Synthesis and Structure–Activity Relationships of Phenyl-Substituted Benzylamine Antimycotics: A Novel Benzylbenzylamine Antifungal Agent for Systemic Treatment

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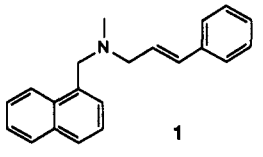
Derivatives of the benzylamine antimycotics with an extra phenyl ring incorporated in the side chain have been prepared and their antifungal activity evaluated. The potency is strongly dependent on the distance between the two phenyl groups and the type of spacer. Linking the aryl rings with a quaternary carbon atom resulted in the identification of highly active compounds **7f** and **12a**, having a novel 4-benzylbenzylamine side chain. Compound **7f** and its 7-benzo[*b*]thienyl analogue **12a** show significantly enhanced efficacy, in particular against *Candida albicans*, and are among the most potent allyl/benzylamine antimycotics identified so far. Extended investigations with the benzylbenzylamine derivative **7f** revealed that, in addition to the enhanced antimycotic profile, the compound is the first representative of the benzylamine antimycotics suitable for systemic treatment.

Introduction

The allylamine derivatives are synthetic antimycotics that selectively inhibit fungal squalene epoxidase.[1] Their use in the systemic and topical treatment of various mycoses is increasing rapidly. The first representative of this class naftifine[2] (**1**, Exoderil) served as a starting point for intensive studies on structure–activity relationships (SAR).[3] This led to the discovery of terbinafine (**2**), which exhibits considerably enhanced antimycotic potency,[4] in particular after oral application.[5] Intensive clinical studies revealed that **2** is extremely potent in the topical and oral treatment of mycoses of the skin and its appendages, especially in the therapy of onychomycoses.[6] Terbinafine (Lamisil) has recently become commercially available.

Subsequent SAR studies demonstrated that high antifungal activity was either retained or further increased when the naphthalene part in **2** was replaced by benzo[*b*]thiophenes with the allyl side chain at position 3, 4, or 7.[7,8] (*E*)-3-Chloro-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-*N*-methylbenzo[*b*]thiophene-7-methanamine[9] (**3**) was shown to be the most potent allylamine antimycotic in vitro identified so far. Further SAR explorations that concentrated on the allyl side chain led to the discovery of the homoproparglyamines[8,10] and the benzylamines.[8,11] With-



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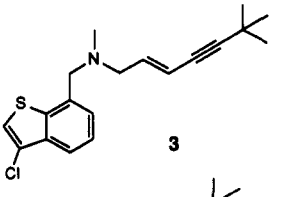

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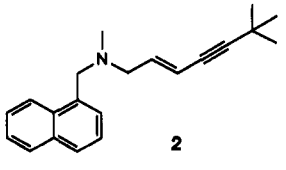

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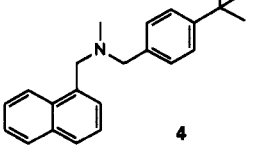

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in the benzylamine derivatives para substitution of the benzyl group is required for high antifungal activity. For example, the *tert*-butylbenzylamine derivative **4** proved to be highly active against a range of human pathogenic fungi. Similar findings were independently found by other groups[12,13] and led to the development of *N*-[[4-(1,1-dimethylethyl)phenyl]methyl]-*N*-methyl-1-naphthalenemethanamine (**4**, butenafine) for the topical treatment of mycoses.

Further synthetic work resulted in a series of derivatives of the benzylamine antimycotics, in which an extra phenyl ring is attached to the para position of the side chain through various spacers. In the present study the SAR obtained for these compounds are reported. As a result of this investigation we have identified a novel representative of the benzylamines that exhibits enhanced activity against yeasts. Additional pharmacological properties indicate that this compound is suitable for systemic use.

Chemistry

In general, the synthesis of the benzylamine derivatives was accomplished by N-alkylation of secondary amines **5** and **9** as shown in Schemes I and II. The side-chain amine **9** of the most active compounds **7f** and **12a,b** was prepared from the corresponding aldehyde **8** via Schiff base formation and reduction (Scheme II). Aldehyde **8** was obtained from 2,2-diphenylpropane using the Duff reaction.[14] Trifluoroacetic acid proved to be the optimal solvent for this particular reaction, producing high yields of **8** and no detectable amounts of possible isomers or dialdehydes. The crude product mixture consisted only of starting material and **8** (average conversion 80–85%) and could be used for the following transformation to **9** without any purification. Isolation of pure **9** was accomplished by crystallization of its hydrochloride salt.

