Review Article

Chemistry and Pharmacological Activities of Pyrazole and Pyrazole Derivatives: A Review

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Received: 02-09-2020; **Revised:** 24-10-2020; **Accepted:** 05-11-2020; **Published on:** 15-11-2020.

ABSTRACT

At the heart of current research is the battle for more efficient and less toxic treatment approaches for diseases. Pyrazole and its derivatives have emerged as an influential scaffold that has drawn the attention of researchers in the field of medicinal chemistry due to its appreciable diversity in biological activities. Pyrazole derivatives have found numerous applications in fluorescent substances, dyes, and agrochemicals. Pyrazole is a multifunction lead compound for efficient biologically active molecules generated by researchers. They have shown a widespread biological and pharmacological activity such as antitumor, analgesic, anti-inflammatory, antimicrobial, antitubercular, antileishmanial activity, ACE inhibitors, antidiabetic, antiparkinsonian and neuroprotective properties. This rational diversity in the pattern of physiological reaction has led many scientists, with far more successful pharmacological intervention, to refine and create new structural alternatives. This Review is important for previous studies and initiatives to explore in the near future the various activities of compounds associated with pyrazole and pyrazole derivatives.

Keywords: Pyrazole, Pyrazole Derivatives, Anti-cancer, Anti-tubercular, Anti-inflammatory, Analgesic, Antimicrobial, Antiviral, Enzyme inhibitors.

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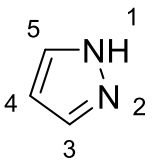
DOI: 10.47583/ijpsrr.2020.v65i01.030

DOI link: http://dx.doi.org/10.47583/ijpsrr.2020.v65i01.030

INTRODUCTION

PYRAZOLE

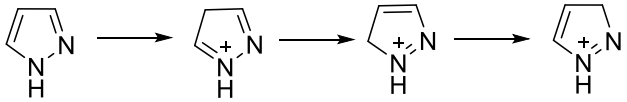
Pyrazoles constitute an essential class of natural and synthetic products, many of which exhibit flexible biological activity. Antitumor, herbicides, antibacterial, antifungal, hypoglycemic, antidepressant, analgesic, anti-inflammatory, anti-cancer, enzyme inhibitor activity are shown among the pyrazoles.[1-3] As represented by the molecular formula, Pyrazole is a five-membered ring structure consisting of three carbon atoms and two nitrogen atoms in adjacent positions. The word pyrazole was first coined by Ludwig Knorr in 1883. They are known as alkaloids because of their structures and unique pharmacological effects on human beings. 1-pyrazolyl-alanine was the first natural pyrazole isolated from watermelon seeds in the year 1959.[4,5]



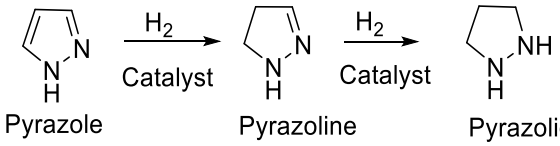
Pyrazole

One that possesses a cyclic structure with at least one heteroatom in the ring is a heterocyclic compound. The most popular heteroatoms are Nitrogen Oxygen and sulphur. In nature, heterocyclic compounds are very widely distributed and important to life in different ways. As is evident from a large number of publications covering their preparation and use, pyrazole constitutes a class of compounds synonymous with widespread use in the field of medicine and agrochemistry.[6]

With a melting point of 70°C, Pyrazole is a colourless solid. This high value is due to intermolecular hydrogen bonding that results in a dimmer (compared with 1-alkyl or aryl-substituted pyrazoles). Pyrazole is a tautomeric substance: in pyrazole itself, the presence of tautomerism cannot be shown but can be inferred by considering pyrazole derivatives. Pyrazole exhibits aromatic properties, e.g., it is readily halogenated, nitrated and sulphonated; the group enters at position 4. The following resonating structures are possible for pyrazole.



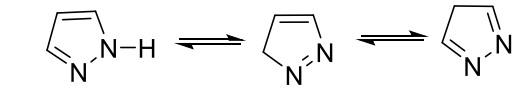
Pyrazole has a weak base and forms salts with inorganic acids; it is possible to substitute imino hydrogen with an acyl group. Pyrazole is highly resistant to oxidizing and reducing agents, but can be catalytically hydrogenated, first with pyrazoline and then with pyrazolidine. But stronger bases than pyrazole are among these compounds.



There are two nitrogen atoms in a five-membered ring in the aromatic organic heterocycle containing pyrazole scaffolds. Pyrazole derivatives are essential in the family of aromatic organic heterocycles. Numerous uses for fluorescent agents, dyes, agrochemicals, and more have been found in pyrazole derivatives. Pyrazole is a multipurpose lead compound for efficient biologically active T-molecules formed by chemical architecture. They have shown a widespread biological and pharmacological activity such as antitumor, anti-inflammatory, antimicrobial, antidepressant antifungal, antimalarial, enzyme inhibitors, antidiabetic, anticonvulsant.

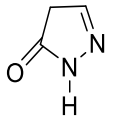
In organic chemistry, the chemistry of heterocyclic compounds remains a blossoming field. One of the heterocyclic compounds is Pyrazole. In the history of heterocyclic chemistry, pyrazole derivatives have played a crucial role and have been extensively studied due to their ready accessibility, diverse chemical reactivity, and extensive biological activity. Pyrazole derivatives are widely applicable in different areas, i.e. Industry, rehabilitation and cultivation in medicine.

In the textile industry, azopyrazolones are the most effective fabric dyes for dyeing cotton, silk, wool, polyester and acrylic fibres, as dyes for leather, rubber products, paint dyes, varnishes, lacquers, natural and synthetic polymers, inks, multi-color jet-printing and hair-dying creams. In rubber technology, the other application of pyrazoles is as anti-aging agents for light coloured rubbers. Pyrazoles are also used in colour photography as colour couplers, sensitizers, super-sensitizers, developers and colour filters. The derivatives of pyrazole are also used as anti-bacterial, diuretic, anti-hypertensive, anti-pyretic, analgesic, tranquillizer, anti-inflammatory, anti-convulsant, anti-thrombotic, anti-tumor and anti-tumor agents in medicinal therapy. In agriculture, pyrazole derivatives have also been used as fungicides, insecticides, pesticides, and herbicides etc. Like other nitrogen involving heterocycles, different tautomeric structures can be written for pyrazoles. The unsubstituted pyrazole has been represented by the following three tautomers with H prefixes to rationalize the nomenclature of the compounds containing this basic skeleton.[4-6]

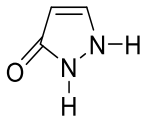


1H-pyrazole 3H-pyrazole 4H-pyrazole

When the carbonyl group is adjacent to nitrogen atoms in the ring, according to the older system of nomenclatures these were named as 5- pyrazolone, pyrazolone-5, pyrazolone-5-one or 3-ones and later on 2- pyrazolin-5-one and the tautomer 3-pyrazolin-5-one.

