7$), 98.1 (C-4), 109.1 (C-11b), 111.1 (C-7), 118.9 (C-10), 120.2 (C-9), 123.4 (NPh C-2,6), 128.0 (NPh C-4), 128.7 (C-6a), 129.7 (NPh C-3,5), 138.9 (NPh C-1), 139.4 (C-3a), 141.4 (C-8), 142.2 (C-5), 146.8 (C-1), 146.8 (C-11a), 149.9 (C-10a). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −204.1 (N-6), −183.4 (N-3), −71.5 (N-2), −11.8 (NO_2). MS m/z (%): 400 ([M+H]$^+$, 100). HRMS (ESI) for $C_{23}H_{22}N_5O_2$ ([M+H]$^+$) calcd 400.1768, found 400.1766.



4.1.2.16.9. Bromination of pyrazole 124 and subsequent cross-coupling reactions

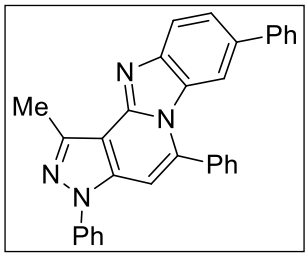
4.1.2.16.9.1. 8-Bromo-1-methyl-3,5-diphenyl-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (119b).

Compound **115** (1.1 g, 4 mmol) was dissolved in DMF (5 mL), and *N*-bromosuccinimide (720 mg, 4 mmol) was added. After stirring for 24 hours at room temperature, water was added; the produced solid was filtered off with suction and subsequently recrystalized from chloroform. White solid, yield 1.20 g, 66%, mp 283 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3054 (CH_{arom}), 2963 (CH_{aliph}), 1652, 1595, 1453, 1262, 1096, 1071, 1023 (C=C, C–N), 802, 761, 707(CH=CH of mono- and disubstituted benzenes). ^{1}H NMR (700 MHz, $CDCl_3$): δ_H ppm 3.05 (s, 3H, CH_3), 6.41



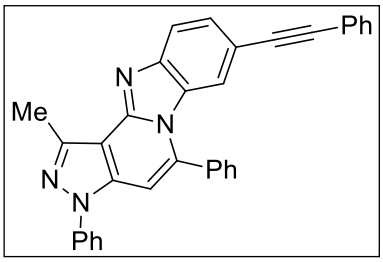
(d, ^4J(7-H,9-H)=1.4 Hz, 1H, 7-H), 6.99 (s, 1H, 4-H), 7.38–7.43 (m, 1H, NPh 4-H), 7.46 (dd, ^3J(9-H,10-H)=8.6 Hz, ^4J(7-H,9-H)=1.5 Hz, 1H, 9-H), 7.51–7.56 (m, 2H, NPh 3,5-H), 7.54–7.58 (m, 2H, CPh 2,6-H), 7.60–7.65 (m, 2H, CPh 3,5-H), 7.68–7.71 (m, 3H, CPh 4-H, NPh 2,6-H), 7.84 (d, ^3J(7-H,8-H)=8.4 Hz, 1H, 10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.7 (CH_3), 100.1 (C-4), 109.5 (C-11b), 113.6 (C-8), 117.0 (C-7), 120.1 (C-10), 123.4 (NPh C-2,6), 127.7 (C-9), 127.8 (NPh C-4), 129.1 (CPh C-2,6), 129.3 (CPh C-3,5), 129.7 (NPh C-3,5), 130.7 (C-6a), 130.5 (CPh C-4), 133.9 (CPh C-1), 138.7 (C-3a), 139.0 (NPh C-1), 139.9 (C-5), 143.0 (C-10a), 146.1 (C-11a), 146.7 (C-1). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −206.6 (N-6), −182.7 (N-3), −71.7 (N-2). MS m/z (%): 455 ($[M+2]^+$, 89), 453 (M^+, 89). HRMS (ESI) for $C_{25}H_{18}BrN_4$ ($[M+H]^+$) calcd 453.0709, found 453.0711.

4.1.2.16.9.2. 1-Methyl-3,5,8-triphenyl-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (120). Into the solution of pyrazole **119b** (227 mg, 0.5 mmol) in



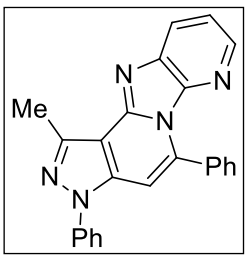
EtOH (2.5 mL) under argon atmosphere, phenylboronic acid (79 mg, 0.65 mmol), 1 M aqueous Cs_2CO_3 solution (1 mL), and $Pd(PPh_3)_4$ (40 mg, 7 mol%) were added, and the reaction mixture was irradiated (50 W) at 100 °C temperature for 10 min. After the completion of reaction as indicated by TLC, the mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, washed with brine, dried over $NaSO_4$, and concentrated under reduced pressure. The obtained residue was purified by column chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:3, v/v). White solid, yield 129 mg, 57%, mp 241 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3056 (CH_{arom}), 2923 (CH_{aliph}), 1651, 1596, 1510, 1495, 1468, 1375 (C=C, C–N), 762, 745, 705 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 3.06 (s, 3H, CH_3), 6.56 (d, ^4J(7-H,9-H)=1.4 Hz, 1H, 7-H), 6.98 (s, 1H, 4-H), 7.23–7.28 (m, 1H, 8-CPh 4-H), 7.29–7.33 (m, 2H, 8-CPh 2,6-H), 7.32–7.37 (m, 2H, 8-CPh 3,5-H), 7.38–7.43 (m, 1H, NPh 4-H), 7.52–7.57 (m, 2H, NPh 3,5-H), 7.61–7.64 (m, 2H, 5-CPh 2,6-H), 7.62–7.66 (m, 2H, 5-CPh 3,5-H), 7.64–7.66 (m, 1H, 9-H), 7.64–7.68 (m, 1H, 5-CPh 4-H), 7.70–7.73 (m, 2H, NPh 2,6-H), 7.99 (d, ^3J(10-H,9-H)=8.5 Hz, 1H, 10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.8 (CH_3), 99.3 (C-4), 109.8 (C-11b), 112.4 (C-7), 113.7 (C-8), 119.3 (C-10), 123.4 (NPh C-2,6), 123.8 (C-9), 126.6 (8-CPh C-4), 126.9 (8-CPh C-2,6), 127.4 (NPh C-4), 128.7 (8-CPh C-3,5), 129.2 (5-CPh C-3,5), 129.3 (5-CPh C-2,6), 129.6 (NPh C-3,5), 130.2 (5-CPh C-4), 130.4 (C-6a), 134.6 (5-CPh C-1), 138.7 (C-3a), 139.1 (NPh C-1), 140.2 (C-5), 141.3 (8-CPh C-1), 144.6 (C-10a), 146.3 (C-11a), 146.6 (C-1). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −205.7 (N-6), −183.0 (N-3), −73.2 (N-2). MS m/z (%): 451 ($[M+1]^+$, 100). HRMS (ESI) for $C_{31}H_{23}N_4$ ($[M+1]^+$) calcd 451.1917, found 451.1920.

