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REVIEW

Exploitation of pyrazole C-3/5 carbaldehydes towards the development of therapeutically valuable scaffolds: a review

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Abstract

Over the past decades, pyrazole has displayed significant importance in various areas of chemistry and industry owing to its unique nature, reactivity, and properties. Pyrazole is versatile compound with a wide range of applications in pharmaceuticals, agriculture, materials science, and various branches of science. Specifically, pyrazole C-3/C-5 carbaldehydes can be used as a building block in organic synthesis to create more valuable and bioactive molecules. In this context, pyrazole C-3/C-5 carbaldehydes may be explored for achieving pyrazole fused/linked heterocyclic skeletons by employing different organic transformations. The investigation of pyrazole C-3/C-5 carbaldehydes has resulted in the formation of a range of biologically potent heterocyclic structures, which include pyrazole C-3/C-5-based silicon derivatives, pyrazole C-3/C-5-based Schiff base derivatives, pyrazole C-3/C-5-based metal complexes, pyrazole C-3/C-5-based imidazo[1,2-a]azines, pyrazole C-3/C-5-based sulphur containing derivatives, and pyrazole C-3/C-5-based thioamide and amides, as well as other pyrazole fused/tethered polycyclic systems. Previous reports have shown that derivatives synthesized from the pyrazole C-3/C-5 carbaldehyde have demonstrated favourable biological uses like 5-HT3A receptor antagonists, allosteric inhibitors, insecticidal activity, antioxidant, antifungal, antiproliferative and antimicrobial. Pyrazole C-3/C-5 carbaldehydes have the potential to be highly utilized in the medical field as well as material science if studied judiciously. This review focuses on the exploration of pyrazole C-3/C-5 carbaldehydes towards the synthesis of highly diversified pyrazole-based molecular hybrids till 2023 and describes their promising utilization in the field of pharmaceutical science.

Keywords Pyrazole · C-3/C-5 Carbaldehydes · Pyrazole tethered/fused derivatives · Medicinal importance · Synthetic practicality · Photophysical properties

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Introduction

Heterocyclic compounds are extensively spread in nature and play a dynamic role in metabolism because their subunits are important constituents of natural products, including hormones, antibiotics, vitamins, and alkaloids (Saini et al. 2013; Al-Mulla et al. 2017). Among heterocycles, nitrogen-containing heterocyclic compounds are the core units of many biologically active compounds and display numerous applications in biology, chemistry and other sciences. Over the decades, research in pyrazole derivatives has significantly increased due to their interesting chemical, physical, and biological properties making them a privileged scaffold (Castillo and Portilla 2018). Pyrazole and its analogues are categorized as alkaloids despite their very low richness in nature as it is very difficult to generate the N–N bond. Moreover, another pyrazole-based alkaloid, l-β-(1-pyrazolyl)alanine, was isolated from the seeds of watermelon (Citrullus Vulgaris, Fig. 1) (Blair and Sperry 2013; Najim et al. 2016). In addition, a few other pyrazole-based natural products are presented in Fig. 1.

Pyrazole is a pattern found in an array of small molecules displaying a vast spectrum of medicinal and pharmaceutical properties (Kumar et al. 2013; Li and Zhao 2014). In past decade, several drugs decorated with the pyrazole framework have been marketed successfully (Fig. 1) (Khan et al. 2016). For example, Rimonabant acts as a cannabinoid ligand and is used to treat obesity (Chamberlain et al. 2010); Celecoxib displays anti-inflammatory effects and inhibits COX-2 (Abadi et al. 2003; Flower 2003); Sildenafil inhibits phosphodiesterase (Dale et al. 2000; Dunn et al. 2004); and Fomepizole inhibits alcohol dehydrogenase. Figure 1 represents a few examples of pyrazole-based drug candidates and bioactive molecules. Moreover, pyrazole and its analogues are well-known to display a vast spectrum of biological properties such as anti-HIV, anticancer, antitumor, anti-inflammatory, antidepressant, antipyretic, antiviral, antifungal, anticonvulsant and antibacterial (Manpadi et al. 2007; Abdel-Aziz et al. 2009; Singh et al. 2013; Schenone et al. 2014; Perez-Fernandez et al. 2014; Qin et al. 2014; Kalaria et al. 2014; Khloya et al. 2015; Kamal et al. 2015; Jha et al. 2016; Lusardi et al. 2023a, 2023b, 2023c).

In addition, pyrazole derivatives are also known to exhibit remarkable electroluminescence (Gao et al. 1999),

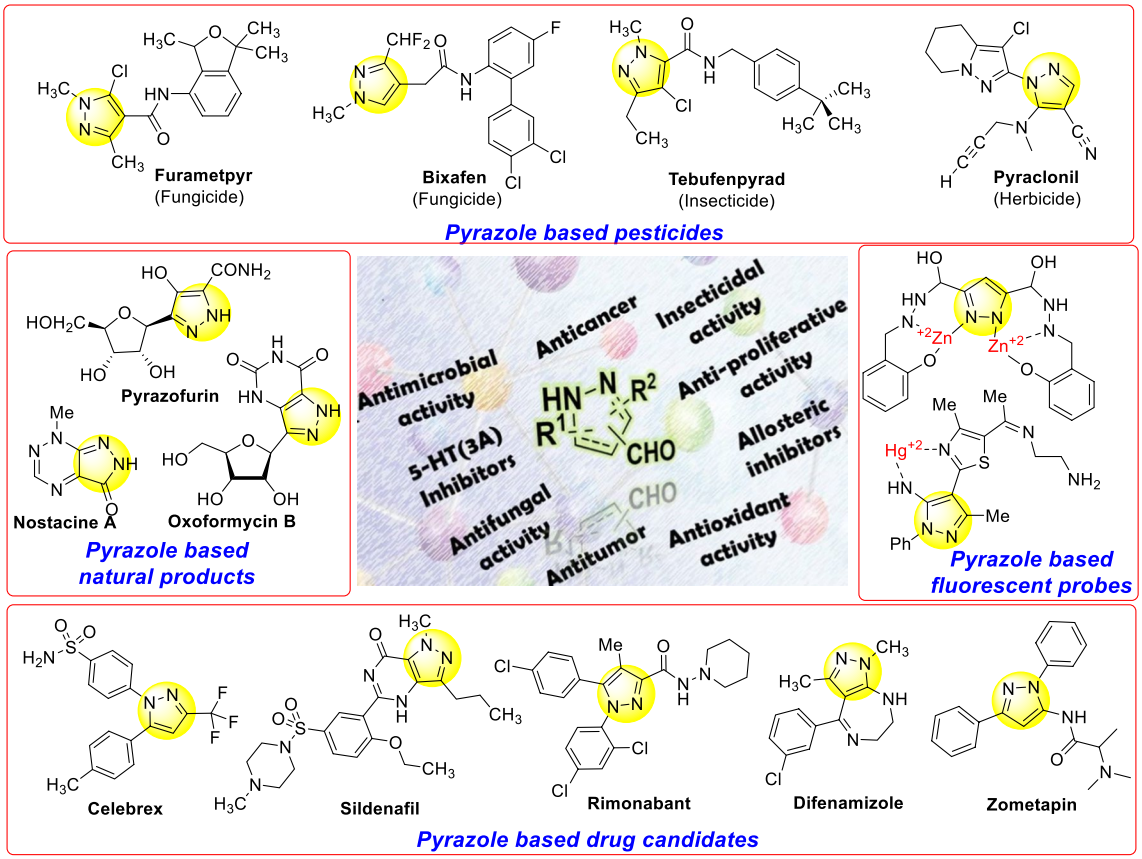
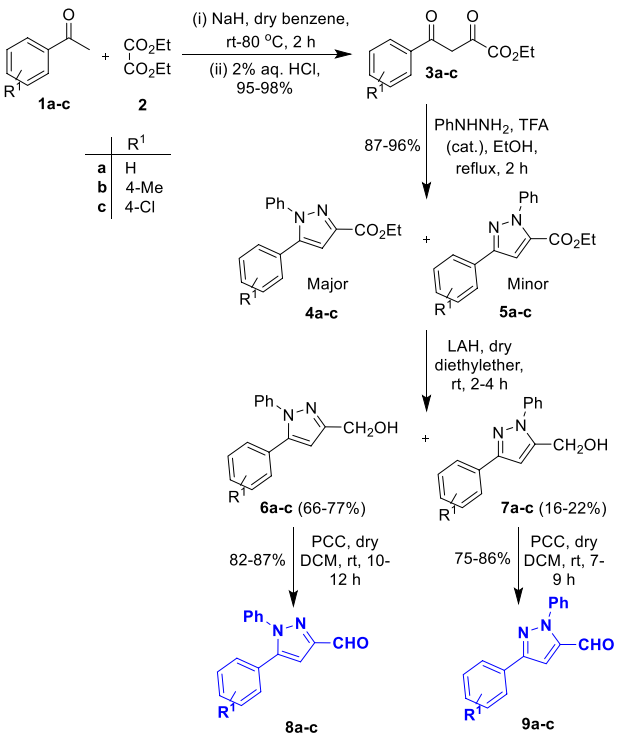


Fig. 1 Pyrazole-based commercial drugs and bioactive molecules

solvatochromic effects (Karci et al. 2013) to get application in the field of material science as brightening agents (Wang et al. 2002). They can act as liquid crystals (Kauhanka and Kauhanka 2006), semiconductors (Burschka et al. 2013) and organic light-emitting diodes (Chou and Chi 2007). Pyrazole and its analogues have also received considerable attention because of their synthetic applications as chiral auxiliaries (Molteni and Buttero 2005), reagents in various multicomponent reactions (Tu et al. 2014) and guanylating agents (Castagnolo et al. 2011). Substituted pyrazoles are also utilized as chelating agents for the detoxification of undesired metal ions (Singh et al. 2006). Besides, pyrazole heterocycles also display fungicidal (Zhuang et al. 2016) (Bixafen, Furametpyr and Penthiopyrad), herbicidal (Fu et al. 2017) (Pyraclonil) and insecticidal (Verma and Nayal 2003; Wang et al. 2017) properties and have contributed to the plant and crop protection (Fig. 1).

Researchers are more interested in designing and making new pyrazole derivatives for drug discovery programmes because pyrazole-based building blocks are easy to make, have good chemical properties, and have many reactive sites. Among pyrazole derivatives, pyrazole C-3/C-5 carbaldehyde has aldehyde functional group at C-3 and C-5 positions of the pyrazole ring, can easily react with nucleophiles to make useful scaffolds based on pyrazoles. Furthermore, it is widely acknowledged that pyrazole C-3/C-5-based molecular hybrids are of great importance because they provide opportunities for multiple reactions such as transition-metal catalysed, coupling approaches, multicomponent that either result in novel tether/fused-pyrazoles derivatives or provide useful intermediates for further complex reactions. Particularly, substituted pyrazole-3/5-carbaldehydes, which can be readily synthesized, possess unique characteristics for the incorporation of desired patterns. Recently, our group comprehensively summarized the synthesis and applications of aldo-X precursors like 4-iodo-pyrazole-3/5-carbaldehydes (Sharma et al. 2020a, 2020b, 2020c).

The synthetic potential of pyrazole-3/5-carbaldehydes has not been previously studied, despite their considerable significance. Several research groups reviewed the synthetic and biological potential of pyrazole derivatives, but these synthetic methods were limited to particular substrates. Recently, our group summarized the exploration of pyrazole carbaldehydes, restricting it to the 4-iodo-pyrazole-3/5-carbaldehydes (Sharma et al. 2020a, 2020b, 2020c). This brief study aims to discuss the synthetic methods employed in the synthesis of biologically active fused and tethered scaffolds, especially based on pyrazole C-3/C-5. To the best of our understanding, this review represents the first synthetic and biological applications of pyrazole-3/5-carbaldehydes till 2023.



Scheme 1 Gram synthesis of pyrazole C-3/C-5 carbaldehydes

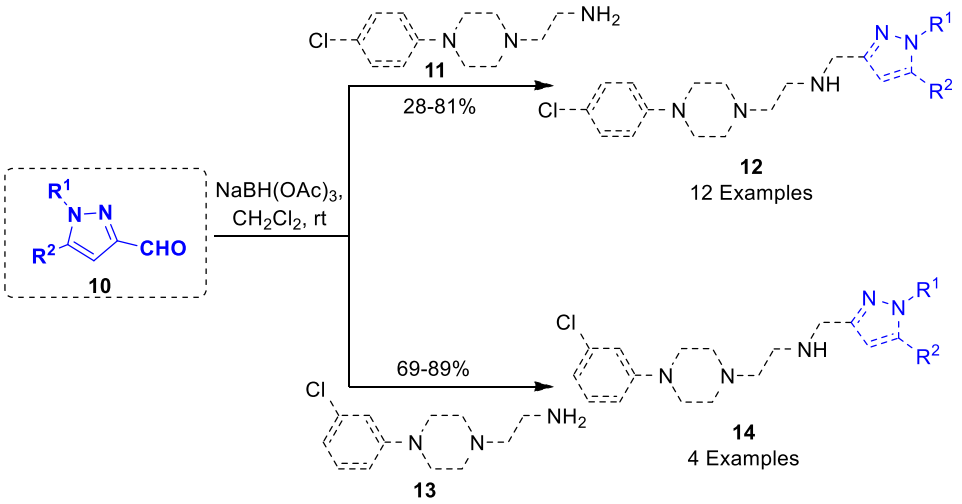
Gram-scale synthesis of pyrazole C-3/C-5 carbaldehydes as a starting substrates

The synthesis of pyrazole-3/5-carbaldehydes is described in Scheme 1 (Nag et al. 2007). The Claisen condensation of various substituted acetophenones **1a-c** with diethyloxalate **2** to furnish the dioxo esters **3a-c** (95–98%) was carried out. Further, the treatment of **3a-c** with phenyl hydrazine afforded the pyrazole derivatives **4a-c** and **5a-c** (87–96%). Next, the pyrazole esters **4a-c** and **5a-c** were subjected to $LiAlH_4$-mediated reduction and PCC-promoted oxidation to afford the pyrazole C-3/C-5 carbaldehydes (**8a-c** and **9a-c**) in 82–87 and 75–86% yields (Scheme 1). Interestingly, the method was also applicable to the electron donating and electron withdrawing groups decorated acetophenones as a starting material.

Synthetic and biological applications of pyrazole-3/5-carbaldehydes

This section describes the synthetic potential of pyrazole C-3/C-5 carbaldehydes towards the development of biologically active scaffolds. Moreover, the results of biological studies of the investigated compounds by the several research groups are also displayed in this section.

Scheme 2 Synthesis of 3-(*N*-arylpiperazinylethyl)aminomethylpyrazole derivatives



R^1 = *t*-butyl, Ph;
R^2 = *p*-ClC_6H_4, *n*-propyl, *i*-butyl, *p*-tolyl, Ph, Me, 2-furyl, (*p*-cyclohexyl)C_6H_4, (*p*-piperidinyl)C_6H_4

Compound	5-HT_{3A} receptor		
	V_{max}	IC_{50}(μM)	nH
12	94.8-104.3	1.3-28.3	1.1-1.9
14	87.6-98.4	9.4-31.0	1.1-1.6

Exploration of pyrazole C-3 carbaldehydes towards the synthesis of biologically active derivatives

Particularly, this part illustrates the exploration of pyrazole C-3 carbaldehydes for the synthesis of biologically active molecular architectures. Additionally, the biological activity of pyrazole C-3-based derivatives is also discussed in this section.

In 2009, Lee et al. stated that a new series of *N*-chlorophenyl tethered piperazinylethylamino pyrazole-based 5-HT_{3A} receptor antagonists **12** and **14** were developed and investigated their potency on the 5-HT_{3A} receptor channel (Scheme 2) (Lee et al. 2009). The reaction of pyrazole C-3 carbaldehydes **10** with chloro-substituted aryl amine **11** delivered pyrazole-based molecular hybrids **12** and **14** in 28–81 and 69–89% yields, respectively. They observed that most of the synthesized derivatives **12** showed high potency towards the inhibition of $I_{5\text{-}HT}$, while derivative **14** with *m*-chlorophenyl group exhibited low potency. These studies suggested that novel chlorophenyl linked piperazinyl-pyrazoles **12** and **14** could be a lead molecule for 5-HT_{3A} inhibition. Moreover, *p*-chlorophenyl moiety might play a major role in enhancing the inhibition activity against 5-HT_{3A}.

