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Synthesis and Antifungal Activity of (z)-3-(bromomethylene)thiochroman-4-ones

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Abstract

Three (z)-3-(bromomethylene)thiochroman-4-ones were designed and synthesized. Their structures were confirmed by MS and ^{1}H NMR. *In vitro* antifungal activities of these synthesized compounds were evaluated against ten species of fungi, and the results showed that the target compounds exhibited activity against fungi tested to some extent. The maximum inhibitory activity was found for **3a** against *C.neoformans*, **3a** and **3c** exhibited more potent antifungal activities against *C.Krusei* than Fluconazole.

Keywords: Antifungal activity, Bromination reaction, Thiochromanones

1. Introduction

In recent years, invasive fungal infections, especially in those individuals with immunocompromised hosts such as cancer patients and patients with AIDS (N. H. Georgopapadakou, 1996), have continued to increase in incidence. Thiochromanones had been reported to possess antifungal activities in patents (Philipp, 1997; Talley, 1997) and papers (Rajasekhar Dodda, 2008). T Al Nakib, *et al*. reported that thiochromanone derivatives have antifungal activities (T Al Nakib, 1990). In particular 3-substituted of thiochromanones had been synthesized and reported had antifungal activities to some extent, such as 3-bromo (QI Ping, 2003), 3-benzylidyne (Yang Liu, 2008; Qi Ping, 2004), 3-mannich base (Zhu Quanhong, 2000), and so on. In this paper, three (z)-3-(bromomethylene)thiochroman-4-ones were designed and synthesized to search for more potential antifungal agents. The synthetic route was outlined in the Scheme 1.

2. Experimental

2.1 Chemistry material

Substituted benzenethiols (chemically pure) were from SHOUERFU LLC (ZHEJIANG, China), and the other reagents were almost from TIANJIN Chemical LLC (TIANJIN, China). ^{1}H-NMR spectra were recorded in $CDCl_3$ on Bruker Avance DMX 400 using TMS as an internal standard (Bruker, Billerica, MA, USA). Mass spectral data were obtained by LC-MSD Trap XCT G2446A (Agilent Technologies, USA). Melting points were determined SGW X-4 microscopic melting point (Shanghai Precision & Scientific Instrument Co., Ltd, China).The IR spectra were recorded in potassium bromide on IRPrestige-21/FTIR-8400S (SHIMADZU CORPORATION, Kyoto, Japan).

*2.2 Preparation of compounds thiochroman-4-ones (**1a-1c**)*

A 1: 1.2: 2.4 molar mixture of substituted benzenethiols (50 mmol), 3-chloropropanoic acid (6.5 g, 60 mmol), and NaOH (4.8 g, 120mmol) in 5 mL water was irradiated under Microwave Irradiation for 5-6 min, the reactant was cooled to ambient temperature and HCl (1 mol/L)was added, maintaining the temperature at < 20 ℃ (pH < 2), a lot of white precipitant were created, filtered and washed with water (Xiao Liwei, 2006), and then, the white precipitant and a solution of concentrated sulfuric acid (40 mL, 98%) were stirred sufficiently. The reaction solution was mixed with ice water(100 mL) after 12 h at room temperature, the solid product formed was collected, washed with water and recrystallized from ethanol water solution (ethanol: H_2O= 8(v): 2(v)) (MA Zhengyue, 2008; Zhu Shiguo, 2008). **1a**, yield 75.1%; **1b**, yield 74.6%; **1c**, yield 72.7%.

*2.3 Synthesis of 3-(carbaldehyde)thiochroman-4-ones (**2a-2c**)*

A suspension of sodium methoxide 2.16g (40 mmol) in toluene (50 mL) and ethyl formate 1.48 g (20 mmol) were taken into a 250 mL round-bottomed flask, after which, a solution of compound **1** (10 mmol) in toluene (20 mL) were added over 20min in ice bath, and then the mixture was stirred for 12h at the temperature < 15 ℃. The organic phase was extracted twice with water (20 mL per time), the combined aqueous phase was added with HCl (0.1 mol/L), maintaining the temperature at < 5 ℃ (pH = 4), the solvent was placed for 2h to give the product of compound **2**. **2a,** yield 87.6%; **2b**, yield 90.2%; **2c**, yield 80.5%.

