Synthesis and Structure–Activity Relationships of the Novel Homopropargylamine Antimycotics

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Analogues of the antimycotic allylamine terbinafine were prepared in which the naphthalene and the *tert*-butylacetylene moieties were preserved, but the spacer between these two groups was varied, and the antifungal activity of the new compounds was evaluated. All modifications of the original spacer such as reduction of the double bond, switching the position of the nitrogen atom, shortening, and elongation resulted in decreased potencies with one exception: Compounds with the $CH_2NMeCH_2CH_2$ group between the 1-naphthalene and the optionally substituted *tert*-butylacetylene function demonstrated high antifungal activity in vitro. The new homopropargylamine derivatives are more potent than terbinafine against *Aspergillus fumigatus*. The results support the hypothesis that two lipophilic domains linked by a spacer of appropriate length and a polar center at a defined position in the spacer are the general requirements for high activity of allylamine antimycotics.

Introduction

Naftifine[1] (1, Figure 1; exoderil) was the first representative of the allylamine antimycotics, known to act by selective inhibition of the fungal squalene epoxidase.[2] The new class of synthetic antifungal agents were named "allylamine" derivatives[3] because the tertiary (*E*)-allylamine structural element was found to be essential for antifungal activity. Extensive studies on structure–activity relationships[4–6] (SAR) led to the discovery of terbinafine (2, Figure 1; lamisil), which is considerably more potent than the original lead structure 1, particularly after oral administration.[7] Intensive clinical studies revealed 2 to be effective in the topical and oral treatment of mycoses of the skin and its appendages, especially in the therapy of onychomycoses.[8]

Subsequent SAR explorations demonstrated that high antifungal activity was either retained or further increased when the naphthalene moiety in 2 was replaced by benzo[*b*]thiophenes with the allylamine side chain at position 3, 4, or 7.[9,10] In particular, (*E*)-3-chloro-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-*N*-methylbenzo[*b*]thiophene-7-methanamine[11–13] (3, Figure 1) exhibited considerably increased in vitro potency against yeasts, relative to 2. Furthermore, formal replacement of the (*E*)-1,3-enyne structural element of terbinafine (2) by a phenyl group resulted in the discovery of the antifungal benzylamines,[10,14,15] represented by the derivative 4 (Figure 1).

All SAR studies to date indicate that only allyl/benzylamine derivatives with a lipophilic bicyclic aromatic ring system (naphthalene, benzo[*b*]thiophene) exhibit high antifungal activities. Furthermore, the side chains of all potent representatives feature a bulky, lipophilic group (phenyl for 1, *tert*-butyl for 2–4; Figure 1). Lipophilic domains L1 and L2 (general structure A, Figure 1) are linked by very similar spacers containing the NMe group as a polar center P. The present study comprises of the SAR investigation on compounds of the general structure B. Varying the distances between L1 (1-naphthalene), P (primarily NMe), and L2 (*tert*-butylacetylene) resulted in the identification of a novel antifungal subclass, the homopropargylamines.

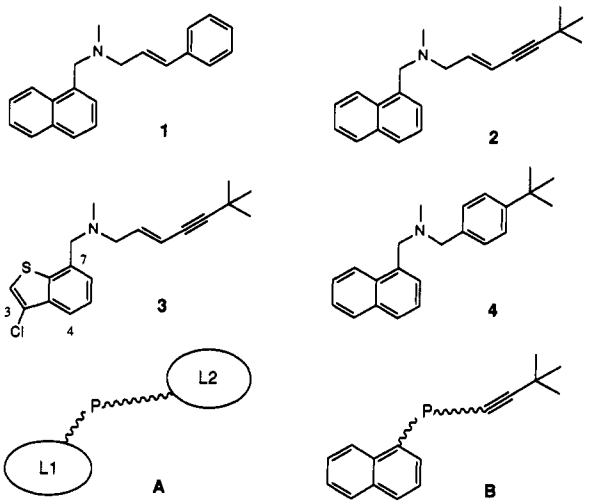

Figure 1. Common structural features of the representatives of potent allyl/benzylamine antimycotics.

