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Synthesis and antifungal activity of 3-halogenomethylene-6-fluoro-thiochroman-4-one

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ABSTRACT

New 3-halogeno-methylene-6- fluoro-thiochroman-4- one were designed and synthesized. In the synthesis of these compounds, Acetyl halides were used as halogenated reagents, and the reaction mechanism was discussed. The results of antifungal activities showed that these compounds had good antifungal activity.

KEYWORDS

Thiochromanones;
Synthesis;
Antifungal activity.

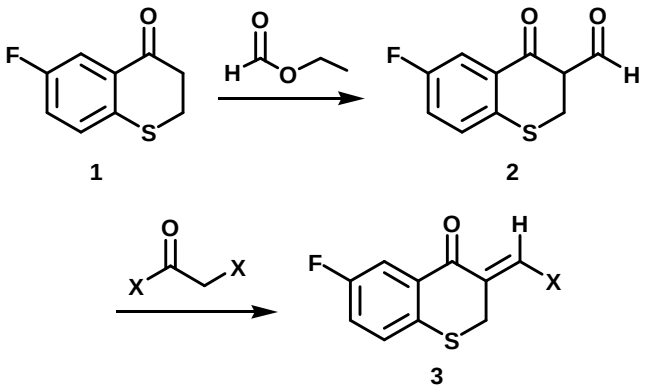
INTRODUCTION

Recently, misusing of antibiotics and the immuno-suppressive agent and anti-tumor chemotherapy drugs used widely which result in fungal infections and the rate of cancer incidence increased greatly[1-3]. Hence, the research on finding new antibiotics is pressing.

It is reported that thiochromanone derivatives have broad biological activities[4]. In our previous studies 3-substituted-thiochromanones have been prepared and shown good antifungal activities in vitro[5-7], such as 3-bromo[8], 3-mannich base[5], 3-benzylidyne[4,9] and so on.

In this paper, 3-halogenomethylene-6-fluoro-thiochroman-4-one is designed and synthesized (Figure 1). The reaction mechanism of the synthesis of compound **(3)** from compound **(2)** have not been reported and it is investigated in this study.

The antifungal activities of the new compounds called 3-halogenomethylene-6- fluoro-thiochroman-4-one were evaluated according to the M27 and M38 program made by the U.S. National Committee for Clinical Laboratory Standards (NCCLS) by using microdilution method[10] with ten kinds of common fungi.



