Regular Article

Design, Synthesis, Antifungal Activity and Molecular Docking of Thiochroman-4-one Derivatives

Yifan Zhong,[a] Xiaoyan Han,[a] Shengbin Li,[a] Hui Qi,[a] Yali Song,*[,a,b] and Xiaoqiang Qiao*[,a,b]

[a] *Key Laboratory of Pharmaceutical Quality Control of Hebei Province, College of Pharmaceutical Sciences, Hebei University; Baoding, Hebei 071002, China: and* [b] *Key Laboratory of Medicinal Chemistry and Molecular Diagnosis of Ministry of Education, Hebei University; Baoding, Hebei 071002, China.*
Received March 29, 2017; accepted June 28, 2017

***N*-Myristoyltransferase (NMT) has been validated pre-clinically as a target for treatment of fungal infections. Various substituted thiochroman-4-one derivatives have been synthesized by an efficient method. The synthesized compounds 7a–y and 8a–t were evaluated for their *in vitro* antifungal activity against the *Canidia albicans, Cryptococcus neoformans, Epidermophyton floccosum, Mucor racemosus, Microsporum gypseum* and *Aspergillus nigerstrain*. A series of compounds exhibited significant activity (minimal inhibitory concentrotion (MIC)=0.5–16 μg/mL) against *Canidia albicans* and *Cryptococcus neoformans*. The antifungal activity of compound 7b was reached to that of fluconazole, which can serve as a good starting point for further studies of structural diversity of the NMT inhibitors. The molecular docking studies revealed an interesting binding profile with very high receptor affinity for NMT of *Canidia albicans*.**

Key words thiochroman-4-one; antifungal; molecular docking; *N*-myristoyltransferase; inhibitor

The infection rate of fungi has increased significantly in the past decades.[1)] In fact, nasty infection of fungus has increased dramatically in recent years to become an important cause of morbidity and mortality in patients. *Aspergillus* and *Candida* spp. account for the majority of documented infections. Recent epidemiological trends indicate a shift towards infections by *Aspergillus* spp., *non-albicans Candida* spp. and previously uncommon fungi that often have diminished susceptibility to current antifungal agents.[2–6)] Whereas, available antifungal drugs for such infections essentially have three molecular targets: 14α-demethylase (azoles), ergosterol (polyenes) and β-1,3-glucan synthase (echinocandins).[7)] Unfortunately, none of them is ideal in terms of efficacy, antifungal spectrum or safety.[8)] To overcome the deficiency of the current antifungal drugs and to obtain more high activity and low side-effect drugs, an antifungal drug having a novel mode of action should be developed.

Myristoyl-CoA : protein *N*-myristoyltransferase (NMT) is a cytosolic monomeric enzyme that catalyzes the transfer of the myristoyl group from myristoyl-CoA to the N-terminal glycine of a number of eukaryotic cellular and viral proteins.[9–12)] NMT is a promising target enzyme[13,14)] for the development of novel fungicidal drugs having a broad antifungal spectrum. Four kinds of NMT inhibitors have been reported (Fig. 1), peptidomimetics (SC58272),[15)] benzothiazole (FTR1335),[16,17)] tetrahydrocarbazole (compound **10c**)[18)] and benzofuran (R64).[19)] Biological of R64 including quasi *in vivo* antifungal activity assay (IC_{50}=3.0 μM), *in vitro* antifungal activity assay (IC_{50}=0.12 μM), and CaNMT inhibitory activity (IC_{50}=0.0012 μM) were reported.[19)] Structure of FTR1335 and R64 shares three important chemical elements (Fig. 1), a benzoheterocyclic core (B), a secondary amine at its side chain (A), and a hydrophobic group (C) through various linkers. According to these characteristics, Sheng *et al.*[20)] designed and synthesized a series NMT Inhibitors (compound **8f**, Fig. 1).

