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Original article

Design and synthesis of novel triazole derivatives containing γ-lactam as potential antifungal agents

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ABSTRACT

A series of novel triazole derivatives containing γ-lactam were designed and synthesized, and their structures were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. The *in vitro* antifungal activities of the target compounds were evaluated. The results showed that all of the compounds exhibited stronger activity against the six clinically important fungi tested than fluconazole. **3D** and **3E** showed comparative activity against the fungi tested except for *Candida glabrata* and *Aspergillus fumigatus* as voriconazole. In addition, the docking model for **2A** and CYP51 was investigated.

1. Introduction

In recent years, the population of immunocompromised individuals, such as AIDS and organ transplants recipient, is increasing. This fact makes the invasive fungal infection become a global threat to human health [1,2]. Among the drugs to treat fungal infection, triazole derivatives as potent and safe antifungal agents have attracted attention for a long time [3,4]. Fluconazole, voriconazole, and itraconazole (Fig. 1) have been widely used in clinical therapy. But some impediments of these drugs still remain to be resolved. Firstly, with the extensive use of triazole antifungal drugs, the rate of drug resistance mutation is also increasing gradually [5,6]. Secondly, the poor water-solubility and drug–drug interactions are a common problem of triazole antifungal drugs [7]. Therefore, the discovery and development of novel antifungal agents for clinical treatment has important realistic meanings.

Albaconazole (Fig. 1) is one of the most potent antifungal agents reported, which has potent activity against many fungi such as *Candida* spp and *Aspergillus* spp [8]. A quinazolinone unit rather than a pyrimidine unit of voriconazole is the structure characteristic of albaconazole. Literatures have disclosed the important interaction between the carbonyl of quinazolinone unit with the His310 of CYP51, the target enzyme of triazole antifungal agents [9]. Our lab also has done some work in this area [10,11]. For example, the pyridine-substituted analogues of itraconazole, some of which showed good activities against pathogenic fungi. Unfortunately, all of those derivatives have poor water-solubility. Our previous studies found that the triazole derivatives containing 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine motif have good activities against *Candida* spp *in vitro* [12]. Compound **1** (Fig. 2) has the most potent activity among those derivatives. What is important is that the disulfate salt of compound **1** has good water-solubility, which can be given through intravenous injection.

Herein, we designed and synthesized two series of triazole derivatives featuring 5,6-dihydro-4*H*-pyrrolo[3,4-d]thiazol-4-one moiety **2** and 4,5-dihydro-6*H*-pyrrolo[3,4-d]thiazol-6-one moiety **3** (Fig. 2) on the basis of the structure characteristics of **1** and albaconazole. We hypothesized that the carbonyl of γ-lactam could interact with the His310 of CYP51, which can enhance the antifungal activity.

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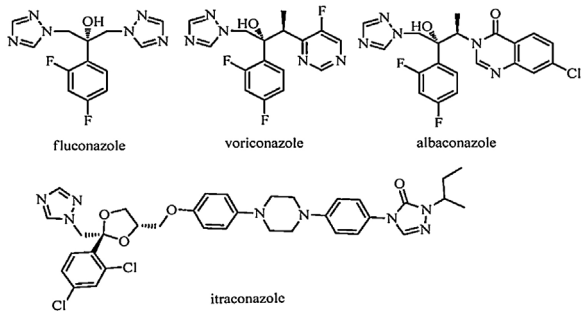


Fig. 1. Chemical structure of fluconazole, voriconazole, albaconazole, and itraconazole.

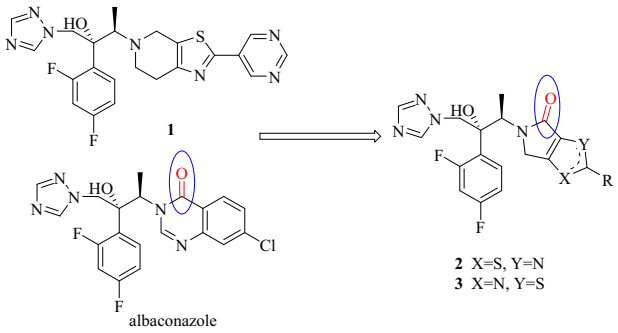
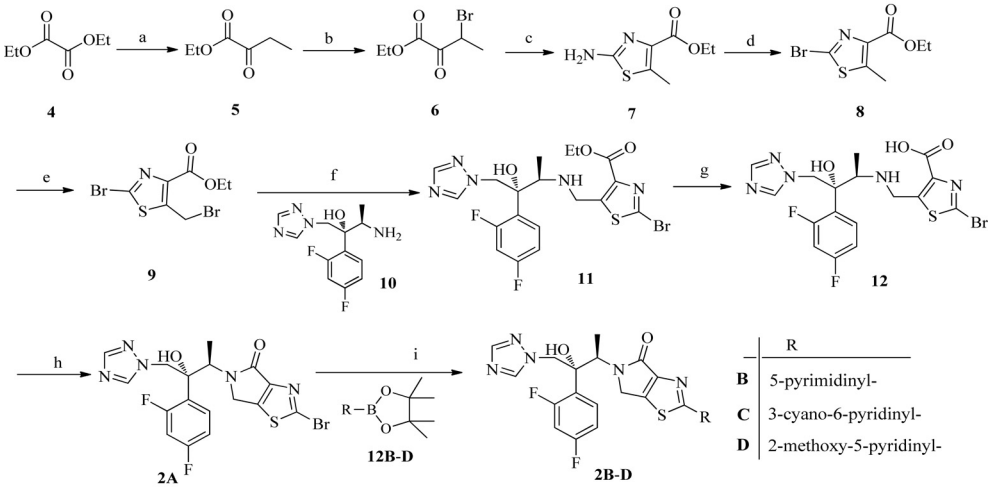


