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A valuable insight into recent advances on antimicrobial activity of piperazine derivatives

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ABSTRACT

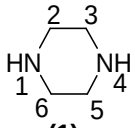
The worldwide problem of microbial resistance has drawn utmost attention for medicinal chemists because of failure of currently available antimicrobial therapy against microbial infections. Therefore, there is an urgent need to develop novel antimicrobial agents with different mode of actions. In the search of better antimicrobial agents, different heterocyclic compounds have been explored and out of them piperazine derivatives have shown a broad spectrum of pharmacological activities like antibacterial, antifungal, antitubercular, anticancer, antiviral, antioxidant activities etc. This communication is focused on to review antimicrobial activities of different piperazine derivatives in detail and the valuable information provided in this manuscript may help in the drug design and development of better antimicrobial agents.

Keywords: Piperazine, antibacterial, antifungal, antitubercular activity.

INTRODUCTION

Treatment of microbial infections including bacterial, fungal, and tubercular is becoming difficult because of everlasting problem of microbial resistance towards antibiotics hence the need for new generations of anti-infective agents, and in particular new antimicrobial agents, is constant for effective treatment of microbial infections [1]. Medicinal chemists have been highly successful in the recent years in reshaping the scaffolds of earlier antibiotics, both natural and synthetic in which heterocyclic nucleus constitutes a part of pharmacophore which is essential for a particular pharmacological activity [2, 3].

A heterocyclic compound is a cyclic compound that has hetero atoms such as N, O and S as members of its ring(s) having medicinal importance [4], Piperazine **(1)** is such a medicinally important heterocyclic nucleus which consists of a six-membered ring containing two nitrogen atoms at opposite positions in the ring. The piperazine nucleus has been classified as a privileged structure and is frequently found in biologically active compounds across a number of different therapeutic areas [5]. Some of these therapeutic areas include antimicrobial, anti-tubercular, antipsychotic, anticonvulsant, antidepressant, anti-inflammatory, cytotoxic, antimalarial, antiarrhythmic, antioxidant and antiviral activities etc. possessed by the compounds having piperazine nucleus [6, 7].

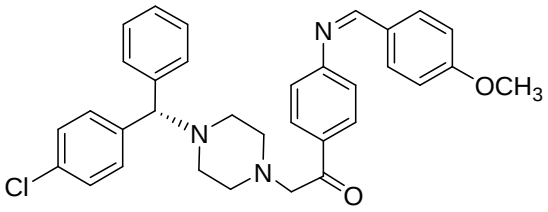


(1)

Antimicrobial Activities

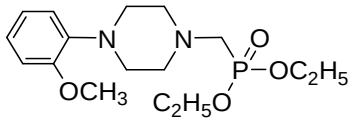
Piperazine derivatives are a broad class of chemical compounds, many with important pharmacological properties, which contain a core piperazine heterocyclic nucleus. A slight change in the substitution pattern in the piperazine nucleus causes distinguishable difference in their pharmacological activities. Literature survey of the recent studies done on piperazine derivatives indicates that they have antimicrobial activities like anti-bacterial and antifungal activities which have been summarized as given below:

Patil *et al*. synthesized a novel series of substituted phenyl acetamide piperazine derivatives **(2)**. The antimicrobial activities for all the synthesized compounds were evaluated against Gram-positive bacteria *(Styphylococcus aureus, Sterptococcus pyrogenes)* and Gram-negative bacteria *(Escherichia coli, Pseudomonas aeruginosa).* The antibacterial activity was evaluated using Ciprofloxacin as a standard drug. The antifungal activity was studied against *Candida albicans* and *Aspergillus niger*. One compound showed good antifungal activity against *Aspergillus niger* when compared with standard drug Greseofulvin [8].



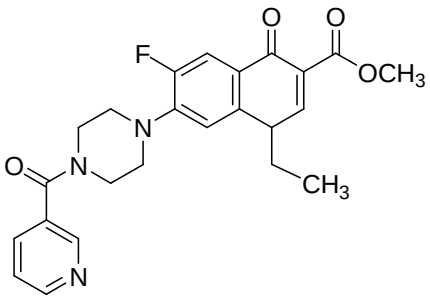
(2)

A series of substituted piperazine derivatives **(3)** were synthesized by Chaudhary *et al.* and tested for antimicrobial activity. The antibacterial activity was tested against *Staphylococcus aureus, Pseudomonas aeruginosa, Streptomyces epidermidis* and *Escherichia coli* whereas antifungal activity against *Aspergillus fumigatus, Aspergillus flavus* and *Aspergillus niger*. All synthesized compounds showed significant activity against bacterial strains by using Gentamycin as standard drug but were found to be less active against tested fungi [9].



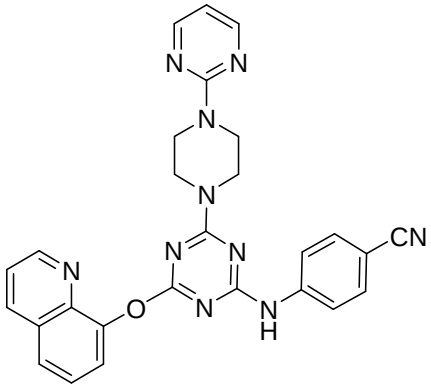
(3)

Sharma *et al.* synthesized a series of *N*-nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxylates **(4)**. All the synthesized compounds were evaluated for antibacterial activity against four different stains of bacteria. Some compounds exhibited moderate to significant minimum inhibitory concentration (MIC) values when compared with standard drug [10].



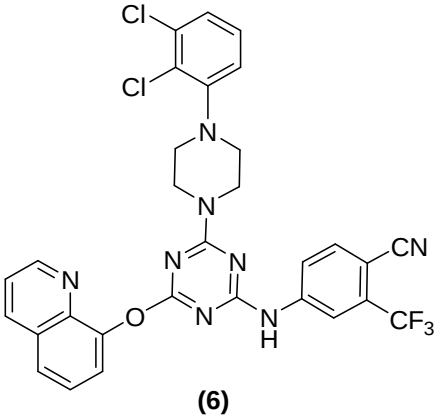
(4)

A novel series of [1,3,5]triazinyl piperazine analogues **(5)** was synthesized by Patel *et al*. and evaluated for their *in-vitro* antibacterial activity against two Gram-positive (*S. aerues, B. subtilis*), two Gram-negative *(E. coli, P. aeruginosa)* and for antifungal activity against two fungal species (*C. albicans* and *A. niger*) by making use of Ciprofloxacin and Griseofulvin as their respective standard drugs. Most of the synthesized compounds showed promising antimicrobial activity [11].



