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AN OVERVIEW OF TRIAZOLE SCAFFOLD: SYNTHESIS AND PHARMACOLOGICAL SIGNIFICANCE (2010-2020)

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Abstract

Among heterocyclic compounds, triazole has become an important one in the development of new drugs. A wide array of drugs comprising triazole nuclei display wide range of pharmaceutical applications which include anticonvulsants, antimalarial, antimicrobial, antitumor, antiviral, antiproliferative , anticancer , antioxidants, analgesics, antifungal , antiplasmodial , antibacterial , immunostimulants and antidiabetic. This pharmacological significance of the triazole nucleus has driven the interest of researchers to develop potent triazole derivatives with auspicious biological activities.

Keywords:
Triazole, Various synthetic methods, antibacterial activity, anti-fungal activity.

Introduction:

Synthesis of heterocyclic compound is of huge attention in synthetic organic chemistry as it possesses variety of therapeutic applications and their existence in numerous natural products like vitamins, hormones, antibiotics and alkaloids.[1] Triazole is a significant class of heterocyclic compounds revealing an extensive range of pharmacological activities. It is otherwise known as pyrrodiazoles and is a five-membered, di unsaturated ring system comprising three nitrogen atoms in a heterocyclic core. [2] Triazole is a white to pale yellow crystalline solid with a weak, characteristic odour, it is soluble in water and alcohol, melts at 120°C and boils at 260°C. It occurs as a pair of isomeric chemical compounds 1,2,3-triazole and 1,2,4-triazole with molecular formula $C_2H_3N_3$ and a molecular weight of 69.06.Two isomers of triazole nucleus exist that differ in the 'position of nitrogen atoms' in the nucleus. These are 1,2,3 triazoles and 1,2,4 triazoles [3]. The structure–activity relationship (SAR) of triazole derivatives have exposed that substitutents on the triazole nucleus at the 1, 3 and 5 positions can be diverse but the greatest difference in structure and properties is exerted by the groups linked to nitrogen atom at the first position [4].

Pharmacological activities

Antibaterial activity:

*Güzeldemirci et al.*reported a synthesis of series of 4-alkyl/aryl-2,4-dihydro-5-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-3H-1,2,4-triazole-3-thiones (3a–i)starting from 6-(4-bromophenyl)imidazo [2,1-b]thiazole-3-acetic acid hydrazide. All the synthesized compounds were examined for in vitro antibacterial activity against Staphylococcus aureus ATCC 29213, Pseudomonas aeruginosa ATCC 27853 and Escherichia coli ATCC 25922 by microbroth dilution

technique.The results exposed that some of the compounds showed promising antimicrobial activities against S. aureus ATCC 29213and E. coli ATCC 25922. [5]

