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Review

Thiazole and thiadiazole: A promising moeity for antimicrobial activity

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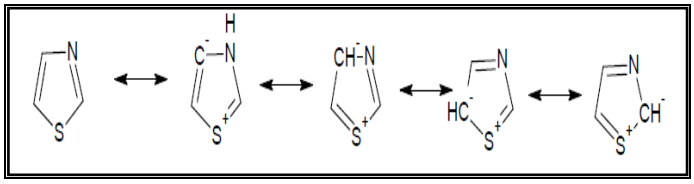
Heterocyclic compounds have a special place in pharmaceutical field. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs. A wide range of thiazole and thiadiazole heterocyclic ring system has been studied for the development of novel chemical entities as a lead molecule in the drug discovery paradigm and these moieties can be found in a large number of compounds which display biological activity. The biological activity of the compounds is mainly dependent on their molecular structures and these both of nucleus are well known antimicrobial agents. Since the beginning of the search of medicinally important synthetic compounds heterocyclic chemistry always remained the point of attraction because of their diverse biological properties. Substitution of heterocyclic compounds on various positions produced medicinally important analogues which are used in the treatment of various diseases.

Key words: Thiazole, thiadiazole, antimicrobial, heterocyclic.

Thiazole or 1,3 Thiazole is a heterocyclic compound that contains both sulfur and nitrogen. It also refers to as a large family of derivatives. Modification of thiazole ring have proven highly effective with improved potency and lesser toxicity. Thiazole is aromatic, heterocyclic organic compound that have five membered molecular ring structures C_3H_3NS. Thiazole was first described by Hantzch and Weber in 1887 and confirmed its structure in 1889. The numbering of thiazole starts from sulphur atom. Numerous reports have appeared in the literature which highlights their chemistry and pharmacological uses. They have greater aromaticity which is evidenced by the chemical shift of the ring protons in proton NMR spectroscopy indicating strong diamagnetic current. In the continuation of our drug research program, the present work is aimed towards the construction of novel heterocyclic compounds of anticipated utility as anticancer agents (Siddiqui et al, 2011; Yadav et al, 2011; Gupta et al, 2013). Thiazole is aromatic on the basis of delocalization of a lone pair of electrons from the sulfur atom completing the need of 6 π electrons to satisfy Huckel's rule. The resonance forms are:



Thiazole and their derivatives have attracted continuing interest over the years because of their varied biological

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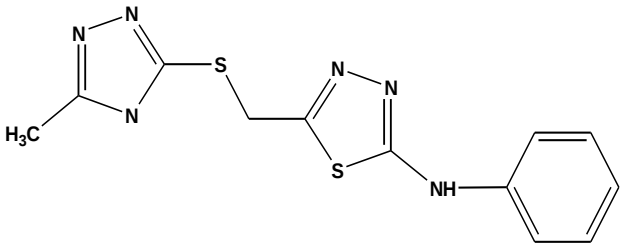
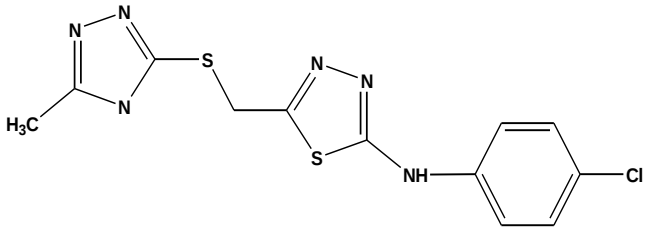
activities. Thiazole derivatives as potential drugs were taken into account in the beginning of 20th century. They are easily metabolized by routine biochemical reactions, are non-carcinogenic in nature. Some recent studies have shown the synthesis of some new thiazoles candidates used as antimicrobial and anticancer agent. Thiazole are basic class of heterocyclic moieties which possess a wide range of therapeutic interest and their importance is also very much established in medicine (Barry et al, 1976; Chawla et al, 2014Sarayanam et al, 2011; Samadhiya et al, 2011).

