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Biological potential of pyrazole, and triazole derivatives: A mini review

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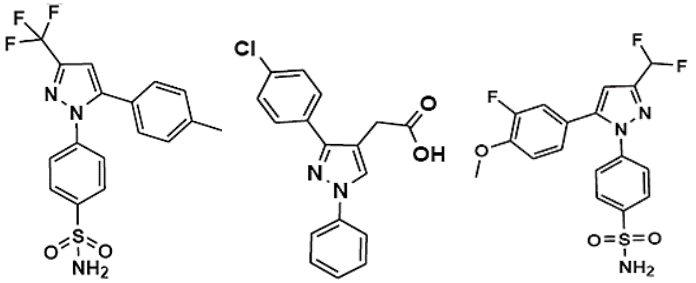
Abstract
The main objectives of this review to study of synthetic routes and biological activities of substituted Pyrazole, and 1, 2, 4-Triazole derivatives. These Pyrazole, and 1, 2, 4-Triazole derivatives have various types of biological activities such as antibacterial, antifungal. Analgesic, antimicrobial, anti-inflammatory, anticancer, antidepressant, anticonvulsant, anti-hyperglycemic, antipyretic, fungicidal, anti-arthritic and other biological activities. Moreover, some of the currently available drugs have been shown to exhibit unfavourable side effects and toxicity. It is well established that small modifications in the structure of the targets are altering their biological character as well as their physiochemical properties.

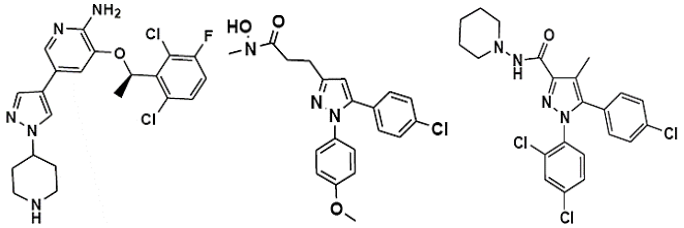
Keywords: biological potential, heterocyclic, Pyrazoles, Triazole, drugs

Introduction
Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents [1]. It is well-known that heterocyclic compounds having azole nucleus are important pharmacophore that appear extensively in various types of pharmaceutical agents, widely implicated in biochemical processes and display diversity of pharmacological activities. These heterocyclic compounds form a major part of organic chemistry; they are widely distributed in nature and play a vital role [2, 3]. Their practical applications range from extensive clinical use to fields as diverse as medicine, agriculture, photochemistry, biocidal activities. Many heterocyclic compounds synthesized have been successfully used as clinical agents. The chemistry of heterocycles has played a vital role in combating many deadly diseases. Various heterocyclic compounds are essential to our life and their functions are often of fundamental importance for living systems [4]. Amongst the heterocyclic compounds pyrazoles and Triazoles have attracted a tremendous attention, in the biological and industrial applications [5, 6]. The biological activities are invariably associated with a large variety of heterocyclic systems such as Pyrazole and Triazole. Various new derivatives have been synthesized and extensively studied for various pharmacological properties.

Biological importance of Pyrazoles
The pyrazole ring system consists of a doubly unsaturated five member ring containing two adjacent nitrogen atoms. The procedures for its synthesis have been extensively studied and such studies have been stimulated by various promising applications, especially in the case of highly substituted pyrazole derivatives. In fact, certain substituted pyrazoles are used as antimicrobial [7], anticancer [8], anti-inflammatory [9], antidepressant [10], anticonvulsant [11], antihyperglycemic [12], antipyretic [13], antibacterial [14], antifungal [15, 16], anti-arthritic [17] activities. The applications has pointed out that trisubstituted pyrazole are important target to be prepared to our interest on synthesis and molecular structure determination of some types of pyrazole. A synthetic approach on medicinal properties of pyrazole derivatives that having wide varieties of activities.



Celecoxib | **Lonazolac** | **Deracoxib** (Anti-inflammatory drugs)

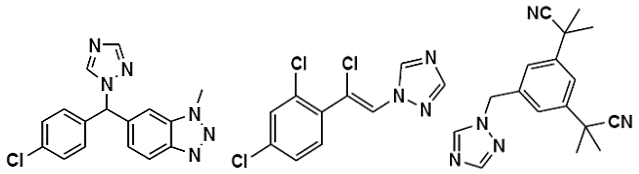


Crizotinib (Lung carcinoma) | **Tepoxalin** (NSAIDs-veterinary use) | **Rimonabant** (Anti-obesity)

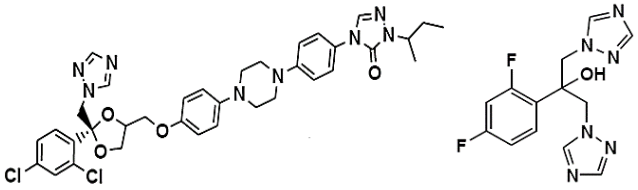
Fig 1: Some Pyrazole containing drugs.

Biological importance of 1, 2, 4-Triazole
The drug molecule is one of the most challenging tasks to the medicinal chemist. The synthesis of high nitrogen containing heterocyclic systems has been attracting increasing interest over the past decade because of their utility in various applications, such as propellants, explosives, pyrotechnics and especially chemotherapy. The chemistry of Triazoles and their fused

heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance. The derivatization of Triazole is considered to be based on the phenomenon of bioisosterism in which replacement of oxygen of oxadiazole nucleus with nitrogen atom yields triazole analogue. 1, 2, 4-Traizole moiety is of great importance to chemists as well as biologist as it is chemically useful molecules having diverse biological activities. Triazole, a heterocyclic nucleus has attracted a wide attention of the medicinal chemist in search for the new therapeutic molecules. Out of its two possible isomers, 1, 2, 4-triazole is which possess almost all types of biological activities. Some of the drugs which are having Triazole as core molecule are given below (Figure 2), several 1, 2, 4-Traizole containing compounds are used as drugs for instance Fluconazole is used as an antimicrobial drug, while Vorozole, Letrozole and Anastrozole are used as non-steroidal drugs used for the treatment of cancer. Loreclezole is used as an antifungal agent.



