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Novel hybrids of fluconazole and furanones: Design, synthesis and antifungal activity

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ABSTRACT

During our efforts to develop new antifungal agents, a number of hybrid molecules containing furanones and fluconazole pharmacophores were designed and synthesized. The new chemical entities thus synthesized were tested for their potential as antifungal agents against various fungal strains and it was observed that the compounds with general structure **7** were potent inhibitors of *Candida albicans* ATCC 24433, *Candida glabrata* ATCC 90030, *Candida tropicalis* ATCC 750 and *Candida neoformans* ATCC 34664 while the fluconazole analogues **12** exhibited antifungal activity against *Candida albicans* ATCC 24433 and *Candida glabrata* ATCC 90030. The structure–activity relationship for these compounds is discussed. The synthetic strategies used in the present work have potential to prepare a large number of compounds for further refinement of structures to obtain molecules suitable for development as antifungal drugs.

In recent years there is an increase in the number of immunocompromised patients, such as those infected with HIV and undergoing organ transplantations or cancer chemotherapy and they have to undergo long term antifungal therapy to fight against opportunistic fungi. Though there are effective antifungal agents available in the market, they have quite a few shortcomings such as toxicity, limited range of activity for the fungal strains, high price and limited penetration through central nervous system. Also, the extensive use of antifungal agents like fluconazole (**1**)[1,2] (Fig. 1) has increased the number of resistant fungi due to mutations. This has made it necessary to design and synthesize new drugs that can be used in place of current antifungal drugs like amphotericin B or azole antifungals, for example, fluconazole (**1**), against the mutated resistant fungal strains and as a result of world-wide efforts, a number of fluconazole analogues have been reported.[3]

Furanones are known to exhibit antifungal activity and there are a number of papers describing synthesis, structure–activity relationship study and modifications of various antifungal furanones **2** and **3** based on structural features of incrustoporin (**4**).[4] A recent publication by Pour and co-workers[5] describing antifungal activity of 5-methylene-3-aryl-2,5-dihydrofuran-2-ones **3** prompted us to report our work in this field.

As a part of our efforts[3i,6a–f] to develop new antifungal drugs, we are in a process of exploring potential of various classes of compounds. During the course of our work, we synthesized a number of furanones **2b** for structure–activity relationship study from substituted phenylacetic acids via the intermediates **2c** by a novel synthetic strategy[6a,f] and observed that these compounds exhibited good antifungal activity against *Candida*, *Aspergillus* or *Fusarium* strains. It was also observed (Unpublished results) that some of the compounds from this group exhibited antifungal activity against various strains of dermatophytes like *Microsporum, Trichophyton, Epidermophyton* etc. During the esterification of **2c**, many times we used to get the corresponding 5-methylene-3-aryl-2,5-dihydrofuran-2-ones **3** in considerable amounts. The 5-methylene-furanones **3** used to polymerize/decompose in a few days and hence were not suitable for further development as antifungal drugs. Therefore, we felt it necessary to modify these molecules in order to get stable molecules and evaluate their potential as antifungal agents.

Also, it is known in literature that structural features of molecules from two different classes having a particular biological activity can be combined to generate novel molecules with increase in that particular biological activity in some cases.[7] The research in this direction in the area of antifungal activity has resulted in some promising candidates suitable for further development for example, Jiang and co-workers[8] reported that ZJ-522 (**5**), a hybrid of fluconazole (**1**) and butenafine (**6**), was about 50-fold more potent than fluconazole against yeasts and 2- to 16-fold more potent than fluconazole against filamentous fungi (Fig. 2).