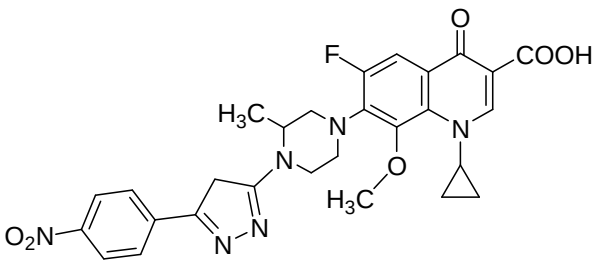
(5)

A novel series of 2-(4-cyano-3-trifluoromethylphenyl amino)-4-(quinoline-4-yloxy)-6-(piperazinyl/piperidinyl)-S-triazines **(6)** were synthesized by Patel *et al*. Preliminary screening of test compounds against eight bacteria *(Staphylococcus aureus, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella typhi, Proteus vulgaris, Shigella flexneria)*, four fungi *(Aspergillus niger, Aspergillus fumigatus, Aspergillus clavatus, Candida albicans)* and *Mycobacterium tuberculosis* indicated that among twenty one studied compounds, few were the most active. Ciprofloxacin and Pyrazinamide were used as standard drugs [12].



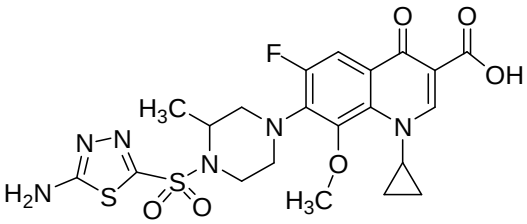
(6)

Kumar *et al*. synthesized a series of 7-[4-(5-aryl-1,3,4-oxadiazole-2-yl) piperazinyl] quinolones **(7)**. The antibacterial activities of all the synthesized compounds were evaluated against identifiable bacterial strains using Ciprofloxacin as standard drug showing inhibition of growth of microbes. Some compounds showed better activity than the parent compound against all the selected stains [13].



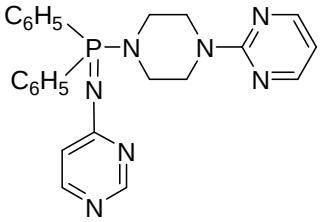
(7)

Talah *et al*. synthesized a series of 7-[4-(5-amino-1,3,4 thiadiazole-2-sulfonyl)]-1-piperazinyl fluoroquinolonic derivatives **(8)** and evaluated for their preliminary *in-vitro* antibacterial activity against some Gram-positive and Gram-negative bacteria and selected compounds were screened for antitubercular activity against *Mycobacterium tuberculosis* stain by broth dilution assay method. The antibacterial data of the tested compounds indicated that all the synthesized compounds showed better activity against Gram-positive bacteria *S. aureus, E. faecelis, Bacillus sp*. having MIC values in range of 1-5 µg/ml respectively when compared to their respective standard drugs. The MIC values of tested derivatives denoted that Sparfloxacin and Gatifloxacin derivatives were most active against the tested Gram-positive bacterial strains (MIC = 1-5 µg/ml). All the tested compounds showed poor activity against the Gram-negative bacteria. The *in-vitro* antitubercular activity reports of selected compounds against *Mycobacterium tuberculosis* strain showed moderate activity at MIC of 10 µg/ml when compared with standard drug [14].



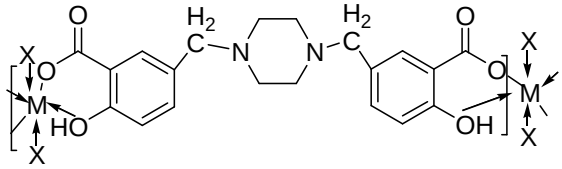
(8)

Chinnam *et al*. synthesized a series of novel iminophosphorane derivatives of piperazine **(9)** accomplished through Staudinger reaction with high yields (70-80%). The chemical structures of synthesized compounds were established by IR, ^{1}H, ^{13}C, ^{31}P-NMR, mass spectral studies and elemental analysis. All the titled compounds showed promising anti-microbial activity by using Streptomycin as a standard drug [15].



(9)

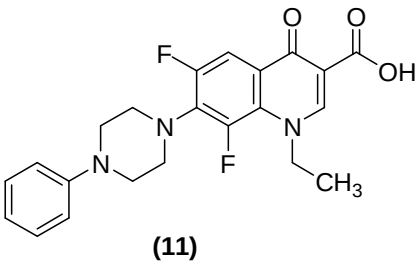
A novel tetradentate salicylic acid–formaldehyde ligand containing piperazine **(10)** moiety was synthesized by Khan *et al*. The antimicrobial screening of the ligand and coordination polymers was done by using Agar well diffusion method against various bacteria and fungi. It was evident from the data that antibacterial and antifungal activity increased on chelation and all the polymer metal complexes showed excellent antimicrobial activity than their parent ligand [16].



M= Mn(II), Co(II), Cu(II); X= H_2O

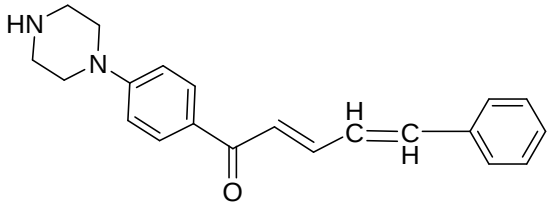
(10)

A series of 1-ethyl-6,8-difluoro-4-oxo-7(4-arylpiperazin-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid derivatives **(11)** were synthesized by Srinivasan *et al.* and evaluated for antibacterial activity by using Ciprofloxacin and Norfloxacin as standard drugs. The antimicrobial activities of the compounds were assessed by the micro broth dilution technique. The compounds were also evaluated for antifungal activity against *Candida albicans* and *Cryptococcous neoformans* pathogens. The preliminary *in-vitro* evaluation studies revealed that some of the compounds had promising antimicrobial activities [17].



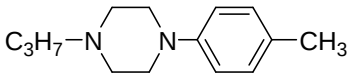
(11)

Two new series of chalcones containing piperazine moiety **(12)** were synthesized by Tomar *et al*. All the synthesized compounds were evaluated for antimicrobial activity. Some of these derivatives were found to be potentially active against *Staphylococcus aureus* and *Escherichia coli*. One compound was found to be most potent compound having MIC value of 2.22 µg/mL against *Candida albicans*. The MIC value was comparable to that of Ciprofloxacin, Amoxicillin and Fluconazole as respective standard drugs [18].



