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Novel Piperazine Derivatives as Anti Microbial Agents: A Comprehensive Review

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Abstract

Over the past decade, there has been an increased development of resistance in organisms that are typical pathogenic in humans. This increased resistance has limited the selection of antimicrobials that may be used to treat specific organisms. Therefore, there is demanding to develop novel classes of drugs, with fewer side effects, and shorter lengths of treatment are key in continuing the fight against infectious disease. In the search of newer antimicrobial agents, various heterocyclic compounds have been examined and out of them, Piperazine derivatives have exhibited diverse biological activities such as antibacterial, antifungal, antitubercular, anticancer, antiviral, and antioxidant activities. In this work, we provide a summary of the recent advances of Piperazine derivatives exhibits anti-microbial activity and significant information of piperazine derivatives which may assist in the drug design and development of potent antimicrobial agents.

Keywords: Anti-microbial activity, Biological activities, Heterocyclic Compounds, Piperazine

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Introduction

The heterocyclic ring comprises the key of the active molecule. Especially big attention is given to nitrogen-containing heterocyclic compounds, as they belong to various biological activities, and are used in various fields of health science.

In the field of pharmaceutical chemistry, it concerns with the discovery, development, interpretation, and the identification of the mechanism of action of biologically active compounds at the molecular level. Various Pharmacological active synthetic compounds have six-membered two nitrogen-containing heterocyclic ring in their structures, for example, Piperazine. Piperazine is a heterocyclic organic compound, which consists of a six-membered ring containing two nitrogen as hetero atoms at the first and fourth position in the ring.[1]

The piperazine nucleus has been classified as a privileged structure and is frequently found in biologically active compounds. Some of these important biologically activities such as antimicrobial, anti-tubercular, antipsychotic, anticonvulsant, antidepressant, anti-inflammatory, cytotoxic, antimalarial, antiarrhythmic, antioxidant, and antiviral activities. possessed by the compounds having piperazine nucleus.[2]

Piperazines were originally named because of their chemical similarity with piperidine, part of the structure of piperine in the black pepper plant (*Piper nigrum*). The -az- infix added to "piperazine" refers to the extra nitrogen atom, compared to piperidine. It is important to note, however, that piperazines are not derived from plants in the *Piper genus*.[3]

Piperazine derivatives are broad class of chemical compounds, many with important biological properties, which contain a core piperazine heterocyclic moiety. A slight change in the substitution pattern in the piperazine nucleus causes recognizable difference in their biological activities. In the recent years a number of Piperazine derivatives have been synthesized and found anti-microbial activity:

Chaudhary *et al.*, synthesized series of Piperazine derivatives and evaluated for antimicrobial activity. All synthesized compounds showed significant activity against bacterial strains but were found to be less activity against tested fungi strain.[4]

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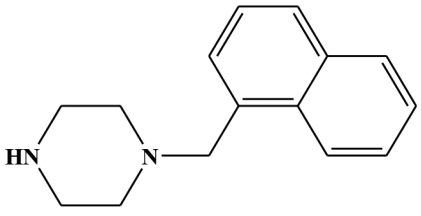
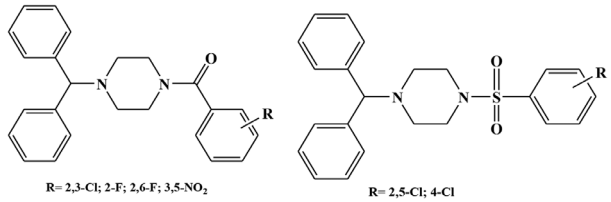
Schumacher *et al.*, studied on 1-(1-Naphthylmethyl)-piperazine has average activity in reversing Multiple Drug Resistance in many but not all members of the *Enterobacteriaceae* family including clinical isolates. Its effects on resistance reversal depend on bacterial species and drug molecules, and are different from those seen with Phe-Arg-b-naphthylamide.[5]



