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Articles

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, antiiflammatory, 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.

1. Introduction

Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents (Harikishan, Kapoor, 2008). 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 (Agarwal, 2002; Kalpesh et al., 2009). 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 (Ravindra et al., 2006). Amongst the heterocyclic compounds pyrazoles and Triazoles have attracted a tremendous attention, in the biological and industrial applications (Chen et al., 1999; Moise et al., 2009). 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.

2. Results and discussion

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

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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 (Pimerova, Voronina, 2001), anticancer (Magedov et al., 2007), antiinflammatory (Rovnyak et al., 1982), antidepressant (Prasad et al., 2005), anticonvulsant (Ozdemir et al., 2007), antihyperglycemic (Ozdemir et al., 2007), antipyretic (Sener et al., 2002), antibacterial (Liu et al., 2008), antifungal (Akbas, Berber, 2005; Delany, 1991), anti-arthritic (Rangari et al., 1990) 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.

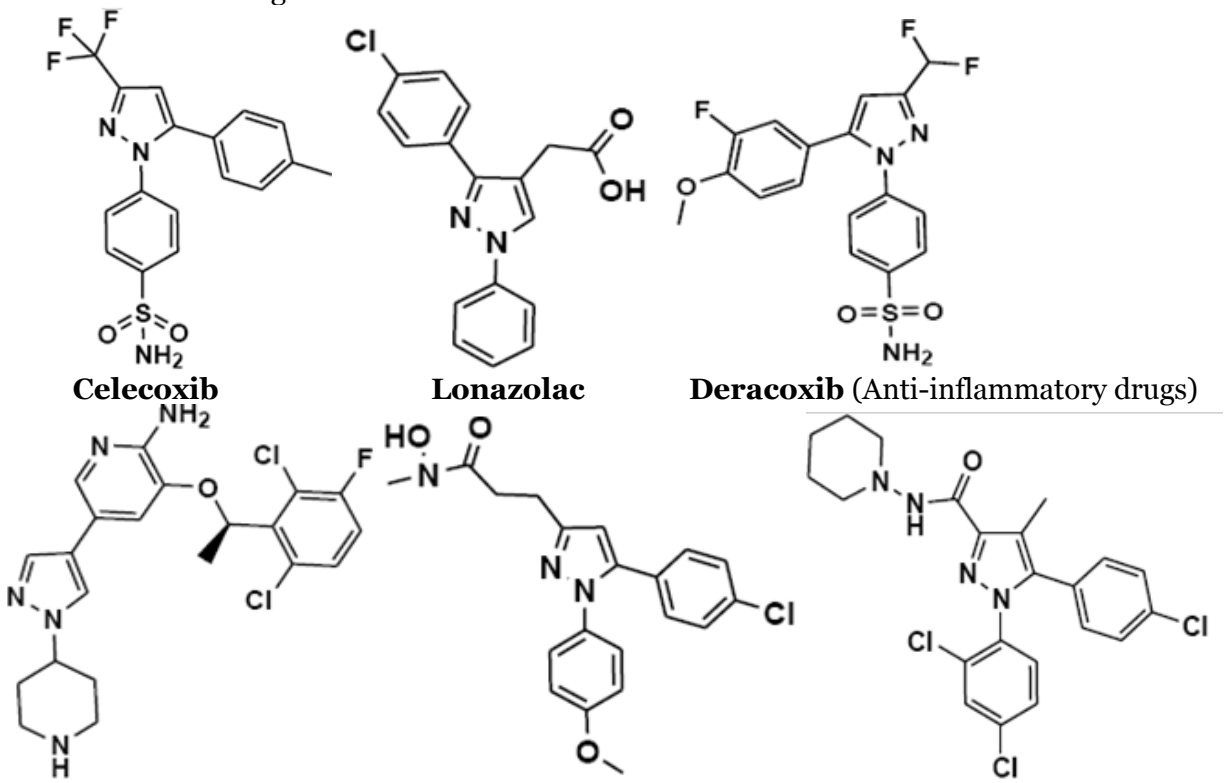


Fig. 1. Some Pyrazole containing drugs

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 posses 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.

