A Review on Pyrazole chemical entity and Biological Activity

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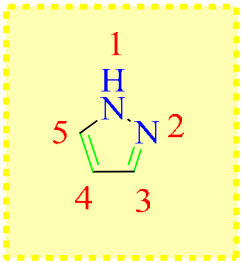
Abstract

Aromatic organic heterocycle containing pyrimidine scaffolds possesses two nitrogen atoms of Five-membered ring. These Pyrazole skeletons comprise various ranges of pharmacological activities such as analgesic, antipyretic, anticancer, antiviral, anti-inflammatory, antioxidants, antimicrobial, anti-diabetic, anticonvulsant, ant arrhythmic activities. Pyrazole is a multipurpose lead compound developed by chemical architecture for effective molecules which are biologically active. Several synthetic routes are accorded to the development of pyrazole containing reactions to afford a novel molecule which is an enormous opportunity in the field of medicinal chemistry. The existing collection of exertions on research to provide information about the synthesis and innumerable biological activities of pyrazole and their outcomes during the past year.

Keyword: Pyrazole, Heterocyclic and Biological activity

Introduction

The term Pyrazole was given by Ludwig Knorr in 1883. Pyrazole refers to the class of simple aromatic ring organic compounds of the heterocyclic series characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions. Being so composed and having pharmacological effects on humans, they are classified as alkaloids, although they are rare in nature. In 1959, the first natural pyrazole, 1-pyrazolyl-alanine, was isolated from seeds of watermelons (Eicher et al., 2003)[1]



PYRAZOLE

Fig.1

Pyrazole derivatives have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals. The recent success of pyrazole COX-2 inhibitor has further highlighted the importance of these heterocyclic rings in medicinal chemistry. A systematic investigation of this class of heterocyclic lead revealed that pyrazole containing pharmacophore active agents play important role in medicinal chemistry. The prevalence of pyrazole cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead.

Physical and chemical properties of Pyrazole moieties: Pyrazole is a π-excessive heterocycle and contains two nitrogen atoms; pyrrole type and pyridine type, at positions 1 and 2. Pyrazole exists in three partially reduced forms.

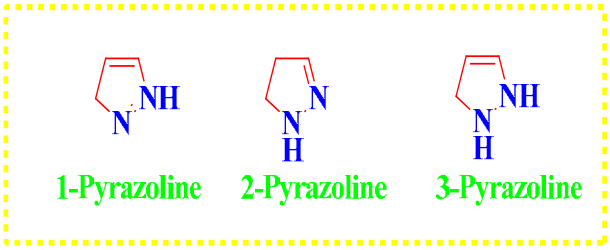


Fig.2

Pyrazole is a colourless solid with m.p. 69-70°**C,** boiling point of pyrazole (186-188°**C)** is due to intermolecular hydrogen bonding, Pyrazole exist in two identical and non-separable tautomers due to rapid interconversion of tautomers.

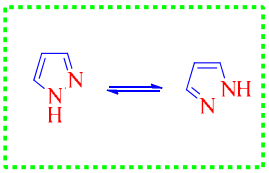


Fig.3

Pyrazoline contain two types of nitrogen atom, pyrrole and pyridine at position 1 and 2 respectively. Pyridine type nitrogen is susceptible to electrophilic attack, and the hydrogen atom attached to the nitrogen at position 1 is more acidic than pyrrolic N-H, so easily removed by nucleophiles. Pyrazole is weaker base (pKa= 2.52), lower basicity is due to extra destabilization of π-bonding after protonation. Pyrazole is very weak acid (pKa=14.21), introduction of electron withdrawing group (-I & -M effect) increase the acidity.

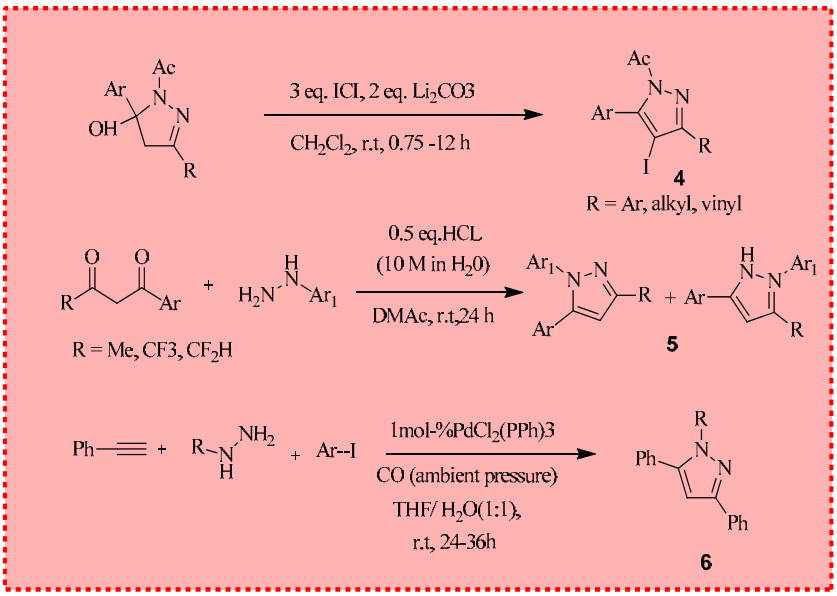


Fig.4 General method for Pyrazole preparation [2, 3, 4]

