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Recent Therapeutic Potential of Multi-functional Pyrazole Motifs in Drug Design

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Abstract

The pyrazole nucleus is a special structural scaffold that makes a great and intriguing template for both material science and pharmaceutical chemistry. The present work presents a comprehensive review of the pharmaceutical applications of pyrazole and substituted pyrazole motifs, alongside the diversity of synthetic pathways showing how substances are synthesized. Additionally, it covers the most current studies and showcases the remarkably efficient synthetic approach as successful green chemistry resulting in accessing new pyrazole-bearing compounds in encouraging yields. The structural activity relationship (SAR), molecular docking, and ADMET for pyrazole derivatives were presented as a way to further demonstrate the interactions and safety of these compounds in biological systems in preparation for future drug development. This survey uncovers that pyrazole is an undeniable pharmacophore due to its huge benefits in restorative chemistry inquire about and other important areas of human endeavour.

Keywords: Pyrazole; synthesis; medicinal chemistry; pharmacological activities; SAR study

1. Introduction

Over the years, consistent effort in synthesizing organic compounds is to develop a novel alternative to treat various diseases to combat the problems of drug resistance that has become more prominent [1].This may be due to improper use of antibiotics, inadequate dosing, or prolonged exposure of agricultural produce to antibiotics over an extended time.

Heterocyclic compounds offer excellent activities in drug design to fight drug resistance and in corrosion inhibition research [2] Pyrazoles are important associates of heterocyclic compounds with two nitrogen heteroatoms in positions-1 and -2 of five-membered unsaturated aromaticmolecules capable of undergoing addition reactions.

The aromatic behaviour can be associated with their two-dimensional structures (pyrazoline and pyrazolidine) [3].The aromaticity of pyrazole is accounted for by the presence of these six electrons which contains four pi-electrons(C=N and C=C) and a lone pair of electrons on the NH. The partially saturated form of pyrazolesiscalled pyrazolines and the saturated form isknown as pyrazolidine (Figure 1). Tautomerization in pyrazole is shown in Figure 2.

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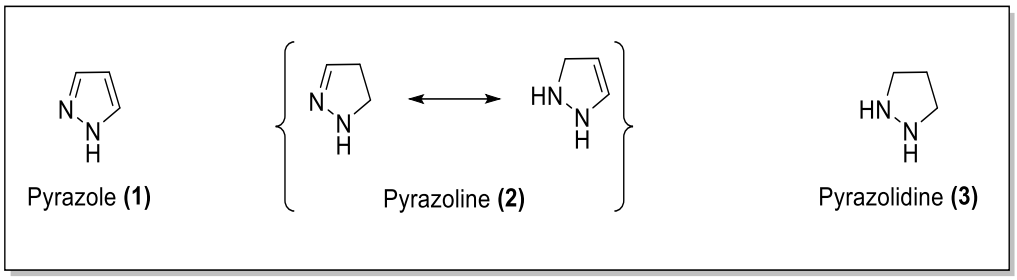


Figure 1: Structures of Pyrazole and Hydrogenated Pyrazole Derivatives

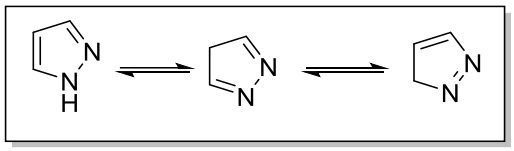


Figure 2: Tautomerization Effect in Pyrazole

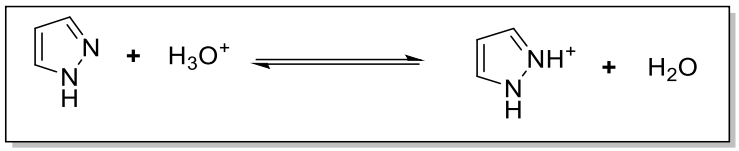


Figure 3: Acidic Behaviour of Pyrazole

The NH-pyrazoles behave as weak bases and weak acids due to their pyridine-cation-receptor, C═N and N–H with proton-donor behaviour as shown in (Figure 3). Pyrazole scaffold is highly viable in medicinal chemistry for its easy way synthetic procedure availability and various clinical applications [4-6]. Pyrazole as a term was conceived in 1883.by Ludwig Knorr[7].They are categorised as alkaloids due to their distinctive pyrazole composition, as well as their potential therapeutic utility. In 1959, the first known pyrazole (1-pyrazolyl-alanine) was isolated from watermelon seeds [7,8].The resourcefulness of pyrazolemotifs in researchandorganicapplications has been well documented as one of the utmostconsideredblendsin the azole family [9-12],though samples of natural plantsassociatedwith pyrazole molecule are limited in number [13].The review presents methods for deriving motifs that have the potential to be very useful in pharmaceutical chemistry and the development of drugs. This review work also showcases the remarkably efficient synthetic approach as successful green chemistry that gave rise to the preparation of new pyrazole-based derivatives in good to outstanding yields. These methods of preparation are via conventional heating and microwave-assisted approach which areeconomical and highly accelerated reactions, as the products were obtained within minutes to a few hours.

Pyrazole is a good member of the heterocyclic family with a varied scope of synthetic and natural product representations with innumerable agrochemical, physiological, and therapeutic applications. Pyrazole moieties also continue to attract attention owing to their viable functional properties suchas antibacterial [3,14], antifungal [15-17],anti-inflammatory [18,19],anti-cancer [20-23],anti-tubercular [24,25], anti-viral[26], antioxidant [27,28], antidiabetic/hyperglycaemic, antidepressant, anticonvulsant, antipyretic, anti-helminthic and herbicidal properties [3].

Numerous therapeutic drugs have been successfully derived from compounds containing pyrazole; some of these drugs are **Sildenafil (Viagra),4**which impedes phosphodiesterase and is used for the treatment of male erectile dysfunction, **Celecoxib,5** a non-steroidal drug that demonstrates anti-inflammatory effects and inhibits COX-2; **Fomepizole, 6**which inhibits alcohol dehydrogenase; **Rimonabant, 7**is

utilized for the treatment of obesity**, Betazole, 8is** used clinically to test gastric secretory function; **Epirizole, 9**is an anti-inflammatory drug used for muscle and joint pain(Figure 4) [24].

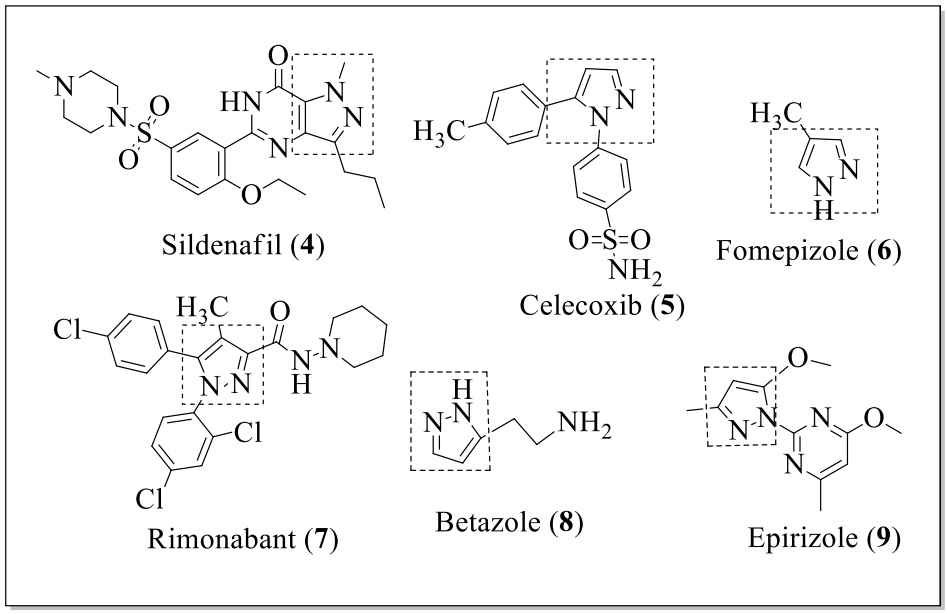


Figure 4: Selected commercially available Drugs Containing Pyrazole Ring

In other studies, theinvestigation ofthe corrosion inhibitory ability of pyrazolo[3,4-b]pyridine was reported and the report showed the surface behavioural pattern of this compound to be very good on stainless steel in HCl [29-31].Some pyrazole moieties possess prominent solvatochromic properties and are useful semiconductor materials [32]. Thus, it is very essential to continually look into the chemistry and pharmacological diversity of pyrazole to harness and tap into the potential of this class of heterocycle for future drug development and application in material science.

1. Chemistry

Pyrazole and other heterocyclic-based framework are the centremechanismsand core focus in therapeutic medicine.Among thefive-membered heterocyclic compounds, pyrazoleis less identified, and investigated as characteristic core in the structure of few commercial drugs. The deficiency of naturally occurring pyrazoles has been attributed to difficulties in establishing the configuration of the N–N bond by living organisms [33].

In any case, compounds **10, 11, 12**, and **13** are pyrazolemotifs that are identified in some alkaloids (Figure 5). Compound **10**, 3-phenyl-5,6-dihydro-4*H*-pyrrolo[1,2-b]pyrazole isapapaverine-like narcotic which occurs within the roots of *Withaniasomnifera* [34], the root bark of *Newbouldialaevis* [35],and in *Elytrariaacaulis* [36].The compounds**11**,**12** and **13** are 1,3,5-trimethylpyrazole alkaloids which can also be referred to as cinachyrazoles (Figure5) and are separated from ocean wipe species of the class called Cinachyrella with no significantly known biological activity as at 2017[37].