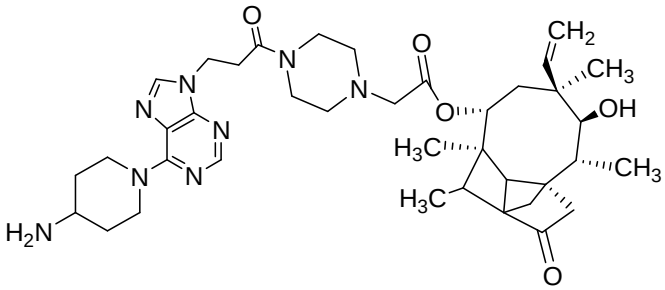
(12)

Jain *et al*. synthesized some 4-substituted-1-(4-substituted phenyl)-piperazine **(13)** derivatives. The synthesized compounds were studied for antibacterial activity using Ampicillin as standard drug against four strains like *S aureus, S. epidermidis, P. aeruginosa* and *E. coli*. One compound showed excellent antibacterial activity when compared with standard drug [19].



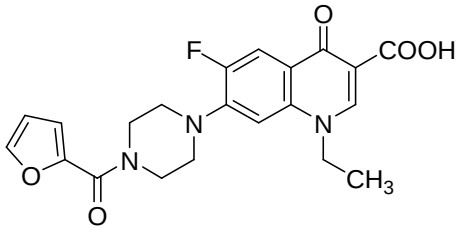
(13)

Hirokawa *et al*. studied SAR on the water-soluble thioether pleuromutilin analogue, which has excellent *in-vitro* and *in-vivo* antibacterial activities, led to discovery of the novel pleuromutilin derivatives having a piperazine ring spacer **(14)**. These derivatives displayed potent and well-balanced *in-vitro* antibacterial activity against various drug-susceptible and resistant Gram-positive bacteria. The pleuromutilin analogues were found to exhibit strong *in-vivo* efficacy against *Staphylococcus aureus* [20].



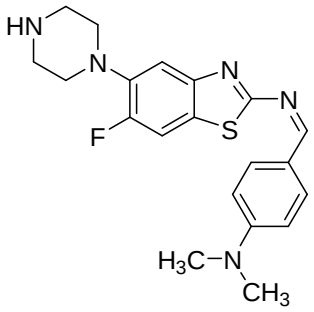
(14)

A series of 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)quinoline-3-carboxylic acid (Norfloxacin) **(15)** derivatives were prepared by Yu *et al*. according to the principle of combinating bioactive substructures and tested for their activities against five plant pathogenic bacteria and three fungi *in vitro*. The activities of compounds against *Xanthomonas oryzae* were better than norfloxacin and some tested compounds were better in antibacterial activities as compared to the agricultural streptomycin sulfate against *X. oryzae, Xanthomonas axonopodis* and *Erwinia aroideae*. One compound displayed good antifungal activities against *Rhizoctonia solani* having 83% inhibition of fungal growth [21].



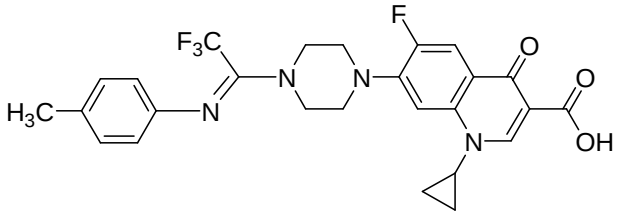
(15)

The synthesis of titled compound 2-N-[aryl-methylidene]-6-fluoro-5-piperazinyl[1,3]-2- amines **(16)** was carried out by Chaithanya *et al* and evaluated for antibacterial and antifungal activities. Some compounds showed significant antimicrobial activity when compared with respective standard drugs like Ofloxacin, Ampicillin and Fluconazole [22].



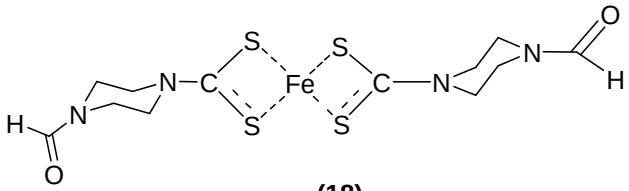
(16)

Some novel N-aryl-2,2,2-trifluoroacetimidoyl piperazinylquinolone derivatives **(17)** were synthesized by Darehkordi *et al*. Two selected compounds were evaluated for their antibacterial activities using the Ciprofloxacin and Vancomycin as standard drugs. These compounds displayed good antibacterial activities [23].



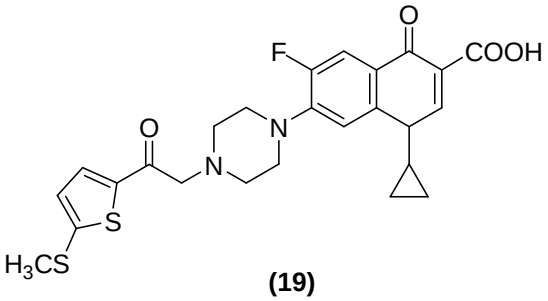
(17)

Mohammad *et al*. synthesized a series of 3d-transition metal complexes of 1-acetylpiperazinyldithioc arbamate **(18)**. The ligand and its 3d-transition metal complexes were tested for their antifungal activity by *agar well* diffusion method using *Fusarium* and *Sclerotina* species. One compound showed maximum activity when compared with standard drug [24].



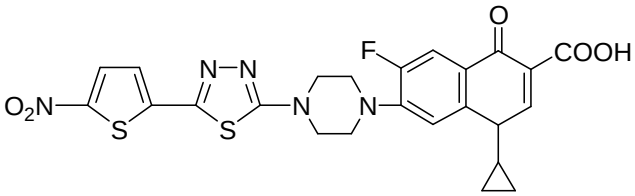
(18)

A number of N-substituted piperazinylquinolone derivatives **(19)** were synthesized by Foroumadi *et al*. and evaluated for antibacterial activity against Gram-positive and Gram-negative bacteria. It was showed in preliminary that most compounds tested in this study demonstrated comparable or better activity against *Staphylococcus aureus* and *Staphylococcus epidermidis* than their parent piperazinyl quinolones as standard drugs. Among these derivatives, Ciprofloxacin derivative showed significant improvement of potency against *Staphylococci*, maintaining Gram-negative bacteria coverage [25].



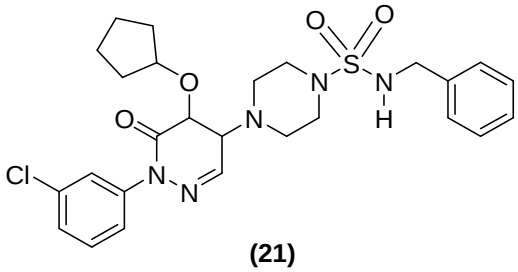
(19)

A series of N-[5-(5-nitro-2-thienyl)-1,3,4-thiadiazole-2-yl]piperazinyl quinolones **(20)** were synthesized by Foroumadi *et al*. and evaluated for *in-vitro* antibacterial activity against some Gram-positive and Gram-negative bacteria. The antibacterial data revealed that compounds had strong and better activity against tested Gram-positive organisms than quinolones based standard drugs such as Ciprofloxacin, Norfloxacin and Enoxacin. However, all the compounds were nearly inactive against Gram-negative bacteria. One compound was found to be most active compound against Gram-positive bacteria having MIC value of 15 µg/L [26].



