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Triazole Compounds: Recent Advances in Medicinal Research

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ABSTRACT:
Biological enzymes and proteins may be readily bound by non-covalent interactions to triazole compounds, which contain three nitrogens in their five-member heterocyclic azole rings, and these compounds can carry out a broad variety of biological tasks. Some impressive outcomes have been reached using triazole-based derivatives as medicinal treatments due to the extensive research that has been conducted. There have been several clinical studies with a wide variety of triazole compounds, revealing both their high development value and their broad therapeutic potential. As well as antibacterial and antiviral characteristics, antifungal and anticancer effects were discovered in triazole compounds. Additionally, antibacterial, antitubercular, antiviral, anti-inflammation, anticonvulsive, antihelmintic, antidiabetic, anti-obesity, anti-histaminic, and antihypertensive characteristics were examined. There are also predictions for the near future of triazole-based chemical medicinal medicine research and development. This review is aimed at generating new ideas for the creation of the more active and dangerous triazole pharmaceutical drugs.

Keywords: Antifungal, anticancer, antibacterial, antitubercular, antiviral,

I. INTRODUCTION

As a result of the potential medical, agricultural, synthetic, artificial acceptor, supramolecular ligand, and biomimetic catalyst applications of triazole heterocyclic [1–2], this has been a popular area of research [1–2]. The triazole ring is an important five-membered heterocyclic with three atoms, aromaticity, and a large number of electrons. Many enzymes and receptors in living organisms interact with triazole derivatives through covalent bonds and hydrogen bonds, for example, because of their unique structure. [3-5], and hence demonstrate a wide range of biological activities [5-6]. Despite this, the triazole ring's particular characteristics make it an ideal candidate for the formation of supramolecular aggregates [6,7], which in turn may lead to the production of supramolecular medicines [8-11]. It is also possible to employ the triazole ring to create novel bifunctional medicinal compounds by linking together diverse pharmacophore fragments, making it an interesting linker for the creation of numerous bioactive and functional molecules. Imidazole, oxazole, pyrazole, thiazole, and amide moiety are all essential isosteres of the triazole ring for developing novel therapeutic compounds. Triazole-based compounds, one of the most active fields in drug research and development, have been widely synthesized and explored for their biological activity. Since its discovery, triazole compounds have been widely used in clinical practise as an antifungal drug of choice for a wide variety of fungus-infected patients. Clinical trials and therapeutic candidates for a broad variety of disorders have been made possible by novel triazole compounds with significant action, low toxicity, and minimal unwanted effects. This is due to their ability to be administered in a wide range of ways and their ability to be targeted to specific cells. All of this demonstrated the enormous therapeutic potential of triazole-based drugs. A thorough analysis of the research and development of triazole compounds as medicines during the last five years was conducted in light of this. The following aspects were examined: First, antifungal, then anti-cancer, then anti-bacterial, then anti-viral, then anti-inflammatory and analgesic, then anti-inflammatory and analgesic, then anticonvulsant, then antiparasitic, then antidiabetic, then anti-obesity, and so on. There were also a few remarks on the connections between structure and activity.

II. THE ANTIFUNGAL PROPERTIES OF TRIAZOLE COMPOUNDS

Toxicologically, triazole chemicals are among the safest and most effective antifungal drugs available. One of the most diverse classes of chemicals is triazole. Management of fungal infections has greatly benefited by the widespread clinical use of a large variety of triazole antifungal medications., and their associated research is now the most active field in the creation of antifungal treatments. Antifungal resistance, particularly multidrug-resistant fungi, is on the rise, and new,