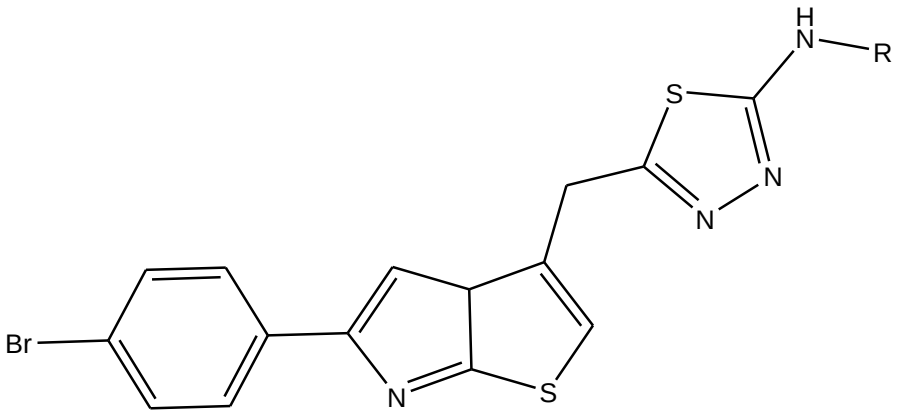
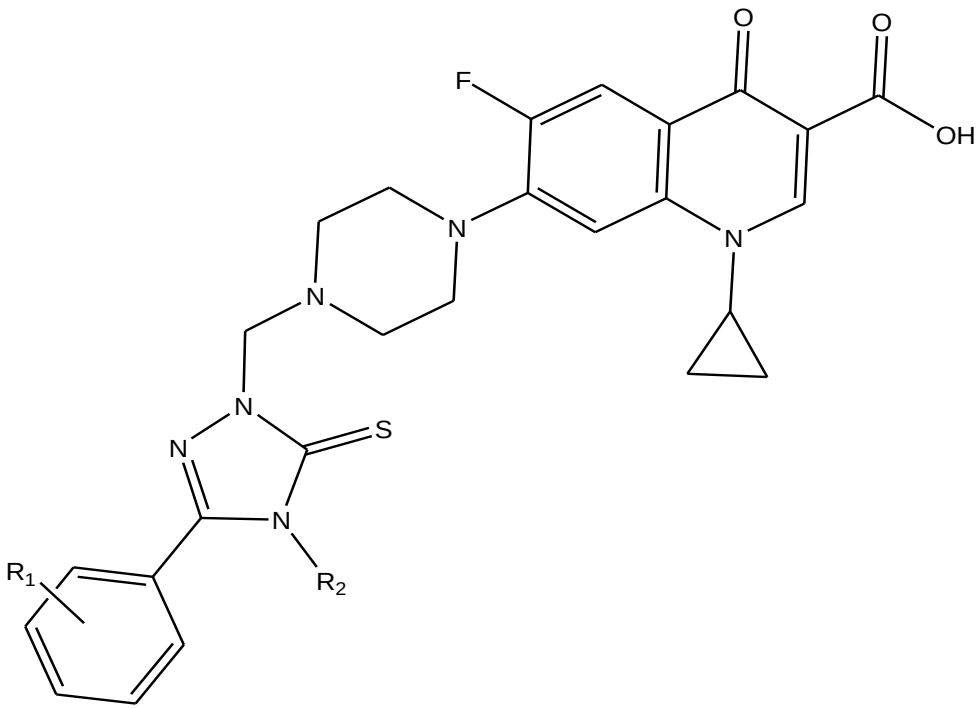


Fig: 1 1,2,4-triazoles bearing imidazo[2,1-b]thiazole moiety

Plech et al. utilized molecular hybridization approach to synthesize a series of 1,2,4-triazole-based compounds as potential antibacterial agents. The aimed compounds were synthesized by Mannich reaction of 1,2,4-triazole-3-thione derivatives with ciprofloxacin (CPX) and formaldehyde. Their active antibacterial effect on Gram-positive bacteria was accompanied by similarly strong activity against Gram-negative strains. The toxicity of the CPX-triazole hybrids for bacterial cells was 18930 times greater than the toxicity for humancells. The results of enzymatic studies revealed that the antibacterial activity of the CPXtriazole hybrids is not dependent only on the degree of their affinity to DNA gyrase and topoisomerase IV.[6]



. **Fig: 2** 1,2,4-triazole-ciprofloxacin hybrids

Gupta et al. synthesized a series of Schiff bases based 4-(benzylideneamino)-5-phenyl-4H-1,2,4-triazole-3-thiol scaffold by heating thiocarbohydrazide and substituted benzoic acid and subsequently, treating with Substituted benzaldehydes. All the synthesized seventeen derivatives were biologically screened for antibacterial activity. Most of the synthesized compounds exhibit strong antibacterial activity against S. aureus and were superior or comparable to standard drug streptomycin. These made the new molecule as a potential antimicrobial agent.[7]

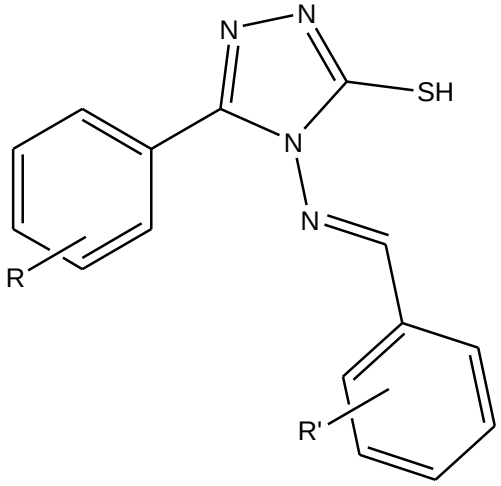


Fig: 3 4-(benzylideneamino)-5-phenyl-4H-1,2,4-triazole-3-thiol

Gao et al. designed a series of potent twelve moxifloxacin-amide-1,2,3-triazole-isatin hybrids. All the synthesized compounds were screened for invitro antibacterial activity against clinically important Gram-positive and Gram-negative bacteria including drug-resistant pathogens. All the

hybrids exhibited significant activity against the tested pathogens with MICvalues of ≤0.03 to 128μg/mL, and some of hybrids activity were comparable to or better than the parent moxifloxacin (MIC:≤0.03–8μg/mL).[8]