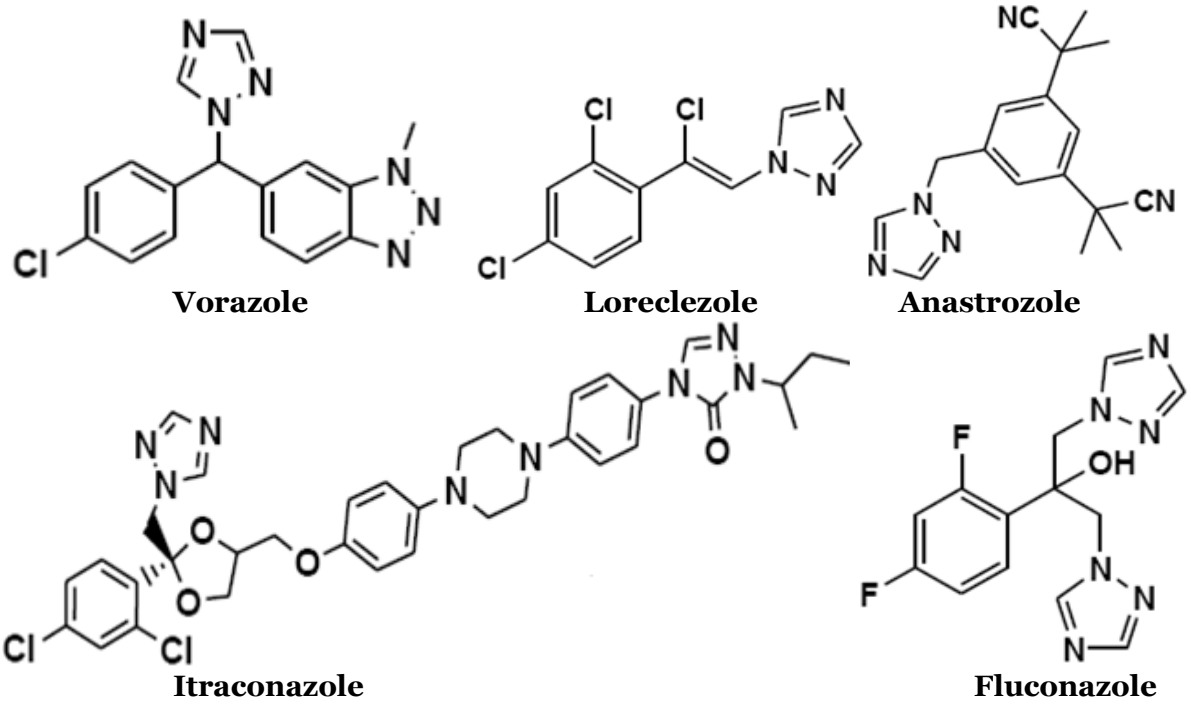
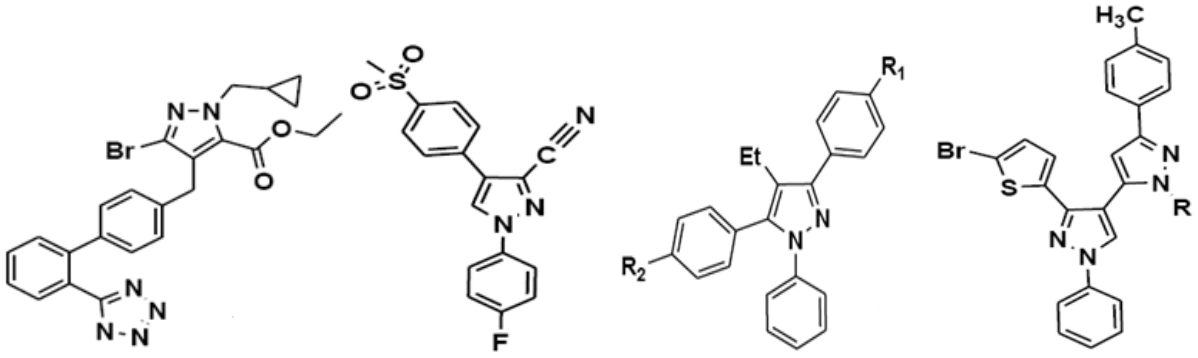


Fig. 2. 1,2,4-traizole containing drugs

The N- alkyl biaryl tetrazoles containing pyrazole nucleus, among the synthesized compound, (**1)** was found to be highly potent antagonists of angiotensin II (Watson et al., 1994). 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 (Kiyoshi et al., 1997). The 4-alkyl-1,3,5-triarylpyrazoles (**3**) which are useful as estrogen receptor (Huang, Katzenellenbogen, 2000). 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 (Bekhit, Abdel-Aziem, 2004).



