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Preliminary communication

Imidazolylchromanones containing non-benzylic oxime ethers: Synthesis and molecular modeling study of new azole antifungals selective against *Cryptococcus gattii*

Mojtaba Babazadeh-Qazijahani [a], Hamid Badali [b], Hamid Irannejad [c], Mohammad Hosein Afsarian [b], Saeed Emami [c,*]

[a] Student Research Committee, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[b] Department of Medical Mycology & Parasitology/Invasive Fungi Research Center (IFRC), Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[c] Department of Medicinal Chemistry and Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran

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ABSTRACT

A series of imidazolylchromanone oximes containing phenoxyethyl ether moiety, as found in omoconazole, were synthesized and evaluated against yeasts (*Candida albicans* and *Cryptococcus gattii*) and filamentous fungi (*Aspergillus fumigatus* and *Exophiala dermatitidis*). Although the title compounds showed marginal activity against filamentous fungi but all of them exhibited potent activity against *C. gattii* (MIC values ≤4 μg/mL). Among them, (3-chlorophenoxy)ethyl analog **7c** with MIC value of 0.5 μg/mL was the most potent compound. Further molecular docking studies provided a better insight into the binding of designed compounds within the homology modeled active site of CnCYP51 (*Cryptococcus* CYP51-14α-demethylase).

1. Introduction

Fungal infections cause a persistent burden on human and animal health, plants and agricultural economy [1]. In human, many fungal infections are caused by opportunistic pathogenic fungi that may be endogenous flora or acquired from the environment. The incidence of fungal infections has significantly increased in recent years. The vast majority of fungal infections are due to *Candida*, *Aspergillus* and *Cryptococcus* species, especially in all categories of immunocompromised patients [2]. The immunocompromised patients including cancer patients receiving chemotherapy, organ transplant recipients and patients with AIDS are prone to fungal infections [3].

Cryptococcus neoformans is encapsulated basidiomycetous yeast that infects pulmonary organs and can disseminate widely, most commonly to the brain and skin [4–6]. Two predominant varieties are recognized for *C. neoformans*: var. *neoformans* and var. *gattii* [7]. *C. gattii* has recently received widespread attention owing to outbreaks in British Columbia, Canada and the US Pacific Northwest, and is believed to be clinically more virulent than *C. neoformans* [8]. Infections with *C. gattii* in patients can be severe and often fatal if untreated [1].

Many drugs are available for the treatment of systemic or superficial fungal infections, but only a limited number of them are effective in the treatment of cryptococcal infections [9]. The polyene drugs such as amphotericin B and azole antifungals such as fluconazole are the most widely used drugs to treat cryptococcosis. Severe side effects such as nephrotoxicity limit the clinical usefulness of polyene drugs. Azole antifungals are generally considered as fungistatic agents and act by inhibiting lanosterol 14α-demethylase in the ergosterol biosynthetic pathway [10]. The emergence of resistance and fungistatic rather than fungicidal activities represent limitations of current azole antifungals. Moreover, the pharmacokinetic deficiencies of azole may have a profound effect on the

* Corresponding author.
E-mail address: sd_emami@yahoo.com (S. Emami).

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apparent drug resistance of azoles. For example, oral itraconazole may be less effective in the treatment of cryptococcal meningitis because of its variable oral absorption and poor cerebrospinal fluid levels [11]. Therefore, there remains an urgent need for finding new antifungal agents with proper safety and pharmacokinetics to overcome this situation and develop effective therapies especially against cryptococcal infections.

In our quest to develop new azole antifungal agents, recently we have designed 3-imidazolylchromanone oxime ethers (Fig. 1, structure **A**) as conformationally constrained analogs of oxiconazole [12]. Oxiconazole and most of imidazole antifungals such as miconazole, econazole, isoconazole, sulconazole and fenticonazole contain benzyl ether side chains (Fig. 1). Besides azole antifungals with benzyl ether side chains, omoconazole is a distinct azole antifungal with non-benzylic side chain namely 2-(4-chlorophenoxy) ethyl ether. In continuation of our research program on azole antifungals, we focused our modifications mainly on the side chains of imidazolylchromanone oxime ethers, and attached 2-phenoxyethyl ether moiety to the imidazolylchromanone oxime scaffold instead of benzyl ether residue. Thus, we report here, synthesis and antifungal activity of imidazolylchromanone *O*-(phenoxyethyl)oxime ethers (Fig. 1, structure **B**).

2. Chemistry

The synthesis of target compounds imidazolylchromanone *O*-(phenoxyethyl)oxime ethers **7**, starting from 4-chromanone (**1**) and phenol derivatives **5** is outlined in Scheme 1. Firstly, 4-chromanone (**1**) was brominated with copper (II) bromide to give 3-bromo-4-chromanone (**2**). Compound **2** was reacted with hydroxylamine hydrochloride in methanol to afford the corresponding oxime **3**. Reaction of 3-bromo-oxime derivative **3** with imidazole in DMF offered 3-imidazolyl-4-chromanone-(*E*)-oxime (**4**) [12]. On the other hand, phenol derivatives **5** were refluxed with 1-bromo-2-chloroethane in butan-2-one and converted to the corresponding phenoxyethyl chloride derivatives **6**. In the final step, (*E*)-oxime **4** was reacted with phenoxyethyl chloride derivatives **6** in the presence of NaH in DMF to give (*E*)-oxime ether derivatives **7**.