In 2011, Rodionov et al. a new ferrocene-based pyrazole compound in the form of 5-ferrocenyl-1-phenyl-1*H*-pyrazole-3-carbaldehyde **15** Synthesized and as presented in Scheme 3 (Rodionov et al. 2011). The one-pot reaction of pyrazole C-3 carbaldehyde **15** and secondary amine **16** in the presence of DCE at room temperature delivered the pyrazole tethered amino derivatives **17** in 70–91% yields. The electrochemical data of 5-ferrocenyl-1-phenyl-1*H*-pyrazole-3-carbaldehyde **17** are shown in Scheme 3. The anodic electrochemical properties of compound **17** were measured by cyclic voltammetry in CH_3CN solution with [*n*-Bu_4N][PF_6] as a secondary electrolyte. The involvement of electron-donating or electron-withdrawing groups in the phenyl ring of pyrazole derivatives does not impact the oxidation potential.

In another study, the authors (Osipova et al. 2011) synthesized a modified pyrazole-ferrocene-based porphyrin **19** via a similar reductive amination approach to ferrocenyl-pyrazole carbaldehyde **15** and tetraphenyl porphyrinamine **18** (Scheme 4). The reductive amination of pyrazole carbaldehyde **15** was carried out in the presence of $NaBH(OAc)_3$ in DCE at room temperature. It was revealed that the reaction only proceeded with ferrocenylformaldehydes that did not have any steric hindrances between substituents in the pyrazole unit. Therefore, the steric environment created by the ferrocene-pyrazole framework **15** was observed to play an important role in this reductive amination reaction.

Next, they (Osipova et al. 2012) also synthesized a ferrocene-pyrazole-based framework **21** via the reductive amination reaction of 5-ferrocene-1*H*-pyrazole-3-carbaldehyde

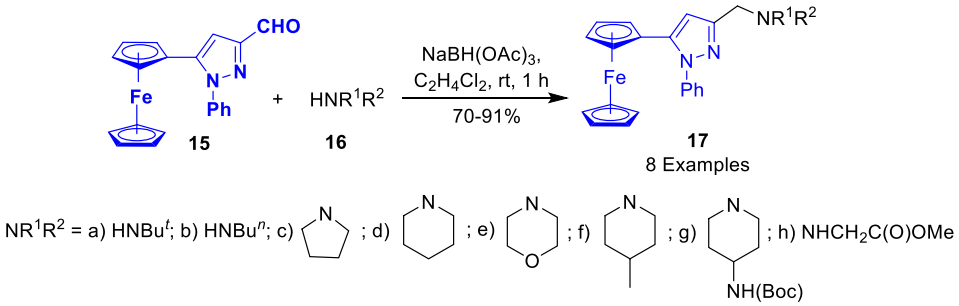
15 with *p*-chloroaniline **20,** as presented in Scheme 5. The targeted compound **21** was afforded in 63% yield under similar reaction conditions.

The authors extended the study to include the formation of metalloporphyrin **22** as outlined in Scheme 6. Initially, the reaction of ferrocenylpyrazole-3-carbaldehyde **15** with porphyrin **18** resulted in the formation of the anticipated product **19** with a 62% yield. Thereafter, porphyrin-modified ferrocene **20** was subjected to interaction with three transition metal salts (Zn^{2+}, Cu^{2+} and Mn^{2+}). The desired products **22** were achieved with excellent yields (95–98%). Osipova et al. also studied the electrochemical properties of newly synthesized metalloporphyrin **22**. The incorporation of an electron-donating fragment into the ferrocene unit of the complex does not impact the oxidation and reduction potentials of the porphyrin fragment. However, the oxidation potential of ferrocene is slightly moved towards the cathode region. The results of electrochemical experiments in terms of oxidation and reduction potential are summarized in Scheme 6.

Here, an elegant metal-free approach for transforming aldehydes **23** into trifluoromethyl tethered pyrazole **24** has been presented (Qiao et al. 2014) (Scheme 7). The multistep reaction of pyrazole C-3 carbaldehyde **23** afforded the trifluoro methyl pyrazoles **24** in 69% yield. This transformation provided additional advantages such as (1) less time for reaction completion; (2) low operational and labour cost; (3) metal-free; (4) less waste during workup; (5) easy-to-perform reactions; (6) nontoxic and stable reagents; and (7) one-pot procedure.

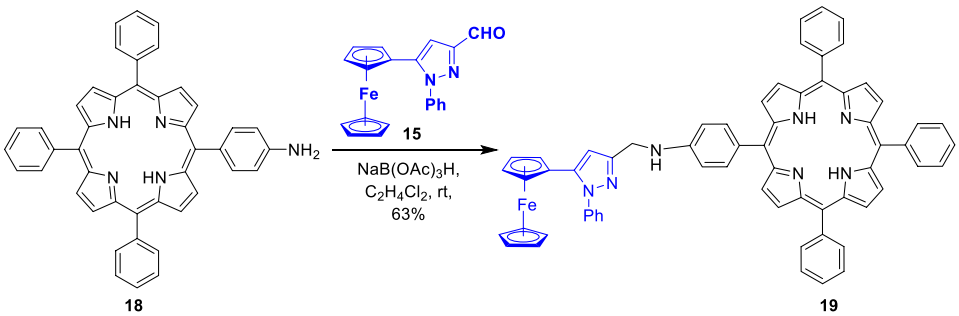
A novel pyrazole-based molecular hybrids **30** have been synthesized as outlined in Scheme 8 (Yao et al. 2014).

Scheme 3 Reductive amination reaction of 5-ferrocenyl-1-phenyl-1*H*-pyrazole-3-carbaldehyde

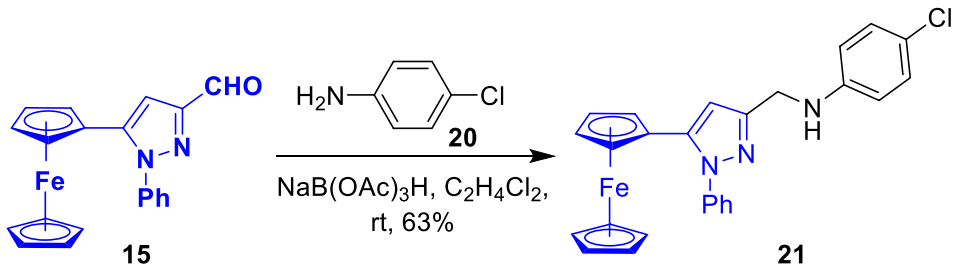


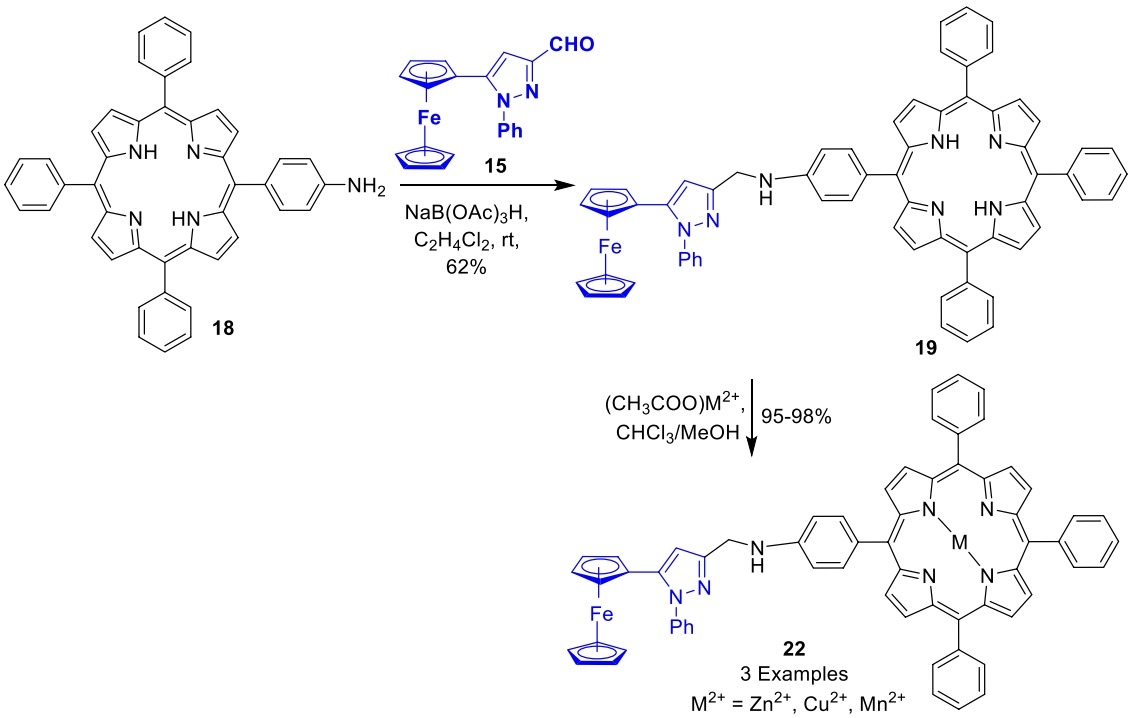
Compound	Oxidation $E_{1/2}$, V	$\triangle E_{1/2}$, V	Reduction E_p, V
17	0.54	0.08	-2.05

Scheme 4 Synthesis of modified ferrocene-pyrazole-based porphyrins



Scheme 5 Synthesis of ferrocene-pyrazole-based framework





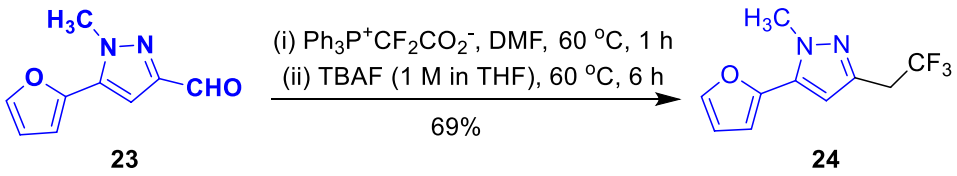
Oxidation potential of the complexes of Fc-TPP-X (X = Cu^{2+}, Mn^{2+})

Substance	E_1^{ox}, mV	E_2^{ox}, mV,	E_3^{ox}, mV	E_4^{ox}, mV	$-E_1^{Red}$, mV	$-E_2^{Red}$, mV
Fc-TPP	640/560	920	1130	-	1120/1050	1450/1350
Fc-TPP-Cu	630/550	960	1160	1420	1190/1130	1530/1450
Fc-TPP-Mn	650/550	920	1120	1380	1100/1020	1430/1320

In solution 0.2 M Bu_4NPF_6 in CH_2Cl_2, Potassium electrode, referred to Fe/Fe^+

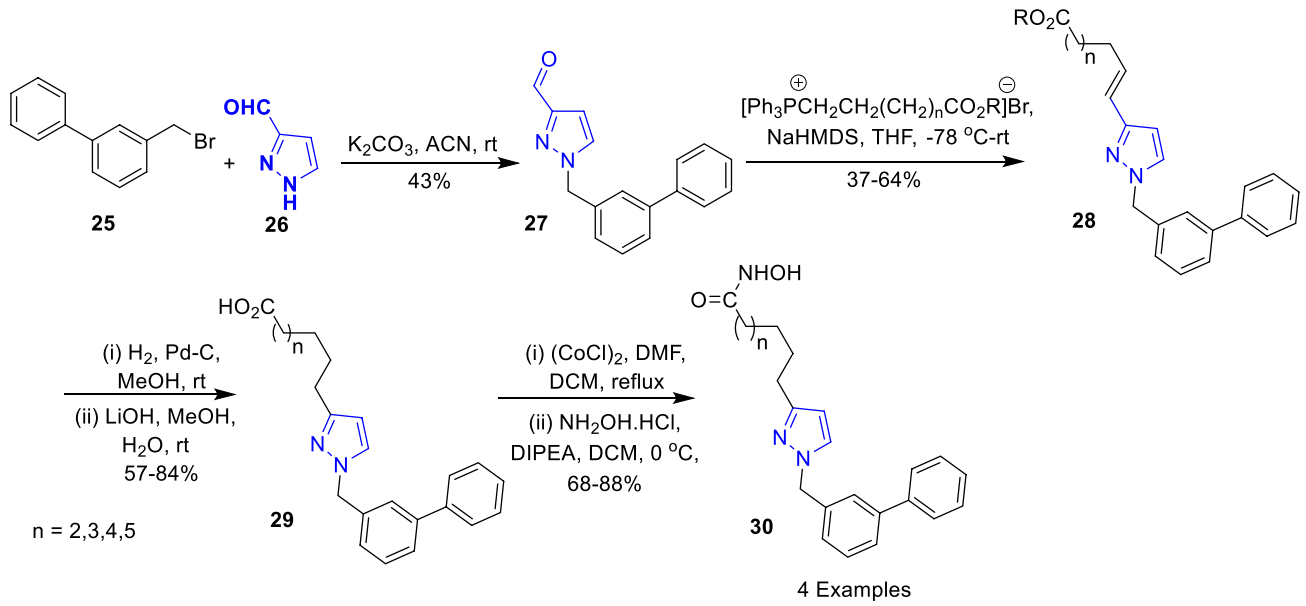
Scheme 6 The metalation method of 3-(5-(*p*-aminophenyl)-10,15,20-triphenylporphyrin)-5-ferrocenyl-1-phenylpyrazole (**19**)

Scheme 7 Synthesis of 5-(furan-2-yl)-1-methyl-3-(2,2,2-trifluoroethyl)-1*H*-pyrazole



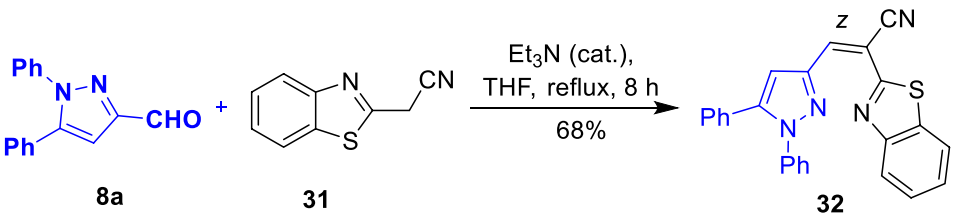
Briefly, the condensation of bromo compound **25** and pyrazole C-3 carbaldehyde **26** led to intermediate **27** that was converted by Witting reaction to derivatives **28** in 37–64% yields. The subsequent reduction of alkene functionality and the hydrolysis of the ester group led to the isolation of acid derivatives **29** in 57–84% yields. Compounds **29** treated with $CoCl_2$, $NH_2OH.HCl$, DIPEA in the presence of dry DCM resulted in the formation of final pyrazole-based molecular hybrids **30**. In addition to this, the synthesized compounds **30** showed better selectivity for class I and IIb over class IIa HDAC isoforms compared to the FDA approved HDAC targeting drug SAHA. This work could serve as a fundamental platform for further exploration of selective HDAC inhibitors using designed molecular scaffold.

In another study, the authors (Refat and Mohamed 2015) established an efficient and convenient strategy for the preparation of (*Z*)-2-(benzo[*d*]thiazol-2-yl)-3-(1,5-diphenyl-1*H*-pyrazol-3-yl)acrylonitrile (**32**) (Scheme 9). The reaction of 1*H*-pyrazole-C3-carbaldehyde **8a** and 2-(benzo[*d*]thiazol-2-yl)acetonitrile (**31**) delivered the targeted framework **32** in the presence of catalytic TEA (triethylamine). The pyrazole C3 tethered benzothiazole **32** was obtained in 68% yield after refluxing.



