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Facile One-pot Synthesis of Some Novel Thiazolylpyrazole Derivatives with Antifungal Activity

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A series of novel 1-(4-phenylthiazol-2-yl)-1,4-dihydrothiochroman[4,3-*c*]pyrazole have been prepared by a three-component reaction of thiochromanone-3-carbaldehyde, phenacyl bromide, and thiosemicarbazide. The reaction was in one-pot and did not require any additional catalyst with moderate yields. This method provided several advantages such as environment friendliness and simple work-up procedure. The compounds were assayed for antifungal activity and some of the new compounds can be further utilized as lead compounds.

Fungal infections are a growing problem because of extensive use of antibiotic drugs and medical instruments.[1] However, clinically used antifungal drugs widely exhibit low bioavailability, narrow antimicrobial spectrum, toxic side effects, and other problems.[2] Therefore, new effective antifungal drugs are desired all the time.

Thiochromanone is a versatile reagent that has been extensively utilized in heterocyclic synthesis.[3] It had been reported to possess important biological activities such as antifungal[4] and anticancer[5] activities. Thiazole and pyrazole are also the key scaffolds of many biological molecules and pharmaceutical products because of their ubiquitous nature. Many of their derivatives had been reported with fantastic bioactivities. A large number of thiazole derivatives obtained from microbial and marine origins exhibit important biological effects such as antibacterial,[6] antifungal,[7] antitumor,[8] and antihypertensive[9] activities. Pyrazole derivatives have been also reported to exhibit significant antimicrobial[10] and antifungal[11] activities.

In view of the various biological activities of thiazole and pyrazole, we were tempted to synthesize a series of compounds constructed of thiochromanone combined with thiazolylpyrazole as potential antifungal agents. To the best of our knowledge, these thiazolylpyrazole derivatives containing thiochromanone have not been reported to date.

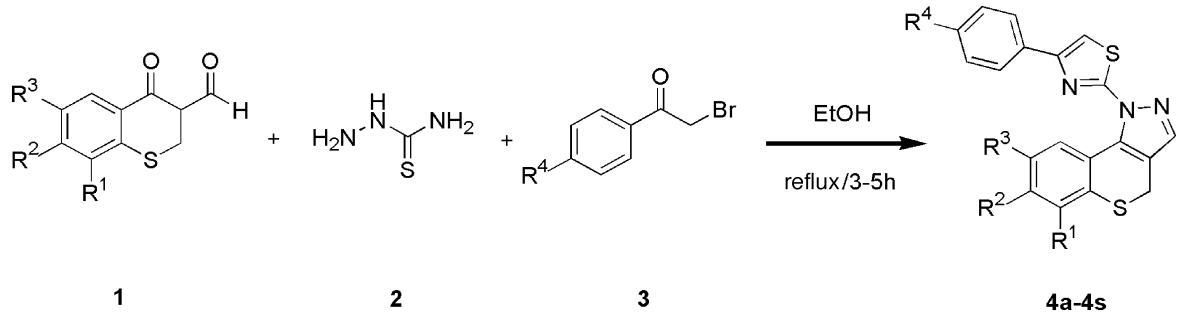
Commonly, thiazolylpyrazole derivatives are formed via base-catalyzed or acid-catalyzed reaction of α,β-unsaturated ketones with thiosemicarbazide generating thiosemicarbazone, which on reaction with phenacyl bromide gives the products.[12] Some literature describes the one-pot synthesis of thiazolylpyrazole derivatives recently, but all of them need additional catalyst.[13] Herein, we efficiently synthesized some thiazolylpyrazole derivatives containing thiochroman skeleton by a one-pot three-component reaction without additional catalyst, some of which shows antifungal activity.

Reaction of an equimolar mixture of thiochromanone-3-carbaldehyde,[14] phenacyl bromide, and thiosemicarbazide under reflux in EtOH gave the final products (Scheme 1). In this reaction, the assembly of thiazolylpyrazole derivatives **4** comprises the following key steps (Scheme 2): intermediate **I**, the adduct of thiochromanone-3-carbaldehyde **1** to thiosemicarbazide **2**, reacts with phenacyl bromide **3** to give the intermediate **II** undergoing the final ring closure. Likely the HBr eliminated from the Hantzsch thiazole synthesis (**I** → **II**) plays a role of catalyst in the cyclocondensation of pyrazole.

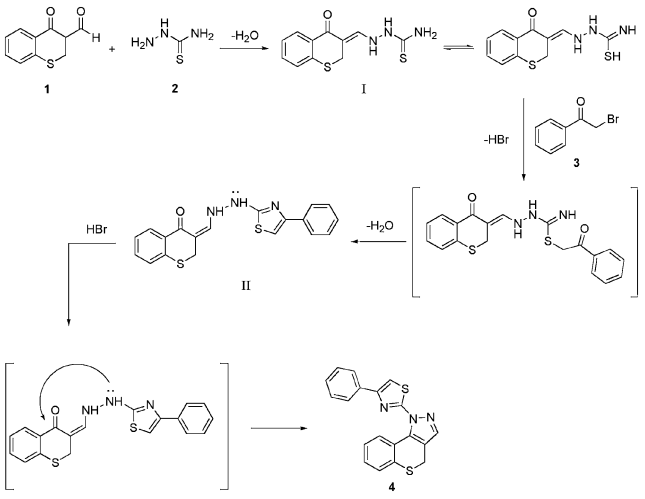
This rationale has been proven by the synthesis of intermediate **I** from 6-chloro-4-methoxythiochromane-3-carbaldehyde and thiosemicarbazide in EtOH without any catalyst. That means thiochromanone-3-carbaldehyde and thiosemicarbazide cannot cyclize to pyrazole without catalyst. Intermediate **I** readily cyclizes to the corresponding thiazolylpyrazole derivative after adding phenacyl bromide thus confirming the cyclocondensation of pyrazole is catalyzed by in situ generated HBr as the above rationale suggests.