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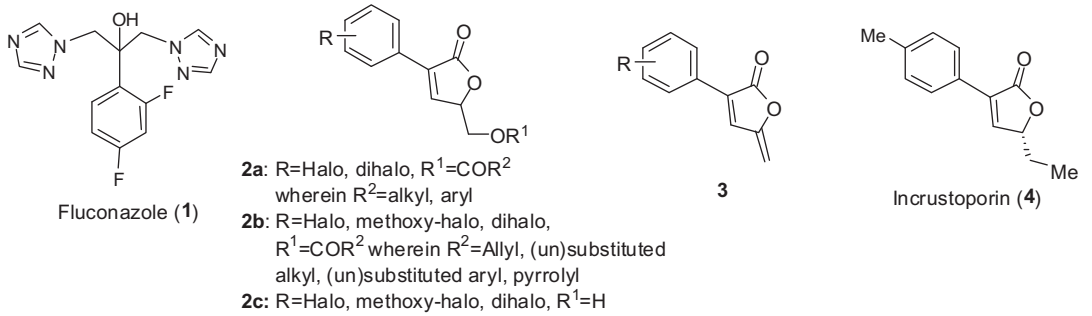


Figure 1. Structures of fluconazole, incrustoporin and incrustoporin analogues **2** and **3**.

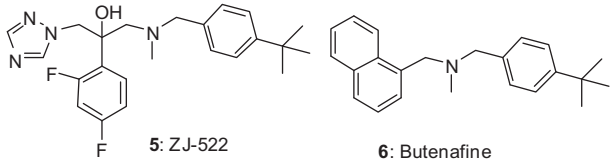


Figure 2. Structures of ZJ-522 and butenafine.

New drug development is a lengthy process and a slight change in structure of a particular molecule results in dramatic increase/decrease in biological activity in many cases making it necessary to screen various molecules with similar structural features and study the structure–activity relationship. The hybrid molecules described in the present work are novel compounds prepared in an effort to come out with new antifungal drugs effective against various fungal strains. The concept involves the incorporation of various pharmacophores in a single molecule with the intention of developing new compounds with dual drug action that is, single drug capable of interacting simultaneously with multiple targets.

In order to study the antifungal activity of hybrid molecules containing furanones and fluconazole pharmacophores, new molecules with general structures **7, 8**, and **9** (Fig. 3) were designed. It was found that some of the synthesized molecules exhibited significant antifungal activity against various fungal strains and the results are presented herein.

The synthetic sequence used for preparation of hybrid molecules **7** containing fluconazole pharmacophores and furanones is shown in Scheme 1. Thus, the known epoxide **10**[9] was reacted with hydroxybenzaldehydes **11a–b** to afford the fluconazole analogues **12a–b** which upon reaction[10a] with hippuric acid in presence of acetic anhydride and sodium acetate provided the azlactones **13a–b**. The substituted phenylacetic acids **14a–b** were obtained by subjecting the azlactones **13a–b** to heating with sodium hydroxide followed by reaction with hydrogen peroxide in presence of sodium hydroxide at room temperature.[10a] The reaction[11] of phenylacetic acids **14a–b** with suitable chloroketones in presence of potassium carbonate afforded the desired hybrid molecules **7**. The structures of these molecules were confirmed by spectral methods.

The significant antifungal activity[5] exhibited by compounds with general structure **3** with exocyclic double bond prompted us to synthesize the hybrid molecules **8** containing furanones with exocyclic double bonds employing the synthetic strategy[12] shown in Scheme 2. The interesting observation was that this class of compounds did not undergo elimination of tertiary hydroxyl group present at the benzylic carbon.

The compound **8a** decomposed in a few days at rt. The other compounds from this class (**8b** and **8c**) were also found to decompose slowly at rt.

The synthetic strategy employed for the preparation of the fluconazole analogues **9a–c** containing trisubstituted furanones is shown in Scheme 3.

The reaction[13] of aldehyde **12** with furanones **18a–c**[12] in methanol in presence of piperidine afforded the desired fluconazole analogues **9a–c** respectively.

It is known in literature[10b] that compounds having azlactone moiety exhibit antifungal activity. The azlactones **13a–d** were prepared and screened for antifungal activity as analogues of hybrid molecules **7**, by synthetic sequence elucidated for **13a** in Scheme 1, by employing required substituted benzaldehyde that is, 4-hydroxybenzaldehyde, 4-hydroxy-3-methoxybenzaldehyde, 3,5-dimethoxy-4-hydroxybenzaldehyde and 3-hydroxy-4-methoxybenzaldehyde respectively (Fig. 4).