Thiochroman-4-one, which is heterocyclic compound containing sulfur atom has been reported to possess wide biological activity.[21–28)] In an effort to investigate the importance of the benzoheterocyclic core on the antifungal activities, we designed and synthesized thiochroman-4-one derivatives as bioisostere of benzoheterocyclic NMT inhibitors. The double bond connection between ring B and ring C could the lost partial flexibility, but the molecular docking showed that the steric configuration of molecule is similar to R64 such as residues Phe240 produced Pi–Pi interaction with ring. Compared with R64 (C4-side chain), the location of side chain of thiochroman-4-one (C6-side chain) is different. It cannot be sure whether three or four carbons might be better for the chain length between hetero-cyclic core and amine side chain. Moreover, thiochroman-4-one with high-fat-soluble[29)] can easily cross cellular membranes and exert bioactivity. The structure–activity relationships (SARs) and molecular docking studies of the thiochroman-4-one derivatives were investigated.

Results and Discussion

Chemistry According to the report,[30)] using the mercaptophenol (**1**) as the starting materials, the intermediate compound **3** (Chart 1) were synthesized *via* two steps. Compound **4** was obtained by aldol condensation of compound **3** with a substituted benzaldehyde. Compound **5** or **6** obtained by etherification reaction of 1,3-dibromopropane or 1,3-dibromobutane with compound **4**.

In the final, the preparation of compound **7a**–**y** and **8a**–**t** would be carried out by a suitable base. In order to study the optimum conditions of substitution reaction, taking (*E*)-3-benzylidene-6-(3-bromopropoxy)thiochroman-4-one (compound **7b**) for instance, base, solvents and temperature were respectively investigated. As shown in Table 1, triethylamine as an organic weak base was not an efficient catalyst for this reaction, and the reaction was failed. Inorganic strong base such as NaOH or KOH can increase the yield to reach 40%. When the solvent was 1,4-dioxane, the yield was highest (51.2%). Optimum reaction temperature for the synthesis was 85°C

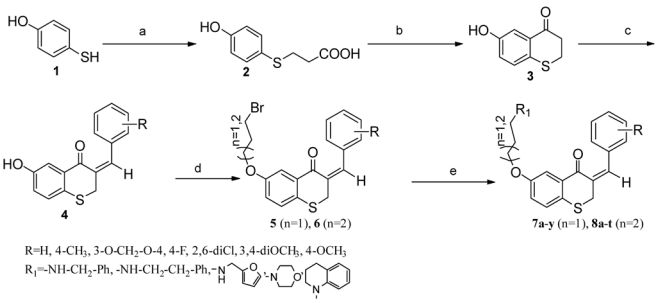
* To whom correspondence should be addressed. e-mail: yalisong@hbu.edu.cn; xiaoqiao@hbu.edu.cn

and the yield was highest (58.3%). Compounds **7a**–**y**, or **8a**–**t** were obtained by treating compounds **5** or **6** with primary or secondary amine and KOH in 1,4-dioxane for 6–9 h at 85°C. The product was isolated and purified by silica gel column chromatography.

A nuclear Overhauser effect (NOE) enhancement (*e.g.* compound **7b**) was observed (Fig. 2 where the arrow point) between the -S-CH_2-(δ_H 3.92) and -C=CH-(δ_H 8.22), indicating a *trans*-form double-bond configuration.

Biological Activity The antifungal activity of each compound against *Candida albicas* (*C. alb*), *Cryptococcus neoformans* (*C. neo*) *Mucor racemosa* (*M. rac*), *Microsporum gypseum* (*M. gyp*), *Epidermophyton floccosum* (*E. flo*) and *Aspergillus niger* (*A. nig*) was expressed as the minimal inhibitory concentration (MIC). *In vitro* antifungal activity assay (Table 2) indicated that these compounds were more active against *C. alb* and *C. neo* than *M. rac, M. gyp* and *E. flo*. Compounds **8a**–**t** (*n*=2) showed moderate antifungal activity against *A. nig*, while compound **7a**–**t** (*n*=1) the marginal activity. In general, all compounds are more antifungal active against deep fungi than superficial except for *E. flo*. The compounds **7a**–**y** (*n*=1) were more active than compounds **8a**–**t** (*n*=2).

Compounds **7a**–**y** (*n*=1) showed good potency inhibitor against *C. alb* and *C. neo* with MIC in the range of 0.5–16 μg/mL. For example, when the concentration of com-



Reagents and conditions: (a) $ClCH_2CH_2COOH$, NaOH, H_2O, 100°C, 3h, 90–95%; (b) H_2SO_4, 12 h, 78–85%; (c) substituted benzaldehyde, KOH, EtOH, r.t., 65–85%; (d) 1,3-dibromopropane or 1,3-dibromobutane, K_2CO_3, 1,4-dioxane, reflux, 4–6 h, 25–30%; (e) benzylamine/phenethylamine/furfurylamine/morpholine/tetrahydroquinolines, KOH, 1,4-dioxane, 85°C, 6–9 h, 40–60%.