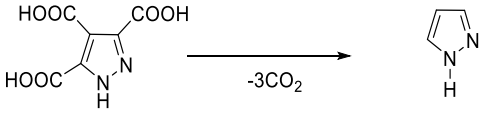


1H-Pyrazol-5(4H)-one



1,2-Dihydropyrazol-5-one

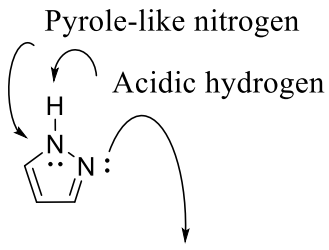
The first known 5-pyrazolone is obtained by Ludwig Knorr, who made the condensation of the acetoacetic ester with phenylhydrazine (in 1883). Pyrazole was first synthesized by Buchner, who in 1889 discovered it by decarboxylation of 3,4,5-tricarboxylic acid with pyrazole.



1H-pyrazole-3,4,5-tricarboxylic acid 1H-Pyrazole

PROPERTIES OF PYRAZOLE

Pyrazole has a five-membered aromatic ring structure consisting of two atoms of vicinal nitrogen, acidic pyrrole-like nitrogen with a single pair of aromatic electrons, simple sp^2-hybridized nitrogen-like pyridine and three atoms of carbon,[7] and these combined features must be carefully taken into account in the context of reactivity. In the first instance, N-unsubstituted pyrazoles possess amphoteric properties, acting as both acids and bases, considering the presence of nitrogen.[8] While the proton is easily donated by the acidic pyrrole-like NH group, the simple pyridine-like nitrogen can accept protons even more readily, and thus the basic character is typically prevalent. Nevertheless, substitutions on the ring can modulate these properties, as, for instance, electron-donating groups were shown to increase the acidity of the pyrrole-like -NH group.[9-10]



In addition to the previous, the combination of two dissimilar and adjacent nitrogen atoms in this azole (-N-N(H)- moiety) allows it to simultaneously donate and accept hydrogen bonds, which favors the establishment of intermolecular interactions, either among pyrazole molecules themselves and the nature of the substituents in the ring or between pyrazoles and neighboring molecules that participate in proton transfer processes.[11-13] Regarding the aggregation pattern of pyrazole in the solid-state, X-ray crystal studies unraveled the formation of linear catemers as well as of cyclic dimers, trimers, tetramers and hexamers.[14] In solution, both linear and cyclic oligomers can form, but in this case the associations between pyrazole molecules depend strongly on the type

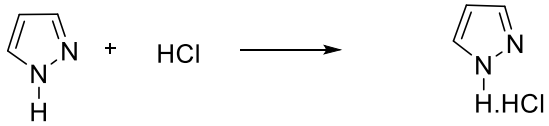
of solvent, since more polar protic solvents can divert the intermolecular interactions towards themselves, favoring the pyrazole-solvent hydrogen bonding rather than the formation of pyrazole-pyrazole clusters.[12,13] In the gas-phase, and intermolecular interaction also needs to take place to allow for proton transfer, whether it occurs with another pyrazole molecule or with a third molecule, or even results from collisions with the analytical instrument's walls.[15] Pyrazole-based self-aggregates in the gas-phase have been detected by Infrared (IR) spectroscopy, for the parent pyrazole and 3,5-dimethyl pyrazole, as an equilibrium between monomers, dimers and trimmers.[16] Also, several theoretical studies were performed regarding intermolecular interactions in pyrazoles, leading to proton transfers in the gas phase.[17]

Chemical Properties

The chemical properties of the pyrazole molecule can be explained by the effect of individual atoms. The N-atom at position-2 with two electrons is basic and therefore reacts with electrophiles. The N-atom at position-1 is unreactive but loses its proton in the presence of a base. The combined two N-atoms reduce the charge density at C-3 and C-5, making C-4 available for electrophilic attack. Deprotonation at C-3 can occur in the presence of a strong base, leading to ring-opening. Protonation of pyrazoles leads to pyrazolium cations that are less likely to undergo electrophilic attack at C-4, but an attack at C-3 is facilitated. The pyrazole anion is much less reactive towards nucleophiles, but the reactivity to electrophiles is increased.[18] Some of the more general chemical properties of the pyrazole molecules are as follows:

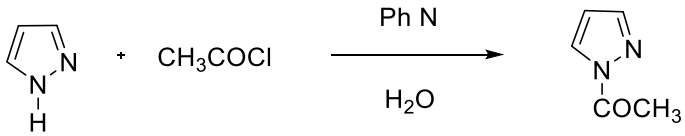
Basic Character

Pyrazole is a weakly basic compound and form pyrazole hydrochloride salts with inorganic acids.[19]



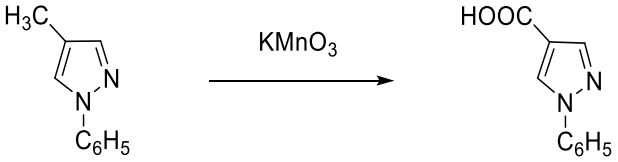
Acylation

The introduction of the acyl or phenyl sulfonyl group into pyrazole nitrogen is usually achieved in the presence of a weak base such as pyridine. Thus, in acylation iminohydrogen atom of the pyrazole nucleus is replaced by an acyl group, to give N-acetyl pyrazole.[19]



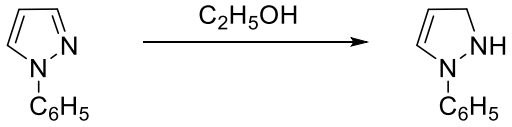
Oxidation

Pyrazoles are mostly stable to oxidation and only C–alkylated side chains are attacked by oxidizing agents alkaline $KMnO_4$ to yield the corresponding carboxylic acid pyrazole.[20]



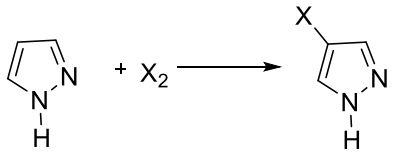
Reduction

Although pyrazole itself is resistant to reduction by sodium-ethanol, its N-phenyl derivative may be reduced by sodium-ethanol to yield the corresponding pyrazoline.[21]



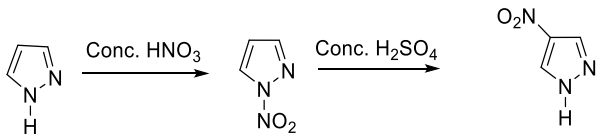
Halogenation

Halogenation of pyrazole gives 4-mono halo pyrazoles e.g. 4-chloro, 4-iodo or 4-bromo pyrazole under controlled conditions but poor yields are obtained on the reaction of isothiazole and isoxazole. Bromine will attack at C–4, but with activating groups, present halogenation proceeds better. 3,4,5-tribromo pyrazole is formed efficiently in an alkaline solution; presumably, the pyrazole anion is the reacting species.[22]



Nitration

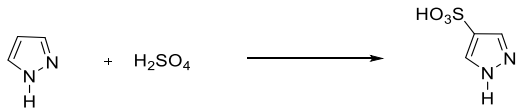
Pyrazole undergo straight nitration at C-4, it gives 1-nitro-pyrazole but this can be rearranged to 4-nitropyrazole in acid at low temperature.[23]



1H-Pyrazole 1-Nitro-1H-pyrazole 4-Nitro-1H-pyrazole

Sulphonation

Pyrazole reacts with fuming sulphuric acid to yield pyrazole 4–sulphonic acid.[24]