Chemistry

The amine derivatives 7 were prepared by *N*-alkylation of the secondary amines 5a–c with the appropriate acetylenic mesylates 6 in *N*,*N*-dimethylformamide (Scheme 1). In general, an organic base (e.g. triethylamine or a second equivalent of the amines 5a–c) was used to neutralize the methanesulfonic acid formed in the reaction. Use of sodium or potassium carbonate instead of the amine resulted in lower yields of 7 and the formation of the corresponding carbamate derivatives, such as 11, which was isolated as byproduct from the reaction of 5c with 6b and sodium carbonate. The ether derivative 10 was prepared from the alcohol 9a and 1-(chloromethyl)-naphthalene (8) via the alcoholate.

Most of the acetylenic alcohol intermediates (9, 14, 17, Scheme 2), which were converted into the corresponding mesylates 6 by treatment with methanesulfonyl chloride and triethylamine, were new. The homopropargylic alcohols 9a–e were prepared via the ring-opening reaction

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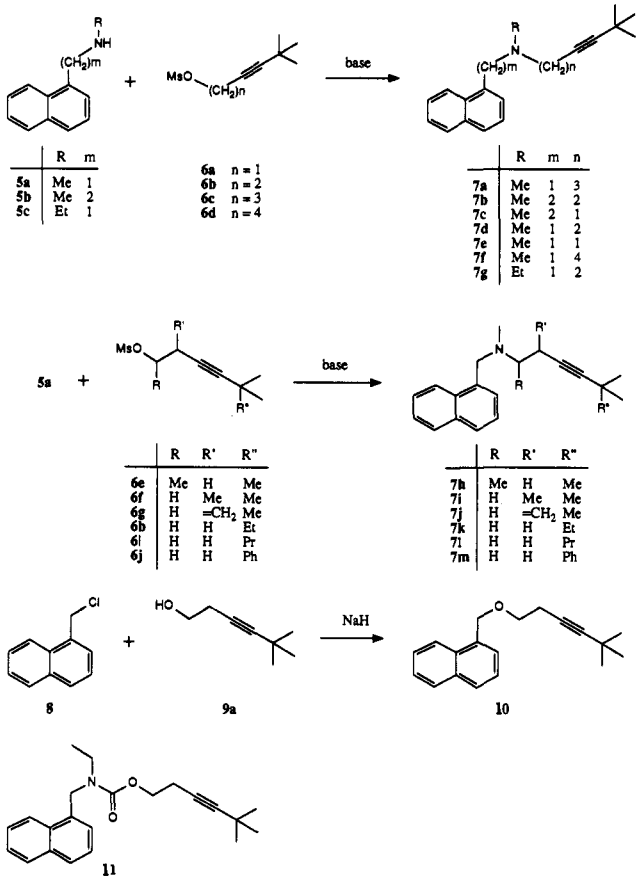
Scheme 1. Synthesis of the Acetylenic Amines 7 and the Ether 10



