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Amide analogs of antifungal dioxane–triazole derivatives: Synthesis and in vitro activities

Takuya Uchida, Yoshiko Kagoshima, Toshiyuki Konosu *

Medicinal Chemistry Research Laboratories II, Daiichi Sankyo Co., Ltd, 1-16-13, Kitakasai, Edogawa-ku, Tokyo 134-8630, Japan

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ABSTRACT

A new series of triazole compounds possessing an amide-part were efficiently synthesized and their in vitro antifungal activities were investigated. The amide analogs showed excellent in vitro activity against *Candida*, *Cryptococcus* and *Aspergillus* species. The MICs of compound **23d** against *C. albicans* ATCC24433, *C. neoformans* TIMM1855 and *A. fumigatus* ATCC26430 were ⩽0.008, 0.031 and 0.031 μg/mL, respectively, (MICs of fluconazole: 0.5, >4 and >4 μg/mL; MICs of itraconazole: 0.125, 0.25, 0.25 μg/mL). Furthermore, compound **23d** was stable under acidic conditions.

The growing population of immunocompromised patients due to transplantation, AIDS and cancer chemotherapy, has resulted in an increase in severe fungal infections.[1] In many cases, it is not the AIDS or cancer itself but the mycoses that are lethal to these patients. Triazole compounds are an important class of antifungal agents because of their generally broad antifungal spectrum, high potency and low toxicity.[2] Triazole derivatives displace lanosterol from lanosterol 14-demethylase, a cytochrome P450-dependent enzyme, and block the biosynthesis of an essential component of the fungal cell membrane, ergosterol.[3] Previously, we synthesized a series of dioxane–triazole compounds possessing an olefin part, as depicted by general formula **A** (Fig. 1).[4] We varied the length of the side chains ($n = 0, 1, 2$) and the substituents on aromatic ring Ar. From these compounds, CS-758 was chosen as a candidate compound on the basis of minimum inhibitory concentrations (MICs), solubility and chemical/metabolic stability. CS-758 is currently under development as an antifungal agent against systemic mycosis.

In parallel to the development study of CS-758, we continued to explore additional compounds with excellent antifungal activity and good pharmacokinetics. Although there is a fear of acid instability in the 1,3-dioxane ring in structure **A**, the ring is crucial to the antifungal activity, and the extent of the acid stability varied enormously between compounds.[5] We assumed that the acid-stability of CS-758 could be ascribed to its electron-withdrawing CN and F groups on the ring Ar, and designed a novel series of compounds as depicted by general structure **B**, wherein electron-withdrawing groups **X** such as an amide group or a sulfonyl group are situated in closer proximity to the 1,3-dioxane ring. In this Letter, we describe the synthesis and the in vitro antifungal activities of such a novel series of triazole derivatives.

First, we synthesized compounds **1a**–**d**, which have various electron-withdrawing groups **X**, and compared their MICs (Fig. 2). The Ar group was fixed to the 4-fluorophenyl group. Synthesis of **1a** was conducted as shown in Scheme 1. Alcohol **4**, which was synthesized from ethyl bromocrotonate **2** in two steps, was oxidized with MnO_2 to give corresponding aldehyde **5**. The aldehyde **5** was coupled with triol **6**[4a] in the presence of *p*-toluenesul-

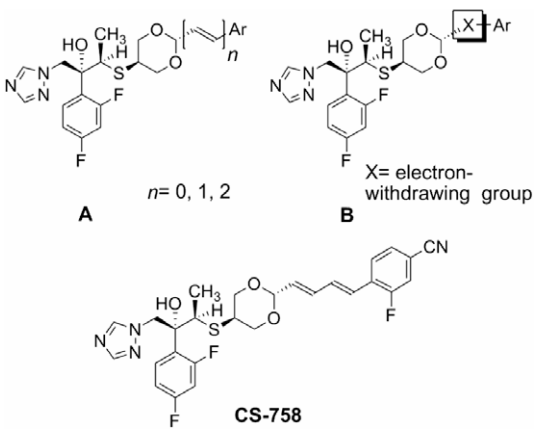

Figure 1. Structural formulas of dioxane–triazole derivatives.