Several title compounds were prepared by individual methods (Scheme I). Analogue **7d** was synthesized by a Wittig reaction from **7c** using the appropriate instant ylide.[15] *N*-Acetyl compound **7j** was treated with base to generate the corresponding secondary aniline **7k** or was reduced to the *N*-ethyl derivative **7l** using the borane dimethyl sulfide complex. As cyclopropanation of **7d** could

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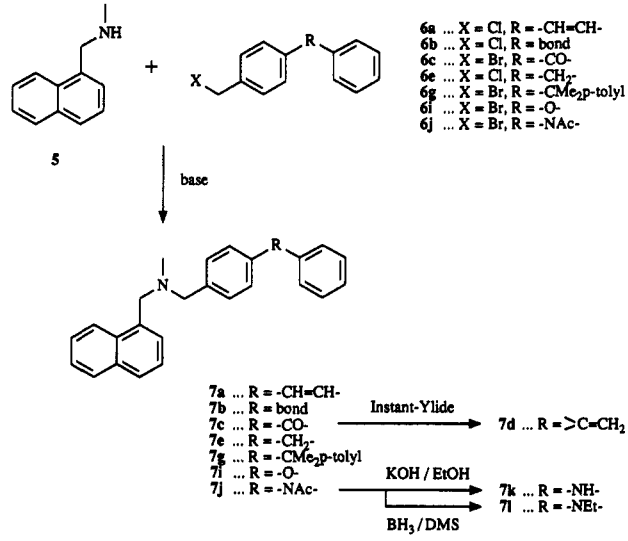
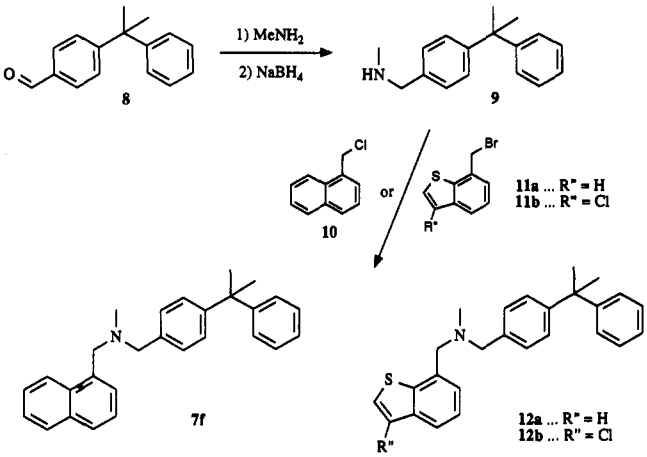
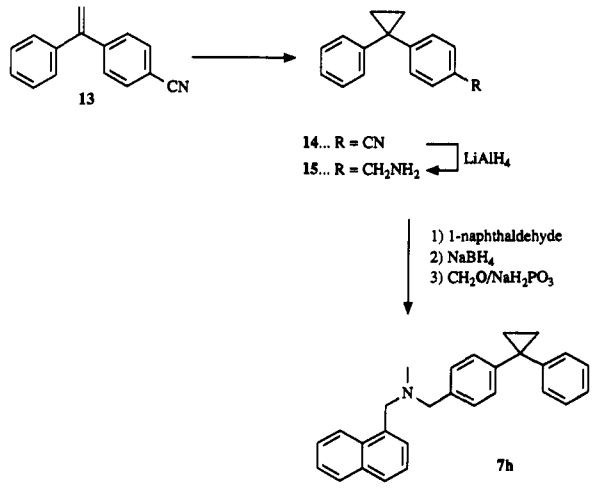
Scheme I. Synthesis of Benzylamine Derivatives 7 by N-Alkylation of 5



Scheme II. Synthesis of Benzylamine Derivatives 7f and 12 by N-Alkylation of 9



Scheme III. Synthesis of Benzylamine Derivative 7h



not be achieved in high yield, a different procedure was developed for the synthesis of **7h** (Scheme III). After successful cyclopropanation of diphenylethylene derivative **13** to produce **14**, the cyano function was converted into the primary amine **15**. Condensation with 1-naphthaldehyde, followed by reduction with sodium borohydride in methanol and N-methylation,[16] yielded **7h**.

Mycology

The in vitro antifungal activity of the allylamine derivatives was investigated against isolates of *Trichophyton mentagrophytes*, *Microsporum canis*, *Sporothrix schenckii*, *Aspergillus fumigatus*, *Candida albicans* Δ124, *Candida albicans* Δ9, and *Candida parapsilosis* Δ39. Minimum inhibitory concentrations (MIC) were determined using Sabouraud's dextrose broth (pH 6.5) for dermatophytes, aspergilli and *S. schenckii* and malt extract broth (pH 4.8) for yeasts in glass tubes. The test compounds were dissolved in DMSO and serially diluted with the growth media. The growth control was read after a 48 h (yeasts), 72 h (molds) or 7 day (*S. schenckii* and dermatophytes) incubation at 30 °C. The MIC was defined as the lowest substance concentration where fungal growth was macroscopically undetectable.

