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REVIEW ON SUBSTITUTED 1,2,4 -TRIAZOLES AS POTENT ANTI-FUNGAL AND ANTI-VIRAL AGENTS

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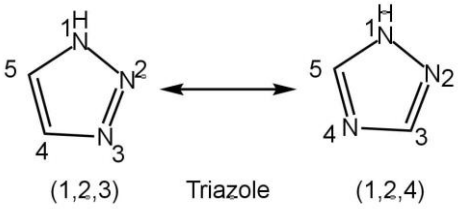
ABSTRACT
For the past few decades, modification of 1,2,4-triazole nucleus have made a tremendous significance in medicinal chemistry. 1,2,4-triazoles and their derivatives are found to have wide variety of pharmacological uses. From literature survey it is well known that triazole heterocycles exhibit manifold importance in the field of medicinal chemistry as a potent chemotherapeutic agent. Triazole is a synthetically versatile substrate used for the synthesis of a large variety of heterocyclic compounds, such as triazole fused with thiadiazole, oxadiazole, and has a raw material for drug synthesis. Much work has been carried out on triazoles as potent antifungal and antiviral agents and many drugs with triazole nucleus having antifungal properties have come into the market (e.g. Voriconazole, Itraconazole, Fluconazole, derivatives) as well as having antiviral properties (e.g. ribavirin, doravirin, derivatives) and their pharmacological profiles which may contribute in future to synthesize various analogs and to develop new pharmacologically less toxic medicines.

KEYWORDS: 1,2,4-antifungal; antiviral; Triazole.

INTRODUCTION

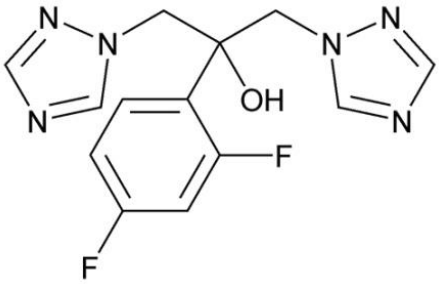
TRIAZOLE

Triazoles are the five membered heterocyclic compounds with three Nitrogen (N) atoms and two double bonds. The chemistry of 1,2,4-triazole and their fused heterocyclic derivatives has drawn a lot of attention in recent decades of their significance in synthesis and biology. Numerous therapeutically intriguing drug candidades, such as antifungal, antibacterial. analgesic. anti-inflammatory. antineoplastic. antiviral. anticonvulsant. anxiolytic. antihistaminic. CNS stimulants and others. have included the 1,2,3-trizole moiety.[1-8] Life-threatening systemic viral and fungal infections have grown more prevalent in immune compromised hosts The InhA inhibitory action of triazole derivatives is being investigated more and more. Isoniazid typically inhibits InhA. an important enzyme in the FASH system that is involved in the formation of mycobacterial mycolic acids. The possible antiviral and anti-tumoral properties of 1,2,4-triazole in general are being investigated. Examples of these substances with 1,2,4-triazole residues include the strong antiviral N-nucleoside ribavirin and the azole antifungal fluconazole.[9]