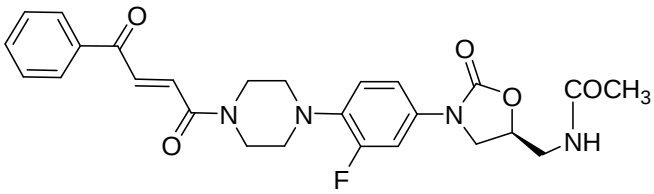
(20)

Zych *et al*. carried out SAR studies of a novel sulfonylurea series of piperazine pyridazine-based **(21)** small molecule as glucan synthase inhibitors. The optimization of pK profiles within the series led to the discovery of several compounds with improved pharmacokinetic profiles which demonstrated *in-vitro* potency against clinically relevant strains. However, the advancement of compounds from this series into a non-lethal systemic fungal infection model failed to show *in-vivo* efficacy when compared with standard drug [27].



(21)

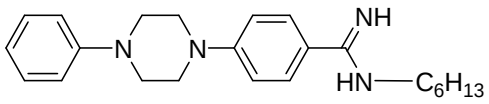
Some substituted piperazinyl phenyl oxazolidinone compounds **(22)** having substitution on the distant nitrogen atom of piperazine ring scaffold were synthesized by Lohray *et al*. and evaluated for their antibacterial activity in Gram-positive bacteria. Few compounds showed superior *in-vitro* antibacterial activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis* and *Streptococcus pyogenes* than standard drugs like Linezolid and Eperezolid [28].



(22)

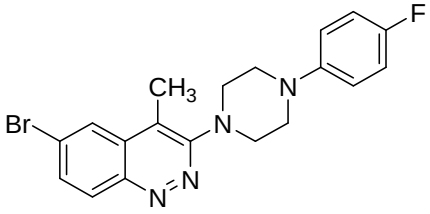
A small library of novel series of 1,4-diarylpiperazines and analogs **(23)** were screened by Forge *et al*. in a rapid luminometric *in-vitro* assay against the laboratory *Mycobacterium tuberculosis* stain. The most promising compounds were evaluated for activity against a multi-drug resistant clinical isolate. The group of amidines were also tested for their ability to kill intracellular *Mycobacterium tuberculosis* residing in mouse macrophages using

first line drug isoniazid as a standard drug. Finally, a correlation between the structural differences of the compounds and their anti-mycobacterial activity were reported [29].



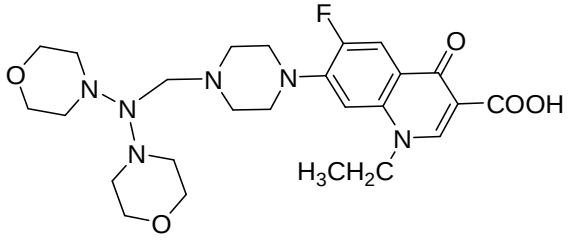
(23)

A new series of 6-substituted-4-methyl-3-(4-arylpiperazin-1-yl) cinnolines **(24)** were synthesized by Awad *et al*. and evaluated as potential antifungal agents when compared with standard antifungal drug [30].



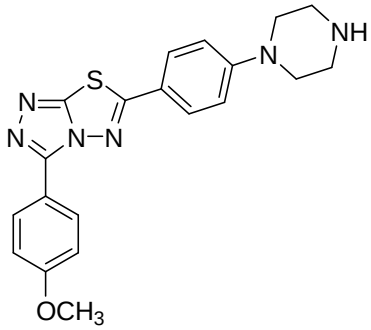
(24)

El-Din *et al*. reported the synthesis of some novel N-4-piperazinyl derivatives of norfloxacin **(25)**. The antibacterial activities of newly synthesized compounds were evaluated and correlated with their physicochemical properties. Results revealed that some of the tested compounds exhibited better inhibitory activities than standard drug Norfloxacin against *pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumonia* and *Staphylococcus aureus* stains. Correlation results showed that there is no single physicochemical parameter that can determine the effect of *N*-4 piperazinyl group on the activity of these fluoroquinolones, where lipophilicity, molecular mass and electronic factors may influence the antibacterial activity [31].



(25)

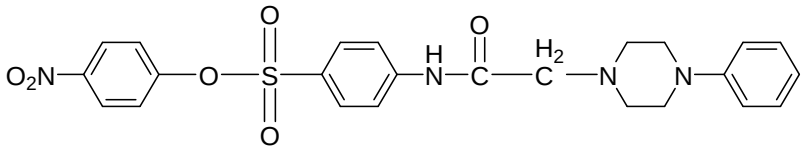
Hu *et al*. synthesized 6/3-(4-Chlorophenyl)-*s*-triazolo[3, 4-*b*][1, 3, 4]thiadiazoles containing piperazine **(26)** in good yields. The *in-vitro* biological results showed that piperazine group conjugated with the above fused heterocycles played an important role in antibacterial activity. *In-vitro* inhibitory activity of one compound was found to be comparable to that of standard drug Ciprofloxacin at the concentration of 0.1 mg/L [32].



(26)

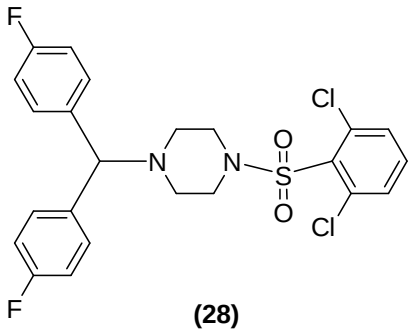
Novel *N*-substituted piperazine derivatives containing sulfonyloxy aniline moiety **(27)** were synthesized by Patel *et al*. Antibacterial activities of all the compounds were studied against Gram-positive bacteria *(Bacillus subtillis* and

Staphylococcus aureus) and Gram-negative bacteria *(E.coli* and *Salmonella typhi)* using Sulfanilamide as a standard for comparison [33].