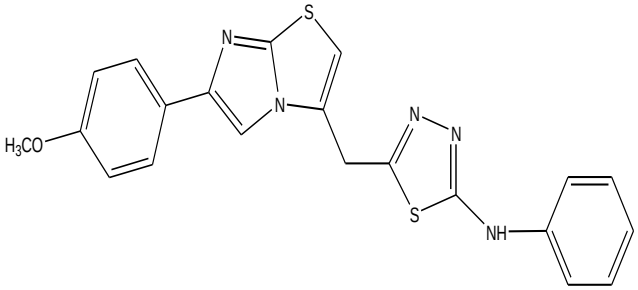
It was thought of interest to accommodate thiazole moieties in a single molecular frame work to synthesize some new heterocyclic compounds with potential biological activity. Heterocyclic rings containing nitrogen, sulfur and oxygen have been under investigation for a long time because of their important medicinal properties and also contributed to the society from biological and industrial point which helps to understand life processes. Thiazole derivatives are considered as one of the most important classes of heterocyclic compounds. Their derivatives are characterized by high biological activity in pharmaceutical fields and have shown antibacterial activity (Vasu et al, 2013; Adki et al, 2012; Patel et al, 2013).

The synthesis, spectral analysis and antimicrobial evaluation of a novel series of substituted 1,2,4- triazole and 1,3,4-thiadiazole derivatives was carried cyclization reaction of acyl thiosemicarbazide derivatives in the presence of alkaline and acidic media results in synthesis of new compounds screening of all synthesized compounds was done for their *in vitro* antimicrobial activities. The potential activity of the following compounds against Gram-positive bacteria and showed good activity especially against: *Micrococcus luteus, Bacillus subtilis* and *Staphylococcus aureus* (Popiolek *et al* 2013).

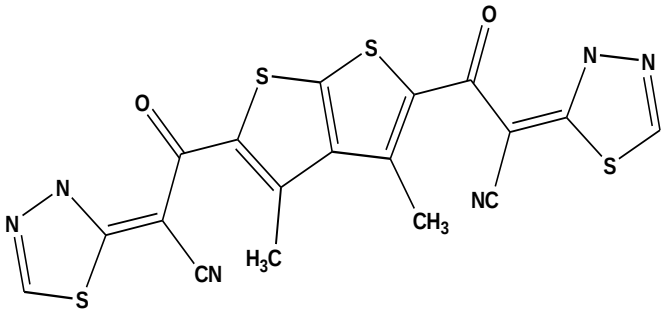




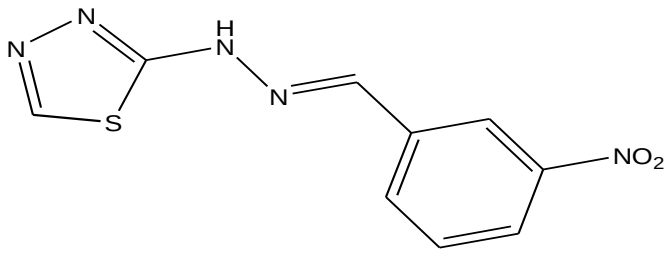
In this work, three new compound series obtained from 6-(phenyl/4-chlorophenyl) imidazo[2,1]thiazole-3-acetic acid hydrazide: 2-{[6-(phenyl/4-chlorophenyl)imidazo[2,1]thiazol-3-yl]acetyl}-N-alkyl/arylhydrazinecarbothioamides, 4-alkyl/aryl-2,4-dihydro-5-{[6-(phenyl/4-chlorophenyl)imidazo[2,1]thiazol-3-yl]methyl}-3*H*-1,2,4-triazole-3- thiones and 2-arylamino-5-{[6-(phenyl/4-chlorophenyl)imidazo[2,1]thiazol-3-yl]methyl}-1,3,4-thiadiazoles were synthesized and evaluated as antibacterial and antifungal activity. Characterization of the newly synthesized compounds was done by IR, ^{1}H NMR, ^{13}C NMR, MASS and elemental analysis. Evaluation of their antibacterial and antifungal activities was done against *Staphylococcus aureus, Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans*, *C. parapsilosis*, *C. krusei*, *Trichophyton mentagrophytes var. erinacei*, *Microsporum gypseum* and *T. tonsurans* (Guzeldemirci *et al* 2013).