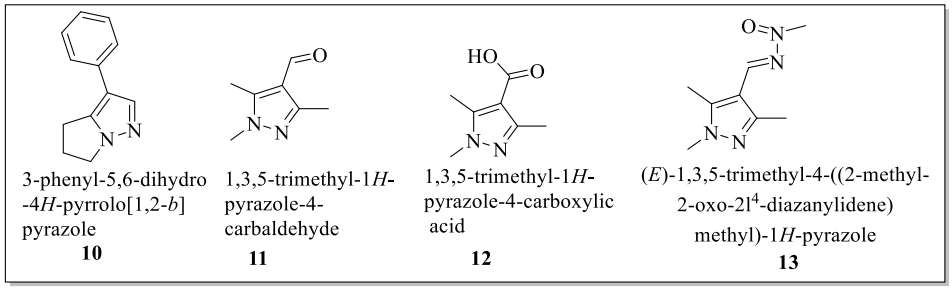


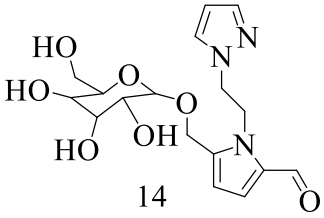
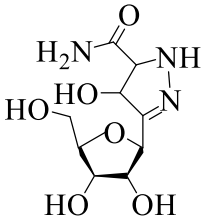
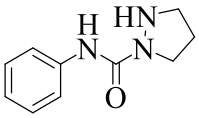
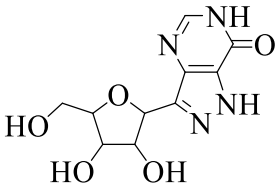
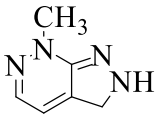
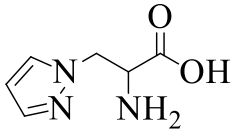
Figure 5: Structures of Bioactive Alkaloids **10-13** having Pyrazole Core

In addition, galactosylated derivative **14**was recently isolated from watermelon seed [38].The report indicated that compound **14** showed moderate viability with 70.4% developed restraint atan inhibitory concentration of 100 μM against

mouse B16 melanoma, 4A5 cell line) (Table 1). *Streptomyces* is the highest producer of new secondary metabolites [39] and pyrazofurin**15**is produced by*Streptomyces candidus;* although,L-glutamate is the precursor to the nucleobases in pyrazofurin [40].

It is altogether known for its antimicrobial, antiviral, and antitumor properties [26].Investigation showed that the naturally occurring pyrazole motif,*N*-phenyl-1-pyrazolidinecarboxamide **16** in Mangrove tree *Rhizophoraapiculata showed*tumour-reducing properties in mice [25] (Figure 6). Formycin B **17** is isolated from *Streptomyces lavendulae* and *Streptomyces candidus*and is known for antiviral and antitumor activity [24]. NostacineA**18** isextracted from *Nostocsponiiaeforme* with a cytotoxic effect [41]. Also, compound**19** with viable antidiabetic was extracted from *Citrullus vulgaris* [33].

Table 1: Natural products containing pyrazole moieties, isolation and uses

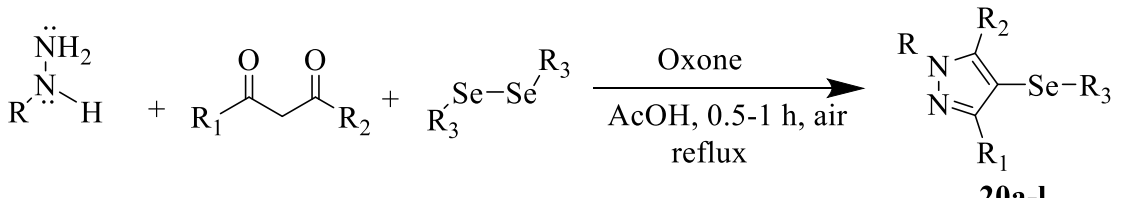
Structures	Name	Isolated from	Uses
 14	Galactosylated pyrazole derivative	Seeds (watermelon) of *Citrulluslanatus*	Anticancer [38].
 **15**	Pyrazofurin	*Streptomyces candidus*	antimicrobial, antiviral, and antitumor [26].
 **16**	*N*-phenyl-1-pyrazolidinecarboxamide	(Mangrove tree)*Rhizophora Apiculeta*	Antitumour (Prabhu and Guruvayoorappan[25].
 **17**	Formycin B	*Streptomyces lavendulae* and *Streptomyces candidus*	Antiviral, antitumour[24].
 **18**	Nostacine A	*Nostocsponiiaeforme*	Cytotoxic [41].
 **19**	l-α-amino-β-(pyrazolyl-*N*)-propanoic acid	*Citrullus vulgaris*	Antidiabetic [33].

2.1 Synthesis of pyrazole derivatives

Pyrazoles have basic chemistry which encourages a few substitutions on their centre ring throughfacilesynthesis. Right now, diverse strategies are utilized for the synthesis of pyrazole and its derivatives. Some of them are detailed in the later writing below.

(a) Synthesis via Oxone-Mediated Method

A successful protocol for the single-pot preparation of a number of 4-organylselanylpyrazoles **20**was described by ozone-mediated multicomponent response of substituted hydrazine, 1,3-diketones and diorganyldiselenides. These results were achieved without using any metal catalyst via smooth set-up, short response period and excellent yields of 98% (Scheme 1) [42].

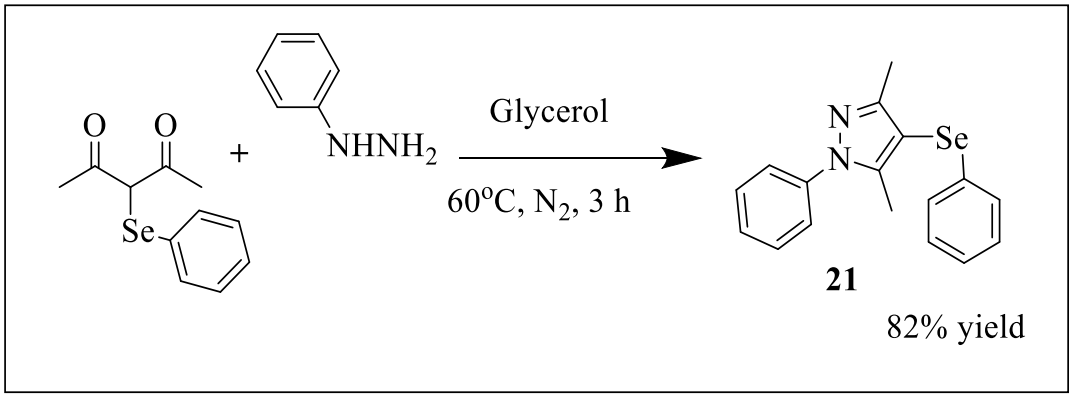


20a: R=C_6H_5, R_1=R_2=Me, R_3=C_6H_5. time=0.5 h, yield=98%
20b: R=C_6H_5, R_1=R_2=Et, R_3=C_6H_5, time=0.5 h, yield=90%
20c: R=C_6H_5, R_1=Ph; R_2=Me (96:4), R_3=C_6H_5. time=0.5 h, yield=89%
20d: R=2,4-dimethylphenyl, R_1=R_2=Me, R_3=C_6H_5, time=1 h, yield=69%
20e: R=2,4-dichlorophenyl, R_1=R_2=Me, R_3=C_6H_5. time=1 h, yield=44%
20f: R=H, R_1=R_2=Me, R_3=C_6H_5, time=1 h, yield=75%
20g: R=C_6H_5, R_1=R_2=Me, R_3=4-methylphenyl. time=0.5 h, yield=77%
20h: R=C_6H_5, R_1=R_2=Me, R_3=4-methoxylphenyl. time=0.5 h, yield=84%
20i: R=C_6H_5, R_1=R_2=Me, R_3=4-chlorophenyl. time=0.5 h, yield=81%
20j: R=C_6H_5, R_1=R_2=Me, R_3=4-florophenyl. time=0.5 h, yield=90**%**
20k: R=C_6H_5, R_1=R_2=Me, R_3=C_4H_9. time=0.5 h, yield=90%
20l: R=C_6H_5, R_1=R_2=Me, R_3=pyridyl. time=0.5 h, yield=58%

Scheme 1: Single-Pot Three Components Synthesis of TetrasubstitutedPyrazole

(b) Synthesis via Glycerol as Sustainable Solvent

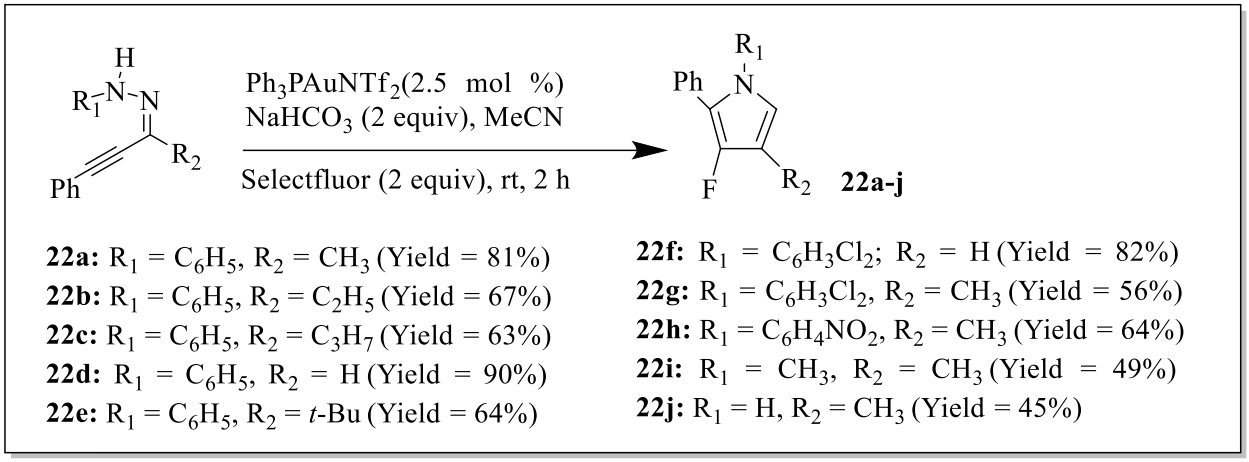
A novel strategy for the preparation of pyrazole derivative **21** by utilizing glycerol, PEG-400, H_2O, and EtOH as sustainable solvents for green chemistry at room temperature, 60°C and 90°Cwere reported respectively. In this strategy, 4-arylselanylpyrazoles were synthesized by a conventional cyclo-condensation of α-arylselanyl-1,3-diketones with arylhydrazines without utilising any corrosive catalyst. The best yield of the product was obtained in 82% at 60°C in 3 h under nitrogen atmosphere (Scheme 2) [43].



Scheme 2: Glycerol Sustainable Synthesis of TetrasubstitutedPyrazole

(c). Synthesis via Select fluor Supported Approach

The synthesis of a well-planned procedure to access ten fluoro-pyrazole**22a-j (**Scheme 3)involved amino-fluorination of alkynes in Selectfluorusing gold-catalysed. The ten pyrazole products **22a-j** were attained in yields ranging from 45% for compound **22j** up to an excellent yield of 90% for pyrazole**22d.** The reaction was driven at room temperature within two hours reaction time [44].

