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Synthesis, biological activity and structure activity relationship studies of novel conazole analogues via conventional, microwave and ultrasound mediated techniques

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ABSTRACT

1,2,4-Triazole derivatives containing a piperazine nucleus (4a-d and 10) were prepared starting from 1-(2-methoxyphenyl)piperazine or ethyl 4-(4-amino-2-fluorophenyl)piperazine-1-carboxylate via several steps. The synthesis of fifteen compounds (7a-l and 13a-c), which can be considered as new analogues of azole class antifungals was performed starting from 1,2,4-triazoles (4a-d and 10) via three steps containing the condensation with 2-bromo-1-(4-chlorophenyl)ethanone, reduction of carbonyl group to alcohol and alkylation of OH group, respectively. All the reactions were examined under conventional, ultrasound and microwave irradiation conditions as green chemistry techniques, and optimum conditions were defined. The newly synthesized compounds were screened for their biological potentials including antimicrobial, antioxidant, antiurease and anti α-glucosidase activities and promising results were obtained. The enzyme inhibitory potentials of these compounds were further validated through molecular docking.

1. Introduction

At present, although humans have been accustomed to fight with the invasion of pathogens with both inherent defenses and medical protections, many pathogenic bacteria have been resistant to most of synthetic or natural antibiotics caused by the excessive and prolonged use of them, and this made microbial infections one of the foremost health crises worldwide. Literature survey reveals that bacterial infections cause to hundreds of thousands of deaths annually and billions of dollars in healthcare expenses emphasizing the urgent need to constant push to discover and improve strategies to counter these threats [1–5]. Similarly, Although various antibacterial and antifungal drugs with different structures and mode of action have been marketed, their clinical implementation have been limited by drug resistance, high risk of toxicity, insufficiencies in their efficacy and side effects [6–8]. One of the most common classes of antifungal agents, azoles play a leading role for the treatment of invasive fungal infections, and act by inhibit the synthesis of ergosterol, the bulk sterol in fungal membranes, by binding to the heme cofactor located in the active site of the cytochrome P450 14α-demethylase (CYP51). Several of these novel azole antifungal agents (Fig. 1), such as Econazole, Miconazole, Itraconazole, Voriconazole, and Ketoconazole have launched (see Fig. 1).

But as in all antimicrobial therapies, the overuse of azole class antifungals has resulted in the development of severe resistance, which significantly reduced their efficacy [7–13]. This has motivated the researchers to design and synthesis of novel and efficient drug candidates with different mode of action, more bioactivity and lowest side effects [14]. In the medicinal chemistry field, homology modeling and pharmacophore modeling techniques have been intensively used for design and development of new antimicrobial drug candidates [15]. According to these models depicted in Fig. 2 schematically, the fundamental azole drugs should have at least three basic pharmacophore groups: (1) imidazole or triazole unit (triazoles in recent years) for binding with CYP51 active side through coordination to hemeiron; (2) a hydrophobic, preferably aromatic group near the azole ring; (3) a second aromatic (preferably halogenated) region to increase the lipophilicity of the molecule, because it is well known that the lipophilic character of a bioactive molecule facilitates the penetration into the cell. Moreover, certain active compounds contain an additional hydrophobic substituent, and the presence of an —O— atom in the structure is necessary

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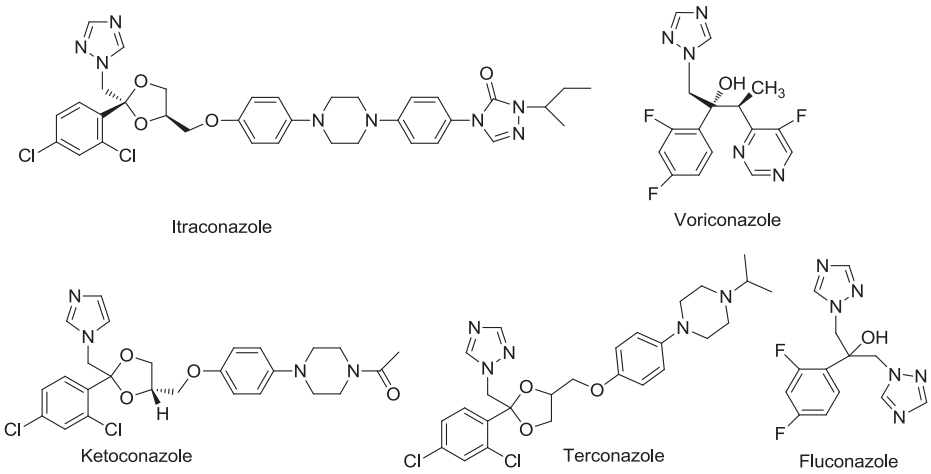

Fig. 1. Some known azole class antifungal drugs.