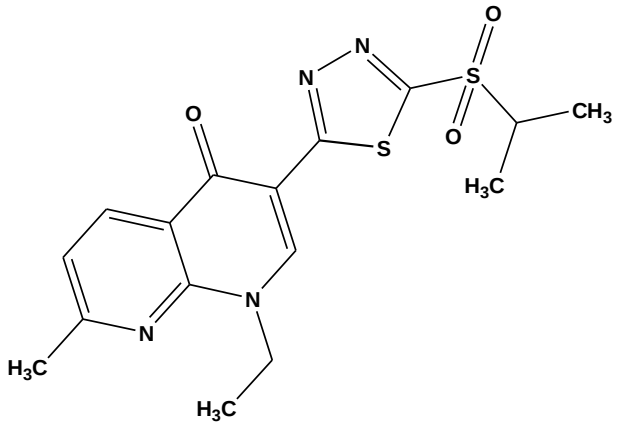
3,3'-(3,4-dimethylthieno[2,3-*b*]thiophene-2,5-diyl)bis (3-oxopropanenitrile) was used as synthetic utility for the synthesis of some novel bis-[1,3,4-thiadiazole] and bis-thiazole and derivatives with thieno[2,3]thiophene moiety is reported. Antimicrobial evaluation of some selected examples of some synthesized products was done and showed promising results.(Kheder *et al* 2012).



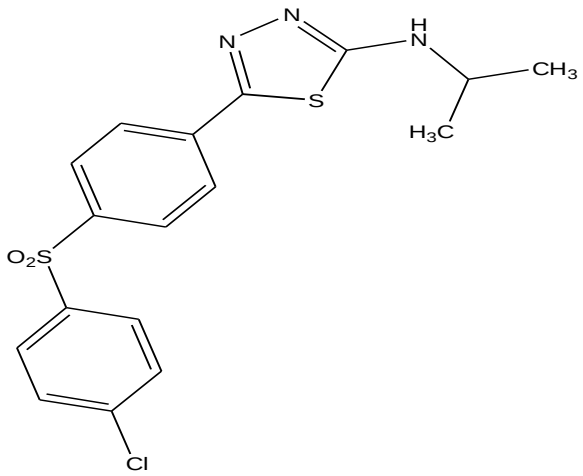
By considering the structural features of a group of known potent inhibitors of human platelet aggregation containing hydrazone structural backbone, synthesis of a series of new hydrazone derivatives of 2-hydrazinyl-1,3,4- thiadiazole was done using one-pot process and testing is done for their inhibitory activity against platelet aggregation induced by arachidonic acid and ADP. Highest antiplatelet aggregation activity among the derivatives was exhibited by the following compound . Screening of the derivatives was done for their potential antimycobacterial activity and compounds were found to be the most active compounds (Tehrani *et al* 2013).



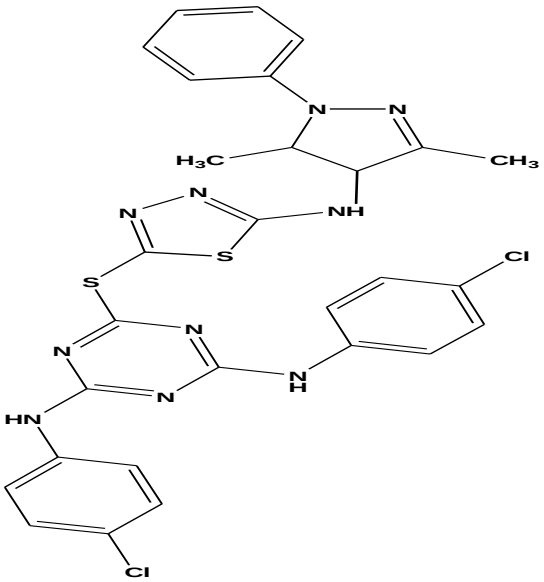
Sysnthesis and characterization of novel nalidixic acid-based 1,3,4-thia(oxa) diazoles, their thio ethers, sulfones, bis mercapto, and mannich bases was done by infrared spectra, ^{1}H NMR, ^{13}CNMR, and elemental analysis. Evalaution of these compounds was done for their antibacterial activity against two Gram-positive and three Gram-negative bacteria. The most of the compounds had better antibacterial activity than the parent compounds, 1,3,4-thia(oxa)diazoles was shown by preliminary bioassay. Maximum antibacterial activity exihibited by Four Mannich bases of nalidixic acid-based 1,3, 4-thiadiazole against *Bacillus subtilis, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* with minimum inhibitory concentration (Aggarwal *et al* 2012).