* Corresponding author. Tel.: +81 3 3680 0151; fax: +81 3 5496 8344.

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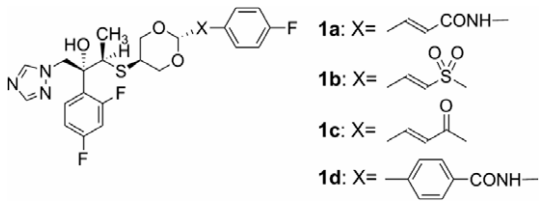


Figure 2. Structural formulas of **1a**–**d**.

fonic acid hydrate and molecular sieves 4 Å to give **1a**. The *trans* dioxane isomer **1a** was predominantly produced over its cis isomer, and was easily separated by silica gel column chromatography.[6]

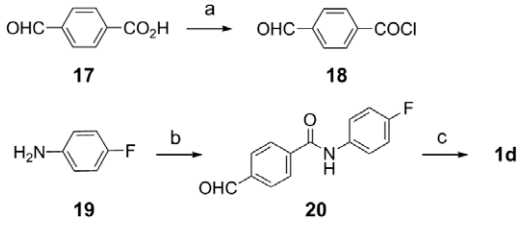
Synthesis of **1b** was conducted as shown in Scheme 2. Sodium 4-fluorophenylsulfinate obtained from **7** was allowed to react with epichlorohydrin to afford alcohol **9**.[7] **9** was oxidized to give corresponding aldehyde **10**. Though **10** did not react with triol **6** in the presence of *p*-toluenesulfonic acid hydrate and molecular sieves 4 Å in dichloromethane, compound **1b** was afforded by acetalization using trimethylsilyl chloride and a catalytic amount of trimethylsilyl trifluoromethanesulfonate.

Synthesis of **1c** was conducted as shown in Scheme 3. Compound **13**, obtained in two steps from **11**, was treated with *n*-BuLi and 4-fluorobenzoyl chloride to afford **14**. The tosyl group and the dimethylacetal group in **14** were removed in a single step by treatment with hydrochloric acid at 60 °C to give aldehyde **16**. The aldehyde **16** was acetalyzed with triol **6** by treatment with *p*-toluenesulfonic acid hydrate and molecular sieves 4 Å.

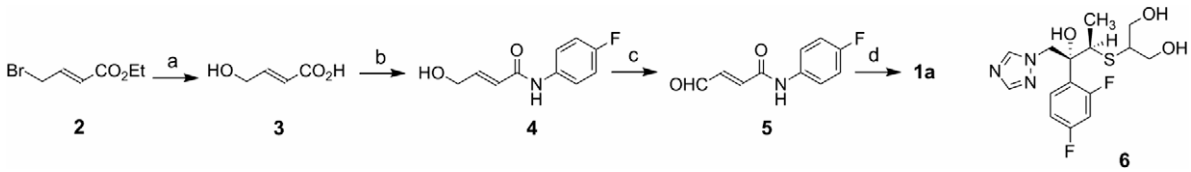
Synthesis of **1d** was conducted as shown in Scheme 4. The amine **19** was coupled with acid chloride **18** to give amide **20**. Compound **20** was acetalyzed with triol **6** to give compound **1d**. The acetalization reaction was driven in the presence of *p*-toluenesulfonic acid in tetrahydrofuran using a rotary evaporator to remove the water. The *trans* dioxane isomer **1d** was predominantly produced over its cis isomer.

The MICs of compounds **1a**–**d** were determined[8] against *Candida*, *Cryptococcus* and *Aspergillus* species and compared with those of our former compound **1e** (Table 1). The MICs of compounds **1a**–**c** were higher than those of **1e**. This difference was most clear in the activity against *Aspergillus flavus* SANK18497. Compound **1d**, which has an aryl-amide group, showed good MICs, which are almost comparable to those of **1e**. In particular, the MICs against *Candida albicans* TIMM3164 (fluconazole resistant strain) and *C. tropicalis* ATCC750 were remarkable. Against *C. glabrata*, the MIC of **1d** was slightly inferior to that of **1e**.