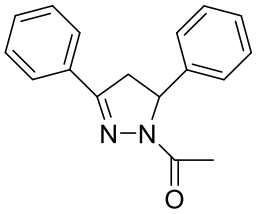


1H-Pyrazole Sulfuric acid Pyrazole-4-sulphonic acid

APPLICATIONS OF PYRAZOLE AND PYRAZOLE DERIVATIVES

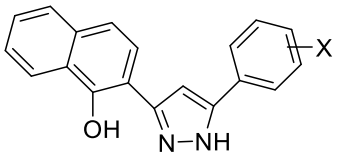
Derivatives of pyrazoles have played a key role and have been used as essential pharmacophores and synthons in the field of organic chemistry and drug design. A series of 1- acetyl-3,5-diphenyl-4,5-dihydro-(1*H*)-pyrazoles were investigated for their ability to inhibit selectively

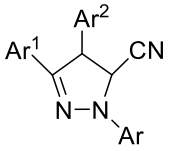
monoamine oxidases, swine kidney diamine oxidase and bovine serum amine oxidase. These compounds were reversible and non-competitive inhibitors of all types of the assayed amine oxidases. In particular 1-acetyl-3-(2,4-dihydroxyphenyl)-5-(3-methylphenyl)-4,5-dihydro-(1H)-pyrazole showed I50 values of 40nM accompanied by a selectivity factor of 4000 for MAOs (mitochondrial monoamine oxidases). By replacing the substituted phenyl ring at N1 by an acetyl group increased the inhibitory activity and selectivity towards MAOs of pyrazoles likely taking part in the interaction with the isoalloxazine nucleus.[25]



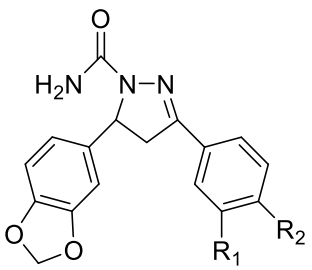
1-(4,5-dihydro-3,5-diphenylpyrazol-1-yl)ethanone

2-(5-Substituted-1*H*-pyrazol-3-yl) naphthalen-1-ol derivatives, a non-vicinal diaryl heterocycle synthesized were evaluated for *in-vivo* anti-inflammatory activity by acute carrageenan-induced paw edema standard method in rats using Indomethacin as a standard drug. The compounds containing electron-donating methyl and halogen functional group showed more activity than that of electron-withdrawing nitro and dinitro functional groups.[26] A series of nine tetrasubstituted pyrazolines synthesized by 1,3-dipolar cycloaddition of aromatic aldehyde phenyl hydrazones and cinnamonitrile with chloramine-T as a catalytic dehydrogenating agent has shown promising antifungal, antibacterial and antioxidant activities.[27]

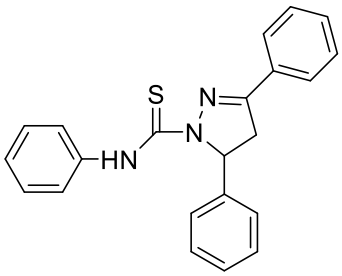




The anticancer activity of the pyrazole analogs of piperine was determined by MTT (3-(4,5- Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay method. The anti-inflammatory activity of the compounds was determined by the Human Red Blood Cell (HRBC) membrane stabilization method at doses of 100 µg, 500 µg and 1000 µg. These analogs also showed a good binding affinity with Cyclooxygenase and farnasyl transferase receptors, which was proved from the docking studies.[28]

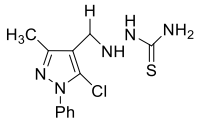


Pyrazole derivatives synthesized were screened for anti-tubercular activity. The minimal inhibition concentration was used to evaluate the anti-tuberculosis activity.[29]

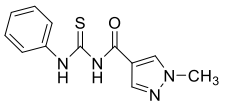


4,5-Dihydro-N,3,5-triphenylpyrazole-1-carbothioamide

Abdel Hameed and co-workers reported 5-chloro-1-phenyl-3-methyl-pyrazolo-4 methinethiosemicarbazone as corrosion inhibitors for carbon steel in 1M HCl by chemical and electrochemical method. The corrosion rate decreased and inhibition efficiencies and surface coverage degree increased with increase in inhibitor concentration and temperature.[30] The protective film of these compounds formed on the carbon steel surface is stable at higher temperatures. Nitulescu and co-workers (2010) synthesized N- (1-methyl-1*H*-pyrazole-4-carbonyl)-thiourea derivatives and evaluated for their analgesic and sedative effects. The compounds showed promising activities.[31]

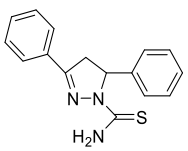


1-((5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl)thiosemicarbazide

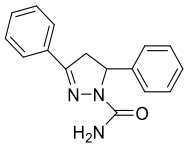


N- (1-Methyl-1H-pyrazole-4-carbonyl)-thiourea

The synthesis and structure-activity relationship of pyrazole derivatives as anticancer agents that may function as inhibitors of EGFR and kinases was reported. Some of them exhibited significant EGFR inhibitory activity. 3-(3,4-Dimethylphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide displayed the most potent EGFR inhibitory activity with IC_{50} of 0.07 µM, which was comparable to the positive control erlotinib. The compound also showed significant antiproliferative activity against MCF-7 with IC_{50} of 0.08 µM and potent inhibitory activity in tumor growth inhibition.[32]



4,5-Dihydro-3,5-diphenylpyrazole-1-carbothioamide



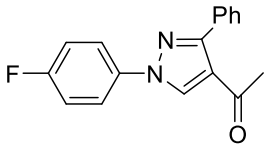
4,5-Dihydro-3,5-diphenylpyrazole-1-carboxamide

Anti-inflammatory Activity

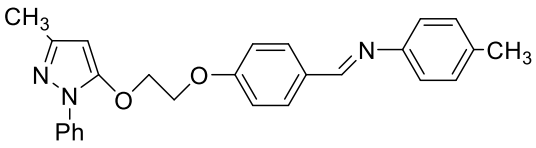
Inflammation is a multi-stage process that in the critical step is supposed to be powered by acutely released arachidonic acid and its prostaglandin-like metabolites. Two cyclooxygenase (COX) isozymes are known to catalyze

the rate-limiting stage of prostaglandin synthesis, COX-I and COX-II.[33] Nonsteroidal anti-inflammatory drugs (NSAIDs) alleviate pain by counteracting the cyclooxygenase (COX) enzyme. Some common example of NSAIDs is aspirin, ibuprofen, and naproxen.[34]

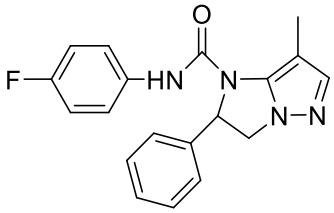
A series of 1-(4-substituted-phenyl)-3-phenyl-1H-pyrazole-4-carbaldehydes were prepared and tested for their anti-inflammatory and analgesic activities. Among the prepared compound exhibited the maximum anti-inflammatory activity.[35] A novel series of pyrazole derivatives were reported by Tewari et al (2014) and evaluated *in vivo* for their anti-inflammatory activity. Among the compounds N-(4-(2-(3-methyl-1-phenyl-1H-pyrazol-5-yloxy)benzylidene)-4-methylbenzenamine showed comparable anti-inflammatory.[36] Brullo et al, (2012) reported and synthesized the anti-inflammatory evaluation of new 2,3-dihydro-imidazo[1,2-b]pyrazole derivatives in which compound N-(4-fluorophenyl)-2,3-dihydro-7-methyl-2-phenylimidazo[1,2-b]pyrazole-1-carboxamide showed an interesting dual activity inhibiting both Fmlp-Ome and IL8-induced chemotoxis with IC_{50} values of 3.8 and 1.2 Nm, respectively.[37]