Scheme 8 Synthesis of pyrazole tethered molecular architectures

Scheme 9 Reaction of pyrazole C-3 carbaldehyde and benzothiazole

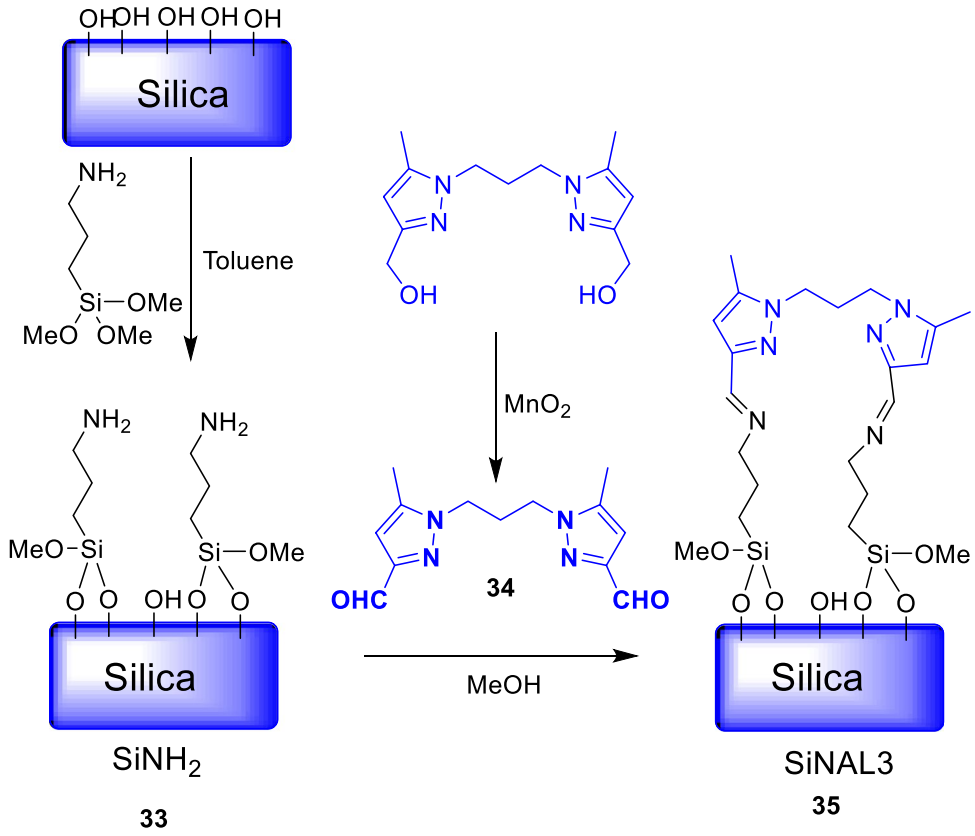


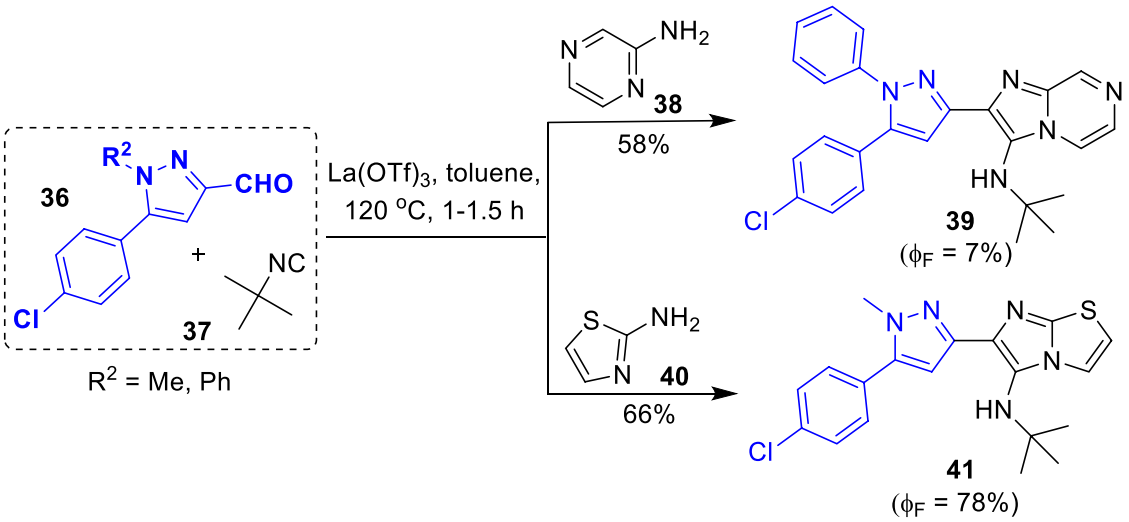
In 2018, a synthetic route for the synthesis of pyrazole silica based molecular hybrids **35** has been described (El-Massaoudi et al. 2018). The reaction of bis-pyrazole C-3 carbaldehyde **34** and $SiNH_2$ **33** delivered the pyrazole-Schiff base containing silico compounds **35** (Scheme 10). The synthesized hybrid material **35** was studied for its ability to uptake Zn (II), Cu (II), Pb (II) and Cd (II) ions in an aqueous solution via kinetics studies. The highest capacity for adsorbing Zn (II), Cu (II), Pb (II), and Cd (II) metals was determined to be 1.23, 0.32, 0.29, and 0.23 mmol g^{-1}, respectively. In addition, hybrid material has demonstrated excellent recyclability and reusability, maintaining its performance up to five cycles.

In 2020, our group (Sharma et al. 2020a, 2020b, 2020c) explored the pyrazole C-3 carbaldehydes **36** towards the synthesis of highly fluorescent pyrazole tethered imidazo[1,2-*a*] azines **39** and **41** as presented in Scheme 11. The reaction of pyrazole C-3 carbaldehydes **36**, *tert*-butyl isocyanide **37** and 2-aminopyrazole **38** or thiazol-2-amine **40** in the presence of $La(OTf)_3$ led to the fluorescent pyrazoles **39** and **41** that displayed excellent photophysical properties (fluorescence quantum yield up to 78%).

Next, the authors (Wassel et al. 2021) designed and synthesized a novel pyrazole-based carbonic anhydrase inhibitor **44** as demonstrated in Scheme 12. The reaction of adamantane-based hydrazide **42** and pyrazole C-3 aldehyde **43** afforded the final pyrazole-adamantane-based molecular hybrid **44**. The simple condensation of the starting substrate in the presence of EtOH and acetic acid accomplished the present reaction. Furthermore, the novel derivative **44** was investigated for its antitumor activity against three cell lines (MCF-7, HepG-2 and A549). The synthesized scaffolds **44** displayed good IC_{50} values (3.75 to 7.46 µM) in comparison with Doxorubicin (3.58–8.19 µM) (Scheme 12). The molecular docking was performed to evaluate the binding modes and possible interactions of the adamantane derivatives within the active site of CAIX/XII and CAXII (PDB codes 3IAI and 1JD0 respectively). The results of molecular docking revealed that the binding affinity was enhanced by the presence of a pyrazole derivative due to its ability to form multiple interactions. Additionally, the presence of a carbonyl group, either at a side chain or directly attached to the pyrazole ring, further increased binding within the pocket.

Scheme 10 Synthesis of silica gel bonded bis-pyrazolyl-propane

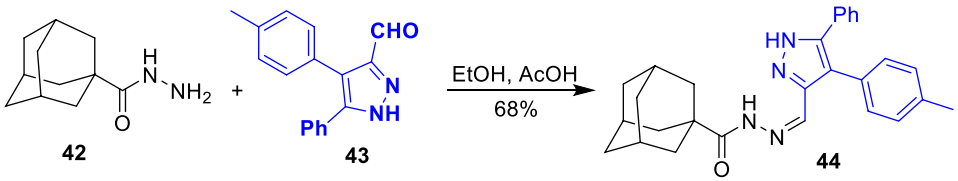




Scheme 11 Synthesis of pyrazole C-3 substituted imidazo[1,2-*a*]azine derivatives

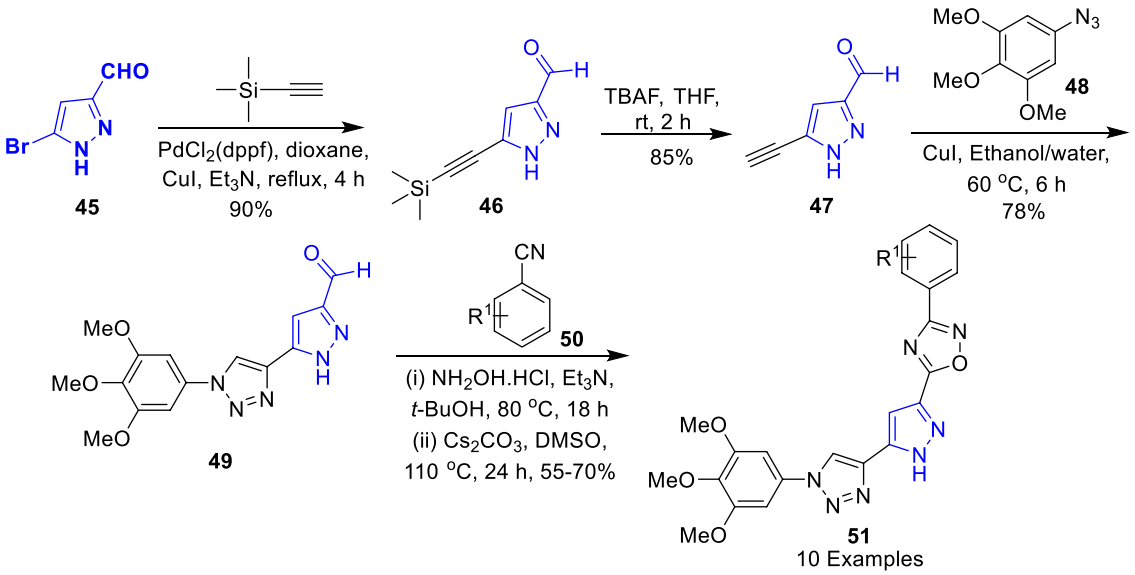
In the following year, the synthesis of novel anticancer agent as pyrazole containing hybrid molecules **51** reported as mentioned in Scheme 13 (Mohan et al. 2021). Firstly, the coupling reaction of bromo containing pyrazole C-3 carbaldehyde **45** with ethynyltrimethylsilane delivered intermediate **46** was further deprotected to afford compound **47**. The treatment of aryl azide **48** with **47** in the presence of CuI, ethanol and water at 60 °C resulted in the formation of pyrazole tethered triazole compound **49** that was converted into the desired derivatives **51** by reacting with aryl cyanides **50** via a two-step reaction (Scheme 13). Additionally, the synthesized compounds were tested for their anticancer

Scheme 12 Reaction of adamantane-1-carbohydrazide with pyrazole C-3 carbaldehyde



Antitumor activity

Compound	IC_{50} (μM)		
	MCF-7	HepG-2	A549
44	7.46	5.11	3.75



R^1 = 4-NO_2, 3,5-$(NO_2)_2$, 3,4,5-$(OMe)_3$, 3,5-$(OMe)_2$, 4-OMe, 4-Cl, 4-Br, 4-Me, 4-$N(Me)_2$, 3,5-$(Me)_2$

Anticancer activity

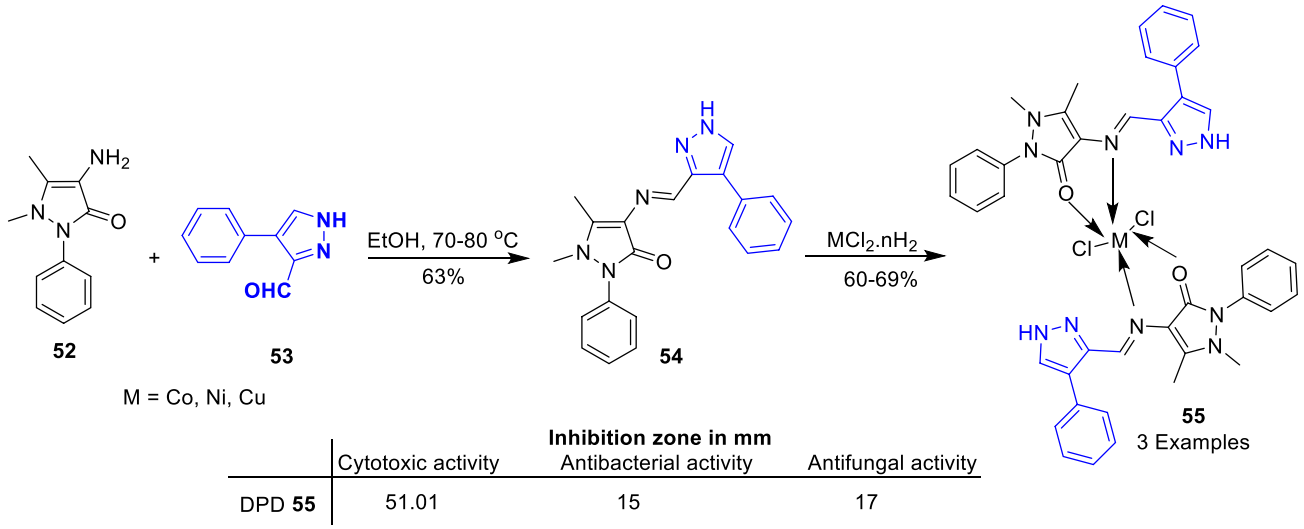
Compound	IC_{50} (μM)			
	[a]PC3	[b]A549	[c]MCF-7	[d]DU-145
51	0.01-9.30	0.27-12.7	0.08-14.2	0.63-34.6
Etoposide	2.39	3.08	2.11	1.97

[a]PC3 : human prostate cancer cell line
[b]A549 : human lung cancer cell line
[c]MCF-7 : human breast cancer cell line
[d]DU-145 : human prostate cancer cell line

Scheme 13 Synthesis of 1,2,4-oxadiazole incorporated 1,2,3-triazole-pyrazole derivatives

properties towards human cancer cell lines (PC3, DU-145 (prostate cancer), A549 (lung cancer) and MCF-7 (breast cancer)) by using MTT method with etoposide as a standard reference. The data from this study are summarized in Scheme 13.