Chart 1. Reagents and Conditions of the Synthetic Compounds

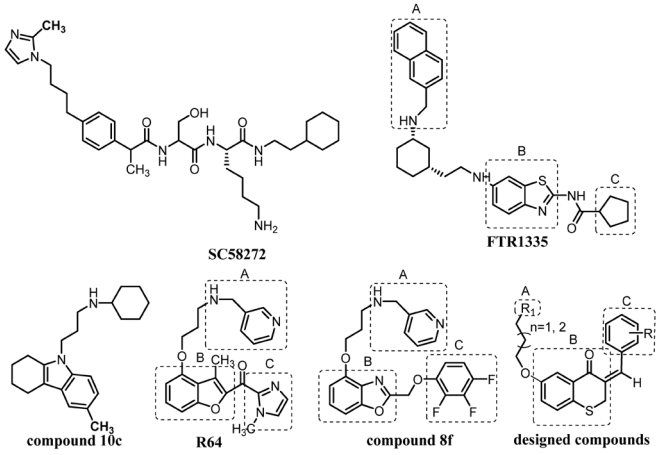


Fig. 1. NMT Inhibitors

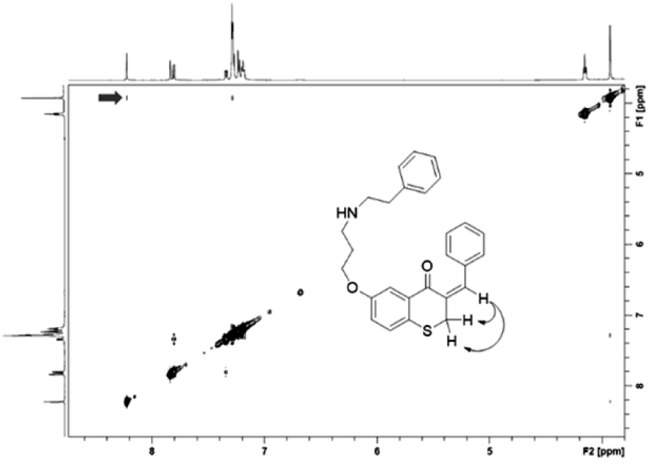
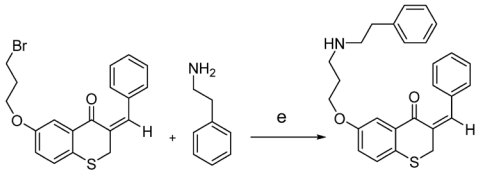


Fig. 2. NOESY Spectrum of Compound **7b**

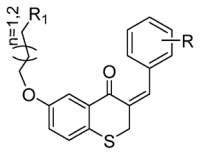
Table 1. The Effect of Different Conditions on Reaction **e**[a)]



Entries	Base	Solvent	Temp (°C)	Time (h)	Isolated yield (%)
1	Et_3N	Acetonitrile	70	—	—
2	K_2CO_3, KI	Acetonitrile	70	7.5	6.2
3	NaOH	Acetonitrile	70	8	40.3
4	KOH	Acetonitrile	70	8	46.8
5	NaH	Acetonitrile	70	6	11.5
6	KOH	Ethanol	70	—	—
7	KOH	Tetrahydrofuran	70	8	43.4
8	KOH	1,4-Dioxane	70	7.5	51.2
9	KOH	1,4-Dioxane	80	7.5	54.6
10	KOH	1,4-Dioxane	90	7	49.5
11	KOH	1,4-Dioxane	85	7.5	58.3

a) 3-Benzylidene-6-(3-bromopropoxy)thiochroman-4-one (1 mmol), phenethylamine (1.5 mmol), amount of base (200 mol%) and solvent (8 mL).