For further structure–activity relationship study, hybrid molecules **19** containing 2-thioxothiazolidin-4-one moiety were prepared[14a] as there are reports[14b,c] that the molecules containing this structural feature exhibit antifungal activity. The reactions used for preparation of these molecules, starting from the aldehydes **12** and rhodanine **20**, are shown in Scheme 4.

The hybrid molecules synthesized were screened[15] for antifungal activity (Table 1) against *Candida albicans* ATCC 24433, *Candida glabrata* ATCC 90030, *Candida krusei* ATCC 6258, *Candida tropicalis* ATCC 750, *Candida neoformans ATCC 34664*, *Aspergillus fumigatus ATCC 46645*, *Aspergillus niger* ATCC 16404 and *Fusarium proliferatum* ATCC 10052. The compounds screened were racemic and the chemical purity of the compounds prepared was checked by HPLC and only the compounds with purity in the range of 95–100% were screened for antifungal activity. It was found that the compounds with general structure **7** exhibited very good antifungal activity against *C. albicans* ATCC 24433 and *C. glabrata* ATCC 90030 and many compounds from this class had MIC_{50} values comparable to fluconazole (Table 1, entries 3–12) indicating that the replacement of one of the triazoles in fluconazole with the groups present in the molecules **7** is tolerated. The compounds from this class exhibited significant antifungal activity against *C. tropicalis* ATCC 750 and *C. neoformans* ATCC 34664 also.

The fluconazole analogues with general structure **12a–d** exhibited antifungal activity against *C. albicans* ATCC 24433 and *C. glabrata* ATCC 90030 (Table 1, entries 13–16) while the corresponding azlactones **13a–d** showed no antifungal activity[12] showing that conversion of aldehyde moiety into the azlactone is not tolerated. The fluconazole analogues **19a–b** exhibited good antifungal activity against *C. albicans* ATCC 24433 (Table 1, entries 18 and 19) while the compounds **19c–d** did not show any antifungal activity[12] against the fungal strains studied in the present work. The furanones **16a** and **17a** exhibited good antifungal activity against *C. albicans* ATCC 24433 and *C. glabrata* ATCC 90030 but they did not exhibit any antifungal activity against rest of the fungal strains studied in the present work.