Further, in 2022, a novel ligand synthesized 1,5-dimethyl-2-phenyl-4-{[(*E*)-(4-phenyl-1*H*-pyrazol-3-yl) methylidene] amino}-1, 2-dihydro-3H-pyrazol-3-one (DPD) **54** as illustrated in Scheme 14 (Ranjitha et al. 2022). Initially, a simple condensation reaction in EtOH of pyrazole amine **52** and pyrazole C-3 carbaldehyde **53** afforded the pyrazole-based imine intermediate **54** with a 63% yield. Imine intermediate **54** was further subjected to the chelation reaction for the synthesis of pyrazole complex **55**. Interestingly, the redox

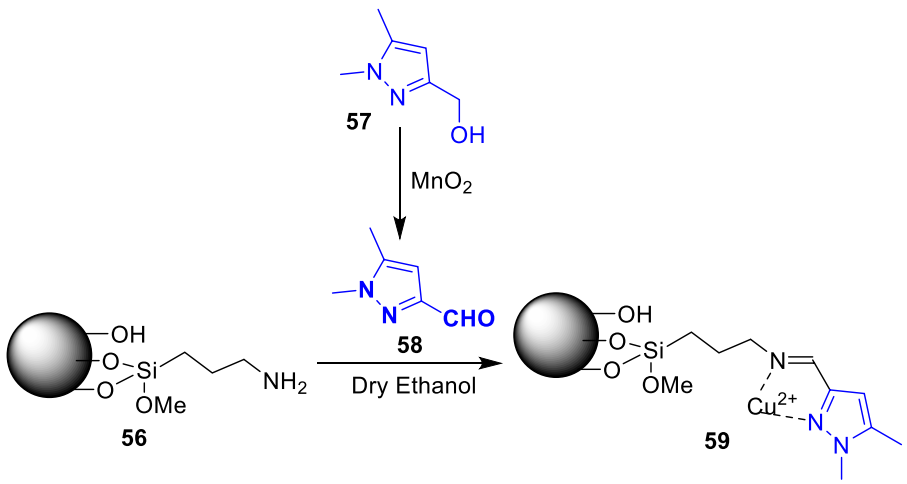


Scheme 14 Synthetic route for the formation of pyrazole based Co (II), Ni (II) and Cu (II) complexes

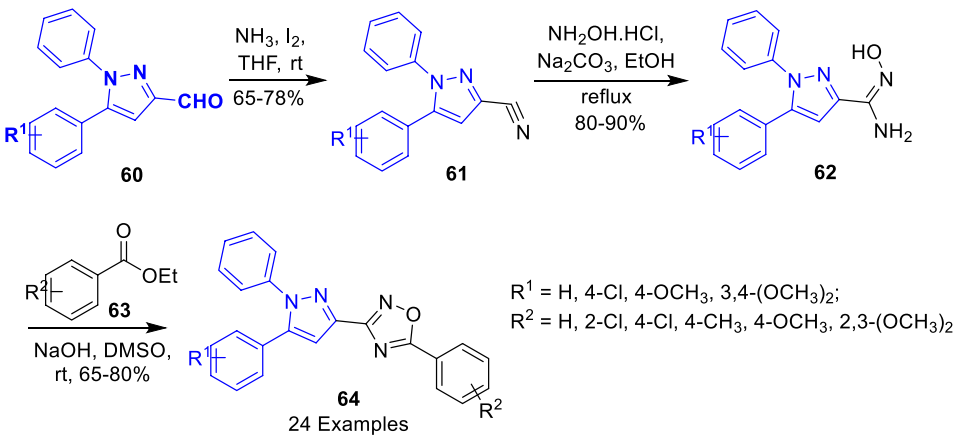
nature of complex **55** was evaluated via a cyclic voltammogram method and it was noted that the physico-chemical characterization of the modified electrode displayed significant results with a long linear range 0.2–1.5 µM/L, sensitivity 1.65 $\mu A \mu M^{-1}$ cm^{-2}. Moreover, the antibacterial, antioxidant and cytotoxic activities of the ligand and its metal complexes were investigated through the agar well diffusion method against *S. aureus*, *B. licheniformis*, A. Sp and *P. aeruginosa* as well as antifungal *P. expansum*, *A. flavus* strains. The biological experiments demonstrated significant activity of the metal complexes **55** in comparison with the reference drug.

In the same year, the authors (Jodeh et al. 2022) developed a route for the formation of pyrazole-based silico complex **59** as presented in Scheme 15. In the first step, the oxidation reaction of pyrazole alcohol in the presence of MnO_2 yielded pyrazole C-3 carbaldehyde **58**. After that, pyrazole C-3 carbaldehyde **58** reacted with organically modified silica to form the final pyrazole-silica-based copper complex **59**. The synthesized materials **59** adsorbed a high percentage of TMP (trimethoprim), reaching more than 94% with increasing pH.

A series of pyrazole tethered 1,2,4-oxadiazole derivatives **64** has been synthesized (Kulkarni et al. 2023). Firstly, the reaction of pyrazole C-3 carbaldehydes **60** with NH_3 and iodine in dry THF at room temperature led to the corresponding pyrazole C-3 nitrile derivatives **61** (Scheme 16). The treatment of **61** with hydroxylamine hydrochloride and sodium carbonate in refluxing ethanol resulted in the formation of key intermediates **62** that were subjected to a base-mediated reaction with aryl ester **63** to form the final pyrazole tethered 1,2,4-oxadiazole **64** in 65–80% yields.



Scheme 15 Simple and efficient synthesis of pyrazole-silica-based copper complex



Scheme 16 Base-mediated reaction for the synthesis of pyrazole C-3 tethered 1,2,4-oxadiazoles

Exploration of pyrazole C-5 carbaldehydes towards the synthesis of pharmaceutically active scaffolds

This section provides a summary of the exploration of pyrazole C-5 carbaldehydes for the preparation of pharmaceutically active molecular architecture and structures. Additionally, the results of the biological study for the synthesized compounds are also discussed in this section.

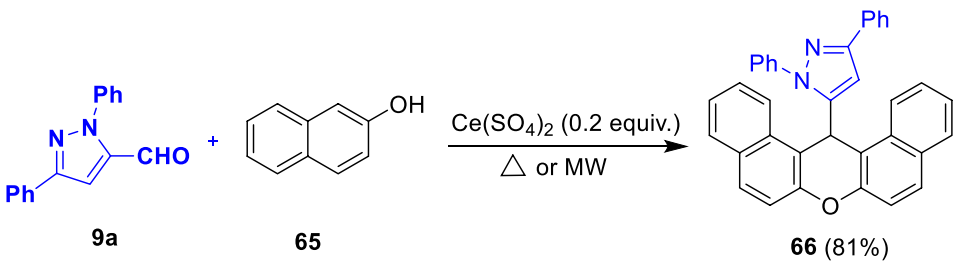
In 2007, Selvam's group (Selvam et al. 2007) unfolded a simple and facile method for the construction of pyrazole C5 tethered xanthene derivative **66** as displayed in Scheme 17. This one-pot procedure was involved for the condensation of pyrazole-5-carbaldehyde **9a** with 2-napthol **65** in the presence of 20 mol% anhydrous $Ce(SO_4)_2$ as the catalyst under solvent-free conditions. The resulting product **66** was obtained in high yield (81%) under conventional as well as microwave heating. The current protocol offers several advantages, such as mild reaction condition, shorter reaction time, high yield, general applicability, use of inexpensive and commercially available cerium(IV)sulphate.

Next, in 2008, Montalban and team (Montalban et al. 2008) described a protocol for the formation of pyrazole C-5 tethered ketoamide derivatives **72–74**, which showed activity against p38 MAP kinase (Scheme 18). Initially, the reaction of pyrazole aldehydes **67** with trimethylsilyl cyanide (TMSCN) resulted in the formation of pyrazole-cyanohydrins **68**; further simultaneous de-protection and hydrolysis of **68** furnished the pyrazole-α-ketoacids **70**. The treatment of intermediates **70** with 4-(2-morpholinoethoxy) naphthalen-1-amine (**71**) afforded the targeted pyrazol-α-ketoamide **72** which was transformed into the corresponding oxime **74** and alcohol **73**.

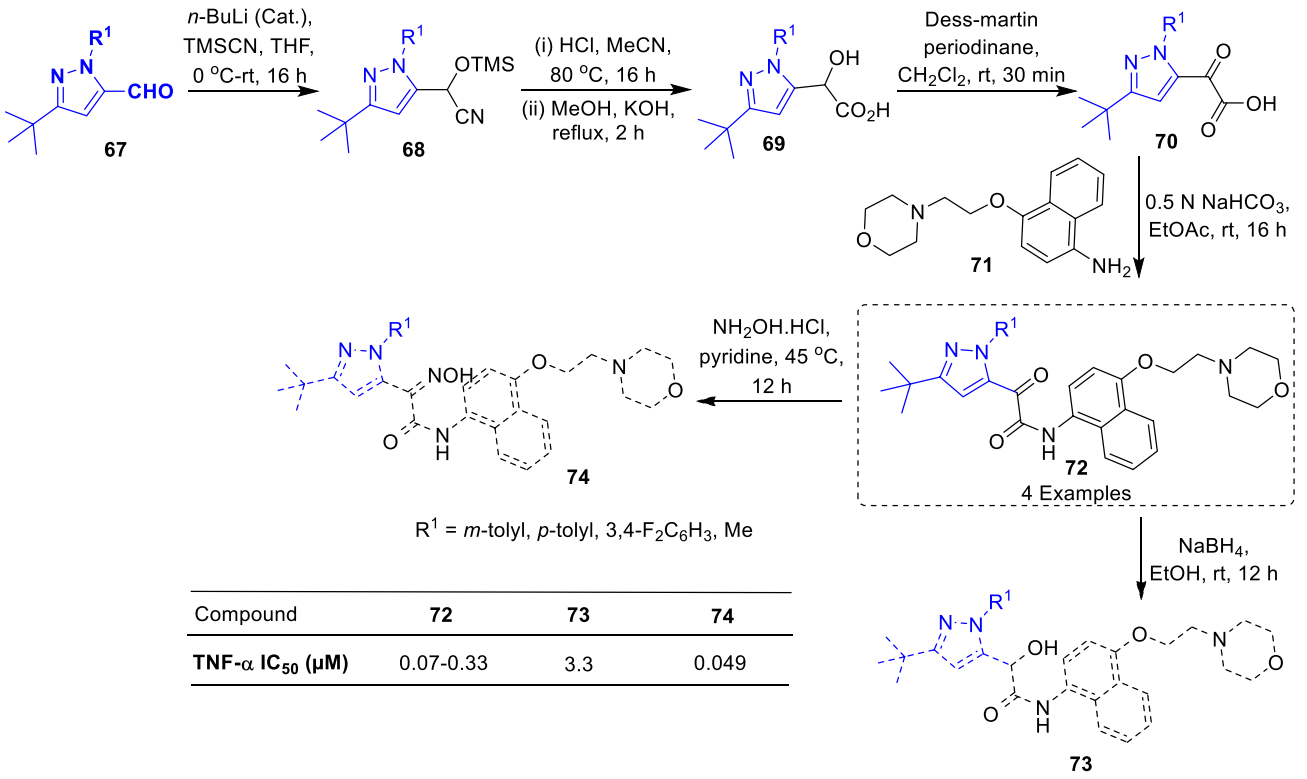
The synthesized derivatives **72–74** were investigated for their biological profile towards the inhibition of mitogen-activated protein (MAP) kinase p38. Additionally, these compounds **72–74** were found to be novel allosteric inhibitors and displayed potential for the better treatment of inflammatory conditions. The quantitative data of the experiment are summarized in Scheme 18.

In 2008, the Murano's group reported the synthesis of *tert*-butyl (2-(1-methyl-1*H*-pyrazol-5-yl)ethyl)carbamate (**76**) (Murano et al. 2008). In this work, Horner-Emmons reaction of 1-methylpyrazole-5-carbaldehyde (**75**) was performed to afford the *tert*-butyl (2-(1-methyl-1*H*-pyrazol-5-yl)ethyl)carbamate (**76**), followed by hydrogenation reaction, hydrolysis, and Curtius rearrangement. The final product as **76** was obtained with 86% yield. Moreover, the chemical transformations involved in this study are presented in Scheme 19.

In the following year, the authors (Schlager et al. 2008) synthesized a pyrazole-based molecular hybrids **84** as demonstrated in Scheme 20. Initially, the formylation of substituted pyrazole **77** led to pyrazole C-5 carbaldehyde **78** that reacted with tosyl hydroxide, $HC(OMe)_3$ and pyridinium bromide in the presence of MeOH to afford the

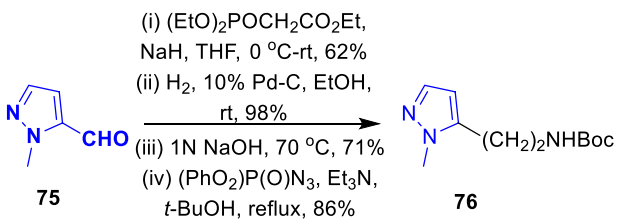


Scheme 17 Synthesis of pyrazolyl xanthene



Compound	72	73	74
TNF-α IC_{50} (μM)	0.07-0.33	3.3	0.049

Scheme 18 Synthesis of pyrazole C5-based α-ketoamides

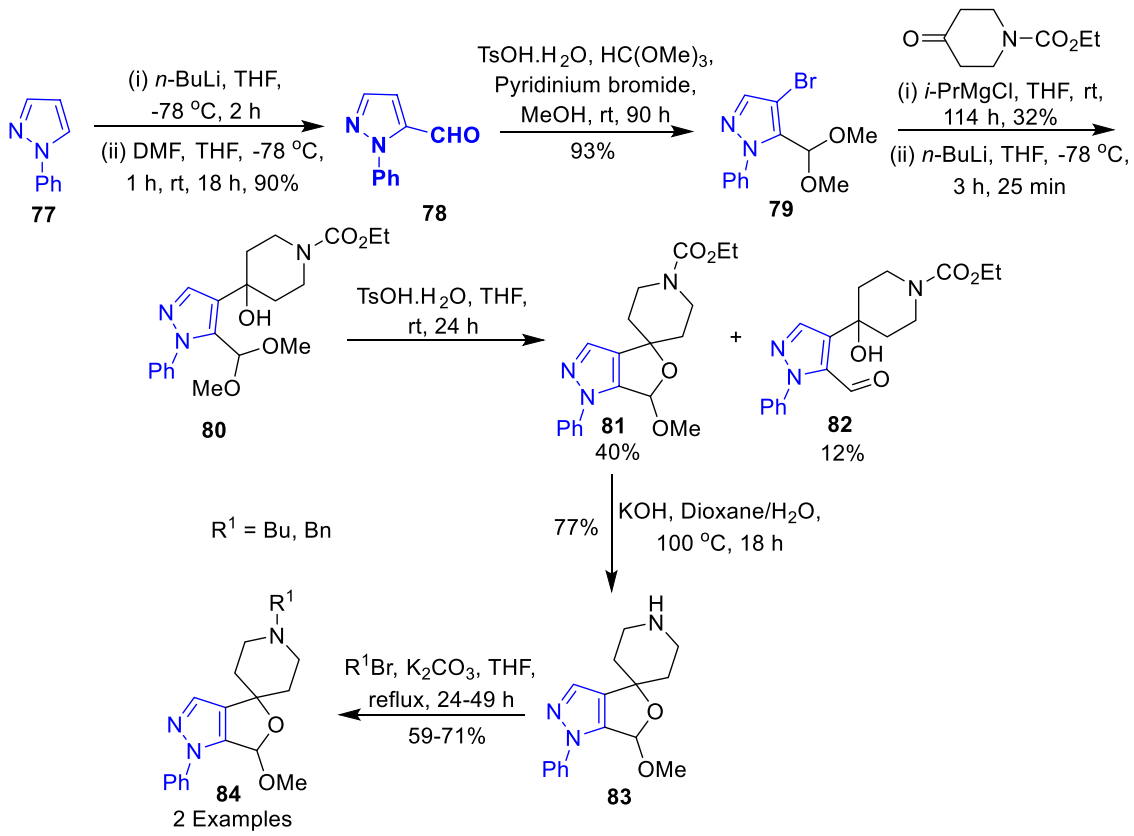


Scheme 19 Synthesis of Boc-protected pyrazole derivative

pyrazole acetal **79**. Next, the reaction of pyrazole acetal **79** with *i*-PrMgCl and *n*-BuLi delivered the intermediate **80**, which was transformed into fused compound **81** and tether pyrazole framework **82**. Furthermore, the treatment of pyrazole fused framework **81** with KOH in the presence of dioxane and H_2O provided the N–H free pyrazole **83**. Finally, the intermediate **83** was subjected under alkylation reaction to achieve the N–H protected pyrazole-based product **84**. The affinity of the spirocyclic pyrazoles to the σ receptors was determined in receptor binding studies with radioligands. Moreover, the calculation of crucial distances of the spirocyclic pyrazole derivatives demonstrated a good correlation with the pharmacophore model of Glennon.