Table 2. Antifungal Activities of Compounds



7a-y (n=1), **8a-t** (n=2)

Compd	R	R_1	MIC (μg/mL)					
			C. alb	*C. neo*	*A. nig*	*M. rac*	*M. gyp*	*E. flo*
7a	H	-NH-CH_2-Ph	4	4	16	4	4	4
7b	H	-NH-CH_2-CH_2-Ph	0.5	1	>128	>128	8	16
7c	H	-NH-CH_2-2-furan	4	8	>128	4	4	8
7d	H	-*N*-Morpholine	16	4	>128	>128	16	8
7e	3-CH_2-O-CH_2-4	-NH-CH_2-Ph	2	2	>128	8	2	8
7f	3-CH_2-O-CH_2-4	-NH-CH_2-CH_2-Ph	8	8	>128	32	8	16
7g	3-CH_2-O-CH_2-4	-NH-CH_2-2-furan	>128	32	>128	32	32	16
7h	3-CH_2-O-CH_2-4	-*N*-Morpholine	>128	32	>128	64	64	32
7i	3-CH_2-O-CH_2-4	-*N*-1,2,3,4-Tetrahydroquinoline	>128	>128	>128	>128	>128	32
7j	3,4-diOCH_3	-NH-CH_2-Ph	4	4	32	4	8	8
7k	3,4-diOCH_3	-NH-CH_2-CH_2-Ph	4	4	>128	16	8	16
7l	3,4-diOCH_3	-NH-CH_2-2-furan	4	4	64	8	2	8
7m	3,4-diOCH_3	-*N*-Morpholine	>128	16	>128	>128	128	32
7n	4-OCH_3	-NH-CH_2-Ph	4	16	>128	8	2	4
7o	4-OCH_3	-NH-CH_2-CH_2-Ph	4	2	>128	8	8	8
7p	4-OCH_3	-NH-CH_2-2-furan	4	4	>128	8	8	4
7q	2,6-diCl	-NH-CH_2-Ph	32	64	>128	64	>128	64
7r	2,6-diCl	-NH-CH_2-CH_2-Ph	16	32	>128	32	32	32
7s	2,6-diCl	-NH-CH_2-2-furan	16	32	>128	32	64	32
7t	4-CH_3	-NH-CH_2-Ph	16	32	16	32	64	16
7u	4-CH_3	-NH-CH_2-CH_2-Ph	64	>128	>128	>128	>128	>128
7v	4-CH_3	-NH-CH_2-2-furan	16	32	16	32	32	8
7w	4-F	-NH-CH_2-Ph	16	64	>128	64	>128	2
7x	4-F	-NH-CH_2-CH_2-Ph	32	16	>128	32	>128	8
7y	4-F	-NH-CH_2-2-furan	64	64	>128	64	64	8
8a	H	-NH-CH_2-Ph	16	32	32	32	32	16
8b	H	-NH-CH_2-CH_2-Ph	16	>128	>128	>128	32	8
8c	H	-NH-CH_2-2-furan	32	32	>128	32	64	64
8d	3-CH_2-O-CH_2-4	-NH-CH_2-Ph	64	32	32	32	32	16
8e	3-CH_2-O-CH_2-4	-NH-CH_2-CH_2-Ph	32	32	>128	32	>128	4
8f	3-CH_2-O-CH_2-4	-NH-CH_2-2-furan	64	128	>128	>128	>128	>128
8g	3,4-diOCH_3	-NH-CH_2-Ph	8	16	32	16	>128	16
8h	3,4-diOCH_3	-NH-CH_2-CH_2-Ph	>128	>128	>128	>128	>128	>128
8i	3,4-diOCH_3	-NH-CH_2-2-furan	32	>128	>128	64	128	64
8j	4-OCH_3	-NH-CH_2-Ph	16	32	32	32	32	4
8k	4-OCH_3	-NH-CH_2-CH_2-Ph	16	32	>128	32	16	32
8l	4-OCH_3	-NH-CH_2-2-furan	32	32	32	32	32	32
8m	2,6-diCl	-NH-CH_2-2-furan	>128	>128	>128	>128	>128	>128
8n	2,6-diCl	-NH-CH_2-CH_2-Ph	16	32	>128	>128	>128	>128
8o	2,6-diCl	-NH-CH_2-Ph	16	>128	>128	>128	>128	>128
8p	4-CH_3	-NH-CH_2-Ph	4	32	32	32	64	16
8q	4-CH_3	-NH-CH_2-CH_2-Ph	8	8	16	16	16	2
8r	4-CH_3	-NH-CH_2-2-furan	>128	>128	>128	32	>128	16
8s	4-F	-NH-CH_2-Ph	16	16	32	32	32	4
8t	4-F	-NH-CH_2-CH_2-Ph	4	8	16	32	32	4
Fcz[a)]	—	—	16	32	>128	32	16	32
AmB[b)]	—	—	1	1	2	1	2	2

a) Fcz: Fluconazole, *b*) AmB: Amphotericin.