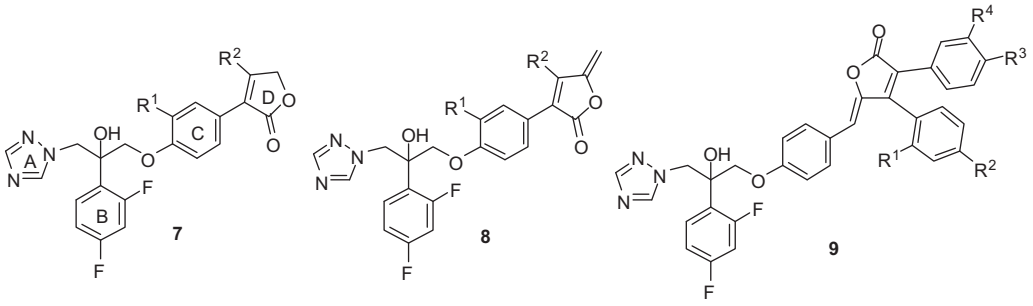
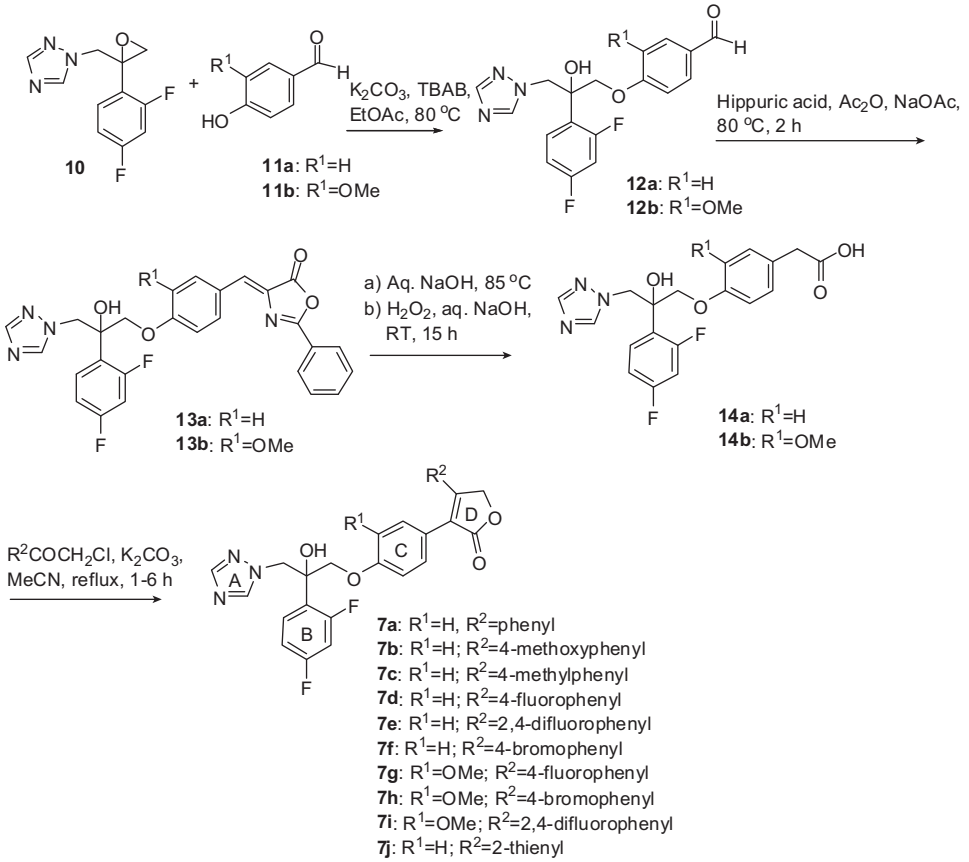


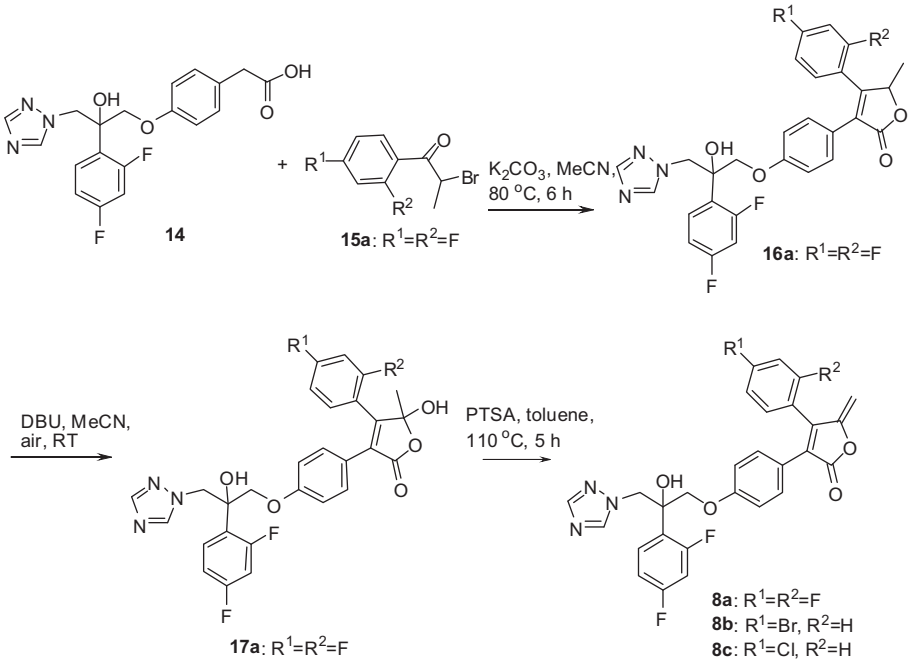
Figure 3. Structures of fluconazole analogues **7**, **8**, and **9**.