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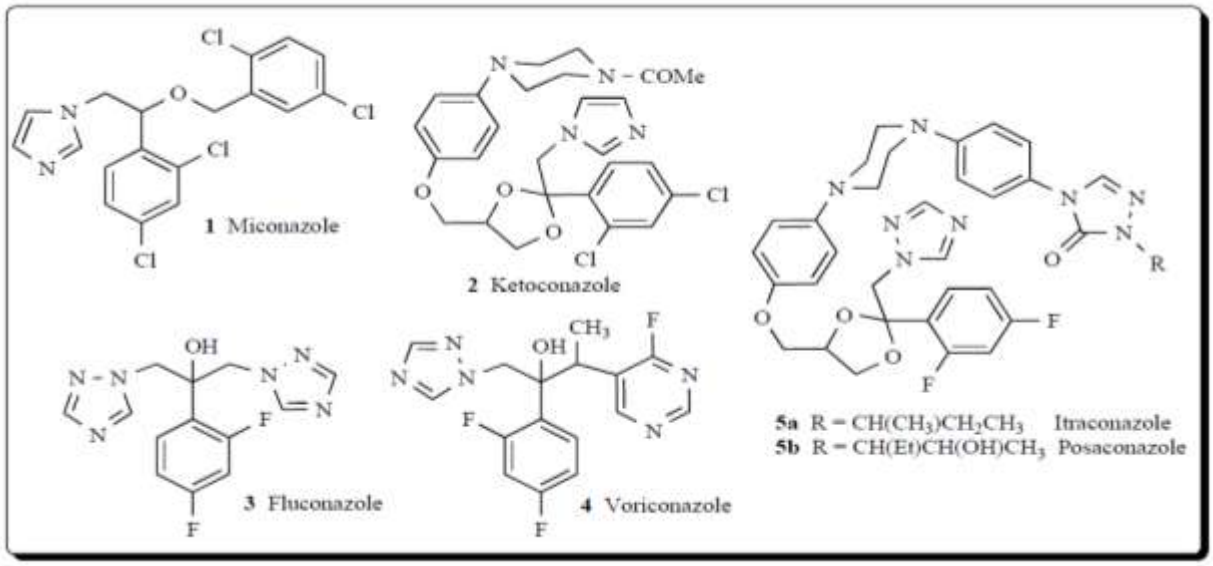
more effective, less toxic, and safer antifungal medicines are urgently needed. New triazole antifungal medication research has been separated into the following 2 ways in the last few years:
(1). Altering the structure of azole antifungal medicines for therapeutic use Toorder to raise their biological activity and widen their active range, this technique is to improve their physicochemical properties and binding affinity. With this approach, we want to preserve the benefits of current azole antifungal medicines while also addressing some of their drawbacks. (2). New triazole antifungal drugs may be used in the fight against fungi. Existing triazole compounds might have a novel mode of action [12,13]. Using this technique, triazole rings are combined with various pharmacophores, novel structural triazoles with distinctive skeletons are developed, triazole-based supramolecular medicines are developed.. etc. New lead compounds and a new approach to produce novel antifungal drugs are the goals of this donation, which aims to alleviate an expanding issue of drug-resistant infections.

2.1. Pharmacological Modification of Azole Antifungal Drugs in Clinical Practice

Two primary classes of antifungal azoles can be identified, the imidazoles [14-17], which include miconazole (1) and ketoconazole (2) as exemplary examples, and the triazoles [4,5,18,19], which includefluconazole.



(**3**), In the near future, itraconazole (5a) and Posaconazole (5b) will be available. For the treatment of a broad range of fungal diseases, triazole compounds with a lower toxicity than imidazole's are commonly employed in the clinic. Death rates from fungal infections are still too high, despite the fact that flaws in present therapeutic antifungal medicines, such as their restricted antifungal range, high toxicity and side effects, and single dose form, have been steadily revealed. Consequently, novel antifungal medicines are being sought after. The structural alteration of clinical azole antifungal medications, notably the further development of clinically prevalent fluconazole, is one of the most successful ways for their treatment.

2.1.1. A Fluconazole Structural Modification Method

Fluconazole, a WHO-recommended antifungal, is the medicine of choice for treating infections and diseases responsible for The infection of Albicans and Cryptococcus neoformans. Infectious candida infections of various sorts may be treated well with this medicine because of its potency, great safety profile, and favorable pharmacokinetic features. Contrarily, the use of fluconazole has led to increased numbers of bacteria that are resistant to the drug. Albicans. The limited water solubility of fluconazole means it is not effective against invasive fungus, as defined by the term "gloss"[20]. In toorderorder to improve fluconazole's antimicrobial range and therapeutic index, several researchers have been working to further modify its structural makeup. A number of fluconazole analogues, such as ravuconazole, albaconazole, and isavuconazole, have been investigated as antifungal

