Brief Review on 1,2,4-Triazoles and Piperazines: Versatile Scaffolds in Medicinal Chemistry

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***Abstract*- 1,2,4-Triazoles and piperazine derivatives are critical heterocyclic designs with wide applications in pharmaceuticals, materials science and agrochemicals. The review details synthetic approaches to these compounds, with an emphasis on classical methods, modern advances, and alternatives to green chemistry. Integration of 1,2,4-triazole and piperazine frameworks in drug discovery and other areas with future perspectives is also discussed.**

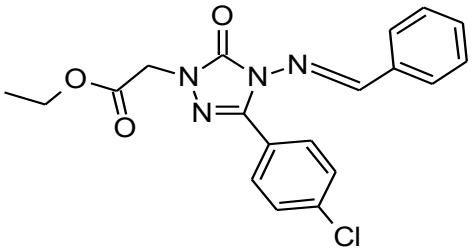
***Index Terms*- 1,2,4-Triazol-3-one Piperazine; Biological activities; Antipsychotic Activity**

I. INTRODUCTION

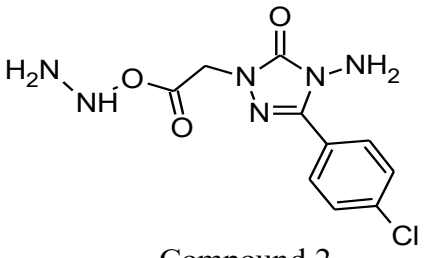
Heterocyclic compounds are the largest family of organic molecules in organic chemistry. A heterocyclic compound is formed when a carbon atom is replaced by an atom of oxygen, nitrogen, sulfur, or the same element. Heterocyclic compounds play an important role in everyday life. It is widely used in chemical and pharmaceutical industries. Triazole and piperazine are chemical compounds with molecular formula C2H3N3 and CH8N2. 1,2,4-Triazole and piperazine are basic heterocyclic scaffolds. Because of its structural properties, these parts are valuable in chemistry, and because of its widespread use in chemistry, it can also be easily synthesized from available compounds. This literature review highlights that the hetero compounds 1,2,4-triazole and piperazine are highly acceptable and have strong diverse activities such as antimicrobial, antibacterial, anticancer, antifungal, antipsychotic, etc. Finally, several biological activities of piperazine and 1,2,4-triazole derivatives of heterocyclic compounds were detailed and reviewed in this review.

II. A REVIEW ON SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1,2,4-TRIAZOLE DERIVATIVES

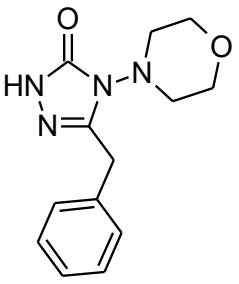
Demirbas, N., et al 4. synthesized a series of novel 1,2,4-triazole compounds and evaluated their antimicrobial properties against various micro-organisms. The results of their study show that compounds 1 and 2 interact with Enterobacter aerogenes, Staphylococcus aureus, Enterococcus faecalis and Bacillus cereus. These compounds effectively inhibited the growth of these test microbes, suggesting their potential as promising antimicrobial agents. On the other hand, compounds 3 and 4 showed only moderate antimicrobial activity. Their effectiveness is particularly important in the treatment of Escherichia coli and Klebsiella pneumoniae were found to have a relatively low inhibitory effect on these bacterial strains. Compounds 3 and 4 may still have some antibacterial properties, but their activity was not as significant as compounds 1 and 2. Overall, this study highlights the varying degrees of antibiotic effectiveness exhibited by different 1,2,4-triazole derivatives, with some showing strong potential for further development as antibacterial agents, while others may require modifications to increase their effectiveness