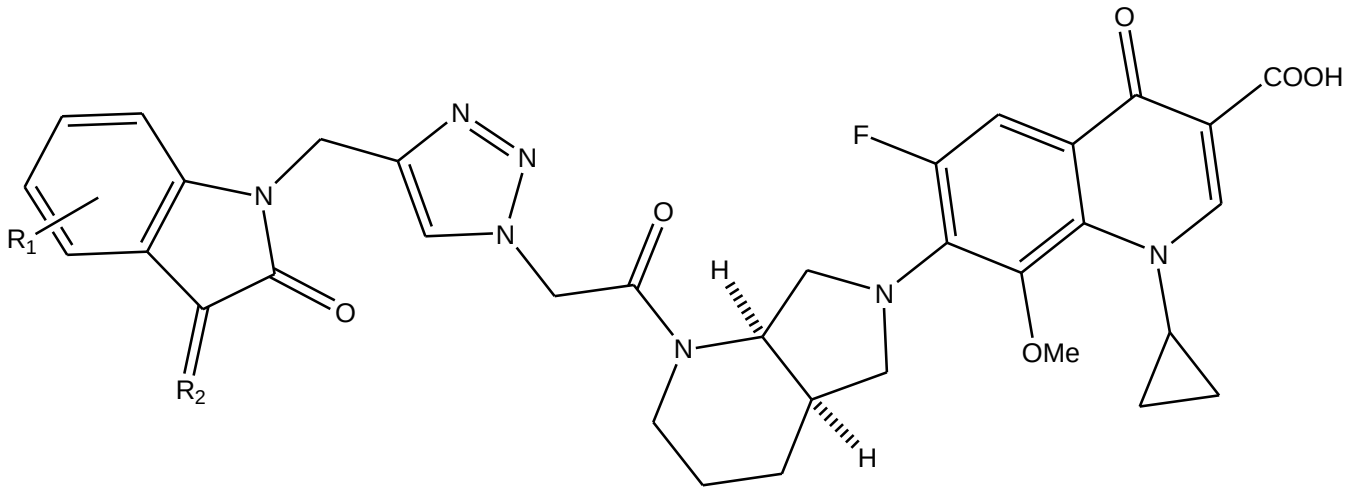


Fig: 4 moxifloxacin-amide-1,2,3-triazole-isatin hybrids

Wang et al. synthesized a series of potent sulfanilamide-derived 1,2,3-triazoles with different lengths of alkyl chains and halo benzyl groups in good yields via cyclization of azides and terminal alkyne by click chemistry. The structure of the synthesized derivatives was confirmed by MS, IR and NMR spectra as well as elemental analyses. All the synthesized compounds were screened in vitro for their antimicrobial activity against *S.aureus, MRSA, E-typhosa,P.aeruginosa,S.dysenteria,B.Subtilis,E.Coli* as well as *C.albicans* and *C.mycoderma* using the two-fold serial dilution technique. The results revealed that the synthesized compounds bearing dodecyl,2,4-dichlorobenzyl and 2,4-diflurobenzyl group showed the powerful antibacterial activities against all the tested bacterial strains with the MIC values ranging from 32 to 128 μg/mL. The antimicrobial activity of the synthesized compound mainly depends on the length of the alkyl chain and substitution in the benzyl moiety.[9]