pound **7l** was 4 μg/mL, *C. alb* was absolutely inhibited (Fig. 3c) as same as 1 μg/mL amphotericin B (Fig. 3d). Moreover, the antifungal activity of compound **7b** against *C. neo* (MIC=1 μg/mL) and *C. alb* (MIC=0.5 μg/mL) had reached or exceeded the MIC of amphotericin B. As compared with *C. alb*, the activity of the compound **7a**–**y** (*n*=1) against *C.*

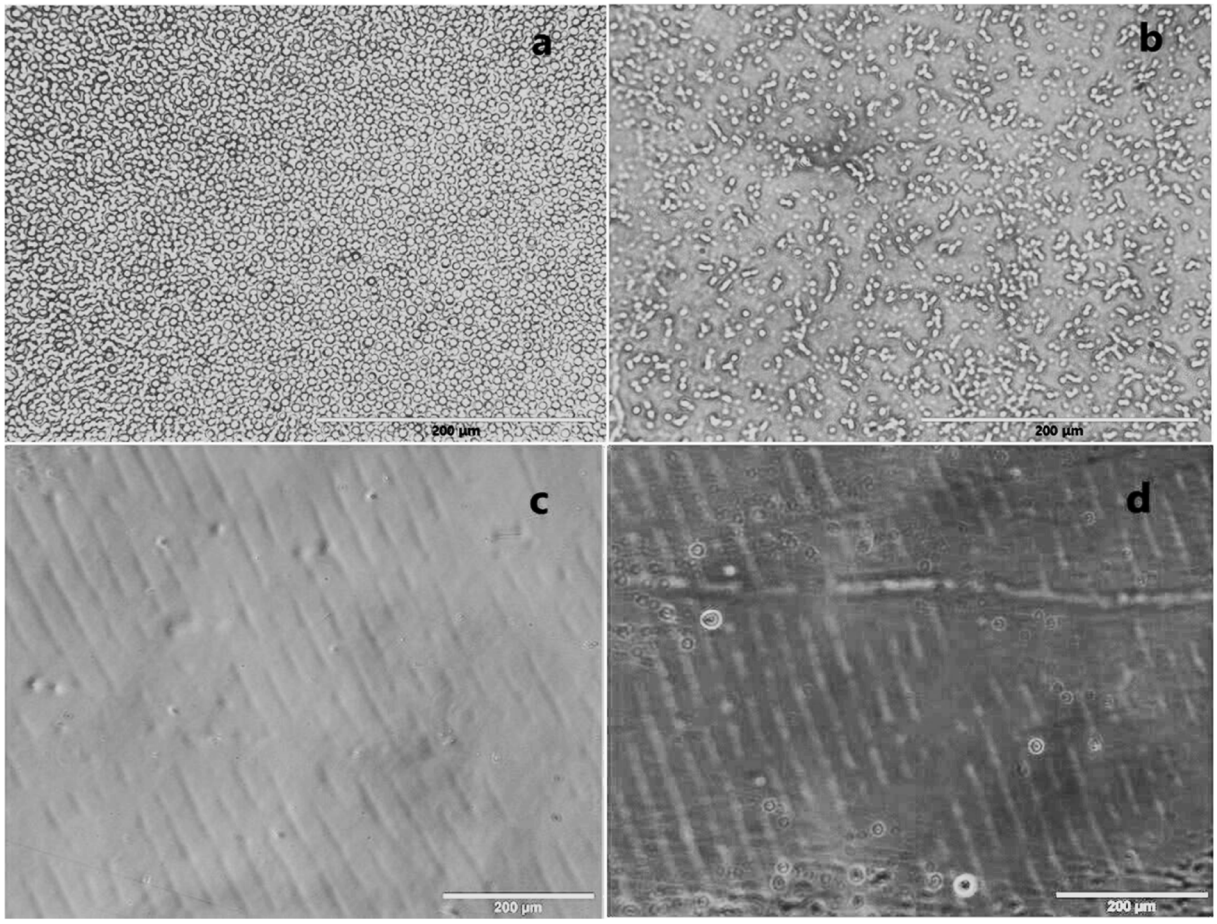


Fig. 3. *C. alb* Was Inhibited in Different Concentrations by Compound **7l** (**a**, 1 μg/mL; **b**, 2 μg/mL; **c**, 4 μg/mL) and Amphotericin B Was Used as Control (**d**, 1 μg/mL)