A method developed for the synthesis of tri-substituted pyrazole derivatives is depicted in Scheme 21 (Rikimaru et al. 2012). Initially, the pyrazole ester **87** was obtained through the reaction of DMAD **85** and hydrazine **86** at room temperature, followed by the formation of pyrazole acetal **88**. As mentioned in Scheme 21, next, the pyrazole C-5 carbaldehyde **89** was achieved through a two-step synthetic process of **88**. Horner–Wadsworth–Emmons and catalytic hydrogenation reaction resulted in the formation of pyrazole keto ester **90** via pyrazole carbaldehyde **89**. Finally, compound **92** was formed from the reaction of **90** with NaH and DMF at room temperature followed by the two-step reaction of pyrazole N-benzylated compound **91.**

The author also developed another pyrazole-based bioactive compound **100** through the various chemical transformations. The formation of key intermediate **96** as pyrazole C-3 carbaldehyde was achieved by using the various organic transformations of starting materials **93–95** as mentioned in Scheme 22. After that, the esterification and reduction of compound **96** were performed to afford another intermediate **97**. Subsequently, the catalytic hydrogenation and hydrolysis of compound **97** delivered pyrazole-alcohol **98**. Further, **97** underwent two-step synthesis process to achieve the pyrazole intermediate **99**. Finally, the treatment of **99** with NaOH, THF, EtOH and 1-pentasulfonamide delivered



Scheme 20 Synthesis of pyrazole-based spirocyclic derivatives

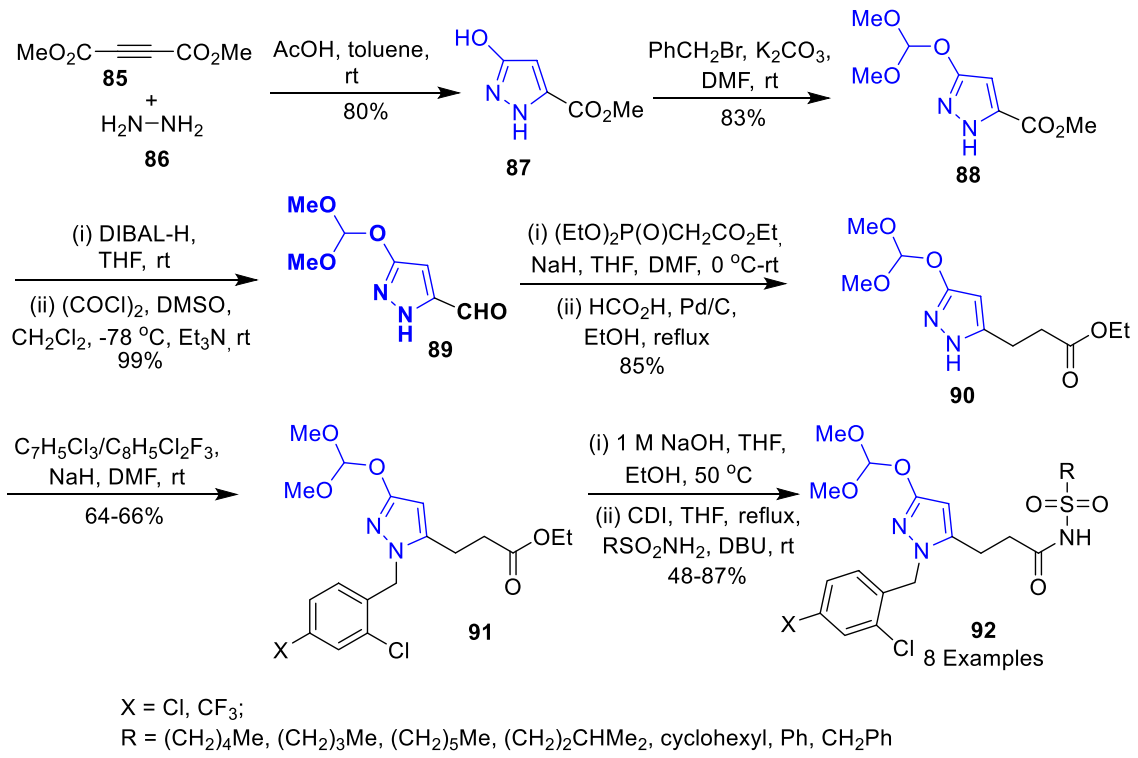
the pyrazole tethered sulphonamide derivatives **100** in 66–94% yield. The optimization study of the synthesized derivatives **100** revealed SAR findings such as 3-substituent on the pyrazole ring being important for potent PPARγ agonism and substitution of a trifluoromethyl group for the *para*-chlorine atom of the benzyl moiety tending to enhance in vitro potency.

In 2013, the authors (Fustero et al. 2013) reported a new approach towards the synthesis of 2,4-disubstituted pyrazole[1,5-*a*]pyridines, pyrazole[1,5-*a*]azepines, dienylpyrazoles and peptidomimetics by a ring-closing metathesis (RCM) method (Schemes 23, 24, 25). Initially, the dienylpyrazoles **103** were prepared in high yields by the addition of allyl- and vinyl-magnesium bromide **102** to form pyrazole-3-carbaldehyde **101** (Scheme 23). Intermediates **103** were then treated with 5 mol% Hoveyda Grubb's catalyst to afford bicyclic alcohols **104** in high yields via the RCM reaction. Finally, the pyrazolo[1,5-*a*]pyridines **105** and pyrazolo[1,5-*a*]azepines **106** were obtained by using the dehydration reaction of intermediate **104** in the presence of 1 M HCl in dry THF.

Next, the author also achieved the diastereoselective synthesis of dienylpyrazoles **109** and **110**. The condensation of pyrazole-5-carbaldehyde **101** with substrate **107** resulted in the formation of the imine intermediate **108**. Further, diastereomers of dienylpyrazoles **109** and **110** were obtained by employing different reaction conditions as outlined in Scheme 24.

To further demonstrate the scope of this protocol, the authors synthesized the peptidomimetics **115**. Firstly, the treatment of dienylpyrazoles **109** and **110** with HCl-dioxane in methanol, followed by reactions with *N*-Boc-L-alanine, HBTU and DIEA in DMF led to the formation of intermediates **111**. Thereafter, the RCM reaction of intermediates **111** was followed by reduction and treatment with ozone, resulted in the formation of bicyclic carboxylic acids **114**. The final peptidomimetics product **115** was obtained by the reaction of ethyl glycinate salt with intermediates **114** in the presence of HBTU in DMF at room temperature, as illustrated in Scheme 25.

Next, Zhou and co-workers (Zhou et al. 2013) synthesized a series of biologically active compounds **118** containing dihydroquinazolinone skeletons, as illustrated in Scheme 26. The reaction was performed between pyrazole-5-carbaldehydes **117** and 2-aminobenzamide **116** substrate in the presence of *p*-toluenesulfonic acid as a catalyst in dry toluene to afford the final products **118** in 65–92% yields. The synthesized derivatives **118** were screened for insecticidal



Scheme 21 Multi-step synthesis of pyrazole and sulphonamide-based molecular hybrids

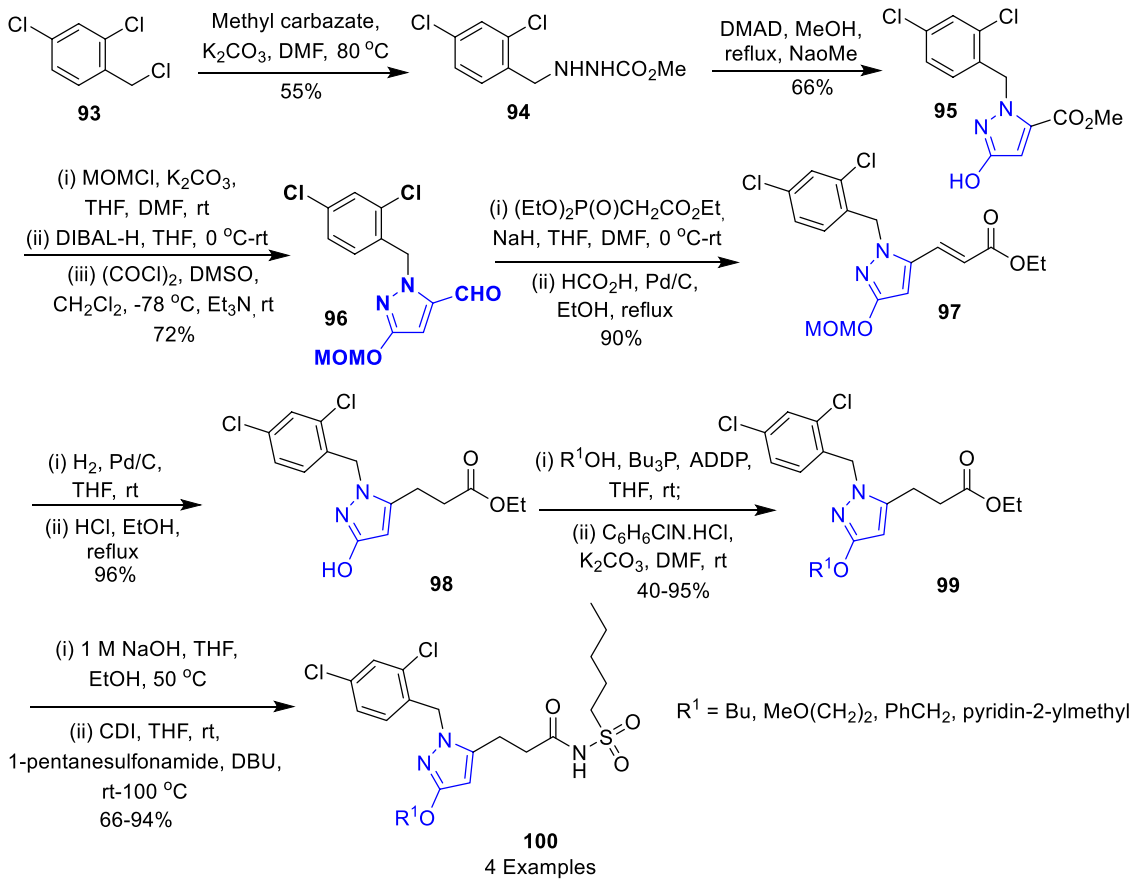
activity against oriental armyworm (*Mythimna separata*). The quantitative data indicated that most of the synthesized compounds **118** exhibited moderate to high activity at different concentrations (5, 10, 25 and 50 mg/L). The results from the current study revealed that the synthesized compound weakly affected the high voltage-gated calcium channel in the central neurons of *S. exigua*. During this study, it was observed that the maximal value of calcium currents (I_{Ca}) was not shifted after the neurons were treated with **118**.

In this study, a protocol presented a simple and convenient route towards the synthesis of pharmaceutically active pyrazole C5 substituted thiazolidinones **121** (Scheme 27) (Hamama et al. 2013). Briefly, the one-pot multicomponent reaction of 1,3-diphenyl-1*H*-pyrazole-5-carbaldehyde (**9a**), 2-mercaptoacetic acid (**119**) and 1,3,4-thiadiazol-2-amine (**120**) in the presence of pyridine allowed for the isolation of derivative **121** in 80% yield. 2-(1,3-diphenyl-1*H*-pyrazol-5-yl)-3-(1,3,4-thiadiazol-2-yl)thiazolidin-4-one (**121**) was investigated for its antioxidant and antitumor activity. The results of the study revealed that the compound **121** had weak antioxidant and antitumour activity in comparison with ascorbic acid and 5-fluorouracil, respectively.

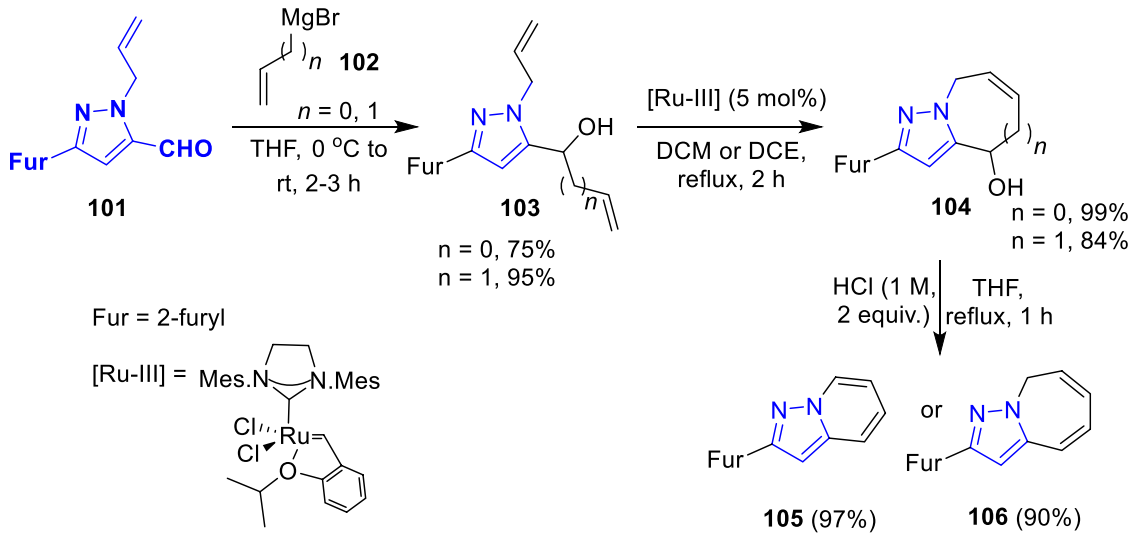
In 2015, the authors (Gouda et al. 2015) disclosed a method for the formation of pyrazole derivative (*E*)-2-cyano-*N*-(3-cyano-4-(furan-2-yl)-5,6-dimethylpyridin-2-yl)-3-(1,3-diphenyl-1*H*-pyrazol-5-yl)acrylamide (**123**) via the reaction of 1,3-diphenyl-1*H*-pyrazole-5-carbaldehyde (**9a**) with 2-cyano-*N*-(3-cyano-4-(furan-2-yl)-5,6-dimethylpyridin-2-yl)acetamide (**122**) in the presence of catalytic piperidine in ethanol as outlined in Scheme 28. They also evaluated the quantum mechanical parameters of compound **123** by using the PM3 (Parametric Method 3) semiempirical molecular model and the results are shown in Scheme 28. This study clearly indicated that compound **123** was found in *E* configuration.

Next, the research group of Ibrahim et al. (2017) reported a simple and convenient method for the synthesis of Schiff base **125** (Scheme 29) through the one-pot condensation of 1*H*-pyrazole-5-carbaldehyde **9a** and 5-phenyl-5*H*-thiazolo[4,3-*b*][1,3,4]thiadiazol-2-amine (**124**) in the presence of catalytic sulphuric acid. The newly synthesized compound **125** was screened for in vitro antifungal activity against the fungus, *Candida albicans* with clotrimazole as a reference drugs. The compound **125** has moderate antifungal activity against *Candida albicans*. The results of the antifungal study are summarized in Scheme 29.