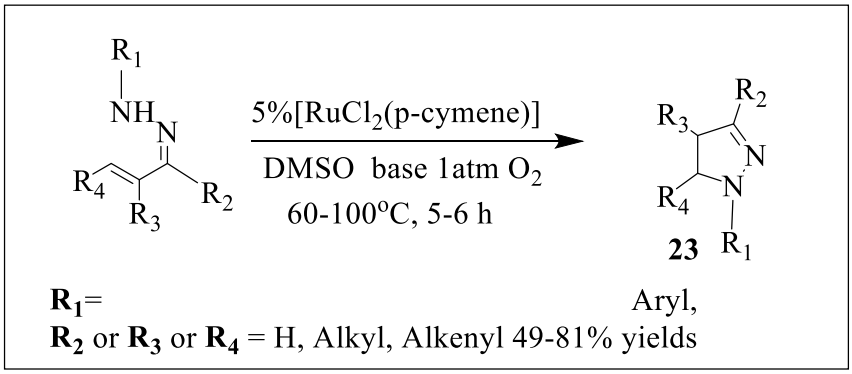


Scheme 3: Selectfluor Supported Synthesis of Fluorinated Pyrazoles

(d). Synthesis via Ruthenium-Catalyzed Oxidative Coupling Approach

A new Ru(II) catalysed oxidative C-N coupling technique detailed for the formation of profoundly broadened tri- and tetra-substituted pyrazoles from readily availa- ble starting materials has been detailed [45].

In the study, molecularoxygen is utilized as the oxidizing agent that showcases basic role within catalytic cycle of C-H activation(Scheme 4). This method has been used in the synthesis of several pyrazole motifs with amazing reactivity, wide range of biodiversity, good tolerance for functional groups insertion and excellent yields [45].

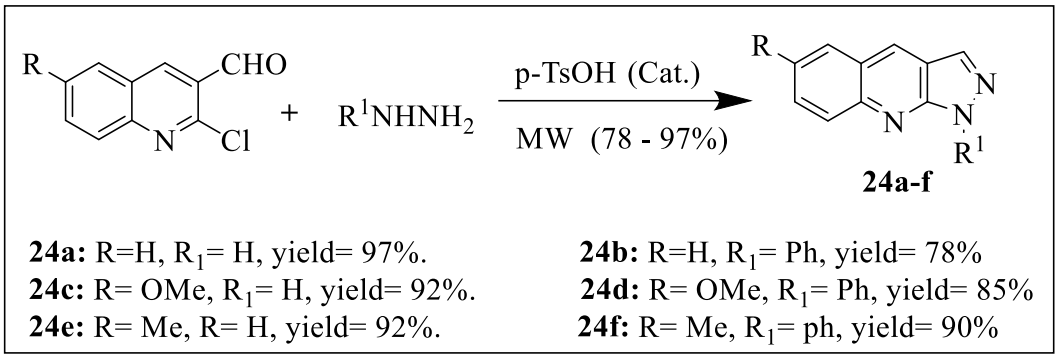


Scheme 4: Ruthenium-Catalysed Synthesis of TetrasubstitutedPyrazoles

(e). Microwave Synthesis via p-TsOH Aided Approach

Pyrazole-fused quinolines**24a-f**were prepared from microwave assisted irradiation of specialized 2-chlorinated 6-substituted quinoline-3-aldehydes and arylated hydrazine using a catalytic quantity of *p*-TsOH in solvent-free medium (Scheme 5).

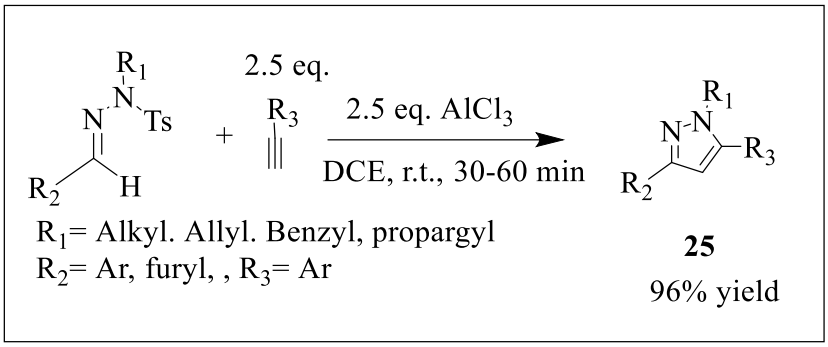
The six quinoline-fused pyrazole motifs**24a-f** were obtained in excellent yields ranging from 78% pyrazole**24b**to 97%for pyrazole**24a**[46].



Scheme 5: Synthesis of Pyrazolo[3,4-*b*]quinolines

(f). Synthesis via Aluminium chloride mediated

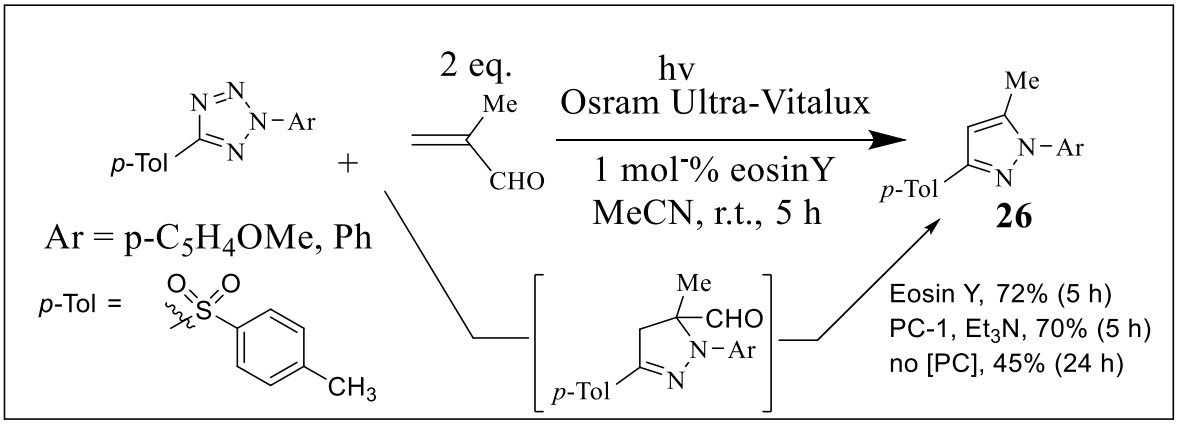
N-Alkylated tosylhydrazones and terminal alkynes reacted through the use of aluminium chloride as the catalyst to produce a succession of 1,3,5-trisubstituted pyrazoles with great regioselectivity in exceptionally great yields of over 90% (Scheme 6). The reaction took place at room temperature between 30-60 min with dichloroethane (DCE) as the solvent, the method exhibited great functional group interaction and can be used on a variety of substrates [47].



Scheme 6: Synthesis of 1,3,5-trisubstituted pyrazoles with great regioselectivity

(g). Synthesis under green light irradiation

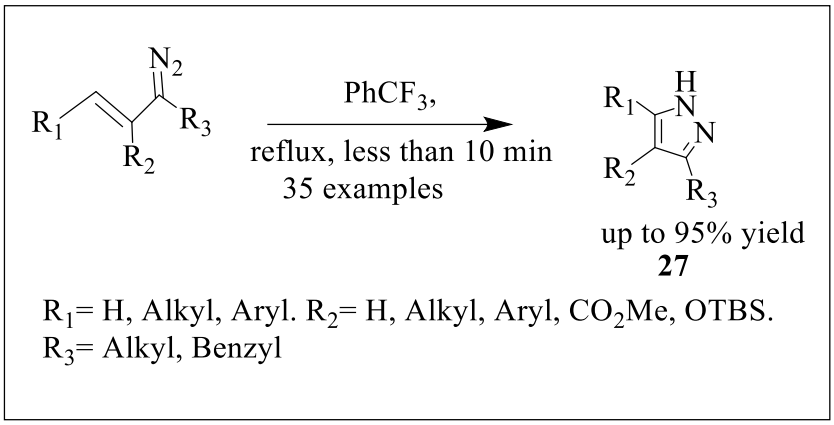
Photo click cycloaddition, subsequent to photocatalyzed oxidative deformylation, allows for the efficient regioselective production of pyrazoles (Scheme 7). This procedure allows the utilization of unsaturated aldehydes as synthetic alternatives to alkynes and offers a novel photoredox-catalyzed Norrish sort fracture under green light irradiation with good yield [48]. When iridium photocatalyst-1 (PC-1)was used in the presence oftriethylamine affording **26**in 70% yield within 5 h reaction time; however, in the absence of PC the yield reduced drastically to 45% even the reaction time became prolonged to 24 h.



Scheme 7: Simple regioselective synthesis of pyrazoles

(h). Synthesis via thermal electrocyclization of vinyl-diazo

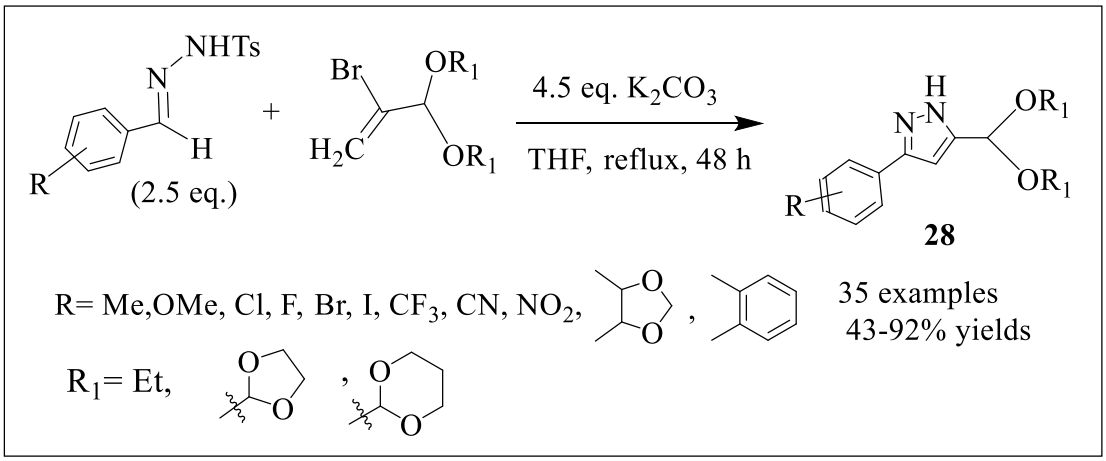
Pyrazoles are produced in good yields by the thermal electrocyclization of vinyl-diazo compounds (Scheme 8). These straight-forward, commonly accessible starting materials and catalyst-free reactions allow the production ofpyrazolederivative**27**(mono-, di-, and tri-substituted)in excellent yield and within a short time of less than 10 min using $PhCF_3$ as a solvent [49].