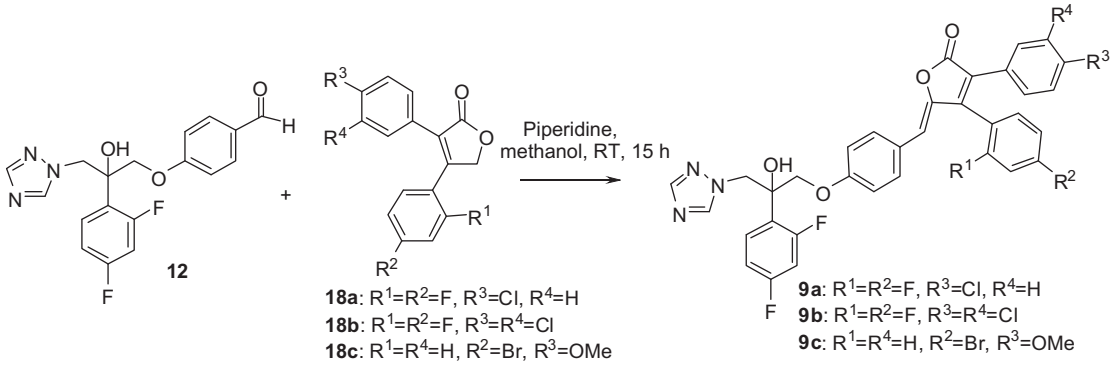
Scheme 1. Synthesis of fluconazole analogues **7**.

The above results indicated following points regarding the structure–activity relationship of the compounds studied in the present work.

1. The hybrid molecules with general structure **7** exhibited very good antifungal activity against *C. albicans* ATCC 24433 and *C. glabrata* ATCC 90030 and significant antifungal activity against *C. tropicalis* ATCC 750 and *C. neoformans* ATCC 34664.
2. The introduction of methoxy group on the aromatic ring C adjacent to fluconazole pharmacophores in the molecules with general structure **7** decreased the antifungal activity (compound nos **7d** v/s **7g**, **7e** v/s **7i** and **7f** v/s **7h**).
3. The substituents on the phenyl ring at 4-position of the furanone ring D in compounds **7** also affected the antifungal activity to some extent. The 4-fluoro or 2,4-difluoro groups on this phenyl ring were tolerated and the resultant compounds exhibited antifungal activity similar to the parent compound **7a** (compound nos **7a** v/s **7d** or **7e**) while the 4-methoxy, 4-methyl or 4-bromo substituent reduced the antifungal activity slightly (compound nos **7a** v/s **7b**, **7c** or **7f**).
4. The replacement of phenyl ring at 4-position of the furanone ring D in **7** with a thiophene ring did not have any effect on antifungal activity showing that the phenyl and thiophene moieties are bioisosteric (compound no **7a** v/s **7j**).
5. The fluconazole analogues **12** exhibited antifungal activity of varying degree. The compounds **12a–c** containing phenyl ring with aldehyde functionality at *para* position exhibited antifungal activity against *C. albicans* ATCC 24433 and *C. glabrata* ATCC 90030 while the analogue **12d** with phenyl ring having aldehyde functionality at *meta* position exhibited less antifungal activity (Table 1, entries 13–16).
6. The antifungal activity of compounds **12a–d** was lost completely when the aldehyde functionality was converted into an azlactone moiety.[12]



Scheme 2. Synthesis of fluconazole analogues **8**.



Scheme 3. Synthesis of fluconazole analogues **9**.