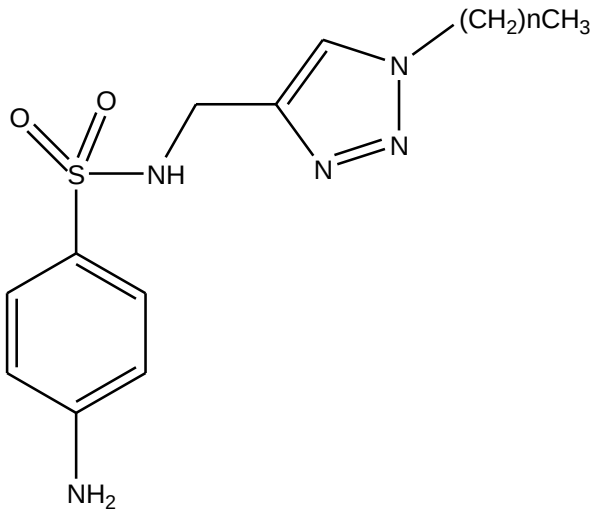


Fig: 5 sulfanilamide-derived 1,2,3-triazoles

Plench et al. reported a fast and efficient synthesis of 1,4-disubstituted thiosemicarbazide derivatives by the reaction of 3-chlorobenzoic acid hydrazide with various aryl isothiocyanates. A series of new Mannich bases related to the structure of 1,2,4-triazole has been also synthesized. All the synthesized compounds were screened for their in vitro antibacterial activity against the reference strains of aerobic bacteria - 6 Gram-positive and 3 Gram-negative ones, 12 Staphylococcus aureus. The results revealed that the antibacterial activity of the title compound mainly depends on the substituent and their position. The introduction of halogen group and electron withdrawing group at para position enhances the antibacterial activity of the title compounds. Also the introduction of the substituent at N-2 position enhances the antibacterial activity of the synthesized compounds on the gram negative bacteria.[10]

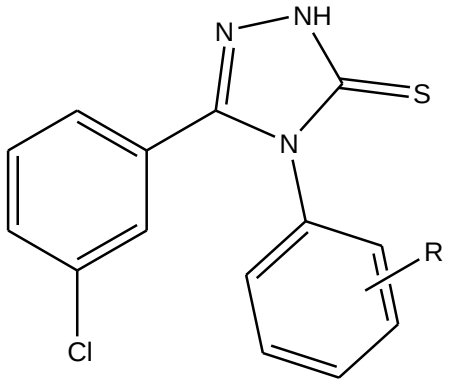


Fig: 6 5-(3-chlorophenyl)-4-substituted-2,4-dihydro-3H-1,2,4-triazole-3-thiones

Tang et al synthesized a series of amide derivatives comprising a triazole moiety through the reaction of intermediate 3 with different acyl chlorides and anhydrous potassium carbonates in anhydrous tetrahydrofuran at 50°C, using 2,4-dichloroacetophenoneas as a starting material . The structure of all the synthesized derivatives was characterized by proton and carbon NMR spectroscopy, IR spectroscopy and elemental analysis. Preliminary antibacterial activity results revealed that some of the synthesized compounds showed high antibacterial activity against *R. solanacearum* at 200 mg/L. Compounds 4m and 4q showed high antibacterial activity against R. solanacearum, with 71% and 65% inhibitory rates respectively.[11]

Antifungal activity:

Junqi Wu et al. developed a two series of (2R,3R)-1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-(N-substitutied)-2-butanols (3a-o, 5a-f, 8a-u) which were analogues of voriconazole. The structure of the synthesized compounds was confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. The MIC_{80} values showed that the synthesized compounds 3a-o showed potent activities than fluconazole on three important fungal pathogens. Significant activity of some of the synthesized compounds was observed on the Aspergillus fumigatus strain (MIC80 range: 1e0.125 mg/ml). [12]

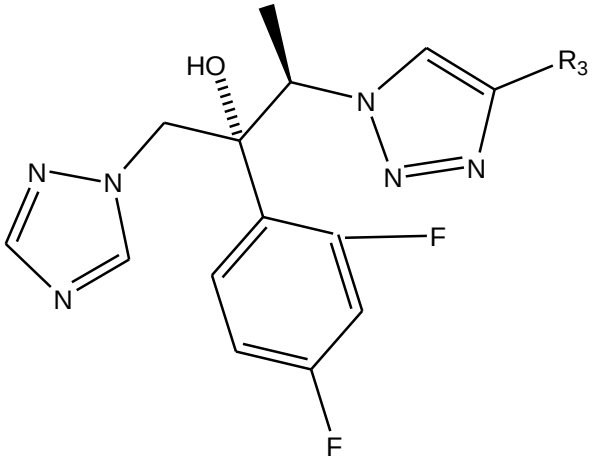


Fig: 7 Synthesis of (2R,3R)-1-(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-(N-substitutied)-2-butanols