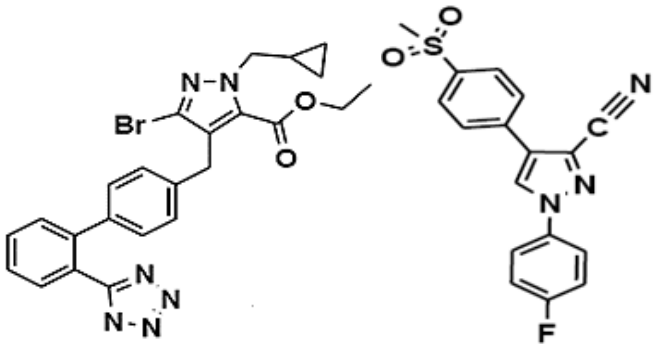
Vorazole **Loreclezole** **Anastrozole**



Itraconazole **Fluconazole**

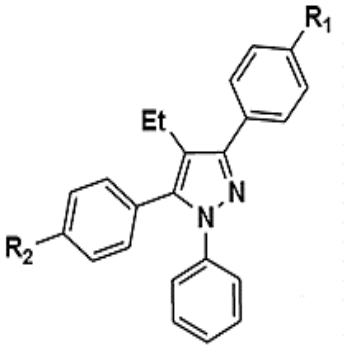
Fig 2: 1, 2, 4-traizole containing drugs

The N- alkyl biaryl tetrazoles containing pyrazole nucleus, among the synthesized compound, (1) was found to be highly potent antagonists of angiotensin II [18]. 1, 4-Diaryl pyrazole derivative (2) was tested for anti-inflammatory and analgesic activities to develop anti-inflammatory agents with fewer side effects than existing non-steroidal anti-inflammatory drugs [19]. The 4-alkyl-1, 3, 5-triarylpyrazoles (3) which are useful as estrogen receptor [20]. The novel series of structurally related 1*H*-pyrazolyl derivatives (4) were tested for their anti-inflammatory and antimicrobial activities. COX-1 and COX-2 inhibitory activities, ulcerogenic effects and acute toxicity were also determined [21].

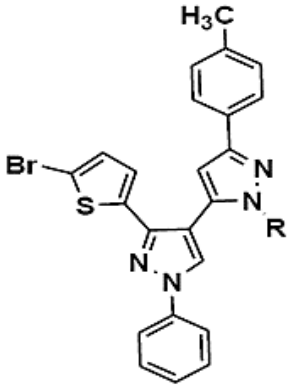


1

2



3 R_1=H, OH, OMe
R_2=H, OH, OMe



4 R=H, C_6H_5CO, C_6H_5NHCS, CH_3CO CHO, CH_3SO_2, 4-$CH_3C_6H_4SO_2$

A series of Pyrazole oxime ether derivatives (5) were examined its cytotoxicity activities. Among those, 5-phenoxypyrazole exhibited very potent cytotoxicity comparable to Doxorubicin (Scheme-1) [22].

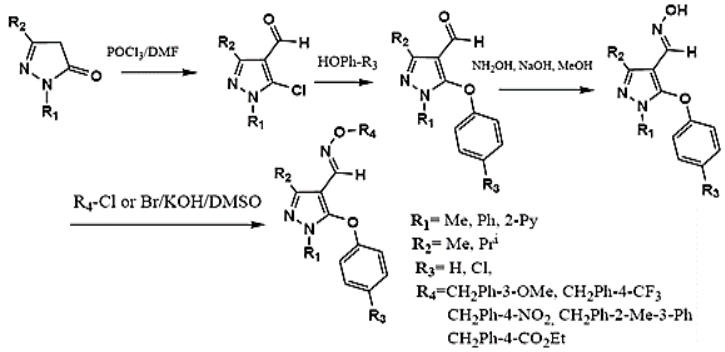
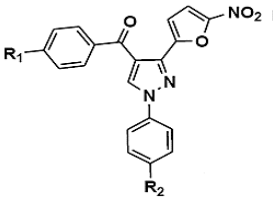
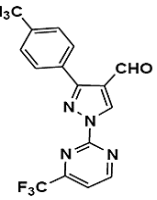
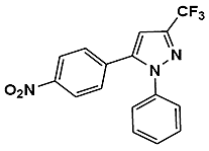


Fig ?: Scheme 1.4: pyrazole oxime ethers derivatives

A series of pyrazole derivatives (6) via 1, 3-dipolar addition of sydnone and nitro furan acetylenic ketones were reported [23]. A series of 1, 5-diaryl and 1, 3-diaryl substituted pyrazoles were evaluated for their ability to inhibit enoyl-ACP reductase of *Plasmodium falciparum*. The inhibitory activity of these compounds was evaluated in a continuous spectrophotometric assay. Of all the tested compounds (7) and (8) inhibited the enzyme with IC50 values of 30μM and 50μM, respectively [24].

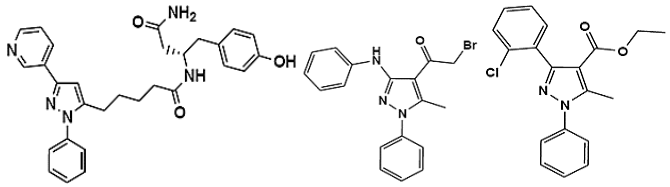






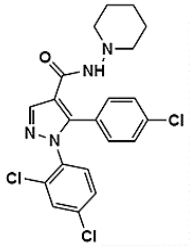
6 R_1=H, CH_3, Cl; R_2=H, CH_3, OCH_3 **7** **8**

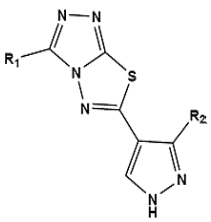
The pyrazole compounds (9) as low molecular weight luteinizing hormone receptor agonists [25]. The N-pyrazole derivatives were used as antimicrobial. Among the compounds tested for antimicrobial, compound (10) shown very good activity against pathogenic mould (*Aspergillus*) [26]. Synthesized and discovered a novel pyrazole derivative (11) as an inhibitor of apoptosis through modulating integrin β4, ROS, and p53 levels in vascular endothelial cells [27].