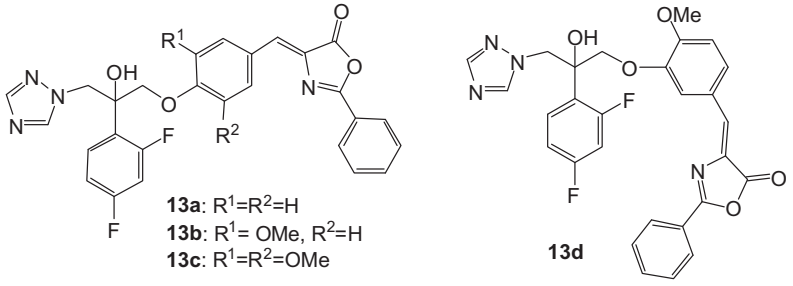
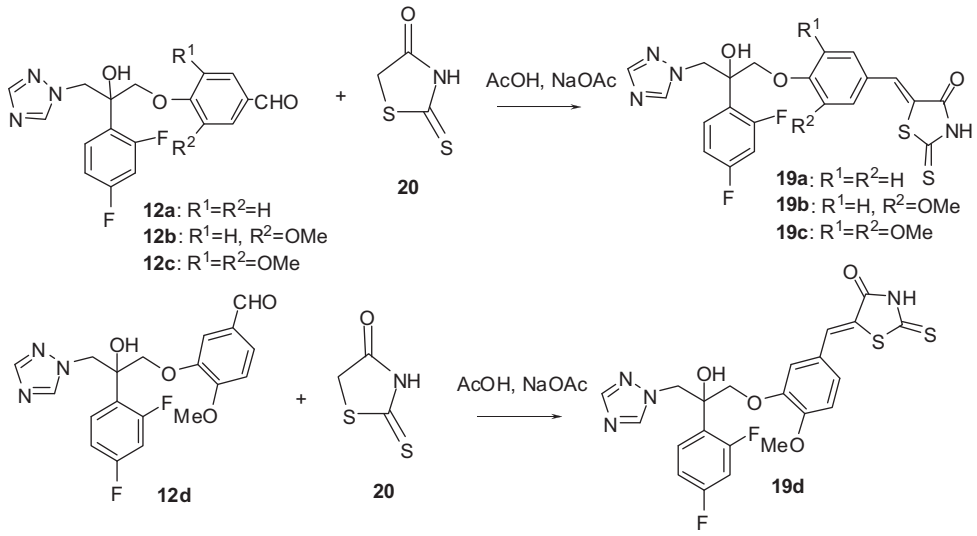


Figure 4. Structures of fluconazole analogues **13a–d** containing azlactone moiety.

7. The conversion of the aryl aldehyde functionality of compounds **12** into arylacetic acid **14** resulted into complete loss of activity.[12]
8. The antifungal activity of compounds **12a–d** was decreased or lost completely when the aldehyde functionality was converted into compounds **19** containing 2-thioxothiazolidin-4-one moiety[12] (compound nos **12a** v/s **19a**, **12b** v/s **19b** and **12c** v/s **19c**).
9. The fluconazole analogues with general structure **8** were not enough stable to screen for antifungal activity while the compounds **9** were stable but did not exhibit any antifungal activity.[12]

In conclusion, we have synthesized a number of compounds with different structural features and evaluated their antifungal activity against various fungal strains using fluconazole and



Scheme 4. Synthesis of fluconazole analogues **19**.

