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A REVIEW ON BIOLOGICAL ACTIVITIES OF PIPERAZINE DERIVATIVES

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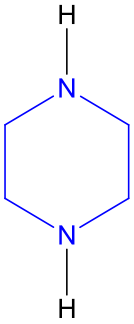
ABSTRACT

Piperazine is a nitrogen-containing heterocyclic compound with six members that contains two nitrogens and four carbons in a cyclic configuration, with nitrogens at the first and fourth positions of the cyclic ring. A saturated heterocyclic compound is a piperazine moiety. It's used in the creation of rational drugs. This molecule may be present in a range of well-known medications, antipsychotic, anti-histaminic, anti-bacterial, anti-fungal, anti-viral, anti-cancer, anti-microbial, and anti-inflammatory action. Piperazine molecule is also used in medicinal and phytochemical chemistry. Benzylpiperazine, Phenylpiperazine, (1-(3-trifluorophenyl piperazine), (1-(3-chlorophenyl piperazine), Methoxyphenyl piperazine are several piperazine variants. This compound is the most common ingredient in competitive medicines, and it has mild stimulant and euphoric effects. This study looked at certain piperazine derivatives and how they could be Buspirone is used as an anxiolytic, while vortioxetine is an antidepressant and clozapine is an antipsychotic. It is possible to remove it from black piper plants (family piperaceae).

KEYWORDS: Piperazine derivatives Synthesis, Antimicrobial activity, Chemistry of piperazine.

1. INTRODUCTION OF PIPERAZINE

The organic molecule Piperazine is a heterocyclic compound containing six members. Component with two atoms of nitrogen in opposition positions in the ring and four carbon atoms attached.[1]



(Figure-1 Piperazine)

Piperazine and their derivatives have a broad the variety of biological effects, including anti-bacterial, anti-malarial, anti-neoplastic, anti-inflammatory, antimicrobial, and anti-fungal drugs.[2] Because of their acceptable pka, the piperazine moiety has two main nitrogen molecules that are used in the pharmacokinetic features of drugs application.[3] These nitrogen moiety cause A considerable rise in the drug's water solubility, and they Play a key part in bioavailability. The shape of a drug, such as moiety, is an essential factor in the design and manufacture of new medicine in order to maintain a balance between pharmacokinetic and pharmacodynamics. The aim of these synthesised drugs is to create compounds having a strong affinity for their target.[4] Each year, approximately Cancer kills 8.2 million people annually, representing about 13% of all deaths worldwide. The global cancer burden continues to rise, and it's estimated that cancer incidence could increase by up to 70% in the coming decades. With over 100 different types of cancer identified, managing and treating these diseases remains a major challenge for healthcare systems worldwide.[5] The World Health Organization (WHO) considers seasonal influenza to be an important global health concern, leading to an estimated 1 billion cases annually. Of these, approximately three to five million are serious illnesses, leading in 290,000 to 650,000 respiratory fatalities each year.[6] Antifungal[7], Anticancer[8], Antimalarial[9], Antibacterial[10], Anticonvulsant.[11] Oxazolidinones are a new class of antibacterials. Linezolid (Figure 6) was the first of the oxazolidinones to be licensed for clinical usage, and it is particularly efficient against Staphylococci, streptococci, and enterococci are all examples of drug-resistant Gram positive bacteria.[12]

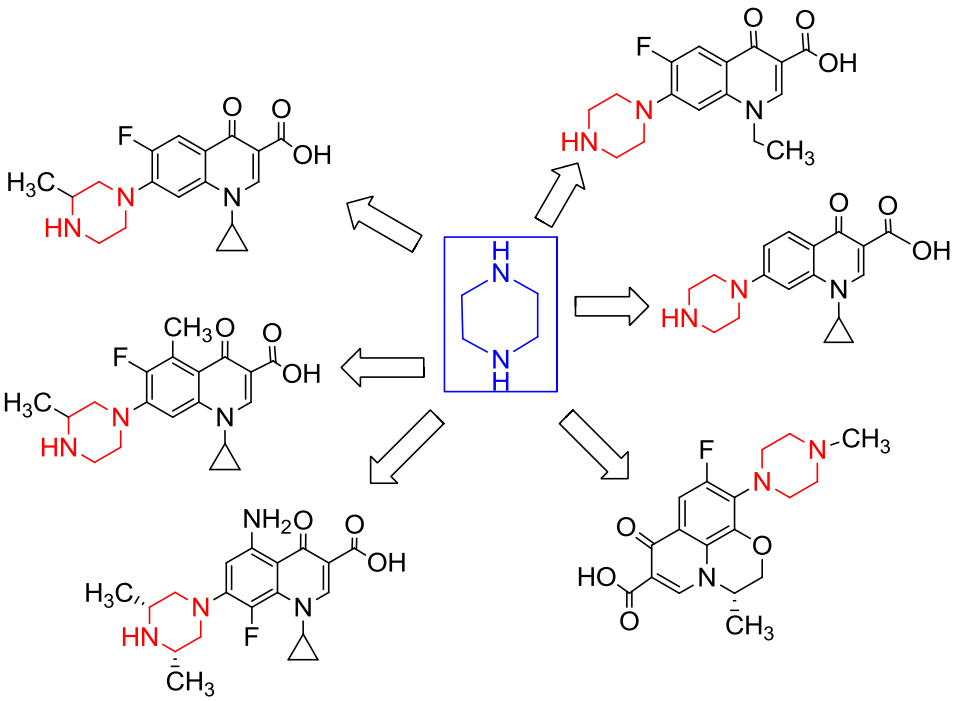


Figure 2: Antibiotics containing piperazine derivatives. Singh V et al (2019) Patil. M et al. (2019).[13]