Cyclization of new N-[4-(4-X-phenylsulfonyl)benzoyl]-N-4-thiosemicarbazides forms some new 5-(4-(4-X-phenylsulfonyl)phenyl)-4-2H-1,2,4-triazol-3-thiones and 5-(4-(4-X-phenylsulfonyl)phenyl)-N-(R)-1,3,4-thiadiazol-2-amines. Intramolecular cyclization of acylthiosemicarbazides synthesize1,2,4- triazoles, in basic media. On contrast, 1,3,4-thiadiazoles were also obtained from same acylthiosemicarbazides, in acidic media. These novel intermediates from thiosemicarbazide class were obtained by the reaction of 4-(4-X-phenylsulfonyl) benzoic acids hydrazides (X, H, Br) 1a,b with 4-trifluoromethoxyphenyl or 3,4,5-trimethoxyphenyl isothiocyanate. The caharterization of newly synthesized compounds was done by IR, 1H NMR, 13C NMR, MS and elemental analysis. Screening of all the new compounds was done for their antimicrobial activity against some bacteria (*Staphylococcus aureus, Bacillus cereus, Escherichia coli, Enterobacter cloacae, Acinetobacter baumannii and Pseudomonas aeruginosa* and yeasts (*Candida albicans and Candida parapsilosis*) (Barbuceanu *et al* 2012).

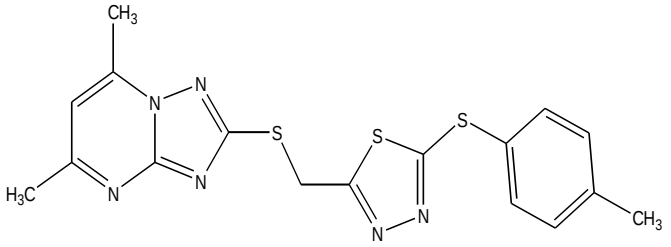


Synthesis and Characterization of some hybrid 1,3,4-thiadiazole-1,3,5-triazine derivatives tethered via –S– bridge was done with the aid of spectroscopic and elemental analysis. The investigation of these hybrid conjugates was done for their antibacterial activity against selected Gram-positive and Gram negative bacteria. Terget compounds presented Excellent to moderate antibacterial activity (Dubey *et al* 2012).

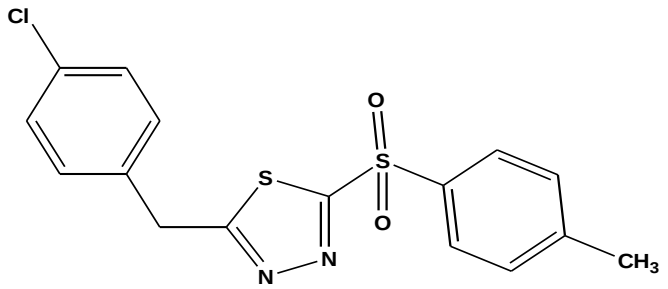


Synthesis of a series of new 1,3,4-thiadiazole derivatives bearing 1,2,4-triazolo pyrimidine moiety was done by the method of splicing active substructures. The following compound was firstly reported among all these compounds. Assay of all the compounds was performed for antimicrobial activities against five fungi strains and four bacteria strains. Good antifungal activities were indicated

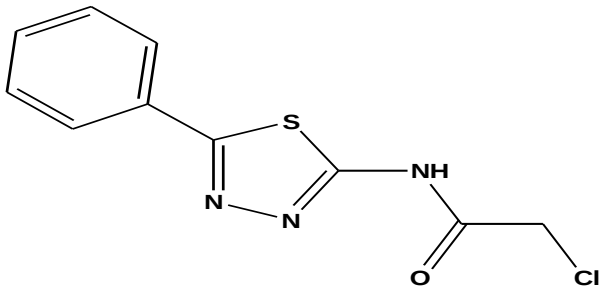
by the preliminary results that compounds showed against *Physaclospora piricola and Rhizoctonia solani*. Good antifungal activity was exhibited by compound against *Cercospora beticola*. Antibacterial activities were shown by most of the compounds against Gram-negative bacteria strains than Gram-positive bacteria strains. Best activities showed by compounds against *Pseudomonas fluorescence* while compounds showed good activities against *Escherichia coli* (Luo *et al* 2013).