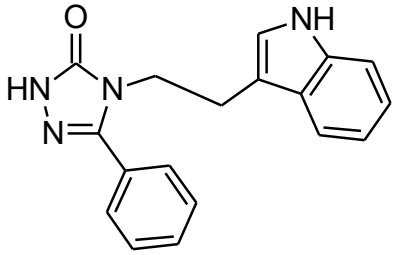
Compound 1



Compound 2



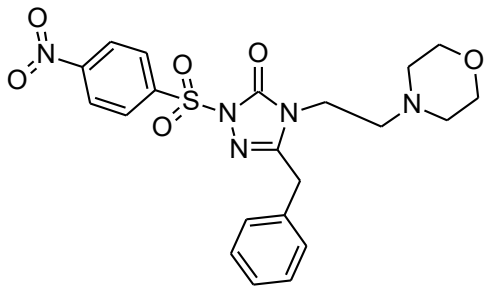
Compound 3



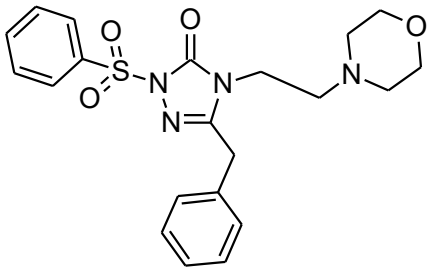
Compound 4

D. Sahin et al.5 integrated 1,2,4-triazole derivatives incorporating morpholine nuclease and evaluated their antibacterial properties. Among the synthesized compounds, Compound 5 demonstrated the highest level of efficacy against a wide range of bacterial strains tested. This suggests that the structural changes introduced in Compound 5 significantly enhanced its antimicrobial potential.

Additionally, Jacob H. J. et al. 6 assessed the antibacterial activity of selected 1,2,4-triazole derivatives against various bacterial strains, including common, environmentally and medically relevant pathogens. In their study, compound 5 was found to be the most potent among the above tested compounds. Notably, this compound has been identified as Bacillus cereus (B. showed antibacterial activity compared to Cereus) vs. Penicillin G, and Pseudomonas aeruginosa (P. also outperformed the effectiveness of penicillin G-positive control against Aeruginosa). These findings highlight the potential of 1,2,4-triazole derivatives, particularly Compound 5, as an effective antimicrobial agent. Its excellent activity against the pathogen P. aeruginosa, known for its resistance to many antibiotics, highlights its importance in the discovery of new antibiotic therapies. Further studies, including the mechanism of action analysis and evaluation of toxicity, can help determine its suitability for drug use.

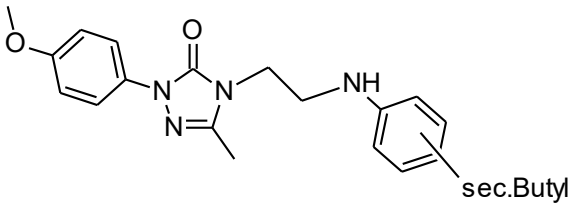


Compound 5

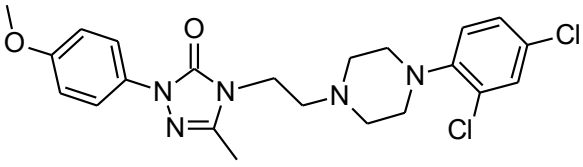


Compound 6

B. S. Patil et al.2 synthesized some novel 1,2,4-triazole derivatives. The antimicrobial activity of these newly developed compounds was thoroughly evaluated to determine their effectiveness against various bacterial strains. Among the synthesized derivatives, compound 7 demonstrated the highest potency against Staphylococcus aureus and Escherichia coli, demonstrating significant antibacterial effects. Meanwhile, compound 8 showed the greatest inhibitory activity against Pseudomonas aeruginosa, making it the most effective derivative against this bacterial strain. These findings highlight the potential of these 1,2,4-triazole derivatives as promising antimicrobial agents for further pharmaceutical development.