Scheme 8: Synthesis of 3,4,5-trisubstituted pyrazole Motifs

(i). Synthesis viaunactivatedbromovinylacetals

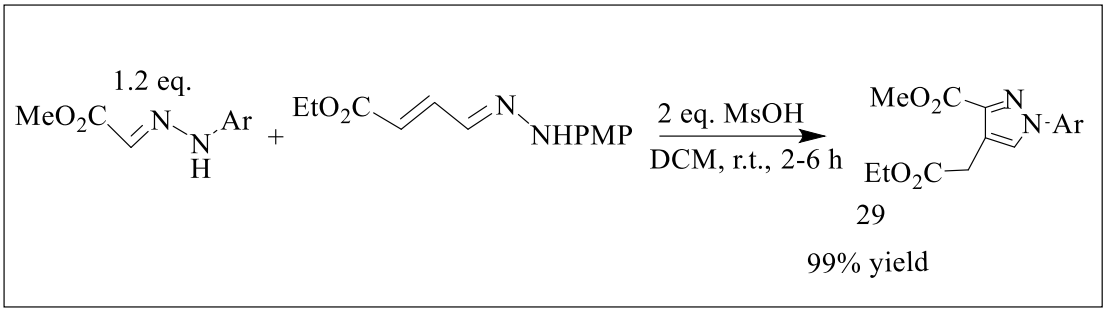
Good yields of 3,5-disubstituted pyrazoles 28are generated in situ by reacting N-tosylhydrazones with unactivatedbromovinylacetals, which stand in for alkynes (Scheme 9). This reaction was carried out using 4.5 equivalents K_2CO_3 as the base and THF as the solvent. The reaction produced a variety of 3,5-disubstituted pyrazoleviathe condensation of *N*-tosylhydrazones with different substituted benzylidene groups[50].



Scheme 9: Synthesis of 3-argio-5-(1,3-dioxan-2-yl-1*H*-pyrazoles

(j). Synthesis via both self- and cross-condensation

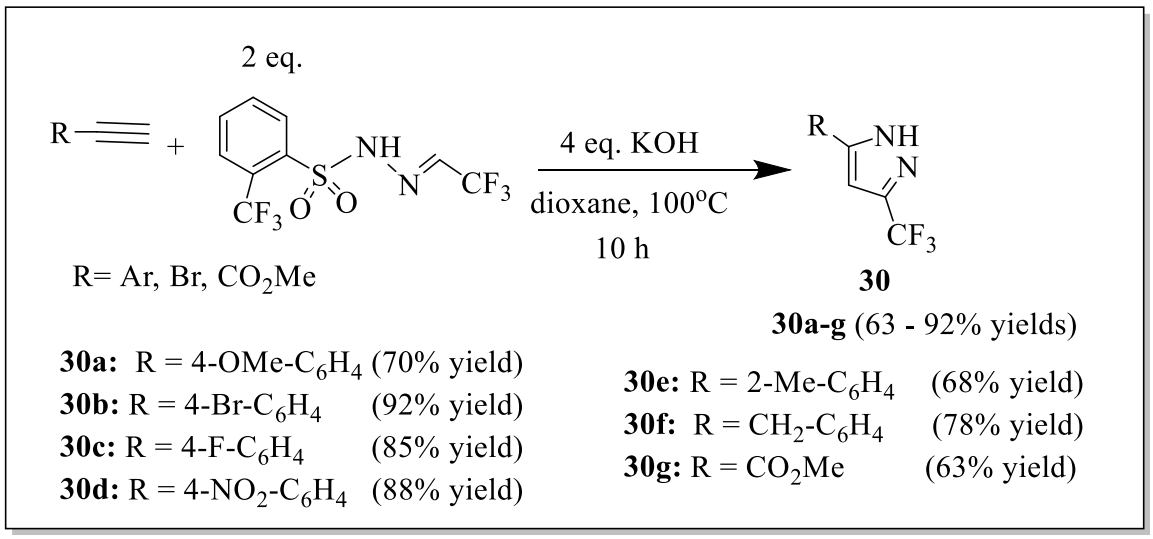
Hydrazones'amphiphilic reactivity allows for both self- and cross-condensation, producing various derivatives of multi-substituted pyrazoles**29** in excellent yields with a diversity of substrates. The easy nucleophilic addition/cyclization/aromatization/-protonation sequence drives this Bronsted acid-mediated reaction under benign circumstances. This reaction occurred at room temperature under a mild state reaction [51].



Scheme 10: Synthesis of multi-substituted pyrazoles

(k). Synthesis via trifluoroacetaldehyde*N*-triftosylhydrazone

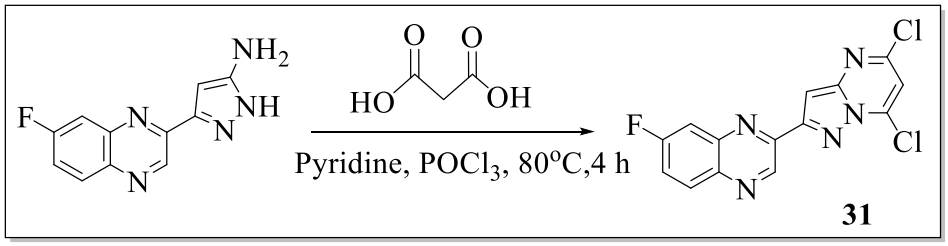
Alkynes and trifluoroacetaldehyde*N*-triftosylhydrazone were reacted in the company of KOH as a base/catalyst using dioxane as reacting medium at 100°Cfor 10 hr to produce 3-trifluoromethylpyrazoles, **30** in excellent yields (Scheme 11) with a variety of substrates, such as aryl, heteroaryl, and alkyl terminal alkynes as well as internal alkynes that are electron-deficient [52]. This operationally simple operation afforded seven pyrazoles**30a-g** in 63 to 92% yields.



Scheme 11: Synthesis of 3-trifluoromethylpyrazoles

(l). Synthesis via Thermal Cyclization of 5-amino-3-hetarylpyrazole

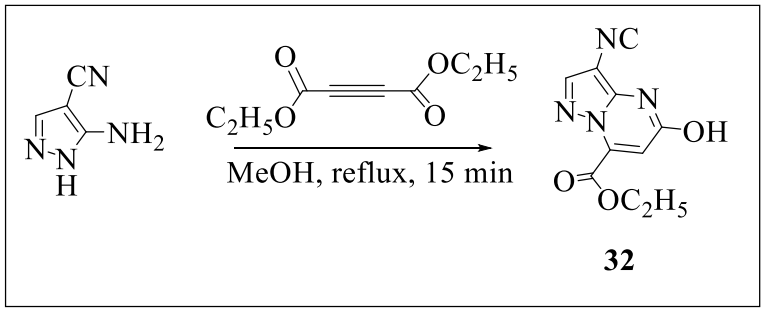
The reaction of5-amino-3-hetarylpyrazole, malonic acid with pyridine catalyst produced compound **31** (Scheme 12). $POCl_3$ is added to produce an enacted class of malonic acid phosphoric ester. This compound gave an excellent yield (>87%)and in less time than under different conditions for dimethyl malonate under basic media [53].



Scheme 12: Synthesis of 5,7-dichloro-2-hetarylpyrazolo[1,5-*a*] pyrimidine.

(m). Synthesis of ethyl 2-((2λ^3ethynyl)- λ^7-oxidanyl)-2-oxoacetate compound with ethene

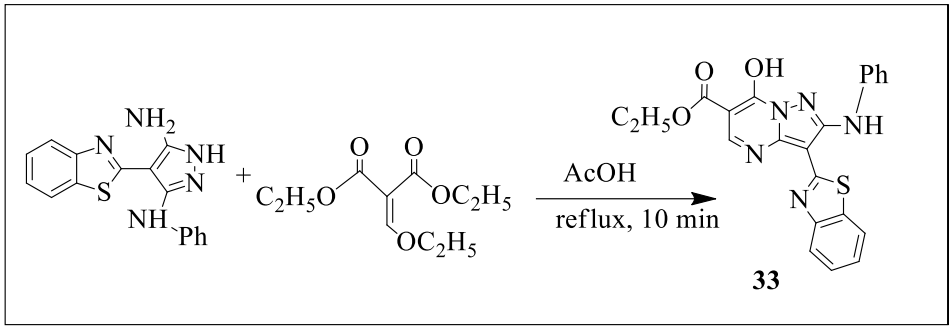
Ethyl-5-hydroxy-3-isocyanopyrazolo[1,5-a]pyrimidine-7-carboxylate**32**was synthesized by reacting diethyl acetylenedicarboxylate and the aminopyrazole using MeOH as solvent at moderate heating for 15 min. Compound **32**was obtained in an excellent yield of 99%due to effective reaction optimization through careful adjustment of solvent, temperature, and time (Scheme 13) [54].



Scheme 13:synthesis of ethyl 5-hydroxy-3-isocyanopyrazolo[1,5-a]pyrimidine-7-carboxylate

(n). Synthesis via diethyl ethoxymethylenemalonate

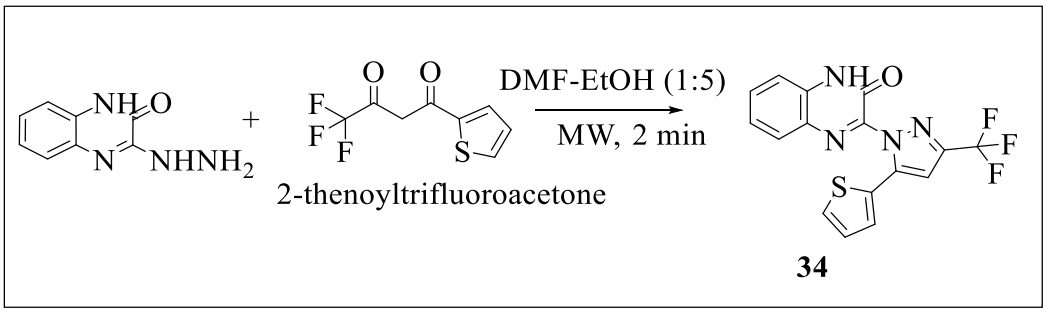
The synthesis of pyrimidine base pyrazole**33** was accessed via the condensation reaction ofdiethylethoxymethylenemalonateand 4-(benzo[d]thiazol-2-yl)-N^3-phenyl-1*H*-pyrazole-3,5-diamine.This was refluxed in acetic acid for 10 min to produce compound **33** in83 % yield as shown (Scheme 14) [21].