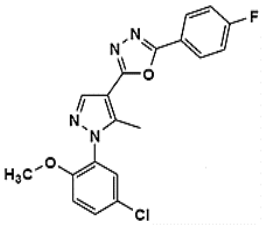


9 **10** **11**

A set of 1-(2, 4-dichlorophenyl)-5-arylpyrazoles were evaluated *in vitro* for their affinity on human CB1 and CB2 receptors. Among the compounds (12) was the closest rimonabant analogue and showed competitive binding of 79% and 37% against CB1 and CB2 receptor respectively [28]. The synthesis and anticancer activity of 3, 6-disubstituted 1, 2, 4-triazolo [3, 4-b]-1, 3, 4-thiadiazoles containing pyrazole moiety (13) [29]. A series of 1, 3, 4-oxadiazole containing pyrazole derivatives and studied its antibacterial activities. Among the compounds, 2-[1-(5-chloro-2-methoxyphenyl)-5-methyl-1*H*-pyrazol-4-yl]-5-(4-fluorophenyl)-1, 3, 4-oxadiazole (14) was found to exhibit significant antibacterial activity [30].







12 **13** **14**

A series of 1, 5-diary pyrazole derivatives (Scheme-2) (15) and screened for their antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*. Similarly all these compounds were screened for their antifungal activity against *Aspergillus flavus*, *Aspergillus fumigates*, *Penicillium marneffei* and *Trichophyton mentagrophytes*. Some of the synthesized compounds exhibited good antibacterial and antifungal activity [31].

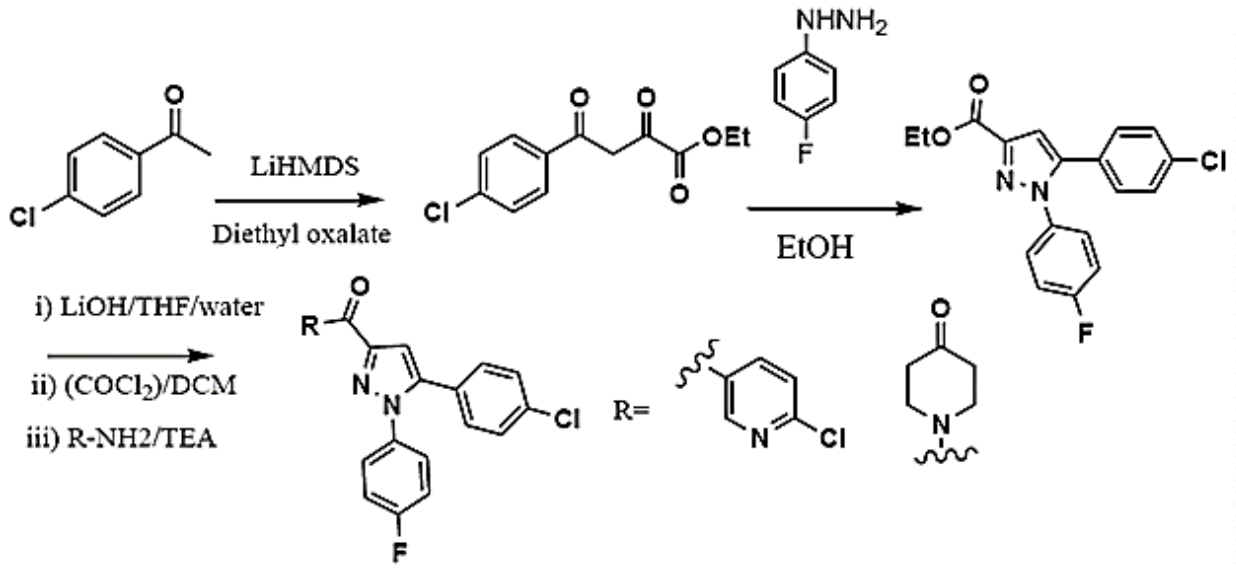
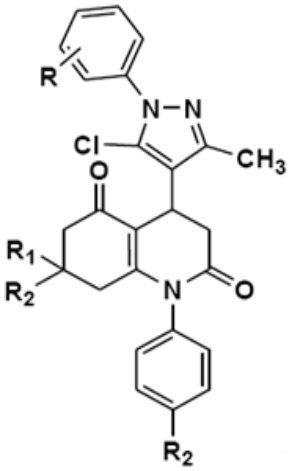


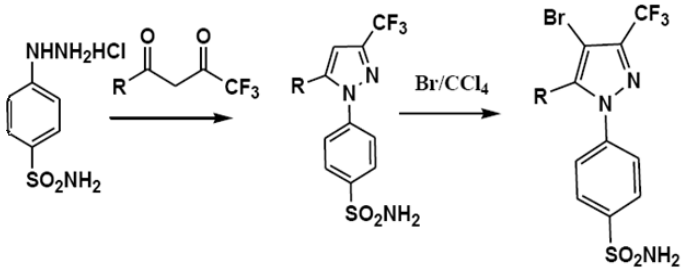
Fig ?: Scheme-2 Synthesis of novel 1, 5-diaryl pyrazoles

A series of 4-pyrazolyl-*N*-arylquinoline-2, 5-dione derivatives **(16)** and are screened, against some of the bacterial pathogens. Some of the compounds were found to be equipotent or more potent than commercial drugs [32].



16 R=3-Cl, 4-Me R1=H, Me R2=F, OMe,

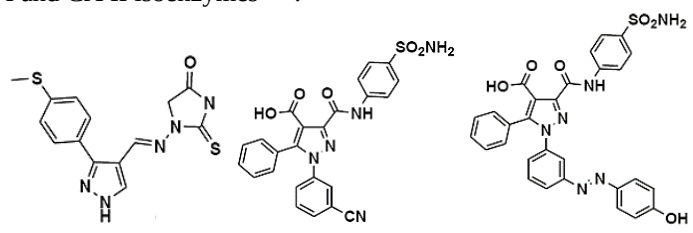
The fluorinated pyrazoles (17) (Scheme-3) has been observed that Preliminary biological screening of the compounds revealed significant antidiabetic and antibacterial activities [33].