neo was decreased. To *M. rac*, compounds **7a**, **b**, **e**, **j**, **l**, **n**, **o** and **r** still showed more active (MIC=4–8 μg/mL) than fluconazole but 2-fold less active than amphotericin B. Among these compounds, **8a**–**t** (n=2) exhibited a moderate fungal activity (major MIC in the range of 32–128 μg/mL) against *C. neo*, *A. nig*, *M. rac* and *M. gyp.* As for *C. alb*, these compounds with major MIC in the range of 8–32 μg/mL were slightly better than other fungus. Remarkably, the activity of compound **8q** against *E. flo* reached the level of amphotericin B (MIC=2 μg/mL). Interestingly, the activity of compound **9** against *C. alb*, *A. nig* and *M. rac* was lost, but it was meaningful antifungal activity against *C. neo*, *M. gyp* and *E. flo.* These results encouraged us to further research their antifungal mechanism in other ways.

SARs of the Thiochroman-4-one Derivatives *In vitro* antifungal estimate showed that when the benzofuran scaffold was replaced bythiochroman-4-one, the antifungal was retained. Various substituents on the C3-aromatic ring, C6-N-terminal linked groups and carbon in the C6-side, were investigated that various by representative antifungal activity of *C. alb* and *C. neo.*

The compounds **8a**–**t** (n=2) were obvious less activity than compounds **7a**–**y** (n=1). Antifungal activity of some compounds **8a**–**t** (n=2) were lost, such as compounds **8k**, **m** and **r**. Obviously, the length of the C6-side chain affect greatly on antifungal activity. But, the partial compounds **8a**–**t** (n=2), like **8e**, **j**, **s**, **q** and **t**, were more antifungal active against *E. flo* than compounds **7a**–**y** (n=1). Compounds with electron-donating and hydrophobic group at the C3-phenyl group, such as -OCH_3, exhibited higher antifungal activity than those with electron-withdrawing groups such as -F and -Cl. Moreover, compounds **7j**–**m** and **8g**–**i** with di-OCH_3 substituents showed no advantage compared to -OCH_3 substituent. Among these electron-donating aryls, compounds **7b** substituents showed the best antifungal activity (MIC=0.5 μg/mL). Replacing the benzyl and phenylethyl of C6-N-terminal with a morpholinyl (such as compounds **7d**, **h** and **m**) and furfuryl (such as compounds **7g**, **p** and **s**) resulted in an obvious decrease in activity. As for *N*-1,2,3,4-tetrahydroquinoline, compound **7i** showed marginal antifungal activity. It suggested the C6-N-terminal nonheterocycle aromatic ring and secondary amine at its C6-side chain made a substantial contribution to the activity. Interestingly, the amine of compound **9** was lost, but the antifungal activity was partial retained against *C. neo, M. gyp* and *E. flo.* It showed that the thiochroman-4-one core with C6-side chain might be a key for antifungal selectivity.

Molecular Docking For further understand the SARs observed *in vitro* antifungal activity assays, compounds **7b**, **e**, **8t** and original ligand **R64** were selected to be performed molecular docking studies. The docking results were showed in Fig. 4 and Table 3. Obviously, compound **7b** was absolutely embedded in NMT of *C. alb.* (CaNMT, PDB ID: 1IYL).[13]

The thiochroman-4-one ring was located at the center of the active site, surrounded by some hydrophobic residues, such