Scheme 14: Synthesis of the 2-(benzothiazol-2-yl)pyrazolo[1,5-*a*]pyrimidine.

(o). Synthesis via DMF–ethanol (1:5) solvent dependent mixture

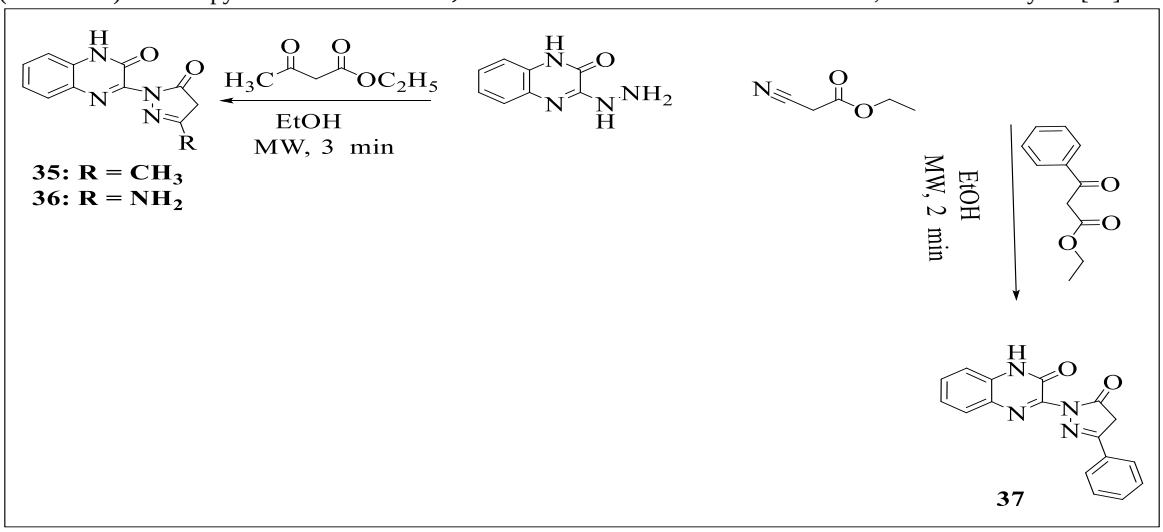
3-(5-(Thiophen-2-yl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)quinoxalin-2-(1*H*)-one**34** was synthesized via equimolar mixture of 3-hydrazino-2-quinoxalinone with 2-thenoyltrifluoroacetone using DMF–ethanol (1:5) as solvent.This was achieved within 2 min under microwave irradiation to afford pyrazole derivative **34**as an orange crystalline compound in 97% yield (Scheme 15). The product was purified by recrystallization on ethanol [55].



Scheme 15: A tri-fluorinated pyrazole derivative and its synthesis

(p). Synthesis via microwave irradiation

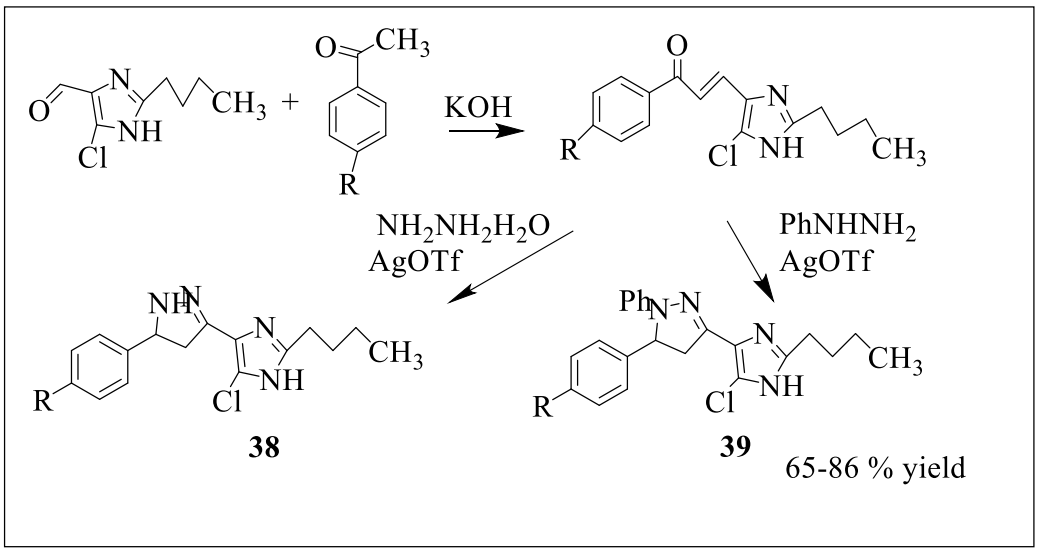
A homogeneous mixture of 3-hydrazino-2-quinoxalinoneand β-keto esters in ethanol using microwave irradiation afforded 3-(5-oxo-3-substituted-4,5-dihydropyrazol-1-yl)quinoxalin-2(1*H*)-ones, **35-37**.This was achieved by the condensation reaction of 3-hydrazino-2-quinoxalinone with ethyl acetoacetate, ethyl cyanoacetate and ethyl benzoylacetate (Scheme 16)to afford pyrazolone derivatives**35,36**and **37** in ethanol for 2 - 3 min with 94%, 50% and 99% yield [55].



Scheme 16: Synthetic method for the production of 3-substituted pyrazolone derivatives **35, 36** and **37**

(q). Synthesis via Silver Triflate-Supported Approach

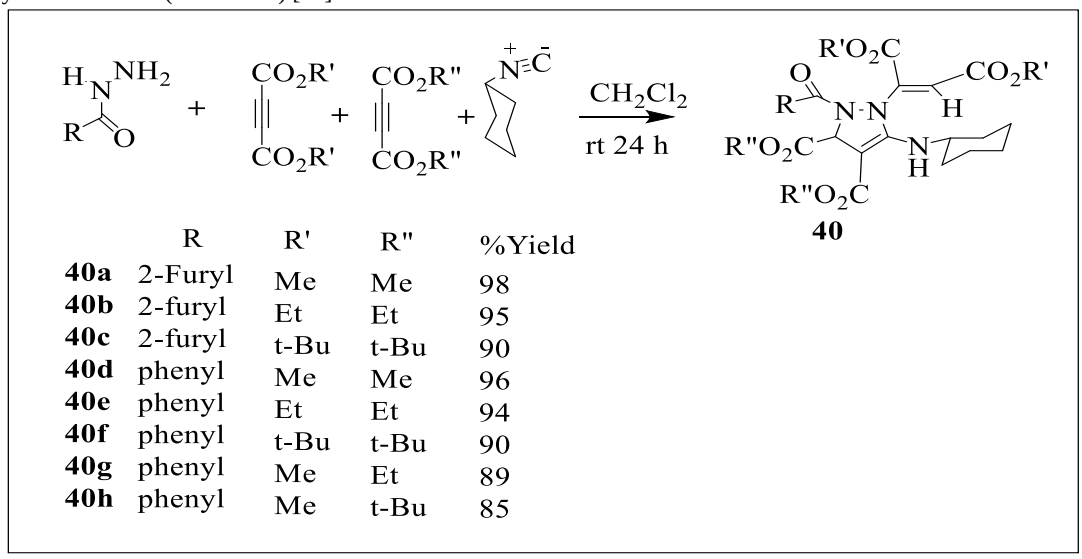
The preparation of a series of imidazole-pyrazole derivatives**38** and **39**occurred via the use of silver(i)trifluoromethanesulfonate (AgOTF)as a catalyst (Scheme17) through a condensation reaction of acetophenones with imidazole aldehydes via KOH andEtOH at room temperature in good yield [56].



Scheme 17: Silver Triflate Synthesis of Imidazole-based Pyrazoles

(r). Synthesis via Isocyanide-based Cascade Approach

An excellent approach leading to the formation of polysubstituted-pyrazole derivatives**40a-h**via a one-potreaction of arylcarbohydrazides, di-alkyl acetylenedicarboxylates, and isocyanido-cyclohexane at room temperature for 24 with excellent yield of 85-98% (Scheme 18) [57].

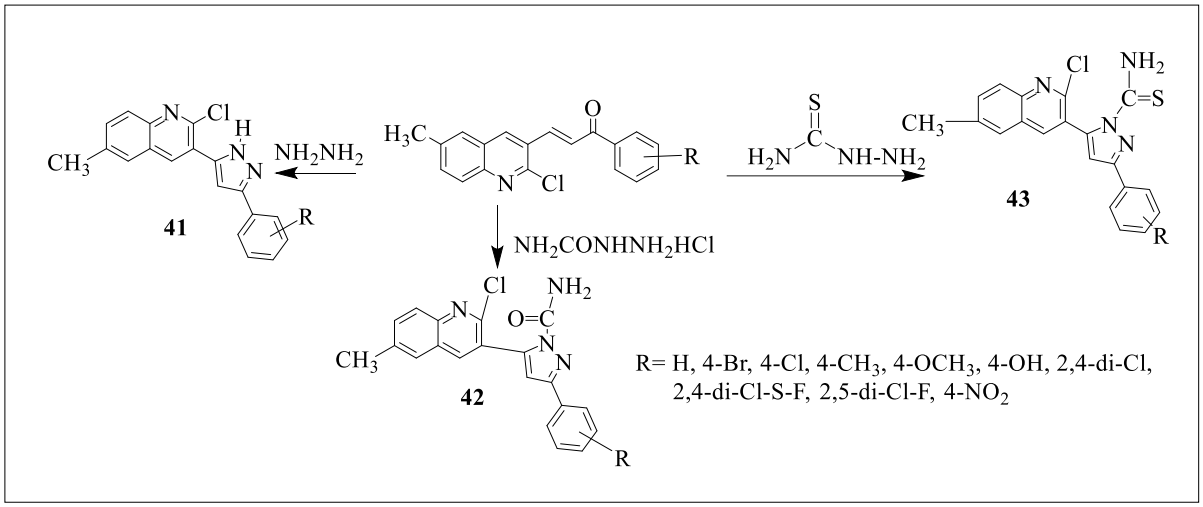


	R	R'	R"	%Yield
40a	2-Furyl	Me	Me	98
40b	2-furyl	Et	Et	95
40c	2-furyl	t-Bu	t-Bu	90
40d	phenyl	Me	Me	96
40e	phenyl	Et	Et	94
40f	phenyl	t-Bu	t-Bu	90
40g	phenyl	Me	Et	89
40h	phenyl	Me	t-Bu	85

Scheme 18: Isocyanide-based Cascade Synthesis of PolyfunctionalizedPyrazoles

(s). Microwave Synthesis via hydrazinolysis Approach

Microwave approach produced polyfunctionalizedpyrazole derivatives**41, 42** and **43**in 4-7 min whereas the same products were synthesized under the conventional heating method in 5-7 hours which is a testimonial to the efficiency and kinetically favoured reaction under microwave irradiation (Scheme 19) [58].