The structures of final compounds **7a**–**f** were fully characterized by IR, ^{1}H NMR, ^{13}C NMR and MS spectral data. Representatively, the spectral studies of compound **7a** are discussed here. In the IR spectrum of compound **7a**, a medium band due to the C=N of oxime moiety was appeared at 1601 cm^{-1}. In the ^{1}H NMR, the CH_2CH_2 unit of phenoxyethyl moiety displayed two triplet signals at 4.32 and 4.54 ppm with coupling constants of 4.4 Hz. The hydrogens located on the C-2 position of chroman ring were appeared at 4.70 and 5.01 ppm as doublets of doublets. The geminal coupling constant of the latter hydrogens was 12.0 Hz. The observed peak at 5.64 ppm was attributed to the H-3 of chroman ring. The resonances of *ortho* and *para* hydrogens of phenoxy group and H-6 and H-8 of chroman ring were occurred in the range of 6.90–7.18 ppm. The H-3 and H-5 of phenoxy group showed absorption at 7.28 ppm. A triplet at 7.46 ppm is attributed to the H-7 of chroman structure. The H-5 of chroman ring was appeared downfield at 8.57 ppm due to the deshielding of (*E*)-oxime functionality. The hydrogens of imidazole ring were observed at 7.68, 7.72 and 9.22 ppm. Since the compound **7a** was prepared as nitrate salt, thus the downfield shift of the latter protons is due to the protonation of imidazole ring.

In the ^{13}C NMR of compound **7a**, the aliphatic carbons of chroman core (C-2 and C-3) showed upfield signals at 74.0 and

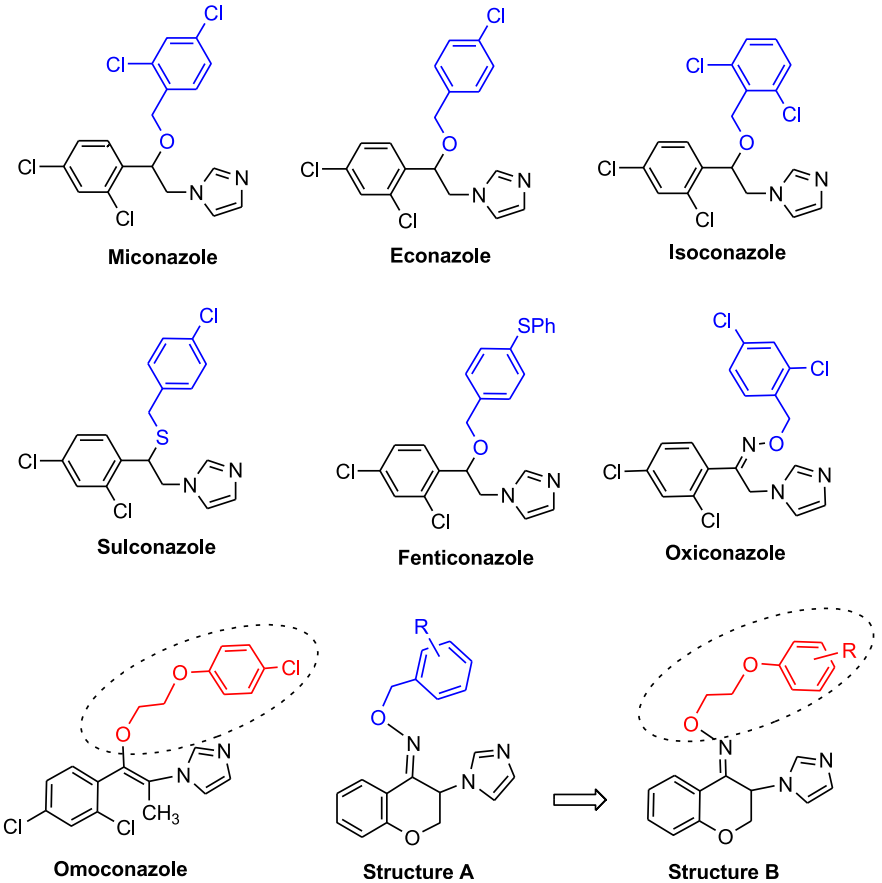

Fig. 1. Structures of representative azole antifungals containing benzyl ether side chain, omoconazole as azole antifungal bearing 2-(4-chlorophenoxy)ethyl ether fragment, and designed 3-imidazolylchromanone oxime ethers (structure B) as non-benzylic analogs of structure A.