Table 1
Antifungal activity data

Sr. no.	Compd no.	MIC_{50}* (μg/ml)							
		Ca01	**Cg01**	**Ck01**	**Ct01**	**Cn01**	**An01**	**Afm01**	**Fp01**
1	**AMB**	**0.25**	**0.25**	**0.5**	**0.5**	**0.5**	**0.25**	**0.5**	**2**
2	**FLU**	**0.25**	**1**	32	**1**	**2**	NI 128	NI 128	NI 128
3	**7a**	**0.5**	**0.5**	NI 4	**2**	NI 4	NI 4	NI 4	NI 4
4	**7b**	**1**	**1**	NI 8	**4**	**2**	NI 8	NI 8	NI 8
5	**7c**	**0.5**	**1**	NI 4	**2**	**2**	NI 4	NI 4	NI 4
6	**7d**	**0.25**	**0.5**	**8**	**1**	**1**	NI 8	NI 8	NI 8
7	**7e**	**0.5**	**0.5**	**8**	**2**	**2**	NI 8	NI 8	NI 8
8	**7f**	**0.5**	**2**	**8**	**4**	**1**	NI 8	NI 8	NI 8
9	**7g**	**0.5**	**0.5**	NI 16	**2**	**2**	NI 8	NI 8	NI 8
10	**7h**	**1**	**2**	NI 4	**4**	**8**	NI 4	NI 4	NI 4
11	**7i**	**1**	**1**	NI 8	NI 8	NI 8	NI 8	NI 8	NI 8
12	**7j**	**0.5**	**0.5**	NI 8	**2**	NI 8	NI 8	NI 8	NI 8
13	**12a**	**0.5**	**0.5**	**16**	**4**	**2**	NI 128	NI 128	NI 128
14	**12b**	**0.5**	**1**	128	**8**	**16**	NI 128	NI 128	NI 128
15	**12c**	**1**	**1**	NI 128	**64**	**8**	NI 128	NI 128	NI 128
16	**12d**	**2**	**2**	NI 128	NI 128	**16**	NI 128	NI 128	NI 128
17	**13a**	**4**	**4**	NI 4	NI 4	NI 4	NI 4	NI 4	NI 4
18	**19a**	**0.5**	**4**	NI 32	**8**	NI 32	NI 32	NI 32	NI 32
19	**19b**	**1**	**8**	NI 16	NI 16	NI 16	NI 16	NI 16	NI 16
20	**19c**	NI 16	NI 16	NI 16	NI 16	NI 16	NI 16	NI 16	NI 16
21	**14a**	**8**	**8**	NI 128	64	64	NI 128	NI 128	NI 128
22	**9a**	NI 4	NI 4	NI 4	NI 4	NI 4	NI 4	NI 4	NI 4
23	**16a**	**1**	**1**	NI 8	**8**	**4**	NI 8	NI 8	NI 8
24	**17a**	**2**	**2**	NI 16	**8**	NI 16	NI 16	NI 16	NI 16

Ca01: *C. albicans* ATCC 24433; **Cg01**: *C. glabrata* ATCC 90030; **Ck01**: *C. krusei* ATCC 6258; **Ct01**: *C. tropicalis* ATCC 750; **Cn01**: *C. neoformans* ATCC 34664; **An01**: *A. niger* ATCC 16404; **Afm01**: *A. fumigatus* ATCC 46645; **Fp01**: *F. proliferatum* ATCC 10052.

* The highest concentration level tested was 128 μg/ml. Some of the compounds precipitated out above certain concentration. The values of concentration till which there was no inhibition and/or above which there was partial/complete precipitation are indicated by "NI ..." for example NI 16 means that there was no inhibition till 16 μg/ml and/or compound started precipitating out at that concentration.The values for activity data for selected compounds are given here; the values for all the compounds screened in the present work are given in the Supplementary data.

amphotericin B as standards. The hybrid molecules **7a–j** exhibited significant antifungal activity against *C. albicans* ATCC 24433, *C. glabrata* ATCC 90030, *C. tropicalis* ATCC 750 and *C. neoformans* ATCC 34664 with MIC_{50} values comparable to fluconazole. As the present MIC_{50} values are for racemic compounds, there is a definite possibility of having more active compounds after preparing the corresponding enantiomers of the active compounds. Thus the present work would be very useful to get potential antifungal agents.

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Supplementary data

Supplementary data (experimental procedures and spectral data for all compounds prepared for antifungal activity testing)

associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.06.022.

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