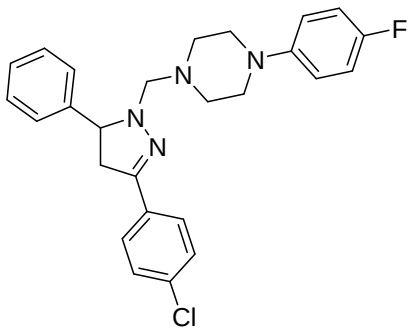
(27)

A series of novel substituted 1-[bis(4-fluorophenyl)-methyl]piperazine derivatives **(28)** were synthesized by Chandra *et al*. All the synthesized compounds were evaluated *in-vitro* for their efficacy as antimicrobial agents against representative strains of Gram-positive *(Staphylococcus aureus*, *Streptococcus pneumoniae*, *Bacillus cereus*, and *Bacillus subtilis*) and Gram-negative bacteria *(Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, and *Salmonella typhi*) by paper disc diffusion and microdilution methods. Among the newly synthesized compounds, one showed potent antimicrobial activities, when compared to the standard drug Streptomycin as standard drug [34].



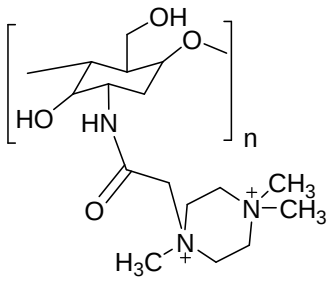
(28)

Ten new fluorine-containing 2-[4-(4-flourophenyl) piparazine-1-yl-methyl]-3,5-substituted phenylpyrazolines **(29)** were synthesized by Parmar *et al*. in yield 80-85%. The structures of synthesized compounds were confirmed by UV, IR, ^{1}H NMR and Mass spectral data. The compounds were evaluated for *in-vitro* antibacterial activity**.** Some compounds showed significant antibacterial activity when compared with standard drug [35].



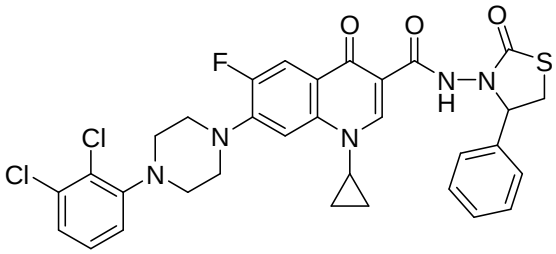
(29)

Well characterized methylpiperazine, mono-quaternary dimethylpiperazine and di-quaternary trimethylpiperazine derivatives of chitosan **(30)** with different degrees of substitutions were investigated by Masson *et al*. for antibacterial activity against different stains of Gram-positive and Gram-negative bacteria. The most active compound induced gradual decrease in the count of viable bacteria as compared to standard drug. It was found that di-quaternary trimethylpiperazine moiety was contributing most to antibacterial activity of the test compounds [36].



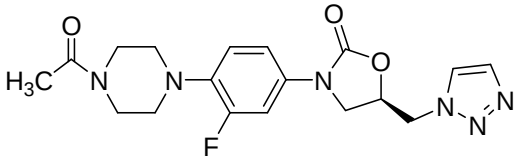
(30)

The title compounds, 2-substituted phenyl-3-{1-cyclopropyl-6-fluoro-7-[4-(2,3-dichloro phenylpiperazin- 1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-1,3-thiazolidin-4-ones **(31)** were synthesized by Patel *et al*. and tested for their antibacterial and antifungal activity *in-vitro* against microorganisms *viz. S. aureus*, *S. pyogenes*, *E. coli*, *P. aeruginosa*, *C. albicans*, *A. niger* and *A. clavatus* by taking Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin, Nystatin and Greseofulvin as their respective standard drugs [37].



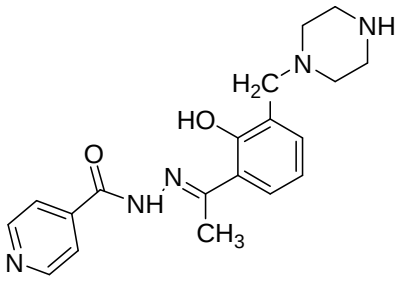
(31)

Phillips *et al*. synthesized a series of novel arylcarbonyl-piperazinyl-5-triazolylmethyl oxazolidinones **(32)** and tested against a panel of Gram-positive and Gram-negative bacterial clinical isolates. Some derivatives showed strong *in-vitro* antibacterial activity against susceptible and resistant Gram-positive pathogenic bacteria and were more active derivatives than others as compared with standard drug. SAR studies concluded that substitution varied on the phenyl ring in the arylcarbonyl series did not alter antibacterial activity significantly [38].



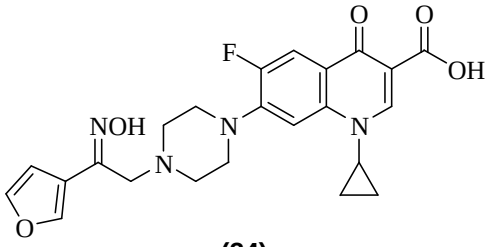
(32)

Sriram *et al*. synthesized some novel *N*-{1-[2-hydroxy-3-(piperazin-1-ylmethyl) phenyl] ethylidene} isonicotinohydrazide derivatives (**33)** which were evaluated against *M. tuberculosis* using the alamar blue susceptibility test. The synthesized compounds inhibited *Mycobacterium tuberculosis* stain with MIC values ranging from 0.56 to 4.61µM. One compound was found to be the most active compound with an MIC of 0.56µM, and was more potent than standard drug Isoniazid having MIC value of 2.04 µM [39].



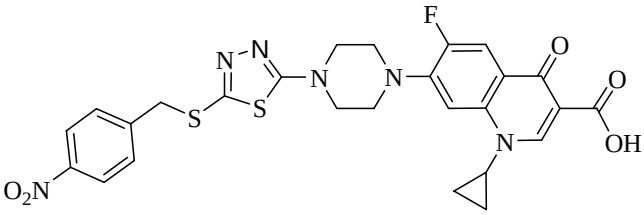
(33)

Foroumadi *et al*. prepared a novel array of 7-piperazinylquinolones carrying a functionalized 2-(furan-3-yl)ethyl moiety attached to the piperazine ring (**34)** and screened them for anti-bacterial activity against a panel of Gram-positive and Gram-negative bacteria. Most of the synthesized compounds displayed significant anti-bacterial activity and this activity can be modulated through the nature of the functionality on ethyl spacer attached to piperazine ring and the type of side chain present at the *N*-1 position of quinolone ring [40].



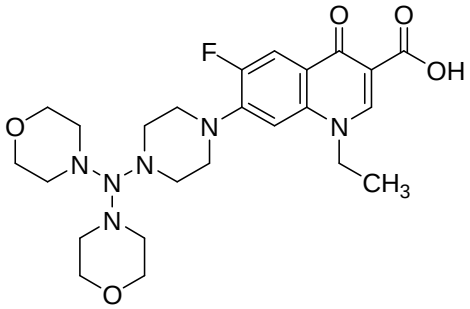
(34)

Foroumadi *et al*. synthesized a series of N-(5-benzylsulfonyl-1,3,4-thiadiazol-2-yl) derivatives of piperazinyl quinolones **(35)** and evaluated for antibacterial activity against Gram-positive and Gram-negative microorganisms. Most of the derivatives displayed high activity against Gram-positive bacteria; *Staphylococcus aureus* and *Staphylococcus epidermidis*. The major findings indicated that both the structure of the benzyl unit and the sulphur linker significantly improved anti-bacterial activity [41].