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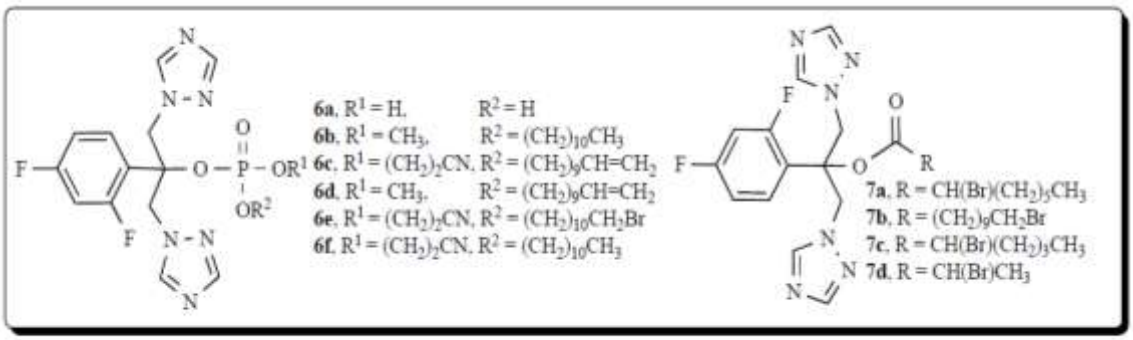
medication candidates. Fluconazole research has recently focused on three primary aspects: It is hoped that the advancement of fluconazole prodrugs will increase the drug's bioavailability and therapeutic effect. Fluconazole's side chain is also anticipated to be crosslinked, which might lead to novel fluconazole derivatives with enhanced binding to the active center of the fungus's lanosterol 14-demethylase enzyme..

2.1.1.1. Fluconazole Prodrugs Research

Fluconazole's prodrug research has been a hot issue in recent years, and it may be broken down into two categories:

(a). In fluconazole, the esterification of the tertiary hydroxyl group gives its ester type prodrugs. Chemical stability, action time, drug intermiscibility, absorption strength, bioavailability, toxicity reduction, and security are all goals of this sort of study. When compared to fluconazole, an ester prodrug released in 2003 for the treatment of C. albicans and Cryptococcus, fluconazole (6a) exhibits a broader antifungal range and is equally effective in preclinical models of fungal illness [23]. Fluconazole's commercial success has sparked a flurry of activity in the field of fluconazole prodrugs, including phosphate and carboxylic ester derivatives. While the aryl and glycosyl phosphate ester derivatives of fluconazole were more active, the alkyl derivatives 6b-f performed better than the others [24], the aryl and glycosyl compounds did not. There were no significant differences in efficacies between compounds 6b and 6c when tested against the strain of As per gillusnigerATCC 16404; the MIC values of these two compounds were much lower than those of fluconazole. (MIC



greater than or equal to 580 ng/mL). Against C. Albicans ATCC 14053 in SDBmedium, the carboxylic acid ester compounds demonstrated strong antifungal effectiveness, as well. More than 40 times more potent than fluconazole, ester compound 7a had a MIC of 111 g/mL. While fluconazole had lower lipophilicity and dermal permeability, all of these compounds had improved lipophilicity and dermal permeability. Alternatealternate therapy for fungal treatment might be photodynamic inactivation (PDI), which generates a cytotoxic impact on cells via the use of light. However, in the presence of light, the antifungal effects of the porphyrin-derived fluconazole 8via an ester link connection became poor [25].

(b). Fluconazole quaternization of the triazole ring More strong and widespread antifungal activity was shown when the triazolyl ring was transformed into thiazolium [26,27]. Higher water solubility and permeability with the electropositive triazole moiety imimprovetheir antibacterial efficacy[28]. Quaternization products derived from two fluconazole rings by different halides showed strong and broad-spectrum antibacterial activity, with low MIC values ranging from 0.5 to 64 g/mL against C. Albicans and Aspergillus fumigates, respectively, in vitro. Naphthalimino, Octyl, and Dichlorobenzyl fluconazole's demonstrated equivalent or superior efficacy against C. Albicans and A.fumigatus compared to fluconazole [29]. [20, 21] In the creation of prodrugs, natural glucose with numerous hydroxyl groups and strong water solubility is often employed [30]. To make water-soluble fluconazole with high biological activity, this natural chemical might be incorporated into fluconazole through an alkyl spacer. Glycose-derived fluconazole 9d showed superior antifungal activity and water solubility as compared to fluconazole. This, of course, is in favor of a more flexible administration model. glucose is also easy to create hydrogen bonds with enzymes and receptors because of the presence of multi hydroxyl multihydroxyl groups.