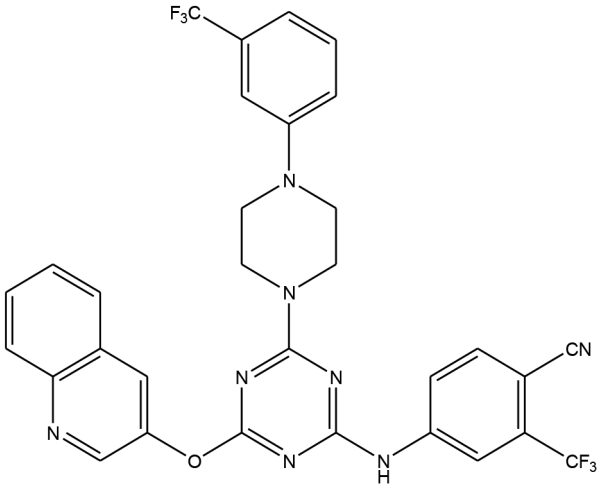
1-(1-naphthylmethyl)-piperazine

Kumar *et al.*, synthesized new 1-benzhydryl-piperazine sulfonamide and carboxamide derivatives. And evaluated their antimicrobial activities by agar disc diffusion and broth dilution method against Gram-positive (*Staphylococcus aureus*, *Staphylococcus epidermis*, *Bacillus cereus*, *Bacillus substilis*) and Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris,* and *Salmonella typhi*) bacterial strains.[6]

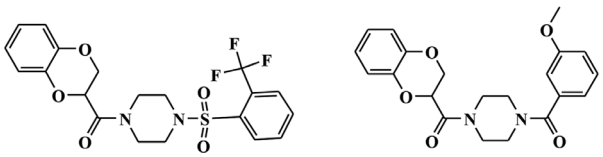


Kumar *et al.*, synthesized new 1-benzhydryl piperazine derivatives and evaluated their antimicrobial activity. The SAR studied proved that both linkage and substituents on phenyl ring are accountable for the antimicrobial activity for these classes of agents.[7]

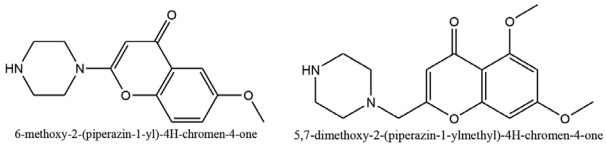
Patel *et al.*, synthesized novel 2-(4-cyano-3-trifluoromethylphenyl amino)-4-(quinoline-4-yloxy)-6-(piperazinyl)-s-triazines derivatives, studied their anti-microbial, anti-mycobacterial, and anticancer activity.[8]



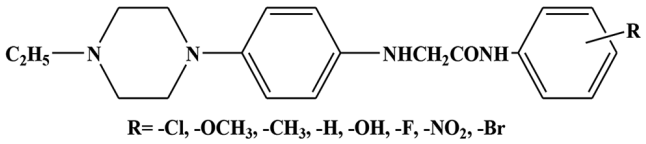
Mallesha and Mohana synthesized novel 1- (1, 4-benzodioxane-2-carbonyl) piperazine derivatives, evaluated their antimicrobial and antioxidant activities. Compound, 4-(2-trifluoromethyl) -benzenesulfonyl-1- (1, 4-benzodioxane -2-carbonyl) piperazine exhibited significant antimicrobial activity against tested pathogenic bacterial and fungal strains.[9]



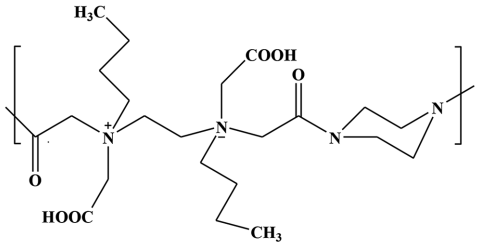
Hatnapure *et al.*, synthesized series of novel 6-methoxy-2-(piperazin-1-yl)-4H-chromen-4-one and 5, 7-dimethoxy-2-(piperazin-1-ylmethyl)-4H-chromen-4-one derivatives; evaluated their screened for their pro-inflammatory cytokines (TNF-α and IL-6) and antimicrobial activity (antibacterial and antifungal).[10]



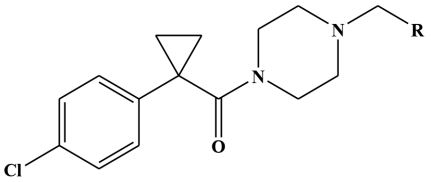
Somashekhar *et al.*, synthesis and antimicrobial activity of Piperazine derivatives. The final product 1- [2-(aryl amino -2-oxoethyl) - amino -4- (n-ethyl piperazine)] benzene derivatives were screened for their antibacterial activity.[11]