4.1.2.16.9.3. 1-Methyl-3,5-diphenyl-8-(phenylethynyl)-3*H*-pyrazolo[4',3': 3,4]pyrido[1,2-*a*]benz-imidazole (121). Into the solution of **119b** (227 mg, 0.5 mmol) in dry DMF (2.5 mL) under argon atmosphere triethylamine (0.11 mL, 0.75 mmol), phenylacetylene (0.08 mL, 0.75 mmol), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol), and CuI (10 mg, 0.05 mmol) were added, and the reaction mixture was irradiated (100 W) at 130 °C temperature for 10 min. After the completion of reaction as indicated by TLC, the mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by column chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:5, v/v). White solid, yield 140 mg, 59%, mp 245 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3057 (CH_{arom}), 2922 (CH_{aliph}), 2210 (C≡C), 1651, 1596, 1510, 1493, 1375 (C=C, C–N), 808, 763, 703 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 3.05 (s, 3H, CH_3), 6.51–6.52 (m, 1H, 7-H), 6.97 (s, 1H, 4-H), 7.29–7.33 (m, 1H, C≡CPh 4-H), 7.31–7.35 (m, 2H, C≡CPh 3,5-H), 7.39–7.44 (m, 1H, NPh 4-H), 7.42–7.46 (m, 2H, C≡CPh 2,6-H), 7.52–7.55 (m, 1H, 9-H), 7.52–7.57 (m, 2H, NPh 3,5-H), 7.57–7.60 (m, 2H, 5-CPh 2,6-H), 7.61–7.66 (m, 2H, 5-CPh 3,5-H), 7.65–7.70 (m, 1H, 5-CPh 4-H), 7.68–7.72 (m, 2H, NPh 2,6-H), 7.89 (d, ^3J(10-H,9-H)=8.4 Hz, 1H, 10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.8 (CH_3), 88.0 (C≡*C*Ph), 90.3 (*C*≡CPh), 99.8 (C-4), 109.7 (C-11b), 115.0 (C-8), 117.4 (C-7), 119.2 (C-10), 123.4 (NPh C-2,6), 123.5 (C≡CPh C-1), 127.7 (NPh C-4), 127.9 (C-9), 128.1 (C≡CPh C-4), 128.3 (C≡CPh C-3,5), 129.1 (5-CPh C-2,6), 129.3 (5-CPh C-3,5), 129.6 (NPh C-3,5), 129.7 (C-6a), 130.3 (5-CPh C-4), 131.4 (C≡CPh C-2,6), 134.2 (5-CPh C-1), 138.8 (C-3a), 139.1 (NPh C-1), 140.2 (C-5), 145.3 (C-10a), 146.7 (C-1), 146.8 (C-11a). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −206.3 (N-6), −182.9 (N-3), −72.7 (N-2). MS m/z (%): 475 ($[M+1]^+$, 100). HRMS (ESI) for $C_{33}H_{23}N_4$ ($[M+H]^+$) calcd 475.1917, found 475.1922.



4.1.2.16.10. Preparation of 3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*']dipyridines

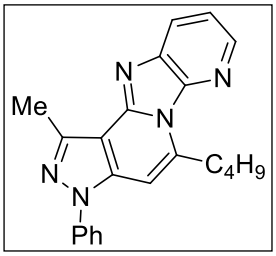
4.1.2.16.10.1. 1-Methyl-3,5-diphenyl-3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*']dipyridine (122).



Compound **122** was synthesized from **113** and pyridine-2,4-diamine in the same manner as described for the preparation of compounds **115–118**, except that the reaction period was 72 hours. White solid, yield 66 mg, 35%, mp 227 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3044 (CH_{arom}), 2959 (CH_{aliph}), 1654, 1598, 1510, 1399 (C=C, C–N), 770, 756, 713, 699 (CH=CH of monosubstituted benzenes). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 3.04 (s, 3H, CH_3), 6.97 (s, 1H, 4-H), 7.32 (dd, ^3J(9-H,10-H)=8.1 Hz, ^3J(9-H,8-H)=4.7 Hz, 1H, 9-H), 7.39–7.45 (m, 1H, NPh 4-H), 7.48–7.54 (m, 2H, CPh 3,5-H), 7.52–7.58 (m, 3H, CPh 4-H, NPh 3,5-H), 7.59–7.63 (m, 2H, CPh

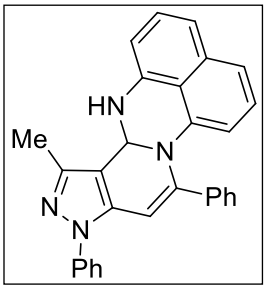
2,6-H), 7.68–7.72 (m, 2H, NPh 2,6-H), 8.11 (dd, ^{3}J(8-H,9-H)=4.7 Hz, ^{4}J(8-H,10-H)=1.5 Hz, 1H, 8-H), 8.21 (dd, ^{3}J(10-H,9-H)=8.1 Hz, ^{4}J(10-H,8-H)=1.5 Hz, 1H, 10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.8 (CH_3), 100.9 (C-4), 109.5 (C-11b), 120.1 (C-9), 126.3 (C-10), 123.5 (NPh C-2,6), 127.8 (NPh C-4), 127.8 (CPh C-3,5), 129.5 (CPh C-2,6), 129.7 (NPh C-3,5), 129.4 (CPh C-4), 134.4 (CPh C-1), 137.1 (C-10a), 139.0 (NPh C-1), 139.3 (C-3a), 140.5 (C-5), 141.3 (C-8), 144.1 (C-6a), 146.4 (C-11a), 146.7 (C-1). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −206.5 (N-6), −182.3 (N-3), −104.3 (N-7), −72.5 (N-2). MS m/z (%): 376 ([M+H]$^+$, 100). HRMS (ESI) for $C_{24}H_{18}N_5$ ([M+H]$^+$) calcd 376.1557, found 376.1559.