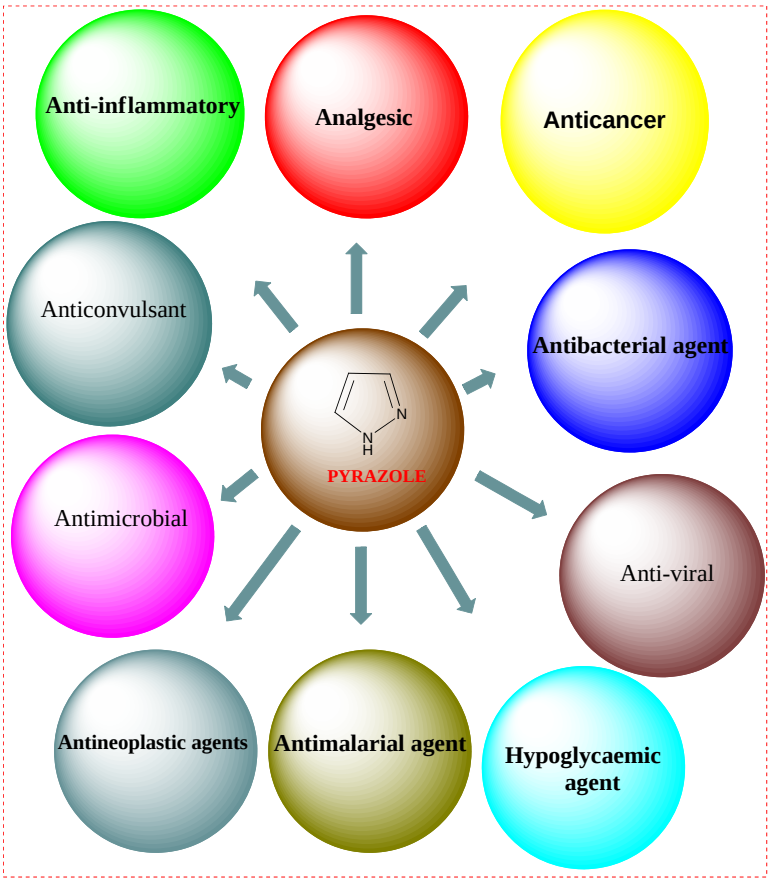
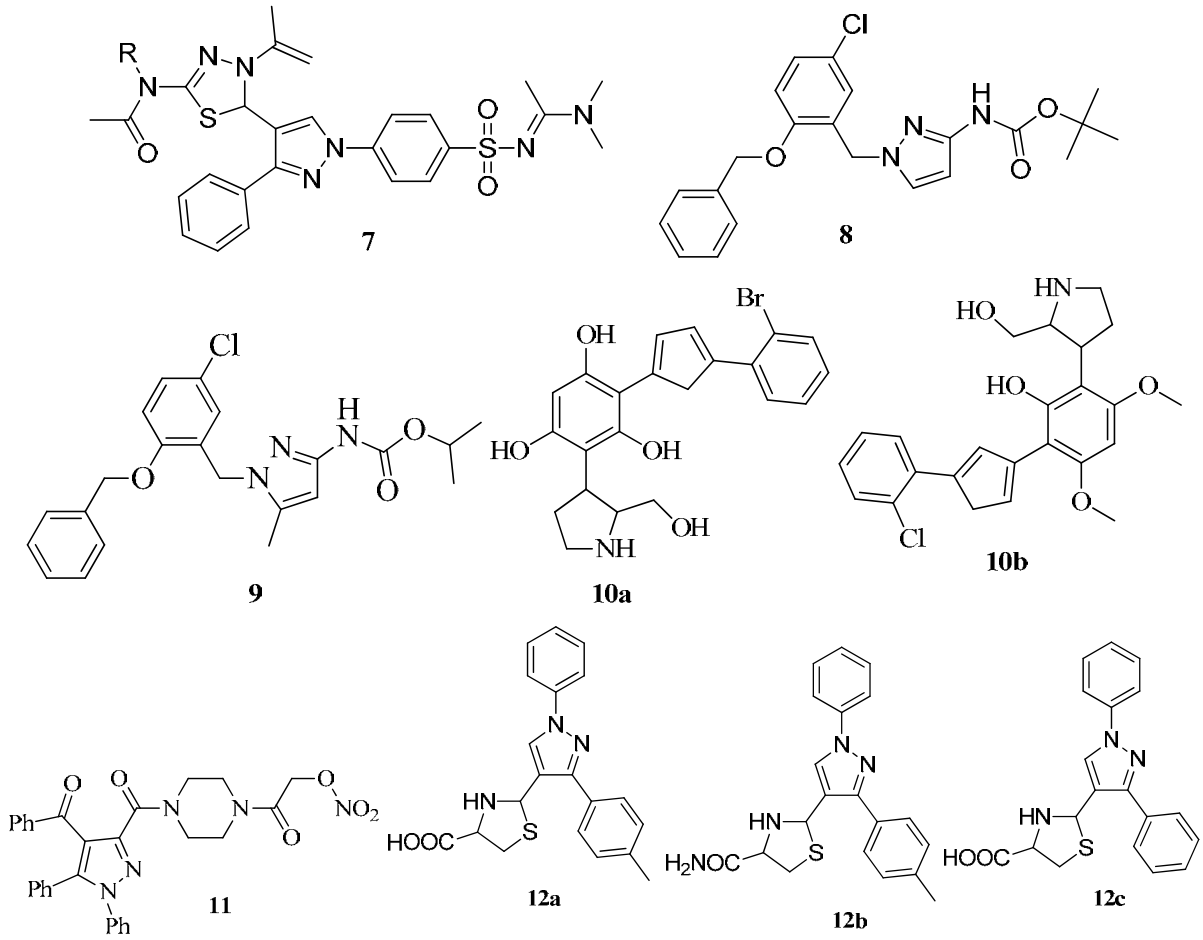