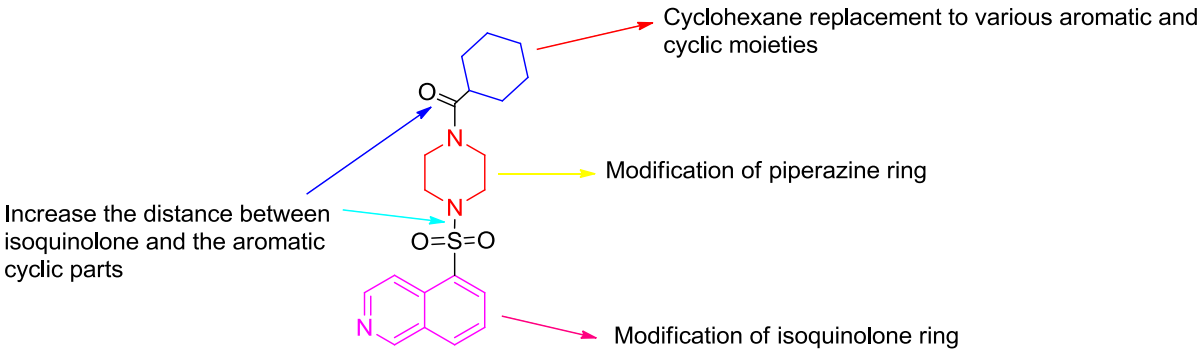


Figure 3: Structure activity relationship of piperazine Singh V et al. (2019).[14]

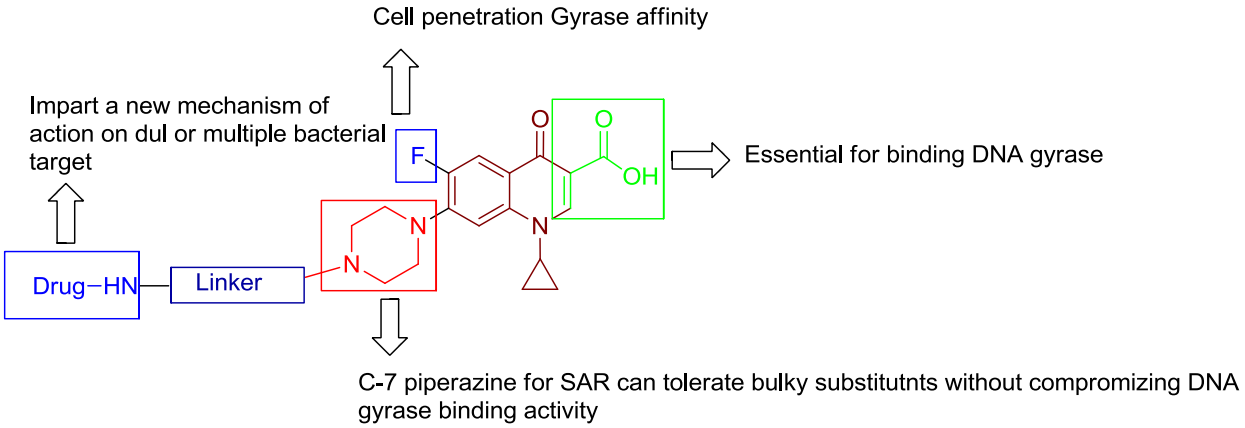
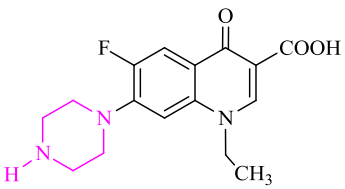
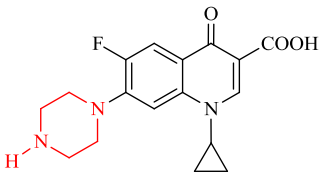


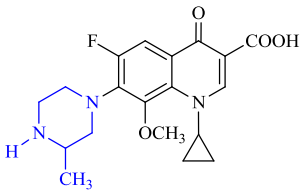
Figure 4: Chemical structures of some piperazine designer drugs Tahir et al. (2019).[15]



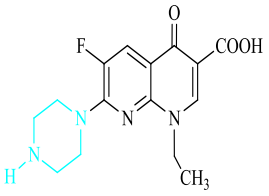
Norfloxacin
1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid



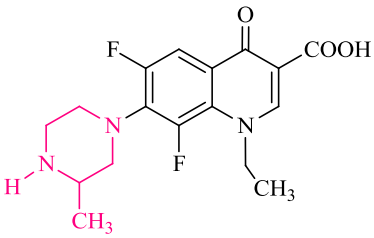
Ciprofloxacin
1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid



Gatifloxacin
1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



Enoxacin
1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid



Lomefoxacin
1-ethyl-6,8-difluoro-7-(3-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

Figure 5 7-piperazinyquinolone derivatives used as antibacterial agents. Emami S et al. (2013).[16]

Chemistry of piperazine: Piperazine is a heterocyclic compound containing four carbon atoms and two nitrogen at 1 and 4 position (as called 1, 4-hexahydropyrazine). The Piperazines or Cyclizines can also be considered as ethylenediamine derivatives or cyclic ethylenediamines (cyclizines); Piperazines are a broad class of chemical compounds with many important pharmacological properties. This dinitrogen moiety has been an inseparable component of plethora of drugs. Piperazine has the chemical similarity with piperidine, a constituent of piperazine in the black piper plant (Piper nigrum). Piperazine introduced into the medicine as a solvent for uric acid. Nitrogen in piperazine ring plays an important role in biological research and drug manufacturing industry including the proportion of Anthelmintic, Antiallergic 4 Antibacterial, Antihistaminic 5, Antiemetic and Antimigrainic agent.

