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Design of new antifungal agents: synthesis and evaluation of 1-[(1*H*-indol-5-ylmethyl)amino]-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ols

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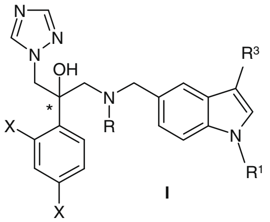
ABSTRACT

We previously reported on the design and synthesis of 1-[((hetero)aryl- or piperidinylmethyl)amino]-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ols showing various degrees of antifungal activity against *Candida albicans* and *Aspergillus fumigatus* strains. Now we have identified a series of 1-[(1*H*-indol-5-ylmethyl)amino] derivatives which exhibited potent MICs (<65 ng mL^{-1}) against *C. albicans* strain. The synthesis and SAR behind the indole scaffold will be discussed.

The growing population of immunocompromised hosts (patients suffering from AIDS or chemotherapy-induced neutropenia or transplant recipients receiving immunosuppressive therapy) has led to an increased incidence of invasive and systemic fungal infections due mainly to *Candida* and *Aspergillus* species which are the most common pathogens.[1] Among the current therapies used in clinics, azoles (the most widely studied class of antifungal agents) target the biosynthesis of ergosterol, a major component of fungal membranes (thereby preventing fungal growth), by inhibiting mainly the cytochrome P450-dependent lanosterol 14α-demethylase (CYP51), encoded by the ERG11 gene. Most azoles are orally active, show a broad-spectrum against most yeasts and filamentous fungi, and are relatively nontoxic. However, increased use of these compounds has likely led to the emergence of resistance showing the need to develop more effective new agents.

We recently reported on the design and synthesis of 1-[((hetero)aryl- or piperidinylmethyl)amino]-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ols showing various degrees of antifungal activity against *Candida albicans* and *Aspergillus fumigatus* strains.[2] SAR studies demonstrated that the benzylamine series bearing H-bond acceptors entities such as NO_2 or CN in *para* position of the benzyl group and a *N*-methyl group in the linker gave the most active compounds with MIC_{80} values of 0.6 and 0.37 ng mL^{-1} on *C. albicans*, respectively. These results confirmed several molecular modeling studies highlighting the importance of hydrogen bonding, π–π stacking and hydrophobic interactions between azole inhibitors and the active site of CYP51-*C. albicans*.[3–6] Compared to their pyridinyl- and piperidinylmethylamine analogues, these compounds also exhibited an emergence of activity on *A. fumigatus* strain with MIC_{80} of 1.96 and 2.41 µg mL^{-1}, respectively.[2]

In this Letter, we describe the design, synthesis and evaluation of 1-[(1*H*-indol-5-ylmethyl)amino] derivatives (**I**, Fig. 1). From a synthetic point of view, these indole-based structures are easily prepared and should keep integrality of the above characteristics depending upon appropriate substituents.



I

X = Cl or F
R = H or CH_3
R^1 = H, Boc or Benzoyl
R^3 = H or $COCF_3$

Figure 1. General structures of synthesized compounds.

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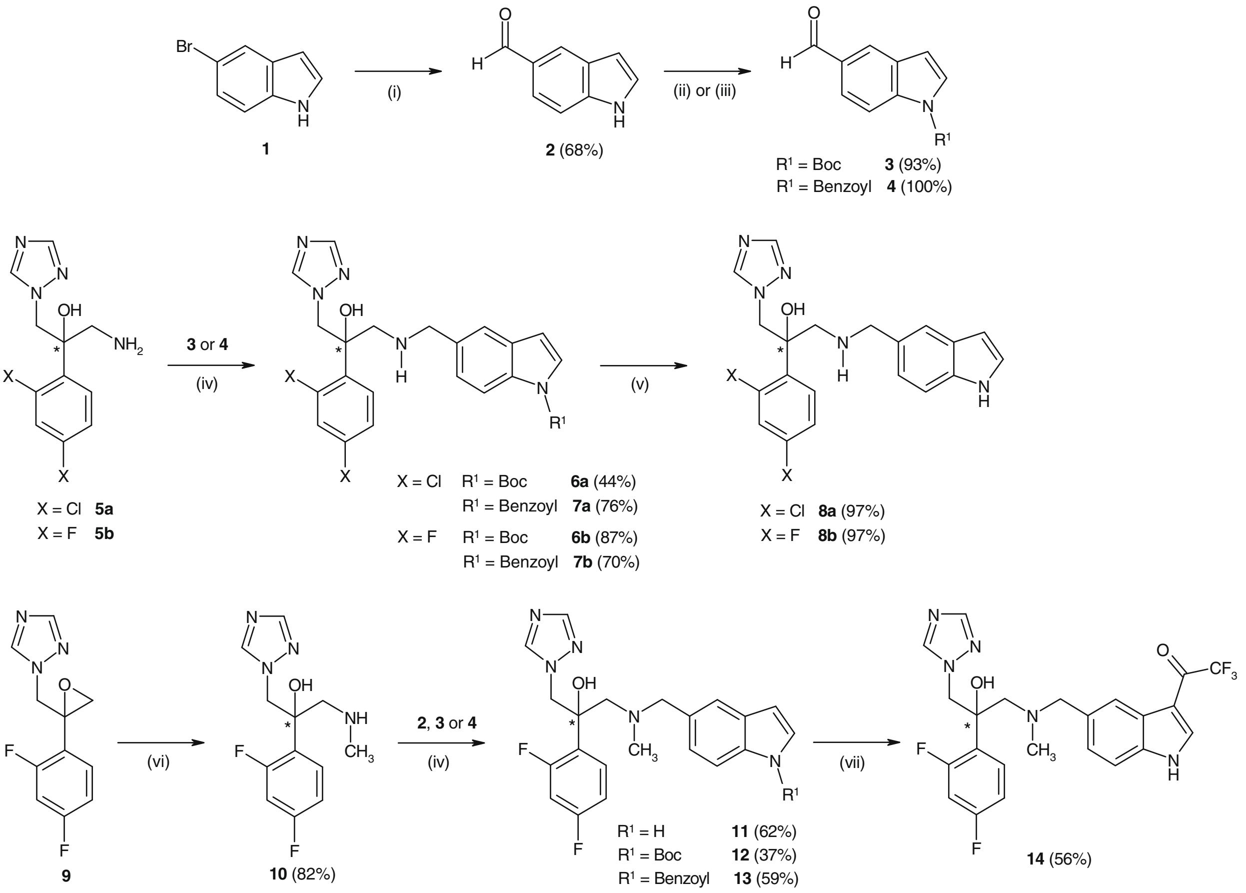