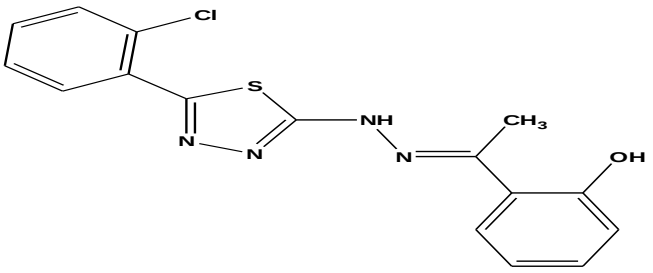
Synthesis of a series of 2,5-substituted-1,3,4-oxadiazole/thiadiazole sulfone derivatives was done and evaluation was done for their antibacterial activities against rice bacterial leaf blight and leaf streak caused by *Xanthomonas oryzae pv. oryzae and Xanthomonas oryzae pv. oryzicolaby* via the turbidimeter test in vitro. The most compounds demonstrated good inhibitory effect antibacterial bioactivities indicated by Antibacterial bioassay results against rice bacterial leaf blight and leaf streak. Among the title compounds, the best inhibitory effect was demonstrated by these compounds against rice bacterial leaf blight and leaf streak with half-maximal effective MIC, it was found to be better than those of commercial agents such as bismerthiazol and thiediazole copper. In vivo ,the controlling effect demonstrated by antibacterial activities tests at greenhouse conditions of the following compound against rice bacterial leaf blight were better than those of bismerthiazole and thiediazole Copper. (Li *et al* 2014)



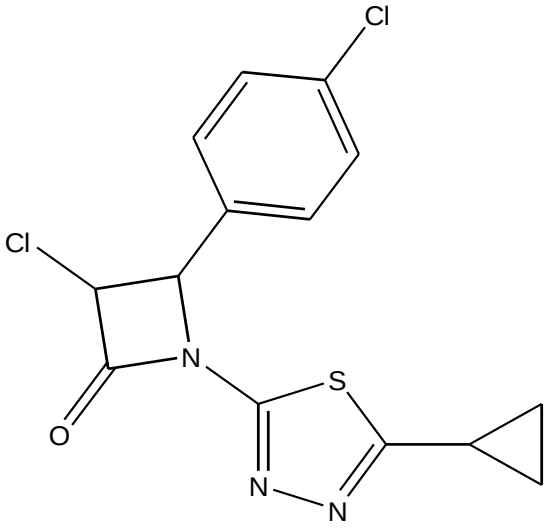
Synthesis of groups of new water soluble chitosan derivatives containing 1,3,4-thiadiazole group were done including 1,3,4-thiadiazole (TPCTS), 2-methyl-1,3,4-thiadiazole (MTPCTS), and 2-phenyl-1,3,4-thiadiazole (PTPCTS).Measurement of their antifungal activity against three kinds of phytopathogens was estimated in vitro, and the synthesized chitosan derivatives have excellent activity against tested fungi showed by fungicidal assessment. All the synthesized chitosan derivatives, the growth of the tested phytopathogens were inhibited most effectively by MTPCTS with inhibitory indices against *Colletotrichum lagenarium.* These indices are higher than those of chitosan. These data also demonstrate the effect to antifungal activity of chitosan derivatives by the hydrophobic moiety (alkyl and phenyl) and the length of alkyl substituent in thiadiazole . It is hypothesized that obviously better antifungal activity and good solubility in water was possessed by thiadiazole groups enable the synthesized chitosan. (Li *et al* 2013).



