Synthesis and Antifungal Activities of Novel 2-Aminotetralin Derivatives

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Novel 2-aminotetralin derivatives were synthesized as antifungal agents. The 2-aminotetralin scaffold was chemically designed to mimic the tetrahydroisoquinoline ring of the lead molecule described before. Their antifungal activities were evaluated in vitro by measuring the minimal inhibitory concentrations (MICs). Compounds **10a**, **12a**, **12c**, **13b**, and **13d** are more potent than fluconazole against seven testing human fungal pathogens. Compound **10b** exhibits much higher antifungal activities against all of the four fluconazole-resistant clinic *Candida albicans* strains than the control drugs including amphotericin B, terbinafine, ketoconazole, and itraconazole. The mode of action of some compounds to the potential receptor lanosterol 14α-demethylase (CYP51) was investigated by molecular docking. The studies presented here provide a new structural type for the development of novel antifungal compounds. Furthermore, **10b** was evaluated in vivo by a rat vaginal candidiasis model, and it was found that **10b** significantly decreases the number of fungal colony counts.

Introduction

Over the past three decades the incidence of severe, invasive, and systemic fungal infections has increased dramatically. Among these, the widespread diffusion of topical and systematic infectious fungal diseases is often related to the use of broad-spectrum antibiotics, immunosuppressive agents, anticancer, and anti-AIDS drugs.[1−4] One of the principal problems in the treatment of fungal infections is the spread of antifungal drug resistance mainly in patients chronically subjected to antimycotic therapy such as HIV-infected people and other immunosuppressed patients.[3] Although the arsenal of antifungal drugs has expanded, currently available antifungal drugs do not meet the increasing requirements of managing infection in the complex patient populations.[5,6] The development of new antifungal drugs has been constantly required in the clinical therapy.

The antifungal agents currently marketed are mainly inhibitors of ergosterol biosynthesis[7] except amphotericin B, which antifungal activity originates from its damaging binding to ergosterol of fungal cell membranes[8] and Echinocandins,[9] such as caspofungin, micafungin, and anidulafungin, which inhibit the biosynthesis β-1,3-glucans,[10] an important structural component of the fungal cell wall. Three different types of inhibitors of ergosterol biosynthetic pathway have been proven to be clinically effective. These are azoles (*N*-substituted imidazoles or 1,2,4-triazoles), which inhibit lanosterol 14α-demethylase (CYP51);[11] allylamines such as terbinafine, which act as a squalene epoxidase inhibitor;[12] and morpholines such as amorolfine, Δ^{14}-reductase and Δ^{8-7}-isomerase inhibitors.[13] Among them, lanosterol 14α-demethylase has been proven to be a prime target for antifungal therapy. Fluconazole and itraconzole are the drugs of choice for the treatment of severe systemic mycoses. Ketoconazole is widely used in the therapy of superficial mycoses.[14] Extensive use and prolonged therapy with azole antifungals have led to resistance.[15] Hence, the second-generation azole compounds[16] such as voriconazole, posaconazole, ravuconazole (BMS-207147; E-1224), and albaconazole (UR-9825) have shown broad-spectrum antifungal activity comparable or superior to itraconazole.[17−19] (Chart 1). Voriconazole has established a role in the antifungal armamentarium. It has been the primary therapy for invasive aspergillosis. Based on clinical studies, posaconazole appears to be a useful alternative in the treatment of invasive aspergillosis, zygomycosis, candidiasis, and cryptococcal meningitis. It is already approved in the EU and FDA. Ravuconazole is undergoing re-evaluation and albaconazole is undergoing Phase II clinical trials.[20] Azoles exert antifungal activity through inhibiting the CYP51 by a mechanism in which the heterocyclic nitrogen atom (*N*-3 of imidazole and *N*-4 of 1,2,4-triazole) binds to the sixth coordination position of the heme iron atom of the prophyrin in the substrate-binding site of the enzyme.[21] The resulting ergosterol depletion and the accumulation of the precursor 14α-methylated sterols interfere with the function of ergosterol as a membrane component. They affect the structure and functions of the plasma membrane, resulting in an inhibition of the growth of fungi.

Differential inhibition of this cytochrome P-450 enzyme between pathogenic fungi and human is the basis for the clinically important activity of azole antifungal agents. The specificity of the inhibitors is determined by the differential complementary between the structure of the azole compound and the active site of the fungal and host enzymes. In fact, one of the reasons to continue the search for better antifungal agents is to increase their specificity toward fungal enzyme. Because CYP51 is a member of the cytochrome P450 superfamily, which exists not only in fungi but in mammals; azole antifungal agents are generally toxic and are hampered in the treatment of deep-seated mycosis and life-threatening systemic infections because of their ability to coordinate with the heme of a lot of host cytochrome P450 enzymes, particularly mammalian CYP3A4.[22,23] Cases of fatal hepatotoxicity have been reported.[24−35] Although the azole ring has been demonstrated to be one of the important pharmacophores for antifungal activity,[36,37] and it is also a key toxicophore for the hepatotoxicity of azole antifungal agents.

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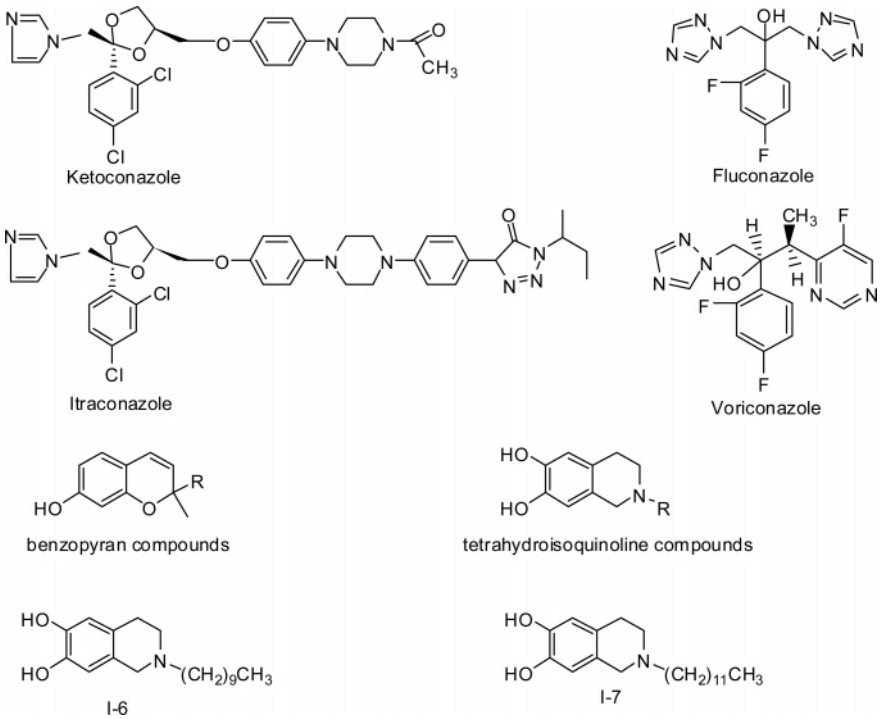
Chart 1