R=CH_3, Furyl

Fig ?: Scheme-3 3-Trifluoromethylpyrazolesulfonyl-urea and thiourea derivatives

A series of novel imidazole derivatives containing substituted pyrazole moiety. Among the compounds, compound (18) was found to be potent antimicrobial agent. The acute oral toxicity study for the compound was carried out and the experimental studies revealed that compound is safe up to 3000 mg/kg and no death of animals were recorded [34]. A series of pyrazole-sulfonamide derivatives (19) and (20) were synthesized and the inhibition effects of the derivatives on human carbonic anhydrases (hCA I and hCA II) were investigated as *in vitro*. Almost all the compounds have good inhibition effects on the CA I and CA II isoenzymes [35].



18 **19** **20**

A concise 'one-pot' synthesis of a variety of 4-substituted 1, 5-diaryl-1*H*-pyrazole-3-carboxylates (21) has been developed in moderate to good yields (Scheme-4) with excellent regioselectivity [36].

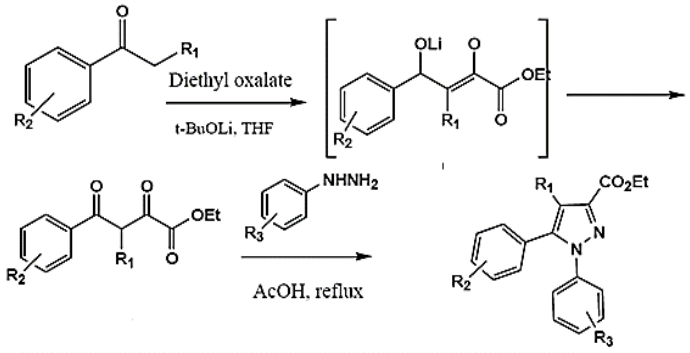
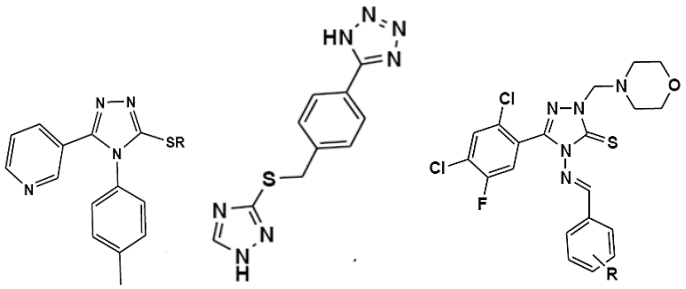


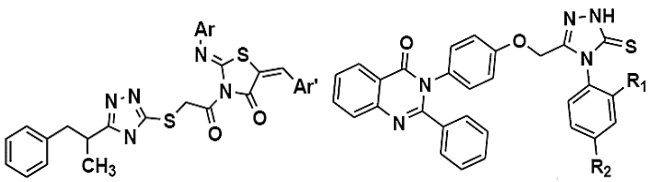
Fig ?: Scheme-4 Synthesis of 4-substituted 1, 5-diaryl-1*H*-pyrazole-3-carboxylates via lithium *tert*-butoxide medium

A series of l, 5-(isomeric pyridyl)-4-aryl-1, 2, 4-triazole-3-thiol, -thioethyl, thiomethyl, thiobenzyl derivatives from pyridine carboxylic acid hydrazide (22) [37]. Series of 3-benzylsulfanyl derivatives of 1, 2, 4-triazole were synthesized by alkylation of starting triazole-3-thiol with appropriately substituted benzyl halide (23). All members of the set were evaluated for *in vitro* anti-TB activity. The compounds exhibited only a moderate or slight anti-TB activity. MICs fall into a range of 32->1000 μmol/l. The most active substances bear two nitro groups or a thioamide group on the benzyl moiety [38]. Some Schiff bases bearing 2, 4-dichloro-5-fluorophenyl moiety (24) by condensing triazole with aromatic aldehydes. Synthesized compounds were tested for their antimicrobial activity [39].



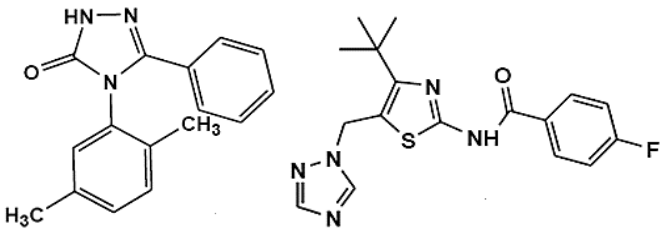
22 R= CH_3, C_2H_5, CH_2Ph, CH_2COOH **23** **24**

Anticonvulsant activity of Thiazolidinone-triazole derivatives (25), by the treatment of (2-chloroacetyl)-2-arylimino-5-[(Z)-arylmethylidene]-1, 3-thiazolan-4-ones with 5-(1-phenoxy-ethyl)-4H-1, 2, 4-triazole-3-thiol in identical conditions provided a set of bulkier derivatives which have also shown the anticonvulsant potential [40]. The 3-[4-(4-substituted phenyl-5-thioxo-4, 5-dihydro-1H-1, 2, 4 triazol-3-ylmethoxy)-phenyl]-2-phenyl-3H-quinazolin-4-one (26). The synthesized compounds were evaluated *in vitro* for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis* by the ditch-plate technique using concentrations of 50 μg/mL. The compounds synthesized were screened for their antifungal activity against. *Aspergillus niger*, *Candida albicans and Cryptococcus neoformans* at concentrations of 50 μg/mL [41].