Scheme 19: Microwave-Assisted Synthesis of PolyfunctionalizedPyrazoles

3. Pharmacological activities

The pyrazole core's convenience and exceptional healing value have long been acknowledged, and its broadest range of applications has been evaluated as crucial pharmacophores. Hence, pyrazole is a possible source of raw materials for the synthesis of targeted molecules and the creation of drugs.Some biological activities associated with pyrazole derivatives that have been described and reported are as follows:

3.1 Anti-inflammatory activities

A good detail showed that compound**44**exhibited excellent anti-inflammatory potential (≥84.2%) as compared to the standard sedate diclofenac (86.72%) when measured 3 h after the carrageenan infusion. Compounds **45** and **46** showed promising anti-inflammatory action of approximately 61–85% tumour necrosis factor and 76–93% interleukin-6 inhibitory action at a concentration of 10 μMwhen compared to the standard sedate dexamethasone (76% and 86% inhibitory movement at 1 μM) [18,19].Investigation showed that compound **47** has the highest potency of 78 % at 3 h when compared to the standard (Ibuprofen) [59].In addition,compound**48** exhibited notableanti-inflammatory and pain-relieving efficacies at doses of25, 50, and 10mg/kg p.o. using phenylbutazone as the standard drug [60].

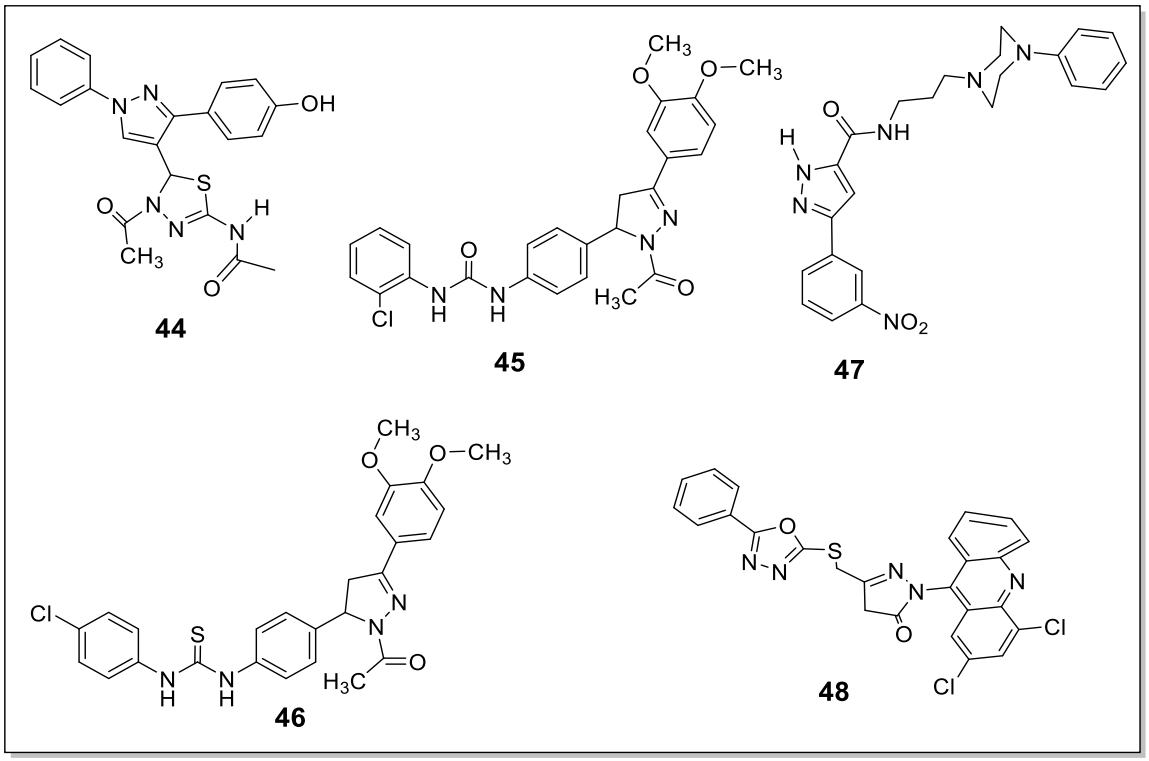


Figure 6: Selected Pyrazole-based Motifs with Analgesic and Anti-inflammatory Properties

3.2 Anti-bacterial activities

Synthetic substance had minimal to moderate antibacterial activity, while compound **49** showed efficacy against *Bacillus subtilis* and compound **50** demonstrated good activity against *Salmonella typhi* [14]. Arange of pyrazoline-based coumarins were produced and their antibacterial activity *invitro* were carried out on six organisms which were *S. aureus, S. faecalis, K. pneumonia, P. vulgaris, P. aeruginosa* and *E. coli*. The foremost dynamic antibacterial representative was compound **51**with a MIC value of 3.92±0.22 µg/mL[3].

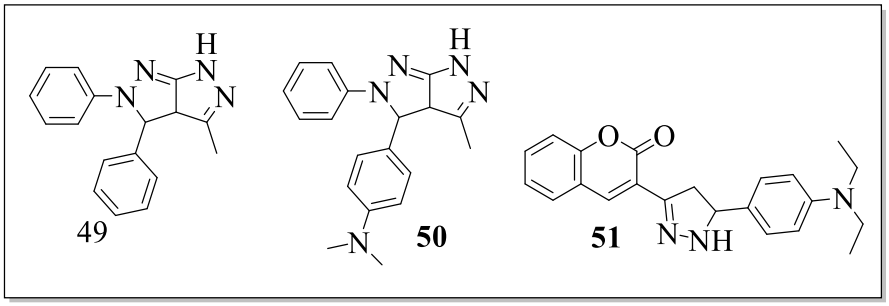


Figure 7: Selected Pyrazole-based Motifs with Antibacterial Properties

3.3 Antifungal activities

Pyrazole derivative**52** (2-NO_2) displayed the most improved antifungal activity exhibited at a minimum inhibitory concentration at 12.5 mg/mL against *A. clavatus* as compared to griseofulvin (100 mg/mL) [61]. The synthesis and evaluation of nine derivatives of pyrazole was carried out, compound**53** showed antifungal activity against *Gibberellanicotiancola*atEC_{50}=0.023µg/mL, EC_{95}=1.766µg/mL than the standard pyraclostrobin (0.226, 4.131µg/mL)[16].Pyrazole motif, **54** was reported to display a better efficacy on *Rhizoctoniasolani* (90% at 10 mg/L), than the clinical standard drug, thifluzamide (80% at 10 mg/L) [15].Additionally, compounds **55** and **56** were identified as the primary protease inhibitors for COVID-19 by ADMET predicted investigation [17].

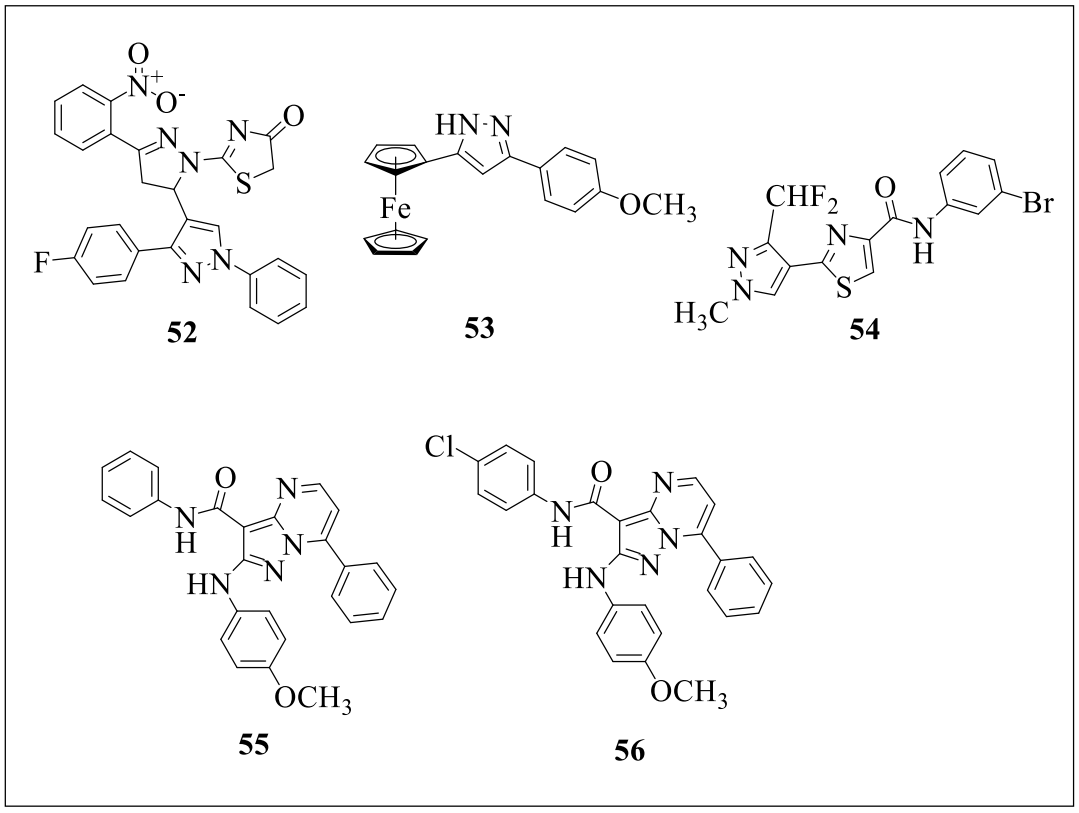


Figure 8: Selected Pyrazole-based Motifs with Antifungal Properties

3.4 Anticanceractivities

Pyrazole motif **57**was reported to show better efficacy as an anticancer agent(IC_{50} =0.3 µg/mL, ED(100, 50, 25)µg =(100, 98.4, 93)%than the clinical standard drug,5-fluorouracil(IC_{50} =32.26 µg/mL, ED(100,50, 25)µg=(98.2, 70.1, 40)%

[62].Compound **58** exhibited effective cytotoxic action against leukaemia CCRF-CEM, lung cancer HOP-92, and liver cancer Hep-G2, with IC_{50} 16.34, 3.45 and 7.79 µM. This showed a moderate to excellent increase in inhibitory action ranging from 44.86 % to 84.59 % [21].The design and synthesis of a number of pyrazole motifs and their targeted findings on the inhibition of the CDK2 enzyme were carried out. Hence, their reports showed that compound **59**, and **60**had higher potency against the tested tumour cell lines EGFR/VEGFR-2 inhibition with IC_{50} values of (0.161 and 0.141 µM) and (0.209 and 0.195 µM) [23].