The fungal strains were obtained either from the American Type Culture Collection, Rockville, MD, from the Centraalbureau voor Schimmelcultures, Baarn, The Netherlands, from the Hygiene-Institut, Würzburg, FRG, or the II. Universitäts-Hautklinik, Vienna, Austria. Filamentous fungi were harvested with a spatula from cultures grown on Kimmig agar (E. Merck AG, Darmstadt, FRG) at 30 °C for 21 days, whereas yeast blastospores were taken from cultures shaken at 37 °C for approximately 30 h in yeast nitrogen base (Difco Laboratories, Detroit, MI).

Results

As shown in Table I, the in vitro antifungal activities of *tert*-butylbenzylamine derivative **4** and terbinafine (**2**) are very similar. Both drugs exhibit very high efficacy against dermatophytes (MIC = 0.003–0.01 mg/L), and are moderately effective against Candida species (MIC = 0.8–25 mg/L).

Within the present study the *tert*-butyl substituent in **4** was replaced by various phenyl-containing residues. These modifications resulted in benzylamine derivatives **7** and **12** bearing side chains with two phenyl groups linked by different spacers. Substitution of the benzylamine side chain at the para position by the (*E*)-cinnamyl residue (**7a**), the phenyl ring (**7b**), or the benzoyl group (**7c**) led to a drastic decrease in antifungal activities. Compounds **7a** and **7c** showed moderate efficacy against dermatophytes, but were inactive against the other strains tested. The biphenyl derivative **7b** was completely ineffective against human pathogenic fungi in vitro. Activity was partially restored when the two aromatic groups in the side chain were linked by the 1,1-ethylene (**7d**) or the methylene function (**7e**). Both compounds showed good activity against dermatophytes and *C. parapsilosis* and moderate efficacy against *S. schenckii*. Formal introduction of two methyl groups at the methylene function in **7e** resulted in a remarkable increase in antifungal activities: Compound **7f** was found to be highly effective against all strains tested. In comparison with **2** and **4**, **7f** demonstrated equal potency against dermatophytes (MIC = 0.003–0.006 mg/L) and *S. schenckii* (MIC = 0.2 mg/L) and showed significantly enhanced activity against *A. fumigatus* (MIC = 0.1 mg/L) and the three *Candida* strains (MIC = 0.1–1.56 mg/L). The increased steric requirement of the side chain caused by an additional methyl group (**7g**) resulted in diminished antifungal activities. In contrast to **7a**,**c**–**e**, the decrease in efficacy of **7g** was more

Table I. In Vitro Activity (MIC, mg/L) of Benzylamine Derivatives 7 and 12

compd	spacer[a]	organisms[b]						
		T. ment.	*M. canis*	*A. fum*	*Sp. sch.*	*C. a.* 124	*C. a.* 9	*C. par.* 39
2	terbinafine	0.003	0.006	0.8	0.4	25	6.25	0.8
4		0.006	0.01	0.4	0.2	25	12.5	0.8
7a	—CH=CH—	0.1	0.01	>200	>200	>200	>200	>200
7b	none	10	>200	>200	>200	>200	>200	>200
7c	—CO—	0.05	0.1	>200	>200	>200	>200	50
7d	—C(=CH_2)—	0.01	0.01	>200	1.56	>200	>200	0.8
7e	—CH_2—	0.05	0.05	>100	1.56	>100	50	6.25
7f	—CMe_2—	0.006	0.003	0.1	0.2	1.56	0.8	0.1
7g	—CMe_2*p*-tolyl	0.1	0.1	12.5	0.4	6.25	6.25	0.1
7h	—C(CH_2CH_2)—	0.006	0.003	1.56	0.1	3.13	1.56	0.1
7i	—O—	0.4	0.8	>200	>200	>200	>200	>200
7j	—NAc—	0.8	3.13	>200	>200	>200	>200	>200
7k	—NH—	>100	>100	>200	>200	>200	>200	>200
7l	—NEt—	0.006	0.006	>200	3.13	>200	>200	3.13
12a	—CMe_2—	0.003	0.003	0.1	0.2	0.8	0.4	0.05
12b	—CMe_2—	0.02	0.02	0.2	0.8	1.56	1.56	0.1

[a] Groups between the two phenyl rings of the benzylamine side chain. [b] Abbreviations: *T. mentagrophytes*, *T. ment.*; *M. canis*, *M. canis*; *A. fumigatus*, *A. fum.*; *S. schenckii*, *Sp. sch.*; *C. albicans* Δ124, *C. a.* 124; *C. albicans* Δ9, *C. a.* 9; *C. parapsilosis* Δ39, *C. par.* 39.