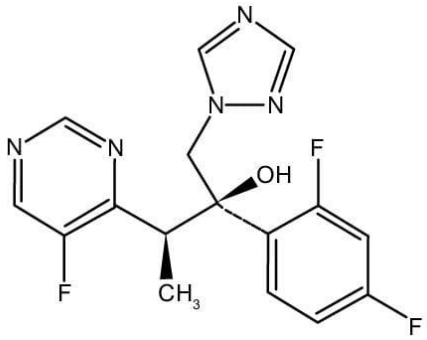


ANTIFUNGAL ACTIVITY

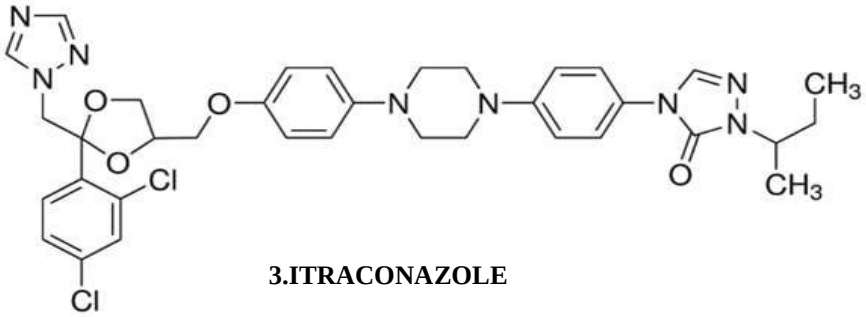
In clinical settings, triazole medications – fluconazole(1), voriconazole(2), itraconazole(3) and posaconazole - are the most often used antifungals. By blocking the activity of the cytochrome p-450 enzyme lanosterol 14α-demethylase, the triazoles work on the fungal membrane. Triazoles cause hepatotoxicity in addition to having strong antifungal action with a narrow antifungal range. Despite its toxicity, amphotericin B a polyene macrolide, is still the most effective medication, Synthesis and bioactivity of 2,5-disubstituted-1,3,4-oxadiazoles and their N,N′-diacylhydrazine precursors.[10]



1.FLUCONAZOLE



2.VORICONAZOLE

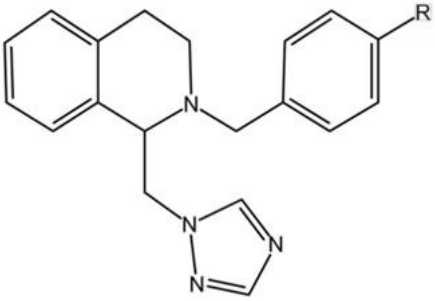


3.ITRACONAZOLE

Azoles are the most often utilized antifungals for treating fungal infections due to their low cost and oral availability.[11]

Numerous studies on triazole derivatives with a broad variety of biological activity have been published since triazoles were first used as pharmaceuticals.[12]

Novel 1,2,3 and 4-tetra series Azoles produced from hydro isoquinolines are antifungal drugs that may block lanosterol 14α-demethylase, which is dependent on cytochrome P-450. According to invitro experiments, a few of these chemicals (4) successfully stop the growth of certain mold and yeast strains. Numerous triazoles containing sulfur were synthesized, and research was done on the structure-activity connections of these potentially effective antifungal drugs. The pentylthio, heptylthio or nonylthio substituted triazole and the addition of a hydroxyl group (5) at the end of their alkyl chain enhanced their efficacy both candidiasis and aspergillosis, according to some significant findings from the SAR.[13]



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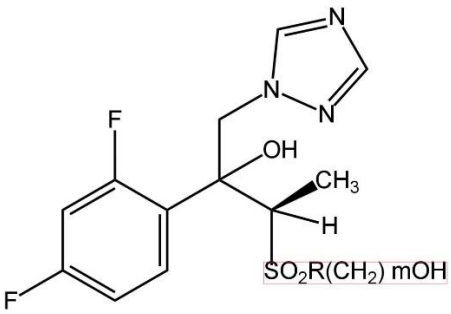
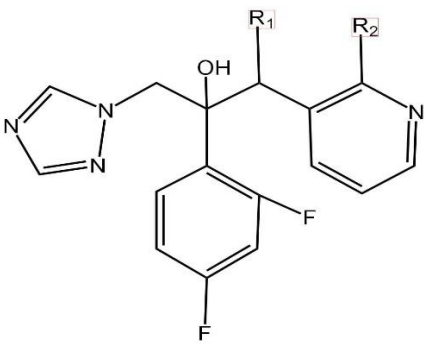


(5)