Pyrazole derivatives among which compounds **61**,**62**, and **63**showed better and viable activities against hepatocellular carcinoma Huh-7 with IC_{50} = 6.3 µM as against the standard doxorubicin (IC_{50} = 3.2 µM), cervical adenocarcinoma HeLa with IC_{50} = 7.8 µM as against the standard doxorubicin (IC_{50} = 8.1 µM) and breast adenocarcinoma MCF-7(IC_{50} = 3.0 µM) whereas IC_{50} of doxorubicin = 5.9 µM. Also, compounds **62** and **63** showed viable activities against the MDA-MB231 cell line with IC_{50} = 4.32 and 5.74 µM in comparison with doxorubicin as the standard with IC_{50} = 6.0 µM [22].Additionally, compounds **64**, **65,** and **66** were found to be viable tyrosine kinase inhibitors for treating various cancers [20].

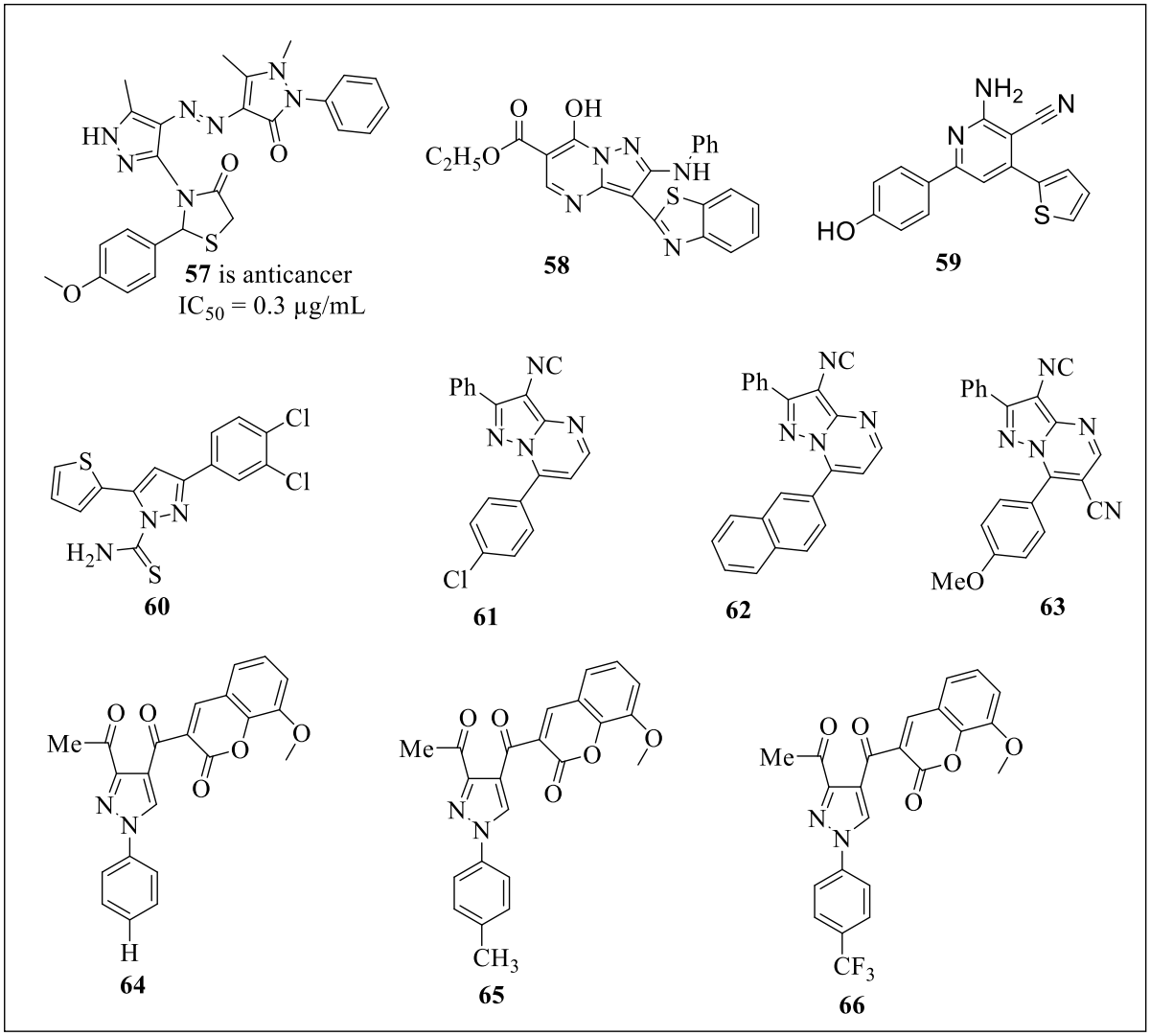


Figure 9: Selected Pyrazole-based Motifs with Anticancer Properties

3.5 Antioxidantactivities

The synthesis oftwelvederivativesof tetrasubstitutedpyrazole**67a-l**were reported, theantioxidantpropertiesofthe moleculeswereevaluated using DPPH,nitricoxide,superoxide,andperoxidemethods. Theresult showed thatcompound**67a** has maximum radicalscavengingactivity(GI_{50}=15.6 µM) against MCF7 [28].Inaddition, compound **68**via evaluation by DPPH, lipid peroxidation,and ABTSmethods showedvery goodantioxidativeactivitywith IC_{50}=9.0,4.3and18.9µM,respectively compared to the standard butylatedhydroxy anisole (BHA)with IC_{50} of 12.5, 5.4 and 20.9 µM, owingtothepresenceof3,5-

dinitrobenzylgroup at1-position ofpyrazole [63].Likewise using similar antioxidant screening procedure,the compound **69** shows excellent antioxidant activity (92.64%) followed by **70** (72.25%) among the serial of sulphonamide-containing pyrazole designed and synthesized from ampyrone. The two chloro substituents presence in **69** might have contributed to the antioxidant efficacy through there electron withdrawing effect[63].

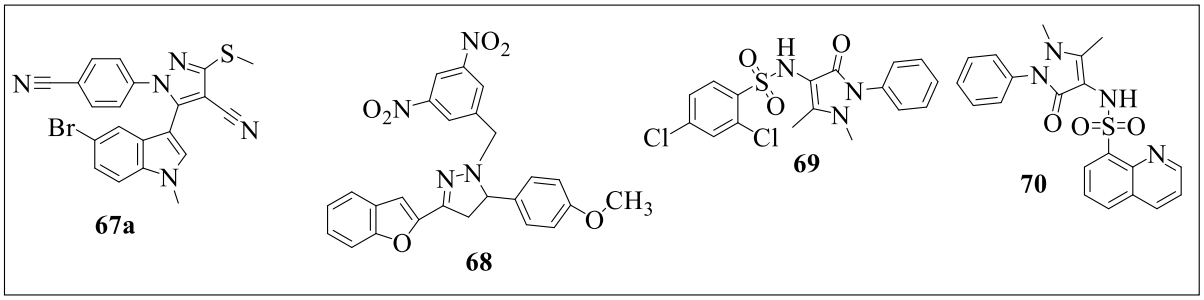


Figure 10: Selected Pyrazole-based Motifs with Antioxidant Properties

3.6 Structure activity relationship (SAR) study

The antifungal agent **54** was the subject of the SAR investigation.It was reported that the activity of this pyrazole motif was enhanced by the presence of a methyl group (electron donating group) on the N1 position of pyrazole moiety as shown in Figure 11. Also, the position of R on the aniline moiety contributed to the activity of the compound. Ortho position and meta positions favoured the antifungal activity while the para position either with electron withdrawing or donating group did not contribute to the antifungal activity of the compound(Figure 11) [15].In a similar observation, the antiproliferative activity of pyrazolemotifs was enhanced by the presence of chloro-group as indicated in **61** (IC_{50} = 6.3 µM) while the bromo and the fluorogroup were of less activity. The replacement of pyrimidine with acetamido group as indicated in **71** (IC_{50} = 10.2 µM) reduce the antiproliferative activity. In addition, the introduction of CN in of the pyrimidine ring as shown in**63**increased the antiproliferative activity (Figure 12) [22].

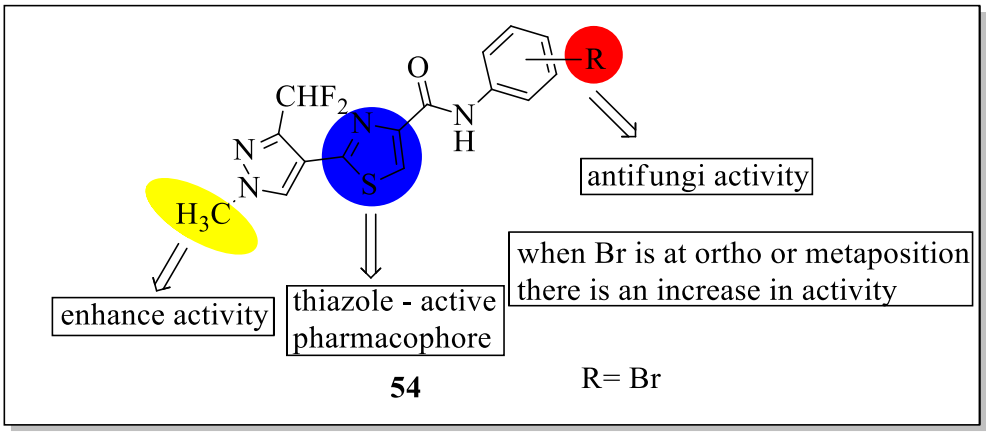


Figure 11: SAR study of pyrazole-thiazole derivatives with antifungal properties

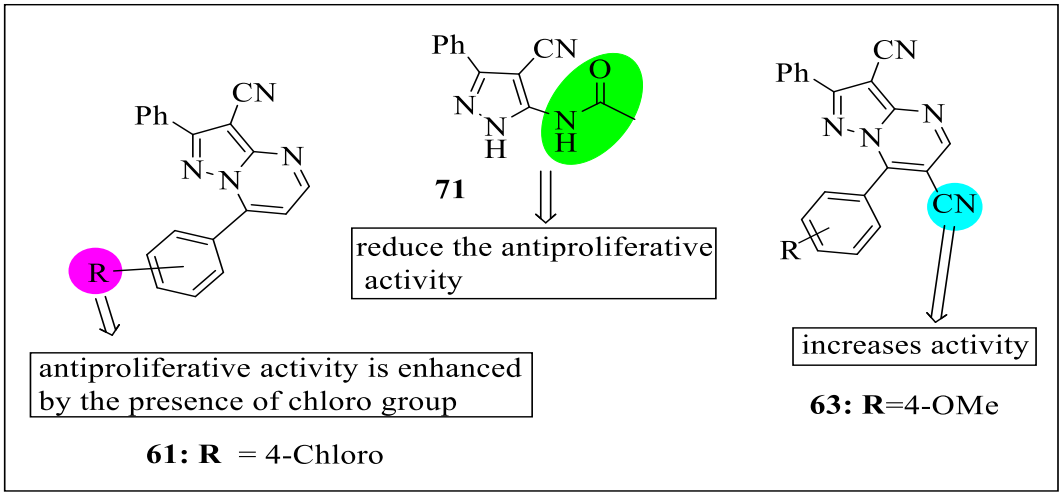


Figure 12: SAR of 2-phenylpyrazolo[1,5-a]pyrimidine-3-carbonitrilederivatives containing pyridine moiety with antiproliferative activity