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REFERENCES

[1]. Bai, X.; Zhou, C.H.; Mi, J.L. Research and application of triazoles. Chem.Res. Appl., **2007**, 19, 721-729(in Chinese)

[2]. Chang, J.J.; Wang, Y.; Zhang, H.Z.; Zhou, C.H.; Geng, R.X.; Ji, Q.G. Recentadvances in researches of triazole-based supramolecular chemistry andmedicinal drugs. Chem. J. Chinese U., **2011**, 32, 1970-1985(in Chinese)

[3]. Mi, J.L.; Wu, J.; Zhou, C.H. Progress in anti-tumor agents: triazoles. WestChina J. Pharm. Sci., **2008**, 23, 84-86(in Chinese)

[4]. Mi, J.L; Zhou, C.H.; Bai, X. Advances in triazole antimicrobial agents. Chin.J. Antibiot., **2007**, 32, 587-593(in Chinese)

[5]. Wang, Y.; Zhou, C.H. Recent advances in the researches of triazolecompounds as medicinal drugs. Scientia SinicaChemica, **2011**, 41, 1429-1456(in Chinese)

[6]. Ouellette, W.; Jones, S.; Zubieta, J. Solid state coordination chemistry ofmetal-1,2,4-triazolates and the related metal-5-(pyrid-4-yl)tetrazolates.CrystEngComm, **2011**, 13, 4457-4485

[7]. Liu, K.; Shi, W.; Cheng, P. The coordination chemistry of Zn(II), Cd(II) andHg(II) complexes with 1,2,4-triazole derivatives. Dalton Trans., **2011**, 40,8475-8490

[8]. Rodriguez-Fernandez, E.; Manzano, J.L.; Benito, J.J.; Hermosa, R.; Monte,E.; Criado, J.J. Thiourea, triazole and thiadiazine compounds and their metalcomplexes as antifungal agents. J. Inorg. Biochem., **2005**, 99, 1558-1572

[9]. Zhou, C.H.; Zhang, Y.Y.; Yan, C.Y.; Wan, K.; Gan, L.L.; Shi, Y. Recentresearches in metal supramolecular complexes as anticancer agents. Anti-Cancer Agents Med. Chem., **2010**, 10, 371-395

[10]. Zhou, C.H.; Gan, L.L.; Zhang, Y.Y.; Zhang, F.F.; Wang, G.Z.; Jin, L.; Geng,R.X. Review on supermolecules as chemical drugs. Sci. China, Ser B:Chem., **2009**, 52, 415-458

[11]. Zhou, C.H.; Zhang, F.F.; Gan, L.L.; Zhang, Y.Y.; Geng, R.X. Research insupermolecular chemical drugs. Sci. China, Ser B: Chem., **2009**, 39, 208-252(in Chinese)

[12]. Fera, M.T.; Camera, E.L.; Sarro, A.D. New triazoles and echinocandins:mode of action, in vitro activity and mechanism of resistance. Expert Rev.Anti Infect. Ther., **2009**, 7, 981-998

[13]. Kumari, S.; Kumar, N.; Drabu, S.; Sharma, P.K. Advances in syntheticapproach to and antifungal activity of triazoles. Beilstein J. Org. Chem.,**2011**, 7, 668-677

[14]. Cai, J.L.; Li, S.; Zhou, C.H.; Wu, J. Advance in research of imidazolesasanti-tumor agents. Chin. J. New Drugs, **2009**, 18, 598-608(in Chinese)

[15]. Wu, J.; Mi, J.L.; Zhou, C.H. Avance in H3 histamine receptor ligands. Chin.Pharm. J., **2007**, 42, 404-409(in Chinese)