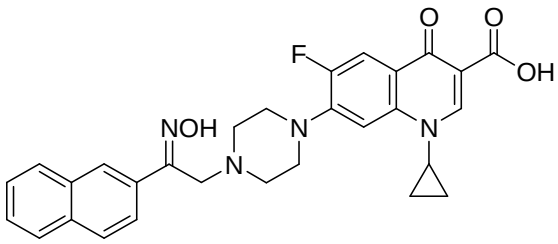
(35)

Abuo-Rahma *et al.* reported the synthesis of some novel *N*-4-piperazinyl derivatives of norfloxacin (**36)**. Some of the compounds exhibited better antibacterial activity than standard drug norfloxacin against *Pseudomonas aeruginosa*, *Esherichia coli*, *Klebsilla pneumonia* and *Staphylococcus aureus* stains [42].



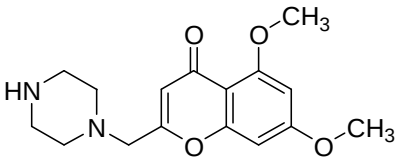
(36)

Shafiee *et al*. reported a series of *N*-[2-(2-naphthyl)ethyl]piperazinyl quinolones **(37)** containing acarbonyl related functional group (oxo- or oxyimino-) on the ethyl spacer and evaluated for antibacterial activity. Anti-bacterial data indicated that some compounds showed good antibacterial activity and modification of the position 8 and N-1 substituent on quinolone ring and ethyl spacer functionality produced significant improvement in antibacterial activity against Gram-positive and Gram-negative bacteria [43].



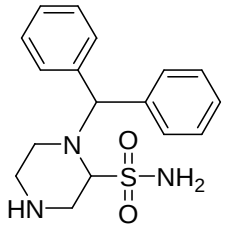
(37)

A series of novel 6-methoxy-2-(piperazin-1-yl)-4*H*-chromen-4-one **(38)** of biological interest were prepared by Hatnapure *et al*. and screened for their antibacterial and antifungal activities. Some compounds were found to be potent antibacterial and antifungal agents showing even 2 to 2.5-fold more potency than standard drugs Ciprofloxacin and Miconazole respectively [44].



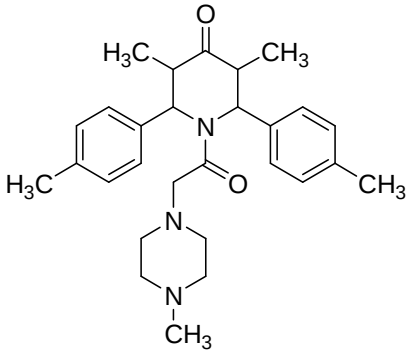
(38)

Kumar *et al*. synthesized a series of novel substituted 1-benzhydryl-piperazine sulfonamides **(39)** and evaluated their antimicrobial activities *in-vitro* by paper disc diffusion and micro dilution method against standard strains of Gram-positive *(Staphylococcus aureus, Staphylococcus epidermis, Bacillus cereus, Bacillus substilis)* and Gram-negative *(Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris* and *Salmonella typhi*) bacteria. Among the synthesized some new compounds showed potent antimicrobial activities compared to the standard drug Streptomycin [45].



(39)

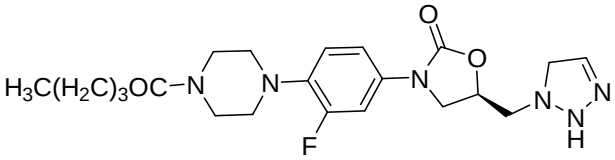
A series of N-(N-methylpiperazinoacetyl)-2,6-diarylpiperidin-4-ones **(40)** were synthesized by Aridoss *et al*. All the compounds were screened for their possible antibacterial and antifungal activities against a spectrum of microbial agents. Biological studies proved that some compounds against bacterial and others against fungal stains exhibited promising antimicrobial activities when compared with their respective standard drugs [46].



(40)

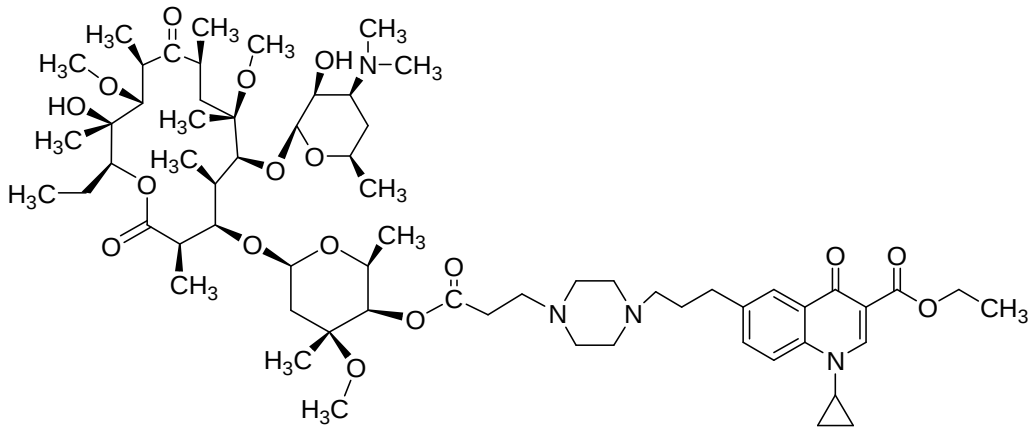
A series of new piperazinyl 5-triazolylmethyl oxazolidinones containing long chain acyl group at the piperazine N-4 position **(41)** were synthesized by Phillips *et al*. and evaluated against a panel of standard and clinical isolates of

Gram-positive and Gram-negative bacteria. Derivatives having long chain acyl groups with nine or more number of carbon atoms showed significant decrease in antibacterial activity. Antibacterial activity correlated positively with heat of formation of the compounds [47].