	R	m
5a	Me	1
5b	Me	2
5c	Et	1

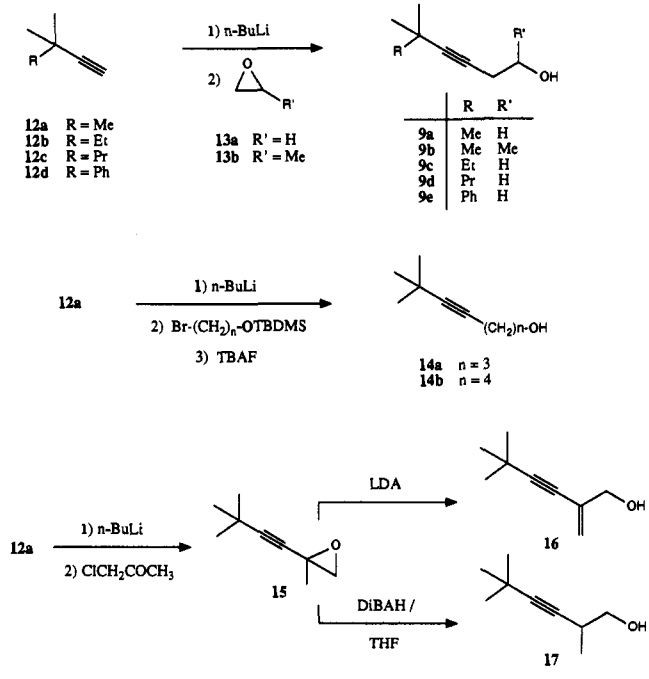
	n
6a	1
6b	2
6c	3
6d	4

	R	m	n
7a	Me	1	3
7b	Me	2	2
7c	Me	2	1
7d	Me	1	2
7e	Me	1	1
7f	Me	1	4
7g	Et	1	2

	R	R'	R"
6e	Me	H	Me
6f	H	Me	Me
6g	H	=CH$_2$	Me
6h	H	H	Et
6i	H	H	Pr
6j	H	H	Ph

	R	R'	R"
7h	Me	H	Me
7i	H	Me	Me
7j	H	=CH$_2$	Me
7k	H	H	Et
7l	H	H	Pr
7m	H	H	Ph

Scheme 2. Synthesis of the Acetylenic Side Chain Intermediates



	R	R'
9a	Me	H
9b	Me	Me
9c	Et	H
9d	Pr	H
9e	Ph	H

of the oxiranes **13a,b** with the appropriate lithium acetylides. The higher homologues **14a,b** were synthesized by alkylation of the lithium derivative of alkyne **12a** with O-silylated ω-bromoalkanols and subsequent deprotection. The branched enyne alcohol **16** was obtained from acetylenic oxirane **15** by lithium diisopropylamide-induced rearrangement.[16]

For the preparation of the β-substituted homopropargylic alcohol **17**, a new method had to be developed. Thus, treatment of the α-acetylenic epoxide **15** with diisobutylaluminum hydride in tetrahydrofuran produced alcohol **17** in high yield (Scheme 2). The high regioselectivity and the very low degree of isomerization to allenic products in this reaction together with its general applicability make this an efficient method for the synthesis of 2-substituted 3-butyn-1-ols.[17]

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, *C. 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 incubation for 48 h (yeasts), 72 h (molds), or 7 days (*S. schenckii* and dermatophytes) at 30 °C. The MIC was defined as the lowest substance concentration at which fungal growth was macroscopically undetectable.

The fungal strains were obtained from the following centers: the American Type Culture Collection, Rockville, MD; the Centraalbureau voor Schimmelcultures, Baarn, The Netherlands; 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. Yeast blastospores were taken from cultures shaken at 37 °C for approximately 30 h in yeast nitrogen base (Difco Laboratories, Detroit, MI).

Results

The antifungal activities of the compounds **7a–m**, **10**, and **11** against a panel of human pathogenic fungi are summarized in Table 1. Compound **7a**, differing from terbinafine (**2**) only by the absence of the double bond, showed remarkably low antifungal activities relative to **2**, except against *C. parapsilosis*. Shifting the position of the NMe group by one carbon (**7b**), resulted in further reduction of potency. In compounds **7c** and **7d** the spacer between the 1-naphthyl and the alkynyl residues was shortened by one carbon atom, relative to **2**. Whereas **7c** showed very weak activities, the homopropargylamine derivative **7d** was almost as active as **2**. Strikingly, the MIC against *A. fumigatus* for **7d** (0.1 mg/L) was substantially lower than that of terbinafine (0.8 mg/L). Shortening the spacer to three atoms (**7e**) or lengthening to six atoms (**7f**) resulted in drastic loss of activities.

Replacement of the polar center (NMe) of **7d** by oxygen produced **10**, which exhibited only very low antifungal potency. Antimycotic properties were also reduced by introduction of an ethyl group at the amino function (**7g**); however, high activity against *A. fumigatus* was observed for **7g** (MIC = 0.2 mg/L). Branching of the spacer by a methyl substituent either at the α- or the β-position of the homopropargylamine side chin of **7d** led to significantly decreased potency (**7h,i**). Compound **7j**, which contained an enyne structural element, was more active than the

Table 1. In Vitro Activity (MIC, mg/L) of the Acetylenic Amines 7 and Ether 10

		organisms[a]						
no.	spacer[b]	T. ment.	M. canis	A. fum.	Sp. sch.	C. a. 124	C. a. 9	C. par. 39
2	CNCC=C	0.003	0.006	0.8	0.4	25	6.25	0.8
7a	CNCCC	0.05	0.2	50	1.56	200	>200	0.8
7b	CCNCC	0.8	3.13	50	12.5	200	100	100
7c	CCNC	1.56	1.56	>50	6.25	100	50	50
7d	CNCC	0.006	0.01	0.1	3.13	50	50	1.56
7e	CNC	12.5	25	>200	>200	>200	200	>200
7f	CNCCCC	12.5	25	>200	>200	>200	200	>200
7g	CN(Et)CC	0.05	0.02	0.2	12.5	200	50	3.13
7h	CNC(Me)C	1.56	1.56	>200	>200	>200	200	100
7i	CNCC(Me)	0.8	0.8	>200	12.5	>200	>200	200
7j	CNCC(=CH_2)	0.05	0.05	50	1.56	>200	>200	6.25
7k	CNCC—Et[c]	0.006	0.01	0.1	3.13	50	12.5	1.56
7l	CNCC—Pr[c]	0.003	0.003	0.05	1.56	25	12.5	0.4
7m	CNCC—Ph[c]	0.01	0.006	0.2	3.13	12.5	6.25	0.4
10	COCC	0.4	0.4	1.56	>200	>200	200	>200
11	CNCOOCC	100	100	>200	>200	>200	>200	25