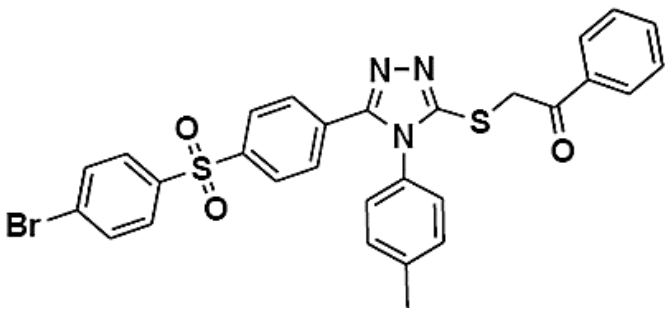
25 **26**

Some substituted diphenyl-1, 2, 4-triazole-3-ones by the condensation of substituted benzoyl chlorides and substituted phenyl semicarbazides. The anticonvulsant activities of these compounds were screened by using different animal models. Results show that compound (27) exhibited anticonvulsant activity in all the four animal models of seizure. A series of N-(5-((1H-1, 2, 4-triazol-1-yl) methyl)-4-tertbutylthiazol-2-yl)-4-carboxamide derivatives from 3, 3-dimethyl butan-2-one. The presence of fluorine atom at position 2, 3, 4 of phenyl ring are crucial for exhibited plant-growth regulatory activities and the substitution with chlorine atom at both 2nd position and 4th position of benzene ring caused a decrease of the activity while the presence of a strong electron-withdrawing group such as nitro-group led to decrease in activity. Compound (28) having fluorine atom at 4th position connected to the phenyl ring produced excellent plant-growth regulatory activity [42].



27 **28**

The 1, 2, 4-triazoles incorporated diphenyl sulfone was synthesized. The compounds were tested for its antibacterial activity. The compounds were tested for their *in vitro* growth inhibitory activity against the following Gram-negative bacteria and Gram-positive bacteria using the paper disk diffusion method. Among these compound (29) showed more active against the tested strains [43].



29

Some new 1, 2, 4-triazoles and their Schiff and Mannich bases (Scheme-5) (30-32) and screened for their antimicrobial activities. Some of the screened compounds showed good activity [44].

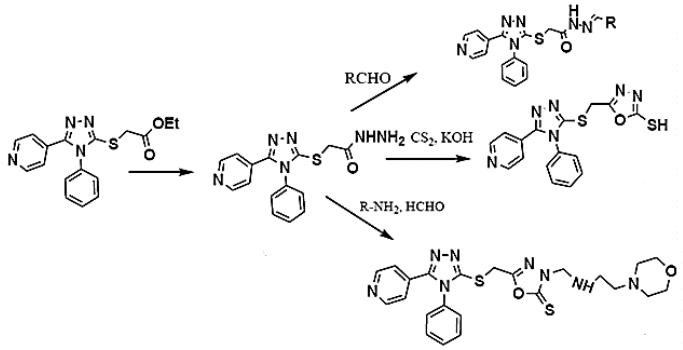
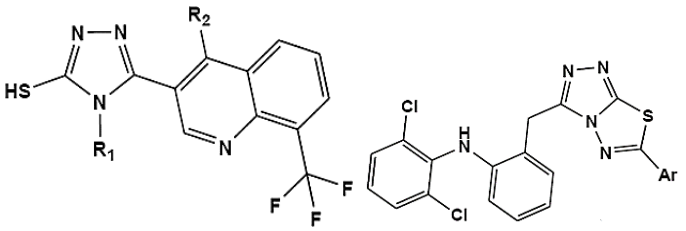


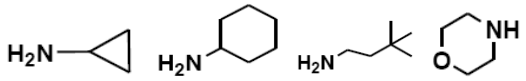
Fig ?: Scheme-5 1, 2, 4-Triazoles, their Schiff and Mannich bases

A class of quinoline derivatives containing 1, 2, 4-triazole moiety (33). The compounds were tested for their *in vitro* antibacterial and antifungal activities against four strains each. Preliminary results indicated that most of the compounds demonstrated very good antimicrobial activity, comparable to the first line standard drugs. The most effective compounds have exhibited activity at MIC of 6.25 μg/mL [45]. A series of 3, 6-disubstituted-1, 2, 4-triazolo-[3, 4-b]-1, 3, 4-thiadiazoles. The compounds (34) were screened for antifungal activity against *Candida albicans* and *Aspergillus Niger* using Ketoconazole as standard and antioxidant activity by DPPH and Nitric oxide methods using Ascorbic acid standard [46].



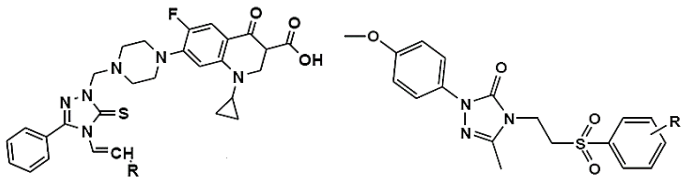
33 R_1= Ph,-CH_2PH, -CH_2-CH_2OMe

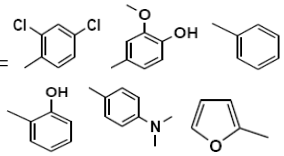
34



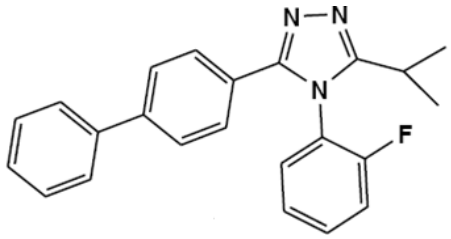
R_2=

Some novel Ciprofloxacin analogues (35) as antimicrobial agents, Ciprofloxacin have been incorporated to the new series of Schiff and Mannich reaction. The compounds have been evaluated *in vitro* for their antimicrobial activity against *B. subtilis*, *K. pneumoniae*, and *P. aeruginosa* at 10μg/mL concentration. All the compounds showed *in vitro* gram positive and gram negative activity generally comparable or superior to that of reference ciprofloxacin [47]. A series of sulfone containing 1, 2, 4- triazole derivatives. The compounds were screened for their antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli* and *Pseudomonas aeruginosa.* The antifungal activity was tested against *Rhizopus oryzae*, *Aspergillus Niger*, *Aspergillus flavus*, *Candida albicans* and *Saccharomyces cerevisiae.* Among all the compounds synthesized, compound (36) exhibited significant antibacterial activity [48].