On the basis of the analysis for the toxicity and activity of azole antifungal agents, we believe that the search of novel nonazole antifungal compounds with structural specificity to the amino acids within the substrate-binding site of fungal CYP51 (by the removal of the coordination binding to the heme iron atom of CYP51) is meaningful in the separation of antifungal activity from their hepatotoxicity. In the previous study,[38] we reported the design of nonazole antifungal lead compounds based on the constructed three-dimensional model of *Candida albicans* CYP51 by coupling structure-based de novo design and found nonazole lead molecules with a benzopyran scaffold. The biological evaluation of these compounds illustrates that the benzopyran derivatives are the novel nonazole inhibitors specific for the CYP51 of fungi. The affinity of the lead molecules for CYP51 was mainly attributed to their nonbonding interaction with the residues of apoprotein without binding with the heme.[38]

Subsequently, another series of nonazole tetrahydroisoquinoline compounds were designed and synthesized, and **I-6** and **I-7** in Chart 1 are the most potent compounds discovered.[39] The antifungal activities of tetrahydroisoquinoline compounds were better compared to those of the benzopyran derivatives, which encouraged us to make further effort to explore more potent nonazole antifungal lead compounds. Herein, the tetrahydroisoquinoline scaffold described in previous study was replaced with a 2-aminotetralin nucleus, and novel derivatives were designed based on the constructed structure of the active site of CYP51 of *Candida albicans* in the previous study.[40,41] The antifungal activities were evaluated in vitro and their structure−activity relationship (SAR) was discussed.

Chemistry

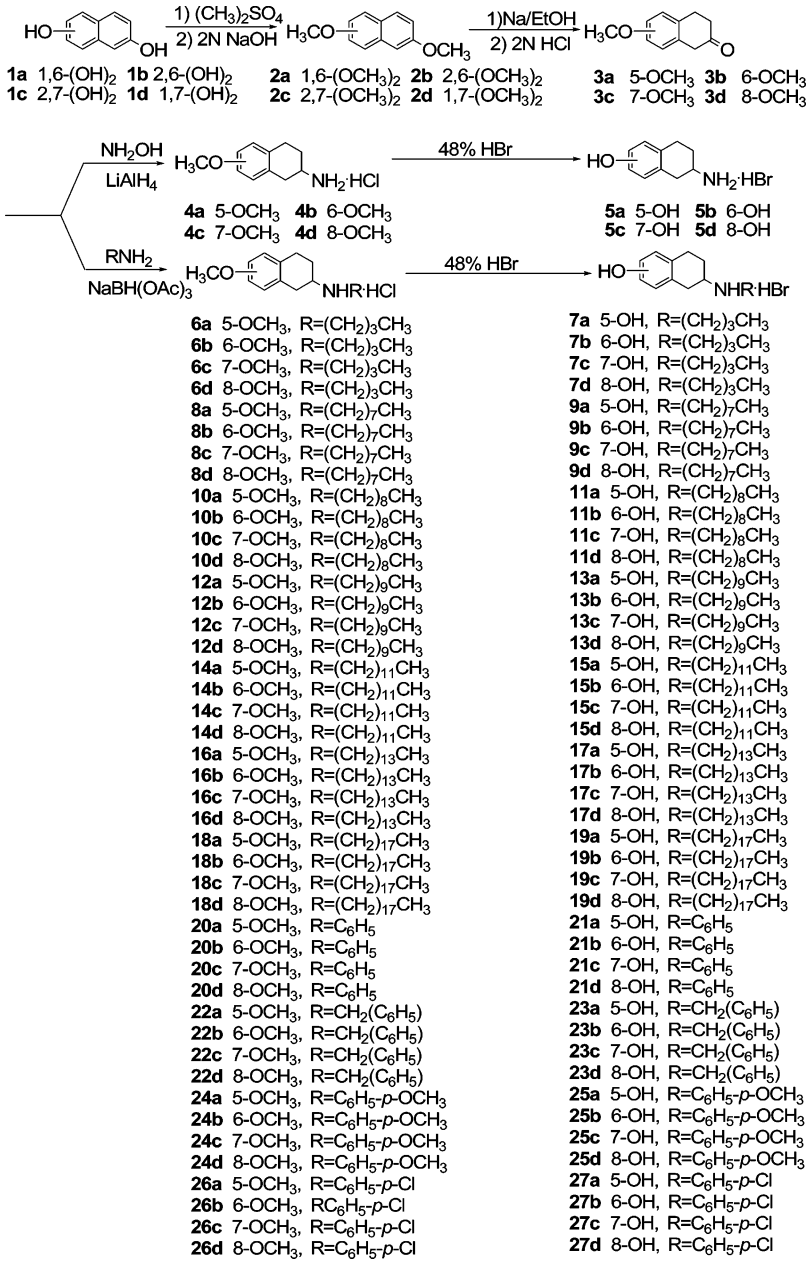
A series of novel 2-aminotetralin compounds were synthesized according to Scheme 1. The appropriate dihydroxy naphthalenes **1a**−**1d** were methylated with dimethyl sulfate to generate **2a**−**2d**, which were subsequently reduced according to the method of Cornforth et al. to afford the desired methoxy substituted-2-tetralones **3a**−**3d**.[42] The 2-amino methoxytetralins **4a**−**4d** were obtained followed by a condensation reaction of tetralones with hydroxylamine hydrochloride and a reduction with metal hydrides, such as $LiAlH_4$. *N*-Substituted 2-aminomethoxy tetralin compounds **6a**−**6d**, **8a**−**8d**, **10a**−**10d**, **12a**−**12d**, **14a**−**14d**, **16a**−**16d**, **18a**−**18d**, **20a**−**20d**, **22a**−**22d**, **24a**−**24d**, and **26a**−**26d** were prepared in high yields by a direct reductive amination reaction of appropriate intermediates **3a**−**3d** with primary amines in anhydrous solvent. Sodium triacetoxyborohydride was used as the reductive reagent. *N*-Substituted 2-amino hydroxyltetralin compounds **7a**−**7d**, **9a**−**9d**, **11a**−**11d**, **13a**−**13d**, **15a**−**15d**, **17a**−**17d**, **19a**−**19d**, **21a**−**21d**, **23a**−**23d**, **25a**−**25d**, and **27a**−**27d** were obtained by the demethylating of the appropriate *N*-substituted 2-amino-methoxytetralins **6a**−**6d**, **8a**−**8d**, **10a**−**10d**, **12a**−**12d**, **14a**−**14d**, **16a**−**16d**, **18a**−**18d**, **20a**−**20d**, **22a**−**22d**, **24a**−**24d**, and **26a**−**26d** with 48% hydrobromic acid under reflux.