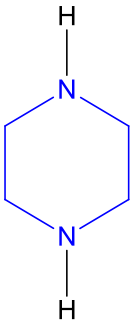


Figure: 6

BIOLOGICAL ACTIVITY

2. Anti-microbial agents

Patil et *al.* (2019) synthesised the derivatives of piperazine and tested them for antimicrobial action. Substance 1 inhibited the development of K. pneumonia in the medium.[17] Piperazine derivatives were synthesized and tested as antimicrobial agents by Patil et *al.* (2019). Compound 2 showed and demonstrated excellent growth inhibition against C. albicans fungi.[18]

2.1 Antibacterial activity

Tahir et *al.* (2019) Piperazine derivatives were produced and analyzed in terms of antibacterial properties. Among the tested chemicals, 1a, 1b, and 1d failed to produce the desired results, exhibiting little activity against all bacteria strains studied. In contrast, Compound 1c displayed moderate antimicrobial activity specifically towards the screened Gram positive strains, minimum inhibitory concentrations (MIC) differ of 16–32 µg/ml.[19] The Mannich base analogues of ciprofloxacin displaying a MIC range of 0.5–32 µg/ml, demonstrating noteworthy anti-microbial properties against all of the tested strains. Compound 2b, the strongest of the chain, was synthesised and analyzed for action against both Gram negative and Gram positive bacteria, which is having MIC value of 0.5g/ml for Gram-negative bacteria and 1g/ml for Gram-positive bacteria. Compound 2c, on the other hand, displayed moderate efficacy against Gram-negative bacteria, with the MIC of 32g/ml.[20] Wang et *al*. (2019) produced and analyte antibacterial activity. Cyanomethyl derivatives compound 4d demonstrated increased antibacterial action towards k pneumonia with a MIC of 0.005 mm. Compound 4d displayed 2.5-fold inhibition efficacy against E. coli all the test strains, with MIC value of 0.025Mm.[21] Hojat Allah Arab et *al.* (2018) synthesised and investigated for antibacterial action. Compound 3 have MIC value of 0.097µg/ml was the strong action chemical opposed to gram-positive bacteria. It was 2-4

times more effective against these microorganism than norfloxacin.[22] Chander et al. (2016) synthesised antibacterial agents and tested them. Compound 4 had a moderate inhibitory potential towards S aureus development, with the MIC range of > 128g/ml.[23] Chander et al. (2016) developed antibacterial agents and tested them. Compound 5 showed a weak inhibitory action towards S aureus development, with the MIC value of >128 g/ml.[24] Substance 6 which Wang et *al.* (2014) synthesised and tested, and 0.355g/ml, respectively. The methoxy group is bound to the benzene ring at para-position in this compound.[25] Compound 7 defined by Wang et *al*. (2014) for anti-microbial action, has a CH_3O group linked at the position-3 of the benzene ring and has minimum inhibitory concentration ranges of 0.612g/ml and 2.523g/ml.[26] Patel and Park et *al.* (2014) identified a new piperazine derivative, compound 8 that has good potency and MIC values of one and two g/ml towards S aureus and Bacillus subtilis exhibited greater anti-bacterial properties towards B subtilis and S aureus was observed, with MIC values of 0.236g/ml cereus.[27] For antibacterial function, Wang et *al.* (2014) synthesised metronidazole derivatives with a piperazine skeleton. Compound 9 is the most potent, with minimum inhibitory concentration values of 0.003g/mL and 0.0024g/ml vs ATCC 25923 and S. aureus TyrRs,[28] With MIC ranges of 0.142g/ml, Wang et *al.* (2014) synthesised compound 10 chlorine atom linked at position-ortho of the benzene ring. Substances with ortho and para position substitutions had higher antibacterial activity than those with meta position substitution.[29] Compound 11 was created by Wang et *al.* (2014) and has a MIC value of 0.272g/mL. This substance has a CH_3O group linked to the otho-position of the benzene ring, which has strong anti-bacterial properties.[30] Compound 12, attached with two chlorine atoms at 3, 4 positions in the benzene ring, was manufactured and evaluated by Wang et *al.* (2014). Compounds substituted at 3, 4 positions had a strong inhibitory effect. Substitution at the para position yielded the highest antibacterial activity as compared to substitution at the 3- position.[31] Mohammadhosseini et *al.* (2012) synthesised and tested levofloxacin derivatives for antibacterial activity. Compound 13 is a solid compound with a MIC of 1.56-6.25g/ml against Escherichia coli, K.pneumoniae, and P.aeruginosa.[32] Patel et *al.* (2012) synthesised derivatives of piperazine and tested them for anti-microbial action. Substance 14 screened as having the maximum action against S. aureus, with a MIC of 6.25g/ml.[33] Ciprofloxacin analogues obtained by Wang et *al.* (2012) and their anti-microbial action was estimated. Compound 15 displayed strong antimicrobial action in vitro against all Gram-positive bacterial strains. The minimum inhibitory concentration differ 0.5 to 4 g/ml.[34] Emami et *al.* (2009) calculated the antibacterial efficacy of piperazinylquinolones manufactured by Emami et al. Compound 16

was it was shown to be the most efficient against Gram-positive bacteria. Methicillin resistance staphylococcus aureus, S. epidermidis, E. coli, and B. subtilis had MIC ranges of 0.049, 0.098, 0.049, 0.024, 0.78, 0.098, and 50g/ml.[35] Foromomaudi et *al.* (2006) manufactured differns piperazinyl quinolone analogues, substance 17 shown excellent Antimicrobial actions against Gram-positive bacteria and also Gram negative bacteria and the minimum inhibitory concentration value is 0.03-1.00µg/ml.[36] Fluoroquinolone derivatives are manufactured by Foroumadi et *al.* (2006) for anti-bacterial properties. Compound 18 was identified as a highest active substance against Pseudomonas aeruginosa with a MIC of 1.56g/mL.[37] Compound 19 was reported to be most active anti-microbial drugs among Phillips et al. (2005) produced chemicals that limit bacterial growth by 10%, 98%, and 100% at concentrations of 0.12 and 0.25 and 0.5µg/mL.[38] Kerns et *al.* (2003) synthesised several piperazinyl attached ciprofloxacin dimers, one of which, Compound 20, is stated to be active against drug-resistant S. Aureus strains.[39] Foroumadi et al. (2003) indeed worked on piperazinyl quinolones, modifying their structures to enhance antibacterial activity. The MIC (Minimum Inhibitory Concentration) value you mentioned — 0.008 g/mL — for compound 21 against *Staphylococcus aureus* is quite significant.[40] Chen et al. (2001) produced and investigate a series of piperazine analogues for antibacterial activity. Among them, compound 22 demonstrated notable actions Against methicillin resistant Klebsiella pneumoniae Staphylococcus aureus (MRSA) is resistant to erythromycin and penicillin *Streptococcus pneumoniae*, and vancomycin-resistant strains, with MIC values of 0.005 *µM*, 0.55 *µM*, 1.82 µM, and 5.47 *µM*, respectively.[41]