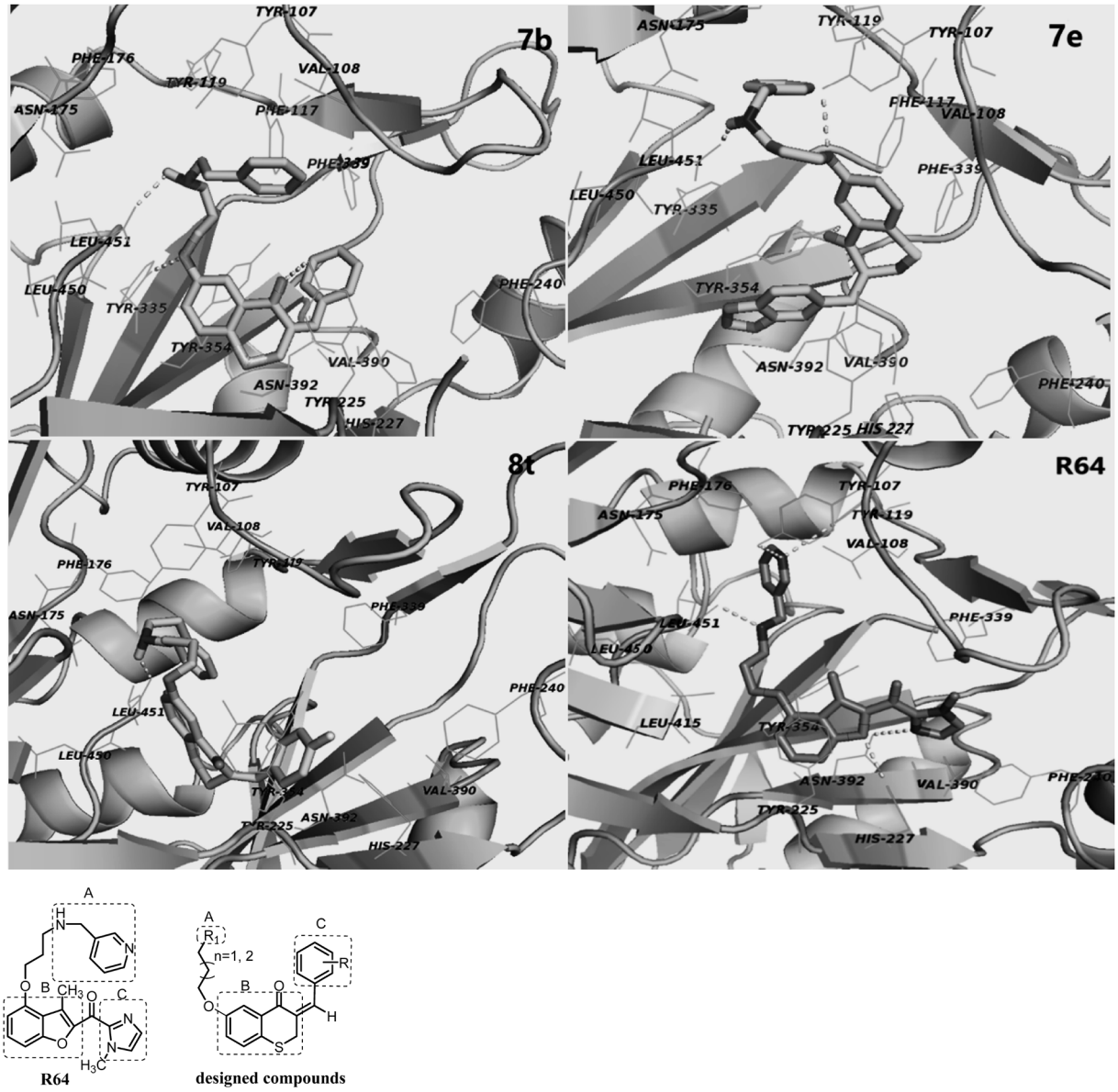


Fig. 4. Docking of Compounds **7b**, **e**, **8t** and Ligand **R64**

Table 3. Ligand–CaNMT Interactions of the Four Compounds

Compd	Binding free energy (kcal/mol)	Ligand efficiency	Interacting amino acids		Residues providing hydrophobic interaction or van der Waals contact without Pi–Pi interaction
			HBD	Pi–Pi	
7b	−12.28	−0.40	Leu451, Tyr335, Tyr225	—	Leu450, Phe175, Phe117, Phe240, Phe339, Tyr119, Val390, Asn392, Val108, His227
7e	−11.88	−0.36	Leu451, Tyr354, Tyr107	A-Tyr107, B-Tyr354	Leu450, Phe117, Phe175, Phe176, Phe339, Tyr119, His227, Val390, Asn392, Val108, Tyr107
8t	−11.48	−0.32	Leu451	B-Tyr354, B-Tyr225	Asn392, Leu450, Phe117, Phe175, Phe176, Phe339, Phe240, Tyr119, Val390, Val108, His227
R64	−11.81	−0.35	Leu451, Tyr107, His227, Tyr119, Asn392	B-Tyr225, B-Phe240	Leu415, Leu450, Phe117, Phe175, Phe176, Phe339, Val390, Val108, His227, Tyr354