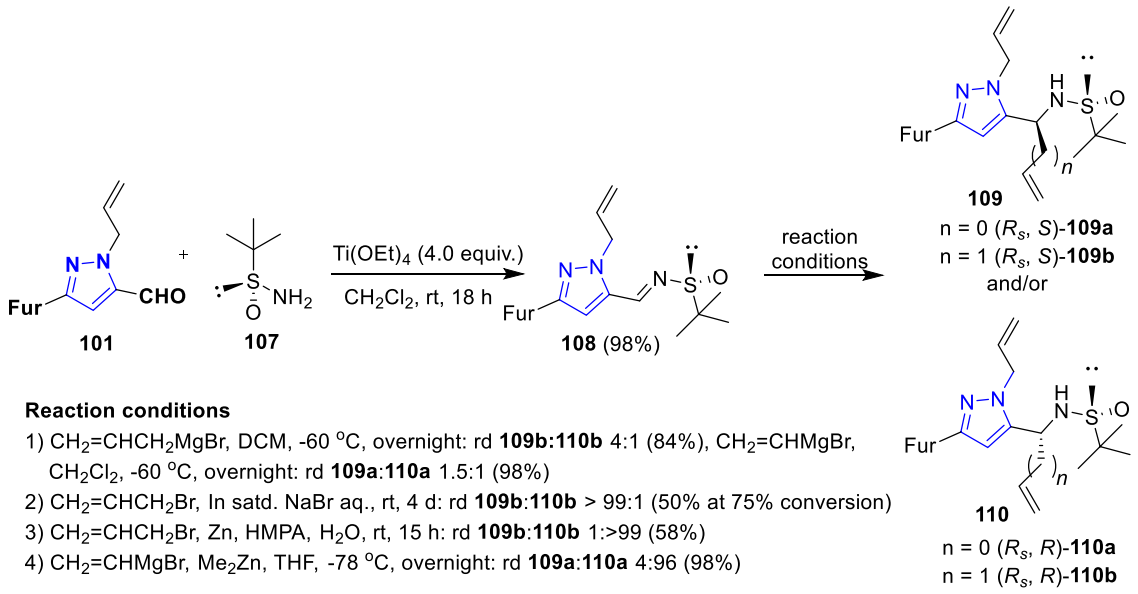
A protocol for the synthesis of biologically active pyrazole derivatives **129** via a two-step operation has been developed as described in Scheme 30 (Cisar et al. 2018). Initially, the reaction of pyrazole-5-carbaldehyde **126** with *N*-Boc-piperazine **127** under reductive amination in the presence of $NaBH(OAc)_3$ delivered the intermediate



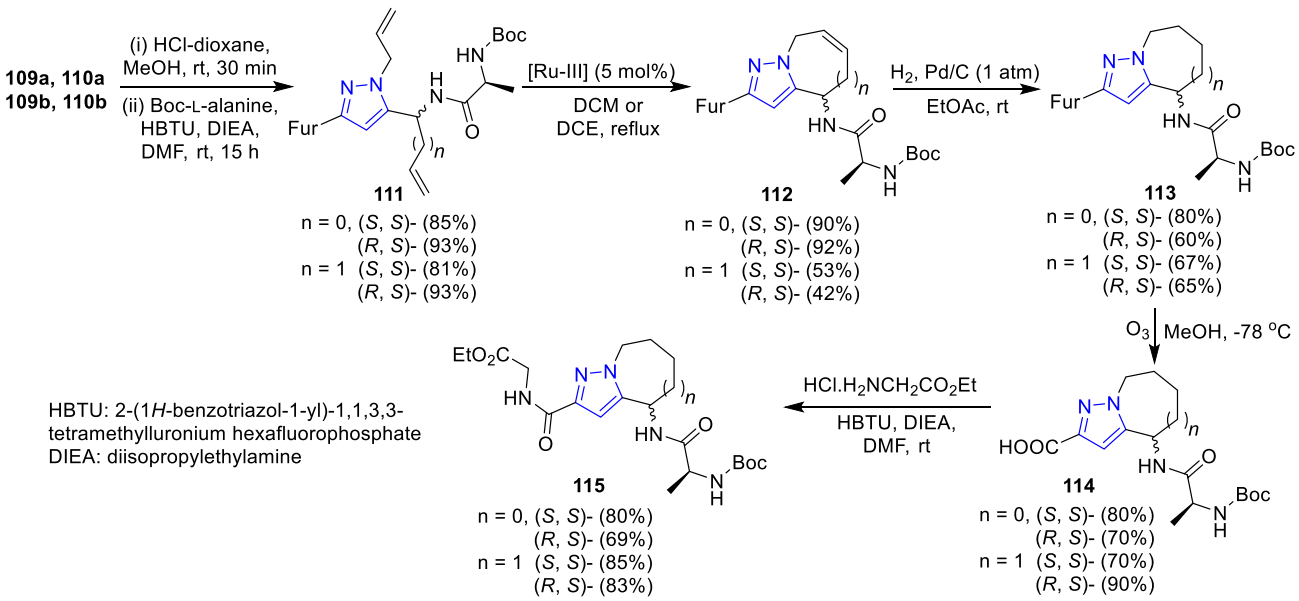
Scheme 22 Synthesis of pyrazole based derivatives



Scheme 23 Synthesis of pyrazolo[1,5-*a*]pyridine and pyrazolo[1,5-*a*]azepine derivatives



Scheme 24 Synthesis of dienylpyrazoles **109** and **110**

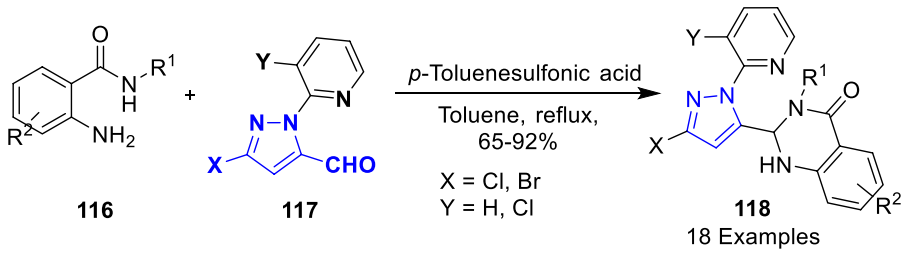


Scheme 25 Synthesis of peptidomimetics **115**

128. Subsequently, deprotection and carbamoylation were achieved. 1,1,1,3,3,3-Hexafluoropropan-2-yl-4-((1-methyl-3-phenyl-1*H*-pyrazol-5-yl)methyl)piperazine-1 carboxylate (**129**) that was tested with respect to monoacylglycerol lipase (MGLL) potency and also for tolerance to PLA2G7 and ABHD6 off-target selectivity. The compound **129** was potentially inhibiting the MGLL, whereas it was weakly effective in inhibiting of PLA2G7 and ABHD6. MGLL is a serine hydrolase enzyme responsible for the proper functioning of the central nervous system (CNS) by controlling the signalling of the endogenous cannabinoid 2-arachidonoylglycerol (2-AG); further ABHD6 also plays a role in the signalling and function of CNS. Additionally, PLA2G7 is a gene that plays a crucial role in smooth muscle cell differentiation from stem cells. The results of these studies are depicted in Scheme 30.

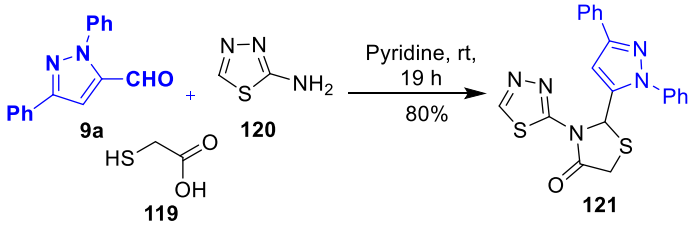
In the following year, the authors (Ammar et al. 2018) set up a synthetic method for the formation of pyrazole-based

Scheme 26 Synthesis of pyrazole-based 2,3-dihydroquinazolinone derivatives



R^1 = H, CH_3, CH_2CH_3, OCH_3, *i*-Pr, *t*-Bu, cyclopropyl, *n*-Pr, 2-thiazolyl, cyclohexyl;
R^2 = H, 6-Cl-8-CH_3, 8-CH_3, 6-Br-8-CH_3

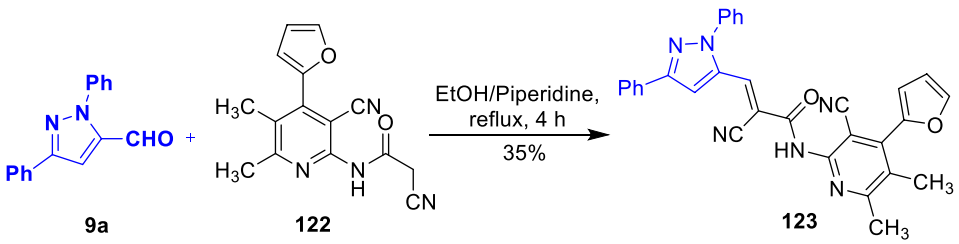
Compound	Larvicidal activity (%) at a concentration og (mg/L)			
	50	25	10	5
118	0-100	0-100	0-100	0-80



Compound	Antioxidant activity assay			In vitro cytotoxicity (Ehrlich ascites cells dead %)			Assay for bleomycin-dependent DNA damage
	Absorbance of sample	% Inhibition	IC_{50} (ug/mL)	ED_{100} (ug/cm^3)	ED_{50} (ug/cm^3)	ED_{25} (ug/cm^3)	Absorbance of sample
121	0.360	26.12	1935.8	43.7	26.1	23.0	0.158 ± 0.003

Scheme 27 Multicomponent synthesis of 2-(1,3-diphenyl-1*H*-pyrazol-5-yl)-3-(1,3,4-thiadiazol-2-yl)thiazolidin-4-one (**120**)

Scheme 28 One-pot condensation for the preparation of pyrazole-based arylidene

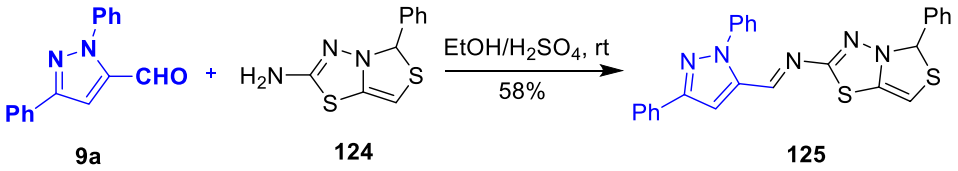


Quantum mechanical data obtained from PM_3 semiempirical molecular orbital calculations of the configurations of 123

Compound	Configuration	Total energy (kcal/mol)	Binding energy (kcal/mol)
123	*E*	-128366.8125	-7063.554688
	Z	-128227.6406	-6934.38623

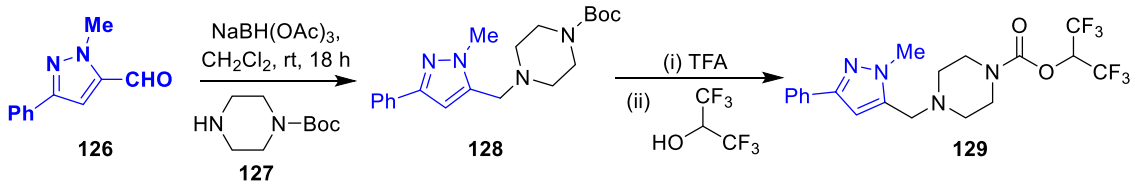
metal complex **132** as illustrated in Scheme 31. The simple condensation of 2-hydrazineylquinoline **130** and pyrazole C-5 carbaldehyde **9a** resulted in the formation of pyrazole-quinoline compound **131** that was complexed with Cr, Cu, Ni, Zn and Co in the presence of EtOH:THF. The pyrazole-based metal complexes **132** were obtained

Scheme 29 One-pot synthesis of *N*-((1,3-diphenyl-1*H*-pyrazol-5-yl)methylene)-5-phenyl-5*H*-thiazolo[4,3-*b*][1,3,4] thiadiazol-2-amine (**125**)



Antifungal activity

Compound	Fungi *Candida albicans* % Activity Index
125	21.42



***In vitro* potency for MGLL and the off-targets ABHD6 and PLA2G7**

Compound	IC_{50} (μM)[a]			
	hMGLL	hABHD6	hPLA2G7	cLogP[b]
129	0.028	0.290	0.580	3.7

[a]IC_{50}s determined using ABPP with a 30-min inhibitor preincubation in PC3 lysate.
[b]cLogP value calculated using XLogP[52] (Dotmatics)

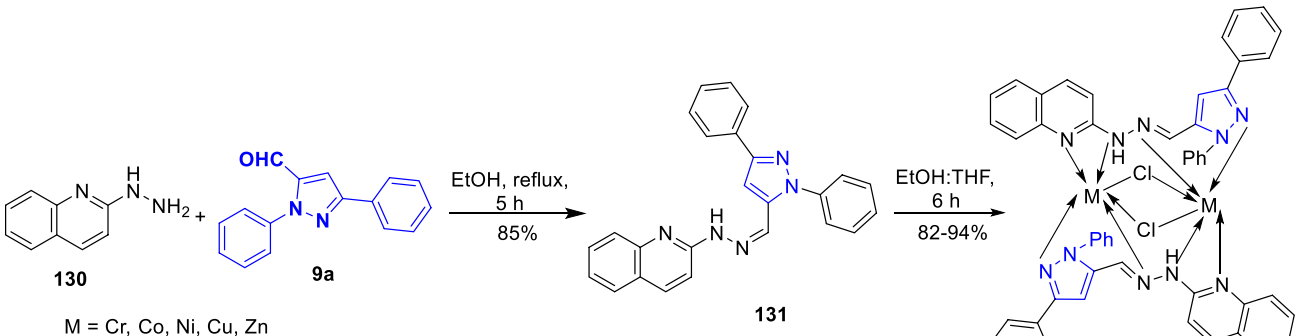
Scheme 30 Synthesis of 1,1,1,3,3,3-hexafluoropropan-2-yl-4-((1-methyl-3-phenyl-1*H*-pyrazol-5-yl)methyl)piperazine-1-carboxylate (**129**)

in 82–94% yield. The molar conductance data displayed that all the metal chelates **132** were non-electrolytes, except the Cr(III) complex, which presents a ΛM value of 146.82 Ω^{-1} cm^2 mol^{-1}, showing that it is a 1:2 electrolyte. Moreover, all compounds showed significant antiproliferative activity against MCF-7 (breast cancer) and A549 (lung cancer) cell lines, still resulting in less effectiveness than cisplatin (Scheme 31).

In this work, a method has been reported for the synthesis of pyrazole derivatives as new anti-proliferative agent as displayed in Scheme 32 (Eldehna et al. 2018). The condensation of indolin-2-one **133** and pyrazole C-5 carbaldehyde **134** in refluxing MeOH afforded pyrazole and indolin-2-one-based molecular hybrids **135** (yield range: 74–85%). The synthesized derivatives **135** were evaluated in vitro for their anti-proliferative activity towards lung A-549, colon HT-29, and breast ZR-75 human cancer cell lines. The results of this study are summarized in Scheme 32.

The authors (Khan et al. 2019) synthesized bioactive bis-pyrazole linked hydrazides **138** by condensing pyrazole benzohydrazides **136** and pyrazole C-5 carbaldehydes **137** in the presence of EtOH and acetic acid (Scheme 33). The bis-pyrazoles **138** were obtained in 60–80% yields and were evaluated for their antimicrobial activity against a panel of Gram-positive and Gram-negative bacteria along with *Candida albicans MTCC 3017* strain (Scheme 33). The results showed excellent anti-Candida activity with MICs values of 3.9 μg/mL, which was equipotent to that of the standard Miconazole (3.9 μg/mL). Silico computational studies were carried out to predict the binding sites (Tyr116, Leu130, Ala291, Gly424, His420, Thr299, Ile423, etc.) and pharmacokinetic parameters of these conjugates **138**. The molecular docking was performed with protein 3GW9.