Table II. Physicochemical Properties of Benzylamine Derivatives 7 and 12

no.	morphology, mp (°C)	NMR ($CDCl_3$) δ	yield[a] (%)	anal.
7a	colorless crystals, 93	8.15–8.45 (m, 1H), 7.65–8.00 (m, 2H), 7.15–7.65 (m, 13H), 7.10 (s, 2H), 3.95 (s, 2H), 3.60 (s, 2H), 2.20 (s, 3H)	88	$C_{27}H_{25}N$ (363.50: C,H,N
7b	colorless crystals, 44–46	8.26–8.33 (m, 1H), 7.75–7.88 (m, 2H), 6.84–7.52 (m, 13H), 3.96 (s, 2H), 3.63 (s, 2H), 2.23 (s, 3H)	56	$C_{25}H_{23}N$ (337.47): C,H,N
7c	oil	8.25–8.43 (m, 1H), 7.64–7.95 (m, 6H), 7.30–7.62 (m, 9H), 4.00 (s, 2H), 3.66 (s, 2H), 2.24 (s, 3H)	68	$C_{26}H_{23}NO$ (365.45): C,H,N
7d	oil	8.24–8.35 (m, 1H), 7.74–7.92 (m, 2H), 7.12–7.60 (m, 13H), 5.42–5.47 (m, 2H), 3.95 (s, 2H), 3.60 (s, 2H), 2.20 (s, 3H)	63	$C_{27}H_{23}N$ (363.50): C,H,N
7e	oil	8.10–8.32 (m, 1H), 7.68–7.96 (m, 2H), 7.05–7.59 (m, 13H), 3.98 (s, 4H), 3.63 (s, 2H), 2.23 (s, 3H)	66	$C_{26}H_{25}N$ (351.50): C,H,N
7f	oil, (HCl) 170–172	8.15–8.24 (m, 1H), 7.76–7.85 (m, 1H), 7.70–7.76 (m, 1H), 7.32–7.48 (m, 4H), 7.10–7.28 (m, 9H), 3.91 (s, 2H), 3.56 (s, 2H), 2.20 (s, 3H), 1.67 (s, 6H)	72	$C_{26}H_{29}N$·HCl (416.10): C,H,N,Cl
7g	oil	8.16–8.28 (m, 1H), 7.74–7.90 (m, 2H), 7.10–7.57 (m, 12H), 3.96 (s, 2H), 3.60 (s, 2H), 2.25 (s, 3H), 2.21 (s, 3H), 1.64 (s, 6H)	64	$C_{28}H_{31}N$ (393.57): C,H,N
7h	oil	8.16–8.27 (m, 1H), 7.70–7.88 (m, 2H), 6.84–7.52 (m, 13H), 3.88 (s, 2H), 3.50 (s, 2H), 2.25 (s, 3H), 1.22–1.28 (m, 4H)	57	$C_{28}H_{27}N$ (377.53): C,H,N
7i	oil	8.19–8.38 (m, 1H), 7.70–7.97 (m, 2H), 6.83–7.62 (m, 13H), 3.96 (s, 2H), 3.58 (s, 2H), 2.23 (s, 3H)	69	$C_{25}H_{23}NO$ (353.47): C,H,N
7j	colorless crystals, 88–92	8.18–8.38 (m, 1H), 7.72–7.98 (m, 2H), 7.06–7.60 (m, 13H), 3.96 (s, 2H), 3.58 (s, 2H), 2.22 (s, 3H), 2.05 (s, 3H)	90	$C_{27}H_{26}N_2O$ (394.52): C,H,N
7k	oil	8.20–8.38 (m, 1H), 7.70–7.96 (m, 2H), 6.82–7.60 (m, 13H), 5.68 (br s, 1H), 3.95 (s, 2H), 3.56 (s, 2H), 2.22 (s, 3H)	60	$C_{25}H_{24}N_2$ (352.48): C,H,N
7l	oil	8.20–8.36 (m, 1H), 7.70–7.96 (m, 2H), 6.83–7.61 (m, 13H), 3.95 (s, 2H), 3.77 (qua, J = 7 Hz, 2H), 3.57 (s, 2H), 2.22 (s, 3H), 1.20 (t, J = 7 Hz, 3H)	64	$C_{27}H_{26}N_2$ (380.53): C,H,N
12a	oil, (HCl) 156–158	7.65–7.86 (m, 1H), 7.15–7.55 (m, 13H), 3.82 (s, 2H), 3.59 (s, 2H), 2.18 (s, 3H), 1.66 (s, 6H)	76	$C_{28}H_{27}NS$·HCl (422.04): C,H,Cl,N,S
12b	oil	7.74–8.02 (m, 1H), 7.12–7.45 (m, 12H), 3.79 (s, 2H), 3.56 (s, 2H), 2.15 (s, 3H), 1.66 (s, 6H)	77	$C_{28}H_{26}ClNS$ (420.01): C,H,Cl,N,S