4.1.2.16.10.2. 5-Butyl-1-methyl-3-phenyl-3*H*-pyrazolo[4,3-*c*]imidazo[1,2-*a*:5,4-*b*']dipyridine (123). This compound was synthesized in analogy to **122**, except that **114** was used as the educt. White solid, yield 71 mg, 40%, mp 161 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3031 (CH_{arom}), 2966 (CH_{aliph}), 1655, 1596, 1504, 1397 (C=C, C–N), 758, 696 (CH=CH of monosubstitu-ted benzenes). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 0.99 (t, J=7.4 Hz, 3H, $C_3H_6CH_3$), 1.50–1.60 (m, 2H, $C_2H_4CH_2CH_3$), 1.76–1.86 (m, 2H, $CH_2CH_2C_2H_5$), 2.98 (s, 3H, 1-CH_3), 3.68–3.74 (m, 2H, $CH_2C_3H_7$), 6.85 (s, 1H, 4-H), 7.38–7.42 (m, 1H, 9-H), 7.41–7.46 (m, 1H, NPh 4-H), 7.55–7.61 (m, 2H, NPh 3,5-H), 7.67–7.71 (m, 2H, NPh 2,6-H), 8.19–8.23 (m, 1H, 10-H), 8.40–8.43 (m, 1H, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.8 (1-CH_3), 13.9 ($C_3H_6CH_3$), 22.3 ($C_2H_4CH_2CH_3$), 30.9 ($CH_2CH_2C_2H_5$), 32.8 ($CH_2C_3H_7$), 97.2 (C-4), 108.8 (C-11b), 119.9 (C-9), 123.4 (NPh C-2,6), 126.1 (C-10), 127.6 (NPh C-4), 129.6 (NPh C-3,5), 137.1 (C-10a), 139.2 (NPh C-1), 139.6 (C-3a), 141.3 (C-8), 143.8 (C-5), 144.8 (C-6a), 146.5 (C-11a), 146.6 (C-1). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −204.9 (N-6), −184.1 (N-3), −104.8 (N-7), −74.6 (N-2). MS m/z (%): 356 ([M+H]$^+$, 100). HRMS (ESI) for $C_{22}H_{22}N_5$ ([M+H]$^+$) calcd 356.1870, found 356.1872.



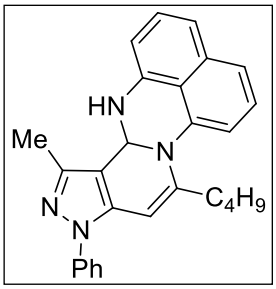
4.1.2.16.11. Preparation of 13,13a-dihydro-3*H*-pyrazolo[4',3':3,4]pyrido [1,2-*a*] perimidines.

4.1.2.16.11.1. 1-Methyl-3,5-diphenyl-13,13a-dihydro-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]perimidine (124). Compound **124** was synthesized from **113** and 1,8-naphthalenediamine in the same manner as described for the preparation of compounds **115**, except that CuI (10 mg, 10 mol%) was used as a catalyst, and the reaction mixture was stirred in DMF (2 mL) for 40 min at 140°C temperature under microwave irradiation (150 W). White solid, yield 96 mg, 45%, mp 257 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3234 (N-H), 3052 (CH_{arom}), 2920 (CH_{aliph}), 1592, 1562, 1413, 1300, 1278 (C=C, C–N), 815, 770, 760, 704 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 2.42 (s, 3H, CH_3), 4.58 (br s, 1H, N-H), 5.69 (s, 1H, 4-H), 6.22 (d, ^{3}J(7-H,8-H)=7.4 Hz, 1H, 7-H), 6.41 (s,



1H, 13a-H), 6.81 (dd, ^{3}J(12-H,11-H)=6.5 Hz, ^{4}J(12-H,10-H)=1.8 Hz, 1H, 12-H), 6.85–7.02 (br m, 2H, CPh 2,6-H), 6.93–6.97 (m, 1H, 8-H), 7.06–7.14 (m, 2H, CPh 3,5-H), 7.14–7.20 (m, 1H, CPh 4-H), 7.30–7.35 (m, 1H, NPh 4-H), 7.36–7.42 (m, 2H, 10,11-H), 7.40 (d, ^{3}J(9-H,8-H)=8.3 Hz, 1H, 9-H), 7.44–7.50 (m, 2H, NPh 3,5-H), 7.58–7.62 (m, 2H, NPh 2,6-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 12.0 (CH_3), 66.5 (C-13a), 91.2 (C-4), 106.6 (C-13b), 109.0 (C-12), 118.4 (C-7), 119.2 (C-10), 120.1 (C-12b), 123.0 (C-9), 123.2 (NPh C-2,6), 124.8 (C-8), 126.7 (C-11), 126.8 (NPh C-4), 127.7 (CPh C-4), 127.8 (CPh C-3,5), 128.5 (CPh C-2,6), 129.3 (NPh C-3,5), 134.6 (C-9a), 137.8 (CPh C-1), 138.0 (C-3a), 138.4 (C-6a), 139.7 (NPh C-1), 141.5 (C-12a), 144.5 (C-5), 145.5 (C-1) ppm. ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −293.2 (N-13), −275.7 (N-6), −181.2 (N-3), −85.5 (N-2). MS m/z (%): 427 ($[M+H]^+$, 100). Calcd for $C_{29}H_{22}N_4$ (426.51): C, 81.66; H, 5.20; N, 13.14. Found: C, 81.73; H, 5.60; N, 13.05.