X = Cl, Br

Figure 1 : Synthetic route of the target compounds

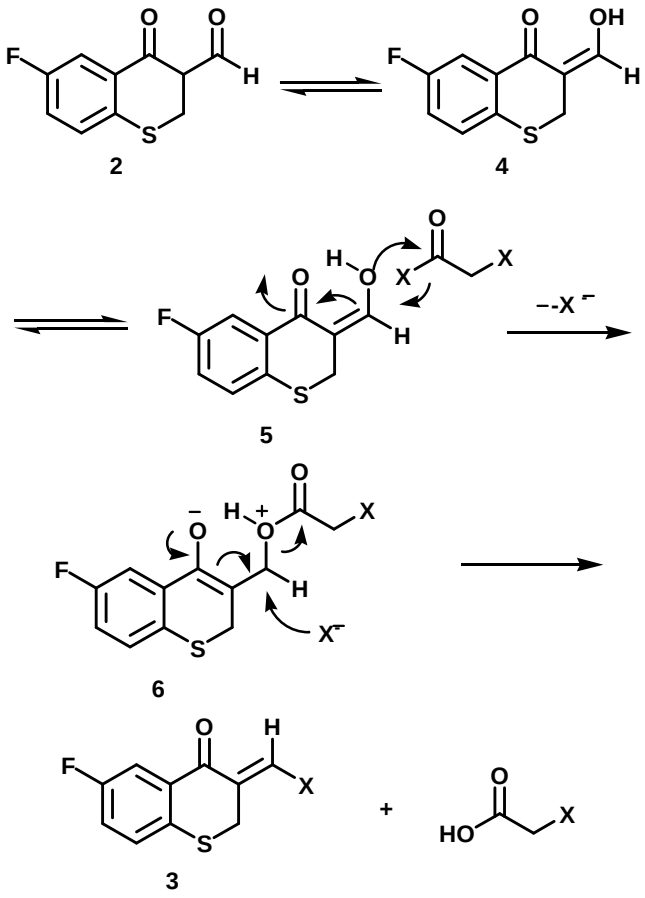
RESULTS AND DISCUSSION

Reaction mechanism

The reaction mechanism of the synthesis of compound **(3)** have not been reported. A postulated mechanism was shown in Figure 2.

It involved tautomeric transformation of compound **(2)** into the intermediate enol 4. Hydroxyl group and carbonyl group in the 4 form the intramolecular hydro-

gen bond give intermediate 5. The latter step presumably involves C=O carbon atom of 2- acyl halide were attacked by the enolate oxygen to generate the intermediate 6. Finally, 6 was attacked by bromine ionic to give compound **(3)**.



X = Cl, Br

Figure 2 : Postulated mechanism for compound (4) synthesis

Antifungal activity in vitro

The test showed that they have certain antifungal activity to most fungal strains, in which 3-chloromethylene-6-fluoro-thiochroman-4-one (A) displayed excellent activity (against S. schenekn, C. glabrata, C. parapsilosis, C. krusei.), its MICs value were equal to amphotericin B (AmB), and against M. gypseum its MIC value was below to the AmB, while A was a little better than fluconazol (FCZ) . 3-bromomethylene-6-fluoro-thiochroman-4-one (B) also showed good activity against filamentous fungi (A. niger, S. schenekn, M.gypseum, E. floccosum), its MICs value were equal or below to FCZ.. They were worth to do further study.

EXPERIMENTAL

TLC was used to monitor the reaction process. TLC was HF_{254} thin layer chromatography with ethyl acetate / petroleum ether (1 / 10) used as eluent. Melting pointing were determined with SGW X-4 micro melting point apparatus. Microwave installations occurred in the family-type of Galanz microwave oven (G7020IITL 2, power 700W) ; The 1H-NMR spectra were obtained on a Bruker AVANCE (400MHz) spectrometer using TMS as internal standard and CDCl3 as solvent. The mass spectra were obtained on an Agilent LC- MSD Trap XCT G2446A HPLC-MS spectrometer.; The IR spectra were recorded in KBr on a SHIMADZU FTIR-8400S spectrometer with Fourier transform. 4-Fluorobenzenethiol is chemically pure, others are analytically pure. Compound 3-(4-Fluoro-phenylsulfanyl) - propionic acid was prepared as previous literature[11].

Synthesis of compound (1)

Taken the compound 3-(4-Fluoro-phenylsulfanyl) - propionic acid (40.3mmol) and dissolved it in concentrated sulfuric acid (70ml) at room temperature, placed it 12h, then treated it with ice. Then yellow precipitation appeared, filtrated, washed with 5% $NaHCO_3$ and water to neutral, recrystallized from alcohol gave light yellow solid compound **(1)** in 51-73% yield.

Synthesis of compound (2)

A mixture of ethyl formate (36.6mmol), fresh Sodium methoxide (54.9mmol) and toluene (100ml) was taken into a 250ml round bottom flask, with the dropwise addition of compound **(1)** which dissolved in the toluene. The temperature was controlled at 0-10 °C and the reaction mixture was further stirred over 10h. And then reaction solution washed twice with water and 5% of NaOH once. Combined aqueous phase, washed twice with ether, adjust PH to weak acid. Solution brought out a lot of bright yellow precipitation. Filtrated and dried to obtain yellow solid compound **(2)** in 71- 92% yield.