[a] Abbrevations: *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. [b] Group of atoms between the 1-naphthyl and the alkynyl residue in general structure B (Figure 1), the third substituent at the nitrogen generally being methyl, except for **7g**. [c] Substituents at the original *tert*-butyl group.

Table II. Physicochemical Properties of the Acetylenic Amines 7, Ether 10, and Carbamate 11

no.	morphology, mp (° C)	NMR ($CDCl_3$) δ	yield[a] (%)	anal.
7a	oil	8.26–8.46 (m, 1H), 7.68–7.96 (m, 2H), 7.28–7.64 (m, 4H), 3.89 (s, 3H), 2.58 (t, *J* = 7 Hz, 2H), 2.18 (s, 3H), 2.08–2.30 (m, 2H), 1.55–1.90 (m, 2H), 1.17 (s, 9H)	73	$C_{21}H_{27}N$ (293.44): C, H, N
7b	oil, 192–196 (HCl)	7.97–8.15 (m, 1H), 7.29–7.94 (m, 6H), 2.56–3.41 (m, 6H), 2.42 (s, 3H), 2.23–2.42 (m, 2H), 1.18 (s, 9H)	46	$C_{21}H_{27}N$·HCl (329.91): C, H, Cl, N
7c	oil, 182–184 (HCl)	8.04–8.25 (m, 1H), 7.32–7.98 (m, 6H), 3.46 (s, 2H), 2.66–3.42 (m, 4H), 2.42 (s, 3H), 1.24 (s, 9H)	62	$C_{20}H_{25}N$·HCl (315.88): C, H, Cl, N
7d	oil, 181–183 (HCl)	8.20–8.40 (m, 1H), 7.65–7.95 (m, 2H), 7.25–7.60 (m, 4H), 3.93 (s, 2H), 2.25–2.80 (m, 4H), 2.24 (s, 3H), 1.18 (s, 9H)	71	$C_{20}H_{25}N$ (279.43): C, H, N
7e	oil, 173–175 (HCl)	8.25–8.45 (m, 1H), 7.68–7.96 (m, 2H), 7.29–7.64 (m, 4H), 3.97 (s, 2H), 3.30 (s, 2H), 2.35 (s, 3H), 1.32 (s, 9H)	86	$C_{19}H_{23}N$·HCl (301.86): C, H, Cl, N
7f	oil	8.24–8.44 (m, 1H), 7.68–7.96 (m, 2H), 7.30–7.65 (m, 4H), 3.88 (s, 2H), 2.49 (t, *J* = 7 Hz, 2H), 2.20 (s, 3H), 2.14 (t, *J* = 6.5 Hz, 2H), 1.32–1.90 (m, 4H), 1.19 (s, 9H)	58	$C_{22}H_{29}N$ (307.46): C, H, N
7g	oil, 149–152 (HCl)	8.24–8.44 (m, 1H), 7.69–7.94 (m, 2H), 7.30–7.65 (m, 4H), 4.03 (s, 2H), 2.20–2.85 (m, 6H), 1.16 (s, 9H), 1.06 (t, *J* = 7 Hz, 3H)	63	$C_{21}H_{27}N$·HCl (329.91): C, H, N
7h	oil	8.20–8.42 (m, 1H), 7.30–7.96 (m, 6H), 4.04 (s, 2H), 2.86–3.26 (m, 1H), 2.10–2.66 (m, 2H), 2.20 (s, 3H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.21 (s, 9H)	35	$C_{21}H_{27}N$ (293.44): C, H, N
7i	oil	8.28–8.48 (m, 1H), 7.68–7.95 (m, 2H), 7.30–7.63 (m, 4H), 3.96 (s, 2H), 2.34–2.75 (m, 3H), 2.22 (s, 3H), 1.18 (s, 9H), 1.10 (d, *J* = 6.5 Hz, 3H)	42	$C_{21}H_{27}N$ (293.44): C, H, N
7j	colorless crystals, 43–47	8.27–8.48 (m, 1H), 7.68–7.94 (m, 2H), 7.28–7.63 (m, 4H), 5.40 (s, 2H), 3.98 (s, 2H), 3.16 (s, 2H), 2.25 (s, 3H), 1.24 (s, 9H)	63	$C_{21}H_{25}N$ (291.41): C, H, N
7k	oil, 171–173 (HCl)	8.22–8.43 (m, 1H), 7.68–7.96 (m, 2H), 7.30–7.66 (m, 4H), 3.95 (s, 2H), 2.30–2.84 (m, 4H), 2.25 (s, 3H), 0.84–1.58 (m, 5H), 1.14 (s, 6H)	71	$C_{21}H_{27}N$·HCl (329.91): C, H, Cl, N
7l	oil	8.20–8.41 (m, 1H), 7.68–7.96 (m, 2H), 7.30–7.63 (m, 4H), 3.94 (s, 2H), 2.30–2.84 (m, 4H), 2.25 (s, 3H), 1.20–1.50 (m, 4H), 1.14 (s, 6H), 0.80–1.00 (m, 3H)	39	$C_{22}H_{29}N$ (307.46): C, H, N
7m	oil, 106–110 (HCl)	8.22–8.43 (m, 1H), 7.68–7.96 (m, 2H), 7.10–7.64 (m, 9H), 3.97 (s, 2H), 2.40–2.90 (m, 4H), 2.28 (s, 3H), 1.56 (s, 6H)	46	$C_{25}H_{27}N$·HCl (376.94): C, H, Cl,[b] N
10	oil	8.05–8.26 (m, 1H), 7.70–7.98 (m, 2H), 7.33–7.68 (m, 4H), 5.01 (s, 2H), 3.65 (t, *J* = 7 Hz, 2H), 2.50 (t, *J* = 7 Hz, 2H), 1.20 (s, 9H)	59	$C_{19}H_{22}O$ (266.38): C, H
11	oil	7.95–8.18 (m, 1H), 7.76–7.92 (m, 2H), 7.30–7.60 (m, 4H), 4.98 (s, 2H), 4.24 (t, *J* = 7 Hz, 2H), 3.15–3.40 (br m, 2H), 2.42–2.60 (br m, 2H), 1.18 (s, 9H), 1.00–1.20 (br m, 3H)	–	$C_{22}H_{27}NO_2$ (337.46): C, H, N