2.2 Anti-inflammatory activities

Sultana et al. (2013) manufactured a number of piperazine substance were investigated for anti-inflammatory efficacy. Among these, compound 1 exhibited significant anti-inflammatory effects.[42] Kono et *al.* (2013) synthesised various piperazine analogues. In an Acetic acid-induced writhing in mice, compound 2 displayed the most potent anti-inflammatory activity.[43] Withan IC50 of 12.5g/mL, compound 3 showed promising anti-inflammatory activities. Piperazine analogues were manufactured by Sultana et al. (2010).[44]

2.3 Anticancer activity

An analogue with a bulky substituent, compound 1 reported by Patel et al. (2016) was found to be inactive in anticancer assays, showing an IC_{50} value greater than 8 µg/m. Both cervical cancer cell lines tested were resistant to this treatment.[45] Patel et *al.* synthesized (2016) and

tested compound 2 for anticancer activity, finding a desirable degree of cytoxicity at 323.1 3.772g/mL of CC50, with a SI of 57.23 and a CC50 of 10.26 0.062 mg/mL of CC50 against hBM- MSCS cells.[46] Compound 3 was synthesised and investigate for anticancer action by Murty et *al.* (2011), and it was identified as the most active compound.[47] Shaharyar et *al.* (2007) synthesised derivatives of piperazine and tested them against human lung tumour cell lines for anti-proliferative properties. Substance 4 was shown to be the greatest active, with an IC50 of 9.0g/ml.[48] Compound 5 was identified as the most potent, exhibiting 79% inhibition against SGC cells with an IC_{50} value of 0.032 µM. Thiosemicarbazone substance were manufactured and evaluated for anti-neoplastic action by Hu et al. (2006).[49]

2.4 Antipsychotic activity

Btito et al. (2019) synthesized compound 1, a piperazine-based derivative with potential antipsychotic activity. Antipsychotic drugs are generally used for the treatment of both positive and negative signs of schizophrenia. Piperazine analogues with antipsychotic effects are typically multimodal agents, acting on multiple receptor systems—primarily as dopaminergic D_2 receptor antagonists and 5-HT_2 serotonergic receptor blockers.[50-53] Of all the piperazine derivatives, Pompeu et *al.* (2013) were synthesised. Compound 2 was discovered to be the most effective antipsychotic agent.[54] Kumar et al. (2011) synthesised a number of piperazine compounds and examined their antipsychotic characteristics. Among them, compound 3 was identified as the most active agent.[55] Among the compound, Tu et*al.* (2011) created. Substance 4 was shown to have the highest activity for the D3 receptor.[56] Compound 5 was synthesised and identified by Park et *al.* (2005) as a highly effective antipsychotic agent.[57] Smid et al. (2005) developed a variety of piperazine derivatives, among which compound 6 was identified as one of the most potent antipsychotic agents.[58] Many piperazine derivatives have antipsychotic properties. Clozapine, quetiapine, and trifluoperazine, for example, are often used as dopaminergic antagonists.[59] Piperazine derivatives used as antipsychotics are multimodal medications that function on several different receptors, primarily as D2 dopaminergic antagonists, and also as 5-HT2 serotonergic blocked antipsychotic drugs for the treated of positive and negative symptoms.[60]

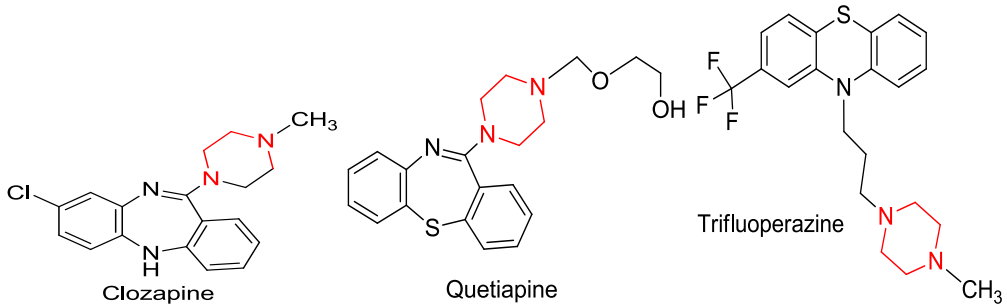
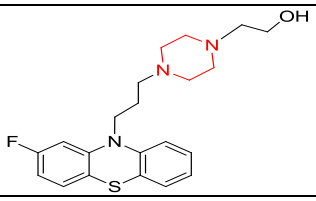
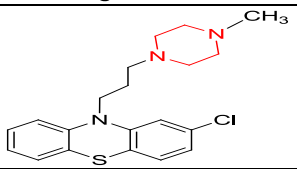
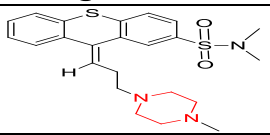
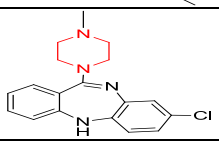
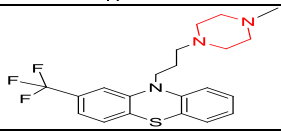
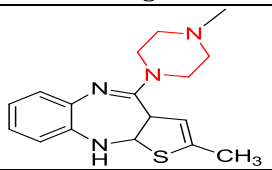
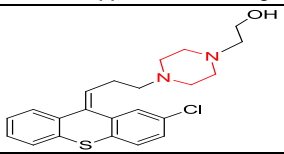
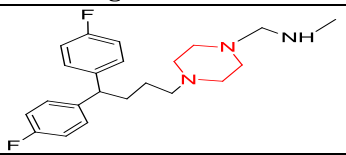


Figure 7: Various piperazine derivatives used for antipsychotic studies.