1-(1-(4-fluorophenyl)-3-phenyl-1H-pyrazol-4-yl)ethanone

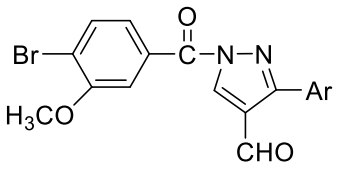


(E)-N-(4-(2-(3-methyl-1-phenyl-1H-pyrazol-5-yloxy)ethoxy)benzylidene)-4-methylbenzenamine

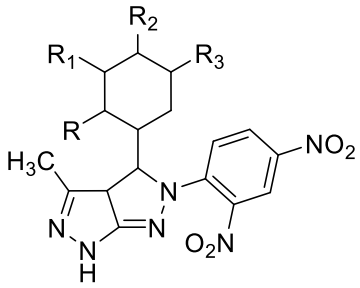


N-(4-fluorophenyl)-2,3-dihydro-7-methyl-2-phenylimidazo[1,2-b]pyrazole-1-carboxamide

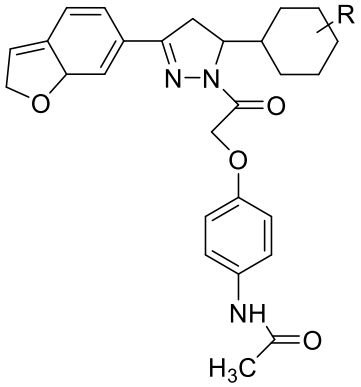
Freddy et al (2001) have synthesized the series of 1-(3-bromo-4-methoxybenzyl)-4-formyl-3-(substituted phenyl) pyrazole and their anti-inflammatory activity.[38] Bhaskar et al (2007) have reported the synthesis of 4,5-disubstituted-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c] pyrazoles and their anti-inflammatory activity.[39] Nargund et al (1992) evaluated the fluorinated phenyl styryl ketones and N-phenyl-5-substituted aryl-3-P-(fluorophenyl) pyrazoline and reported anti-inflammatory activity *in vivo*.[40]



1-(3-bromo-4-methoxybenzyl)-4-formyl-3-(substituted phenyl) pyrazole

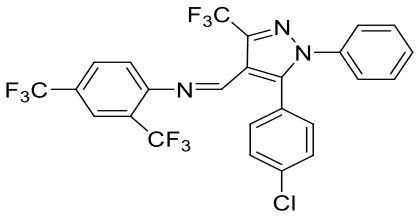


4,5-disubstituted-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c] pyrazoles

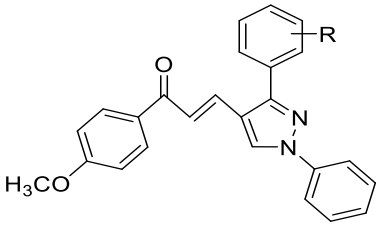


N-Phenyl-5-substituted aryl-3-P-(fluorophenyl) pyrazoline

Sayed et al (2012) reported a series of new pyrazole derivatives characterized as N-((5-(4-chlorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene)-3,5bis (trifluoromethyl) aniline which exhibited optimal anti-inflammatory activity as compared with reference drugs diclofenac sodium and celecoxib.[41] Bandgar et al (2009) evaluated the series of novel 1-(2,4-dimethoxy-phenyl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)-propenone by the Claisen-Schmidt condensation of 1-(2,4-dimethoxy-phenyl)-ethanone and substituted 1,3-diphenyl-1H-pyrazole-4-carbaldehyde. All the synthesized compounds were evaluated for anti-inflammatory activity.[42]



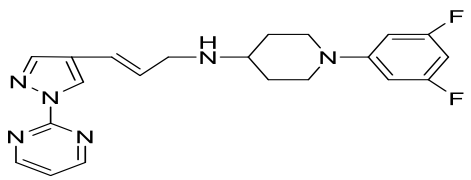
N-((5-(4-chlorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene)-3,5bis (trifluoromethyl) aniline



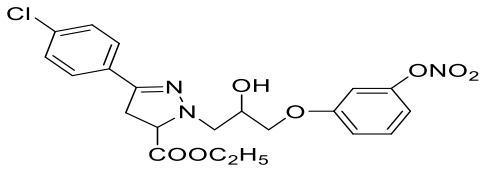
1,3-diphenyl-1H-pyrazole-4-carbaldehyde

Anti-cancer Activity

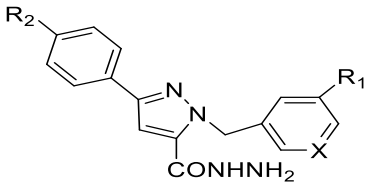
Different derivatives of pyrazole are generated by linking pyrimidine, carboxyhydrazide, as well as ferrocenyl molecule with pyrazole cap and all that are particularly effective against carcinoma of lung cells. Ohki et al (2002) synthesized the pyrimidinyl pyrazole derivatives 1-(3,5-difluorophenyl)-N-(E)-3-(1-pyrimidin-2-yl)-1H-pyrazol-4-yl)piperidin-4-amine as a new scaffold of an anti-tumor agent, which also showed antiproliferative activity against human lung cancer cell lines and inhibited tubulin polymerization.[43] Wei et al (2006) reported a series of novel small molecules of compound ethyl1-[20-hydroxy-30-aroxypropyl]-3-aryl-1H-pyrazole-5-carboxylate derivatives which have its potency to suppress lungs cancer cell growth.[44] Xia et al (2007) prepared a series of novel 1-arylmethyl-3-aryl-1H-pyrazole-5-carbohyrazide derivatives which had inhibitory effects on the growth of A549 cells and induced the cell apoptosis.[45] Fan et al (2008) reported a series of novel 1-(3-(4-chlorophenoxy)phenyl)-3-(4-chlorophenyl)-1H-pyrazole-5-carbohydrazide which is inhibiting the growth of A549 cells.[46]



1-(3,5-Difluorophenyl)-N-((E)-3-(1-(pyrimidin-2-yl)-1H-pyrazol-4-yl)allyl)piperidin-4-amine

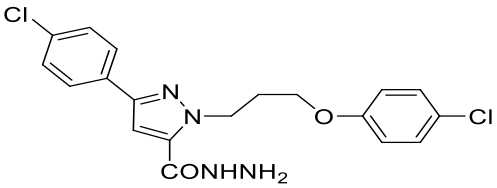


Ethyl1-[20-hydroxy-30-aroxypropyl]-3-aryl-1H-pyrazole-5-carboxylate



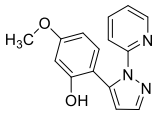
R1,R2 = CH3, NH3

1-Arylmethyl-3-aryl-1H-pyrazole-5-carbohyrazide

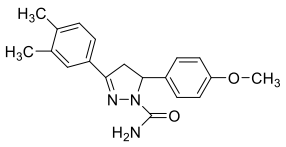


1-(3-(4-chlorophenoxy)propyl)-3-(4-chlorophenyl)-1H-pyrazole-5-carbohydrazide

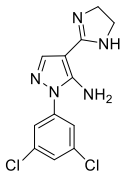
Balbi et al (2011) prepared a novel pyrazole derivatives 5-methoxy-2-(1-(pyridine-2-yl)-1H-pyrazol-5-yl)phenol and reported their antiproliferative activity in human ovarian adenocarcinoma A2780 cells, human lung carcinoma A549 cells, and murine P388 leukemia cells.[47] Lv et al (2010) reported and synthesized two series of pyrazole derivatives4,5-dihydro-5-(4-methoxyphenyl)-3-(3,4-dimethylphenyl)pyrazole-1-caboxamide which are designing for potential EGFR kinase inhibitors, as well as antiproliferative activity against MCF-7 with potent inhibitory activity in tumor growth inhibition, would be a potential anticancer activity.[32] Bandgar et al (2010) developed a new series of 3, 5-diaryl pyrazole derivatives 1-(3,5-dichlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazol-5-amine and evaluated for their anticancer activity.[48]