Fig. 2. The design of title compounds.

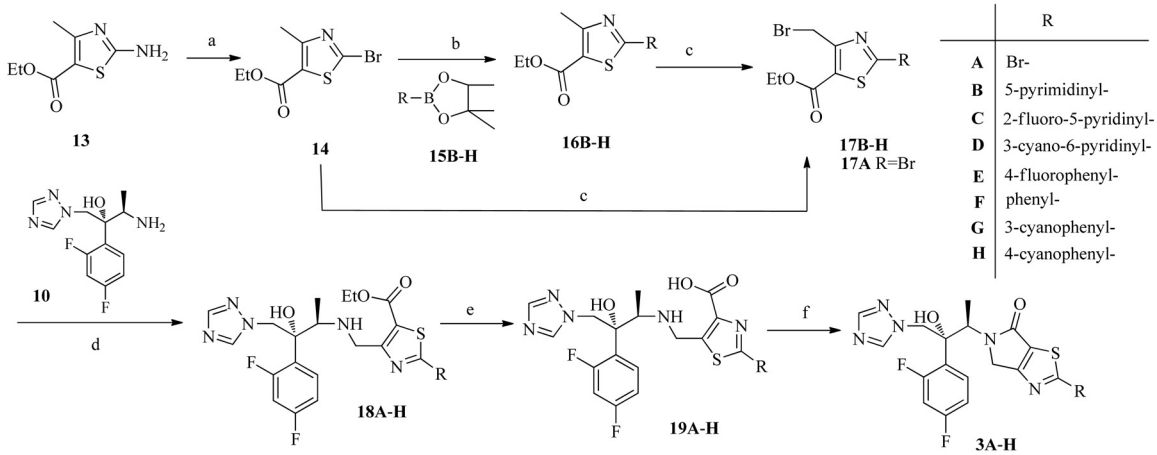
2. Experimental

The synthetic route of title compounds **2A–D** is outlined in Scheme 1. The reaction of compound **4** with ethylmagnesium bromide yielded **5**. Then compound **5** reacted with $CuBr_2$ to give **6**, which underwent annelation to obtain **7**. Compound **7** underwent a Sandemyer reaction and bromination by NBS sequentially to afford **9**. The key intermediate **9** reacted with compound **10** [13] to give **11**, which underwent a hydrolysis and condensation to obtain compound **2A**. Compounds **2B–D** were obtained by treating **2A** with different boronic acid pinacol ester **12B–D** in 1, 4-dioxane and water.

The synthetic route of compounds **3A–H** is showed in Scheme 2. Commercially available compound ethyl 2-amino-4-methylthiazole-5-carboxylate (**13**) underwent a Sandemyer reaction to give compound **14**, which was treated with different boronic acid



Scheme 1. Synthetic route for title compounds **2A–D.** Reagents and conditions: (a) ethylmagnesium bromide, THF, −78 °C then −10 °C, 2 h; (b) $CuBr_2$, EtOAc/$CHCl_3$, reflux, 12 h; (c) thiourea, EtOH, reflux 2 h then r.t., 12 h; (d) ^tBuONO, $CuBr_2$, CH_3CN, r.t. then 60 °C, 6 h; (e) NBS, BPO, CCl_4, 60 °C, 12 h; (f) **9**, K_2CO_3, CH_3CN, 0 °C then r.t. overnight; (g) NaOH, THF, MeOH, 0 °C then r.t. overnight; (h) EDCI, HOBt, TEA, CH_2Cl_2, 0 °C then r.t. 2 h; (i) **12B–D**, Pd[$P(Ph_3)_4$], Cs_2CO_3, 1, 4-dioxane/H_2O,70 °C, 12 h.



Scheme 2. Synthetic route for title compounds **3A–H**. Reagents and conditions: (a) ^tBuONO, $CuBr_2$, DMF, CH_3CN, 0 °C then 60 °C, 1 h; (b) **15B–H**, Cs_2CO_3, Pd(PPh_3)$_4$, 1, 4-dioxane/H_2O, 80 °C, 12 h; (c) NBS, AIBN, CCl_4, r.t., overnight; (d) K_2CO_3, CH_3CN, 0 °C then r.t. overnight; (e) NaOH, MeOH, THF, 0 °C then r.t. 8 h; (f) EDCI, HOBt, TEA, 0 °C then r.t. 2 h.