Drugs that contain piperazine: Table.1

Medicines	Structures	Pharmacological class
Perphinazine[61]		Typical anti-psychotic
Prochloperazine[62]		Typical anti-psychotic
Thiothixene[63]		Typical anti-psychotic
Clozapine[64]		Atypical Antipsychotic
Trifluoperazine[65]		Typical anti-psychotic
Olanzapine[66]		Atypical Antipsychotic
Zuclopenthixol[67]		Typical Antipsychotic
Amperozide[68]		Atypical Antipsychotic

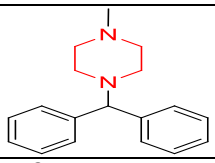
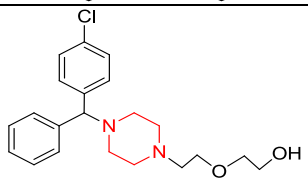
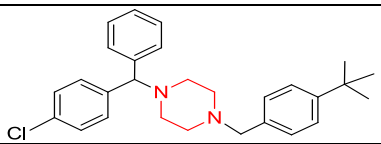
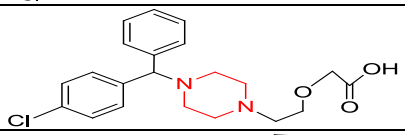
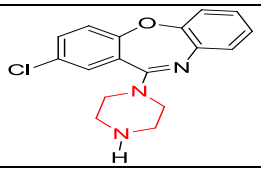
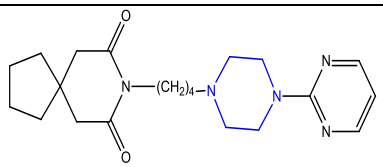
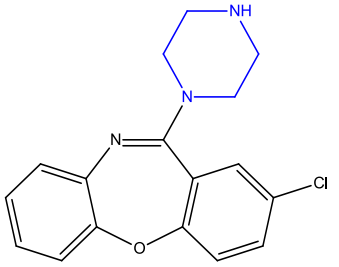
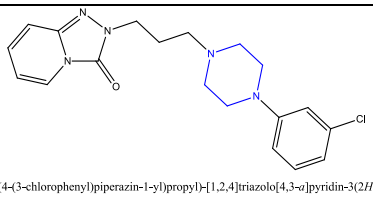
Cyclizine[69]		Antihistamine
Hydroxyzine[70]		Antihistamine
Buclizine[71]		Antihistamine
Cetrizine[72]		Antihistamine
Amoxapine[73]		Antidepressant

Table 2: Various piperazine based drugs on the market.

Drug Name	Structure	Mechanism of action	Development year	Ref.
Buspirone	 8-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)butyl)-8-azaspiro[4.5]decane-7,9-dione	5-HT1 Aagonist	1986	[74]
amoxapine	 2-chloro-11-(piperazin-1-yl)dibenzo[*b*,*f*][1,4]oxazepine	Serotonin reuptake inhibitor (SERT),5-HT_{1A} partial agonist	1992	[75]
Trazodone	 2-(3-(4-(3-chlorophenyl)piperazin-1-yl)propyl)-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one	5-HT_{1A}R agonist and 5-HT_2R antagonist	1981	[76]

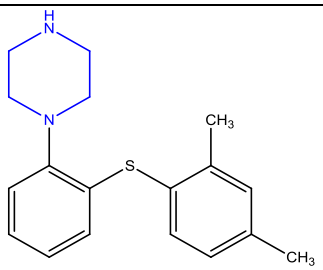
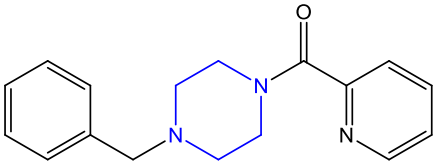
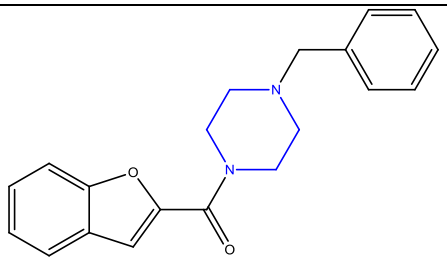
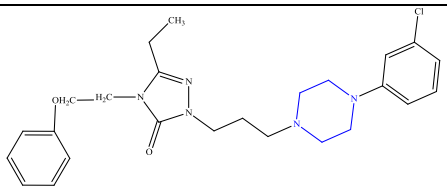
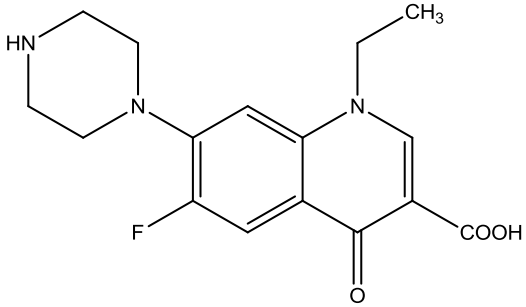
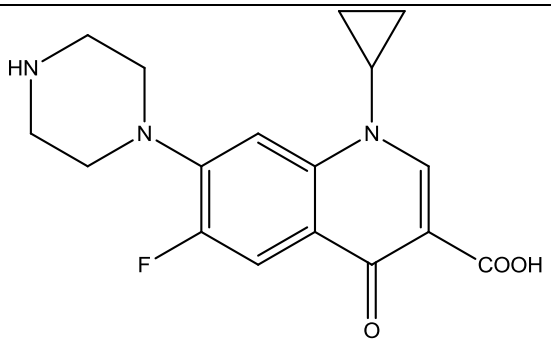
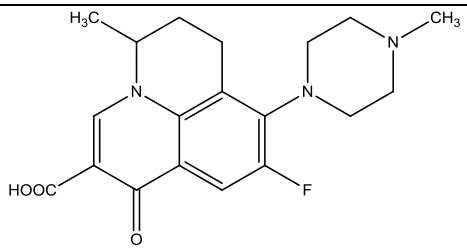
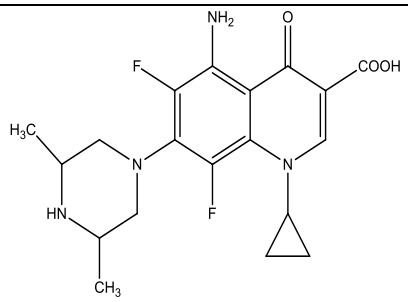
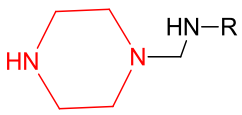
Vortioxetine	 1-(2-((2,4-dimethylphenyl)thio)phenyl)piperazine	Serotonin reuptake inhibitor (SERT), 5-HT_{1A}R partial agonist, 5-HT_3 R agonist	2017	[77]
Piberaline	 (4-benzylpiperazin-1-yl)(pyridin-2-yl)methanone	Serotonin reuptake inhibitor (SERT), norepinephrine reuptake inhibitor(NET)	1980s	[78]
Befuraline	 benzofuran-2-yl(4-benzylpiperazin-1-yl)methanone	Serotonin reuptake inhibitor (SERT), norepinephrine reuptake inhibitor (NET)	1970s	[79]
Nefazodone	 1-(3-(4-(3-chlorophenyl)piperazin-1-yl)propyl)-3-ethyl-4-(2-phenoxyethyl)-1*H*-1,2,4-triazol-5(4*H*)-one	5-HT_{1A}R agonist and 5-HT_2R antagonist	1994	[80]