Voriconazole is a potent and wide spectrum triazole that shows activity against Candidia species and Aspergillus species. They have shown a good bioavailability after oral and intravenous administration and also reduced toxicity.[14]

When a triazole ring of fluconazole was substituted with a 4-pyridinyl moiety, purimidinyl moiety, and α-methyl group, the activity against Aspergillus fumigates increased in the fluorine – containing triazole. Thus, it was discovered that the triazole analo-guesses pyridinyl (6) and pyrimidinyl (7) exhibited a wide spectrum of activity against fungal infections, such as A funigatus and Candida krusei.[15]



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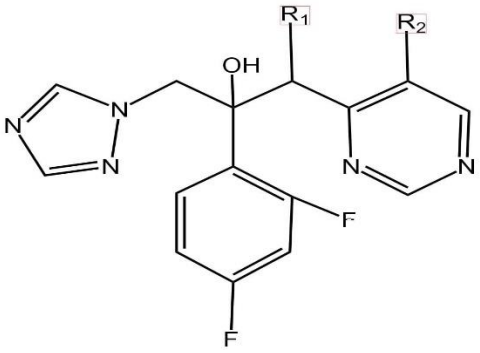
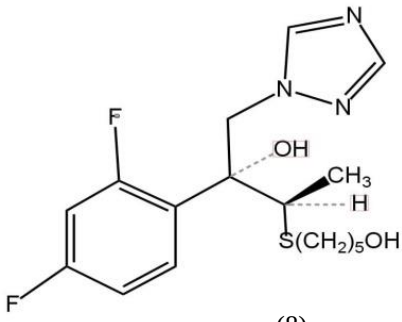


(7)

Triazole derivatives containing fluorine and sulfur, such as 5-hydroxypentylthio (8) and hydroxyheptylythio (9), were shown to be the more effective antifungal compounds; the addition of hydrophilic group to alkyl chains increased the antifungal activity of these compound.[16]



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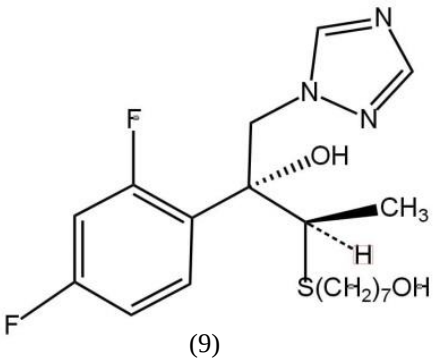
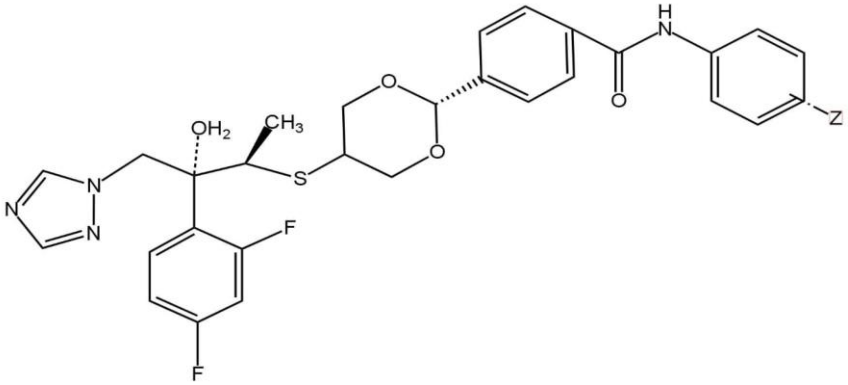