Compound 7



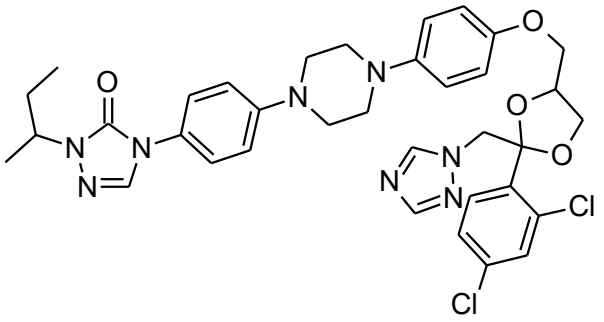
Compound 8

ITRACONAZOLE

Itraconazole is an antifungal drug developed by Janssen Pharmaceuticals in the late 1980s. It is a triazole antifungal agent that is known for its broad-spectrum activity against various fungal infections. works by blocking the enzyme lanosterol 14α-demethylase, which is required to produce ergosterol, a key component of

fungal cell membranes. This disruption weakens the cell membrane, causing the fungal cells to die.

It has a complex structure with three chiral centers and a dioxolane ring. It is available in oral and intravenous form, but its absorption is significantly improved when taken with food. In addition to its antifungal effects, it has also been used to treat hedgehogs and has shown potential for treating non- fungal diseases, such as certain cancers, by inhibiting specific signaling pathways. Its wide range of activity and non-scientific effects make it a valuable antifungal agent with various therapeutic abilities.

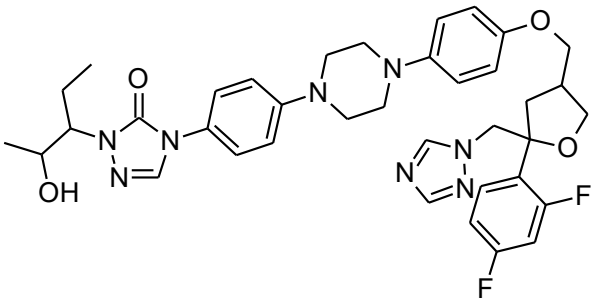


Itraconazole

POSACONAZOLE

Posaconazole is an antifungal drug developed by Schering-Plough in the mid-2000s. This is a new type of triazole antifungal, derived from itraconazole, which has a more complex structure that includes four chiral centers and a long side chain. Posaconazole has a wider range of activities compared to older triazoles. It works by blocking an enzyme necessary for the production of fungal cell membranes, which leads to cell death. In addition to treating fungal infections, posaconazole also treats Chagas disease, leishmaniasis, and hedgehog. It has demonstrated the ability to inhibit signaling pathways. Understanding the properties and structure of posaconazole can help develop better antifungal drugs in the future.

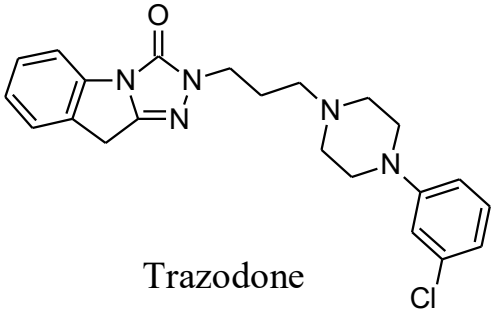
Posaconazole is a broad-spectrum antimicrobial agent with favorable pharmacokinetics and effective activity against various fungal infections. After oral administration, it is absorbed within three to five hours, significantly increasing its bioavailability when taken with a high-fat meal, resulting in a fourfold increase in plasma concentration compared to fasting conditions. With a half-life of 16 to 31 hours, the drug is mainly metabolized by the liver, which allows for continued antifungal activity. Posaconazole works by inhibiting lanosterol 14α-demethylase, a key enzyme in the biosynthesis of ergosterol, an essential component of fungal cell membranes. This disruption compromises the integrity of the membrane, causing the fungal cells to die. It is notoriously more potent at inhibiting 14α-demethylase than itraconazole. Interestingly, posaconazole has shown potential beyond antifungal activity, particularly in the treatment of Trypanosoma cruzi infection, a causative agent of Chagas disease, where it has shown greater efficacy than benznidazole in some cases. Its broad-spectrum activity and emerging applications make posaconazole a valuable agent in the treatment and prevention of invasive fungal and other parasitic infections.