In the same year, a strategy has been unfolded for the synthesis of pyrazole tethered fluoro derivatives as outlined in Scheme 34 (Nosik et al. 2019). In the first step, the treatment of pyrazole tethered alkene **139** with LDA and DMF resulted in the formation of pyrazole C-5 carbaldehyde **140**. Next, the compound **140** was treated with $HC(OMe)_3$ and TsOH to afford the pyrazole C-5 acetal **141** in 86% yield. The pyrazole C-5 acetal **141** was transformed into a pyrazole containing cyclopropyl **142** in the presence of sodium iodide. Finally, the **142** got converted into final pyrazole-based compound **143** with a 93% yield. Additionally, the

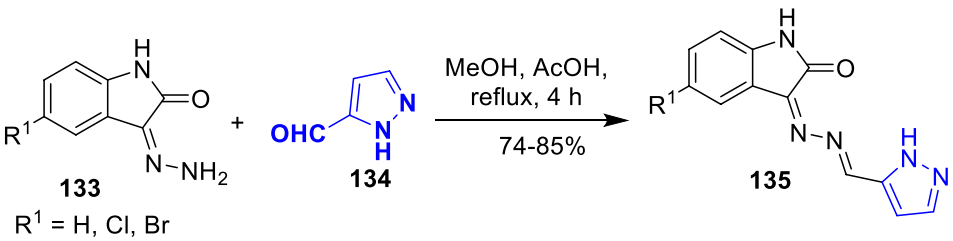


Anticancer activity

Compound	IC_{50} (μM)	
	MCF-7	A-549
131	25 ± 1.2	28 ± 1.4
132 (M = Cr)	17 ± 1.6	20 ± 1.7
132 (M = Co)	19 ± 1.7	22 ± 1.9
132 (M = Ni)	21 ± 1.7	28 ± 1.4
132 (M = Cu)	26 ± 1.5	37 ± 0.8
132 (M = Zn)	29 ± 1.7	38 ± 1.2
Cisplatin	13 ± 0.5	12 ± 0.9

Scheme 31 Synthesis of Schiff base metal(II/III) complexes

Scheme 32 Synthesis of the pyrazole containing hydrazonoindolin-2-ones



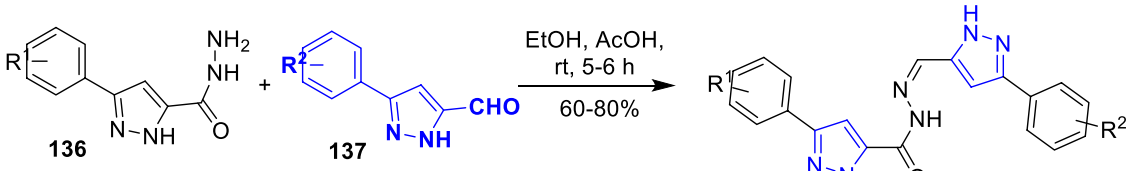
Anti-proliferative activity cell growth inhibitory activity at 30 μM concentration

Compound	IC_{50} (μM)			
	A-549	ZR-75	HT-29	Average growth inhibition (%)
135	8.2-91.5	19.2-82.3	28.8-94.9	26.9-89.6
Sunitinib	59.5 ± 2.3	90.7 ± 4.5	85.7 ± 2.7	78.7

approach demonstrated high efficiency when applied on a gram scale and could be utilized for the synthesis of several functionalized regioisomeric pyrazole derivatives containing a gemdifluorocyclopropane group, such as amines, carboxylic acids, aldehydes, bromides, and boronic esters.

In the following year, a novel pyrazole fused oxazines have been developed as presented in Scheme 35 (Lindsay-Scott et al. 2020). Initially, the reaction of di-substituted pyrazoles **144** and bromo-containing compound **145** in the presence of cesium carbonate and acetonitrile afforded tri-substituted pyrazoles **146** that were converted into pyrazole C-5 carbaldehydes **147** in 74–94% yields. These intermediates underwent intramolecular cyclization, leading to the formation of pyrazolo[5,1-*c*][1,4]oxazines **148** that were reduced to the final compounds **149** in 68–84% yields.

Thereafter, in 2022, a route was developed for the synthesis of pyrazole-based molecular hybrids **154** as shown in Scheme 36 (Khidre et al. 2022). In the first step,



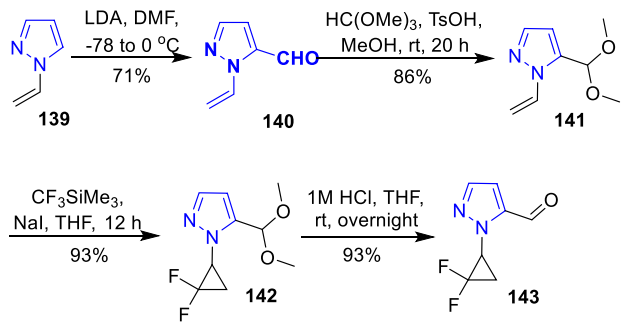
R^1 = H, OCH_3, 3,4,5-$(OCH_3)_3$, CF_3, 3,4-$(Cl)_2$;
R^2 = 3,4-$(OCH_3)_2$, 3,4,5-$(OCH_3)_3$, CF_3, 3,4-(OCH_2O)

Antimicrobial activity

Compound	Minimum Inhibitory Concentration (MIC, ìg/mL)							
	ML	SA	SL	BS	EC	PA	KP	CA
138	3.9-125	3.9-125	7.8-125	7.8-125	3.9-125	7.8-125	3.9-125	3.9-125
Ciprofloxacin	0.9	0.9	0.9	0.9	0.9	0.9	0.9	–
Miconazole	–	–	–	–	–	–	–	3.9
Fluconazole	–	–	–	–	–	–	–	3.9
Clotrimazole	–	–	–	–	–	–	–	7.8

ML = Micrococcus luteus MTCC 2470, SA = Staphylococcus aureus MTCC 96, SL = Staphylococcus aureus MLS-16 MTCC 2940, BS = Bacillus subtilis MTCC 121, EC = Escherichia coli MTCC739, PA = Pseudomonas aeruginosa MTCC 2453, KP = Klebsiella planticola MTCC 530

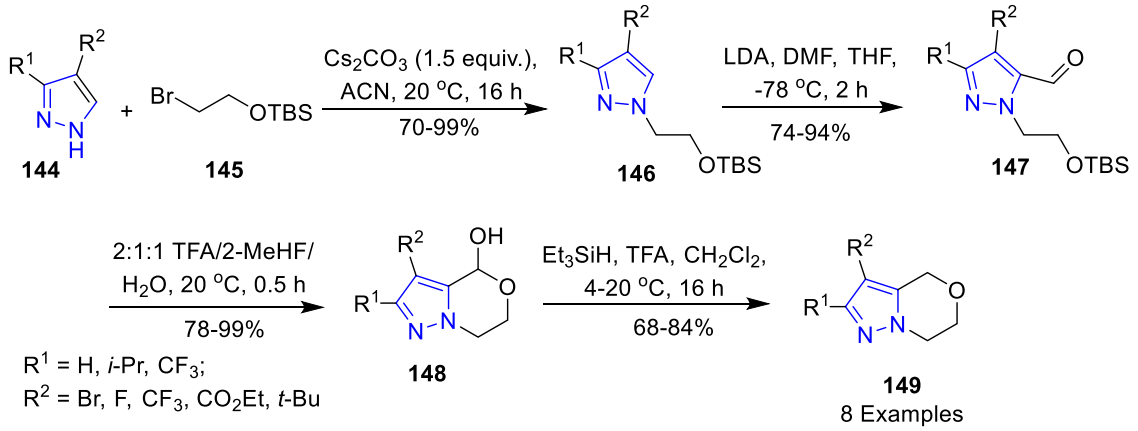
Scheme 33 Simple condensation reaction for the synthesis of bis-pyrazole hydrazide derivatives



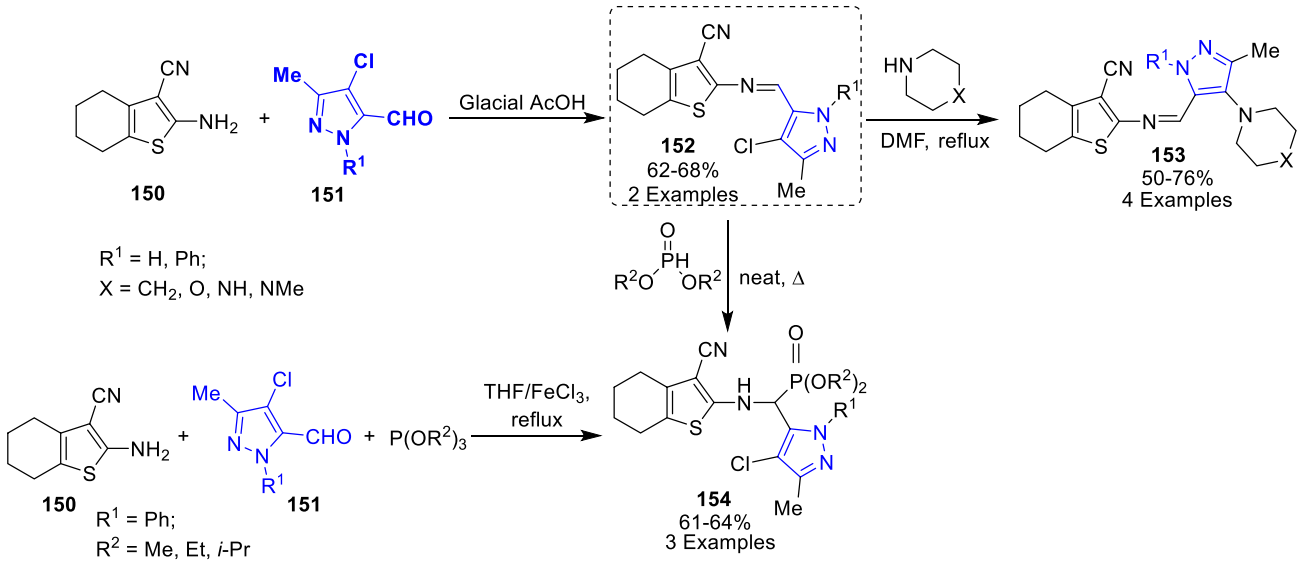
Scheme 34 Synthesis of 1,5-disubstituted N-(gem-difluorocyclopropyl)pyrazole derivatives

amino thiophene carbonitrile **150** reacted with chloropyrazole carbaldehydes **151** to generate the Schiff bases **152** in good yield via the condensation approach. Next, compounds **152** were treated with secondary amines in the presence of DMF to form pyrazole derivatives **153**. On the other hand, one-pot operation was involved in the synthesis of pyrazolo-α-aminophosphonates **154** by the reaction of pyrazole-5-carbaldehydes **151,** N-heterocyclic amines **150** and trialkylphosphites in the presence of THF and $FeCl_3$. In another route, α-Aminophosphonates **154** were also achieved in high yields by reacting Schiff bases **152** directly with dialkylphosphites. Next, the molecular modelling of the compounds **154** was studied to evaluate the binding interactions for the target protein quinone reductase-2 (4ZVM) and revealed that the synthesized compounds **154** were the most promising candidates compared with Doxorubicin. Anti-proliferative activity of newly synthesized derivatives **154** was investigated on three cell lines of liver such as HepG2, MCF7 and HCT-116 in comparison with human healthy cell line (BJ-1) by using the MTT assay method. The present studies showed that compound **154** exhibited strong activity towards the HepG2 and HCT-116 while having weak efficiency for the MCF7 in comparison with the reference drug.

In 2023, a novel anticancer agent **158** was synthesized by condensing coumarins **155**, pyrazole-5-carbaldehydes **156** and malononitrile **157** (Scheme 37) (Srinivas et al. 2023). The multi-component reaction was carried out in the presence of ionic liquid (BMIM[OH]) at 70–75 °C with 87–90% yields of the final product **158**. The cytotoxic activity of the synthesized derivatives against PC-3 and HepG-2 cells was screened by the authors. The investigated compounds demonstrated good to moderate activities against the PC-3 and HepG-2. The data of this study are summarized in Scheme 37.



Scheme 35 Multi-step synthesis of pyrazole fused framework



Anti-proliferative activity

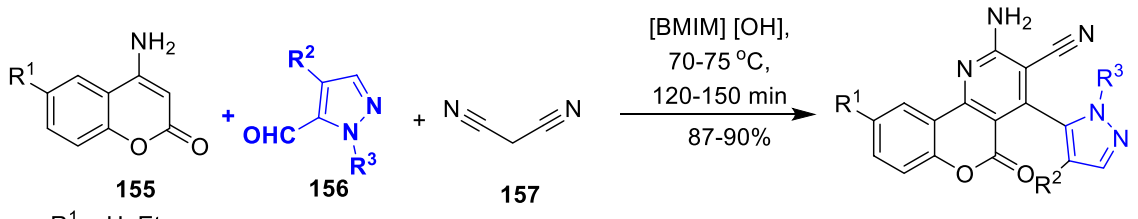
Compound	IC_{50} (μM)		
	MCF-7	HepG-2	HCT-116
154	19.8-20.6	38.8-46.9	10.1-24.8
Doxorubicin	16.7	63.2	21.8

Scheme 36 Synthesis of pyrazole tethered molecular hybrids

Exploration of pyrazole C-3/C-5 carbaldehydes towards the synthesis of valuable molecular architectures

This section presents an analysis of pyrazole C-3/C-5 carbaldehydes for the synthesis of pharmaceutically active molecular architectures and hybrids. Comprehensive findings from numerous international research teams have been presented in a simplified and accessible manner.

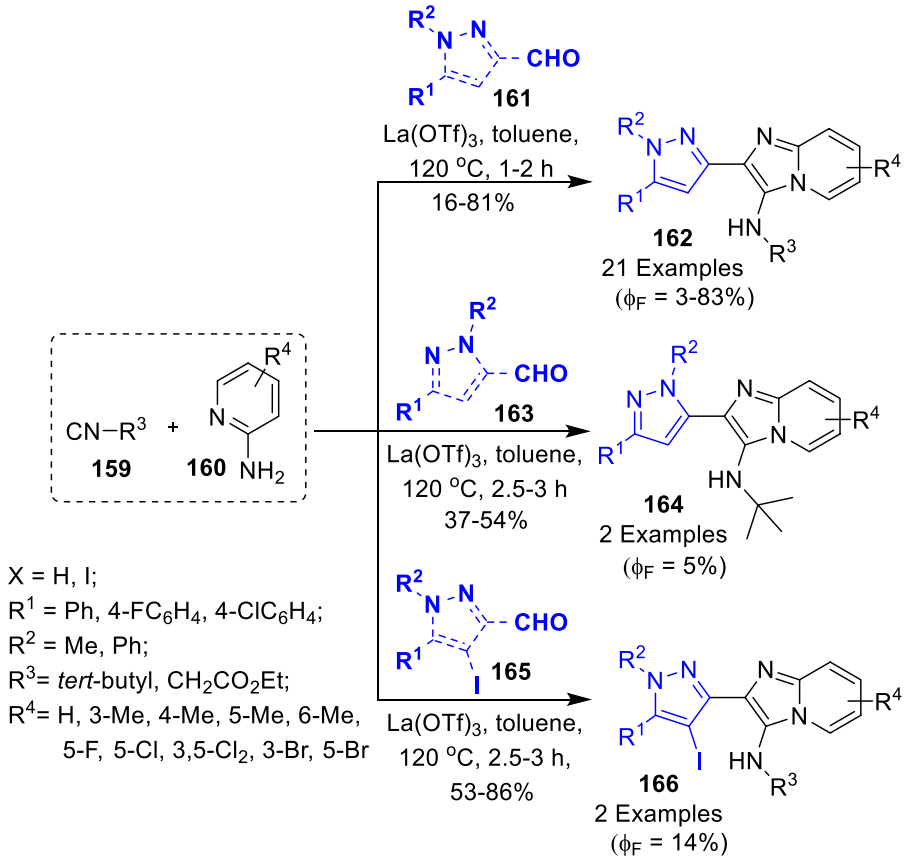
In 2020, our group (Sharma et al. 2020a, 2020b, 2020c) unfolded a method for the preparation of pyrazole linked imidazo[1,2-*a*]pyridine derivatives **162**, **164**, **166** (Scheme 38) and evaluated their photophysical properties. The pyrazole C-3/5 carbaldehydes **161**, **163**, **165** were reacted with isocyanides **159** and substituted 2-aminopyridines **160**, in the presence of lanthanum triflate and pyrazolyl-imidazo[1,2-*a*]pyridines **162**, **164** and **166** were obtained, as illustrated in Scheme 38. The photophysical



Anticancer activity

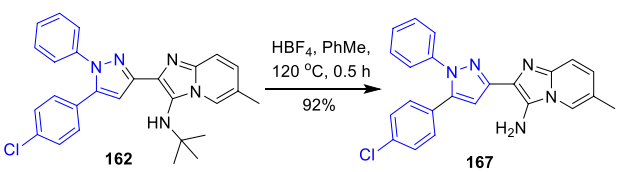
Compound	IC_{50} (μM)	
	PC-3	HepG-2
158	9.2-(>100)	8.9-(>100)
Doxorubicin	0.59	0.61

Scheme 37 Multicomponent reaction for the synthesis of pyrazole containing molecular hybrids



Scheme 38 $La(OTf)_3$-catalysed synthesis of pyrazole C-3/5 tethered imidazo[1,2-*a*]pyridine derivatives

properties of fluorescent pyrazole tethered imidazo-azines **162**, **164** and **166** were investigated in $CHCl_3$ as a solvent; it was found that all the synthesized compounds afforded good to excellent luminescent quantum yields ($\Phi_F = 3–83\%$). The developed methodology provides several advantages including high atom economy, high diversity, high yield of the products, and excellent fluorescence quantum yield.