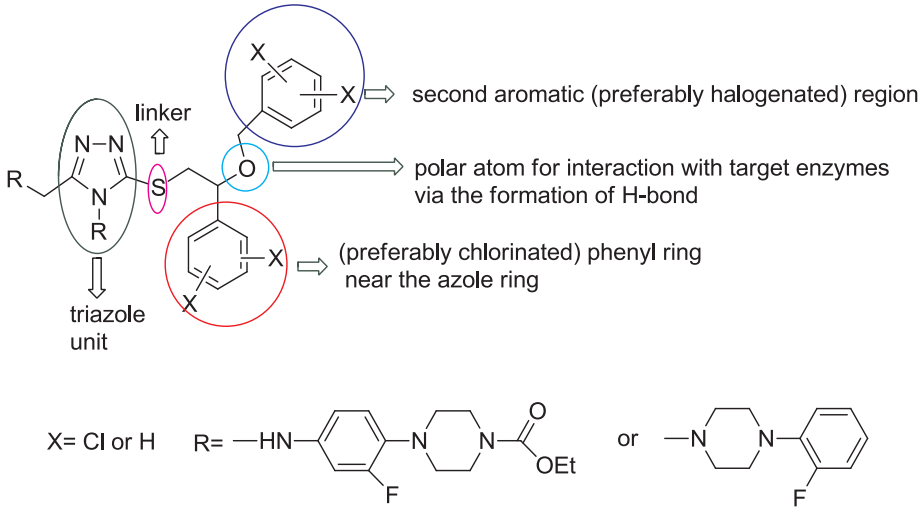

Fig. 2. General representation of the target compounds.

for interaction with target enzymes via the formation of H-bond [15,16].

In recent years, the application of microwave (MW) techniques for organic synthesis has attracted considerable interest due to some superior properties including the low reaction times, improved yields, simplified work-up and designing energy-saving protocols [17]. Moreover, with the development of 'green chemistry', the focus has now shifted to less cumbersome solvent-free methods, undergoing facile reactions to provide high yields of pure products, thus eliminating or minimizing the use of organic solvents [18–22]. Ultrasound mediated procedures constitute another powerful technique used to accelerate organic reactions. The noteworthy properties of sonication, which has been accepted as an important technique for green chemistry procedure, are formation of pure products in high yields, easier work up and enhanced reaction rates [23–26].

Urease, a nickel containing binuclear enzyme, is a virulent factor for human and animal infections containing many urinary and gastrointestinal tracts, hepatic diseaonomic loesses and gastric cancer [27]. α-Glucosidase (EC3.2.1.20) is a crucial enzyme found in the brush border surface of cells in the small intestine. During the digestion of food this enzyme hydrolyzes carbohydrates and produces α-D-glucose, which is absorbed in the blood stream, raises postprandial blood glucose levels and brings about diabetes. Thus, for the control and prevention of diabetes, a-glucosidase inhibitors are of particular interest as they can help to reduce the carbohydrate digestion and subsequent monosaccharide absorption [28–31].

In light of these considerations, as the continuation of our ongoing efforts, we reported here the synthesis and biological activity screening studies of novel analogues of azole class antifungals by conventional method and green chemistry techniques.

2. Result and discussion

2.1. Chemistry

In the present study, traditional and ecofriendly synthesis, antimicrobial, enzyme inhibition and antioxidant activity screening studies of novel analogues of azole class antifungals were intended (Table 1). Synthetic routes leading to the formation of the targeted compounds was presented in Schemes 1–3 and all compounds were presented Table 2. Compounds **2, 3, 4, 8, 9** and **10** were synthesized following the procedure reported by us earlier [27]. The synthesis of novel analogues of azole class antifungals (**7a-l** and **13a-d)** was carried out starting from the corresponding 3*H*-1,2,4-triazoles (**4a-d**, **10)** containing a piperazine nucleus, via three steps. The alkylation of compounds **4a–d** and **10** with 2-bromo-1-(4-chlorophenyl) ethanone in ethanol yielded compounds **5a–d**. The comparison with a conventional heating showed that MW irradiation and sonication decreased the reaction time from 27 h to 10 min and increased the yields from 76–90% to 87–94% (Table 2).

It is well known that mercapto- or oxo-triazoles can exist in (thi)