35 R=  **36** R=2-F, 3-F, 4-F, 4-Br, 3-CF_3, H

A series of glycine transporter 1 inhibitors derived from a high-throughput screening hit. A pharmacokinetic study was showed that compound (37) showed very good oral bioavailability and ameliorated learning impairment in passive avoidance tasks in mice [49].



37

A series of novel isoindoline-1, 3-diones containing 1, 2, 4-triazole moiety were synthesized *via* a one-pot reaction (Scheme-6). Antifungal and cytotoxic activities of these compounds were evaluated. Antifungal studies of the novel compounds showed promising activity (38). Some compounds displayed much stronger antitumor activity than Fluorouracil [50].

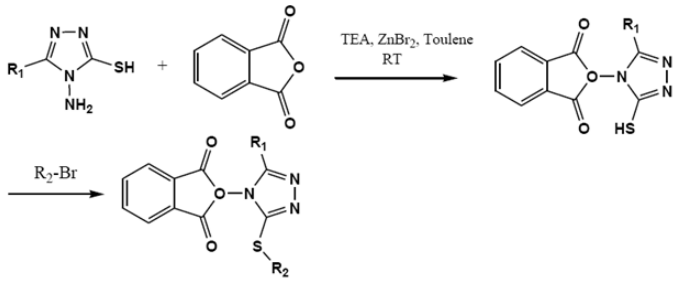


Fig ?: Scheme-6 Novel isoindoline-1,3-dione derivatives bearing 1, 2, 4-triazole derivatives

A two-step synthesis of medicinally important 1, 2, 4-triazoles from isocyanides and thiosemicarbazones (Scheme-7). The method is based on the discovered TMSCl-promoted reaction of isocyanides that yields rare N1, N3-disubstututed formamidrazones (39) [51].

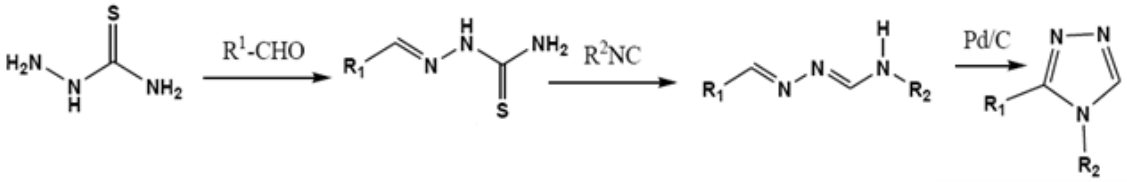
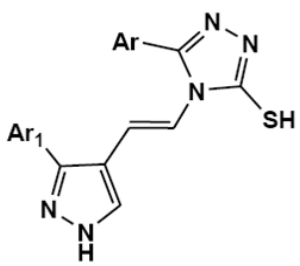


Fig ?: Scheme-7 Synthesis of novel 1,2,4-triazoles from isocyanides and thiosemicarbazones

A series of new 1, 2, 4-triazole derivatives. All the synthesized compounds were screened for their analgesic activity by the tail flick method. The antimicrobial activity of the new derivatives was also performed by MIC by the serial dilution method. The results revealed that the compound having 2, 5-dichlorothiophene substituent on pyrazole moiety and a triazole ring (40) showed significant analgesic and antimicrobial activity [52].



40

Conclusion

The present work, involving design, synthesis and characterization Pyrazole and Triazole derivatives and evaluation of their preliminary antibacterial, antifungal activities, has been aimed at development of new active compounds, which may have future commercial applications. To modify the structure of already existing drugs by improving the binding affinity to the receptor. Also, the correlation between structure activities of the new compounds would impart valuable information to assist the development of new types of drugs in new millennium. Furthermore, the results of research may be useful in understanding the mechanism of drug action. The research study is expected to add some more data to the chemistry of new heterocyclic compounds. The utility of above new heterocyclic compounds may be explored in other area of applications also.

References

1. Harikishan S, Kapoor VK. A text book of medicinal & pharmaceutical chemistry. 2nd edition, 2008, 264-455.
2. Agarwal OP. Organic chemistry reaction and reagents. 34th edition, 2002, 826-828.
3. Kalpesh P, Jayachandran Ravi S. Synthesis, characterization and anthelmintic activity (perituma posthuma) of new oxadiazole incorporated with imidazole and pyrazole Int J Pharm. Bio. Sci, 2009, 957-958.