[a] Yields (not optimized) of isolated, analytically pure products. [b] Cl: calcd, 9.41; found, 8.94.

corresponding saturated yne analogue **7i**, but the MICs were still higher compared to those determined for **7d**.

Replacement of the *tert*-butyl group in **7d** by more bulky substituents led to derivatives with high activities. Compound **7k** showed comparable potency to **7d**, but **7l** demonstrated even improved antifungal properties. With MICs of 0.003 mg/L for dermatophytes, 1.56 mg/L for *S. schenckii*, and 0.4–25 mg/L for Candida species, **7l** so far is the most active representative of the novel homopropargylamine antimycotics exhibiting similar in vitro potency as terbinafine (**2**). In addition, the sensitivity of *A. fumigatus* (MIC = 0.05 mg/L) to **7l** was remarkably enhanced in comparison with **2**. High in vitro potency was also found for the phenyl analogue **7m**.

The carbamate derivative **11** showed no significant inhibition of fungal growth in vitro.

Discussion

Intensive investigations within the allylamine antimycotics[5,9,10,14] so far have revealed that all highly active compounds (represented by prototypes **1–4** in Figure 1) have three structural features in common: (1) a bicyclic aromatic ring system, connected through (2) a tertiary (*E*)-allylamine function to (3) a bulky, lipophilic group. Moreover, studies with the carbon analogue[10,18] of **2** (NMe replaced by CHMe) indicated that the allylamine nitrogen is not essential for enzyme inhibition per se, but is required for fungal cell penetration. These findings stimulated further studies to explore whether the (*E*)-allylamine structural element is absolutely necessary or only the ensemble of a polar center P (NMe for compounds **1–4**, embedded in the linker) with the two lipophilic domains L1, L2 (general structure A, Figure 1) would be sufficient for high antifungal potency. Consequently, we synthesized and evaluated the antimycotic potential of terbinafine analogues not containing the allylamine structural feature (general formula B, Figure 1).