Fig.5 Different Biological activities of pyrazole moiety

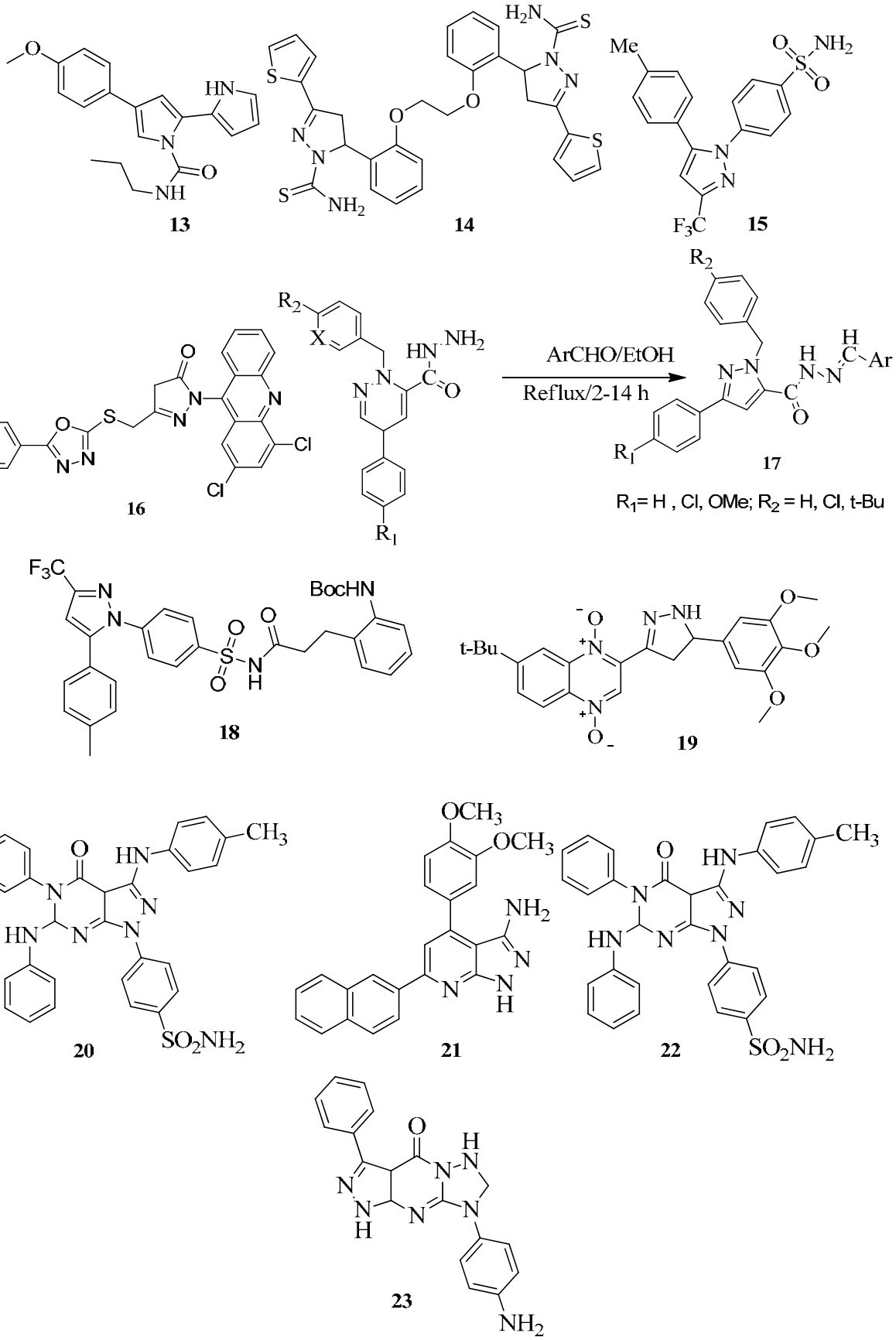
Biological Activities

Anti-inflammatory activity

Bekhit *et al.* (2008) reported a series of thiazolyl and thiadiazolyl derivatives of 1*H*-pyrazole (**7**) and their anti-inflammatory activity. They observed that the compounds were more active than the standard indomethacin and the active compound were found selective towards COX-2 enzyme.[5] A series of compound was synthesized by Balbi *et al.* (2007) 5-(2,6,6- Trimethyl-2-cyclohexen-1-yl)ethenyl-1H-pyrazole (**8**) were also be found to be potent inhibitors of neutrophil chemotactic responsiveness which could be considered as lead compounds and compared to standard Diclofenac.[6] Hall *et al.* (2008) reported compounds in a series of methylene linked pyrazole (**9)** as EP_1 receptor antagonist and discovered compounds of amide, reversed amide and carbamate derivatives and identified as brain penetrant compounds and both demonstrated efficacy in the CFA model of inflammatory pain.[7] A combinatorial library of 3, 5-diaryl pyrazole derivatives (**10**) were synthesized and evaluate them for anti-inflammatory activity against TNF-α and IL- 6. Out of 15 reported compounds few compound showed anticancer activity (61–73% at 10 µM concentration) And IL-6 inhibition (47% and 42% at 10 µM concentration) as in comparison to standard flavopiridol (72-87% inhibition at 0.5 µM) and dexamethasone (85% inhibition at 1 µM concentration), respectively by Bandgar *et al.* (2010).[8] Abdel-Hafez *et al.* (2009) prepared novel pyrazole-NO hybrid molecules 2-(4-(4-benzoyl-1, 5-diphenyl-1H-pyrazole-3-carbonyl)piperazin-1-yl)-2-oxoethyl nitrate (**11)** and evaluated them for nitric oxide release, antibacterial and anti- inflammatory activities. Compound **7** exhibited highest percentage of NO release using Griess diazotization method. Some of the tested compounds are reported with significant anti-inflammatory activity compared to indomethacin using carrageenan induced paw edema method. Structural modification as reported through nitrate ester or oxime hybrids has resulted better anti-inflammatory activity with less ulcerogenic liability.[9] Synthesised a series of 4-thiazolyl pyrazolyl **(12a, 12b & 12c**) and studied there, COX-1, COX-2, ulcerogenic effect and acute toxicity, by Bekhit *et al.* (2010) and Docking study of compounds A, B and C on active site of the human COX-2 enzyme and DNA-gyrase B has revealed that compounds A, B and C exhibited good anti-inflammatory activity with no or minimal ulcerogenic effect. Compound B and C are reported as most potent and selective towards COX-2 compared to indomethacin.[10]