4. Ravindra KC, Vagdevi HM, Vaidya VP, Padmashali B. Synthesis, antimicrobial activities of 1,3,4-oxadiazoles linked to naphtho [2, 1- b] furan Ind. J. Chem. 2006: 45B:2506-2511.
5. Chen HS, Li ZM, Han YF, Wang ZW. New Fungicidally Active Pyrazolyl-Substituted 1, 3, 4-ThiadiazoleCompounds and Their Preparation Chin. Chem. Lett. 1999; 10(5):365-366.
6. Moise M, Sunel V, Profire L, Popa M, Desbrieres J, Peptu C, *et al*. Synthesis and Biological Activity of Some New 1, 3, 4-Thiadiazole and 1, 2, 4-Triazole Compounds Containing a Phenylalanine Moiety Molecules. 2009; 14:2621-2631.
7. Pimerova EV, Voronina EV. Antimicrobial activity of pyrazoles and pyridazines obtained by interaction of 4-aryl-3-arylhydrazono-2, 4-dioxobutanoic acids and their esters with hydrazines Pharm Chem J. 2001; 35:18-20.
8. Magedov IV, Manpadi M, Slambrouck VS, Steelant WFA, Rozhkova E, Przheval ski NM, *et al*. Discovery and Investigation of Antiproliferative and Apoptosis-Inducing Properties of New Heterocyclic Podophyllotoxin Analogues Accessible by a One-Step Multicomponent Synthesis. J Med. Chem. 2007; 50:5183-5192.
9. Rovnyak GC, Millonig RC, Schwartz J, Shu V. Synthesis and anti-inflammatory activity of hexahydrothiopyrano [4, 3-c] pyrazoles and related analogs. J Med. Chem. 1982; 25:1482-1488.
10. Prasad YR, Rao AL, Prasoona L, Murali K, Kumar RV. Synthesis and antidepressant activity of some 1, 3, 5-triphenyl-2-pyrazolines and 3-(2″-hydroxy naphthalen-1″-yl)-1, 5-diphenyl-2-pyrazolines. Bioorg. Med. Chem. Lett. 2005; 15(22):5030-5034.
11. Ozdemir Z, Kandilici B, Gumusel B, Calis U, Bilgin A. Synthesis and studies on antidepressant and anticonvulsant activities of some 3-(2-furyl)-pyrazoline derivatives. Eur. J.Med. Chem. 2007; 42:373-379.
12. Hees KL, Fitzgerald JJ, Steiner KE, Mattes JF, Mihan B, Tosi T, *et al*. New Potent Antihyperglycemic Agents in db/db Mice: Synthesis and Structure Activity Relationship Studies of (4-Substitutedbenzyl) (trifluoromethyl) pyrazoles and pyrazolones. J Med. Chem. 1996; 39:3920-3928.
13. Sener A, Sener MK, Bildirici I, Kasimogullari R, Akcamur Y. Studies on the reactions of cyclic oxalyl compounds with hydrazines or hydrazones : Synthesis and reactions of 4-benzoyl-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid. J Het. Chem. 2002; 39:869-875.
14. Liu XH, Cui P, Song BA, Bhadury PS, Zhu HL, Wang SF, *et al*. Synthesis, structure and antibacterial activity of novel 1-(5-substituted-3-substituted-4,5-dihydropyrazol-1-yl) ethanone oxime ester derivatives. Bioorg. Med. Chem. 2008; 16:4075-4082.
15. Akbas E, Berber I. Antibacterial and antifungal activities of new pyrazolo [3, 4-*d*] pyridazin derivatives Eur. J Med Chem. 2005; 40:401-405.
16. Delany JJ. Selective Pyrazoline Insecticides and Fungicides, compositions and use U. S. Pat 4346, 1991, 97
17. Rangari V, Gupta VN, Atal CK. Synthesis, anti-inflammatory and antiarthritic activity of newer β-Boswellic acid derivatives. Ind. J Pharm. Soc. 1990; 52:158-160.
18. Watson SP, Middlemiss D, Pass M, Hubbard T, Panchai TA, Heron NM, *et al*. Clinked pyrazole biaryl tetrazoles as antagonists of angiotensin II Part II: pharmacokinetics and an efficient regioselective synthesis. Bioorg. Med. Chem. Lett. 1994; 4:51-156.
19. Kiyoshi T, Katasuya N, Nobukiyo K, Takashi T, Takehiro O, Hachiro S, *et al*. Studies on Anti-inflammatory Agents. IV. Synthesis and Pharmacological Properties of 1, 5-Diarylpyrazoles and Related Derivatives Chem. Pharma. Bull. 45, 1997, 987-995.
20. Huang YR, Katzenellenbogen JA. Regioselective Synthesis of 1, 3, 5-Triaryl-4-alkylpyrazoles: Novel Ligands for the Estrogen Receptor. Org. Lett. 2000; 2(18):2833-2836.
21. Bekhit AA, Abdel-Aziem T. Design, synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory-antimicrobial agents. Bioorg. Med. Chem. 2004; 12:1935-1945.
22. Park HJ, Lee K, Park SJ, Ahn B, Lee JC, Cho YY, *et al*. Identification of antitumor activity of pyrazole oxime ethers. Bioorg. Med. Chem. Lett. 2005; 15:3307-3312.
23. Rai G, Puranik VG, Kalluraya B, Hegde JC. Exclusive Formation of 1-Aryl-3-(5-nitro-2-furyl)-4-aroylpyrazoles via Regiospecific 1, 3-Dipolar Cycloaddition of 3-Arylsydnones with α, β-Acetylenic Ketones. Synth. Commun. 2006; 37(9):1285-1290.
24. Kumar S, Kumar G, Kapoor M, Surolia A, Surolia N. Synthesis and Evaluation of Substituted Pyrazoles: Potential Antimalarials Targeting the Enoyl- ACP Reductase of Plasmodium Falciparum. Synth. Comm. 2006; 36(2):215-226.
25. Jorand-Lebrun C, Brondyk B, Lin J, Magar S, Murray R, Reddy A, *et al*. Identification, synthesis, and biological evaluation of novel pyrazoles as low molecular weight luteinizing hormone receptor agonists. Bioorg. Med. Chem. Lett. 2007; 17:2080-2085.
26. Farag AM, Mayhoub AS, Barakat SE, Bayomi AH. Regioselective synthesis and antitumor screening of some novel *N*-phenyl pyrazole derivatives Bioorg. Med. Chem. 2008; 16:881-889.
27. Zhao BX, Zhang L, Zhu XS, Wan MS, Zhao J, Zhang Y, *et al*. Synthesis and discovery of a novel pyrazole derivative as an inhibitor of apoptosis through modulating integrin β4, ROS and p53 levels in vascular endothelial Bioorg. Med. Chem. 2008; 16:5171-5180.
28. Menozzi G, Fossa P, Cichero E, Spallarossa A, Ranise A, Mosti L, *et al*. Rational design, synthesis and biological evaluation of new 1, 5-diarylpyrazole derivatives as CB1 receptor antagonists, structurally related to rimonabant Eur. J. Med. Chem. 2008; 43:2627-2638.
29. Dhanya S, Isloor AM. Shetty P. Synthesis, characterization and anticancer activity of 1, 2, 4-Triazolo [3, 4-b]-1, 3, 4-thiadiazoles on Hep G2 cell lines Der Pharma Chemica. 2009; 1(2):19-26.
30. Rai NP, Narayanaswamy VK, Shashikanth S, Arunachalam PN. Synthesis, characterization and antibacterial activity of 2-[1-(5-chloro-2-methoxy-phenyl)-5-methyl-1*H*-pyrazol-4-yl]-5-(substituted-phenyl)-[1, 3, 4] oxadiazoles Eur. J. Med. Chem. 2009; 44(11):4522-4527.
31. Ragavan RV, Vijayakumar V, Kumari NS. Synthesis and antimicrobial activities of novel 1, 5-diaryl pyrazoles Eur. J. Med. Chem. 2010; 45:1173-1180.