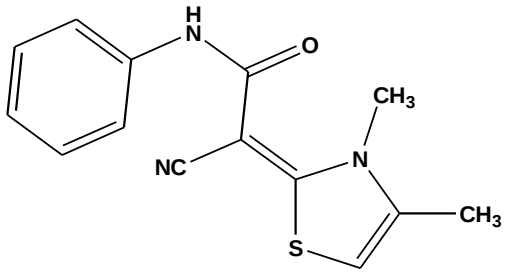
Synthesis of Zn (II) complexes have been done by reacting zinc acetate with schiff bases derived from 2-hydrazino-5-[substituted phenyl]-1,3,4-thiadiazole and 2-hydroxyacetophenone/benzaldehyde/indoline-2, 3-dione. These complexes are soluble in both DMF and DMSO; low molar conductance values show that they are non electrolytes. Elemental analyses suggest that the complexes have 1:2 metal to ligands stoichiometry of the types [ZnL2(H2O)2] (L = monoanionic Schiff bases derived from 2-hydrazino-5-[substituted phenyl]-1,3,4-thiadiazole and 2-hydroxyacetophenone/indoline-2,3-dione) [ZnL0 2(OOCCH3)2(H2O)2] (L0 = neutral Schiff bases derived from 2-hydrazino-5-[substituted phenyl]-1,3,4-thiadiazole and benzaldehyde), and their characterization have been done by IR, 1H NMR, and 13C NMR.Synthesized compound must be tested for Particle sizes which can be measured with dynamic light scattering (DLS) analyser which indicates that particle diameter are of the range 100–200 nm.Screening of all these Schiff bases and their complexes have also been done for their antibacterial (Bacillus *subtilis (B. subtilis), Escherichia coli (E. coli*) and antifungal activities (*Colletotrichum falcatum (C. falcatum), Aspergillus niger (A. niger), Fusarium oxysporium (F. oxysporium) Curvularia pallescence (C. pallescence*). The antimicrobial activities have shown that activity increases upon complexation (Singh *et al* 2013).



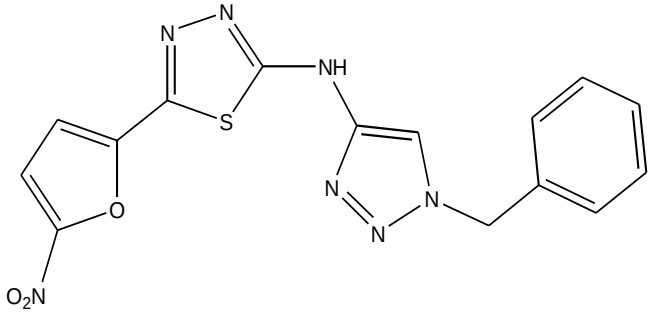
In an attempt to obtain a novel class of antimicrobial agents, synthesis of a series of novel azetidin-2-ones and thiazolidin-4-ones of 2-amino-5-cyclopropyl-1,3,4-thiadiazole was done. Confirmation of the synthesized compounds was done by melting point, IR, 1H NMR, 13C NMR, and mass spectroscopy. The most potnt compound were found to be the b-lactam derivative of the series displaying excellent antibacterial activities against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Pseudomonas aeruginosa* with MIC values of 15.60, 31.50, 62.50, and 125mg/mL, respectively, as compared to the positive control drug ampicillin.Confirmation that the compound inhibit cell wall synthesis by inhibiting PTB (transpeptidase enzyme)as done by Molecular docking studies and determination of the leakage of UV260- and UV280-absorbing material (nucleic acid material and protein). Indication their potential as drug like molecules was given by Lipinski's rule and in silico ADME pharmacokinetic parameters are within the acceptable range defined for human use (Patel *et al* 2014).