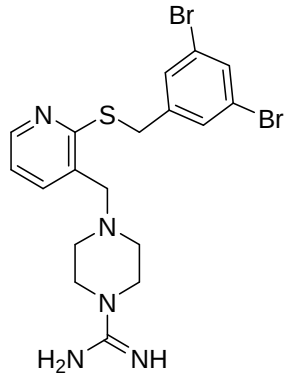
(41)

Some novel macrolones with central piperazine ring in the linker **(42)** were prepared by Kapic *et al*. The final macrolones were differ by macrolide moiety and substituents at the position N-1 of the quinolone attached *via* a linker. It was found in the study that linker flexibility seems to play an important role for potent antibacterial activity against macrolide resistant respiratory pathogens. This finding can be utilized further for the drug design and development of better antibacterial agents [48].



(42)

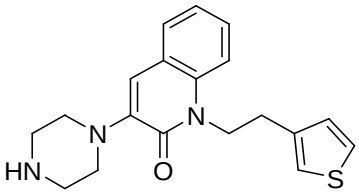
Francois *et al*. screened a library of 500 piperazine-1-carboxamidine derivatives **(43)** for antifungal activity *via* induction of endogenous reactive oxygen species accumulation. Structure-activity relationship studies showed that piperazine-1-carboxamidine analogues with large atoms or large side chains substituted on the phenyl group were characterized by a high reactive oxygen species accumulation capacity in *Candida albicans* and with high antifungal activity. Moreover this could link the fungicidal mode of action of the piperazine-1-carboxamidine derivatives to the accumulation of endogenous reactive oxygen species [49].



(43)

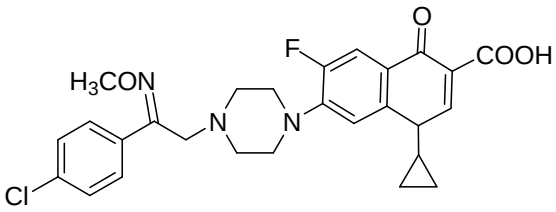
As a part of continuing search for potential antibacterial agents in the quinolones field, Letafat *et al*. synthesized novel quinolone agents bearing *N*-[2-(thiophen-3-yl)ethyl] piperazinyl moiety **(44)** in the 7-position of the quinolone ring. *In-vitro* antibacterial evaluation of the target compounds showed that N-[2-(thiophen-3-yl)ethyl] group attached to piperazine ring served as promising C-7 substituent for piperazinyl quinolone antibacterials. Among

these derivatives, ciprofloxacin analogues, few residues provided a high inhibition against all the tested Gram-positive organisms including methicillin-resistant *Staphylococcus aureus* superior with respect to the standard drugs Norfloxacin and Ciprofloxacin [50].



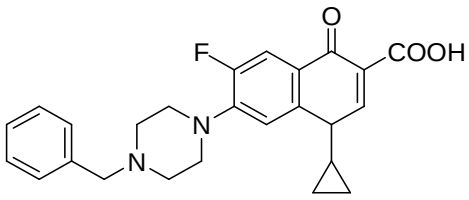
(44)

Foroumadi *et al***.** synthesized *N*-(Phenethyl) piperazinyl quinolone derivatives that bear a methoxyimino-substituent **(45)** and were evaluated for antimicrobial activity against Gram-positive and Gram-negative microorganisms. To define SAR, a few Ciprofloxacin derivatives containing 2-oxo-2-phenylethyl or 2-hydroxyimino-2-phenylethyl moieties at N-4 position of piperazine ring were prepared and tested. Ciprofloxacin derivatives, containing an *N*-(chloro-substituted phenylethyl) piperazine residue showed *in-vitro* Gram-positive and Gram-negative activity generally comparable to that of standard quinolone based drugs [51].



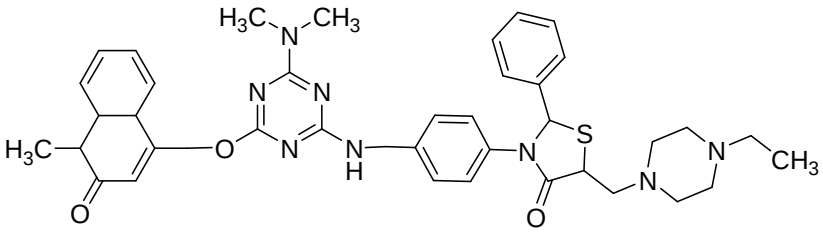
(45)

Wang *et al*. herein designed and synthesized a series of novel Ciprofloxacin derivatives with remarkable improvement in lipophilicity by introducing a substituted benzyl moiety to the N atom on the C-7 piperazine ring of Ciprofloxacin **(46)**. Antimycobacterial and antibacterial activity of the newly synthesized compounds was evaluated. Results revealed that compounds showed good *in-vitro* antibacterial activity against all of the tested Gram-positive stains including MRSA and MRSE with MIC value of 0.06-32 µg/mL which is two to eightfold more potent than the parent drug Ciprofloxacin having MIC value of 0.25-128µg/mL. Some compounds showed better antibacterial activity against Gram-negative bacteria *P. aeruginosa* and *M. tuberculosis* at MIC values of 0.5-4µg/mL and 1µg/mL respectively [52].



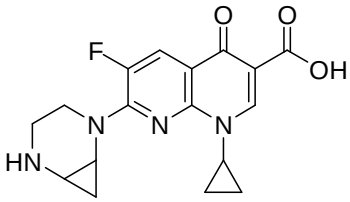
(46)

A novel series of thiazolidinone derivatives namely 4-(4-dimethylamino-6-{4-[5-(4 ethylpiperazin-1- ylmethyl)-4-oxo-2-phenylthiazolidin-3-yl]-phenylamino}-[1,3,5]triazin-2-yloxy)-1-methyl-1H-quinolin- 2-one **(47)** were synthesized by Patel *et al*. The newly synthesized compounds were evaluated for their antimicrobial activity against eight bacterial strains *(Staphylococcus aureus, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella typhi, Proteus vulgaris, Shigella flexneri)* and four fungal strains *(Aspergillus niger, Candida albicans, Aspergillus fumigatus, Aspergillus clavatus)* using the standard drug Ciprofloxacin and Ketoconazole respectively at the concentration of 100µg. Some compounds showed promising antimicrobial activity when compared with standard drug [53].



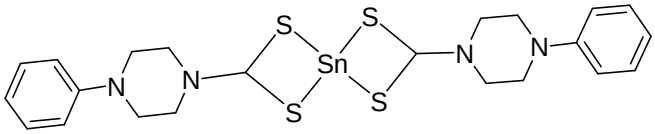
(47)

Piperazines and modified piperazines, such as homopiperazines and 2-methylpiperazines, are found in a wide range of pharmaceutical substances and biologically active molecules. In this study, Taylor *et al*. synthesized 2,5-diazabicyclo[4.1.0]heptanes, in which a cyclopropane ring is fused onto a piperazine ring **(48)** were described as modified piperazine analogues. These analogues demonstrated similar antibacterial activity as compred to the parent drug Ciprofloxacin [54].