Results and Discussion

In Vitro Antifungal Activities. The in vitro antifungal activities of all the title compounds were listed in Table 1, in which fluconazole and **I-6** were used as the controls. All of the title compounds exhibit potent antifungal activities against seven pathogenic fungi, which were found in dermatomycoses (*Trichophyton rubrum*, *Fonsecaea compacta*, and *Microsporum gypseum*) and systemic mycoses (*Candida albicans*, *Candida parapsilosis*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*). Compared to **I-6**, compounds **10a**−**11d**, in which the length of *N*-alkyl side chains at position 2 is as long as that of **I-6**, exhibit much more potent antifungal activities against seven pathogenic fungi.

In the previous study we presented that compound **I-6** exhibited comparable or superior antifungal activities in comparison with fluconazole except against *Candida albicans*.[39] However, **8b**, **8c**, **9b**−**13d**, **14b**−**15b**, **16c**, **16d**, and **17b**−**17d** in Table 1 exhibit higher antifungal activities than fluconazole against *Candida albicans*. Compounds **8a**, **8c**, **8d**, **9d**−**12a**, **12c**, **12d**, **13b**−**13d**, **14c**, **14d**, **15d**, and **17d** exhibit high antifungal activities against *Aspergillus fumigatus*. Especially, compounds

Scheme 1



8b, **9b**, **10a**, **10b**, **11b**, **12a**, **12c**, **13a**, **13b**, and **13d** show their MIC values lower than 0.125 μmol/L against *Candida albicans*. Compounds **10a** and **13d** showed a MIC value of 8 μmol/L against *Aspergillus fumigatus*. Compounds **10a**, **12a**, **12c**, **13b**, and **13d** exhibit more potent antifungal activities against all seven pathogenic fungi than fluconazole.

Structure−Activity Relationship Analysis. The antifungal activities of the compounds with *N*-substituted aromatic groups (**20a**−**21d** and **24a**−**27d**) are lower than those of the compounds that contain *N*-substituted alkyl side chains and the corresponding carbon atom number of the alkyl side chain is between 7 and 13. The antifungal activities of the *N*-unsubstituted compounds **4a**−**5d** are very low. Similarly, compounds **6a**−**7d**, in which the carbon atom numbers of the *N*-substituted alkyl side chain are less than four, exhibit low antifungal activities as well. Compared to **8a**−**15d**, the antifungal activities of compounds **16a**−**19d**, in which the carbon atom numbers of the *N*-substituted alkyl side chain are more than 12, are decreased linearly with the increase of the length of *N*-substituted alkyl side chain. Compounds **10a**−**13d**, in which the carbon atom numbers of *N*-substituted alkyl side chains are between 9 and 10, are of the highest antifungal activity compared to all of the other compounds. Compounds substituted with a hydroxyl or methoxy group at positions 5 and 6 of the tetralin ring, such as **8a**, **8b**, **9a**, **9b**, **10a**, and **10b**, exhibit higher antifungal activities than those of compounds with a hydroxyl or methoxy group at positions 7 and 8, such as **8c**, **8d**, **9c**, **9d**, **10c**, and **10d**. The primary SAR analysis above provides the structural basis for the modification of 2-aminotetralin antifungal derivatives in the future.

The compounds in which antifungal MIC values against the standard *Candida albicans* strain were lower than 0.125 μmol/L were further tested against four fluconazole-resistant clinic *Candida albicans* strains. The results are listed in Table 2. All tested compounds exhibit much more potent antifungal activities than that of fluconazole or itraconazole. Compounds **9b**, **11b**, **12a**, **12c**, and **13b** exhibit comparable or superior antifungal activities than that of terbinafine or ketoconazole. The antifungal activities of compounds **10b** against fluconazole-resistant strains are higher than those of the other testing compounds including

Table 1. In Vitro Antifungal Activities of 2-Aminotetralin Compounds[a]