A novel series of 4-(4-methoxyphenyl)-N-propyl-1H, 1'H-[2, 2'-bipyrrole]-1-carboxamide **(13)** by Go khan-Kelekci *et al.* (2007). They tested synthesised compound for their anti-inflammatory activity against carrageenan-induced oedema and acetic acid-induced increase in capillary permeability in mice.[11] Prepared a series bis (3-aryl-4, 5-dihydro-1*H*-pyrazole-1-thiocarboxamides) and bis (3-aryl-4, 5-dihydro-*1H*-pyrazole-1-carboxamides) (**14**) by Barsoum *et al.* (2009) synthesized compounds were tested for anti-inflammatory activity on carrageenan-induced paw oedema method in rats. The Compound is reported as most potent relative to indomethacin.[12] Aldo Balsamo *et al.* (2003) synthesized several hetero aromatic analogues of (2-aryl-1-cyclopentenyl-1-alkylidene) (arylmethyloxy) amine (**15**) COX-2 inhibitors, in which the cyclopentene moiety was replaced by pyrazole proved to be significantly active only towards COX-1.[13] Chandra *et al.* (2010) reported a series of compounds with anti-inflammatory and analgesic activities. The compound 1-(2, 4-Chloroacridine-9-yl)-3-(5-pyridine-4-yl)-(1,3,4-oxadiazol-2-ylthiomethyl)-pyrazole-5-one (**16**) showed better anti-inflammatory and analgesic activities at the three graded dose of 25, 50 and 100 mg/kg p.o.[14] Ruiz *et al.* (2011) designed, synthesized potential of a new type of benzenesulfonamide **(17)** cyclo-oxygenase-2 (COX-2) inhibitor prodrug is investigated using celecoxib.[15] Burguete *et al.* (2007) synthesized substituted pyrazole derivatives (**18**) and evaluated them for their anti-inflammatory activities. These derivatives showed good anti-inflammatory activity against carrageenan induced rat paw edema test.[16] Sandeep *et al.* (2013) synthesize a novel 3-substituted-1-aryl-5-phenyl-6-anilino-pyrazolo[3,4-d]pyrimidin-4-ones (**19**) and the compounds were screened for the anti-inflammatory activity. The compounds exhibited superior anti-inflammatory activity in comparison with diclofenac sodium and comparable activity with Celecoxib at a dose of 25 mg/kg. The compounds were found as active with inhibition of edema in the range of 35-39 after 3h of administration of test compounds. COX-2 docking score of the active compound was found to be better than standard celecoxib.[17] Hamdy *et al.* (2009) synthesize the reaction of 2-acetyl-5,6,7,8-tetrahydronaphthalene with aldehydes was conducted in the presence of ethyl cyanoacetate and ammonium acetate, yielded the cyanopyridones (**20**) which react with phosphorous pentasulphide to afford the corresponding thioxopyridine derivatives respectively. The findings revealed that the derivatives can be recognized as promising multi-potent anti-inflammatory agents.[18] Russo *et al.* **(**1992**)** synthesized pyrazolotriazolopyrimidine (**21**) derivatives screened for anti-inflammatory analgesic activity.[19] Russo *et al.* **(**1992) have synthesized pyrazolotriazolopyrimidine derivatives (**22**) screened for anti-inflammatory analgesic activity. The results shows good anti-inflammatory activity associated with non-narcotic analgesic property with remarkable systemic and gastric tolerance.[20]