In terbinafine (**2**) the spacer between L1 (1-naphthalene) and L2 (*tert*-butylacetylene) is a five-membered chain including the nitrogen atom (C—NMe—C—C≡C). Keeping the length of the spacer constant but using a saturated carbon chain and varying the position of the polar center (NMe) generated analogues **7a** and **7b**. The observed reduction of the antifungal activities (Table 1) for both compounds were ascribed to the modification of the side-chain geometry. Shortening of the linker by one carbon atom resulted in structures **7c** (C—C—NMe—C) and **7d** (C—NMe—C—C). Whereas **7c** showed only weak activity, the isomer **7d** inhibited fungal growth very effectively. Further shortening of the spacer to a C—NMe—C chain (**7e**) or elongation to yield a six-membered chain (C—NMe—C—C—C—C) as linker (**7f**) caused almost complete loss of activity. These results with **7a–f** demonstrated the importance of the chain length and positioning of the polar center for the antifungal potency. Considering the finding that the nitrogen in **2** should be mainly responsible for cell penetration, the substantial influence of the position of the polar center on the activity (**7a** and **7d** in comparison with **7b** and **7c**, respectively) was remarkable. But this impact might be due to steric interference with the enzyme receptor, as the nitrogen was generally substituted by a methyl group and allyl/benzylamine analogues with branching between P and L2 consistently showed reduced potency. In addition, the shift of the polar center (NMe) within the chain might lead to an imbalance between lipophilic and polar domains and consequently affect the biological activity.

The high potency of the homopropargylamine derivative **7d** stimulated further investigations within this novel subtype of allylamine antimycotics. Introduction of oxygen instead of NMe as polar center (**10**) resulted in drastic reduction of activity. Both electronic (nitrogen versus oxygen) and steric (presence or absence of Me) factors could be responsible for this effect. The importance of the NMe group is evident from the finding that elongation just by one carbon atom to give the *N*-ethyl analogue **7g** led to diminished activity. Reduced potency was also observed for compound **7h** bearing an extra methyl substituent at the α-position of the homopropargylamine side chain of **7d**. The very similar MICs of **7h** and analogue **7c**, in which the *N*-methyl group was located at the same position as the extra methyl substituent in **7h**, suggested that in both cases the weak activity could be due to steric hindrance in binding to the receptor. Branching at the β-position of the homopropargylamine side chain also caused a decrease in potency, which was more pronounced for the methyl derivative **7i** than for the methylene analogue **7j**.

Increase of the bulkiness in the *tert*-butyl region of **7d** led to derivatives with high antifungal potency. Thus, whereas replacement of one methyl group by ethyl (**7k**) did not affect the potency, replacement by *n*-propyl (**7l**) resulted in a slightly improved activity pattern. Derivative **7m**, in which one methyl of the *tert*-butyl group in **7d** was replaced by phenyl, also inhibited fungal growth efficiently and demonstrated increased activity against *Candida* strains. These findings, that high antifungal activity was retained or even enhanced on increasing the bulkiness of the lipophilic domain L2, agreed well with recent SAR results for both the allylamine[19] and the benzylamine[15] antimycotics.

In summary, in addition to the known allylamine antimycotics, which feature an (*E*)-$CH_2NMeCH_2CH{=}CH$ chain between lipophilic domains L1 and L2 (Figure 1), highly active antifungal agents with $CH_2NMeCH_2CH_2$ as spacer between L1 and L2 have been identified. The homopropargylamine derivatives **7d,l–n** inhibited fungal growth very effectively and demonstrated improved potency against *A. fumigatus* compared to the corresponding allylamines. These findings support the hypothesis that the structural requirements for high activity of allylamine antimycotics in the broadest sense can be roughly characterized by the general formula A (Figure 1), where two lipophilic domains are linked by a spacer of appropriate length containing a polar center at a defined position.