4.1.2.16.11.2. 5-Butyl-1-methyl-3-phenyl-13,13a-dihydro-3*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]perimidine (125). This compound was synthesized in analogy to **124**, except that **114** was used as the educt. White solid, yield 90 mg, 44%, mp 194 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3262 (N-H), 3050 (CH_{arom}), 2951 (CH_{aliph}), 1596, 1569, 1505, 1412, 1275 (C=C, C–N), 817, 771, 694 (CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 0.60 (t, J=7.1 Hz, 3H, $C_3H_6CH_3$), 0.83–0.95 (m, 1H, $C_2H_4CH_2CH_3$), 0.98–1.10 (m, 1H, $C_2H_4CH_2CH_3$), 0.98–1.16 (m, 2H, CH_2CH_3), 2.16–2.25 (m, 1H, $CH_2C_3H_7$), 2.35 (s, 3H, 1-CH_3), 2.46–2.54 (m, 1H, $CH_2(C_3H_7)$, 4.36 (br s, 1H, N-H), 5.65 (s, 1H, 4-H), 6.14 (s, 1H, 13a-H), 6.67–6.72 (m, 1H, 12-H), 7.08 (d, ^{3}J(7-H,8-H)=7.4 Hz, 1H, 7-H), 7.30–7.35 (m, 1H, NPh 4-H), 7.33–7.36 (m, 2H, 10,11-H), 7.37–7.42 (m, 1H, 8-H), 7.45–7.51 (m, 2H, NPh 3,5-H), 7.57–7.61 (m, 2H, NPh 2,6-H), 7.59–7.63 (m, 1H, 9-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 11.8 (1-CH_3), 13.6 ($C_3H_6CH_3$), 22.0 ($C_2H_4CH_2CH_3$), 29.5 ($CH_2CH_2C_2H_5$), 33.4 ($CH_2(C_3H_7)$, 66.0 (C-13a), 88.6 (C-4), 106.4 (C-13b), 108.5 (C-12), 118.0 (C-7), 118.5 (C-10), 120.2 (C-12b), 123.1 (NPh C-2,6), 124.4 (C-9), 125.1 (C-8), 126.7 (NPh C-4), 126.9 (C-11), 129.2 (NPh C-3,5), 134.7 (C-9a), 138.2 (C-3a), 138.6 (C-6a), 139.8 (NPh C-1), 141.7 (C-12a), 145.0 (C-1), 146.1 (C-5). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −296.0 (N-13), −276.5 (N-6), −182.4 (N-3), −88.0 (N-2). MS m/z (%): 407 (M^+, 100). HRMS (ESI) for $C_{27}H_{27}N_4$ ($[M+1]^+$) calcd 407.2230, found 407.2233.

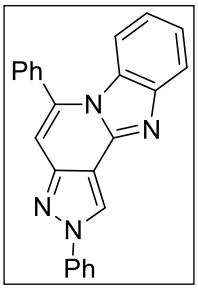


4.1.2.16.12. Typical experimental procedure for the synthesis of tetracycles 126–129.

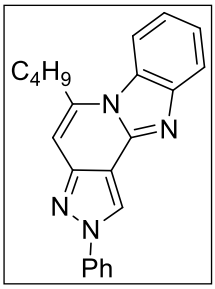
Corresponding alkyne **39** or **42** (0.5 mmol) and the appropriate *o*-aryldiamine (0.6 mmol) were dissolved in absolute DMF (2 mL), and the mixture was stirred at 120 °C temperature for 48 hours. After the completion of reaction as indicated by TLC, the mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by column

chromatography (SiO_2, eluent: ethyl acetate/*n*-hexane, 1:4, v/v) to provide the desired products **126–129**.

4.1.2.16.12.1. 2,5-Diphenyl-2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (126). White solid, yield: 90 mg, 50%, mp 241 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3047 (CH_{arom}), 1663, 1596, 1501, 1448, 1400, 1270 (C=C, C–N), 755, 736, 702, 691(CH=CH of mono- and disubstituted benzenes). ^1H NMR (400 MHz, $CDCl_3$): δ_H ppm 6.28–6.31 (m, 1H, 7-H), 6.93–6.98 (m, 1H, 8-H), 6.97 (d, ^5J(4-H,1-H)=0.8 Hz, 1H, 4-H), 7.30–7.36 (m, 1H, 9-H), 7.39–7.43 (m, 1H, NPh 4-H), 7.52–7.57 (m, 2H, NPh 3,5-H), 7.58–7.62 (m, 4H, CPh 2,3,5,6-H), 7.62–7.66 (m, 1H, CPh 4-H), 7.84–7.88 (m, 1H, 10-H), 7.87–7.89 (m, 2H, NPh 2,6-H), 8.96 (d, ^5J(1-H,4-H)=0.8 Hz, 1H, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 104.5 (C-4), 111.3 (C-11b), 113.9 (C-7), 119.3 (C-10), 120.2 (NPh C-2,6), 121.3 (C-8), 122.9 (C-1), 123.8 (C-9), 127.9 (NPh C-4), 129.0 (CPh C-2,6), 129.3 (CPh C-3,5), 129.7 (NPh C-3,5), 129.9 (CPh C-4), 130.8 (C-6a), 134.8 (CPh C-1), 139.8 (NPh C-1), 139.9 (C-5), 144.3 (C-10a), 145.0 (C-3a), 148.1 (C-11a). ^{15}N NMR (40 MHz, $CDCl_3$): δ_C ppm −210.2 (N-6), −160.3 (N-11), −154.3 (N-2), −97.2 (N-3). MS m/z (%): 361 ($[M+H]^+$, 100). HRMS (ESI) for $C_{24}H_{17}N_4$ ($[M+H]^+$) calcd 361.1448, found 361.1463.