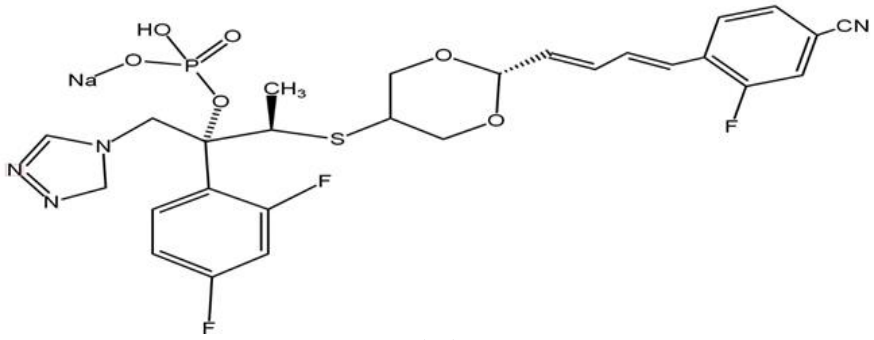
(9)

Using a triazole amide derivative produced outstanding activity against Aspergillus, candidia and Cryptococcus species. Good MICs were displayed by compounds.[10,11,12] that have a halogen atom at the C4 position on the benzene ring. The compound with the best MICs of all, especially against Candidia albicans, was compound[13], which added a cyano group to the C4 position on the benzene ring.[17]



(Z=4-F=10,Z=4-Cl=11,Z=4-Br=12,Z=4-CN=13)

Similar to the sulfur linkage, triazole phosphoryl ester (14) derivatives were synthesized and discovered to have antifungal and injectable prodrug properties.



(14)

When ether linkage was substituted for sulfur linkage, triazole derivatives with sulfur linkage still exhibited antifungal activity against Candida albicans, with certain compounds exhibiting antifungal activity that was greater than voriconazole. These analouges shown enhanced antifungal properties in vitro, particularly against Candida species. As a result of this research, molecules for more optimizations have been discovered.[18]

On Candida albicans and Candida tropicalis, a large number of 3-mercapto-1,2,4-mono/di-substituted tri-azoles derivatives show strong action. The antifungal activity was raised from 30% to 50% by adding a chlorine atom in the para position and a methylene chain between the phenyl and the 1,2,4-triazole cycle.[19]

ANTIVIRAL ACTIVITY

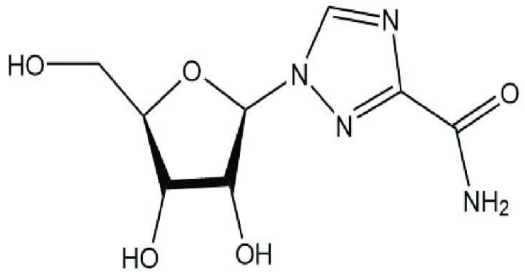
Severe viral infections have become more common in recent years, and antiviral chemotherapeutic medicines are insufficiently effective in treating these infections, which can result in fatalities and major human illnesses. As a result, there is an urgent need for a new antiviral, which is unquestionably necessary for the treatment of numerous deadly and incapacitating viral diseases. Derivatives of 1,2,4-triazoles play a crucial role in contemporary medicinal chemistry and are found in many pharmaceutical products, including antiviral medications. To the best of my knowledge, there aren't many review papers that focus solely on the roles of 1,2,4-triazole nuclei in different types of antiviral drugs during the past few decades, along with some structure-activity connections and examples of logical design.[29]

According to multiple reviews, 1,2,4-triazole derivatives are the preferred structural moiety in the creation of novel medications with a broad spectrum of pharmacological action.[20]

This is because an amide, ester, or carboxyl group can be thought of as a bioisostere of the triazole ring.[21]

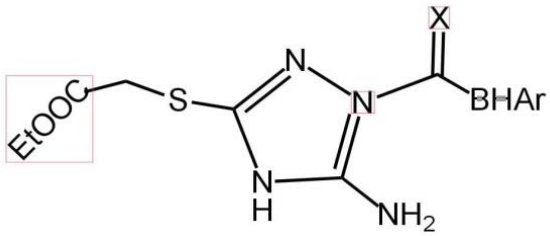
Hepatits C influenza A and B, herpes type 1 and 2 viruses, and other RNA and DNA viruses are susceptible to the antiviral effects of ribavirin (15). It is now being investigated if this drug can be used to treat coronavirus, hantavirus, and other hemorrhagic fevers.[22]