Synthesis of compound (3)

Compound **(2)** (15.1mmol) and chloracetyl chloride or bromoacetyl bromide (22.5mmol) were added in a 50 ml sealed tube. Dissolved in CH_2Cl_2 (15 ml), stirred at 50 °C for 3h. Washed reaction solution with

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$NaHCO_3$ for three times. The organic phase was separated and evaporated the solvent under reduced pressure to obtain the mixture of compound **(3)** and other byproduct. Purified by silicagel column chromatography (dichloromethane / petroleum ether = 1/10), we can obtain3-chloromethylene-6-fluoro-thio-chroman-4-one (A) and 3-bromomethy-lene-6-fluoro- thiochroman- 4- one (B) in 65-90 % yield. The structures all confirmed by MS, IR and ^{1}H-NMR and the data was shown as follow:

3-chloromethylene-6-fluoro-thiochroman-4-one:
mp/°C: 78~80;
yield/%: 39;
APCI: 228.8(m/z+1), 230.8(m/z+1);
IR: (KBr, cm^{-1}): 1662.52 (C=O), 1587.31(C=C);
1H-NMR($CDCl_3$): δ: 4.011-4.013(d,2H), 7.129-7.178(m,1H), 7.281-7.315(q,1H), 7.384 (s,1H), 7.796-7.826(dd,1H)

3-bromomethylene-6-fluoro-thiochroman-4-one:
mp/°C: 85-88;
yield/%: 41;
APCI: 272.7 (m/z+1), 274.7(m/z+1);
IR: (KBr,cm^{-1}): 1647.10 (C=O), 1575.73(C=C);
1H-NMR($CDCl_3$): δ: 4.018(s,2H), 7.131-7.179(m,1H), 7.280-7.314(q,1H), 7.636(s,1H), 7.798-7.828(dd,1H).

Antifungal activity

3.1 Test fungal strains: C. albicas, C. neoformans, A. niger, S. schenekn, M. gypseum, E. floccosum, C. glabrata, C. parapsilosis, C. krusei, C. tropicalis.

3.2 The test used micro-dilution method, the active control is FCZ and AmB. The tested compound is dissolved with DMSO, and diluted with RPMI1640 medium and make the concentration of AmB in the range of 16¡ «0.313μg/ ml, FCZ and the tested compound in the rang of 0.125¡ «64μg/ ml. Adjust the final fungi concentration to $0.5 \times 10^3 \sim 2.5 \times 10^3$CFU / ml for yeast, $0.5 \times 10^4 \sim 2.5 \times 10^4$CFU / ml for filamentous fungi. Every test we did quality control by using C. parapsilosis (ATCC22019) . MICs of the positive control agents against qualify—control strain were shown in TABLE 1. The 96-well plates which we put in fungi solution, tested compound and RPMI1640 medium were incubated in 2-7 days. We determined the destination of test result by visual method. The MIC of AmB and tested compound were determined as there has no visible growth, FCZ determined as restrain 80% compared with blank control. MICs of the positive control drug and the tested compounds were shown in TABLE 2.

TABLE 1: MICs of the positive control agents against the qualify-control strain (μg/ml)

fungi	purpose	drug	MIC
C. parapsilosis (ATCC22019)	qualify-control	AmB	0.5-4.0
		FCZ	1.0-4.0

TABLE 2 : MICs of the positive control drug and the tested compounds (μg/ml)

fungi	positive control drug and compounds			
	FCZ	AmB	A	B
C. albicas	0.125–0.5	0.25-1	4	64
C. neoformans	1–4	0.5-2	4	4
A. niger	---	0.5-1	---	---
S. schenekn	---	1-4	4	64
M. gypseum	64	8-16	2	64
E. floccosum	---	0.5-1	16	64
C. glabrata	4-16	0.5-4	4	8
C. parapsilosis	2-4	0.5-2	2	---
C. krusei	64	4-16	16	8
C. tropicalis	2	16	32	32

(—): no activity

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