32. Thumar NJ, Patel MP. Synthesis, characterization, and antimicrobial evaluation of carbostyril derivatives of 1*H*-pyrazole Saudi Pharmaceutical Journal. 2011; 19:75-83.
33. Faidallah HM, Khan KA, Abdullah MA. Synthesis and biological evaluation of new 3-trifluoromethylpyrazolesulfonyl-urea and thiourea derivatives as antidiabetic and antimicrobial agents J. Fluor. Chem. 2011; 132(2):131-137.
34. Vijesh AM, Isloor AM, Telkar S, Peethambar SK, Rai S, Isloor N. Synthesis, characterization and antimicrobial studies of some new pyrazole incorporated imidazole derivatives Eur. J Med. Chem. 2011; 46:3531-3536.
35. Balseven H, Isgor MM, Mert S, Alım Z, Beydemir Ok SS, Kasimogullari R, *et al*. Facile synthesis and characterization of novel pyrazole sulfonamides and their inhibition effects on human carbonic anhydrase isoenzymes Bioorg. Med. Chem. 2013; 21:21-27.
36. Jiang JA, Huang WB, Zhai JJ, Liu HW, Cai Q, Xu LX, *et al*. One-pot' synthesis of 4-substituted 1,5-diaryl-1*H*-pyrazole-3-carboxylates via lithium *tert*-butoxide-mediated sterically hindered Claisen condensation and Knorr reaction Tetrahedron, 2013, 627-635.
37. Zamani K, Faghihi Sangi MR, Zolgharnein J. Synthesis of Some New Substituted 1, 2, 4-Triazole and 1, 3, 4-Thiadiazole and Their Derivatives Turk J Chem. 2003; 27:119-125.
38. Klimesova V, Zahajska L, Waisser K, Kaustova J, Mollmann U. Synthesis and antimycobacterial activity of 1,2,4-triazole 3-benzyl sulfanyl derivatives IL Farmaco. 2004; 59:279-288.
39. Karthikeyan MS, Prasad DJ, Poojary B, Bhat KS, Holla BS, Kumari NS, *et al*. Synthesis and biological activity of Schiff and Mannich bases bearing 2,4-dichloro-5-fluorophenyl moiety Bioorg. Med. Chem. 2006; 14(22):7482-7489.
40. Shiradhar MR, Nikalje AG. Synthesis and anticonvulsant activity of clubbed thiazolidinone-Barbituric acid and thiazolidinone-triazole derivatives ARKIVOC. 2007; (xiv):58-74.
41. Havaldar FH, Patil AR. Synthesis of 1, 2, 4-triazole Derivatives and their biological Activity E-Journal of Chemistry. 2008; 5(2):347-354.
42. Shalini M, Yogeeswari P, Sriram D, Stables JP. Biomedicine & pharmacotherapy. 2009; 63:187-193.
43. Qin X, Yu H, Liu J, Dai H, Bing G, Qin Z, *et al*. Synthesis and biological activity of novel *N*-(5-((1*H*-1,2,4-triazol-1-yl) methyl)-4-*tert*-butylthiazol-2-yl)-4-carboxamide derivatives ARKIVOC. 2009; (ii):201-210.
44. Barbuceanu SF, Almajan GL, Saramet I, Draghici C, Socoteanu R, Barbuceanu F, *et al*. New S-alkylated 1, 2, 4-triazoles incorporating biphenyl sulfone moieties with potential antibacterial activity J Serb. Chem. Soc. 2009; 74(10):1041-1049.
45. Bayrak H, Demirbas A, Karaoglu SA, Demirbas N. Synthesis of some new 1,2,4-triazoles, their Mannich and Schiff bases and evaluation of their antimicrobial activities Eur. J. Med. Chem. 2009; 44(3):1057-1066.
46. Eswaran S, Adhikari AV, Shetty NS. Synthesis and antimicrobial activities of novel quinoline derivatives carrying 1,2,4-triazole moiety. Eur. J Med. Chem. 2009; 44(11):4637-4647.
47. Ilango K, Valentina P. Synthesis and biological activities of novel 1, 2, 4-triazolo-[3, 4-b]-1, 3, 4-thiadiazoles. Der Pharma Chemica. 2010; 2(2):16-22.
48. Jubie S, Sikdar P, Kalirajan R, Gowramma B, Gomathy S, Sankar S, *et al*. Synthesis and antimicrobial activity of some novel ciprofloxacin analogues. J Pharmacy Res. 2010; 3:511-13.
49. Patil BS, Krishnamurthy G, Bhojya Naik HS, Latthe PR, Gate M. Synthesis, characterization and antimicrobial studies of 2-(4-methoxy-phenyl)-5-methyl-4-(2-arylsulfanyl-ethyl)-2, 4-dihydro-[1, 2, 4] triazolo-3-ones and their corresponding sulfone Eur. J Med. Chem. 2010; 45:3329-3334.
50. Sugane T, Tobe T, Hamaguchi W, Shimada I, Maeno K, Miyata J, *et al*. Synthesis and Biological Evaluation of 3-Biphenyl-4-yl-4-phenyl-4*H*-1, 2, 4-triazoles as Novel Glycine Transporter 1 Inhibitors J. Med. Chem. 2011; 54:387-391.
51. Zhao PL, Ma WF, Duan AN, Zou M, Yan YC, You WW, *et al*. One-pot synthesis of novel isoindoline-1, 3-dione derivatives bearing 1, 2, 4-triazole moiety and their preliminary biological evaluation Eur. J Med. Chem. 2012; 54:813-822.
52. Sarnpitak P, Krasavin M. Synthesis of 1, 2, 4-triazoles employing isocyanides Tetrahedron. 2013; 69:2289-2295.
53. Vijesh AM, Isloor AM, Shetty P, Sundershan S, Fun HK. New pyrazole derivatives containing 1, 2, 4-triazoles and benzoxazoles as potent antimicrobial and analgesic agents Eur. J Med. Chem. 2013; 60:208-215.