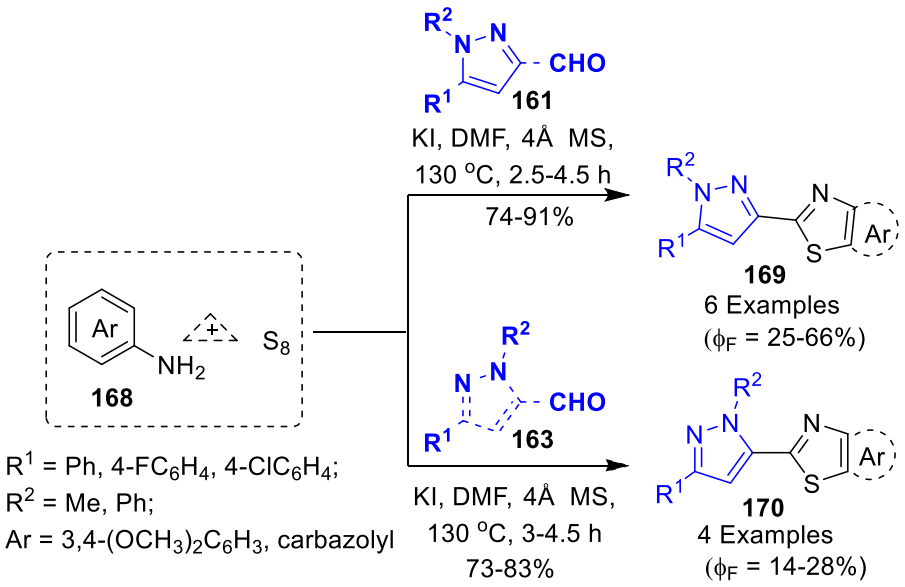
Scheme 39 HBF_4-assisted dealkylation of 2-(5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-3-yl)-6-methylimidazo[1,2-*a*]pyridin-3-amine

To further establish the scope of this protocol, dealkylation of Groebke–Blackburn–Bienayme (GBB) product **162** was studied by using aq. HBF_4 in toluene. Surprisingly, the dealkylation of **162** furnished the 2-(5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-3-yl)-6-methylimidazo[1,2-*a*]pyridin-3-amine **167** in excellent yield (Scheme 39).

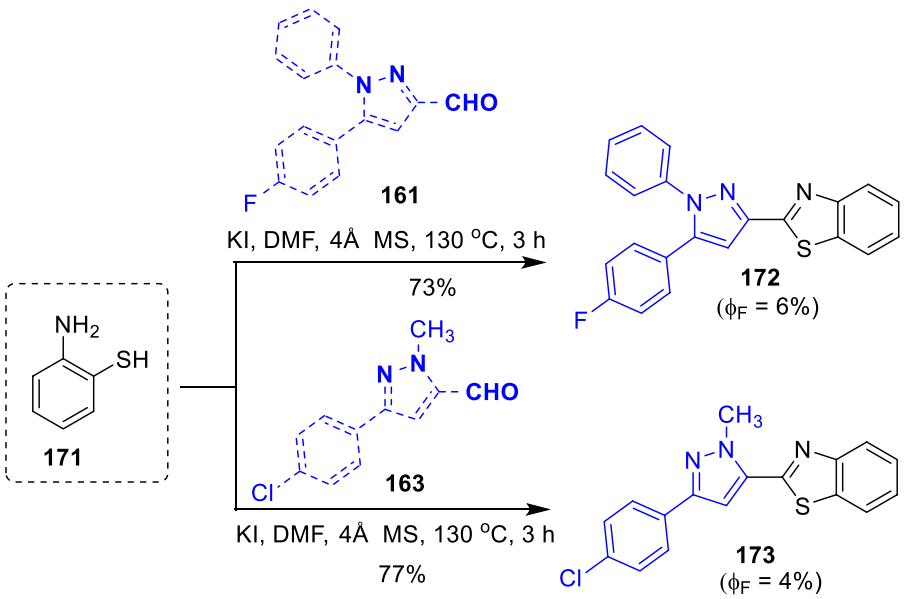
In the same year, our group (Sharma et al. 2020a, 2020b, 2020c) also developed a method for the synthesis of pyrazole C-3/C-5 tethered benzothiazole **169**, **170** as presented in Scheme 40. The reaction of pyrazole C-3/C-5 carbaldehyde **161**, **163**, aryl amines **168** and elemental sulphur yielded pyrazole C-3/C-5 substituted benzothiazole **169**, **170** in the presence of potassium iodide and dry DMF at 130 °C. The pyrazole C-3/C-5 tethered benzothiazole **169**, **170** were obtained in 73–91% yields and investigated for their light-emitting character. Interestingly, the pyrazole C-3 tethered benzothiazoles **169** gave good fluorescence quantum yield in the range of 25–66%, whereas the pyrazole C-5 tethered benzothiazoles **170** gave low quantum yields (14–28%). The current method has several advantages including metal-free reaction, broad substrate scope, a good yield of the products, and excellent fluorescence quantum yield.

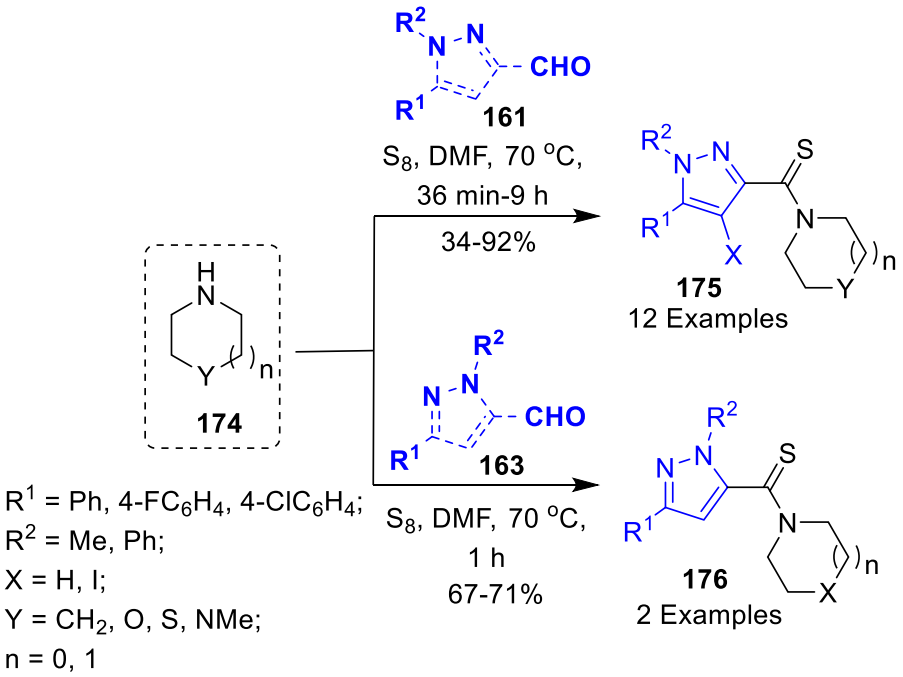
The developed protocol was also applicable for the conventional synthesis of pyrazole tethered benzothiazole frameworks **172**, **173**. The reaction of pyrazole C-3/C-5 carbaldehydes **161**, **163** and 2-aminothiophenol **171** in the

Scheme 40 Synthesis of pyrazole C-3/5 tethered benzothiazole derivatives



Scheme 41 Scope of methodology for conventional synthesis of benzothiazoles using 2-aminothiophenols



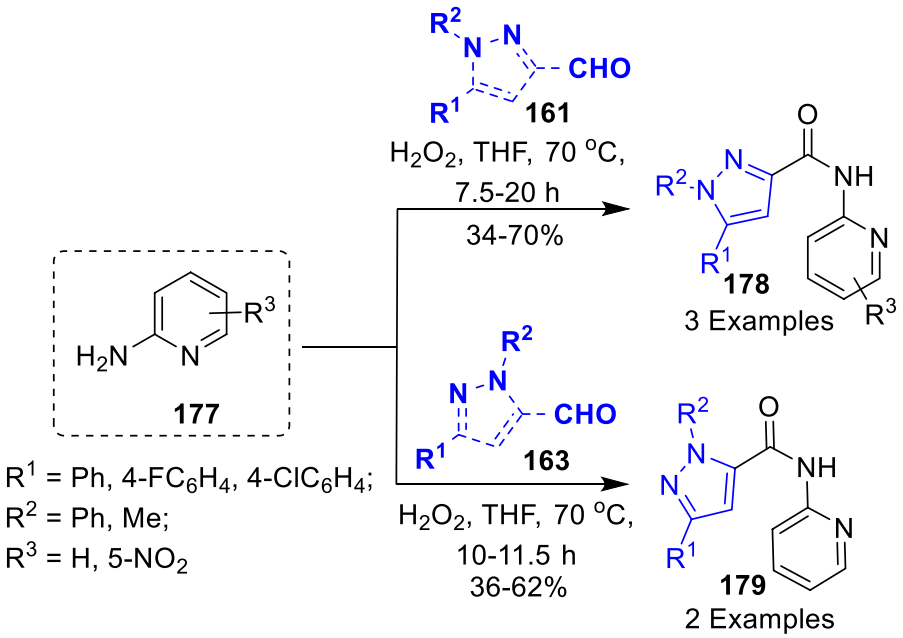


Scheme 42 Metal- and catalyst-free preparation of pyrazole C-3/5-linked thioamide conjugates

presence of KI and DMF led to the corresponding compounds with good yields (73–77%) (Scheme 41).

In 2023, an operationally simple and metal-free approach has been described by our group (Sharma et al. 2023) for the synthesis of pyrazole tethered thioamide and amide conjugates **175**, **176** as depicted in Scheme 42. The thioamides **175**, **176** were generated by employing a three-component reaction of diverse pyrazole C-3/5 carbaldehydes **161**, **163,** secondary amines **174** and elemental sulphur in a single synthetic operation.

Moreover, the pyrazole C-3/5 linked amide conjugates **178**, **179** were also synthesized via an oxidative amination of pyrazole carbaldehydes **161**, **163** and 2-aminopyridines **177** using hydrogen peroxide as an oxidant (Scheme 43).



Scheme 43 H_2O_2-mediated synthesis of pyrazole-pyridine conjugates with amide tethers

Summary and outlook

Over the past decades, the development of pyrazole derivatives has led to several facile, convenient, and useful synthetic methods that have provided access to a broad spectrum of biologically active heterocycles. A number of outstanding contributions from the researchers based on the new, reliable, and efficient methodologies available are highlighted in this review. In this perspective, pyrazole C-3/C-5 carbaldehyde precursors have witnessed a significant and valuable contribution in organic and medicinal chemistry. The exploration of pyrazole C-3/C-5 carbaldehydes afforded a series of biologically potent heterocyclic scaffolds, viz. pyrazole C-3/C-5-based silicon derivatives, pyrazole C-3/C-5-based Schiff base derivatives, pyrazole C-3/C-5-based metal complexes, pyrazole C-3/C-5-based imidazo[1,2-*a*]azines, pyrazole C-3/C-5-based sulphur containing derivatives and pyrazole C-3/C-5-based thioamide and amides other pyrazole fused/tethered polycyclic systems. These synthesized derivatives demonstrated potential applications such as 5-HT_{3A} receptor antagonists, allosteric inhibitors, insecticidal activity, antioxidant, antifungal, antiproliferative and antimicrobial (Fig. 2). This review highlights the approaches towards the diversity-oriented synthesis of pyrazole C-3/C-5 based derivatives and their application in medical science.

Future scope

It is realized that the synthetic and practical utility of pyrazole C-3/C-5 carbaldehydes has not been explored to their potential. Furthermore, exploration of these formyl pyrazoles by employing multicomponent reactions (e.g. Ugi, Passerini, Biginelli, Bucherer–Bergs reaction, and Strecker synthesis) and other currently trending chemistry (C-H activation) remains unrevealed. Based on our in-depth literature analysis, the biological and medicinal potential of pyrazole C-3/C-5-based molecular frameworks has been carried out by a few research groups. It is depicted from the previous reports that the derivatives synthesized from the pyrazole C-3/C-5 carbaldehyde showed promising biological applications. On the basis of previous findings, if pyrazole C-3/C-5 carbaldehydes are explored to their full potential, more promising applications in the various domains of science may be anticipated. Our group has successfully investigated the light-emitting character of pyrazole-3(5)-carbaldehydes linked imidazo[1,2-*a*]azine and benzothiazole derivatives and observed excellent results with luminescence quantum yield up to 83%. Based on photophysical results, it is proposed that highly fluorescent pyrazole-based scaffolds are similar and have applications in the fields of bio-imaging, chemosensors, OLEDs, pH sensors, and material science.

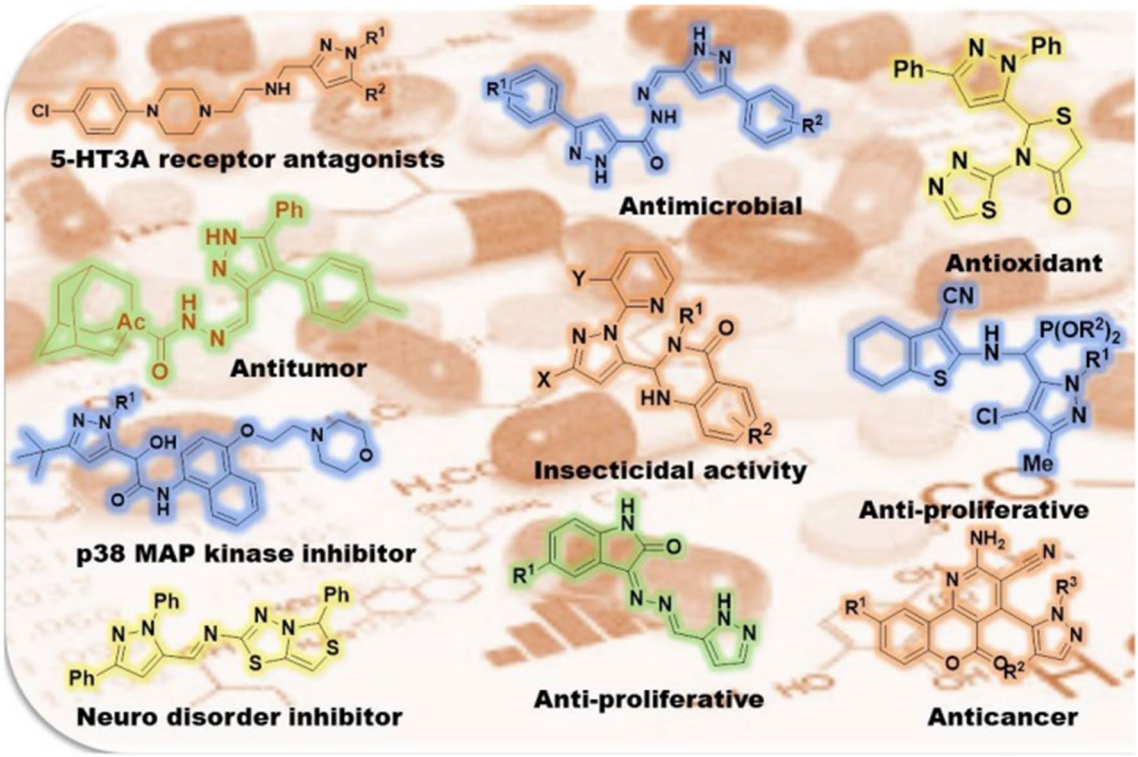


Fig. 2 A glimpse of medicinal attributes of pyrazole C-3/C-5-based molecular architectures

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Declarations

Conflict of interest There is no conflict to declare.

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