[a] Yields (not optimized) of isolated, analytically pure products.

pronounced against dermatophytes and *A. fumigatus*, whereas the activity against the other strains remained nearly unchanged. Formal cyclization of the two geminal methyl groups to the cyclopropane ring system (**7h**) had no effect on the antifungal potencies relative to **7f**, except for the decreased efficacy against *A. fumigatus*.

In a series of compounds the two phenyl groups in the side chain were linked by heteroatoms. The diphenyl ether derivative **7i** and the acetylated aniline **7j** showed only moderate activity against dermatophytes and were ineffective against the other strains. Introduction of the secondary amine function (**7k**) caused complete loss of activity. However, the tertiary amine derivative **7l** exhibited high efficacy against dermatophytes (MIC = 0.006 mg/L), *S. schenckii* (MIC = 3.13 mg/L), and *C. parapsilosis* (MIC = 3.13 mg/L).

To investigate the potential of the novel benzylamine side chain of **7f**, two further derivatives were prepared, in which the naphthalene part was replaced by 7-benzo[*b*]-thiophenes. Compound **12a** with the unsubstituted 7-benzo[*b*]thiophene moiety showed very high efficacy against all strains tested (MICs between 0.003 and 0.8 mg/L), being superior to **2** and **4**, in particular against *A. fumigatus*, *C. albicans*, and *C. parapsilosis*. The 3-chloro-7-benzo[*b*]thiophene derivative **12b**, although highly active, demonstrated decreased efficacy relative to **12a**, especially against dermatophytes.

Compound **7f** (SDZ SBA 586) has also been shown to be highly effective in vivo. In the guinea pig trichophytosis model[5] (treatment once daily for 9 days starting on the day of inoculation) **7f** proved to be significantly superior to griseofulvin and ketoconazole after oral application:

ED_{50} [mg/kg per day] = 4.6 (**7f**), 40.7 (griseofulvin), 50.8 (ketoconazole). With **7f**, 100% mycological cure was already achieved at a dose of 8 mg/kg per day.

In the guinea pig skin candidosis model[5] (topical treatment twice daily for 5 days starting 3 days after inoculation) a 90% mycological cure with **7f** was achieved using a 2% solution (ED_{50} = 1.32%).

Details of the in vivo investigations will be reported elsewhere.

Discussion

The (*E*)-2-en-4-yne structural element of terbinafine (**2**) is replaced by a phenyl ring in the antifungal benzylamine derivative **4**. In this structure the "allylic" double bond is fixed in the *E* configuration, which is essential for high activity within the allylamines.[3] The structural resemblance between **2** and **4** is reflected in similar potencies of the two compounds against human pathogenic fungi in vitro (Table I) and in comparable SAR within the allylamine and benzylamine antimycotics,[3,17] leading to a combined QSAR investigation.[18] These studies disclosed that the benzylamine side chain must be substituted at the para position. Therefore, we synthesized and tested a series of compounds that satisfy this structural requirement and possess benzylamine side chains containing two phenyl groups linked by various spacers.

The antifungal activities listed in Table I revealed that linking the two aromatic rings with either 1,2-ethylene (**7a**), a carbonyl group (**7c**), or no spacer (**7b**) was not tolerated. The presence of one carbon atom between the phenyl groups in derivatives **7d** and **7e** led to improved activity. Finally, the introduction of a quaternary carbon atom as a spacer (**7f**)—being equivalent to formal replacement of one methyl group by phenyl in **4**—resulted in a remarkable increase in antifungal activities. This finding suggested that a fully substituted sp^3 carbon atom is the optimal linker of the two phenyl groups in the side chain and correlated well with the SAR results of terbinafine- and butenafine-related structures that the *tert*-butyl group in the side chain proved to be the optimal aliphatic substituent for high antifungal efficacy.[17,19] The increase in activity of **7f** in comparison with **4** was particularly pronounced against *A. fumigatus* and *C. albicans*. The steric requirement seems to be satisfied optimally by the side chain in **7f**, because (1) an addition of one methyl group (**7g**) caused a decrease in activity and (2) ring closure of the two geminal methyl groups (**7h**) did not improve the antifungal potency.