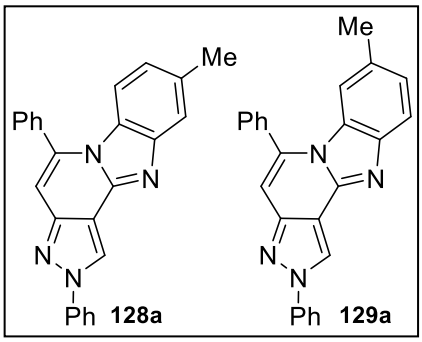


4.1.2.16.12.2. 5-Butyl-2-phenyl-2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (**127**). White solid, yield 143 mg, 84%, mp 180 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3059 (CH_{arom}), 2953 (CH_{aliph}), 1669, 1536, 1504, 1452, 1402, 1274, 1211 (C=C, C–N), 758, 750, 732, 687 (CH=CH of mono- and disubstituted benzenes). ^1H NMR (400 MHz, $CDCl_3$): δ_H ppm 1.04 (t, *J*=7.3 Hz, 3H, $C_3H_6CH_3$), 1.55–1.66 (m, 2H, $C_2H_4CH_2CH_3$), 1.84–1.93 (m, 2H, $CH_2CH_2C_2H_5$), 3.26–3.32 (m, 2H, $CH_2C_3H_7$), 6.86 (d, ^5J(4-H,1-H)=0.8 Hz, 1H, 4-H), 7.31–7.36 (m, 1H, 8-H), 7.36–7.41 (m, 1H, NPh 4-H), 7.42–7.47 (m, 1H, 9-H), 7.49–7.55 (m, 2H, NPh 3,5-H), 7.83–7.87 (m, 2H, NPh 2,6-H), 7.90–7.93 (m, 2H, 7,10-H), 8.87 (d, ^5J(1-H,4-H)=0.8 Hz, 1H, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.9 ($C_3H_6CH_3$), 22.2 ($C_2H_4CH_2CH_3$), 29.4 ($CH_2CH_2C_2H_5$), 33.6 ($CH_2C_3H_6$), 101.5 (C-4), 110.8 (C-11b), 114.0 (C-7), 119.6 (C-10), 120.1 (NPh C-2,6), 121.9 (C-8), 122.7 (C-1), 123.8 (C-9), 127.7 (NPh C-4), 129.7 (NPh C-3,5), 130.8 (C-6a), 139.8 (NPh C-1), 141.7 (C-5), 144.4 (C-10a), 145.3 (C-3a), 148.3 (C-11a). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −209.0 (N-6), −159.9 (N-11), −155.4 (N-2), −97.2 (N-3). MS m/z (%): 341 ($[M+H]^+$, 100). HRMS (ESI) for $C_{22}H_{21}N_4$ ($[M+H]^+$) calcd 341.1747, found 341.1762.



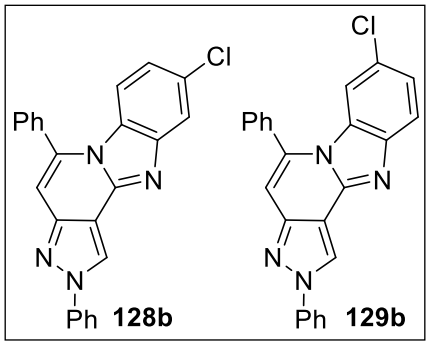
4.1.2.16.12.3. 9-Methyl-2,5-diphenyl-2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (128a) and 8-methyl-2,5-diphenyl-2*H*-pyrazolo[4',3':3,4] pyrido[1,2-*a*]benzimidazole (129a). White solids, yield 112 mg, 60%. Compounds were obtained as an inseparable mixture in the ratio 1:0.62 (**128a**:**129a**).

4.1.2.16.12.3.1. 128a. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 2.45 (s, 3H, CH_3), 6.15 (d, ^{3}J(7-H,8-H)=8.5 Hz, 1H, 7-H), 6.77 (dd, ^{3}J(8-H,7-H)=8.5 Hz, ^{4}J(8-H,10-H)=1.5 Hz, 1H, 8-H), 6.94 (s, 1H, 4-H), 7.38–7.43 (m, 1H, NPh 4-H), 7.51–7.57 (m, 2H, NPh 3,5-H), 7.57–7.60 (m, 4H, CPh 2,3,5,6-H), 7.63 (br s, 1H, 10-H), 7.61–7.67 (m, 1H, CPh 4-H), 7.86–7.90 (m, 2H, NPh 2,6-H), 8.95 (s, 1H, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 21.5 (CH_3), 104.2 (C-4), 111.31 (C-11b), 113.4 (C-7), 112.86 (C-8), 119.0 (C-10), 120.2 (NPh C-2,6), 122.83 (C-1), 127.86 (NPh C-4), 128.85 (C-6a), 128.92 (CPh C-2,6), 129.33 (CPh C-3,5), 129.7 (NPh C-3,5), 129.83 (CPh C-4), 133.7 (C-9), 134.91 (CPh C-1), 139.83 (NPh C-1), 139.88 (C-5), 144.6 (C-10a), 145.0 (C-11a), 148.12 (C-3a). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −210.3 (N-6), −154.3 (N-2).



4.1.2.16.12.3.2. 129a. ^{1}H NMR (400 MHz, $CDCl_3$): δ_C ppm 2.21 (s, 3H, CH_3), 6.02 (br s, 1H, 7-H), 6.94 (s, 1H, 4-H), 7.15 (dd, ^{3}J(9-H,10-H)=8.2 Hz, ^{4}J(7-H,9-H)=1.3 Hz, 1H, 9-H), 7.38–7.43 (m, 1H, NPh 4-H), 7.51–7.57 (m, 2H, NPh 3,5-H), 7.57–7.60 (m, 4H, CPh 2,3,5,6-H), 7.61–7.67 (m, 1H, CPh 4-H), 7.73 (d, 1H, ^{3}J(10-H,9-H)=8.2 Hz, 10-H), 7.86–7.90 (m, 2H, NPh 2,6-H), 8.93 (s, 1H, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 21.9 (CH_3), 104.3 (C-4), 111.4 (C-11b), 114.0 (C-7), 118.7 (C-10), 120.2 (NPh C-2,6), 122.75 (C-1), 125.3 (C-9), 127.84 (NPh C-4), 128.80 (CPh C-4), 128.85 (CPh C-2,6), 129.39 (CPh C-3,5), 129.77 (NPh C-3,5), 130.9 (C-6a), 131.1 (C-8), 134.87 (CPh C-1), 139.83 (NPh C-1), 139.95 (C-5), 142.3 (C-10a), 144.6 (C-11a), 148.05 (C-3a). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −210.3 (N-6), −154.5 (N-2). MS m/z (%): 375 ([M+H]$^+$, 100). HRMS (ESI) for $C_{25}H_{19}N_4$ ([M+H]$^+$) calcd 375.1604, found 375.1621.