Wang et al. designed a series of new conformationally restricted triazole derivatives bearing benzylpiperidin-4-yl methyl amino side chains. All the synthesized compounds were screened for in vitro antifungal activity against the tested pathogenic fungi. Most of the compounds exhibited higher antifungal activity against Candida albicans than fluconazole. Besides, compounds bearing chloro, cyano and bromo substituent also showed good activity against Aspergillus fumigatus with their MIC80 on the level of 1mg/mL. The binding modes of the designed compounds were analyzed by Flexible molecular docking. The results revealed that the aimed compounds intermingled with CACYP51 mainly through hydrophobic and van der Waals interactions. [13]

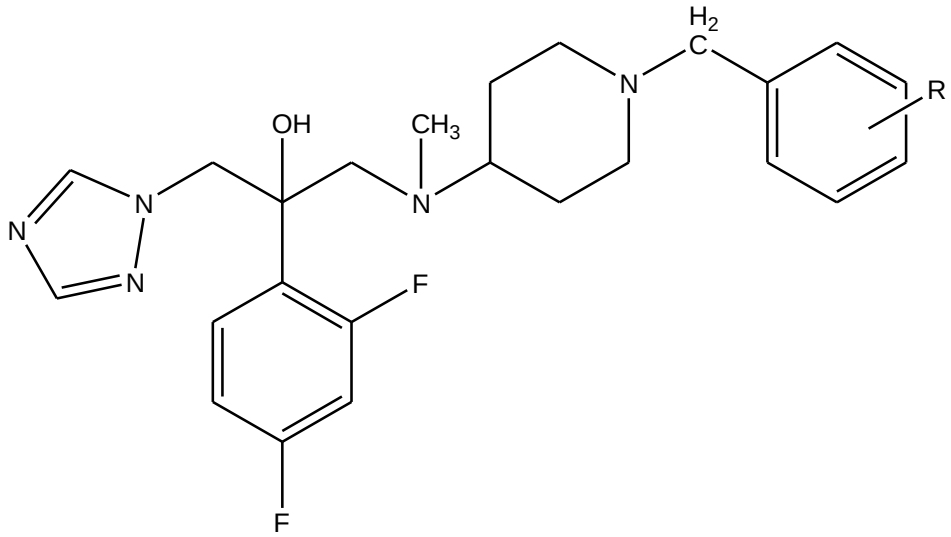


Fig: 8 Design rationales of the new azoles with benzylpiperidin-4-yl side chains

Sheng et al. rationally designed and synthesized a series of new antifungal triazole derivatives with phenylacetamide side chain on the basis of the structural information of lanosterol 14-demethylase (CYP51). In vitro antifungal activity assay showed that many compounds exhibited higher activity than fluconazole. Especially,

compound bearing di chloro substituent exhibited excellent inhibitory activity against Candida albicans and Cryptococcus neoformans (MIC = 0.0156 lg／mL), suggesting that it is a promising lead for the development of novel antifungal agents. The binding mode of compound 8h was investigated by flexible molecular docking. Itinteracted with CACYP51 through hydrophobic and van der Waals interactions.[14]