Table 3: Piperazine Nucleus Based Clinically Used Drugs.[81-84]

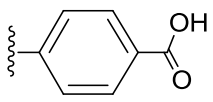
S. No	Drug	Chemical Structure	Pharmacological Activity
1.	Norfloxacin	 1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid	Antibacterial

2.	Ciprofloxacin	 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid	Antibacterial
3.	Ofloxacin	 9-fluoro-5-methyl-8-(4-methylpiperazin-1-yl)-1-oxo-1,5,6,7-tetrahydropyrido[3,2,1-*ij*]quinoline-2-carboxylic acid	Antibacterial
4.	Sparfloxacin	 5-amino-1-cyclopropyl-7-(3,5-dimethylpiperazin-1-yl)-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	Antibacterial

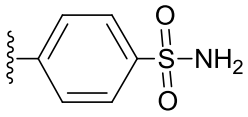


(1a-1d)

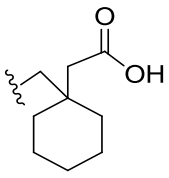
Where, R=



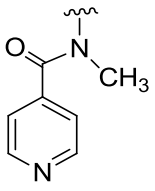
1a



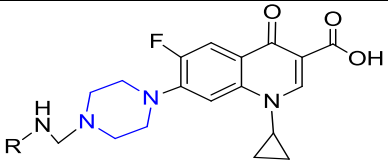
1b



1c

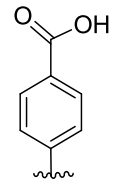


1d

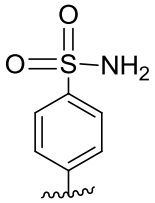


(2a-2d)

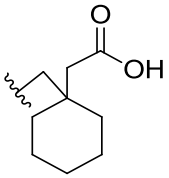
Where, R=



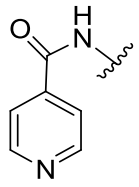
2a



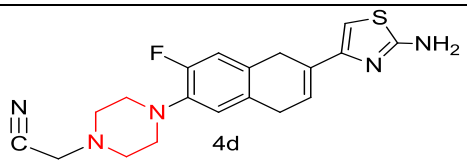
2b



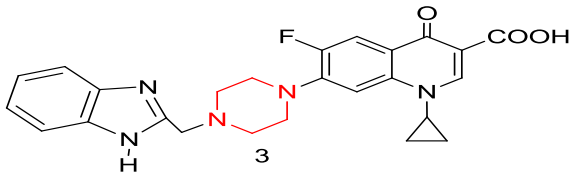
2c



2d



4d



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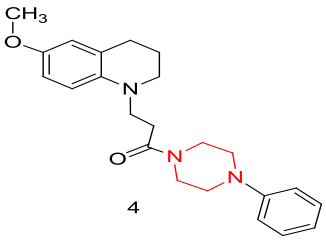

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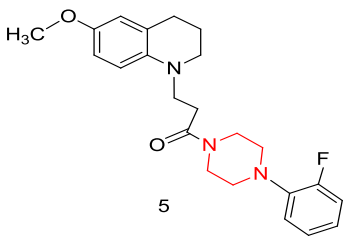

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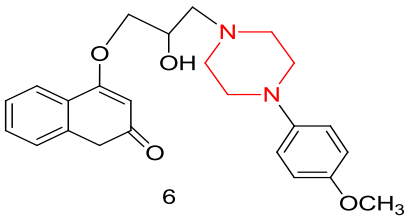

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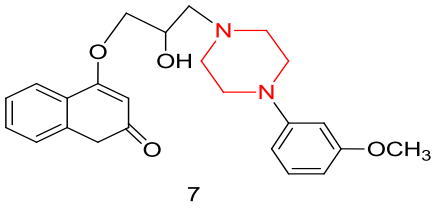

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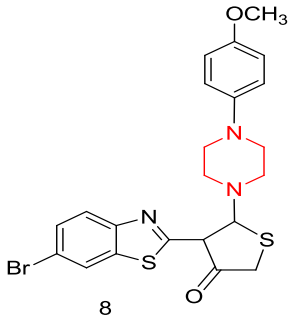

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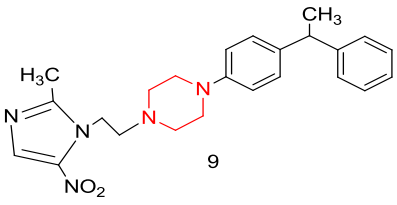