In vitro results for a series of compounds with heteroatoms as linkers of the two aromatic groups in the side chain (**7i–l**, Table I) revealed that these chemical modifications resulted in loss of antifungal activity. The only notable finding was the high and selective efficacy of **7l** against dermatophytes.

Within the terbinafine-related allylamines replacement of the naphthalene moiety by 7-benzo[*b*]thiophenes led to the discovery of compounds with increased antifungal potency in vitro.[7] Therefore, the derivatives **12a** and **12b**, which contain the novel side chain of **7f**, were prepared and tested. The unsubstituted 7-benzo[*b*]thiophene compound **12a** exhibited very high antifungal activity (even slightly superior to **7f**). However, substitution of naphthalene by 3-chloro-7-benzo[*b*]thiophene (**12b**), the most active derivative within the terbinafine-related allylamines, caused some decrease in efficacy. This finding suggested that the overall lipophilicity in **12b** had exceeded the limit tolerated for high antifungal activity in vitro. Nevertheless, the results obtained with **12a,b** confirmed that the novel 4-benzylbenzylamine side chain represents an important contribution in optimizing the antimycotic potency within the benzylamines.

With regard to the spectrum and intensity of efficacy in vitro, compounds **7f** and **12a** were significantly superior to the parent compound **4**, in particular against *A. fumigatus* and *C. albicans*. Thus, these compounds are among the most potent allyl/benzylamine antimycotics identified so far. Preliminary oral pharmacokinetic and tolerability (a 14-day single dose pilot study of 12-week old female Sprague Dawley rats at 300 mg/kg per day) studies proved **7f** (SDZ SBA 586) to be well absorbed (~86%) and well tolerated in rats after administration by gavage. In contrast, treatment with butenafine (**4**), following the same schedule as used for **7f**, caused mortality in two out of five animals.

In summary, the introduction of an extra phenyl group within the benzylamine derivatives succeeded not only in enhancing the antimycotic profile, but also resulted in the identification of a derivative suitable for systemic treatment.

Experimental Section

4-Benzoylbenzyl bromide,[20] 4-benzylbenzyl chloride,[21] 4-bromomethyl diphenyl ether,[22] 7-(bromomethyl)benzo[*b*]thiophene,[7] and 7-(bromomethyl)-3-chlorobenzo[*b*]thiophene[7] were prepared according to published procedures. 4-(Chloromethyl)stilbene and 4-phenylbenzyl chloride were purchased from Aldrich.

Melting points were determined on a Reichert Thermovar microscope and are not corrected. The temperature is given in Celsius units. The purity of the compounds was determined by GLC (Siemens Sichromat 1) using quartz columns (stationary phase OV-101) or RP-HPLC (pump, Waters M 6000; columns, 18 or 10 μm, Partisil ODS-10) using a water/acetonitrile gradient and a Schoeffel SF 770 UV detector (270 nm).

Thin-layer chromatography was performed using silica gel F_{254} plates (Merck) with visualization by UV or iodine vapor. Column chromatography was performed using silica gel 60 (0.040–0.063 mm, Merck) at a pressure of 3–5 bars.

^1H NMR spectra were recorded at 90 MHz (Bruker WH 90) or 250 MHz (Bruker WM 250) in $CDCl_3$ with $(CH_3)_4Si$ as internal standard. Chemical shifts are given as δ units. Elemental analyses were performed by Dr. O. Zak and Mag. J. Theiner, microanalytical laboratory at the University of Vienna, Institute of Physical Chemistry.

Synthesis of Benzylamines (7). (1) N-Alkylation. General Procedure. In a typical procedure, (*E*)-4-(chloromethyl)-stilbene (**6a**; 500 mg, 2.2 mmol) was dissolved in dry dimethylformamide (10 mL) and added slowly to a mixture of *N*-methyl-1-naphthalenemethanamine (**5**; 375 mg, 2.2 mmol) and potassium carbonate (400 mg, 2.9 mmol) in dry dimethylformamide at 0 °C. After stirring overnight at room temperature, the solvent was evaporated in vacuo and the residue partitioned between ether and water. The separated aqueous phase was extracted with ether, and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed (toluene/ethyl acetate, 9/1) to give **7a** (700 mg, 88%) as colorless crystals: mp 90–95 °C.