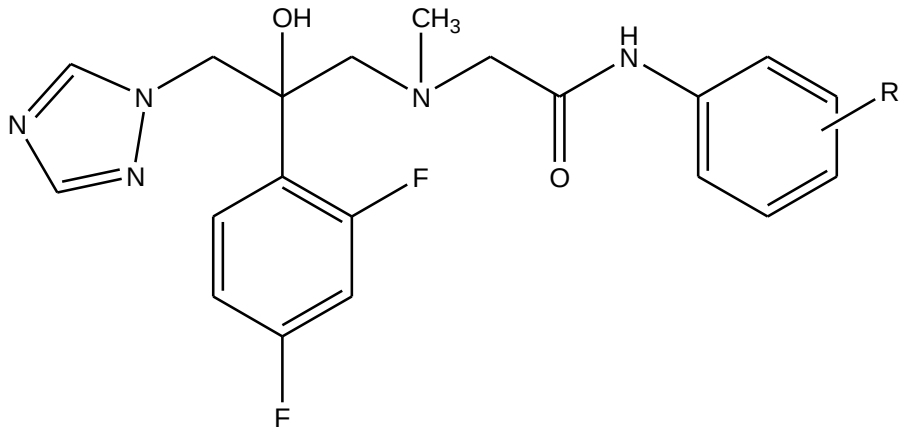


Fig: 9 Triazole derivatives with phenylacetamide side chain

Tan et al. reported a series of 1,2,4-triazole derivatives containing 1,2,3- thiadiazole starting from carbonic acid diethyl ester under microwave irradiation or ultrasonic irradiation as well as by conventional heating. The characterization of the newly synthesized compounds were done by ^{1}H-NMR, MS and elemental analyses. The in vivo fungicidal activities of the title compounds revealed that the synthesized compounds showed good antifungal activity against Pseudoperonospora cubensis. Some of the title compounds displayed moderate antifungal activities against Fusarium oxysporum,Pseudoperonospora cubensis, Sphaerotheca fuligenea, Corynespora cassiicola, and Xanthomonas axonopodis. Moreover the substituted benzene ring compound with p-Cl or 2,4-Cl_2 lead to higher fungicidal activity against P. cubensis. [15]

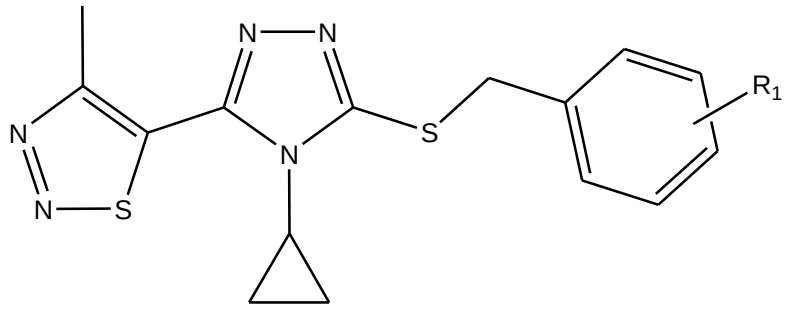


Fig: 10 1,2,4-Triazole derivatives containing 1,2,3-Thiadiazole Moiety.

Lin et al. reported a series of novel myrtenal derivatives bearing 1,2,4-triazole Moiety as potent antifungal agents by multi-step reactions. The structure of the synthesized compounds was confirmed by using UV-vis, FTIR, NMR, and ESI-MS analysis. The preliminary evaluation of antifungal activity of the target compounds were done by using in vitro method against *Fusarium oxysporum f. sp.cucumerinum, Physalospora piricola, Alternaria solani, Cercospora arachidicola,* and *Gibberella zeae* at 50 μg/mL. Among the synthesized Compounds,compound 6c (R = i-Pr), 6l (R = o-NO_2 Bn), and 6a (R = Et) showed tremendous antifungal activity against P. piricola with inhibition rates of 98.2%, 96.4%, and 90.7%, respectively, display better or comparable antifungal activity than that of the commercial fungicide azoxystrobin with a 96.0% inhibition rate, which served as a positive control.[16]

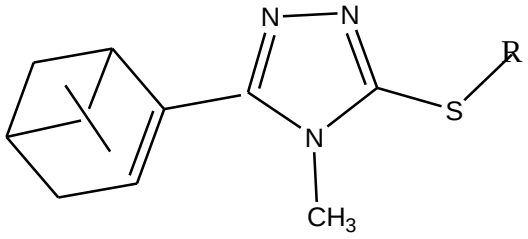


Fig: 11 Myrtenal-based 4-methyl-1,2,4-triazole-thioethers

Yu et al. synthesized a series of fluconazole analogues containing 1,2,3-triazole fragment and on the basis of the active site of the cytochrome P450 14α-demethylase (CYP51). The structures of the title compounds were characterized by ^{1}H NMR, ^{13}C NMR and LC–MS. The MIC_{80} values showed that the target compounds 1a–r exhibited better activities against all the fungi tested to some extent except Aspergillus fumigatus. Compounds 1c, e, f, l and p exhibited 128 times higher activity (with the MIC80 value of 0.0039 mg/mL) than that of fluconazole against Candida albicans and also exposed higher activity than that of the other positive controls.[17]