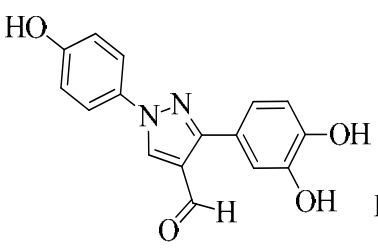


Anticancer activity

Christodoulou *et al*. (2010) Synthesised a series of tri substituted pyrazole derivatives (**24**) and PIFA-mediated conversion of molecules bearing the fused pyrazolo [4,3-c]quinolone ring system and evaluated them for anti-

angiogenic activity by using *in vitro* assays for endothelial cell proliferation and migration, and in the chicken chorioallantoic membrane (CAM) assay. Compounds having fused pyrazolo [4, 3-c]quinoline motifs emerged as potent anti-angiogenic compounds, and also inhibit the growth of human breast (MCF-7) and cervical (Hela) carcinoma cells *in vitro*.[21] Bonesi *et al.* (2010) Prepared a series of chalcones and their pyrazoles derivatives (**25**) and investigated them for Angiotensin I-Converting Enzyme (ACE) inhibitory activity. They have reported the chalcone (a) with highest activity (IC_{50} 0.219 mM), while the most potent pyrazole was (b) (IC_{50} 0.213 mM).[22] Lv *et al.* (2010) designed two series of pyrazole derivatives and evaluated for their potential EGFR kinase inhibitors activity. Compound 3-(3, 4-dimethylphenyl)-5-(4-methoxy phenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**26**) is most potent with IC_{50} of 0.07 μM, as compared to positive control erlotinib.[23] Xia *et al.* (2007) synthesised a series of novel 1-arylmethyl-3-aryl-1*H*-pyrazole-5-carbohydrazide derivatives(**27**) nine compounds of the series are reported to inhibit the growth of A549 cells and induced the cell apoptosis. They also studied the basis of structure–activity relationships and prediction of lipophilicities of compounds. Compounds with logP values in the range of 3.12-4.94 have been found more inhibitory on the growth of A549 cells [25] Havrylyuk *et al.* (2009) examined the anticancer activity of several novel thiazolone-based compounds containing the 5- aryl-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl (**27**) frame work.[26] Zheng *et al.* (2009) synthesised a series of novel 3-aryl-1-(4-tert-butylbenzyl)-1*H*-pyrazole-5-carbohydrazide hydrazone derivatives(**28**) and investigated their effects on A549 cell growth, the compound (E)-1-(4-tert-butylbenzyl)-NO-(1-(5-chloro-2-hydroxyphenylethylidene)-3-(4-chlorophenyl)-1*H*-pyrazole-5-carbohydrazide possessed the highest growth inhibitory effect and induced apoptosis of A549 lung cancer cells.[27] Braulio *et al.*(2010) synthesized novel (E)-1-aryl-3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)prop-2-en-1-ones (**29**) among them some compound showed potent activity against leukemia (K-562 and SR), renal cancer (UO-31) and non-small cell lung cancer (HOP-92) cell lines, with the most important GI_{50} values ranging from 0.04μ to 11.4 lμ, from the *in vitro* assays.[28] Bruno *et al.* (2009) reported the synthesis and the chemo taxis inhibitory activity of number of 1*H* pyrazole-4-carboxylic acid ethyl esters **(30)**. Few compounds have been reported as potent inhibitors of IL8- and fMLPOMe-stimulated Olga neutrophil chemo taxis. Most active compound in the fMLP-OMe induced chemo taxis test showed IC_{50} 0.19 nM^{-2} nM.[29] a new series synthesized by Ronghui Lin *et al.* (2007) 3, 4-disubstituted pyrazole derivatives (**31**).The analogues showed potent and selective cycline dependent kinase inhibitory activities & inhibited *In vitro* cellular proliferation in various human cells.[30] Synthesized new series of preparation of compound 7-phenyl-7HPyrazolo[4,3-e]-[1,2,4,]Triazolo[1,5-c]pyrimidine-2-thione (**32**) by Ghorab *et. al.* **(**2010) and active against Ehrlich Ascites carcinoma (EAC) cell line as compared to standard drug Doxorubicin.[31] Schenone *et al.* (2004) synthesized a new 4-aminopyrazolo[3,4-d]pyrimidine (**33**) bearing various substituents at the position 1 and 6, were synthesized. The new compounds showed antiproliferative activity toward A431 cells, were found to be inhibitors of Src phosphorylation, and induced apoptotic cell death. In particular, 2h was a better inhibitor of Src phosphorylation than the reference compound PP2.[32]