(2) *N*-Methyl-*N*-[[4-(1-phenylethenyl)phenyl]methyl]-1-naphthalenemethanamine (7d). A ready-to-use mixture of methyltriphenylphosphonium bromide/sodium amide (1.37 g, 3.29 mmol) was stirred in dry toluene (7 mL) for 15 min at room temperature, followed by the addition of **7c** (1 g, 2.7 mmol). The mixture was refluxed for 1.5 h and subsequently concentrated in vacuo. The residue was treated with dry ether (10 mL), filtered, and evaporated again to produce the crude product, which on purification by chromatography (toluene) gave **7d** (626 mg, 63%) as a colorless oil.

(3) *N*-Methyl-*N*-[[4-(1-phenylcyclopropyl)phenyl]methyl]-1-naphthalenemethanamine (7h). Following the procedure described for the synthesis of 9, 4-(1-phenylcyclopropyl)-benzylamine (15; 840 mg, 3.76 mmol) and 1-naphthaldehyde (588 mg, 3.76 mmol) were reacted to generate the corresponding Schiff base, which was subsequently reduced using sodium borohydride in methanol to give crude *N*-[[4-(1-phenylcyclopropyl)phenyl]-methyl]-1-naphthalenemethanamine (1.29 g, 94%): NMR δ 8.02–8.12 (m, 1 H), 7.70–7.98 (m, 2 H), 7.10–7.66 (m, 13 H), 4.26 (s, 2 H), 3.90 (s, 2 H), 1.64 (s, 1 H), 1.30 (s, 4 H). This secondary amine (1.15 g, 3.2 mmol) was dissolved in dioxane (20 mL), mixed with 1 N aqueous sodium dihydrogen phosphite solution (20 mL) and formaldehyde (20 mL, 0.24 mol, 36.5% solution in water), and heated to 60 °C for 2 h. The mixture was made alkaline by addition of 1 N aqueous sodium hydroxide solution and extracted with ether. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. The title compound (874 mg, 72%) was obtained as colorless oil after purification by chromatography (dichloromethane/methanol, 100/1).

(4) *N*-Methyl-*N*-[[4-(phenylamino)phenyl]methyl]-1-naphthalenemethanamine (7k). 7j (650 mg, 1.65 mmol) and potassium hydroxide (140 mg, 2.5 mmol) were dissolved in ethanol (10 mL) and heated to reflux for 24 h. The solvent was distilled off in vacuo, and the residue partitioned between ether and water. The layers were separated, and the aqueous phase was extracted with ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (dichloromethane/ether, 10/1) to give 7k (352 mg, 60%) as colorless oil.

(5) *N*-Methyl-*N*-[[4-(*N*'-ethyl-*N*'-phenylamino)phenyl]-methyl]-1-naphthalenemethanamine (7l). Under argon atmosphere 7j (200 mg, 0.5 mmol) was dissolved in dry tetrahydrofuran (20 mL) and treated slowly with borane dimethyl sulfide complex (0.12 mL, 1.3 mmol) at room temperature. After stirring for 2 h at 60 °C, the mixture was quenched with methanol (2 mL) and concentrated in vacuo. The residue was taken up in ethanol (5 mL), treated with 6 N hydrochloric acid (5 mL), and refluxed for 1.5 h. The mixture was poured onto water, made alkaline using 20% aqueous sodium hydroxide solution, and extracted with ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated in vacuo. Purification by chromatography yielded 7l (123 mg, 64%) as colorless oil.

Synthesis of Starting Materials. 2-[4-(2-Bromomethyl)-phenyl]-2-(4-methylphenyl)propane (6g). 2,2-Di(4-methylphenyl)propane (760 mg, 3.4 mmol), *N*-bromosuccinimide (610 mg, 3.4 mmol), and a catalytic amount of dibenzoyl peroxide were mixed in tetrachloromethane (20 mL) and heated to reflux for 4 h. The cooled mixture was filtered and concentrated in vacuo. The crude product (950 mg, 95%) was used in the following alkylation step or purified by chromatography (cyclohexane): NMR δ 7.20 (s, 4 H), 7.10 (s, 4 H), 4.45 (s, 2 H), 2.27 (s, 3 H), 1.62 (s, 6 H).

N-[4-(2-Bromomethyl)phenyl]-*N*-phenylacetamide (6j). Following the procedure described for the synthesis of 6g, reaction of *N*-(4-methylphenyl)-*N*-phenylacetamide[23] (805 mg, 3.2 mmol) with *N*-bromosuccinimide (570 mg, 3.2 mmol), followed by chromatography (hexane/ethyl acetate, 2/1) produced 6j (739 mg, 76%) as colorless crystals: mp 95–97 °C; NMR δ 7.14–7.58 (m, 9 H), 4.49 (s, 2 H), 2.08 (s, 3 H).