[16]. Meng, J.P.; Lu, Y.H.; Halqam, I.; Zhou, C.H. Advances in the research ofbenzimidazole compounds as enzyme inhibitors. Chin. J. Biochem. Pharm.,**2008**, 29, 422-425(in Chinese)

[17]. Meng, J.P.; Geng, R.X.; Zhou, C.H.; Gan, L.L. Advances in the research ofbenzimidazole drugs. Chin. J. New Drugs, **2009**, 18, 1505-1514(in Chinese)

[18]. Shi, Y.; Zhou, C.H. Synthesis and evaluation for a class of new coumarintriazole derivatives as potential antimicrobial agents. Bioorg. Med. Chem.Lett., **2011**, 21, 956-960

[19]. Shi, Y.; Zhou, C.H.; Zhou, X.D.; Geng, R.X.; Ji, Q.G. Synthesis andantimicrobialevaluation of coumarin-based benzotriazoles and theirsynergistic effects with Chlromycin and Fluconazole. Acta Pharm. Sinica,**2011**, 46, 798-810(in Chinese)

[20]. Wan, K.; Zhang, Y.Y.; Zhou, C.H.; Zhou, X.D.; Geng, R.X.; Ji, Q.G. Recentadvances in antifungal Fluconazole. Chin. J. Antibiot., **2012**, 37, (in press).

[21]. Pasqualotto, A.C.; Thiele, K.O.; Goldani, L.Z. Novel triazole antifungaldrugs: focus on isavuconazole, ravuconazole and albaconazole. Curr. Opin.Invest. Drugs, **2010**, 11, 165-174

[22]. Fera, M.T.; La Camera, E.; De Sarro, A. New triazoles and echinocandins:mode of action, in vitro activity and mechanisms of resistance. Expert Rev.Anti-Infect. Ther., **2009**, 7, 981-998

[23]. Sobue, S.; Tan, K.; Haug-Pihale, G. The effects of hepatic impairment on the

[24]. pharmacokinetics of fosFluconazole and Fluconazole following a singleintravenous bolus injection of fosFluconazole. Br. J. Clin. Pharmocol., **2005**,59, 160-166

[25]. Nam, N.-H.; Sardari, S.; Selecky, M.; Parang, K. Carboxylic acid andphosphate ester derivatives of Fluconazole: synthesis

and antifungalactivities. Bioorg. Med. Chem., **2004**, 12, 6255-6269

[26]. Mora, S.J.; Cormick, M.P.; Milanesio, M.E.; Durantini, E.N. Thephotodynamic activity of a novel porphyrin derivative bearing a Fluconazolestructure in different media and against Candida albicans. Dyes Pigments,**2010**, 87, 234-240

[27]. Zhou, C.H.; Yu, K.G.; Meng, J.P.; Fang, B.; Luo, Y.; Zhang, F.F.; Li, T.Q.;Li, J. Dibenzimidazole and onium compound thereof, preparation methodand medical use thereof. CN Patent, **2009**, CN101397276 (A)

[28]. Francavilla, C.; Low, E.; Nair, S.; Kim, B.; Shiau, T.P.; Debabov, D.; Celeri,C.; Alvarez, N.; Houchin, A.; Xu, P.; Najafi, R.; Jain, R. Quaternary ammonium N,N-dichloroamines as topical antimicrobial agents. Bioorg.Med. Chem. Lett., **2009**, 19, 2731-2734

[29]. Zhou, C.H.; Mi, J.L.; Wu, J.; Luo, Y.; Bai, X.; Gan, L.L.; Geng, R.X.Triazole onium compound with antimicrobial activity, preparation methodand medical use. CN Patent, **2009**, CN101391985(A)

[30]. Zhang, Y.Y.; Mi, J.L.; Zhou, C.H.; Zhou, X.D. Synthesis of novelfluconazoliums and their evaluation for antibacterial and antifungalactivities. Eur. J. Med. Chem., **2011**, 46, 4391-4402

[31]. Khalil, N.S.A.M. Efficient synthesis, structure, and antimocrobial activity ofsome novel N- and S-D-glucosides of 5-pyridin-3-yl-1,2,4-triazoles. Carbohydrate Res., **2006**, 341, 2187-2199