5-methoxy-2-(1-(pyridin-2-yl)-1H-pyrazol-5-yl)phenol

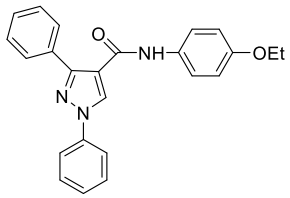


4,5-dihydro-5-(4-methoxyphenyl)-3-(3,4-dimethylphenyl)pyrazole-1-carboxamide



1-(3,5-dichlorophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazol-5-amine

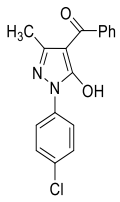
Li et al (2012) developed a series of 1H-pyrazole-4-carboxamide derivatives and reported their potential antiproliferation activity and Aurora-A kinase inhibitory activity. Among the compounds, N-(4-ethoxyphenyl)-1,3-diphenyl-1H-pyrazole-4-carboxamide possessed the most potent biological activity against HCT116 and MCF-7 cell lines with IC_{50} value of 0.39 and 0.46 µM, respectively.[49]



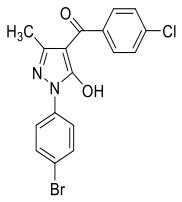
N-(4-ethoxyphenyl)-1,3-diphenyl-1H-pyrazole-4-carboxamide

Anti-tubercular Activity

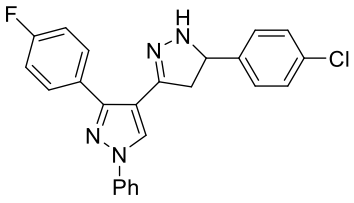
Manetti et al (2006) developed new inhibitors of *Mycobacterium tuberculosis*. The compound (1-(-chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)(phenyl)methanone was found to be the most active agent with a MIC value of 25 µM/ mL.[50] As a continuation of our previous work that turned toward the identification of antimycobacterial compounds with innovative structure, the compound (1-(4-bromophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)(4-chlorophenyl)methanone of pyrazole derivatives were synthesized by Castagnolo et al (2008) and assayed as inhibitors of M. tuberculosis H37Rv. The pyrazole derivatives with the p-bromophenyl group at the N1 position was showed to be very active.[51] A new series of fluorinated pyrazoles were reported and screened by Shelki et al (2012) for their *in vitro* anti-tubercular activities against Mycobacterium tuberculosis H37Rv. Results the compound 4-(5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-3-(4-fluorophenyl)-1-phenyl-1H-pyrazole showed that pyrazoline displayed significant anti-tubercular activities against the M. tuberculosis H37Rv strain (MIC=6.25 µg/mL).[52]



(1-(4-chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)(phenyl)methanone

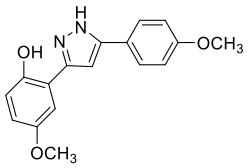


(1-(4-bromophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)(4-chlorophenyl)methanone

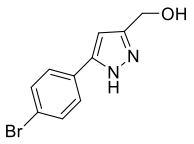


4-(5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-3-(4-fluorophenyl)-1-phenyl-1H-pyrazole

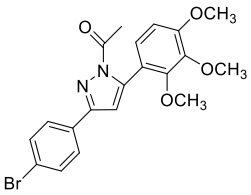
Fullam et al (2013) developed the inhibitory potencies of a novel series of 3,5-diaryl-1H-pyrazoles as specific inhibitors of prokaryotic arylamine N-acetyltransferase enzyme. The compound 4-methoxy-2-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)phenol was found to have good anti-mycobactrium activity and inhibited the growth of both *M. tuberculosis* with an MIC<10µg/mL. Maurya et al (2013) evaluate and reported the various substituted pyrazoles derivatives for their *in vitro* anti-tubercular activity against M. tuberculosis H37Rv strain. The compound (5-(4-bromophenyl0-1H-pyrazol-3-yl-methanol exhibited significant anti-tubercular activity at MIC value 25µM concentration.[54] Pathak et al (2014) synthesized the various substituted 1-(3, 5-diary-4,5-dihydro-1H-pyrazol-1-yl)ethanone derivatives for their *in vitro* anti-tubercular activity against *M. tuberculosis* H37Rv strain.[55]



4-methoxy-2-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)phenol



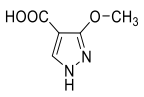
(5-(4-bromophenyl)-1H-pyrazol-3-yl)methanol



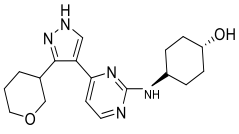
1-(3-(4-bromophenyl)-5-(2,3,4-trimethoxyphenyl)-1H-pyrazol-1-yl)ethanone

Anti-diabetic Activity

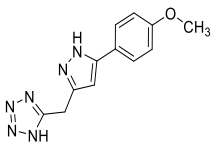
Cottineau et al (2002) were reported and developed a new series of substituted pyrazole-4-carboxylic acids for their antidiabetic activity. The results indicated that the prepared compound 3-methoxy-1H-pyrazole-4-carboxylic acid emerges as the best hypoglycemic agent in the series.[56] Sharon et al (2005) were prepared a new series of 5-[(5-arly-1H-pyrazol-3-yl) methyl]-1H-tetrazoles and isolated them for their *in vivo* anti-hyperglycemic activity. Out of screen compound demonstrated 24.6% of blood glucose-lowering activity at 100 mg/kg.[57] Humphries et al (2009) were synthesized the series of novel 4-pyrazolyl-2-aminopyrimidines as inhibitors of c-Jun-N-terminal kinases. This study led to the identification of compound (1s,4s)-4-(4-(3-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexanol which showed good selectivity across a panel of diverse protein and lipid.[58] Brigance et al were reported several pyrazolopyrimidines and evaluated as inhibitors of dipeptidyl peptidase-4(DPP4). Among the reported compound (7-(2,4-dichlorophenyl)-2-(2-chlorophenyl)-3,3a-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl)methanamine displayed the greatest potency (Ki= 20 Nm) and demonstrated excellent selectivity over the other dipeptidyl peptidase.[59]



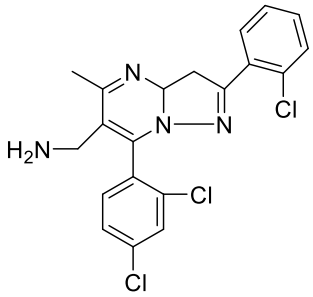
3-methoxy-1H-pyrazole-4-carboxylic acid



(1s,4s)-4-(4-(3-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-4-yl)pyrimidin-2-ylamino)cyclohexanol