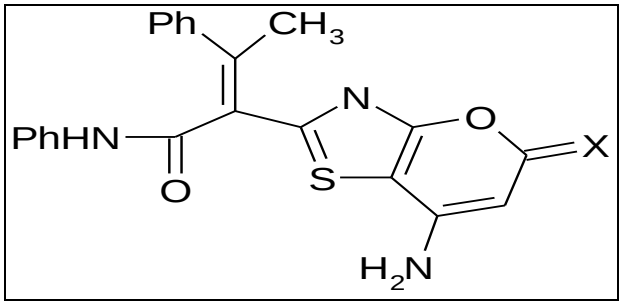
A serious threat to modern medicine is Microbial resistance to the available drugs. The design, synthesis and in vitro antimicrobial evaluation of new functionalized 2,3-dihydrothiazoles and 4-thiazolidinones tagged with sulfisoxazole moiety have been reported. Following Compound was most active against *Bacillis subtilis*. Moreover, significant activity was displayed by these compounds *B. subtilis and Streptococcus pneumonia* versus ampicillin respectively). Compounds were highly potent against *Escherichia coli* versus gentamycin. On the other hand, compounds were found to be four folds more active than amphotericin B against *Syncephalastrum racemosum*. Molecular docking studies revealed that the dihydropteroate synthase (DHPS) enzyme could be the target for inhibition for the synthesized compound. This study is a root for the future design and development of more potent antimicrobial agents (Nasr *et al* 2015).



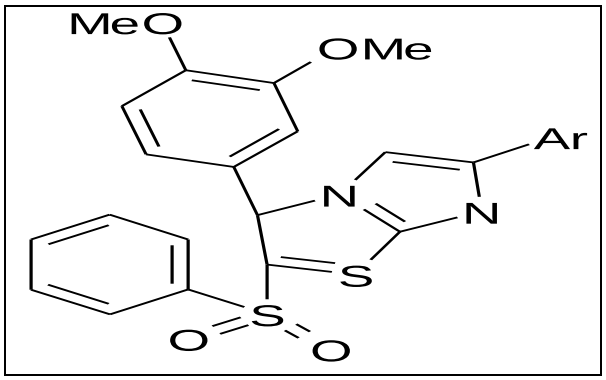
Synthesis of a novel series of 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-amines was done by introducing N-[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl] moiety as a new functionality on the C-2 amine of thiadiazole ring via click chemistry. The title compounds namely, N-[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]-5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-amines were characterized by IR, NMR and MS spectra. In vitro, anti-leishmanial activity of these compounds was against *promostigote* form of the *Leishmania* major.good antileshmanial activity was exhibited by most compounds against the *promastigote* form of L. major. The most active compound found against promostigotes was found to be 4-methylbenzyl analog, which significantly reduces the number of intracellular amastigotes per macrophage, percentage of macrophage infectivity and infectivity index (Tahghighi *et al* 2012).



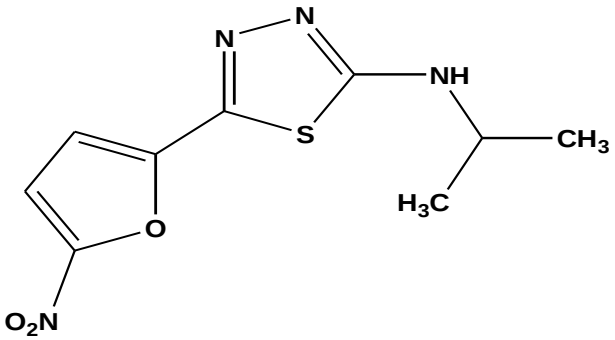
Some compounds were tested *in vitro* for antimicrobial activity against two bacterial isolates, one saprophytic (*Escherichia coli*) and the other parasitic (*Xanthomonas citri*). As can be seen from the results, most of the synthesized compounds showed antibacterial activities. Compounds were highly active against *Escherichia coli* and *Xanthomonas citri*.



Kakrani and Kalyani *et al.* used standard methods for evaluating anthelmintic activity. Earth worms (*Pheritima postuma*) of same size are used for anthemintic activity.and compound showed potent anthelmintic activitiy.



Synthesis and evaluation of a new series of 5-(5-nitrofuran-2-yl)-and 5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazole-2-amines bearing acyclic amine at C-2 position of thiadiazole ring were done *in vitro* against *promastigote* and *amastigote* forms of *Leishmania major*. The investigation of structure-activity of series was done by studying 40 compounds. Hydroxypropylamino- and methoxypropylamino- analogs of 5-(5-nitrothiophen-2-yl)-1,3,4- thiadiazole with highest selectivity index were found to be most active (Tahghighi *et al* 2013).



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