A novel series of N-phenyl-imidazo[4,5-b]pyridin-2-amines, 4-indazolyl-N-phenylpyrimidin-2-amines (**35**) was synthesized by Lukasik *et al.*(2012**)**. Their anti-proliferative activities were tested in HCT-116 human colon carcinoma and MCF-7 breast carcinoma cell lines.**[33]** Radek *et al.* (2011**)** a new potent CDK2 inhibitor with pyrazolo[4,3-d]pyrimidine and imidazolo[4,3-d]pyridine (**36**) scaffold have been synthesized and evaluated in cellular and biochemical assays. Importantly, as the anticancer activities of the pyrazolo [4, 3-d] pyrimidine exceed those of its bioisostere roscovitine.[34] A series of 2, 9-substituted 6-guanidinopurines, structurally related to the cyclin-dependent kinase (CDK) inhibitors olomoucine and roscovitine (**37)** has been synthesized and screened for their CDK1 and CDK2 inhibitory activities, cytotoxicity and antiproliferative effects in the breast cancer-derived cell line MCF-7 [35] by the Dolecková *et al.* **(**2013**)**



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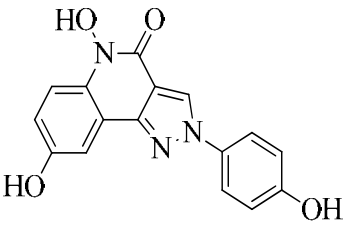

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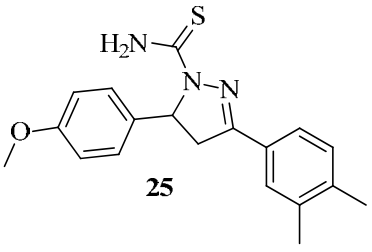

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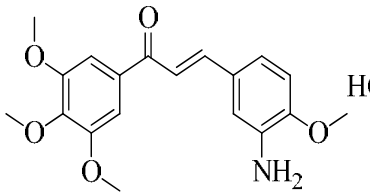

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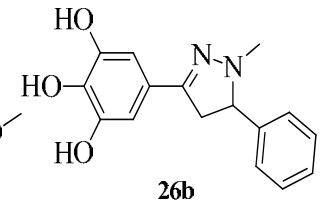

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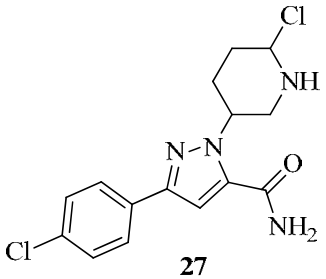

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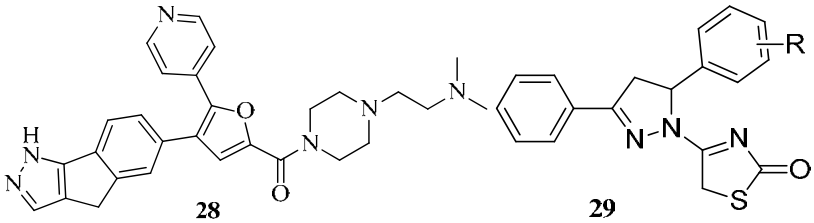

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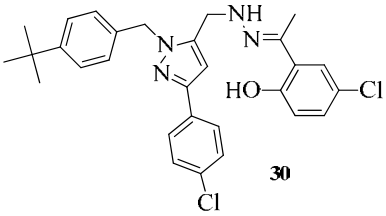

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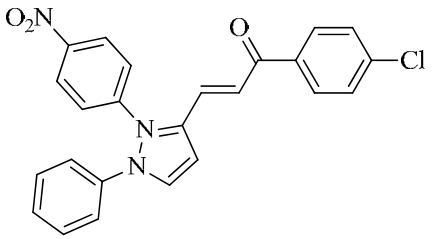

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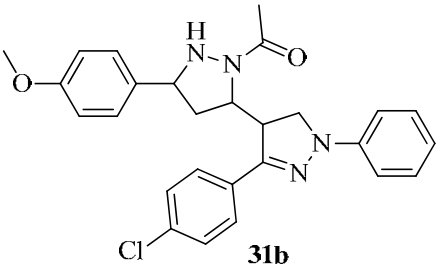

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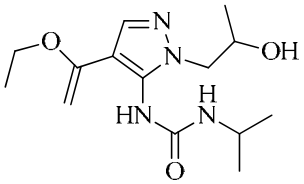

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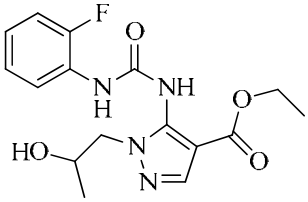