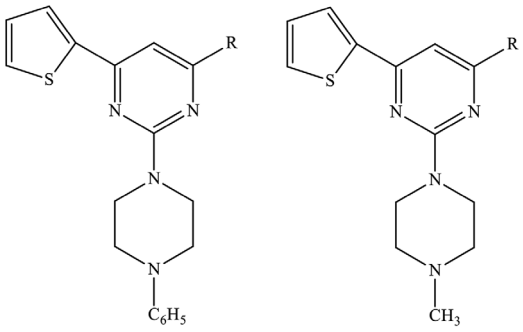
Zhang *et al.*, reported a novel antibacterial piperazine derivative has been synthesized via the nucleophilic substitution reaction of poly (ethylenediaminetetraacetic dianhydride-co-piperazine) with n-butyl bromide and evaluated their antibacterial activity.[12]



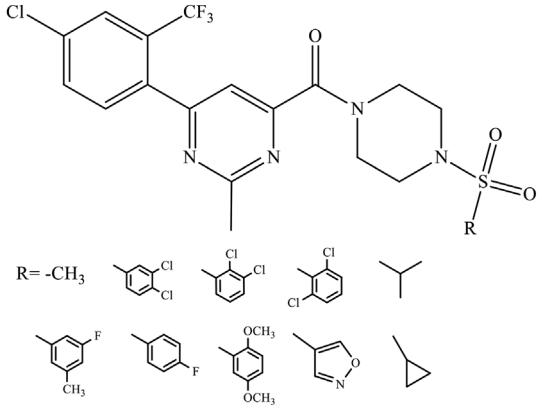
Mallikarjuna *et al.*, A series of novel [1-(4-Chlorophenyl) cyclopropyl] (piperazin-1-yl) methanone derivatives were synthesizing by reductive amination method in presence of sodium triacetoxyborohydride to form piperzine derivatives. Some of the tested compounds have exhibited significant anti-tuberculosis and anticancer activity.[13]



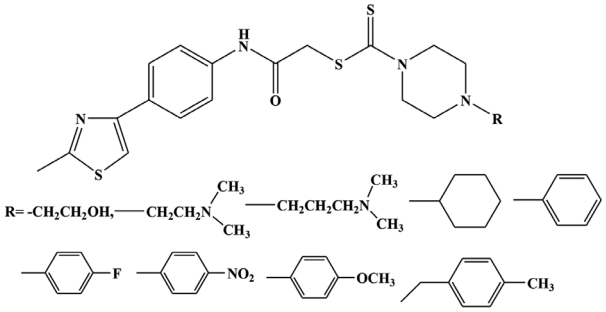
Padmashali *et al.*, synthesis of pyrimidine incorporated piperazine derivatives and their antimicrobial activity. The structures of all the newly synthesized compounds showed good antibacterial activity and significant antifungal activity compared with standard drugs.[14]



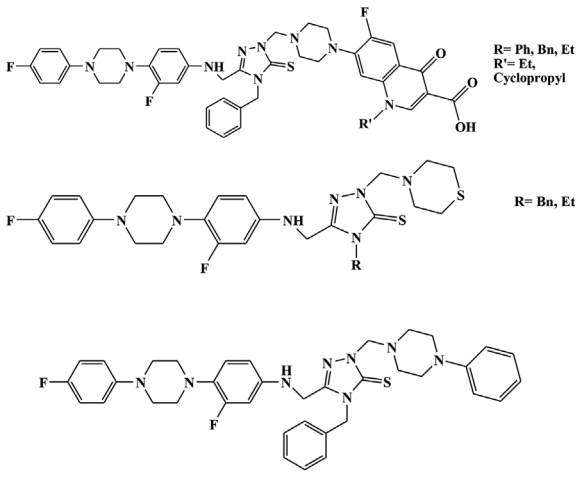
Mohan *et al*., synthesis, antibacterial, anthelmintic and anti-inflammatory studies of new Methylpyrimidine Sulfonyl Piperazine derivatives. Some compounds showed potent anti-microbial activity.[15]



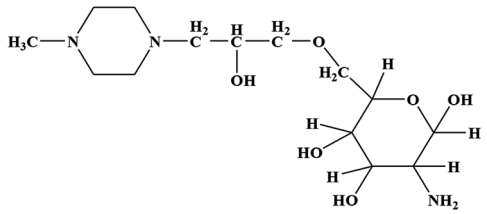
Mohsen *et al.*, synthesized and evaluated antimicrobial activity of some Piperazine Dithiocarbamate derivatives. The antimicrobial activity of the compounds was examined by using the microbroth dilution method. Antimicrobial activity results revealed that synthesized compounds exhibited moderate antimicrobial activity against to *E. faecalis* and *P. aeruginosa*.[16]