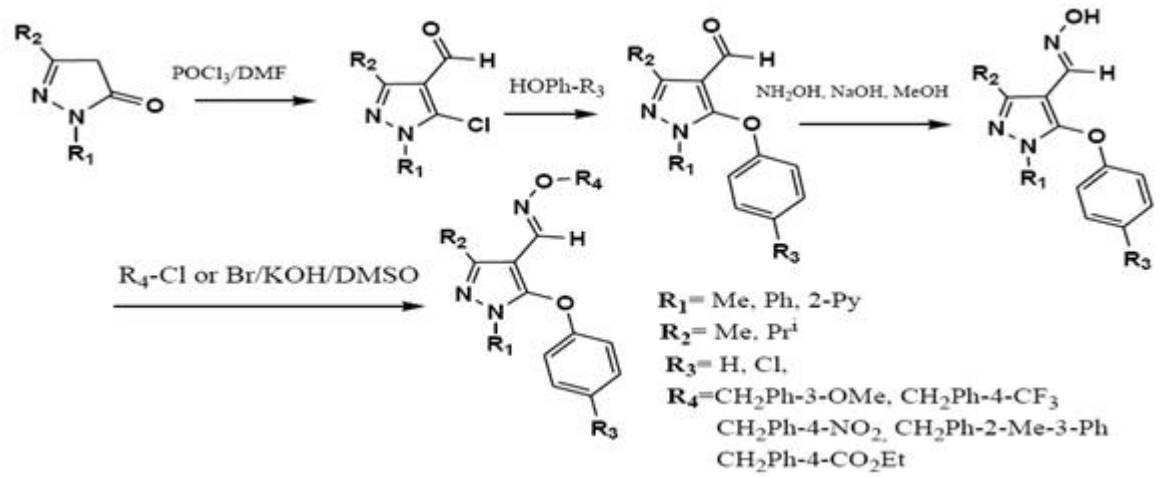
1 **2**

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

4 R=H, C_6H_5CO, C_6H_5NHCS, CH_3CO

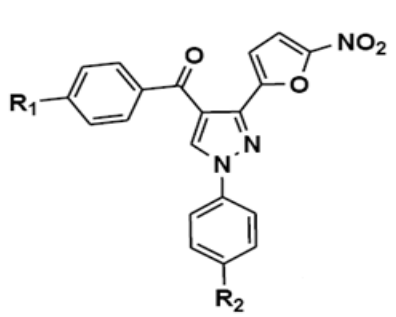
CHO, CH_3SO_2, 4-$CH_3C_6H_4SO_2$

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**) (Park et al., 2005).

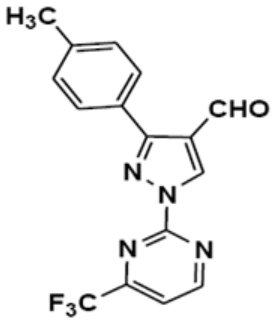


Scheme 1.4: pyrazole oxime ethers derivatives

A series of pyrazole derivatives (**6**) via 1,3-dipolar addition of sydnone and nitro furan acetylenic ketones were reported (Rai et al., 2006). 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 30 μM and 50 μM, respectively (Kumar et al., 2006).



6 R_1=H, CH_3, Cl;
R_2=H, CH_3, OCH_3



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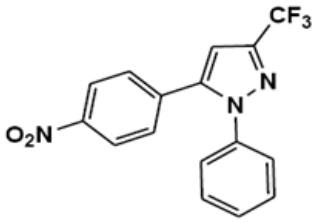
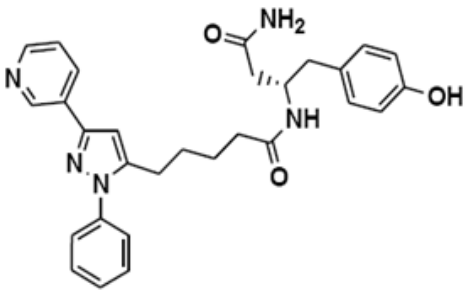


8

The pyrazole compounds (**9**) as low molecular weight luteinizing hormone receptor agonists (Jorand-Lebrun, 2007). The N-pyrazole derivatives were used as antimicrobial. Among the compounds tested for antimicrobial, compound (**10**) shown very good activity against pathogenic mould (*Aspergillus*) (Farag et al., 2008). 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 (Zhao et al., 2008).



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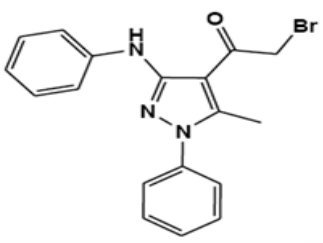

