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Short communication

Azide-enolate 1,3-dipolar cycloaddition in the synthesis of novel triazole-based miconazole analogues as promising antifungal agents

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ABSTRACT

Seven miconazole analogs involving 1,4,5-tri and 1,5-disubstituted triazole moieties were synthesized by azide-enolate 1,3-dipolar cycloaddition. The antifungal activity of these compounds was evaluated *in vitro* against four filamentous fungi, including *Aspergillus fumigatus*, *Trichosporon cutaneum*, *Rhizopus oryzae*, and *Mucor hiemalis* as well as three species of *Candida* spp. as yeast specimens. These pre-clinical studies suggest that compounds **4b**, **4d** and **7b** can be considered as drug candidates for future complementary biological studies due to their good/excellent antifungal activities.

1. Introduction

Miconazole is an azole-type drug with a broad spectrum of antifungal activity [1]. Due to the development of fungal resistance to this drug [2], the medicinal chemistry of anti-fungal agents has become an important field of study in organic synthesis [3]. To design new agents free of antibiotic resistance, the modification of functional groups in lead molecules has been an efficient strategy [4].

The triazole ring system, is a very well-recognized pharmacophore [5], this nitrogen heterocycle is prominent among U.S. FDA approved pharmaceuticals [6]. In particular, the 1,2,3-triazole core has been an increasingly important heterocycle with successful application in medicinal chemistry [7]. There are reports in literature about the biological activity of 1,2,3-triazole derivatives against cancer [8], malaria [9], tuberculosis [10], trypanosomiasis [11], leishmaniasis [12], HIV [13], influenza [14], dengue [15], pain (analgesic) [16], epilepsy [17], obesity [18], inflammation [19] and bacterial infection [20]. On the other hand, the study of 1,2,3-triazole scaffolds for the synthesis of antifungals [21], and particularly for miconazole analogs [22] has represented an ongoing and promising field of research in the last few years.

Cu-catalyzed azide-alkyne cycloaddition (CuAAC) represents the conventional method for obtaining 1,2,3-triazole moieties [23]. In recent years, azide-enolate 1,3-dipolar cycloaddition has emerged as a novel and potent tool for the synthetic approach to these valuable heterocycles [24]. Its application in medicinal chemistry has already been demonstrated [25].

We previously reported the antifungal activity of *benzyloxy* derivatives of miconazole [26]. As part of our ongoing research, we herein describe the synthesis/evaluation of *triazolic* analogs (1,4,5- and 1,5-substituted derivatives) that maintain the 1-(2-phenylethyl)imidazole core responsible for the biological activity of this compound [27] (Fig. 1).

2. Chemistry

From 2,4-dichlorobenzaldehyde **1** [Eq. (1)], the 1-(2,4-

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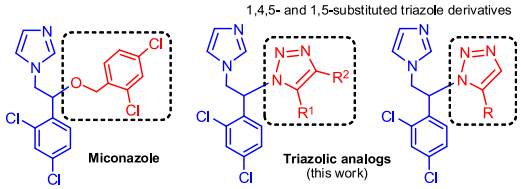
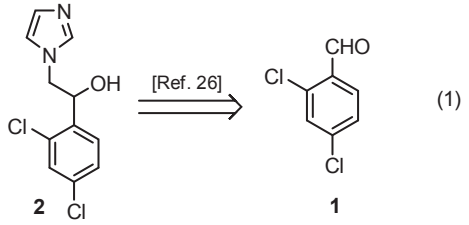
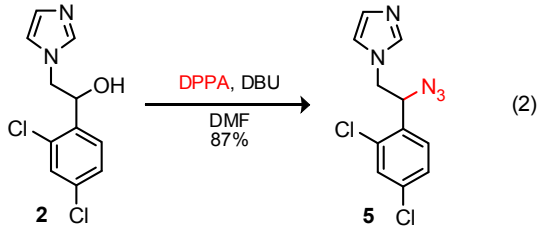


Fig. 1. Proposed triazolic analogs of miconazole.

dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol **2** (key precursor) was obtained in two steps according to our previous report [26]. Previously we published a novel method for preparing 1,4,5-trisubstituted 1,2,3-triazoles from benzylic alcohols *via* an azide-enolate 1,3-dipolar cycloaddition [28]. For this purpose we used diphenylphosphoryl azide (DPPA) as an azidating agent, followed by an efficient cycloaddition in the presence of active ketones. Miconazole analogs **4a**–**d** (1,4,5-trisubstituted derivatives) were synthesized in good yields (Table 1) by coupling acetylacetone **3a**, 2-benzoylacetophenone **3b**, benzoylacetonitrile **3c** and 1-(phenylsulfonyl)heptan-2-one **3d** under the aforementioned protocol.



