Brief Report

Synthesis and antifungal activity of 3-substituted thiochromanones

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ABSTRACT: A series of 3-substituted thiochromanones has been prepared. Their structures were confirmed by H^1-NMR and HRMS. All of the synthesized compounds were screened for antifungal activity against ten fungi species *in vitro*. The compounds 2f and 2g were more efficient than the control drug, ketoconazole.

Keywords: Thiochromanone, Synthesis, Antifungal activity

1. Introduction

In recent years, the incidence of fungal infections has reached alarming proportions. This is largely due to a number of factors such as intensive uses of chemotherapy for bacterial infections and cancers. At the same time, the number of systemic fungal infections has markedly increased; this has been true for large populations of immunocompromised patients as well as those suffering from various hematological malignancies, those with acquired immune deficiency syndrome (AIDS), and those undergoing organ transplantations (*1,2*). An initial study on agricultural antibiotics by the current authors revealed an active ingredient with antifungal activity *in vitro*; this was identified as a compound including a scaffold of thiochromanone. Similarly, Nakazumi H *et al*. also reported that thiochromanone derivatives have broad biological activities (*3,4*). Encouraged by these results, the current authors designed and synthesized a series of 3-substituted thiochromanone derivatives. The preliminary structure-activity relationship has been established based on the results of an *in vitro* antifungal assay. Optimization of the lead scaffold allowed the preparation of several compounds with good antifungal activity *in vitro*.

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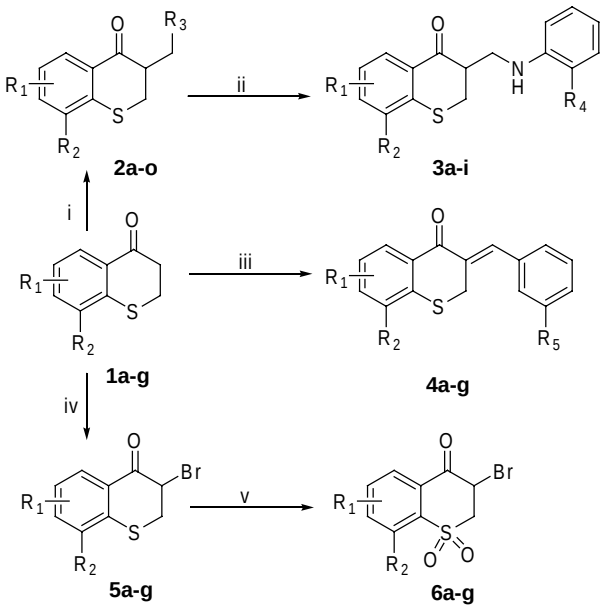
2. Materials and Methods

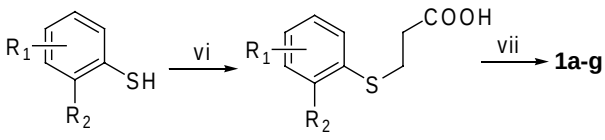
2.1. *Synthesis of 3-substituted thiochromanones*

The 3-substituted thiochromanones (**2**, **3**, **4**, **5** and **6**, Table 1) in this paper were prepared from compound **1** as shown in Scheme 1. The starting material compounds **1a-g** were obtained by a direct method as outlined in Scheme 2 (*5,6*). Commercially available substituted thiophenols were condensed with β-chloro-propionic acid under basic conditions in ethanol, followed by cyclization in H_2SO_4 to give compounds **1a-g**.

The Mannich base derivatives of secondary saturated amines, compounds **2a-o**, were prepared by refluxing the mixtures of **1a-g**, paraformaldehyde, and



Scheme 1. (i) Amines/HCHO/HCl, reflux; (ii) Aromatic amines/EtOH, rt; (iii) Arylaldehydes/H_2SO_4/ EtOH, reflux, 3 h; (iv) Br_2/HOAc, rt, 3 h; (v) H_2O_2/HOAc, rt, 48 h.



Scheme 2. (vi) K_2CO_3/EtOH, reflux, 4 h; (vii) H_2SO_4, rt, 36 h.