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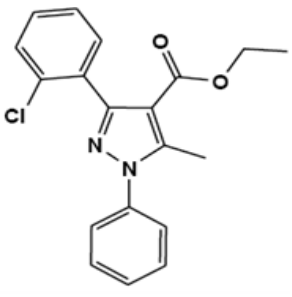
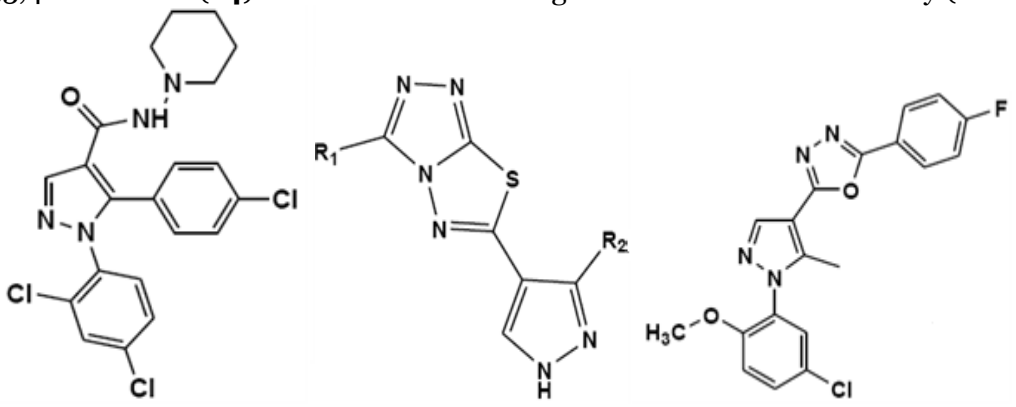


11

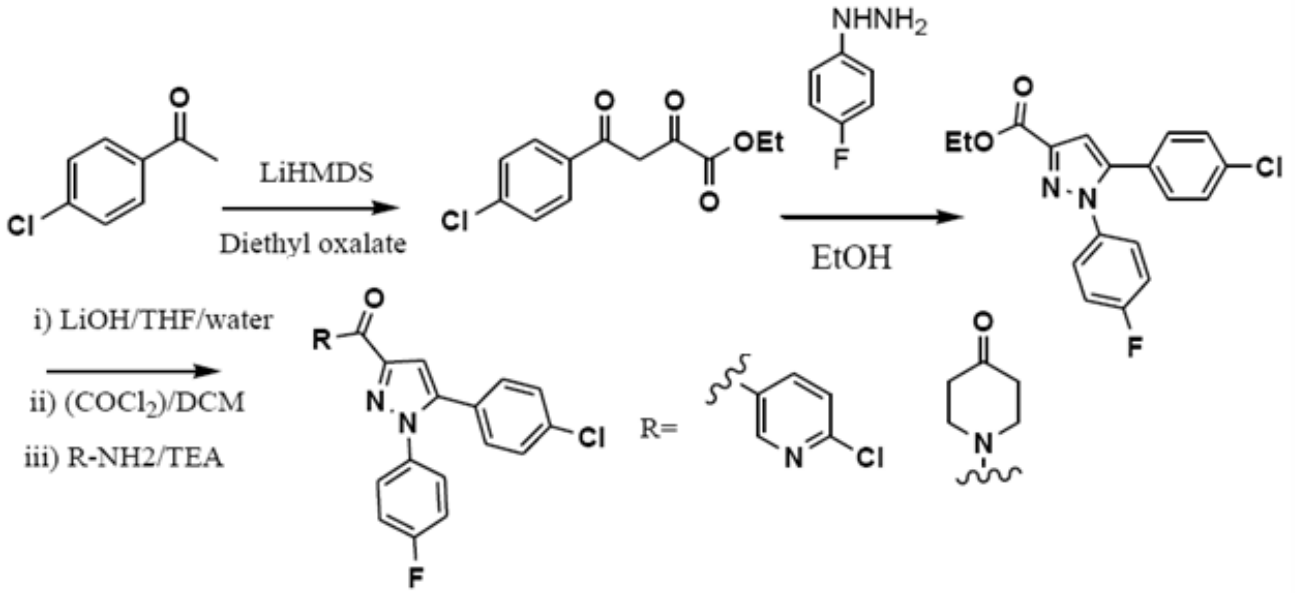
A set of 1-(2,4-dichlorophenyl)-5-arylpyrazoles were evaluated in vitro for their affinity on human CB1 and CB2 receptors. Among the compounds (**12**) was the closest rimonabant analogue

and showed competitive binding of 79 % and 37 % against CB1 and CB2 receptor respectively (Menozzi et al., 2008). The synthesis and anticancer activity of 3,6-disubstituted 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles containing pyrazole moiety (**13**) (Dhanya et al., 2009). 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 (Rai et al., 2009).



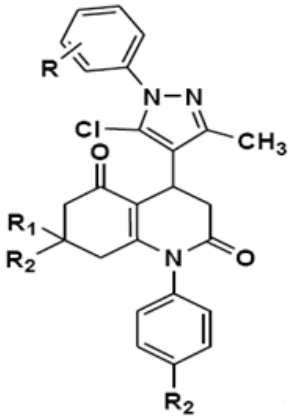
12 **13** **14**

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 (Ragavan et al., 2010).