All of the synthesized compounds in Table 1 gave analytical and spectroscopic data which were consistent with their depicted structures (The analytical data of all the synthesized compounds are given in Supporting Information.)[15]

The ^{1}H NMR spectrum of **4o** showed a sharp singlet at 3.84 ppm due to the C-4 proton of the compound. The singlet at 3.84 ppm is related to a singlet at 7.65 ppm in an NOE experiment, which means the sharp singlet at 7.65 ppm is the proton of pyrazole. Thiazole proton is another singlet at 7.23 ppm. Aromatic proton peaks of two phenyl rings of **4o** appear in the region of 8.69–6.97 ppm as multiplets. The

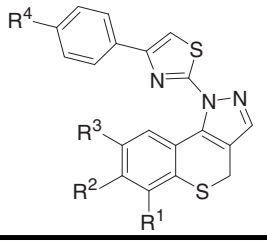


Scheme 1. Synthesis route of thiazolylpyrazole derivatives **4a**–**4s**.



Scheme 2. Plausible key steps of one-pot assembly of thiazolylpyrazole derivatives from thiochromanone-3-carbaldehyde **1**, thiosemicarbazide **2**, and phenacyl bromide **3**.

Table 1. Structure and yield of synthesized compounds



	R^1	R^2	R^3	R^4	Yield/%
4a	H	H	CH_3	H	71
4b	F	H	H	H	79
4c	H	H	F	H	81
4d	Cl	H	Cl	H	80
4e	H	F	CH_3	H	77
4f	CH_3	H	CH_3	H	69
4g	H	H	Cl	H	77
4h	Cl	H	H	H	80
4i	CH_3	H	H	H	75
4j	H	H	Cl	Br	81
4k	H	F	CH_3	Br	74
4l	H	H	F	Br	81
4m	Cl	H	H	Br	80
4n	CH_3	H	CH_3	Br	80
4o	H	H	Cl	OCH_3	78
4p	H	F	CH_3	OCH_3	73
4q	H	H	F	OCH_3	78
4r	Cl	H	H	OCH_3	77
4s	CH_3	H	CH_3	OCH_3	71

^{13}C NMR spectra showed no peaks at about 180 ppm (C=O) in target compound but appearance in compound **I**, which means intermediate **I** closed the loop to the target compound.

All the synthesized novel compounds were tested for in vitro antifungal activity by microdilution broth method.[16] The organisms examined included *C. albicans*, *C. neoformans*, *M. gypseum*, and *A. niger*. From Table 2, it is clear that no target compounds showed antifungal activity against *M. gypseum* and *A. niger*. Only **4a**, **4g**, **4i**, **4k**, and **4s** have weak activity against *C. albicans*. The compounds **4a**–**4s** showed growth-inhibiting activity against *C. neoformans* except **4b**, **4c**, **4e**, **4f**, and **4h**. The substituted phenylthiazole **4j**–**4s** (R^4 = –Br or –OCH_3) showed improvement in the activity when compared to the compounds **4a**–**4i** (R^4 = –H). And **4o**–**4s** showed more inhibitory activity than **4j**–**4n** maybe resulting from an electron-donating substituent at the *para*-position of the aromatic ring (–OCH_3) had better antifungal activity than that with an electron-withdrawing substituent (–Br). Among them, the MIC was 8 μg mL^{-1} for **4s** against *C. neoformans*, a similar level of activity with Fcz.

Table 2. Minimum inhibitory concentrations (MIC μg mL^{-1}) of target compounds

Compound	Antifungal activity			
	C. albicans	*C. neoformans*	*M. gypseum*	*A. niger*
4a	128	128	>128	>128
4b	>128	>128	>128	>128
4c	>128	>128	>128	>128
4d	>128	64	>128	>128
4e	>128	>128	>128	>128
4f	>128	>128	>128	>128
4g	128	32	>128	>128
4h	>128	>128	>128	>128
4i	128	128	>128	>128
4j	>128	64	>128	>128
4k	128	128	>128	>128
4l	>128	64	>128	>128
4m	>128	128	>128	>128
4n	>128	64	>128	>128
4o	>128	64	>128	>128
4p	>128	32	>128	>128
4q	>128	16	>128	>128
4r	>128	64	>128	>128
4s	128	8	>128	>128
Fcz[a]	2	8	64	>128
AmB[b]	0.5	2	8	32

[a]Fcz, abbreviation of Fluconazole. [b]AmB, abbreviation of Amphotericin B.

In conclusion, a simple and friendly one-pot strategy for the synthesis of thiazolylpyrazole derivatives from thiochromanone-3-carbaldehyde, phenacyl bromide, and thiosemicarbazide has been developed. In this method, thiazolylpyrazole derivatives can be synthesized with good yields and without any other additional catalyst. Some compounds prepared in this study exhibited antifungal activity against *C. neoformans*. It seems reasonable that the development of libraries of substituted thiazolylpyrazole derivatives might provide additional lead molecules for use in drug discovery.

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