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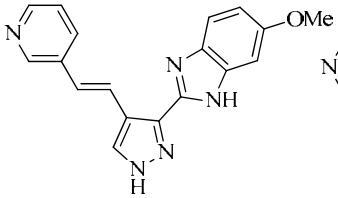

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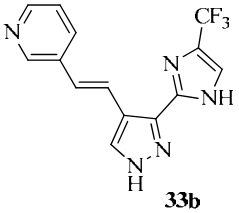

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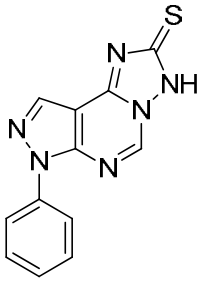

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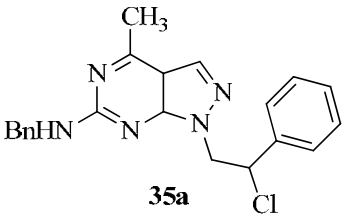

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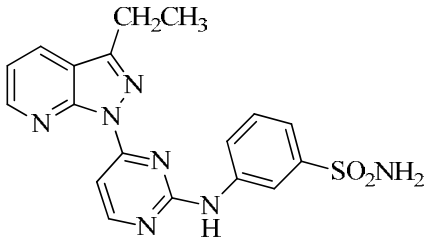

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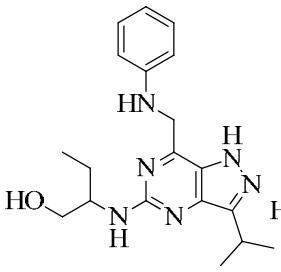

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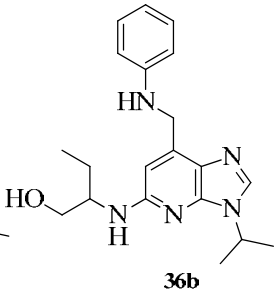

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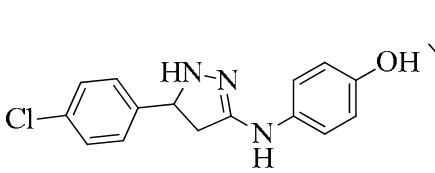
Antimicrobial Activity

A new series of fused pyrazole-pyrimidine derivatives (**37**) was synthesized by Samir Bondock *et al.* (2010). The given compound was found to exhibit the most potent *in-vitro* antifungal activity with MICs (6.25 μ/ml) against *A. fumigatus* & *F. Oxysporum* comparable with Chloroamphenicol.[36] Smaail *et al.* (2010**)** synthesized novel pyrazole derivatives (**38)** and these derivatives were evaluated for their antimicrobial activity determined by agar plate diffusion technique. The antibacterial activity was determined by agar plate method against E.Coli strains *Saccharomyces cereviseae* and *Fusarium oxysporum f. sp.ablicans*. Streptomycin was used as reference compound in performing antimicrobial assay. These derivatives were found to be most potent.[37] Sahu *et al.* (2008) synthesized novel 4-((5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)amino)phenol **(39)**.The derivatives showed potent Antimicrobial activity: Antibacterial activity; by muller hinton agar (Hi media) plates by agar diffusion cup-plate method for Staphylococcus aureus, salmonella typhi & E. coli. Antifungal activity was tested on sabouraud dextrose agar plates by cup-plate method against Candida albicans & Aspergillus niger) In both of these assays ciprofloxacin and cotrimazole was used as standard drugs. Also some potent the compounds showed effective analgesic (by Tail flick method) and anti-inflammatory (by Carageenan induced rat paw edema method).[38]



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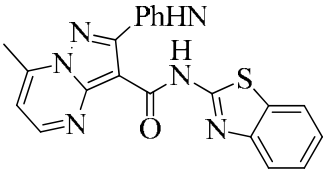

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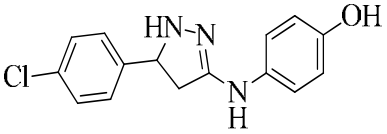

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Anticonvulsant and Antidepressant Activity

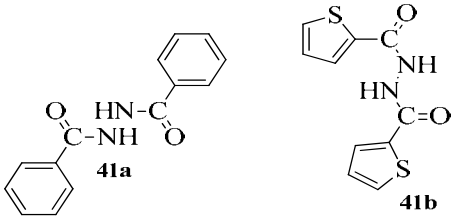
Chimenti *et al.* (2004) Synthesised a novel series of 1-acetyl-3-(4-hydroxy- and 2,4-dihydroxyphenyl)-5-phenyl-4,5-dihydro-(1*H*)-pyrazole derivatives (**40**) and investigated them ability to selectively inhibit the activity of the A and B isoforms of monoamine oxidase (MAO). The new synthesized compound proved to be more reversible, potent, and selective inhibitors of MAO-A than of MAO-B.[39] Abdel-Aziz *et al.* (2009) Described two synthetic paths for the formation of diacylhydrazines, 5amino-1-substiuted pyrazole-3,3,4-tricarbonitriles(**41**) and oxadiazole, pyrazoline derivatives, showing antidepressant activity using tail suspension behavioural despair test and anticonvulsant activity against PTZ induced seizures in mice. Compound **a** and **b** showed antidepressant activity compared to imipramine and their antidepressant activity were twice the activity of imipramine at 10 mg/kg dose level. Compounds **c**, **d** and **e** exhibit protective effect against clonic seizures induced by i.p. injection of PTZ at a dose level of 20 mg/ kg.[40]