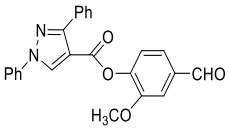


5-((5-(4-methoxyphenyl)-1H-pyrazol-3-yl)methyl)-1H-tetrazole

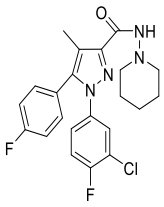


(7-(2,4-dichlorophenyl)-2-(2-chlorophenyl)-3,3a-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl)methanamine

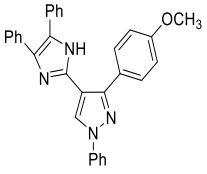
Choi et al (2010) were synthesized the 1, 3-diphenyl-1H-pyrazole derivatives as a new series of potent PPAR partial agonists using an improved virtual screening method combining ligand-centric and receptor-centric methods. The pyrazole compound 4-formyl-2-methoxyphenyl-1,3-diphenyl-1H-pyrazole-4-carboxylate showed relatively strong binding activities against PPAR among the virtual candidates.[60] Hernandez-Vazquez et al (2013) were reported the novel 1, 5-diaryl pyrazole derivatives and identify *in vivo* for their hypoglycemic activity. The compound 1-(3-chloro-4-fluorophenyl-5-(4-fluorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide showed the most significant plasma glucose reduction with a decrease of 60%.[61] Chaudhry et al (2017) were identified the new series of imidazolylpyrazoles and tested for their α-glucosidase inhibitory activity. The compound 3-(4-methoxyphenyl)-1-phenyl-4-(4,5-diphenyl-1H-imidazol-2-yl)-1H-pyrazole showed significant inhibitory potential and the *in vitro* enzyme inhibition indicate binding affinities as compared to that of reference acarbose.[62] Hernandez-vazquez et al (2017) were reported the hybrid novel dual compound that exhibited both anti-diabetic and in vitro antioxidant effects. The compound (E)-N-(3-hydoxy-4-methoxybenzylidene)-1-(3,4-dichlorophenyl)-5-(4-chlorophenyl)-4-methyl-1Hpyrazole-3-carbohydrazide showed a pronounced anti-hyperglycemic effect even at a dose of 5 mg/kg in a glucose tolerance test on normoglycemic rats.[63]



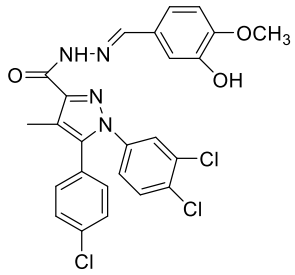
4-Formyl-2-methoxyphenyl 1,3-diphenyl-1H-pyrazole-4-carboxylate



1-(3-Chloro-4-fluorophenyl)-5-(4-fluorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide



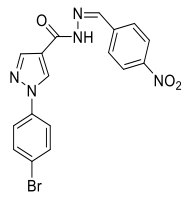
3-(4-Methoxyphenyl)-1-phenyl-4-(4,5-diphenyl-1H-imidazol-2-yl)-1H-pyrazole



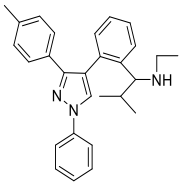
(E)-N'-(3-hydroxy-4-methoxybenzylidene)-1-(3,4-dichlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carbohydrazide

Anti-leishmanial Activity

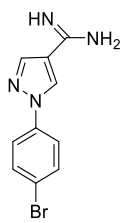
Bernardino et al (2006) were synthesized and reported the *in vitro* leishmanicidal activities of 1H-pyrazole-4-carbohydrazides. Among all the 1H-pyrazole-4-carbohydrazides derivatives examined the compound (Z)-N-(4-nitrobenzylidene)-1-(4-bromophenyl)-1-pyrazole-4-carbohydrazide found the most active against *L. amazonensis, L. chagasi and L. braziliensis* species.[64] Dardari et al (2006) were reported the synthesis of new pyrazole derivatives, compound N-ethyl-2-methyl-1-(2-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)phenyl)propan-1-amine. This compound inhibited the *in vitro* multiplication of *Leishmania tropica, Leishmania major* and *Leishmania infantum* with IC_{50} value of 0.50 µg/mL, 0.65 µg/mL and 0.42 µg/mL, respectively.[65] Dos santos et al (2011a) were reported the synthesis of new 1-Aryl-1H-pyrazole-4-carboximidamide derivatives and evaluated *in vitro* for their anti-leishmanial activities. Compound 1-(4-bromophenyl)-1H-pyrazole-4-carboxamide showed an activity profile that can be improved through medicinal chemistry strategies.[66] Dos santos et al (2011b) were reported the new series of 1-aryl-4-(4 ,5-dihydro-1H-imidazol-2-yl)-1H-pyrazoles and evaluated *in vitro* against three Leishmania species: *L. amazonensis, L. braziliensis* and *L. infantum.* Among the examined compound 1-(4-bromophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole emerged as the most active on promastigotes forms of *L. amazonensis*, with a IC_{50} value of 15 µM.[67]



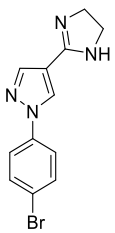
(Z)-N'-(4-nitrobenzylidene)-1-(4-bromophenyl)-1H-pyrazole-4-carbohydrazide



N-ethyl-2-methyl-1-(2-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)phenyl)propan-1-amine

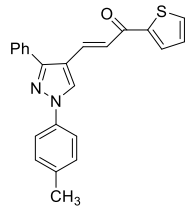


1-(4-Bromophenyl)-1H-pyrazole-4-carboxamidine

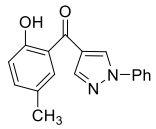


1-(4-Bromophenyl)-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole

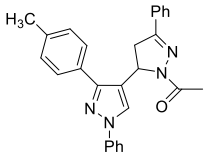
Bekhit et al (2014) were synthesized a novel series of 1H-pyrazole derivatives and tested for their *in vitro* anti-leishmanial activities against *L. aethiopica* promastigots. The highest anti-leishmanial activity was exhibited by compound (E)-3-(3-phenyl-1-p-tolyl-1H-pyrazol-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one with an IC_{50} of 0.08 µg/mL.[68] Figarella et al (2020) were reported and tested pyrazole derivatives for their *in vitro* antiparasitic activity against promatsigotes of *Leishmania maxicana* and epimastigotes of *Trypanosoma cruzi* using a modified MTI assay. Only compound (2-hydroxy-5-methylphenyl)(1-phenyl-1H-pyrazol-4-yl)methanone displayed selectivity on *L. mexicana* with a SI of 3, however, the IC_{50} obtained here was around four times higher.[69] Tuha et al were developed a new series of pyrazole derivatives and tested *in vitro* for their anti-leishmanial activity. Compound 1-(4,5-dihydro-3-phenyl-5-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)pyrazol-1-yl)ethenone was found to be the most active than the standard multefosine and amphotericin B deoxycholate for Leishmania donovani.[70] Reviriego et al (2017) reported the synthesis of some simple dialkyl pyrazole-3,5-dicarboxylates against *Trypanosoma cruzi, Leishmania infantum* and *Leishmania braziliensis.* The compound diethyl-1H-pyrazole-3,5-dicarboxylate showed high efficiency against the mentioned protozoa.[71]