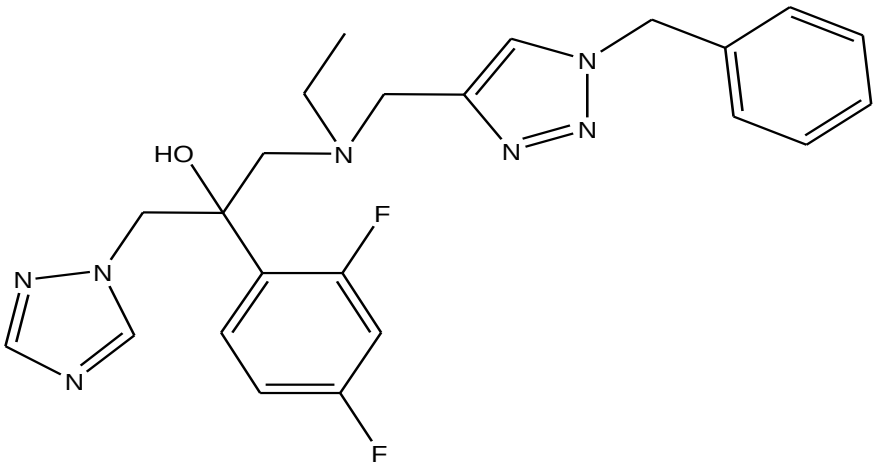


Fig: 12 Fluconazole analogues containing 1,2,3-triazole fragment

Wang et al. reported a novel triazole Compounds containing piperazine Moiety analogues to fluconazole. The structure of the title compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, MS and IR. The impact of piperazine moiety on in vitro antifungal activities of all the target compounds were assessed against eight human pathogenic fungi. [18]

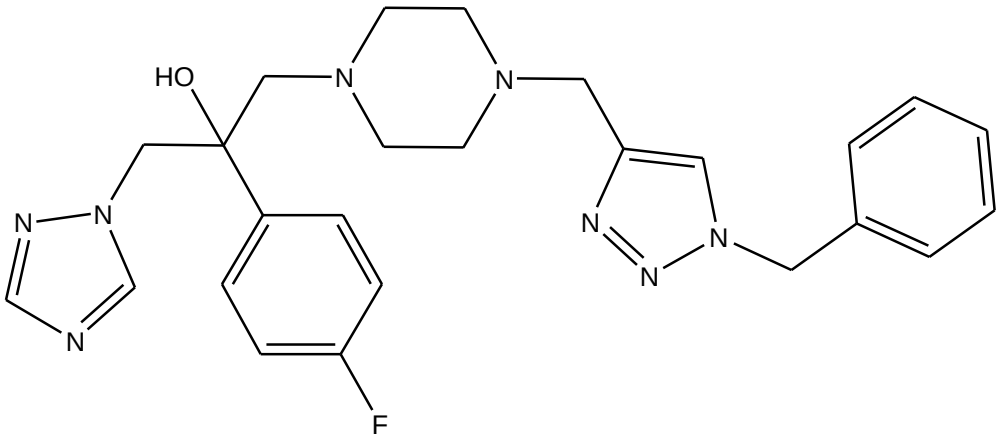


Fig: 13 Structure of the designed fluconazole analogues

Venugopala et al. reported a synthesis of 2,4,5 trisubstituted-1,2,3-triazole analogues and also evaluated the antifungal activity of the title compounds against five fungal strains, Candida parapsilosis, Candida albicans, Candida tropicalis,Aspergillus niger, and Trichophyton rubrum, via a 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazoliumbromide (MTT) microdilution assay. The results of antifungal activity of the title compound revealed that all the test compounds showed potent antifungal activity against the tested ATCC strains. The title compound GKV15 showed as extremely promising, as it exhibited the best antifungal activity against C. parapsilosis, C. albicans, C. tropicalis, A. niger, and T. rubrum at an MIC of 0.98, 0.98, 0.49, 0.98, and 0.98 g/mL, respectively. [19]

Conclusion

This study sketches the synthesis , anti-bacterial and antifungal activity of triazole derivatives. These compounds exhibited a wide range of therapeutic importance. The triazole compounds can be synthesized by many methods and identified to have numerous pharmacological activities such as anticancer, antimicrobial, antiinflammatory,anti- HIV, anti -tubercular, anti -diabetic, antifungal etc. So, study on this molecule is useful to the mankind.

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