Scheme 1. Preparation of targeted compounds **6a**,**b**, **7a**,**b**, **8a**,**b** and **11–14**. Reagents and conditions: (i) KH, *t*-BuLi, DMF, THF, −78 °C to rt, 16 h; (ii) NaH, Boc_2O, DMF, rt, 1 h 30 min; (iii) benzoyl chloride, DMAP, Et_3N, CH_2Cl_2, rt, 2 h; (iv) **2**, **3** or **4**, $NaBH_3CN$, AcOH/MeOH 2% v/v, rt; (v) from compounds **7a**,**b**: NaOH 2 M, MeOH, 60 °C, 4 h; (vi) methylamine (33% in EtOH), EtOH, reflux, 2 h; (vii) from compound **11**: trifluoroacetic anhydride, 1,2-dichloroethane, rt, 3 h.

Scheme 1 outlines the synthesis of compounds **6a,b**, **7a**,**b**, **8a**,**b** and **11–14**. Treatment of the commercially available 5-bromo-1*H*-indole **1** with KH, *t*BuLi and DMF in THF afforded 1*H*-indole-5-carbaldehyde **2** in a 68% yield.[7] Carbamate **3** was prepared from compound **2** using a standard procedure with sodium hydride and di-*tert*-butyl dicarbonate.[8] On the other hand, treatment of **2** with benzoyl chloride in methylene chloride and in the presence of triethylamine and 4-dimethylaminopyridine (DMAP) gave the *N*-benzoylated indole **4**.[9,10] Derivatives **6a,b** and **7a,b** were synthesized from previously described key intermediates **5a** and **5b**[2] by reductive amination with **3** or **4**.[11,12] Removal of the Boc protective group under acidic condition (HCl 3 M/AcOEt)[13] or with tetra-*n*-butylammonium fluoride in THF[14] failed. Thus, targeted compounds **8a**,**b** were obtained by basic hydrolysis of *N*-benzoylated derivatives **7a**,**b**.[15]

N-methylated analogues **11–13** could be obtained from the previously described epoxide **9**[16] which can be opened by methylamine in ethanol to afford 2-(2,4-difluorophenyl)-1-methylamino-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol **10** in a 82% yield,[17] following a reductive amination with compounds **2–4**.[18] Finally, acylation of indole **11** using trifluoroacetic anhydride in 1,2-dichloroethane gave product **14**.[19]

All these compounds were screened for their antifungal activity against *C. albicans* CA98001 and *A. fumigatus* AF98003 strains. Inhibition growth was measured as previously described.[20] Fluconazole and itraconazole were used as positive controls. The minimum inhibitory concentration (MIC_{80}) values (in $ng\,mL^{-1}$) are presented in Table 1.

On *C. albicans* strain, our compounds displayed a high level of activity with MIC values 3- to 60-fold lower than that of fluconazole. Interestingly, the best result is obtained with fluorinated compound **6b** bearing a *N*-Boc protective group on the indole moiety and a N–H linker ($MIC_{80} = 3.0\,ng\,mL^{-1}$). In contrast, neither the *N*-benzoyl **7b** nor the unsubstituted **8b** derivatives improved the inhibitory potency (MIC_{80} of 27.0 and 34.0 $ng\,mL^{-1}$, respectively), suggesting that an appropriate substitution at position 1 of the indole ring should be important for potent antifungal activity.

Moreover, introduction of a *N*-methyl group in the linker (**11–13**) would not play a major role on the two tested strains (*C. albicans* and *A. fumigatus*), even causing a significant decline in activity for compound **12** ($MIC_{80} = 60.0\,ng\,mL^{-1}$) compared to compound **6b** ($MIC_{80} = 3.0\,ng\,mL^{-1}$).

The supposed binding mode of the docked molecule **6b** (GOLD version 4.0; CCDC, Cambridge, UK) in our homology model of CYP51-*C. albicans*[2b] suggests a key hydrogen bonding interaction between the carbonyl group and the protonated imidazole side chain of His377 (Fig. 2). The (*S*)-configuration was retained since in a precedented series, these isomers were much more active than (*R*)-enantiomers.[21] In addition, the pyrrolo portion of indole may be involved in π–π interactions with the phenyl ring of residue Phe380, but not with the phenol group of Tyr118, a highly conserved residue in CYP51 family.

Even if the key elements of this new scaffold were conserved (a H-bond acceptor positioned on an aromatic moiety), the lack of activity on *A. fumigatus* strain could be explained either by a steric hindrance within the active site induced by the bulky indole ring