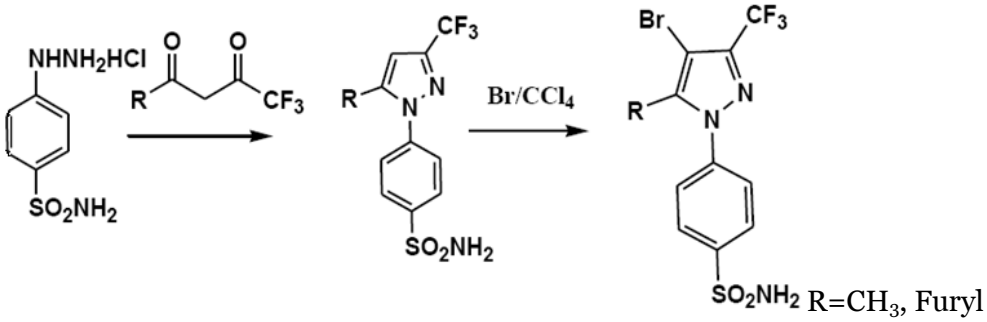
Scheme 2. Synthesis of novel 1, 5-diaryl pyrazoles

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 (Thumar, Patel, 2011).



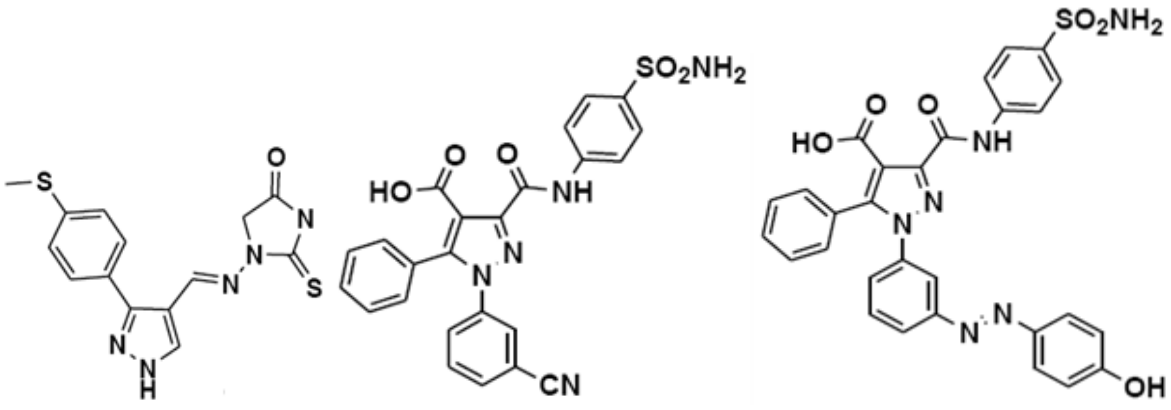
16 R=3-Cl, 4-Me R1=H, Me R2=F, OMe

The fluorinated pyrazoles (**17**) (**Scheme-3**) has been observed that Preliminary biological screening of the compounds revealed significant antidiabetic and antibacterial activities (Faidallah et al., 2011).



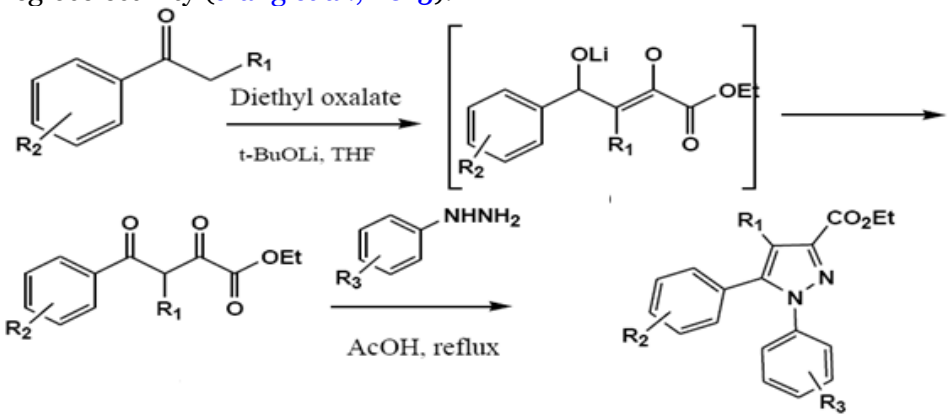
Scheme 3. 3-Trifluoromethylpyrazolesulfonyl-urea and thiourea derivatives

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 (Vijesh et al., 2011). 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 (Balseven et al., 2013).