Ozdemir *et al*., synthesis and antimicrobial activity of new piperazine-based heterocyclic compounds. Here, triazoles reacted with different heterocyclic amines in the presence of formaldehyde to form N-aminoalkylated triazoles. The outcome of various catalysts and solvents on conventional and microwave-prompted reactions was studied. The synthesized compounds were evaluated for their antimicrobial activities.[17]



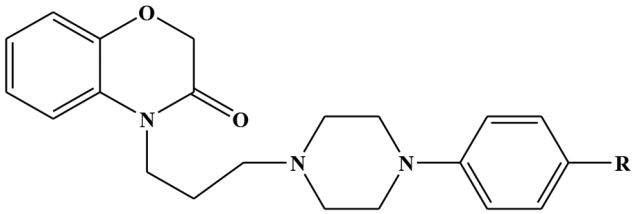
Chauhan *et al*., synthesis, characterization and anti-microbial activity of Chitosan epoxy n-methyl Piperazine.[18]



3-amino-6-((2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy)methyl)-tetrahydro-2*H*-pyran-2,4,5-triol

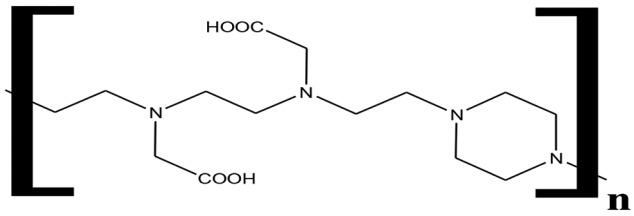
Kale *et al*., heterocyclic compounds especially with benzimidazole, thiophene, and Piperazine moieties were synthesized and screened their antibacterial, antifungal, and antitubercular activities. Most of the compounds have shown significant antibacterial, antifungal, and anti-tubercular activity as compared with the standard drug. QSAR studies were done by using Schrodinger software.[19]

Subramaniyan *et al*., synthesized and studied antimicrobial activity of novel series of benzoxazine containing piperazine derivatives.[20]



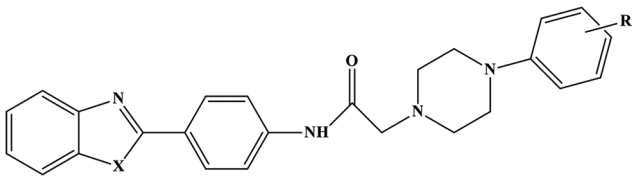
R= -F, -OCH$_3$, -CF$_3$

Zhang *et al*., described the green method synthesis of a new piperazine polymer, which was based on the raw materials piperazine and ethylenediaminetetraacetic dianhydride. The results showed that piperazine polymer exhibited good antibacterial activity against bacterial strains.[21]



Patil *et al*., design, synthesis, and molecular docking study of new piperazine derivative as potential antimicrobial agents. All compounds were screened antibacterial and antifungal activity against bacterial such as *S. aureus*, *E. coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *P. aeruginosa* and fungal strains such as *Candida albicans* and *Cryptococcus neoformans*.[22]

Bari *et al*., synthesized series of N- (4- (benzo[d]thiazol-2-yl) phenyl)-2-[4-(arylsubstituted) piperazines-1-yl] acetamide, N-(4-(benzo[d]oxazol-2-yl) phenyl)- 2-[4-(arylsubstituted) piperazines-1-yl] acetamide, N-(4- (benzo[d]imidazol-2-yl) phenyl)- 2- (4- (arylsubstituted)piperazin-1-yl) acetamide and studied their anti-microbial activity.[23]



Shinde *et al.*, synthesized and studied antimicrobial activity of 2-(4-(benzo[d]thiazol-5-ylsulfonyl) piperazine-1-yl) -N-substituted acetamide derivatives. All compounds were evaluated *in vitro* antimicrobial activity against Gram-positive and Gram-negative pathogenic bacterial strains such as *S. aureus*, *Bacillus subtilis*, *E. coli* and *P. aeruginosa* using ciprofloxacin and fungal strains such as *C. albicans* and *Aspergillus fumigatus* as compared with Clotrimazole. Molecular docking study showed that all these compounds were having good to excellent correlation binding energy as compared with binding energy of standard drugs.[24]

Conclusion

Several developed piperazine derivatives possessed good to superior antimicrobial activities. This review article has complied valuable information about various piperazine derivatives as potent anti-microbial agents and also some of the clinically used drugs having piperazine moiety as per the recent most literature survey. Based on the literature of reviews, it may be concluded that piperazine nucleus is a versatile and medicinally important nuclei having promising antimicrobial compounds 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 mortal and severe microbial infections.

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