4.1.2.16.12.4. 9-Chloro-2,5-diphenyl-2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (137b) and 8-chloro-2,5-diphenyl-2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (138b). Compounds were obtained separately by column chromatography on silica gel (Hex/EtOAc. 4:1 v/v). Yields: 40% (**128b**) and 30% (**129b**).

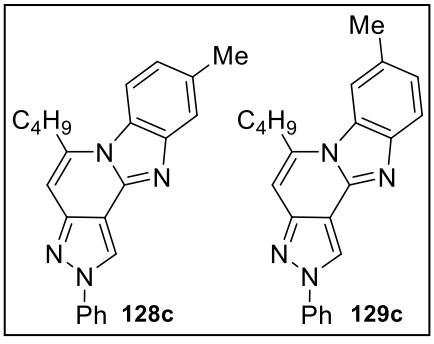


4.1.2.16.12.4.1. 128b. White solid, yield 79 mg, 40%, mp 185 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3062 (CH_{arom}), 1665, 1597, 1501, 1429, 1418, 1403, 1205 (C=C, C–N), 755, 745, 702, 685 (C–Cl, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 6.16 (d, ^{3}J(7-H,8-H)=8.9 Hz, 1H, 7-H), 6.90 (dd, ^{3}J(8-H,7-H)=8.9 Hz, ^{4}J(8-H,10-H)=2.0 Hz, 1H, 8-H), 6.99 (s, 1H, 4-H), 7.39–7.45 (m, 1H, NPh 4-H), 7.52–7.57 (m, 2H, NPh 3,5-H), 7.57–7.62 (m, 4H, CPh 2,3,5,6-H), 7.62–7.68 (m, 1H, CPh 4-H), 7.80 (d, ^{4}J(10-H,8-H)=2.0 Hz, 1H, 10-H),

7.85–7.90 (m, 2H, NPh 2,6-H), 8.94 (s, 1H, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 105.0 (C-4), 111.1 (C-11b), 114.5 (C-7), 118.8 (C-10), 120.3 (NPh C-2,6), 121.7 (C-8), 123.0 (C-1), 128.1 (NPh C-4), 129.1 (CPh C-2,6), 129.3 (CPh C-3,5), 129.39 (C-6a), 129.44 (C-9), 129.8 (NPh C-3,5), 130.1 (CPh C-4), 134.4 (CPh C-1), 139.6 (C-5), 139.7 (NPh C-1), 145.2 (C-10a), 146.0 (C-11a), 148.1 (C-3a). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −210.3 (N-6), −160.8 (N-11), −154.3 (N-2). MS m/z (%): 397 ($[M+2]^+$, 36), 395 (M^+, 100). Calcd for $C_{24}H_{15}N_4Cl$ (394.86): C, 73.00; H, 3.83; N, 14.19. Found: C, 73.33; H, 4.02; N, 14.28.

4.1.2.16.12.4.2. 129b. White solid, yield 59 mg, 30%, mp 229 °C (ethyl acetate). IR (ν_{max}, cm^{-1}): 3059 (CH_{arom}), 1665, 1597, 1501, 1455, 1418, 1273 (C=C, C–N), 758, 702, 687 (C–Cl, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 6.19 (d, ^4J(7-H,9-H)=2.0 Hz, 1H, 7-H), 6.98 (s, 1H, 4-H), 7.28 (dd, ^3J(9-H,10-H)=8.6 Hz, ^4J(9-H,7-H)=2.1 Hz, 1H, 9-H), 7.39–7.44 (m, 1H, NPh 4-H), 7.52–7.57 (m, 2H, NPh 3,5-H), 7.55–7.59 (m, 2H, CPh 2,6-H), 7.60–7.65 (m, 2H, CPh 3,5-H), 7.65–7.70 (m, 1H, CPh 4-H), 7.73 (d, ^3J(10-H,9-H)=8.6 Hz, 1H, 10-H), 7.85–7.89 (m, 2H, NPh 2,6-H), 8.93 (s, 1H, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 105.0 (C-4), 111.1 (C-11b), 114.0 (C-7), 119.8 (C-10), 120.3 (NPh C-2,6), 123.0 (C-1), 124.4 (C-9), 126.7 (C-8), 128.0 (NPh C-4), 129.2 (CPh C-3,5), 129.3 (CPh C-2,6), 129.8 (NPh C-3,5), 130.2 (CPh C-4), 131.1 (C-6a), 134.2 (CPh C-1), 139.6 (C-5), 139.7 (NPh C-1), 142.8 (C-10a), 145.6 (C-11a), 148.0 (C-3a). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −210.5 (N-6), −160.4 (N-11), −153.6 (N-2) ppm. MS m/z (%): 397 ($[M+2]^+$, 36), 395 (M^+, 100). HRMS (ESI) for $C_{24}H_{16}ClN_4$ ($[M+H]^+$) calcd 395.1058, found 395.1062.

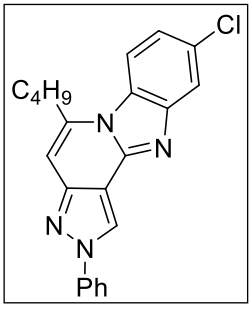
4.1.2.16.12.5. 5-Butyl-9-methyl-2-phenyl-2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (128c) and 5-butyl-8-methyl-2-phenyl-2*H*-pyrazolo[4',3':3,4] pyrido[1,2-*a*]benzimidazole (129c). Yield: 106 mg (60%). Compounds were obtained as an inseparable mixture in the ratio 1:0.25 (**128c**:**129c**).