N-Methyl-[4-(1-methyl-1-phenylethyl)phenyl]methanamine (9). (a) 4-(1-Methyl-1-phenylethyl)benzaldehyde (8). 2,2-Diphenylpropane (3.93 g, 20 mmol) and hexamethylenetetramine (2.8 g, 20 mmol) were refluxed in trifluoroacetic acid (35 mL) for 16 h. After cooling the mixture was poured onto ice/water, stirred for one additional hour, and made alkaline (pH 9) by treatment with solid potassium carbonate. Extraction with ether followed by evaporation of the combined and dried organic layers yielded a product (4.6 g), which was analyzed by ^{1}H NMR spectroscopy to determine the ratio of 8 and starting material (80–85% of 8). The crude product could be used in the following condensation reaction or purified by chromatography (hexane/ethyl acetate, 95/5) or Kugelrohr distillation (0.6 mbar/110 °C): NMR δ 9.98 (s, 1 H), 7.76–7.84 (m, 2 H), 7.37–7.45 (m, 2 H), 7.15–7.34 (m, 5 H), 1.72 (s, 6 H).

(b) *N*-Methyl[4-(1-methyl-1-phenylethyl)phenyl]methanamine (9). Methylamine (7.5 mL, 60 mmol, 8.03 M solution in ethanol) and 4-Å molecular sieve were added to a solution of crude 8 (4 g of 83% purity, about 15 mmol) in dry ethanol (40 mL) and stirred overnight at room temperature. The mixture was filtered over Celite and concentrated in vacuo. The residual Schiff base (4.3 g) was dissolved in dry methanol (20 mL), treated with sodium borohydride (0.7 g, 18.5 mmol) in portions, and heated to 40 °C for 1 h. The solvent was distilled off and the residue partitioned between water and ether. The organic layer was separated, dried over magnesium sulfate, and evaporated. For purification the crude product was dissolved in dry ethanol (10 mL), treated with excess etheric hydrochloric acid solution, and evaporated to dryness. Crystallization from 2-propanol yielded 9-HCl (2.83 g, 73% yield with respect of 83% pure starting material) as colorless crystals: mp 170–172 °C; NMR (free base) δ 7.10–7.40 (m, 9 H), 3.71 (s, 2 H), 2.47 (s, 3 H), 1.68 (s, 6 H), 1.44 (s, 1 H). For the *N*-alkylation reactions in general the free base of 9 was used, which was obtained after treatment of the hydrochloride salt with 2 N NaOH and extraction with ether.

4-(1-Phenylcyclopropyl)benzylamine (15). (a) 4-(1-Phenylethylene)benzonitrile (13). Following the procedure described for the synthesis of 7d, conversion of 4-benzoylbenzonitrile[24] (3 g, 14.5 mmol) with methyltriphenylphosphonium bromide/sodium amide (7.84 g, 18.8 mmol), followed by chromatography (toluene) afforded 13 (1.61 g, 54%) as colorless oil: NMR δ 7.18–7.73 (m, 9 H), 5.60 (s, 1 H), 5.55 (s, 1 H).

(b) 4-(1-Phenylcyclopropyl)benzonitrile (14). Copper powder (2.2 g, 35 mmol) was treated with iodine (30 mg) in dry toluene (30 mL) for 10 min. Diiodomethane (4.12 g, 15.4 mmol) and 13 (1.58 g, 7.7 mmol) were added, and the mixture was heated to reflux for about 6 days. After filtration the solvent was distilled off in vacuo and the residue chromatographed (toluene) to give 14 (1.47 g, 88%) as colorless oil: NMR δ 7.00–7.50 (m, 9 H), 1.32 (s, 4 H).

(c) 4-(1-Phenylcyclopropyl)benzylamine (15). Lithium aluminum hydride (1.06 g, 28 mmol) was suspended in dry tetrahydrofuran and treated with a solution of 14 (1 g, 4.56 mmol) in dry tetrahydrofuran at room temperature. The mixture was stirred for 18 h at 60 °C, hydrolyzed cautiously with 1 N hydrochloric acid and extracted with dichloromethane. The combined organic layers were washed with diluted aqueous sodium hydroxide solution, water, and brine, dried over magnesium sulfate, and concentrated in vacuo. The crude product (840 mg, 82%) thus obtained was used in the following condensation reaction without further purification: NMR δ 7.15–7.25 (m, 9 H), 3.80 (s, 2 H), 1.60 (br s, 2 H), 1.25 (s, 4 H).

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