as Tyr225, His227 and Asn392. The compounds **7e** and **8t** formed Pi–Pi interaction with Tyr354 with benzene of ring B. The carbonyl of compounds **7b** and **e** formed hydrogen bond interaction with residues Tyr225 and Tyr354, while compound **8t** was non-interacting. Ring C of compounds **8t** formed Pi–Pi interaction with residues Phe225. Ring A of compounds was surrounded by residues, such as Phe176, Tyr119, Val108 and Tyr107. Among them, compound **7b** formed Pi–Pi interaction with residues Tyr107. The second amine group of all compounds produced hydrogen bond with the residue Leu451,

which is an important functional residue in the catalytic cycle of CaNMT.[13] As for oxygen of chain between ring A and B, compounds **7b** and **e** formed hydrogen bond interaction with residues Tyr335 and Tyr107, which agree with the binding free energy and antifungal activity.

The conformation of compounds **7b** and **8t** in the active site of CaNMT was similar to the original ligand **R64**, while compound **7e** is different. As compared with original ligand **R64**, compound **7b** has a C1-sulfur atom, which can form additional van der Waals interaction with CaNMT. The carbonyl group of ring B produced extra hydrogen bond interaction. As a result, although missing the nitrogen atom and two hydrogen bonds, compounds showed good binding free energy compared with **R64**.

It was worth mentioning that the docking data (Table 3) showed that the trend of the binding free energy was consistent with the antifungal activity of the compounds. It implied that the hydrogen and Pi–Pi bonding interactions between the ring 2 and CaNMT might be essential for locating the inhibitor to reasonable position and direction. It should be noted that the ligand efficiency of compounds **7b** and **7e** was better than original ligand **R64** and might be a high-performance structure of NMT inhibitor. Overall, the molecular docking study could give a qualitative interpretation of the observed SARs in antifungal activity assay.

Conclusion

Overall, a series of novel thiochroman-4-one derivatives were designed and synthesized by an optimum reaction route. The importance of benzoheterocyclic core on the antifungal activity was investigated by the isostreric design of the thiochroman-4-one. *In vitro* antifungal activity assay indicated that the activity of thiochroman-4-one derivatives were good against four fungi but slightly lower than the benzofuran derivatives. The antifungal activity of compounds 7**a**–**y** (n=1) was better than compounds **8a**–**t** (n=2). Compound **7b** showed the best antifungal activity against *C. alb* (MIC=0.5 μg/mL) and *C. neo* (MIC=1 μg/mL), which was better than amphotericin B (MIC=1 μg /mL). The binding mode of the compounds **7b**, **e** and **8t** was indicated the importance of binding between these compounds and the residues (such as Leu451, Tyr354 and Try225) of CaNMT, and the binding model was consistent with original ligand **R64**. It clearly demonstrated that introduction of appropriate substituents on the C3-phenyl group of (*E*)-3-benzylidene-6-(3-(phenethylamino)propoxy)-thiochroman-4 one (compound **7b**) would lead to the more potent derivatives. It implied that compound **7b** might be considered as new promising lead candidates for further design and synthesis of antifungal agents.

Experimental

General chemistry methods, synthesis procedures, spectral data, biological assays, molecular docking are given in Supplementary materials.

Acknowledgments National Natural Science Foundation of China (21675039), Project funded by China Postdoctoral Science Foundation (2016M591401), Young Talent of Hebei Province, Hebei University Science Fund for Distinguished Young Scholars (2015JQ06) and Natural Science Foundation of Hebei Province (B2015201016). We gratefully acknowledge Dr. Carl LeBlond (Chemistry Department, College of Natural Sciences and Mathematics of IUP) for his helping for grammar and spelling of the paper.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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