Table 1. Structures and antifungal activities of 3-substituted thiochromanones

Compounds	R_1	R_2	R_3	R_4	R_5	Yield (%)	MIC (μM)[a]					
							C.a	*C.n*	*S.s*	*E.f*	*T.r*	*M.g*
1a	5-F	H				50						
1b	5-Cl	H				43						
1c	5-Br	H				47						
1d	6-CF_3	H				59						
1e	5-CH_3	H				61						
1f	5-F	6-Cl				64						
1g	6-Cl	8-Cl				56						
2a	5-F	H	$N(CH_3)_2$			57	10	5	2.5	1.25	1.25	1.25
2b	5-Cl	H	$N(CH_3)_2$			56	10	10	1.25	0.61	0.61	1.25
2c	5-Br	H	$N(CH_3)_2$			78	1.25	5	2.5	0.62	0.08	0.61
2d	6-CF_3	H	$N(CH_3)_2$			67	5	0.61	0.61	0.08	1.25	1.25
2e	5-CH_3	H	$N(CH_3)_2$			49	10	5	1.25	1.25	5	0.61
2f	5-F	6-Cl	$N(CH_3)_2$			67	1.25	0.31	1.25	0.08	0.08	0.61
2g	6-Cl	8-Cl	$N(CH_3)_2$			80	1.25	0.61	1.25	0.08	0.31	0.08
2h	5-F	6-Cl	$N(C_2H_5)_2$			69	5	10	10	1.25	0.61	1.25
2i	6-Cl	8-Cl	$N(C_2H_5)_2$			67	10	5	2.5	1.25	0.08	1.25
2j	5-F	H	Piperidine			65	2.5	2.5	2.5	1.25	0.61	0.61
2k	5-F	6-Cl	Piperidine			67	5	2.5	5	1.25	0.08	0.31
2l	6-Cl	8-Cl	Piperidine			71	1.25	1.25	2.5	0.61	0.61	0.31
2m	5-F	H	Morpholine			62	5	2.5	10	1.25	0.31	1.25
2n	5-F	6-Cl	Morpholine			78	2.5	1.25	1.25	0.61	1.25	1.25
2o	6-Cl	8-Cl	Morpholine			56	2.5	10	10	1.25	1.25	0.31
3a	5-F	H		H		69	10	10	2.5	5	1.25	1.25
3b	5-F	H		4-SO_2NH_2		75	5	10	10	5	2.5	0.61
3c	5-F	H		4-F		75	10	10	10	1.25	1.25	0.61
3d	5-F	H		4-Cl		71	2.5	5	1.25	10	1.25	0.31
3e	5-F	H		4-Br		79	2.5	5	1.25	2.5	0.61	2.5
3f	5-F	H		4-NO_2		78	5	1.25	5	2.5	1.25	5
3g	5-F	H		2-NO_2		75	10	10	5	1.25	0.61	0.61
3h	5-F	H		4-CH_3		80	10	10	5	5	1.25	1.25
3i	5-F	H		4-C_2H_5		69	10	10	10	1.25	2.5	0.61
4a	5-F	H			H	83	5	10	10	1.25	5	5
4b	5-F	H			2-Cl	81	10	10	10	5	0.61	1.25
4c	6-CF_3	H			2-Cl	78	10	10	10	2.5	2.5	1.25
4d	6-Cl	8-Cl			H	76	5	5	1.25	10	2.5	0.61
4e	6-Cl	8-Cl			2-Cl	65	2.5	10	10	5	1.25	10
4f	6-Cl	8-Cl			2-NO_2	76	2.5	10	10	1.25	5	5
4g	6-Cl	8-Cl			4-OCH_3	87	5	10	5	0.61	5	1.25
5a	5-F	H				86	1.25	10	5	5	1.25	0.08
5b	5-Cl	H				81	5	2.5	10	1.25	1.25	5
5c	5-Br	H				85	5	2.5	1.25	5	1.25	0.61
5d	6-CF_3	H				78	10	5	5	1.25	1.25	5
5e	5-CH_3	H				67	5	10	2.5	10	1.25	0.61
5f	5-F	6-Cl				69	2.5	10	10	10	10	5
5g	6-Cl	8-Cl				68	2.5	10	10	1.25	2.5	1.25
6a	5-F	H				80	2.5	10	10	5	5	0.08
6b	5-Cl	H				68	5	5	5	1.25	2.5	5
6c	5-Br	H				79	10	2.5	1.25	2.5	1.25	1.25
6d	6-CF_3	H				75	5	2.5	5	0.61	0.61	0.61
6e	5-CH_3	H				85	2.5	10	5	5	1.25	2.5
6f	5-F	6-Cl				87	5	10	10	2.5	2.5	2.5
6g	6-Cl	8-Cl				79	2.5	1.25	10	1.25	1.25	1.25
Ketoconazole							2.5	1.25	1.25	0.08	0.61	0.61

[a] *C.a, C. albicans*; *C.n, C. newformans*; *S.s, S. schenckii*; *E.f, E. floccosum*; *T.r, T. rubrum*; *M.g, M. gypsum*.

appropriate amines in dry benzene. Primary aromatic amines do not usually give corresponding Mannich bases with the above procedure. However, stirring **2a** with primary aromatic amines in ethanol at room temperature was found to give the corresponding Mannich bases in good yield. The 3-benzylmethylene thiochromanones **4a-g** were obtained from an Aldol-condensation reaction of **1a-g** and appropriate arylaldehydes under catalysis of H_2SO_4. Compounds **1a-g** were treated with an equivalent Br_2 in acetic acid to give 3-bromo thiochromanones, compounds **5a-g**, followed by oxidation with H_2O_2 in acetic acid at room temperature to yield **6a-g**. The structures of all synthesized compounds have been confirmed by elemental analysis, IR, H^1-NMR, and HRMS (*See Supplemental data*).