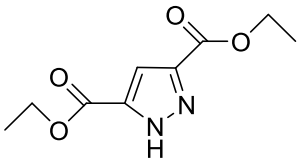
(E)-3-(3-phenyl-1-p-tolyl-1H-pyrazol-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one



(2-hydroxy-5-methylphenyl)(1-phenyl-1H-pyrazol-4-yl)methanone



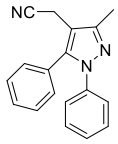
1-(4,5-dihydro-3-phenyl-5-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)pyrazol-1-yl)ethanone



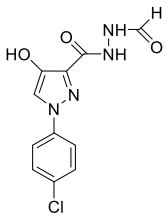
Diethyl 1H-pyrazole-3,5-dicarboxylate

Anti-viral Activity

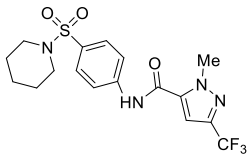
Genin et al (2000) were synthesized a novel 1,5-diphenylpyrazole class of HIV-1 nonnucleoside reverse transcriptase inhibitors. Compound 2-(3-methyl-1,5-diphenyl-1H-pyrazol-4-yl)acetonitrile was found to have good activity verse wild-type and delaviridine-resistant P236L reverse transcriptase.[72] Rostom et al (2003) were reported a new series of 1-(4-chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxylic acid hydrazide analogs and were tested for their *in vitro* effect on the replication of hepatitis-C virus (HCV) in HepG2 hepatocellular carcinoma cell line infected with the virus using the reverse transcriptase-polymerase chain reaction technique. The results revealed that compound 1-(4-chlorophenyl)-N-formyl-4-hydroxy-1H-pyrazole-3-carbohydrazide were capable of inhibiting the replication of both the HCV RNA(+) and (-) stands at 10-100 µg/mL concentration range.[73] Sun et al (2007) were synthesized a novel series of 1-methyl-3-(trifluoromethyl)-N-[4-(pyrrolidinylsulfonyl)phenyl]-1H-pyrazole-5-carboxamide and potent inhibitor against multiple primary isolates of diverse measles virus (MV) genotype currently circulating worldwide. The most active piperidine derivatives, when subjected to a secondary virus titer reduction assay, revealed activity against live MV (0.012-0.017 µM, strain Alaska) and no cytotoxicity.[74]



2-(3-Methyl-1,5-diphenyl-1H-pyrazol-4-yl)acetonitrile

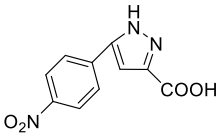


1-(4-Chlorophenyl)-N'-formyl-4-hydroxy-1H-pyrazole-3-carbohydrazide

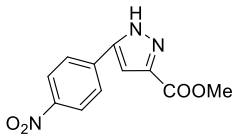


1-Methyl-3-(trifluoromethyl)-N-[4-(pyrrolidinylsulfonyl)phenyl]-1H-pyrazole-5-carboxamide

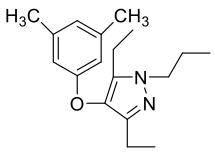
Zeng et al (2008) have been reported novel phenyl-substituted 1H-pyrazole-3-carboxylic acids and were conveniently examined concerning the effect on the IN inhibition and HIV replication. The best antiviral effect was exhibited by 5-(4-nitrophenyl)-1H-pyrazole-3-carboxylic acid and 3-(3-(benzyloxy)phenyl)isoxazole-5-carboxylic acids 46 with an EC_{50} value of 3.7 and 254 µM.[75] Mowbray et al (2009a) was synthesized a new series of N-hydroxyethyl pyrazole derivatives and evaluated *in vivo* for their anti-HIV activity. The compound methyl-5-(4-nitrophenyl)-1H-pyrazol-3-carboxylate demonstrated excellent activities against large panels of wild type and drug-resistant HIV consistent with the encouraging profile demonstrated against the design isolated RT enzymes shown above.[76] Mowbray et al (2009b) described the design and synthesis of a novel series of non-nucleoside HIV reverse transcriptase inhibitors (NNR-TIs) based on a pyrazole template. The compound 4-(3,5-dimethylphenoxy)-3,5-diethyl-1-propyl-1Hpyrazole and 2-(4-(3,5-dichlorophenyl)-3,5-diethyl-1H-pyrazol-1-yl)ethanol are active against wild type reverse transcriptase (RT) and retain activity *against* clinically important mutants. Combining the best 3- and 5-substituted gave the 3,5-diethyl pyrazole as the most potent compound in this early series.[77]



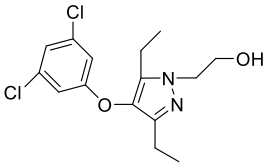
5-(4-nitrophenyl)-1H-pyrazole-3-carboxylic acid



methyl 5-(4-nitrophenyl)-1H-pyrazole-3-carboxylate

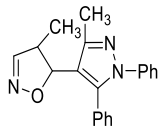


4-(3,5-dimethylphenoxy)-3,5-diethyl-1-propyl-1H-pyrazole

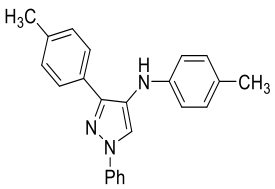


2-(4-(3,5-dichlorophenoxy)-3,5-diethyl-1H-pyrazol-1-yl)ethanol

Tentawy et al (2012) were prepared the new series of 4-substituted 3-methyl-1,5-diphenyl-1H-pyrazole and isolated *in vitro* for antiviral activity against herpes simplex virus type-1 grow on Vero African green monkey kidney cells through plaque-reduction assay method using acyclovir as a positive control. The result of the antiviral activity of the prepared compound 4-(4,5-dihydro-4-methylisoxazol-5-yl)-3-methyl-1,5-diphenyl-1H-pyrazole showed that exhibited strong antiviral activity with IC_{50} value of 0.03 compared to the used reference drug.[78] Fioravanti et al (2015) were reported the series of N-((1,3-diphenyl-1H-pyrazol-4-yl)methyl)anilines and evaluated *in vitro* for cytotoxicity and antiviral activity against a large panel of viruses. Most of the tested compound 1-phenyl-N,3-dip-tolyl-1H-pyrazol-4-amine interfered with RSV replication in the micromolar concentration.[79]



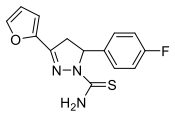
4-(4,5-Dihydro-4-methylisoxazol-5-yl)-3-methyl-1,5-diphenyl-1H-pyrazole



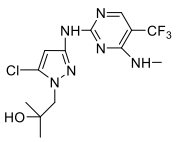
1-Phenyl-N,3-dip-tolyl-1H-pyrazol-4-amine