cmpd	*C. alb.*	*C. par.*	*C. neo.*	*T. rub.*	*F. com.*	*A. fum.*	*M. gyp.*	cmpd	*C. alb.*	*C. par.*	*C. neo.*	*T. rub.*	*F. com.*	*A. fum.*	*M. gyp.*
4a	>64	>64	>64	8	64	>64	>64	**16b**	32	>64	64	16	>64	>64	>64
4b	>64	>64	>64	64	>64	>64	>64	**16c**	4	>64	16	0.0625	64	>64	4
4c	>64	>64	>64	64	>64	>64	>64	**16d**	4	16	32	0.5	32	>64	2
4d	>64	>64	>64	64	>64	>64	>64	**17a**	8	>64	8	0.5	>64	>64	4
5a	>64	>64	>64	>64	32	>64	>64	**17b**	2	32	4	0.5	>64	>64	2
5b	>64	>64	>64	>64	32	>64	>64	**17c**	4	4	8	0.5	8	>64	4
5c	>64	>64	>64	>64	32	>64	>64	**17d**	16	64	32	0.125	16	16	4
5d	>64	>64	>64	>64	32	>64	>64	**18a**	>64	>64	>64	32	64	>64	16
6a	>64	>64	>64	64	>64	>64	>64	**18b**	64	>64	>64	8	>64	>64	>64
6b	64	>64	64	64	>64	>64	>64	**18c**	>64	>64	>64	8	>64	>64	64
6c	64	64	>64	4	4	>64	64	**18d**	>64	>64	64	2	>64	>64	64
6d	>64	>64	>64	16	0.25	64	32	**19a**	64	>64	>64	16	>64	>64	>64
7a	>64	>64	>64	64	64	>64	>64	**19b**	32	>64	>64	8	>64	>64	64
7b	>64	>64	>64	64	>64	>64	>64	**19c**	16	>64	>64	2	64	>64	>64
7c	>64	>64	>64	>64	64	>64	64	**19d**	>64	>64	>64	2	64	>64	>64
7d	>64	>64	>64	>64	>64	>64	64	**20a**	>64	>64	>64	2	>64	>64	32
8a	8	16	16	8	4	16	>64	**20b**	>64	>64	>64	0.5	>64	>64	32
8b	0.0625	16	16	8	8	>64	8	**20c**	>64	>64	64	4	>64	>64	64
8c	1	32	16	4	4	64	8	**20d**	>64	>64	>64	4	>64	>64	32
8d	16	32	16	4	8	32	8	**21a**	>64	>64	>64	8	>64	>64	>64
9a	8	64	32	4	8	>64	8	**21b**	64	64	64	8	64	>64	32
9b	0.0625	16	8	4	2	>64	16	**21c**	32	>64	16	8	32	>64	16
9c	4	32	16	8	8	>64	4	**21d**	>64	>64	32	4	64	>64	32
9d	2	8	8	8	4	16	4	**22a**	32	>64	64	16	32	>64	64
10a	0.0625	0.5	2	2	0.5	8	4	**22b**	30	>64	>64	16	>64	>64	>64
10b	0.0625	0.5	4	1	2	64	4	**22c**	64	>64	>64	4	>64	>64	>64
10c	0.25	4	4	0.0625	2	16	4	**22d**	>64	>64	>64	32	>64	>64	4
10d	0.5	1	4	2	2	16	64	**23a**	64	>64	>64	0.125	>64	>64	8
11a	1	32	8	4	4	64	8	**23b**	64	>64	>64	8	>64	>64	>64
11b	0.0625	4	0.5	0.25	1	32	0.5	**23c**	64	>64	>64	16	>64	>64	>64
11c	1	16	8	4	8	64	8	**23d**	64	>64	>64	0.5	32	>64	32
11d	1	8	8	4	4	16	4	**24a**	>64	>64	>64	2	>64	>64	8
12a	0.031 25	8	1	1	1	16	2	**24b**	>64	>64	>64	8	>64	>64	8
12b	0.25	8	16	1	8	>64	4	**24c**	>64	>64	>64	0.5	>64	>64	16
12c	0.0625	0.25	1	1	1	16	2	**24d**	>64	>64	>64	32	>64	>64	16
12d	0.25	2	1	1	1	16	2	**25a**	>64	32	>64	0.25	>64	>64	16
13a	0.031 25	32	1	4	1	>64	1	**25b**	>64	64	64	0.5	>64	>64	16
13b	0.0625	2	1	0.0625	0.25	16	8	**25c**	>64	64	>64	0.5	>64	>64	32
13c	1	4	4	2	8	32	2	**25d**	>64	>64	>64	2	>64	>64	16
13d	0.0625	4	1	0.25	2	8	4	**26a**	>64	>64	>64	2	>64	>64	16
14a	8	16	8	0.5	8	>64	16	**26b**	>64	>64	>64	1	>64	>64	16
14b	4	32	4	4	64	>64	>64	**26c**	>64	>64	>64	16	>64	>64	16
14c	2	1	1	2	8	16	2	**26d**	>64	>64	>64	>64	>64	>64	32
14d	4	16	16	4	8	32	64	**27a**	2	8	8	2	16	64	0.5
15a	4	>64	>64	32	>64	>64	2	**27b**	8	32	16	0.25	32	64	4
15b	1	8	2	2	4	>64	8	**27c**	8	32	16	2	32	64	4
15c	16	>64	32	1	32	>64	4	**27d**	16	32	32	8	64	>64	8
15d	16	32	32	4	8	32	>64	**I-6**	>64	0.5	1	1	16	16	>64
16a	64	>64	32	8	64	>64	>64	**Flu**	8	0.5	2	1	16	>64	16

[a] MIC, μmol/L. Abbreviations: *C. alb.*, *Candida albicans*; *C. par.*, *Candida parapsilosis*; *C. neo.*, *Cryptococcus neoformans*; *T. rub.*, *Trichophyton rubrum*; *F. com.*, *Fonsecaea compacta*; *A. fum.*, *Aspergillus fumigatus*; *M. gyp.*, *Microsporum gypseum*; Flu, fluconazole.

Table 2. In Vitro Antifungal Activities of Some 2-Aminotetralin Compounds against Four Fluconazole-Resistant *Candida albicans* Strains[a]

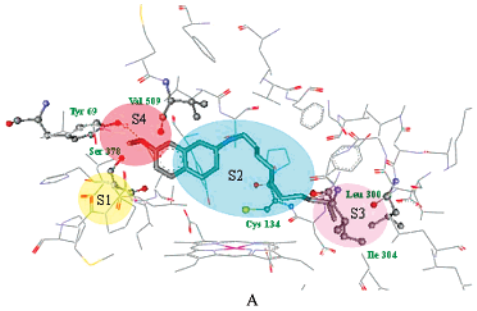
cmpd	0511655	01010	18	25
8b	8	16	8	8
9b	4	4	4	2
10a	16	16	16	8
10b	0.0625	0.125	0.0625	0.0625
11b	4	4	4	2
12a	8	8	4	4
12c	4	4	4	2
13a	32	16	32	32
13b	2	4	2	2
13d	16	16	16	16
fluconazole	>64	>64	>64	>64
terbinafine	8	32	8	4
amphotericin B	0.25	0.64	2	0.5
itraconazole	64	>64	>64	>64
ketoconazole	8	8	4	8

[a] MIC, μmol/L.

the control drug amphotericin B, which is often used in the clinic to treat fluconazole-resistant fungal infection. The results presented here suggest that 2-aminotetralin derivatives have no cross resistance with azoles antifungal agents.