3.7 Molecular Modelling and Binding Study

In order to investigate and predict the primary binding affinity of drug-like compounds to a given protein, docking is an essential tool. When compared to experimentally determined biological activity, this method is efficient in terms of cost, duration, and energy consumption.The molecular docking studies on the homology-modelled SDH crystal structure from *Rhizoctoniacerealis* using **54** and thifluzamide. It was observed that the amide oxygen atom of **54** interacted with the amino acid Trp-B203 via a hydrogen bond. The inhibitor bound to the protein's active site in large part to this interaction, which strengthened its hold over thifluzamide. Other interactions such as the phenyl moiety which formed a Br-π collaboration with the build-up Phe-C65 were reported to be influential in the binding(Figure 13). As a result of the interactions observed between the **54** and the active site of RcSDH, compound**54** was also reported to be more active than the standard thifluzamide after experimental biological validation [15].

In another study, a designed novel*N*-alkylated pyrazole Hybrid Molecules were carried out and docked to establish their antimicrobial activity potential. Compound **72** displayed top inhibiting activity on 1E9X and 3MZD and has proven to possess good *in vitro* antimicrobial activity with binding energy (-13.2 kcal/mol) on interacting residues GLY396/ALA256, CYS394/LEU321,TYR76/LYS97 and VAL395which is lower than the standard Fluconazole (-7.3 kcal/mol)(Figure 14) [64].

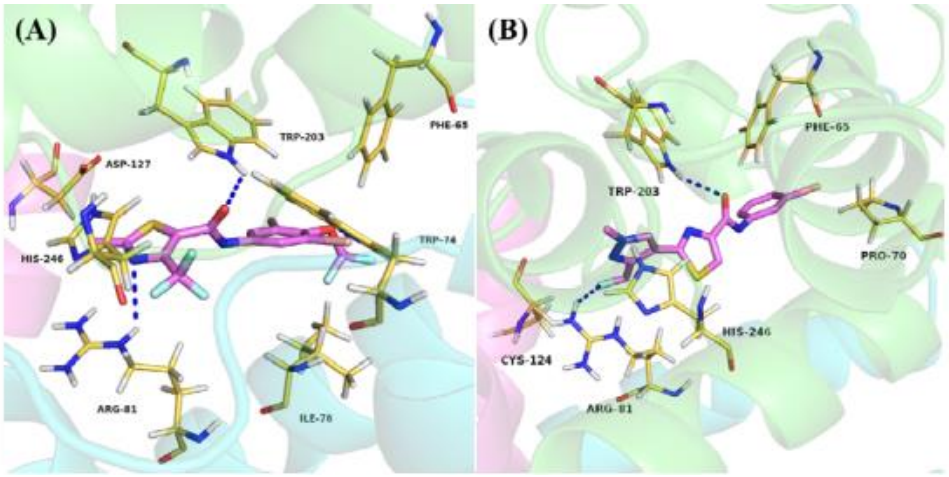


Figure 13: The molecular docking of thifluzamide with RcSDH (A) and **54** with RcSDH (B) showing their interaction and binding affinity.

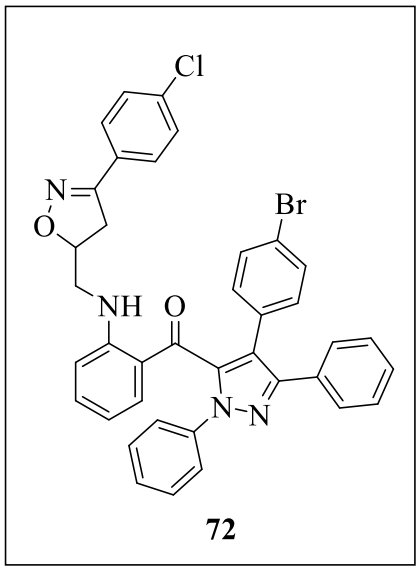


Figure 14a: Compound **72** having good *in vitro* antimicrobial activity with binding energy (-13.2 kcal/mol) as against the standard Fluconazole (-7.3 kcal/mol)

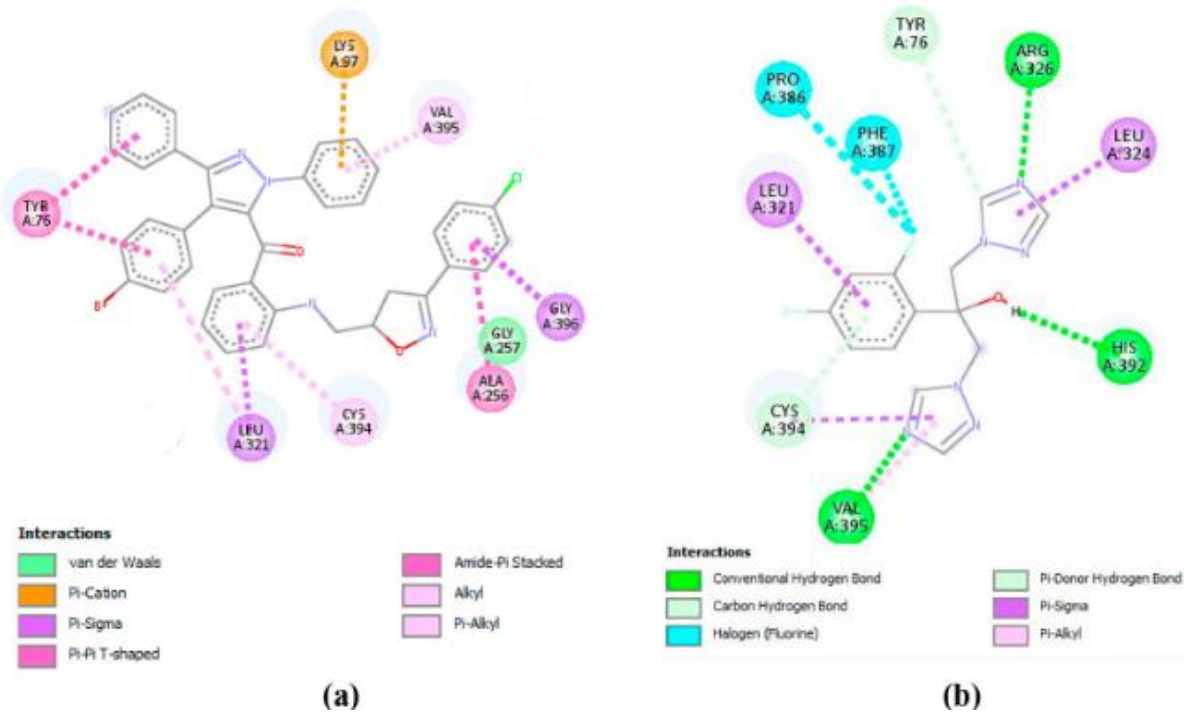


Figure 14b:(a) 2D Diagram of 1E9X-**72** interactions. (b) 2D Diagram of**72** interactions involved between **1**E9X and Fluconazole.

3.8 ADMET Study on Pyrazole Derivatives

ADMET(Absorption, distribution, metabolism, excretion and toxicity**)** studies help researchers and drug developers to establish that a synthesizedpyrazoleis suitable as a drug candidate by assessing the substance's safety and drug-likeness. A new pyrazole-based pyridine-3-carbonitrile derivatives **61**, **62**and**63**were synthesized and tested as an antiproliferative agent. To pass Lipinski's test, a chemical substance needs to have a logP (octanol/water partition coefficient) below 5, a molecular weight of less than 500, and a hydrogen bond donor of less than 5. As a result, it is fairly soluble and works well as a potential drug [22].

In another study,it was reported thatpyrazole derivatives are soluble in H_2O at 25ºC with excellent intestinal absorptionexcept fora few that are slightly skin permeable [64]. All the synthesised compounds statistics showed that most of the projected derivatives have acceptable ADMET profiles without toxic features. It is important to note that inappropriate check always results in an expanded danger of toxicity because of the wrong administration, particularly of those plants and synthetic compounds that are dangerous at low doses [65]. The compounds also have a molecular weight below 500, a hydrogen bond donor below 5, and an octanol/water partition coefficient logP below 5, which all comply with Lipinski's rule of five [64].Additionally, compounds **64**, **65** and **66** are nontoxic and have a better solubility in water as well as outstanding permeability potential with 97 to 100 percent absorption[20].Compounds **55** and **56** also exhibit good ADMET profiles and lack toxic properties [17].

4. Conclusion

Pyrazole is afive-membered heterocyclic compound with two nitrogen hetero-atomsat first and second positions. Due to highly interesting synthetic routes available for the preparation of pyrazole derivatives and their wide spectrum of biological and pharmacological activities, we have devoted some research efforts to these heterocyclic templates. Thus, we have herein dealt with the review of the synthesis of pyrazole motifs by different methods of preparation. The pyrazole derivatives herein discussed are pharmacologically very potent were accessed within less reaction time and with a wide variety of applications in different fields. The therapeutic importance of the locations of the substituents on the pyrazole analogues were disclosed by SAR investigations, and this information may be used to create more active derivatives. The reported drug-likeness of several of the derivatives was also employed to highlight their pharmacokinetic properties, thereby potentially opening the door to long-awaited discovery in restorative pharmaceutical for future therapeutic design and development.

5. Conflict of interest

The authors have declared no conflict of interest.

6. Acknowledgement

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