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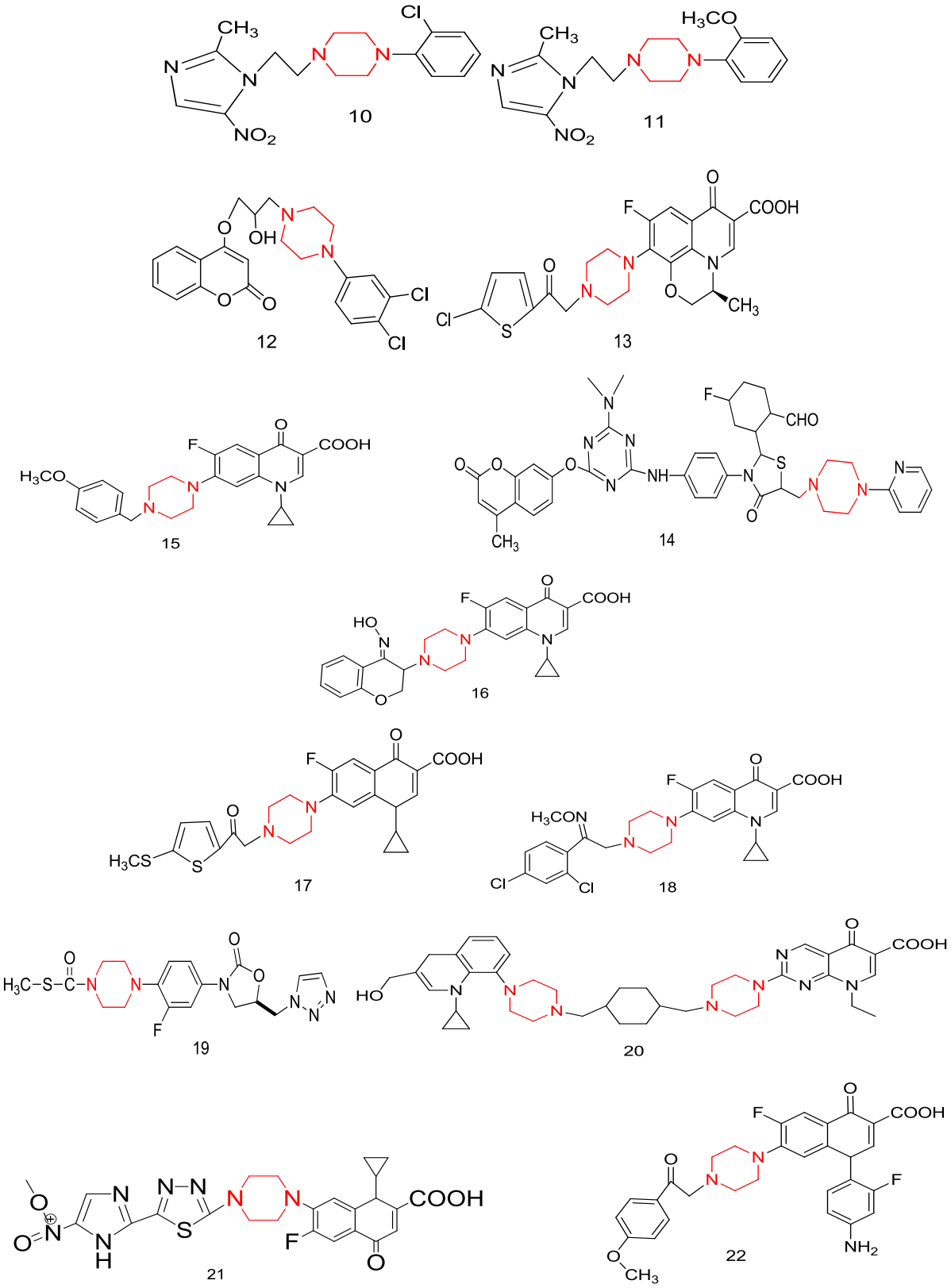


Figure 8: Antimicrobial piperazine derivatives.

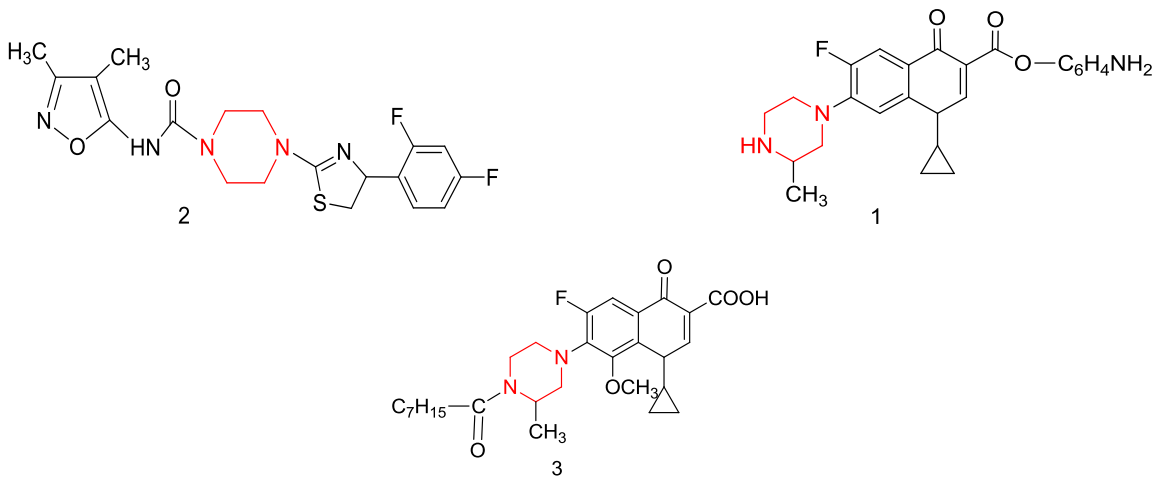


Figure 9: Antibacterial piperazine derivatives.