Binding Mode of the 2-Aminotetralins. The binding mode of 2-aminoteralin derivatives to the active site of CYP51 is explained by the flexible docking using the Affinity module within the Insight II software package (Figure 1). The active site of CYP51 was constructed in the previous studies.[38,40] Because all the title compounds were the racemates, both the *R*- and *S*-isomers were docked into the active site and the interaction energies of the *R*- and *S*-isomers were calculated, respectively. The results show that the overall trend of the interaction energies of both the *S*- and *R*-isomers are in good qualitative agreement with the in vitro antifungal activities. Because the interaction energies of the *R*-isomer of each docked compounds were lower than that of the corresponding *S*-isomers, only the binding mode of the *R*-conformation was displayed in Figure 1.

In previous studies, we found that the regions in the active site of CYP51 for ligand noncovalent binding can be divided into four subsites S1−S4, besides the site coordinating to the



A

Compounds	6c	8c	10c	12c	14c	16c
Energy (kcal/mol)	-53.261	-61.129	-63.789	-66.296	-58.450	-57.646
MIC_{80} (μmol/L)	64	1	0.25	0.125	2	4

B

Figure 1. (A) Binding of compound **12c** to the active site of CYP51 from *C. albicans*. Yellow indicates the S1 subsite. Green indicates the S2 subsite. Pale purple indicates the S3 subsite. Pink indicates the S4 subsite. (B) A comparison of the calculated interaction energies of the *R*-isomers of **6c**, **8c**, **10c**, **12c**, **14c**, and **16c** with CYP51.

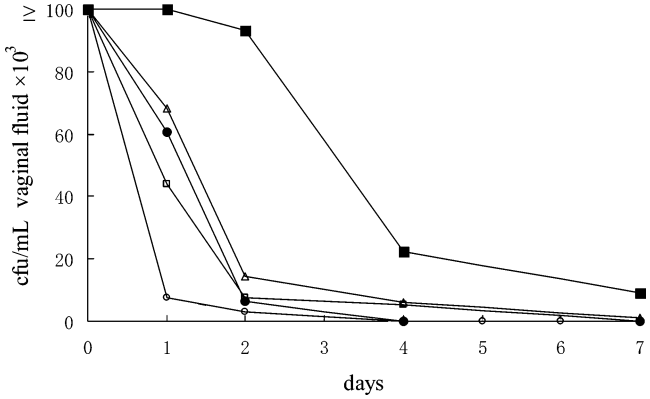


Figure 2. Outcome of vaginal infection by *C. albicans* in oophorectomized, oestradiol-treated rats inoculated intravaginally with compound **10b**: 1% mg/L (white triangles), 4% mg/L (white squares), 10% mg/L (white circles), itraconazole 4% mg/L (black circles), blank suppository (control; black squares) at 1, 2, 4, and 7 days after the drugs were administered. Each curve represents the mean of cfu of six rats.

heme.[38,40] The S1 subsite is a hydrophilic hydrogen-bonding region; the S2 subsite is a hydrophobic region; the S3 subsite is a narrow hydrophobic cleft formed by the residues in the helix B′-Meander1 loop and the N terminus of helix I; and the S4 subsite adjacent to the β6-1/β1-4 sheet is another hydrogen-bonding region in the active site.

The binding mode of the 2-aminotetralin derivatives to CYP51 suggests that the tetralin ring interacts with the hydrophibic S2 subsite. The methoxy group in the benzene ring forms H-bonding interactions with the residues Tyr69 and Ser378 in the S4 subsite. The long lipophilic alkyl side chain interacts with the hydrophobic S3 subsite. No interaction was found between the compound and the heme. It suggests that the affinity of 2-aminotetralin derivatives to the potential receptor CYP51 might be mainly attributed to their nonbonding interaction with the apoprotein part of the active site.

The binding mode of the 2-aminotetralin derivatives with the active site of CYP51 provides reasonable explanation for their antifungal activities. The antifungal activities of compounds **4a**−**7d** and **20a**−**27d** are very low. That is because either none of the alkyl side chains was presented in **4a**−**5d** or *N*-substituted alkyl (**6a**−**7d**) or the aromatic (**20a**−**27d**) side chains are too short to interact firmly with the hydrophobic S3 region. The low antifungal activities of compounds **14a**−**19d** are due to their very long *N*-substituted alkyl side chains that are out of the accommodation by the hydrophobic S3 subsite. Compounds **10a**−**13d**, which *N*-substituted alkyl side chains have 9 to 10 carbon atoms, exhibit the highest antifungal activities, and the antifungal activities of **10a**, **12c**, **13b**, and **13d** are particularly interesting. This result suggests that the appropriate length of the substituents on the amino group of 2-aminotetralin derivatives is important for antifungal activities, and the alkyl side chains with 9 to 10 carbon atoms are optimal for the binding of these types of inhibitors to the receptor.

The S4 subsite is a hydrogen bond donor and acceptor region, which interacts with the functional groups on the phenyl group of the tetralin ring. To study the effect of substitution at different positions of the phenyl ring on their antifungal activities, the analogues with hydroxyl or methoxy group at different positions of the phenyl ring were designed and synthesized. The binding mode of the docked molecules to CYP51 and their corresponding antifungal activities suggest that compounds with hydrogen bonding donor or acceptor substituents at positions 5 and 6, such as **8a**, **8b**, **9a**, **9b**, **10a**, and **10b**, exhibit higher antifungal activities than those compounds with substituents at positions 7 and 8 of the tetralin ring (**8c**, **8d**, **9c**, **9d**, **10c**, and **10d**).

Experimental Vaginal Infection. After establishing activity in vitro, we examined the activity of compound **10b** in vivo. As shown in Figure 2, compound **10b** exerted a marked acceleration of clearance of the yeast, as demonstrated by a statistically significant decrease in colony forming units (cfu) counts throughout the study, compared with the blank control. The parallel curves of clearance with different compound **10b** concentrations suggest a substantial compound **10b** dose dependence of fungus clearance, although the difference was not statistically significant. As with all dose regimens, the infection was cleared in 1 week, whereas the blank control rats remained infected. Itraconazole treatment, as a positive control, shows a pattern of clearance comparable to that induced by **10b**.