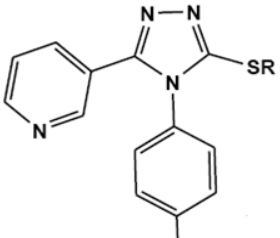
18 **19** **20**

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 (Jiang et al., 2013).

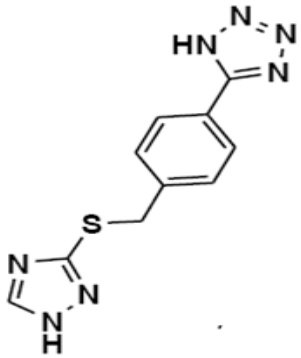


Scheme-4. Synthesis of 4-substituted 1, 5-diaryl-1*H*-pyrazole-3-carboxylates via lithium *tert*-butoxide medium

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)** (Zamani et al., 2003). 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 (Klimesova et al., 2004). 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 (Karthikeyan et al., 2006).



22 R= CH_3, C_2H_5, CH_2Ph, CH_2COOH



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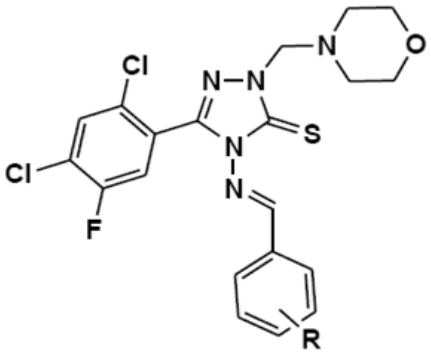
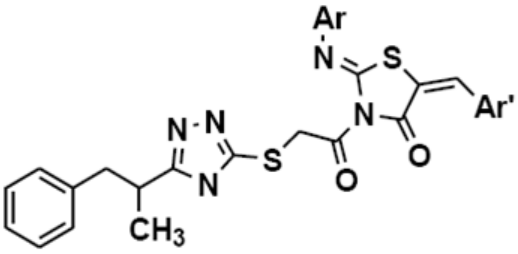


24

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 (Shiradhar, Nikalje, 2007). 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 (Havaldar, Patil, 2008).



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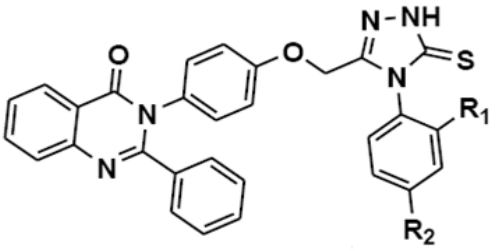
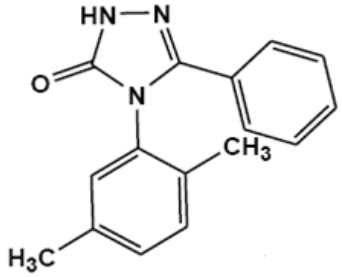


26

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 nitrogroup led to decrease in activity. Compound **(28)** having fluorine atom at 4th position connected to the phenyl ring produced excellent plant-growth regulatory activity (Qin et al., 2009).



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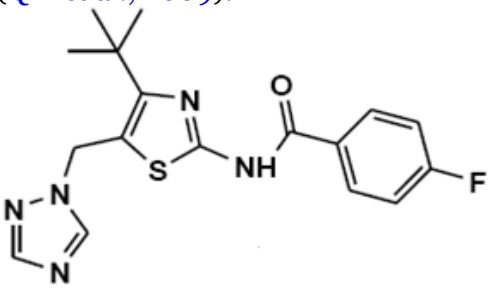
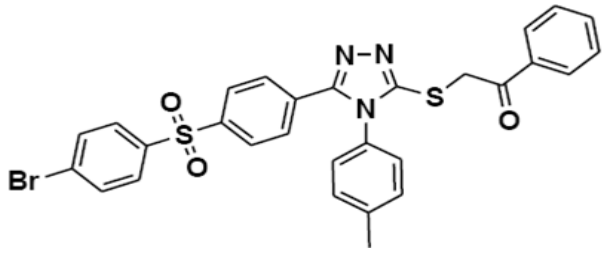


28

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 (Barbuceanu et al., 2009).