*2.4 Synthesis of (z)-3-(bromomethylene)thiochroman-4-one (**3a-3c**)*

In a sealed tube, compound **2** (100 mmol) and dichloromethane (10 mL) were placed, acetyl bromide (150 mmol) was added within 2 min, sealed the tube. After warming it in an oil bath at 50℃ for 2h, the organic phase was extracted twice with 0.5 mol/L sodium carbonate solution (15 mL per time), the organic extracts was removed under vacuum to give the crude product and then purified by silica-gel column chromatography, eluting with dichloromethane: petroleum ether= 1:10 (v/v).

2.4.1 (z)-3-(bromomethylene)-7-fluoro-6-methylthiochro- man-4-one (**3a**)

Yield: 85.6%; HPLC: 95%; mp 81-85 ℃ (yellow solid); IR (KBr, cm^{-1}): 1654.81 (C=O), 1577.66 (C=C); MS (APCI) m/z 288.6[M^++1, base peak), 286.6[M^++1, 98%]; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.30(d, 3H, *J*=1.4Hz, CH_3), 4.00(d, 2H, *J*=0.8Hz, CH_2), 7.14(d, 1H, *J*=6.7Hz,Ar-H), 7.61(s, 1H, C=CH-), 7.76(d, 1H, *J*=10.0Hz, Ar-H).

2.4.2 (z)-3-(bromomethylene)-6-methylthiochroman-4-one (**3b**)

Yield: 84.6%; HPLC: 92%; oily yellow liquid; IR (KBr, cm^{-1}): 1662.52 (C=O), 1581.52 (C=C); MS (APCI) m/z 270.6[M^++1, base peak), 268.6[M^++1, 98%]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.34(s, 3H, CH_3), 3.99(d, 2H, *J*=0.9Hz, CH_2), 7.18- 7.23 (m, 2H, Ar-H), 7.57 (s, 1H, C=CH-), 7.93(d, 1H, *J*=0.6Hz, Ar-H).

2.4.3 (z)-3-(bromomethylene)-6-chlorothiochroman-4-one (**3c**)

Yield: 78.4%; HPLC: 93%; mp 85-89 ℃ (yellow solid); IR (KBr, cm^{-1}): 1660.60 (C=O), 1579.59 (C=C); MS (APCI) m/z 290.7[M^++1, base peak), 288.7[M^++1, 74%]; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.03(s, 2H, CH_2), 7.26(s, 1H, Ar-H), 7.38(dd, 1H, J_1=8.4Hz, J_2=2.4Hz, Ar-H), 7.64(s, 1H, C=CH-), 8.10(d, 1H, *J*=2.3Hz, Ar-H).

2.5 Antifungal Activity in Vitro

In vitro antifungal activities were measured by means of the minimal inhibitory concentrations (MIC) by consecutive double dilution method. The MIC means the lowest concentration of an antimicrobial agent that prevents visible growth of a microorganism in broth dilution susceptibility test (Marcelo C. Murguı´a, 2008).The MIC was determined according to the national committee for clinical laboratory standards (NCCLS) recommendations. Ten human opportunistic pathogenic fungi were tested, Fluconazole was taken as the reference drug for positive control. The compounds were dissolved in dimethyl sulfoxide (DMSO) (1 mL), further progressive dilutions by RPMI 1640 gave the required concentrations(64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.125μg/mL); the fungi were prepared and adjusted to a final concentration of 0.5×10^4-2.5×10^4 CFU /mL. MIC values were determined by visual observation after 2-7d of incubation.

3. Results and discussion

3.1 Reaction mechanism

Compounds **3** were synthesized by bromination reaction of Compounds **2.** In addition, this kind of bromination reaction had no been reported, a plausible mechanism showing the formation of this reaction was supposed in Scheme 2. The proposed pathway involves initial tautomerization of the intermediate enol compounds **4**, it was possible that the nucleophilic attack of the enolate oxygen on the acetyl bromide to generate the intermediate compounds **5**, the latter step presumably involves compounds **5** was attacked by bromine ionic to give compounds **3**.

3.2 Antimicrobial Activity in vitro

The results of antifungal activities *in vitro* were shown in Table 1. The results showed that the target compounds were effective against all of the tested fungi. The maximum inhibitory activity was found for **3a** against *C.neoformans*; **3a** and **3c** had higher inhibitory effects on the growth of *C.Krusei*; **3a, 3b, 3c,** showed a similar level of activity with fluconazole when against *M.gypseum* and showed moderate activity against *C.parapsilosis*. In particular, **3a, 3b, 3c** were active for *E.floccosum* and *S.schenekn* while the activity of Fluconazole was lower. However, all of the tested compounds and Fluconazole were low active against *A.niger*.