Conclusion

In the present study, a novel series of 2-aminotetralin compounds were designed, synthesized and their antifungal activities were evaluated in vitro. The results show that the 2-aminotetralin derivatives exhibit potent antifungal activities, in which the antifungal activities of compounds **10a**, **12a**, **12c**, **13b**, and **13d** against seven pathogenic fungi are higher than those of fluconazole, especially against *Candida albicans* (MIC < 0.125 μmol/L) and *Aspergillus fumigatus* (MIC ≤ 16 μmol/L). Compound **10b** exhibits better antifungal activities against four fluconazole-resistant clinic strains (MIC < 0.125 μmol/L) than amphotericin B, which is often used in the clinic to treat fluconazole-resistant fungal infection. A molecular docking study showed that the affinity of 2-aminotetralin derivatives for CYP51 was mainly attributed to their nonbonding interaction with the apoprotein. The primary SAR analysis provides the reliable clues about how to optimize the structures of 2-aminotetralin compounds. The research presented here affords a new structural type as an antifungal agent, which has some distinguished advantages, such as high antifungal activity, broad antifungal spectra, and potentially low toxicity. Compound **10b** was evaluated in vivo by a rat vaginal candidiasis model, and it was found to have a marked acceleration of clearance of the yeast, as demonstrated by a statistically significant decrease in colony forming unit (cfu) counts. The infection was cleared in one week with all dose regimens.

Experimental Section

Chemistry. General Methods. Melting points were determined on an electrically heated RK-Z melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Brucker Vector II spectrometer. Mass spectra (MS) were measured on a Micromass Qtof-Micro LC-MS instrument. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC-300P spectrometer with Me_4-Si as the internal standard. ^{1}H NMR spectra of some compounds were recorded at 500 MHz on a Bruker AC-500P spectrometer with Me_4Si as the internal standard. Chemical shifts are given in ppm (δ), and the spectral data are consistent with the assigned structures. Elemental analyses were performed with a MOD-1106 instrument and were consistent with theoretical values within 0.4%. Silica gel thin-layer chromatography was performed on precoated plates GF_{254} (Qindao Haiyang Chemical, China). Silica gel column chromatography was performed with Silica gel 60 G (Qindao Haiyang Chemical, China). All compounds were routinely checked by TLC by using silica gel plates GF_{254} (Qindao Haiyang Chemical, China). Commercial solvents and reagents were of reagent grade and, when necessary, were purified and dried by standard protocols. All starting materials were commercially available unless otherwise indicated. Yields of purified products were not optimized. A concentration of solutions after reactions and extractions was executed on a rotary vaporator (Büchi) operating under reduced pressure. Brine is a saturated solution of sodium chloride in water. Organic solutions were dried over anhydrous sodium sulfate.

General Method for the Synthesis of the Methoxy-2-tetralones 3a−3d. The method to synthesize 5-methoxy-2-tetralone (**3a**) is described. 1,6-dimethoxynaphthalene[42] **2a** (30.0 g, 0.16 mol) was added to the refluxing anhydrous EtOH (300 mL) under mechanical stirring. Sodium (28 g, 1.22 mol), cut in small pieces, was added as rapidly as possible to the solution. Refluxing was continued until all sodium disappeared. The reaction mixture was cooled to 10 °C and then 2 N HCl was added dropwise until the pH value was changed to 3. The reaction mixture continued to reflux for 30 min. After cooling, the reaction mixture was extracted with Et_2O (100 mL × 3), the H_2O/EtOH layer was concentrated under reduced pressure, and then the H_2O layer was extracted with Et_2O (100 mL × 3). The Et_2O layers were combined and washed with brine (50 mL × 3), dried over anhydrous Na_2SO_4, and filtrated, and the solvent was evaporated. The residual oil was purified by distillation under reduced pressure to yield 18.3 g (65%) of **3a** as a yellow oil, which solidified under room temperature: bp 160−165 °C (10 mmHg). Recrystallization from petroleum ether (bp 60−90 °C) gave **3a** as a light yellow solid: mp 35−37 [lit.[43,44] bp 118−124 °C (1.1 mmHg); mp 36−37 °C]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.50−7.52 (m, 3H, ArH), 3.82 (s, 3H, OCH_3), 3.42 (s, 2H, CH_2), 3.06 (t, 2H, CH_2), 2.48 (t, 2H, CH_2).

Similarly, **3b−3d** were synthesized from the appropriate dimethoxy-naphthalenes **2b−2d**. Compound **3b**: mp 34−35 °C (lit.[42] mp 36 °C). Compound **3c**: mp 26−27 °C [lit.[43,45] bp 130−136 °C (2.3 mmHg); mp 27−28 °C]. Compound **3d**: mp 56−57 °C [lit.[43,46] mp 58−59 °C; bp 120−123 °C (1.0 mmHg)].

General Method for the Synthesis of the 2-Amino-methoxy-1,2,3,4-tetrahydro-naphthalene 4a−4d. The method to synthesize 2-amino-5-methoxy-1,2,3,4-tetrahydronaphthalene hydrochloride (**4a**) is described. Compound **3a** (5.6 g, 0.032 mol) was added to a solution of hydroxylamine hydrochloride (4.4 g, 0.063 mol) and sodium acetate (8.5 g, 0.104 mol) in 60 mL of EtOH. The mixture was refluxed for 2 h and then diluted with water and extracted with Et_2O. The ether extract was washed with water and dried over anhydrous Na_2SO_4. After removal of solvent, a brown solid was obtained. The crude oxime was dissolved in anhydrous tetrahydrofurane and then $LiAlH_4$ (6 g, 0.158 mol) was added. The mixture was refluxed for 8 h and cooled to 0 °C. Ice water was added carefully to the mixture until no bubbles occurred. The mixture was filtered and evaporated. The residue was dissolved in anhydrous Et_2O and filtered. The filtrate was chilled in an ice water bath, and anhydrous HCl was passed through the solution. The precipitated salt was collected and recrystallized from MeOH/Et_2O to give 3.4 g (50.1%) of **4a** as a white needle: mp 265−267 °C (lit.[43,47] mp 266−267 °C). IR (KBr,ν/cm^{-1}): 3445, 2920, 1585, 1470, 1259, 1078, 766, 685. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.12 (t, J = 8 Hz, 1H), 6.74 (dd, J = 8, 8 Hz, 2H), 3.80 (s, 3H), 3.48 (m, 1H), 3.13 (m, 1H), 3.01∼2.90 (m, 1H), 2.80 (m, 1H), 2.65 (m, 1H), 2.30 (m, 1H), 1.88∼1.72 (m, 1H). MS (ESI) *m*/*z*: 178.12 (M + 1). Anal. ($C_{11}H_{16}ClNO$) C, H, N.