Posaconazole

TRAZODONE

Trazodone is an antidepressant drug developed by Angelini Research Laboratories in the 1960s. It belongs to the class of serotonin antagonists and reuptake inhibitors. Trazodone works by increasing serotonin levels in the brain, preventing the reuptake of serotonin, and acting as an antagonist at certain serotonin receptors, which helps to improve mood and reduce anxiety. Compared to other antidepressants, trazodone has a simple chemical structure and is available in oral form. It is commonly used to treat major depressive disorders, anxiety, and insomnia due to its sedative effects. In addition to its antidepressant action, trazodone has shown benefits in treating sleep disorders and post-traumatic stress disorder. Its double effect on mood and sleep makes it a widely used and versatile drug.



Trazodone

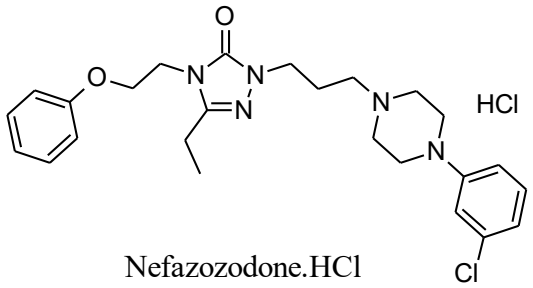
NEFAZODONE.HCl

Nefazodone is an antidepressant drug developed by Bristol-Myers Squibb and approved in the 1990s. It belongs to the class of serotonin antagonists and reuptake inhibitors. Nefazodone works by blocking the reuptake of serotonin and antagonizing the 5-HT2A receptor, which helps to improve mood and reduce anxiety.

Structurally, nefazodone has a complex chemical structure with several chiral centres. It is metabolized in the liver primarily using the enzyme CYP3A4. Although effective for depression and anxiety, in rare cases, its use was reduced due to the risk of liver toxicity. Despite this, the dual action

The effects of nefazodone on serotonin receptors and reuptake give it a unique position among antidepressant drugs.

Nefazodone is a serotonin antagonist and reuptake inhibitor with a unique pharmacological profile. Structurally, it contains a triazolone core, a piperazine ring (which plays a crucial role in serotonin receptor binding), and a chlorophenyl group (which contributes to its receptor affinity). Its mechanism of action involves multiple pathways. First, it blocks 5-HT$_2$A receptors, reducing serotonin overstimulation, which leads to decreased anxiety, improved sleep quality, and mood stabilization. Additionally, it inhibits the reuptake of serotonin and norepinephrine, enhancing their availability in synapses, thus elevating mood. It has minimal dopamine reuptake inhibition, which may help reduce emotional blunting commonly seen with SSRIs. Furthermore, nefazodone exhibits α1-adrenergic antagonism, which may lead to mild sedation and hypotension, contributing to its anxiolytic effects. Compared to trazodone, another serotonin antagonist and reuptake inhibitor, nefazodone has a lower risk of sedation due to reduced H1-histamine receptor binding, causes less sexual dysfunction than serotonin antagonist and reuptake inhibitors, and has a lower likelihood of orthostatic hypotension. However, it carries a higher risk of liver toxicity, which has led to a black box warning and limited its use in some countries.