4.1.2.16.12.5.1. 128c: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, *J*=7.4 Hz, 3H, $C_3H_6CH_3$), 1.53–1.63 (m, 2H, $C_2H_4CH_2CH_3$), 1.80–1.89 (m, 2H, $CH_2CH_2C_2H_5$), 2.52 (s, 3H, 9-CH_3), 3.20–3.25 (m, 2H, $CH_2C_3H_7$), 6.81 (d, ^5J(4-H,1-H)=0.8 Hz, 1H, 4-H), 7.13 (dd, ^3J(8-H,7-H)=8.7 Hz, ^4J(8-H,10-H)=1.3 Hz, 1H, 8-H), 7.34–7.40 (m, 1H, NPh 4-H), 7.48–7.53 (m, 2H, NPh 3,5-H), 7.65–7.67 (m, 1H, 10-H), 7.75 (d, ^3J(7-H,8-H)=8.7 Hz, 1H, 7-H), 7.81–7.85 (m, 2H, NPh 2,6-H), 8.86 (d, ^5J(1-H,4-H)=0.8 Hz, 1H, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.89 ($C_3H_6CH_3$), 21.43 (9-CH_3), 22.2 ($C_2H_4CH_2CH_3$), 29.37 ($CH_2CH_2C_2H_5$), 33.45 ($CH_2C_3H_7$), 101.1 (C-4), 110.71 (C-11b), 113.46 (C-7), 119.26 (C-10), 120.0 (NPh C-2,6), 122.61 (C-1), 123.3 (C-8), 127.64 (NPh C-4), 128.78 (C-6a), 129.6 (NPh C-3,5), 133.64 (C-9), 139.8 (NPh C-1), 141.59 (C-5), 144.64 (C-10a), 145.21 (C-3a), 148.21 (C-11a). ^{15}N NMR (40 MHz, $CDCl_3$): δ_N ppm −209.3 (N-6), −160.9 (N-11), −155.4 (N-2).

4.1.2.16.12.5.2. 129c: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 1.04 (t, *J*=7.4 Hz, 3H, $C_3H_6CH_3$), 1.56–1.65 (m, 2H, $C_2H_4CH_2CH_3$), 1.82–1.91 (m, 2H, $CH_2CH_2C_2H_5$), 2.55 (s, 3H, 8-CH_3), 3.24 (m, 2H, $CH_2C_3H_7$), 6.81 (d, ^{5}J(4-H,1-H)= 0.8 Hz, 1H, 4-H), 7.24–7.26 (m, 1H, 9-H), 7.34–7.40 (m, 1H, NPh 4-H), 7.48–7.53 (m, 2H, NPh 3,5-H), 7.67–7.68 (m, 1H, 7-H), 7.75–7.78 (m, 1H, 10-H), 7.81–7.85 (m, 1H, NPh 2,6-H), 8.84 (d, ^{5}J(1-H,4-H)=0.8 Hz, 1H, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.88 ($C_3H_6CH_3$), 21.43 (8-CH_3), 22.2 ($C_2H_4CH_2CH_3$), 29.44 ($CH_2CH_2C_2H_5$), 33.50 ($CH_2C_3H_7$), 101.3 (C-4), 110.78 (C-11b), 114.0 (C-7), 118.9 (C-10), 120.0 (NPh C-2,6), 122.55 (C-1), 125.27 (C-9), 127.62 (NPh C-4), 129.6 (NPh C-3,5), 130.9 (C-6a), 131.63 (C-8), 139.8 (NPh C-1), 141.67 (C-5), 142.35 (C-10a), 144.9 (C-3a), 148.14 (C-11a). MS m/z (%): 355 ($[M+H]^+$, 100). HRMS (ESI) for $C_{23}H_{23}N_4$ ($[M+H]^+$) calcd 355.1917, found 355.1915.

4.1.2.16.12.6. 5-Butyl-9-chloro-2-phenyl-2*H*-pyrazolo[4',3':3,4]pyrido[1,2-*a*]benzimidazole (128d). White solid, yield 107 mg, 57%, mp 227 °C (ethyl acetate).



IR (ν_{max}, cm^{-1}): 3064 (CH_{arom}), 2960 (CH_{aliph}), 1671, 1596, 1499, 1427, 1209 (C=C, C–N), 798, 767, 747, 690 (C–Cl, CH=CH of mono- and trisubstituted benzenes). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H ppm 1.05 (t, *J*=7.4 Hz, 3H, $C_3H_6CH_3$), 1.57–1.68 (m, 2H, $C_2H_4CH_2CH_3$), 1.85–1.94 (m, 2H, $CH_2CH_2C_2H_5$), 3.26–3.32 (m, 2H, $CH_2C_2H_7$), 6.93 (s, 1H, 4-H), 7.31 (dd, ^{3}J(8-H,7-H)=8.9 Hz, ^{4}J(8-H,10-H)=2.0 Hz, 1H, 8-H), 7.39–7.44 (m, 1H, NPh 4-H), 7.52–7.58 (m, 2H, NPh 3,5-H), 7.82–7.86 (m, 1H, 7-H), 7.85–7.89 (m, 2H, NPh 2,6-H), 7.87–7.89 (m, 2H, 10-H), 8.90 (s, 1H, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 13.9 ($C_3H_6CH_3$), 22.2 ($C_2H_4CH_2CH_3$), 29.3 ($CH_2CH_2C_2H_5$), 33.5 ($CH_2C_3H_7$), 102.0 (C-4), 110.6 (C-11b), 114.7 (C-7), 119.2 (C-10), 120.2 (NPh C-2,6), 122.1 (C-8), 122.9 (C-1), 127.9 (NPh C-4), 129.4 (C-6a), 129.5 (C-9), 129.8 (NPh C-3,5), 139.7 (NPh C-1), 141.3 (C-5), 145.4 (C-10a), 146.4 (C-11a), 148.2 (C-3a). ^{15}N NMR (40 MHz, $CDCl_3$): δ_C ppm −209.2 (N-6), −154.3 (N-2). MS m/z (%): 377 ($[M+2]^+$, 36), 375 ($[M+H]^+$, 100). HRMS (ESI) for $C_{22}H_{20}ClN_4$ ($[M+H]^+$) calcd 375.1375, found 375.1371.

4.2. Biology

4.2.1. Cancer cell lines and cytotoxicity assay

Human cancer cell lines were obtained from the American Type Culture Collection and were cultivated according to the provider's instructions. In brief, MCF-7 and K-562 cell lines were maintained in DMEM medium supplemented with 10% fetal bovine serum, penicillin (100 U/mL), and streptomycin (100 µg/mL) at 37 °C in 5% CO_2. For the cytotoxicity assays, cells were treated in triplicate with six different doses of each compound for 72 hours. After treatment, Calcein AM solution was added for 1 hour, and the fluorescence from live cells was measured at 485 nm/538 nm (excitation/emission) by using a Fluoroskan Ascent microplate reader (Labsystems). The GI_{50} value, the drug concentration lethal to 50% of the cells, was calculated from the dose-response curves that resulted from the assays.