Similarly, **4b−4d** were obtained from the appropriate methoxy-2-tetralones **3b−3d**. Compound **4b** was obtained as a white powder: mp 245−246 °C (lit.[43] mp 243−246 °C). IR (KBr, ν/cm^{-1}): 3440, 3023, 2927, 2610, 1505, 1246, 1161, 1045, 824. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.05 (d, J = 8.4 Hz, 1H), 6.71 (dd, J = 2.7, 8.4 Hz, 1H), 6.66 (d, J = 2.7 Hz, 1H), 3.78 (s, 3H), 3.42 (m, 1H), 3.18∼3.08 (m, 1H), 3.01∼2.90 (m, 1H), 2.88∼2.76 (m, 1H), 2.72∼2.60 (m, 1H), 2.30∼2.16 (m, 1H), 1.88∼1.72 (m, 1H). MS (ESI) *m*/*z*: 178.09 (M + 1). Anal. ($C_{11}H_{16}ClNO$) C, H, N.

Compound **4c** was obtained as a white powder: mp 251−253 °C (lit.[43] mp 213−214 °C). IR (KBr, ν/cm^{-1}): 3436, 2924, 1615, 1493, 1453, 1265, 698. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.16 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.81 (s, 1H), 3.80 (s, 3H), 3.52 (m, 1H), 3.15 (m, 1H), 2.97 (m, 1H), 2.78 (m, 1H), 2.62 (m, 1H), 2.32 (m, 1H), 1.81 (m, 1H). MS (ESI) *m*/*z*: 178.10 (M + 1). Anal. ($C_{11}H_{16}ClNO$) C, H, N.

Compound **4d** was obtained as a white needle: mp 275−277 °C (lit.[43] mp 273−275 °C). IR (KBr, ν/cm^{-1}): 3418, 2918, 1586, 1098, 764, 696. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.15 (dd, J = 8.1, 7.5 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 7.5 Hz, 1H), 3.78 (s, 3H), 3.39 (m, 1H), 3.16 (m, 1H), 3.01∼2.76 (m, 2H), 2.40 (m, 2H), 1.81 (m, 1H). MS (ESI) *m*/*z*: 178.06 (M + 1). Anal. ($C_{11}H_{16}ClNO$) C, H, N.

General Method for the Synthesis of the 2-Amino-hydroxy-1,2,3,4-tetrahydronaphthalene. The method adopted for the synthesis of 2-amino-5-hydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide (**5a**) is described. A mixture of **4a** (1 g, 0.005mol) and 48% HBr (10 mL) was heated at 120−130 °C for 3 h. After removal of solvent, the solid residue was recrystallized from methanol/ether, giving **5a** as a white solid (1 g, 87.7%): mp 250−252 °C (lit.[47] mp 252−253 °C). IR (KBr, ν/cm^{-1}): 3330, 3025, 2926, 1588, 1495, 1464, 1267, 770, 698. ^{1}H NMR (CD_3OD, 500 MHz): δ 6.97 (t, J = 7.8, 7.8 Hz, 1H), 6.61∼6.63 (m, 2H), 3.35∼3.41 (m, 1H), 3.01 (m, 1H), 2.78 (m, 2H), 2.50 (m, 1H), 2.12 (m, 1H), 1.72 (m, 1H). MS (ESI) *m*/*z*: 164.18 (M + 1). Anal. ($C_{10}H_{14}BrNO$) C, H, N.

Similarly, **5b−5d** were obtained from the appropriate **4b−4d**. Compound **5b** was a gray solid: mp > 280 °C. IR (KBr, ν/cm^{-1}): 3324, 3027, 2926, 1613, 1501, 1449, 1285, 1215 1154, 972, 826, 698. ^{1}H NMR (CD_3OD, 300 MHz): δ 6.90 (d, J = 8.0 Hz, 1H), 6.56 (dd, J = 2.7, 8.0 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 3.41 (m, 1H), 2.98 (m, 1H), 2.74 (m, 3H), 2.10 (m, 1H), 1.71 (m, 1H). MS (ESI) *m*/*z*: 164.24 (M + 1). Anal. ($C_{10}H_{14}BrNO$) C, H, N.

Compound **5c** was a gray solid: mp 180−182 °C. IR (KBr, ν/cm^{-1}): 3353, 3027, 2923, 1620, 1592, 1503, 1273, 696. ^{1}H NMR (CD_3OD, 300 MHz): δ 6.89 (d, J = 8.4 Hz, 1H), 6.56 (dd, J = 2.4, 8.4 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 3.40 (m, 1H), 3.06 (m, 1H), 2.74 (m, 2H), 2.42 (m, 2H), 1.72 (m, 1H). MS (ESI) *m*/*z*: 164.26 (M + 1). Anal. ($C_{10}H_{14}BrNO$) C, H, N.

Compound **5d** was a yellow crystal: mp 241−242 °C. IR (KBr, ν/cm^{-1}): 3332, 3013, 2928, 1588, 1493, 1468, 1316, 1275, 766, 698. ^{1}H NMR (CD_3OD, 300 MHz): δ 6.93 (t, J = 7.8, 7.8 Hz, 1H), 6.61 (d, J = 7.5 Hz, 1H), 6.59 (d, J = 7.2 Hz, 1H), 3.39 (m, 1H), 3.06 (m, 1H), 2.74 (m, 2H), 2.40 (m, 2H), 1.71 (m, 1H). MS (ESI) *m*/*z*: 164.21 (M + 1). Anal. ($C_{10}H_{14}BrNO$) C, H, N.