Numerous ribavirin modes of action have been postulated. It is believed that this chemical affects viruses differently. Ribavirin may mimic the purine guanidine cycle, according to one theory.[23]



(15)

It was demonstrated that compound that have had their nitrogen atoms changed both the endocyclic (compound 16) and exocyclic (compound 17) positions are effective against the herpes simplex type 1 virus. With minimal toxicity and great selectively, the highest activity was exhibited by condensed triazolopyrimidines 8(in article), which had structural similarities with purine basis. The study's authors think that another crucial element influencing the antiviral activity is the lipophilicity of substituent R1 and R2. The closest analog of acyclovir, compound, was found to be a viable candidate for additional development as an antiherpetic drug through physiochemical experiments employing the ADMET principle. Additionally, it has been demonstrated that substituting a thiadizole ring for the triazole ring results in the total loss of antiviral.[24]



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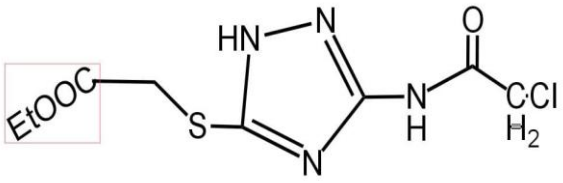


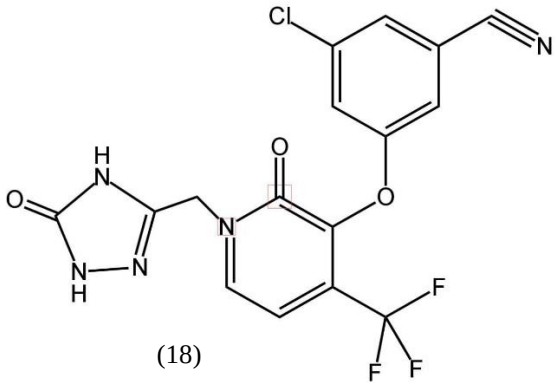
(17)

Suggested two techniques for creating ribavirin analog (chemical and chemoenzymatic) that begin with natural nucleoside substrates and substitute the isostere 1,2,4-oxadiazole ring for the carboxamide fragment. The produced compounds showed strong antiviral efficacy against influenza A, herpes simplex type 1, and hepatitis C viruses that was on par with ribavirin.[25]

Creation of ribavirin analogs with a vinylaryl substituent at triazole ring position 5. It was investigated how the structure and activity of the resulting compounds E/Z-2 related to the herpes simplex, influenza, and hepatitis C viruses. According to the obtained result 6, all active compounds share two characteristics: lipophilic substituent in the para position of the aryl ring and a firm link between the triazole and aryl rings. It was shown that the Z-isomers are inert against the herpes simplex virus, whereas only the E-isomers exhibit high activity on par with ribavirin.[26]

Creation of ribavirin analogs 2 with a vinylaryl substituent at triazole ring position 5. It was investigated how the structure and activity of the resulting compounds E/Z-2 related to the herpes simplex, influenza, and hepatitis C viruses. According to the obtained results6, all active compounds share two characteristics: lipophilic substituents in the para position of the aryl ring and a firm link between the triazole and aryl rings. It was shown that the Z-isomers are inert against the herpes simplex virus, whereas only the E-isomers exhibit high activity on par with ribavirin.[27]

Again a number of doravirine-substituted acetamide analogs, which are strong non-nucleoside reverse transcriptase inhibitors (NNRTIs). The majority of compound 19 that were obtained exhibited HIV-1 inhibitory qualities. Compound 19's 1,2,4-triazole substituent in the amide fragment demonstrated good selectivity and excellent efficacy, on par with doravirine(18) but much better than lamivudine.[28]