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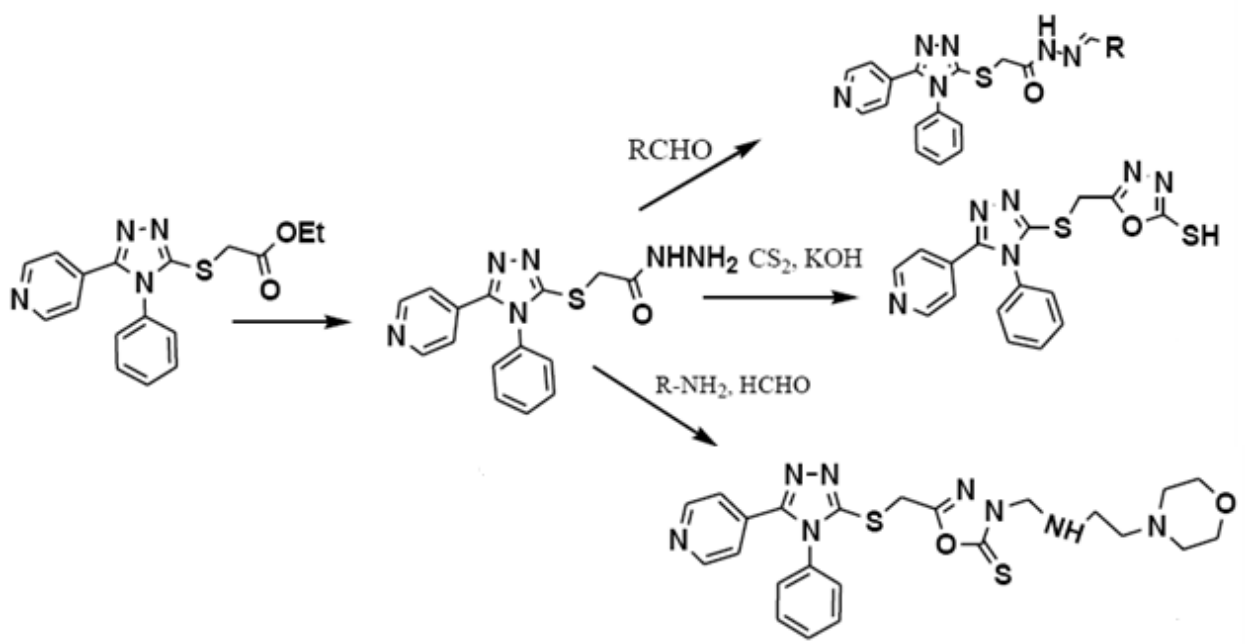
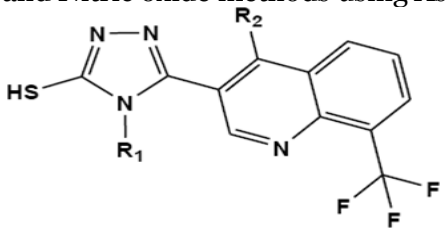
Some new 1,2,4-triazoles and their Schiff and Mannich bases (**Scheme 5)** (**30-32**) and screened for their antimicrobial activities. Some of the screened compounds showed good activity (Bayrak et al., 2009).



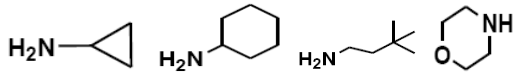
Scheme 5. 1,2,4-Triazoles, their Schiff and Mannich bases

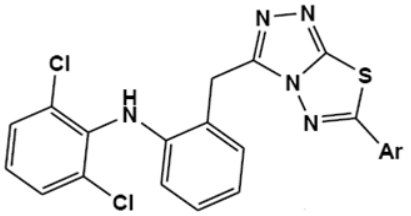
A class of quinoline derivatives containing 1,2,4-triazole moiety (**33**). The compounds were tested for their in vitro antibacterial and antifungal activities against four strains each. Preliminary results indicated that most of the compounds demonstrated very good antimicrobial activity, comparable to the first line standard drugs. The most effective compounds have exhibited activity at MIC of 6.25 µg/mL (Eswaran et al., 2009). 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 (Ilango, Valentina, 2010).



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

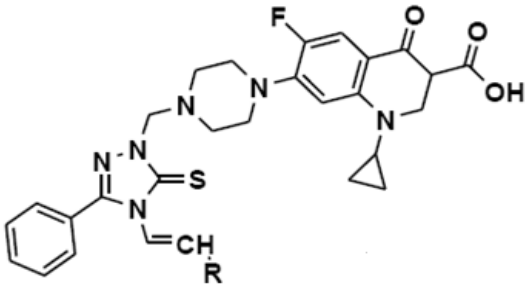
R_2=

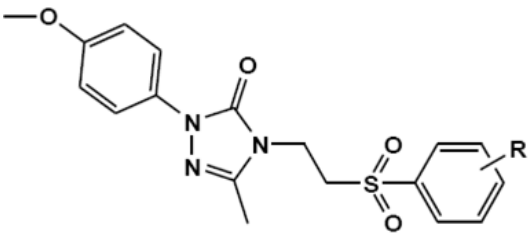




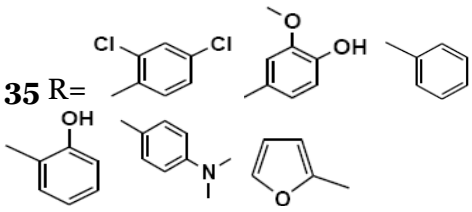
34

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 10 µg/mL concentration. All the compounds showed in vitro gram positive and gram negative activity generally comparable or superior to that of reference ciprofloxacin (Jubie et al., 2010). 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 (Patil et al., 2010).