***N*-Butyl-1,2,3,4-tetrahydro-5-methoxynaphthalen-2-amine Hydrochloride (6a).** To a solution of 5-methoxy-2-tetralone (**3a**; 3.0 g, 0.017 mmol) in dichloroethane (60 mL) was added *n*-butylamine (2 mL, 0.020 mol) followed by sodium triacetoxyborohydride (10.5 g, 0.05 mol) under an inert atmosphere. The reaction was allowed to stir at room temperature for 24 h. The mixture was concentrated and 2 N NaOH was added dropwise until pH = 8 was obtained. The solution was extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with water and dried over

anhydrous Na_2SO_4. After removal of solvent, the residue was taken up in ether (125 mL) and treated with 1 N HCl in ether. The salt was filtered and dried to afford **6a** as a gray solid (5.0 g, 90.1%). Mp 193−194 °C. IR (KBr, ν/cm^{-1}): 3445, 2924, 2450, 1600, 1560 1270, 637. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.14 (dd, J = 7.8, 7.8 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 7.5 Hz, 1H), 3.76 (s, 3H), 3.58 (m, 1H), 3.15∼3.25 (m, 3H), 2.85∼2.94 (m, 3H), 2.27 (m, 1H), 1.84 (m, 1H), 1.69 (m, 2H), 1.40 (m, 2H), 0.95 (t, J = 7.2, 7.5 Hz, 3H). MS (ESI) m/z: 234.21 (M + 1). Anal. ($C_{15}H_{24}$-ClNO) C, H, N.

The synthetic methods for the following compounds **6c**−**6d**, **8a**−**8d**, **10a**−**10d**, **12a**−**12d**, **14a**−**14d**, **16a**−**16d**, **18a**−**18d**, **20a**−**20d**, **22a**−**22d**, **24a**−**24d**, and **26a**−**26d** were similar to the synthesis of compound **6a**.

***N*-Butyl-5-hydroxy-1,2,3,4-tetrahydronaphthalen-2-amine Hydrobromide (7a).** A mixture of **6a** (1.0 g, 0.0037 mol) and 48% HBr (10 mL) was heated at 120−130 °C for 3 h. After removal of solvent, the solid residue was recrystallized from ethanol−ether, giving **7a** as a gray solid (1 g, 90.1%). Mp 130−133 °C. IR (KBr, ν/cm^{-1}): 3300, 2654, 2450, 1600, 1560, 1270, 637. ^{1}H NMR (CD_3-OD, 500 MHz): δ 6.98 (t, J = 7.8, 7.8 Hz, 1H), 6.61∼6.64 (m, 2H), 3.36∼3.40 (m, 1H), 2.95∼3.12 (m, 3H), 2.65∼2.78 (m, 3H), 2.19∼2.25 (m, 1H), 1.58∼1.72 (m, 3H), 1.32∼1.39 (m, 2H), 0.91 (t, J = 7.2, 7.5 Hz, 3H). MS (ESI) m/z: 220.29 (M + 1). Anal. ($C_{14}H_{22}BrNO$) C, H, N.

The synthetic methods for the following compounds **7c**−**7d**, **9a**−**9d**, **11a**−**11d**, **13a**−**13d**, **15a**−**15d**, **17a**−**17d**, **19a**−**19d**, **21a**−**21d**, **23a**−**23d**, **25a**−**25d**, and **27a**−**27d** were similar to that for compound **7a**.

Molecular Docking Simulation. The 3D model of CYP51 from *C. albicans* was constructed in the previous studies.[40,41] All calculations were performed on an Origin 300 server using Insight II 2000 software package.[48] All the ligands were constructed and minimized in the Discover 95.0 module of InsightII 2000. The CVFF force field and a convergence criterion 0.1 kcal/mol·Å was used. The Affinity module was then applied to define the lowest energy position for the generated molecules by using a Monte Carlo and simulated annealing combined protocol. All of the atoms within a defined radius (5 Å) of the lead molecule were allowed to move. The solvation grid was used.[49] The resulting structure was accepted if it passed the Metropolis criterion, and then a check of the rms distance of the new conformation versus the conformations found so far. The final conformations were obtained through a simulation annealing procedure from 500 to 300 K, and then 2000 runs of energy minimization were performed to reach a convergence, where the resulting interaction energy values were used to define a rank order. Each energy-minimized final docking position of the lead molecules was evaluated by using the scoring function in the LUDI module.[50,51]

In Vitro Antifungal Activity Studies. In vitro antifungal activity was evaluated by means of the determination of the minimal inhibitory concentrations (MICs) using the serial dilution method in 96-well microtest plates. The MIC determination was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) method with RPMI 1640 (Sigma) buffered with 0.165 M MOPS (Sigma) as the test medium. Test fungal strains were obtained from the ATCC or clinical isolates. The MIC value was defined as the lowest concentration of test compounds that resulted in a culture with turbidity less than or equal to 80% inhibition when compared with the growth of the control. The testing compounds were dissolved in DMSO serially diluted in growth medium. The yeasts were incubated at 35 °C and the dermatophytes at 28 °C. Growth MIC was determined at 24 h for *Candida* aspecies, at 72 h for *Cryptococus neoformans*, and at 7 d for filamentous fungi. Fluconazol (Pfizer) and **I-6** were taken as the control drugs.

Experimental Vaginal Infection. Experimental vaginal infection in rats was induced basically as reported by Chami et al. with some modifications.[52] Oophorectomized female SD rats weighing 180 to 200 g were injected subcutaneously with oestradiol benzoate, 1 mg for 7 days, and were immunosuppressed by administering dexamethasone in drinking water at a dose of 1 mg per liter throughout the study. Seven days after the first oestradiol dose, all animals were inoculated intravaginally with 107 yeast cells of *Candida albicans* 0511655 in 0.05 mL of saline. The number of cells in the vaginal fluid was counted with 0.05 mL saline by washing the fluid three times up and down in the vagina. A total of 1 μL of the fluid was then plated onto sabouraud dextrose agar containing chloramphenicol (100 mg/L) and incubated for 48 h at 37 °C, and colony forming units (cfu) values were recorded. Compound **10b** was administered intravaginally with 50 μL suppository based with PEG 1500 and PEG 4000 (1:2 [v/v]) at 1% mg/L, 4% mg/L, and 10% mg/L, at 24 h after intravaginal *Candida albicans* challenge and continued 7 days). Rats receiving itraconazole suppository at 4% or blank suppository served as positive or negative controls, respectively. The infection was monitored just before administering suppository as 0 day and 1, 2, 4, and 7 days after the first suppository administered.

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Supporting Information Available: IR, ^{1}H NMR, MS, melting point data, and elemental analysis data for the compounds in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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