4.2.2. Flow cytometry

Asynchronous cells were seeded into a 96 well plate and, after a preincubation period, treated with the tested compounds for 24 hours at a single dose of 10 μM. MCF-7 cells were first washed with PBS, trypsinized, and finally treated with a solution of trypsin inhibitor (0.1%). After the incubation, 5× staining solution (17 mm trisodium citrate dihydrate, 0.5% IGEPAL® CA-630, 7.5 mm spermine tetrahydrochloride, 2.5 mm Tris; pH 7.6 containing 50 μg/mL propidium iodide) was added. K-562 cells were stained directly with the 5x staining solution (i.e., without trypsinization). The cells' DNA content was analyzed by flow cytometry using a 488 nm laser (BD FACS Verse with software BD FACSuite™, version 1.0.6.). Cell cycle distribution was analyzed by using ModFit LT (Verity Software House, version 4.1.7).

For the quantification of histone H3 phosphorylation, the cells were harvested by trypsinization, washed in PBS, fixed with ice-cold 90% methanol, incubated on ice for 30 min, and washed with PBS/BSA containing 0.5% Tween-20. Then, the cells were incubated with the primary antibody raised against histone H3 phosphorylated at Ser10 (Millipore) for 1 hour at room temperature, washed with PBS containing 1% BSA, and incubated with the secondary antibody (goat-anti-rabbit-Alexa Fluor 488, Invitrogen) for 1 hour in the dark. After washing with PBS/BSA, each sample was incubated with propidium iodide (final concentration 10 μg/mL) and RNAse A (final concentration 200 μg/mL) for 30 minutes at room temperature in the dark. Then, the cells were analyzed by flow cytometry using a 488 nm laser (BD FACS Verse with software BD FACSuite™, version 1.0.6.).

4.2.3. Caspase-3/7 assay

Cellular caspase-3/7 activity was measured according to the previously published procedure.[104] K-562 cells were cultivated in a 96-well plate overnight. Next day, the cells were treated with increasing concentrations of compound **5** for the next 24 hours. After the incubation, 3x caspase-3/7 assay buffer (150 mM HEPES pH 7.4, 450 mM NaCl, 150 mM KCl, 30 mM $MgCl_2$, 1.2 mM EGTA, 1.5% Nonidet P40, 0.3% CHAPS, 30% sucrose, 30 mM DTT, 3 mM PMSF) containing 150 μM peptide substrate Ac-DEVD-AMC (Enzo Life Sciences) was added, and after 2 hours incubation, the caspase-3/7 activity was measured by using a Fluoroskan Ascent microplate reader (Labsystems) at 346 nm/442 nm (excitation/emission). The activity was normalized to an untreated control.

4.2.4. Immunoblotting

Immunoblotting was performed as described earlier.[105] In brief, cellular lysates were prepared by harvesting cells in Laemmli sample buffer. Proteins were separated on SDS-polyacrylamide gels and electroblotted onto nitrocellulose membranes. After blocking, the membranes were incubated with specific primary antibodies overnight, washed, and incubated with peroxidase-conjugated secondary antibodies. Finally, peroxidase activity was detected with ECL+ reagents (AP Biotech) by using a CCD camera LAS-4000 (Fujifilm). Specific antibodies were purchased from Santa Cruz

Biotechnology (PARP, β-actin), Cell Signaling (Ser-139 phosphorylated H2AX, Bcl-2), and Sigma Aldrich (peroxidase-labeled secondary antibodies).

5. THE MAIN RESULTS AND CONCLUSIONS

1.Derivatives of the 2*H*-furo[2,3-*c*]pyrazole can be easily obtained *via* the silver (I) or gold (I) ion mediated cyclisation of 4-alkynyl-1-phenyl-1*H*-pyrazol-3-ols.

2. 3-Alkynylpyrazole-4-carbaldehydes and the corresponding alkanones are suitable precursors for the preparation of 2*H*-pyrazolo[4,3-*c*]pyridine derivatives.

3. A simple and straightforward approach to various benzopyrano[2,3-*c*]pyrazol-4(2*H*)-ones starting from easily available 4-aroylpyrazol-3-ols is developed.

4. The reaction of 3- and 5-alkynylpyrazole-4-carbaldehydes with (het)aryl diamines results in the formation of polycylic condensed heterocyclic systems.

5. 1-Methyl-3,5-diphenyl-3*H*-pyrazole[4',3':3,4]pyrido[1,2-*a*]benzimidazole can be functionalized by employing Sonogashira- and Suzuki-type coupling reactions of the corresponding intermediate bromide.

6. 2*H*-Pyrazolo[4,3-*c*]pyridine derivatives exhibit anticancer activity against K-562 and MCF-7 cancer cell lines *in vitro* through arresting the cell cycle in mitosis and induction of apoptosis.

7. 2*H*- and 3*H*-pyrazole[4',3':3,4]pyrido[1,2-*a*]benzimidazole derivatives are novel fluorescent organic compounds characterized by a high quantum yield (Φ_f).

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LIST UF PUBLICATIONS

Publications in the journals inscribed into the list approved by the Information Scientific Institute (ISI)

•**Milišiūnaitė, Vaida**; Arbačiauskienė, Eglė; Řezníčková, Eva; Jorda, Radek; Malínková, Veronika; Žukauskaitė, Asta; Holzer, Wolfgang; Šačkus, Algirdas; Kryštof, Vladimír. Synthesis and anti-mitotic activity of 2,4- or 2,6-disubstituted- and 2,4,6-trisubstituted-2*H*-pyrazolo[4,3-*c*]pyridines // European Journal of Medicinal Chemistry. Paris : Elsevier Masson SAS. ISSN 0223-5234. eISSN 1768-3254. 2018, Vol. 150, pp. 908–919. DOI:10.1016/j.ejmech.2018.03.037.

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