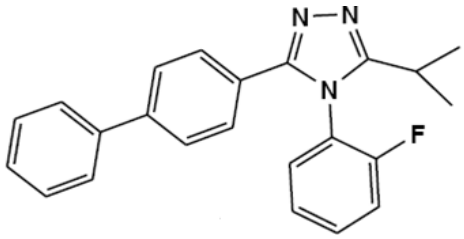


35 R=



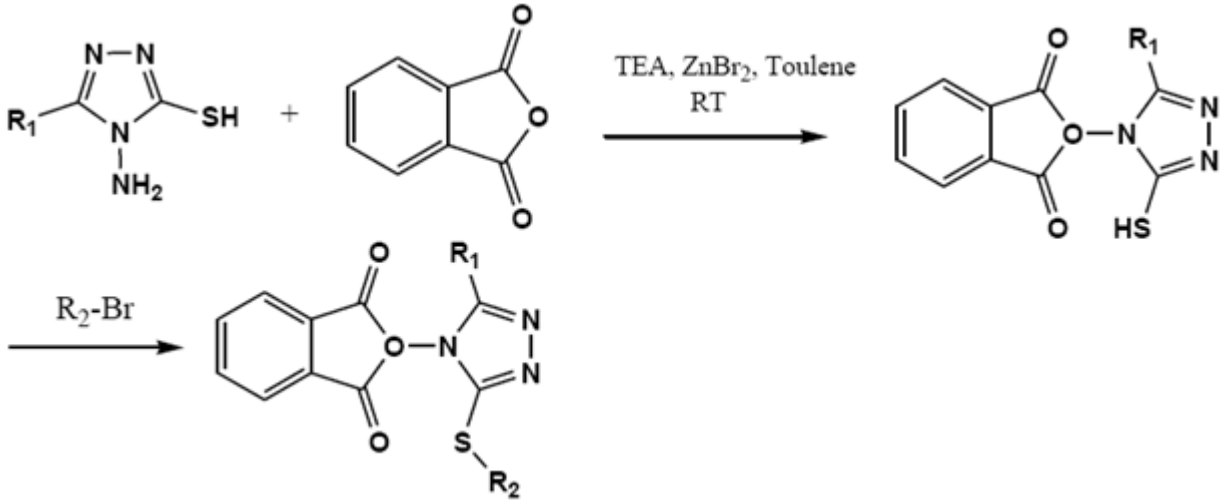
36 R=2-F, 3-F, 4-F, 4-Br, 3-CF_3, H

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 (Sugane et al., 2011).



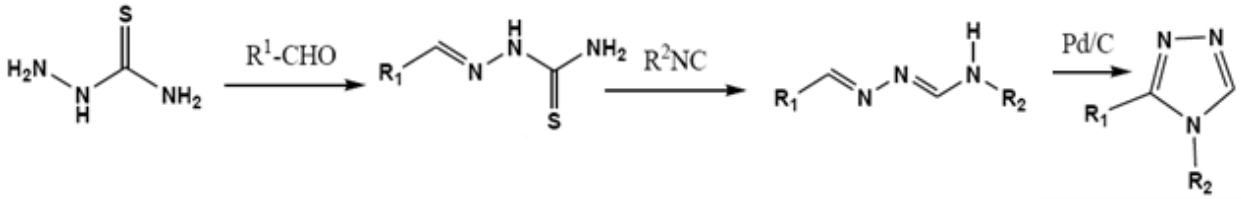
37

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 (Zhao et al., 2012).



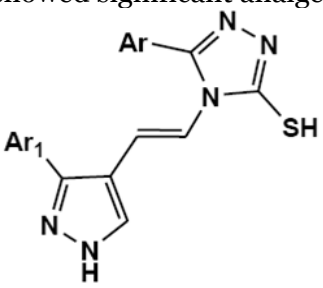
Scheme 6. Novel isoindoline-1,3-dione derivatives bearing 1,2,4-triazole derivatives

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)** (Sarnpitak, Krasavin, 2013).



Scheme 7. Syntheisis 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 (Vijesh et al., 2013).



40

3. 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.

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