(48)

A novel series of organotin (IV) 4-(4-methoxyphenyl) piperazine-1-carbodithioates **(49)** were synthesized by Rehman *et al*. and evaluated for their antimicrobial activities. A subsequent antimicrobial study indicated that these compounds were active biologically active in comparison to standard drug Streptomycin and hence may provide the basis for drug design and development of new class of antimicrobial agents [55].



(49)

Piperazine derivatives are being used successfully in clinical therapy like Ciprofloxacin, Sparfloxacin, Ofloxacin, Norfloxacin, Gatifloxacin, Ketoconazole, Posaconazole and Itraconazole etc. for treatment of various microbial infections. Some of the clinically used piperazine based drugs have been compiled in **Table no. 1**.

Table 1: Piperazine Nucleus Based Clinically Used Drugs [56-58].

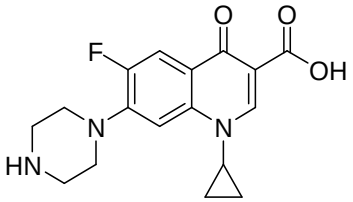
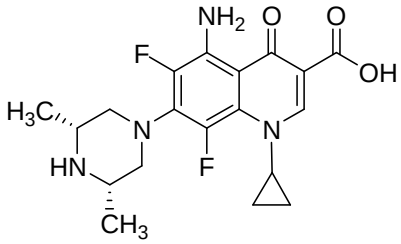
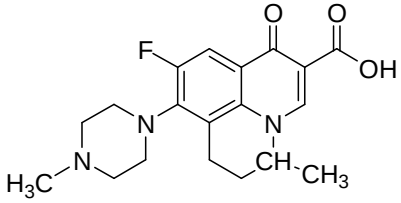
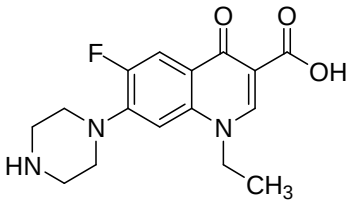
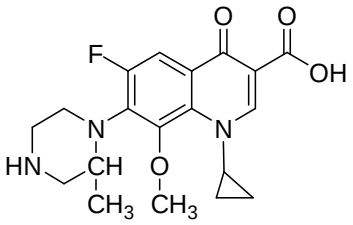
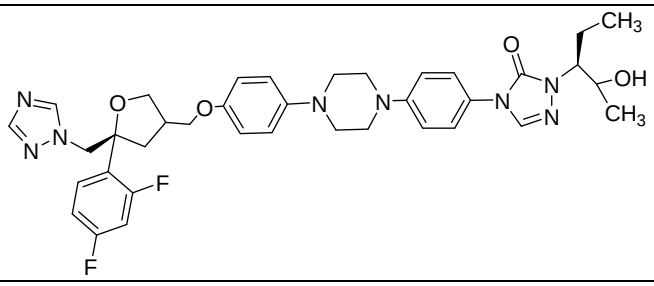
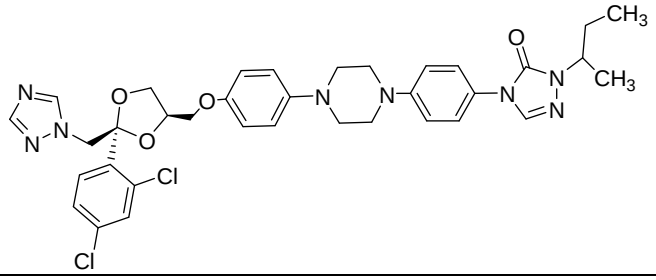
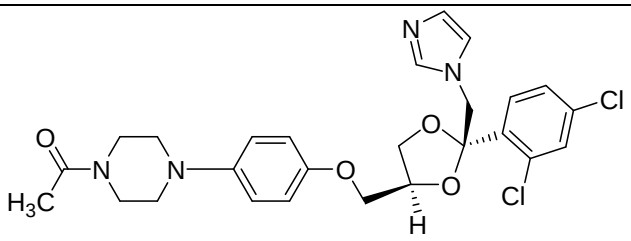
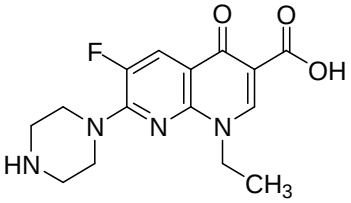
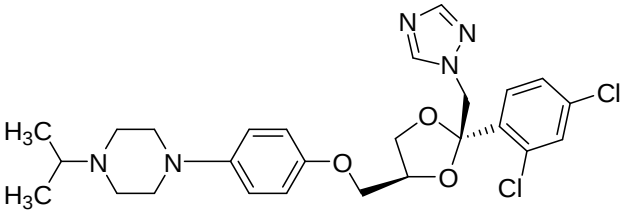
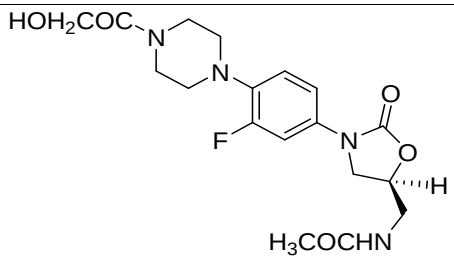
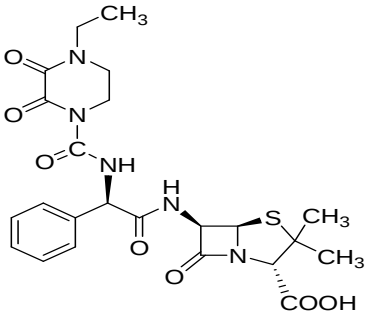
S. No.	Drug	Chemical Structure	Pharmacological Activity
1.	Ciprofloxacin		Antibacterial
2.	Sparfloxacin		Antibacterial
3.	Ofloxacin		Antibacterial
4.	Norfloxacin		Antibacterial
5.	Gatifloxacin		Antibacterial
6.	Posaconazole		Antifungal

Table 1 (Continued)…..

7.	Itraconazole		Antifungal
8.	Ketoconazole		Antifungal
9.	Enoxacin		Antibacterial
10.	Terconazole		Antifungal
11.	Eperezolid		Antibacterial
12.	Piperacillin		Antibacterial

CONCLUSION

This manuscript has complied significant information about antimicrobial activities of various derivatives based on piperazine heterocyclic nucleus and also some of the clinically used drugs having piperazine moiety as per the recent most literature survey. It may be concluded by this present review article that piperazine nucleus is a versatile and medicinally important nuclei having promising antimicrobial potential which may provide lead compounds for drug design and development of potent antimicrobial agents for future to provide effective antimicrobial therapy to the patients suffering from fatal microbial infections.

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