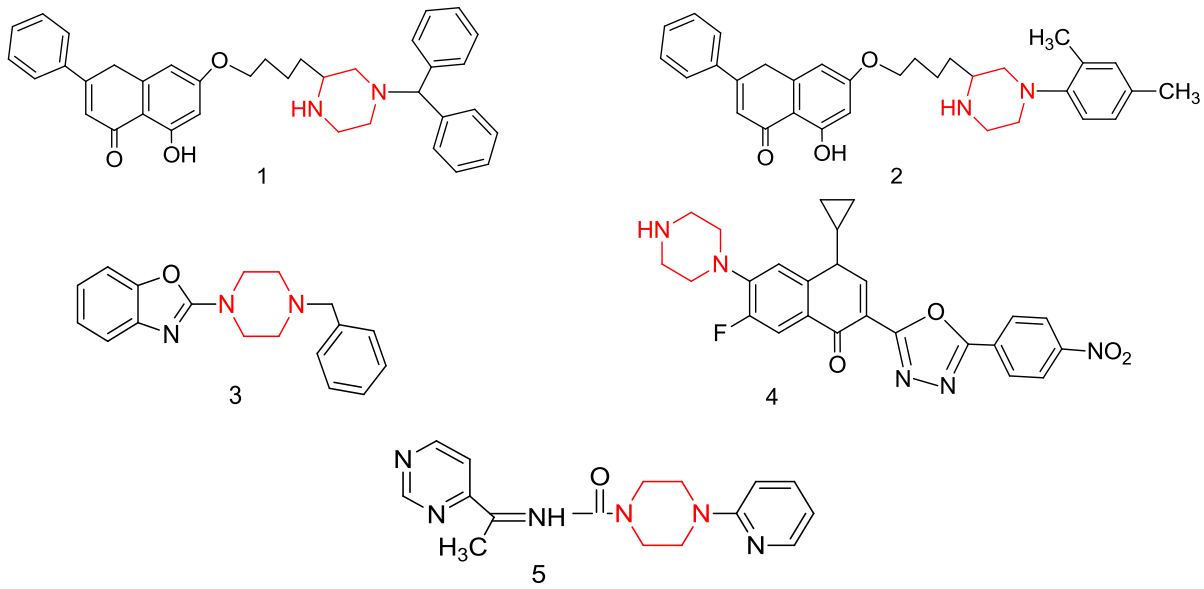
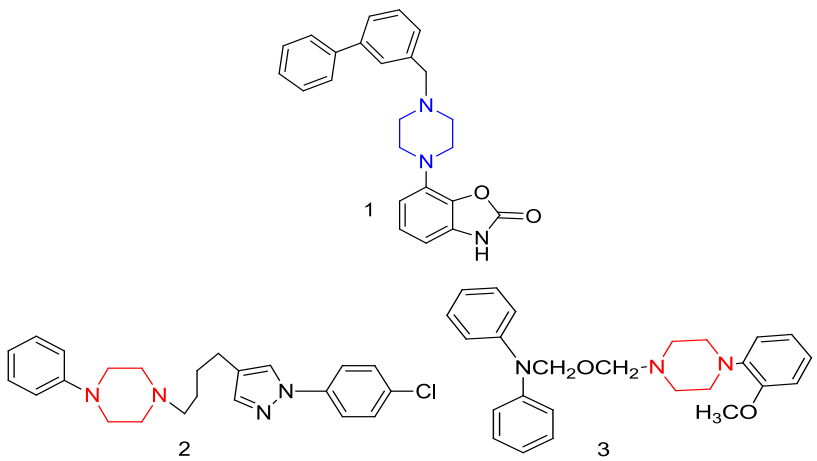


Figure 10: Anti-inflammatory piperazine derivatives.



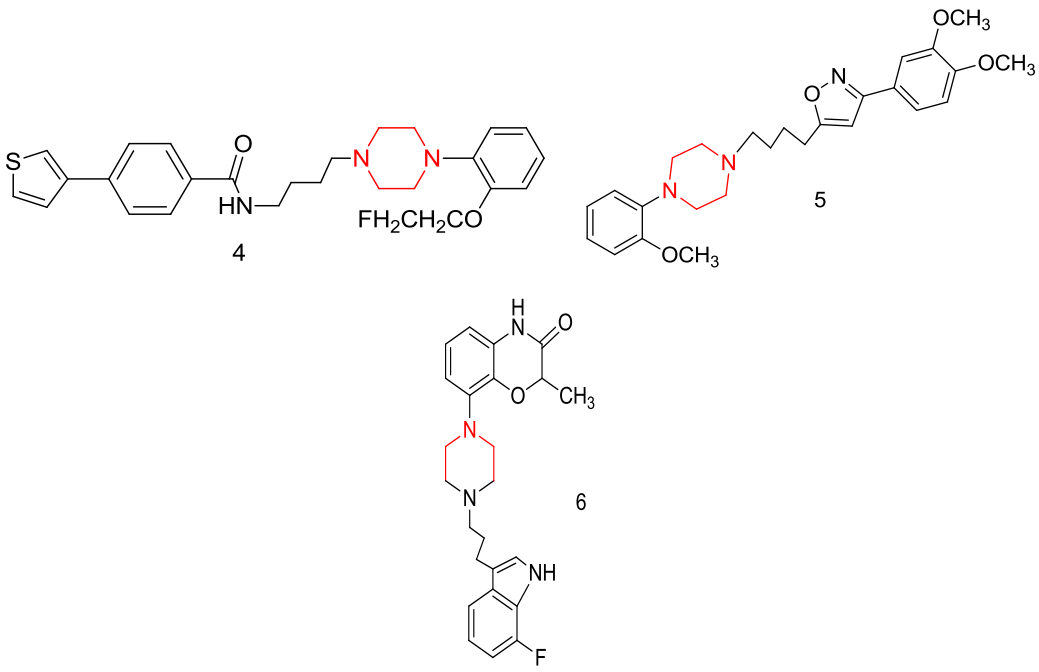


Figure 11: Anticancer piperazine derivatives.

CONCLUSION

Piperazine is an important saturated nitrogen-containing heterocyclic scaffold that plays a significant role in modern medicinal chemistry. Due to the presence of two nitrogen atoms and its structural flexibility, piperazine serves as a key pharmacophore in the design of many therapeutically effective drugs. Numerous piperazine derivatives exhibit a wide spectrum of biological activities, including anxiolytic, antidepressant, antipsychotic, antimicrobial, anticancer, anti-inflammatory, and antiviral effects. Well-known drugs such as buspirone, vortioxetine, and clozapine highlight the clinical importance of the piperazine moiety. The versatility of piperazine and its derivatives makes them valuable components in rational drug design and pharmaceutical research. Overall, piperazine remains a crucial and widely used compound in the development of competitive and effective medicinal agents.

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