Nefazozodone.HCl

III. DISCUSSION

The classification of 1,2,4-triazoles and piperazine highlights their versatility and importance in medicinal chemistry. For 1,2,4-triazoles, substitution patterns such as mono and d-substitution play an important role in determining their biological activity. Functional triazoles with groups such as hydroxyl or amino further increase their medicinal potential, while fused triazoles, combining the triazole ring with other systems, provide unique electronic and medicinal properties. The success of triazole derivatives as antifungal agents, exemplified by drugs such as fluconazole, demonstrates their value. However, the discussion may explore expanding their use to other therapeutic areas.

Similarly, piperazines are extremely versatile due to their ability to accommodate various changes on the nitrogen atoms. The difference between mono- and di-substituted derivatives significantly affects their activity and selectivity. Fused piperazines provide an additional layer of structural complexity, which helps to improve pharmacokinetics. While their widespread use in drugs such as antihistamines (cetirizine) and antipsychotics emphasizes their importance, there is still room to explore their potential in emerging areas.

When comparing triazoles and piperazine, their structural differences - such as the number and location of nitrogen atoms - directly affect their chemical and biological properties. This raises questions about how options and functional groups can be optimized for specific applications. Both classes present opportunities and challenges, especially for achieving regulatory change or incorporating complex alternatives. Advances in computational chemistry and new synthetic methods can help overcome these challenges, making it possible to develop more powerful derivatives for a variety of applications.

Compound / Agent	Structural Class	Target / Activity	Biological Effect	Reference
Compound 1	1,2,4-Triazole	*Staphylococcus aureus*, *Enterococcus faecalis*	Strong antibacterial activity	Demirbas et al. (2004) [4]
Compound 2	1,2,4-Triazole	*Enterococcus faecalis, Bacillus cereus*	Moderate activity	Demirbas et al. (2004) [4]
Compound 3	1,2,4-Triazole	*Escherichia coli*	Potent antibacterial activity	Demirbas et al. (2004) [4]
Compound 4	Triazole morpholine hybrid	*Klebsiella pneumoniae*	Potent antibacterial activity	Sahin et al. (2002) [5]
Compound 5	Triazole morpholine hybrid	*Escherichia coli*	Moderate activity	Sahin et al. (2002) [5]
Compound 6	Triazole– morpholine hybrid	*Klebsiella pneumoniae*	Weak activity	Sahin et al. (2002) [5]
Compound 7	Triazole derivative	*Escherichia coli*, *Staphylococcus aureus*	High potency	Patil et al. (2012) [2]
Compound 8	Triazole derivative	*Bacillus cereus*, *E. coli*	Significant antibacterial activity	Patil et al. (2012) [2]
Posaconazole	Triazole antifungal	*Candida spp.*, *Trypanosoma cruzi*	Broad-spectrum antifungal & antiparasitic	Israel M.Jordi Góm ezi,Prat.(2014) [10]
Itraconazole	Triazole antifungal	*Aspergillus spp.*, *Histoplasma capsulatum*	Potent antifungal	Guanzhao Liang1, Musang Liu1,(2017) [11]
Trazodone	Triazolopyridinone–piperazine	Depression, insomnia	SARI: Serotonin reuptake inhibitor + 5-HT_2A antagonist	Sonia Gervais, Laval; Damon Smith, Saint-Laurent; (2010) [12]
Nefazodone	Triazolone piperazine	Major depressive disorder	SARI; withdrawn in some markets due to hepatotoxicity	Seva E Kostrubsky 1, Stephen CStrom,2006 [13]

IV. CONCLUSION

1,2,4-triazoles and piperazines are versatile heterocyclic compounds with significant potential in medicinal chemistry and pharmaceuticals. Their substitution patterns and functional groups influence their biological activities and therapeutic properties. Advances in synthesis, including green chemistry, have opened new avenues for their application in antifungal, antihistamine, and antipsychotic treatments. There is still considerable potential for these compounds in emerging areas like cancer and antiviral therapies. With further optimization and novel synthetic strategies, both classes of compounds promise to lead to more effective, targeted therapies, offering exciting prospects for the future of drug development.

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