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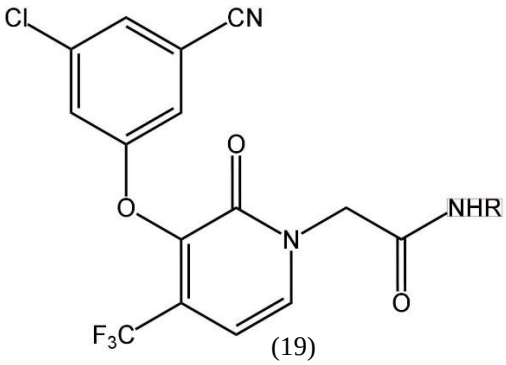

(19)

Triazole scaffolds, whether added to non-nucleosides or nucleoside analogs, show exceptional antiviral activity. Because of their diverse biological role, scientists from all around the world have developed a number of synthetic approaches. In this study, we have attempted to provide a thorough explanation of the role of [1,2,4] and [1,2,3]-triazole derivatives as antiviral medicines, as well as to outline novel synthetic techniques developed by various research groups. Numerous molecular proteins have been demonstrated to be targeted by antiviral triazole drugs. Furthermore, it was shown that a number of virus strains were vulnerable to triazole derivatives, including the immunodefficiency virus, SARS virus, influenza virus, hantavirus, herpes virus, and hepatitis B and C viruses.[29]

CATEGORY	DRUG NAME	MOLECULAR FORMULA	MOLECULAR WEIGHT	MECHANISM OF ACTION	EFFECTIVE AGAISNT
ANTI-FUNGAL AGENTS	FLUCONAZOLE	C13H12F2N6O	306.27 g/mol	Converts lanosterol to ergosterol. interacting with 14-demethylase (P450 enzyme)	Candidia species-C.albicans, C.parapsilosis, C.tropicalls etc.
	VORICONAZOLE	C16H14F3N5O	349.31 g/mol	14-demethylase (P450 enzyme)	C.albicans, C.parapsilosis, C.tropicalls, C.krusei
	ITRACONAZOLE	C35H38C12N8O4	705.6 g/mol	Demethylation	Cryptococcus neoformans, Coccidiodes immitis
	KETOCONAZOLE	C26H28CL2N4O4	531.43 g/mol	Demethylation	Candidia species Dermatophytes
	POSOCONAZOLE	C37H42F2N8O4	700.79 g/mol	Inhibition of ergosterol production (CYP51)	Aspergillus species Candidia species Zygomycetes
ANTI-VIRAL AGENTS	RIBAVIRIN	C8H12N4O5	244.20 g/mol	Inhibit RNA. DNA (IMPDH)	HCV, RSV, HBV
	DORAVIRIN	C17H11C1F3N5O3	425.75 g/mol	Reverse transcription (NNRTI)	Various type of HIV-1
	REMDESIVIR	C27H35N6O8P	602.6 g/mol	Inhibtion of RNA synthesis (RdRp)	SARS-CoV-2 (COVID-19), Ebola virus
	FAVIPIRAVIN	C5H4FN3O2	157.01 g/mol	Inhibit RNA replication and transcription (RdRp)	Influenza virus, Ebola virus

CONCLUSION

The 1,2,4-Triazole moiety has been continuously studying and has found various biological activities. These studies leads to discovery of many novel triazole derivatives which shows potent activities in treatment of various diseases like fungal, viral infections, cancer, tumour, seizers, inflammation, anxiety, etc. These study shows that small changes like linkage between the compounds and substitution in compounds can give a potent drug. Example, compound.[14] Again closest analogs of acyclovir gives potent and more effective compounds[16,17] than other triazole antiviral agents like Ribavirin[15], Doravirin(), etc. Therefore further studies on this novel 1,2,4-triazole may give new or modified compounds having more effective and potent activities.

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