Recently [29] we reported a novel method for obtaining 1,5-disubstituted triazoles from azides by coupling them with β-keto-phosphonates. Therefore, we decided to begin with the synthesis of benzyl azide **5** [Eq. (2)] as a precursor. The azidation of benzyl alcohol **2** was achieved using DPPA and DBU in dry DMF with good yields [30]. The synthesis of alkyl (**7a** and **7b**) and aryl (**7c**) 1,5-disubstituted triazole derivatives was carried out *via* an azide-enolate 1,3-dipolar cycloaddition (Table 2).



An outstanding aspects for compounds **7a**–**c** is a singlet signal in the range δ 7.6–7.4 ppm (^{1}H NMR spectra) attributable to the triazolic hydrogen [Eq. (3)]. Likewise, for all final compounds, the hydrogens H^a, H^b and H^c on the imidazole moiety can be observed in the ranges δ 7.7–7.4, 7.0–6.9 and 6.9–6.6 ppm respectively.

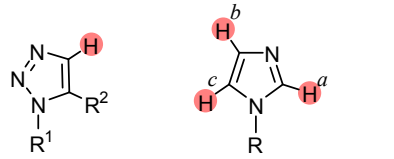
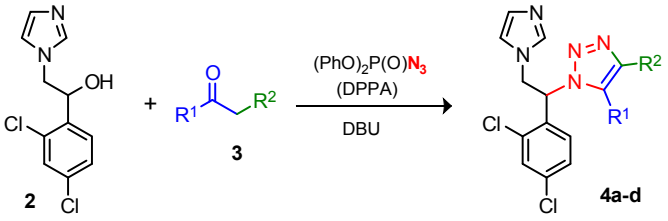


Table 1
Synthesis of 1,4,5-trisubstituted 1,2,3-triazole **4a**–**d** (miconazole analogs) from alcohol 2 by coupling with active ketones 3.



Entry[a]	Ketone	Triazole[b] (Yield%)[c]
1	**3a**: R^1 = CH_3, R^2 = $COCH_3$	**4a** (75%)
2	**3b**: R^1 = Ph, R^2 = COPh	**4b** (67%)
3	**3c**: R^1 = Ph, R^2 = CN	**4c** (63%)
4	**3d**: R^1 = $CH_3(CH_2)_4$–, R^2 = SO_2Ph	**4d** (78%)

[a] *Reaction conditions*: A mixture of compound **2** (1.0 eq), DPPA (1.1 eq), and DBU (2.0 eq) in DMF was stirred at r.t. for 3 h. Then **3** (1.0 eq) was added and the reaction continued at 60 °C for 3 h.
[b] Confirmed by ^{1}H NMR, ^{13}C NMR, and MS.
[c] Yields refer to chromatographically pure isolated compounds.

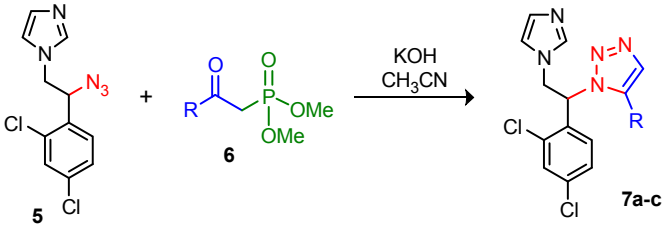
3. Microbiology

Compounds **4a-d** and **7a-c** were evaluated for their *in vitro* antifungal activity against four filamentous fungi (*Aspergillus fumigatus* ATCC-16907, *Trichosporon cutaneum* ATCC-28592, *Rhizopus oryzae* ATCC-10329 and *Mucor hiemalis* ATCC-8690) as well as three yeast specimens (*Candida utilis* ATCC-9226, *Candida albicans* ATCC-10231 and *Candida tropicalis* ATCC-13803).

CLSI standardized methods were adopted to carry out the microbiological tests. The M38-A microdilution method [31] was used to determine the sensitivity of filamentous fungi, and the M27-A3 method [32] for *Candida* yeasts.

The antifungal activity of compounds **4a**–**d** and **7a**–**c** was compared with itraconazole, a standard antifungal drug. The minimum inhibitory concentration (MIC) values of the compounds and standard drugs, expressed in micrograms per millilitre, were determined in 96-well plates by using RPMI 1640 medium buffered with MOPS (3-[N-morpholino]propane sulfonic acid; Sigma-Aldrich).

Table 2
Synthesis of 1,5-disubstituted 1,2,3-triazole **7a**–**c** (miconazole analogs) from azide 5 by coupling with β-ketophosphonates 6.



Entry[a]	Ketone	Triazole[b] (Yield%)[c]
1	**6a**: R = cyclohexyl	**7a** (64%)
2	**6b**: R = $CH_3(CH_2)_3C(CH_3)_2$–	**7b** (70%)
3	**6c**: R = *p*-(CH_3S)phenyl	**7c** (72%)

[a] *Reaction conditions*: A mixture of compound **5** (1.0 eq), **6** (1.0 eq), and KOH (3.0 eq), in CH_3CN was stirred at 60 °C for 5 h.
[b] Confirmed by ^{1}H NMR, ^{13}C NMR, and MS.
[c] Yields refer to chromatographically pure isolated compounds.