2.2. *Evaluation of antifungal activity*

The prepared 3-substituted thiochromanones were evaluated for their *in vitro* antifungal activity against six isolates of fungi in Sabouraud medium according to consecutive double dilution to give their minimum inhibitory concentrations (MIC). Ketoconazole was used as a control drug. In brief, the assay was conducted as follows: the synthesized compounds and

ketoconazole were accurately weighted and dissolved in 0.5 mL of DMSO and diluted with sterile distilled water to 25 mL. The solution was then added to the cells to bring the concentration of tested compound within a range of 0.08 to 10 µM. The cells were incubated at 28°C for 24 h for *C. albicans*, for 48 h for *C. neoformans*, and for 7 days for other fungi. After incubation, MIC values were determined.

3. Results and Discussion

Table 1 summarizes the structures and antifungal activity of 3-substituted thiochromanones synthesized in the present study. All compounds tested had a certain level of antifungal activity against the fungi tested. On the whole, all compounds demonstrated potent activity against *T. rubrum* and *M. gypsum*. The series of Mannich base derivatives displayed better activity against all fungi tested. Antifungal activity of the most potent compounds, **2f** and **2g**, was more effective than that of the control drug, ketoconazole, against *C. albicans*, *C. neoformans*, and *T. rubrum*. This activity was comparable to that of ketoconazole against *S. schenckii*, *E. floccosum*, and *M. gypsum*. The aromatic Mannich base derivatives, compounds **3a-i**, displayed potent activity against *E. floccosum* and *T. rubrum* but weaker activity against *C. albicans*, *C. neoformans*, and *S. schenckii*. The 3-benzylmethylene derivatives, compounds **4a-g**, demonstrated similar activity; however, compound **4b** was as effective as ketoconazole against *T. rubrum*, **4d** was similarly as effective against *S. schenckii* and *M. gypsum*, and **4e** and **4f** were similarly as effective against *C. albicans*. Among the 3-bromo thiochromanones, **5a** displayed excellent activity against *C. albicans* and *M. gypsum* and was twice as active as ketoconazole. Compound **5d** was as effective as ketoconazole against *M. gypsum*, and other compounds had lower activity. The oxidation derivative compounds **6a-g** did not have clearly increased activity, and did not demonstrate the activity that was expected. The current efforts, though not as successful as hoped, should nonetheless help in the discovery of new antifungal agents.

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(*Received July 07, 2008; Accepted August 02, 2008*)

Supplementary data

All final compounds were characterized by elementary analysis, IR, H^1-NMR and HRMS. Data for compound:

1g: m.p. 81-82°C; IR (KBr) 1685, 1557, 1475, 880 cm^{-1}; H^1-NMR (300 MHz, DMSO-d_6) δ 2.9-3.3 (4H, m), 7.6 (1H, d), 8.1 (1H, d); HRMS (M^+) calcd for $C_9H_6Cl_2OS$ 231.9516, found 231.9524.

2f: m.p. 165-166°C; IR (KBr) 2670, 1750, 1580, 1320, 1220, 850 cm^{-1}; H^1-NMR (300 MHz, DMSO-d_6) δ 3.3-3.9 (6H, m), 4.3-4.7 (5H, m), 7.4 (1H, d), 7.9 (1H, d); HRMS (M^+) calcd for $C_{12}H_{13}ClFNOS$ 273.0390, found 273.0411.

2g: m.p. 176-177°C; IR (KBr) 2700, 1575, 1330, 1225, 845 cm^{-1}; H^1-NMR (300 MHz, DMSO-d_6) δ 3.0-3.7 (6H, m), 4.8 (5H, m), 7.3 (1H, d), 7.8 (1H, d); HRMS (M^+) calcd for $C_{12}H_{13}Cl_2NOS$ 289.0095, found 289.0109.

3e: m.p. 110-112°C; IR (KBr) 3400, 1665, 1600, 1470, 1270, 895, 820 cm^{-1}; H^1-NMR (300 MHz, DMSO-d_6) δ 3.1 (3H, m), 3.5-3.7 (2H, q), 4.1-4.8 (1H, s), 6.5 (1H, d), 7.1-7.4 (4H, m), 7.8 (1H, d); HRMS (M^+) calcd for $C_{16}H_{13}BrFNOS$ 364.9885, found 364.9876.

4g: m.p. 148-149°C; IR (KBr) 2830, 1650, 1560, 1545, 1480, 840, 800 cm^{-1}; H^1-NMR (300 MHz, DMSO-d_6) δ 3.6 (3H, s), 4.0 (2H, s), 6.6-7.0 (4H, m), 7.1 (1H, s), 7.8 (1H, d), 8.0 (1H, d); HRMS (M^+) calcd for $C_{17}H_{12}Cl_2O_2S$ 349.9935, found 349.9950.

5g: m.p. 108-109°C; IR (KBr) 1700, 1575, 1470, 880 cm^{-1}; H^1-NMR (300 MHz, DMSO-d_6) δ 3.5-3.8 (2H, m), 4.8-5.0 (1H, m), 7.6 (1H, d), 8.1 (1H, d); HRMS (M^+) calcd for $C_9H_5BrCl_2OS$ 309.8622, found 309.8637.