Anti-Parkinson Activity

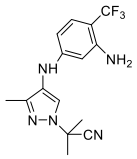
Chimenti et al (2010) were described a new series of N1-thiocarbamoyl-3,5-di(hetero)aryl-4,5-dihydro-(1H)-pyrazole derivatives and evaluated for their ability to inhibit the activity of the A and B isoforms of human monoamine oxidase. Compound 5-(4-fluorophenyl)-3-(furan-2-yl)-4,5-dihydropyrazole-1-carbothioamine was found the most active of the series with IC_{50} value of 2.78 µM and selectivity ratio of 26.[80] Chan et al (2012) were synthesized a new aminopyrazole as a Leucine-Rich Repeat Kinase 2 (LRRK2) inhibitors. In *in vivo* rodent PKPD studies, compound 1-(3-(5-(trifluoromethyl)-4-(methylamino)pyrimidin-2-ylamino)-5-chloro-1H-pyrazol-1-yl)-2-methylpropan-2-ol demonstrated good brain exposure and engendered significant reduction in brain pLRRK2 levels post-ip administration.[81] Estrada et al (2014) were identified as a new aminopyrazoles as Leucine-Rich Repeat Kinase 2 inhibitors. Compound (2-(4-(3-amino-4-(trifluoromethyl)phenylamino)-3-methyl-1H-pyrazol-1-yl)-2-methylpropanenitrile was identified as a highly potent and selective LRRK2 inhibitors with IC_{50} value of 3 nM.[82]



5-(4-fluorophenyl)-3-(furan-2-yl)-4,5-dihydropyrazole-1-carbothioamide

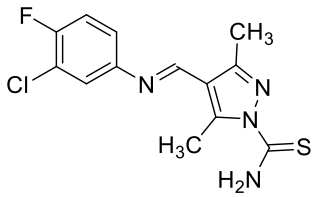


1-(3-(5-(trifluoromethyl)-4-(methylamino)pyrimidin-2-ylamino)-5-chloro-1H-pyrazol-1-yl)-2-methylpropan-2-ol



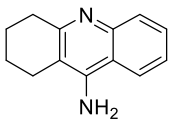
2-(4-(3-amino-4-(trifluoromethyl)phenylamino)-3-methyl-1H-pyrazol-1-yl)-2-methylpropanenitrile

Several new pyrazole derivatives containing a quinolone moiety were synthesized and tested for their anti-inflammatory and ulcerogenic effect. Hussain et al (2015) synthesized pyrazole derivatives and investigated them for their, anti-inflammatory and analgesic activity. Results indicated that (E)-4-(((3-chloro-4-fluorophenyl)imino)methyl)-3,5-dimethyl-1H-pyrazole-1-carbothioamide showed anti-inflammatory activities.[83,84]



(*E*)-4-(((3-chloro-4-fluorophenyl)imino)methyl)-3,5-dimethyl-1*H*-pyrazole-1-carbothioamide

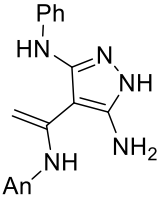
The anti-cholinesterase activity of the target compound was assessed *in vitro* against AchE from Electrophorus electrics and horse serum butyrylcholinesterase in comparison to tacrine as the reference drug.[85]



Tacrine

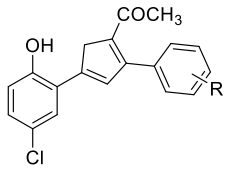
Antimicrobial Activity

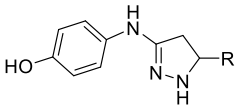
Bondock et al (2008) reported the synthesis and antimicrobial activity of some new heterocycles incorporating antipyrine moiety. 2-cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl) acetamide was utilized as a key intermediate for the synthesis of some new coumarin, pyridine, pyrrole, thiazole, pyrido, pyrazolo triazine and amino pyrazole.[86]



Analgesic Activity

Rajasekaran et al (2012) novel [1-(3-(5-chloro-2-hydroxy phenyl)-5-aryl-4,5-dihydro pyrazol-1-yl] ethanone derivatives has been synthesized and were screened for analgesic activity by acetic acid-induced writhing inhibition method. Results showed that all the synthesized compounds shown significant activity when compared with that of standard drug.[87,88]

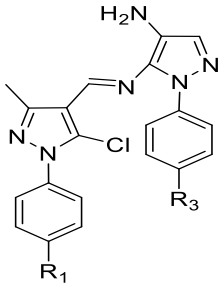




R=C_6H_5, 2-Furyl, 4-$NO_2C_6H_5$

Anti-TMV Activity

The commercially available plant virucide Ningnammycin was used as a positive control. The anti-viral bioassay against TMV is assayed by the reported method and the anti-viral results of all the compounds. the results showed that most of the targets compound present excellent anti-TMV activities at 500mg/L.[89]

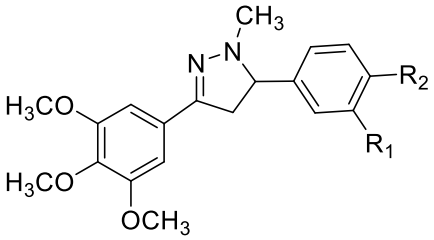


R_1=-H, -Cl, $-CH_3$

R_3=-F, $-CH_3$, -H, $-CF_3$

ACE Inhibitors

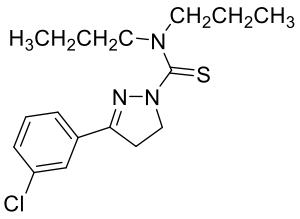
Bonesi et al (2010) produced a series of pyrazole derivatives and examined their potential activity as Angiotensin-I-converting enzyme inhibitory (ACE inhibitors) activity by performance evaluation.[90]



R_1= NO_2 R_2= OCH_3

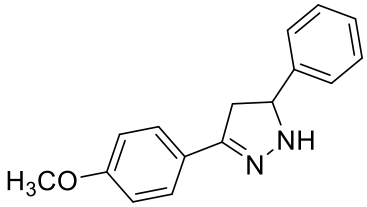
Antiamoebic Activity

Abid et al 2005, reported the synthesis of a series of new 1-N-substituted cyclized pyrazoline analogous to thiosemicarbazole and were evaluated for their antiamoebic activity.[91]

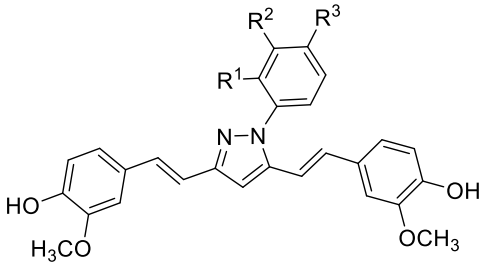


Neuroprotective Activity

Cocconcelli et al (2008), have described the parallel synthesis of aryl azoles. Here substituted phenylhydrazine is made to react with an α, β-unsaturated ketones, which leads to the regioselective formation of 4,5-dihydro-1H-pyrazole and acetic acid was used as a catalyst. Compounds possess good neuroprotective activity.[92]



Scientist reported the therapeutic potential of Curcuminoid pyrazole in the treatment of Parkinson disease. Curcuminoid pyrazole, inhibits the deposition of the neurotoxic α-synuclein aggregates in the brain.[93]



R^1= -H,-Cl R^2= -H, $-NO_2$

R^3=-H, -F

CONCLUSION

The research and other informational data, available in literature so far, have rendered pyrazole a significantly important class of heterocyclic compounds and their applications in ever-challenging chemotherapy of various ailments/ infections since the last three decades immensely hiked interests of medicinal chemist and biochemist. It has been seen that pyrazole derivatives incorporated with different nuclei have shown a variety of pharmacological profile. Pyrazole compound can be used with various heterocyclic systems with enhancing biological activity. This particular review article, established the fact that pyrazole derivatives could be a rich source of potential entities in the research of a new generation of biologically active compounds. Thus, the quest to explore many more modifications to pyrazole moiety needs to be continued.

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Source of Support: None declared.

Conflict of Interest: None declared.