Antiviral Activity

Osama *et al.* (2009) synthesized 4, 5-disubstituted pyrazole derivatives (**42**). The derivative containing R= Cl group showed the potent antiviral activity against a broad panel of viruses in different cell culture (HEL Cell cultures).[41]Aymn E. Rashad *et al.* (2008) synthesized substituted pyrazole derivatives(**43**). These derivatives showed promising antiviral activity against hepatitis A virus and Herpes Simplex virus type-1 using plaque infective assay.[42]

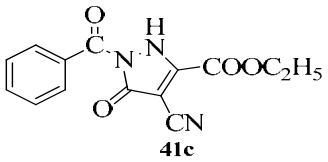
ACE-Inhibitory Activity

Macro *et al.* (2010) synthesized a series of pyrazole derivatives (**44**) and investigated their potential activity as Angiotensin-I-converting enzymes inhibitory activity by performing assay. This derivative of pyrazole showed effective ACE-inhibitory activity with 0.123 mM IC_{50} value.[43] A new molecule designed and developed a series of COX-2 inhibitors. Gao *et al.* (2011) prepared compounds **(45**) were screened for their biological activity, indicated that the synthesized new compounds a and b display similar strong inhibitory effectiveness in the MDA-MB-435 human cancer cell line in comparison with the parent compound celecoxib.[44]

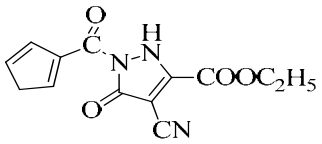


41a

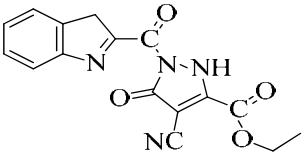
41b



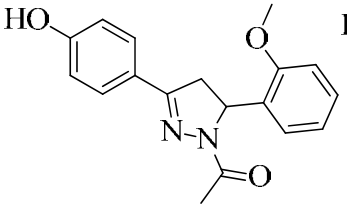
41c



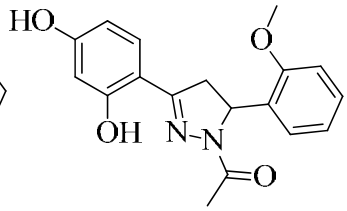
41d



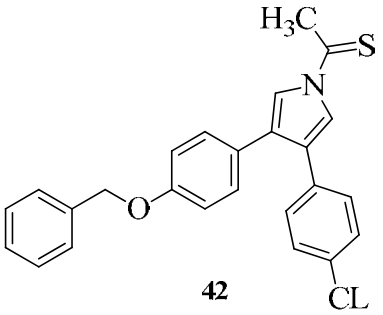
41e



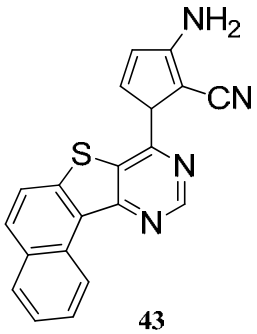
40a



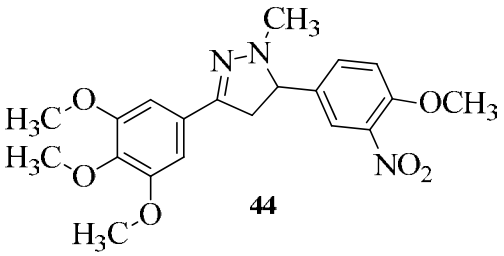
40b



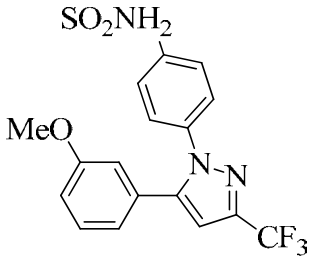
42



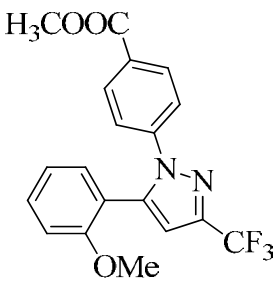
43



44



45a



45b

Conclusion

The review article has been outlined in the biological activities of the pyrazole moiety. This heterocyclic moiety possesses great pharmacological and medicinal significance. An extensive literature has been accumulated over the years and the chemistry of pyrazole continues to be a developing field. The versatile synthetic applicability and biological activity of these heterocyclic will help the medicinal chemists to approach, organize and

implement new scheme. Therefore, by considering all these derivatives viewing different of activities can say that Pyrazole ring have been searched past year is even being used for prospective development of new drug against man more pathological conditions.

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