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Design, synthesis and bio-evaluation of C-1 alkylated tetrahydro-β-carboline derivatives as novel antifungal lead compounds

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ABSTRACT

The field of antifungal agent has become static and development of resistance by the pathogen as well as limited clinical efficacy of marketed drugs demand the constant development of new antifungals. The presence of hydrocarbon chain of specific length linked with various different heterocycles was found to be an important structural feature in various antifungal lead compounds. Based on the prominent antimicrobial activity of β-carboline derivatives, a set of C1 alkylated tetrahydro-β-carboline derivatives were proposed to be active against fungi. To validate and confirm the role of suitable alkyl chains linked to a β-carboline scaffold, few related analogues having C1 aryl substituents were also synthesized in one step *via* classic Pictet-Spengler reaction. The synthesized library was evaluated for its antifungal activity against *C. albicans*, *C. krusei*, *C. parapsilosis*, *C. kefyr*, *C. glabrata*, *C. tropicalis* and *C. neoformans*. One of the library members (compound **12c**), with *n*-alkyl chain of eight carbons exhibited potent antifungal activity against *C. glabrata* and *C. kefyr*. The lead compound, being selectively toxic also demonstrated prominent synergy enhancing the potency of antifungal drugs up to 10-fold. The time kill kinetic studies confirmed the efficacy of compound **12c**, where the results obtained were comparable to that of Amp B. FE-SEM analysis revealed the increased asymmetry, disintegration and roughness of cell surface which could be because of the possible interaction of compound **12c** at membrane level or interference in cell wall structure. Apoptosis/necrosis detection assay confirmed the significant apoptotic activity in *C. glabrata* cells after **12c** treatment which was responsible for the rapid killing of *C. glabrata* cells.

In recent years, fungal infections have emerged as a major cause of death in immunocompromised patients and cause ~1.4 million death globally per year.[1] Most common human fungal pathogens include *Candida albicans* and non-albicans species namely, *Candida krusei* (*C. krusei*), *Candida parapsilosis* (*C. parapsilosis*), *Candida kefyr* (*C. kefyr*), *Candida tropicalis* (*C. tropicalis*), *Candida glabrata* (*C. glabrata*) and *Cryptococcus neoformans* (*C. neoformnas*) representing 4th leading cause of nosocomial disease and accounting for ~75% of all fungal infections.[2] Although a large number of antifungal agents are discovered, the pathogenic fungi are constantly developing resistance to these drugs.[3] Overall, the field of antifungal agent has become static and there are only four major groups of antifungals currently available in the market namely; azoles, polyenes, allylamines and echinocandins.[4] Many of these antifungal agents are associated with drawbacks such as development of resistance, side effects, limited clinical efficacy and poor bioavailability[5] which demand the constant development of new antifungals. Recently well-known clinical antifungals such as amphotericin B and fluconazole were also found less potent due to the development of resistance against the most common fungal pathogens like *C. albicans*, *C. glabrata*, and *C. neoformans*.[6]

During our recent investigation towards the synthesis of tetrahydro-β-carboline (THβC) derivatives as potent indoleamine 2,3-dioxygenase (IDO1) inhibitors,[7,8] it was observed that few IDO1 inhibitors demonstrated promising antifungal activities. In particular, it was interesting to observe potent antifungal activity of novel alkylated azole **1** which demonstrated the inhibition of 14α-demethylase enzyme involved in ergosterol biosynthesis.[9] The presence of such hydrocarbon chain of specific length linked with various different heterocycles was found to be an important structural feature in various other antifungal lead compounds. These structures were proposed to be active using structure-based de novo studies involving lanosterol 14α-demethylase (CYP51) of fungi. Most active analogues in this series include 7-hydroxy-2-heptyl-4-oximinochromane **2**,[10] 2-decyl-tetrahydroisoquinoline-6,7-diol **3**[11] and 5-methoxy-*N*-nonyl-tetrahydronaphthalen-2-amine **4**[12] (Fig. 1).

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