In conclusion, the target compounds had an antifungal effect on most tested fungi *in vitro*. Further biological evaluation of the three compounds is in progress. Moreover, the results should encourage us to design and synthesize more potent antifungal agents.

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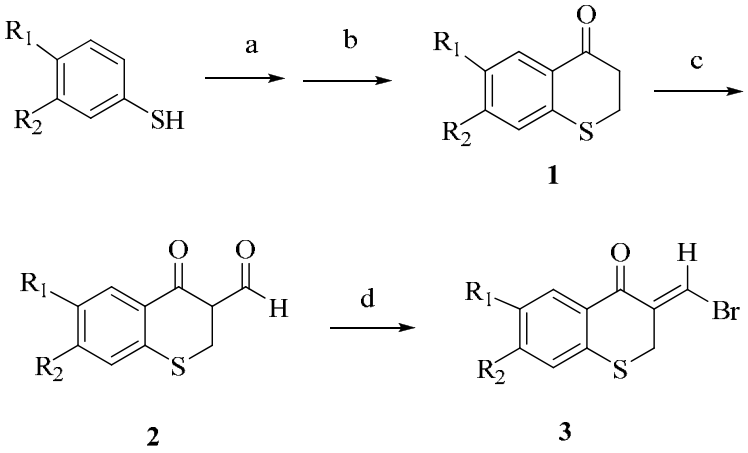
Table 1. Antifungal activity of compounds synthesized *in vitro*

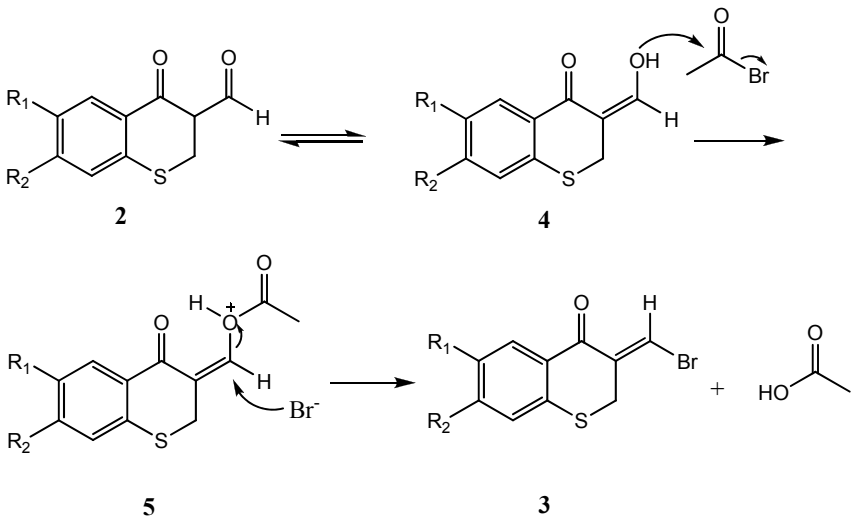
Compound	MIC (μg/mL)									
	Cp	Cg	Ca	Ct	Cn	CK	Ef	Mg	An	Ss
3a	8	64	64	32	1	4	32	64	>64	32
3b	32	>64	32	>64	8	64	64	64	>64	32
3c	8	64	64	32	4	16	64	64	>64	64
Flu	4	16	0.5	2	4	64	>64	64	>64	>64

Abbreviations: Cp, *C.parapsilosis*; Cg, *C.glabrata*; Ca, *C.albicas*; Ct, *C.tropicalis*; Cn, *C.neoformans*; CK, *C.Krusei*; Ef, *E.floccosum*; Mg, *M.gypseum*; An, *A.niger*; Ss, *S.schenekn*; Flu, Fluconazole.



1a, 2a, 3a ($R_1 = CH_3$, $R_2 = F$); **1b, 2b, 3b** ($R_1 = CH_3$, $R_2 = H$);
1c, 2c, 3c ($R_1 = Cl$, $R_2 = H$)

Scheme 1. (a) 3-chloropropanoic acid, NaOH, MV. (b) concentrated sulfuric acid, 12h, rt. (c) $C_6H_5CH_3$, CH_3ONa, $HCOOCH_2CH_3$, 12h, <15℃. (d) $CHCl_3$, acetyl bromide, 2h, reflux



Scheme 2. Plausible mechanism