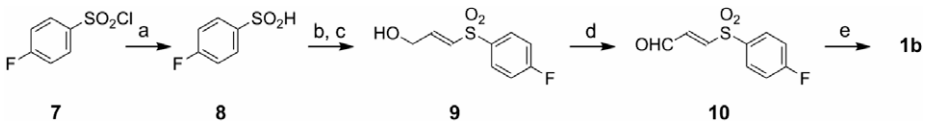
We then fixed **X** to the aryl-amide group, and the substituents on the terminal benzene ring Ar were examined. These compounds (**23a**–**k**) were synthesized in a manner similar to that shown in Scheme 4 or according to the route shown in Scheme 5, wherein common intermediate **22** was prepared by an acetalization reaction of **21** with triol **6**. The intermediate **22** was condensed with the appropriate amine using trimethyaluminum to afford desired



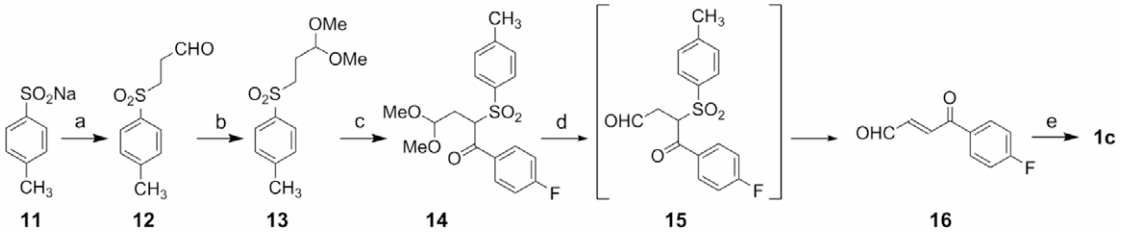
Scheme 4. Synthesis of **1d**. Reagents and conditions: (a) $(COCl)_2$, cat. *N*,*N*-dimethylformamide, THF, rt, 100%; (b) 1.6 equiv Et_3N, 1.5 equiv **18**, THF, rt, 78%; (c) 0.9 equiv **6**, 3.2 equiv *p*-toluenesulfonic acid hydrate, THF, rt, evaporation, 49%.



Scheme 1. Synthesis of **1a**. Reagents and conditions: (a) 2 N KOH, H_2O, reflux, 76%; (b) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, Et_3N, 4-fluoroaniline, THF, 0 °C to rt, 47%; (c) MnO_2, CH_2Cl_2, 70%; (d) **6**, *p*-toluenesulfonic acid hydrate, molecular sieves 4 Å, CH_2Cl_2, 39%.



Scheme 2. Synthsis of **1b**. Reagents and conditions: (a) Na_2SO_3, NaOH, H_2O, 0–40 °C, 58%; (b) NaOH, H_2O, DMF, rt; (c) epichlorohydrin, reflux, 60% (2 steps); (d) MnO_2, CH_2Cl_2, 40%; (e) **6**, *i*-Pr_2NEt, Me_3SiCl, cat. Me_3SiOTf, CH_2Cl_2, *i*-PrOH, 15%.



Scheme 3. Synthesis of **1c**. Reagents and conditions: (a) 0.8 equiv acrolein, AcOH, rt; (b) 2.0 equiv $CH(OMe)_3$, cat. *p*-toluenesulfonic acid hydrate, MeOH rt, 42% (2 steps); (c) 2.0 equiv *n*-BuLi, 1 equiv 4-F-BzCl, THF, −78 °C to rt, 65%; (d) 2 N HCl, THF, 60 °C, 72%; (e) **6**, *p*-toluenesulfonic acid hydrate, molecular sieves 4 Å, CH_2Cl_2, 35%.