Experimental Section

N-Methyl-2-(1-naphthyl)ethanamine (**5b**),[20] *N*-ethyl-1-naphthalenemethanamine (**5c**),[21] 4,4-dimethyl-2-pentyn-1-ol,[22] 3,3-dimethyl-1-pentyne (**12b**),[23] 3,3-dimethyl-1-hexyne (**12c**),[23] and 3-methyl-3-phenyl-1-butyne (**12d**)[24] were prepared according to published procedures. 1-Bromo-3-[(*tert*-butyldimethylsilyl)oxy]propane and 1-bromo-4-[(*tert*-butyldimethylsilyl)oxy]butane were synthesized from the appropriate 1-bromoalkanols in analogy to the reported preparation of the corresponding 1-chloro compounds.[25]

Melting points were determined on a Reichert Thermovar microscope and are not corrected. The temperature is given in Celsius units. Thin-layer chromatography was performed using silica gel F_{254} plates (Merck) visualizing with UV, iodine vapor, or potassium permanganate. Column chromatography was performed using silica gel 60 (0.040–0.063 mm, Merck), pressure 3–5 bar. ^{1}H-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 Amine Derivatives 7: *N*-Alkylation. General Procedure: *N*-(5,5-Dimethyl-3-hexynyl)-*N*-methyl-1-naphthalenemethanamine (7d). In a typical procedure, (5,5-dimethyl-3-hexynyl)methanesulfonate (**6b**; 5.8 g, 28.5 mmol) and *N*-methyl-1-naphthalenemethanamine (**5a**; 12.2 g, 71 mmol) were dissolved in dry dimethylformamide (200 mL) and heated to 100 °C for 4 h. Most part of the solvent was distilled off in vacuo and the residue partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate solution. The organic layer was washed with water, dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by chromatography on silica gel (toluene/ethyl acetate, 9/1) to give **7d** (5.61 g, 70.5%) as colorless oil: mp (HCl) 181–183 °C (2-propanol/ether).

Synthesis of Ether Derivative 10: 5,5-Dimethyl-3-hexynyl 1-Naphthylmethyl Ether (10). Sodium hydride (240 mg of 80% dispersion in mineral oil, 8 mmol) was added to a solution of 5,5-dimethyl-3-hexyn-1-ol (**9a**; 990 mg, 7.8 mmol) in dry tetrahydrofuran (15 mL) at room temperature. After the mixture was stirred for 1.5 h 1-(chloromethyl)naphthalene (8; 1.38 g, 7.8 mmol) in dry dimethylformamide (7 mL) was added and stirring continued overnight. The mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over magnesium sulfate, and evaporated in vacuo. The residue was subjected to chromatography on silica gel (toluene/hexane, 3/1) to obtain **10** (1.23 g, 59%) as colorless oil.

Starting Materials: Synthesis of Acetylenic Mesylates (6). (5,5-Dimethyl-3-hexynyl)methanesulfonate (6b). In a typical experiment, 5,5-dimethyl-3-hexyn-1-ol (**9a**; 7.8 g, 62 mmol) and triethylamine (7 g, 69 mmol) were dissolved in absolute dichloromethane (30 mL) and treated with methanesulfonyl chloride (7.8 g, 68 mmol) at 0 °C under argon atmosphere. The mixture was stirred for additional 30 min and poured onto ice/aqueous sodium hydrogen carbonate solution. The organic layer was separated, washed with brine, dried, and concentrated in vacuo to yield **6b** quantitatively: NMR δ 4.21 (t, J = 7 Hz, 2H), 3.05 (s, 3H), 2.58 (t, J = 7 Hz, 2H), 1.21 (s, 9H). Generally, the crude mesylates thus obtained were used in the following alkylation step without further purification and characterization.

5,5-Dimethyl-3-hexyn-1-ol (9a). n-Butyllithium (28.3 mL of 1.6 M solution in hexane, 45 mmol) was added to a solution of 3,3-dimethyl-1-butyne (**12a**; 3.1 g, 38 mmol) in dry tetrahydrofuran (40 mL) at −20 °C under argon. After 45 min the mixture was cooled to −50 °C and treated subsequently with hexamethylphosphoric triamide (20 mL, dried over 4-Å molecular sieves) and ethylene oxide (40 mL of 1.4 M solution in ether, 56 mmol). Stirring overnight at room temperature was followed by addition of water and extraction with ether. The organic layers were combined and dried over sodium sulfate, and the solvent was distilled off at atmospheric pressure. The residue was fractionated in vacuo to obtain **9a** (3.18 g, 67%) as colorless oil: bp 70–71 °C (20 mbar); NMR δ 3.68 (qua, J = 6.5 Hz, 2H), 2.22 (t, J = 6.5 Hz, 2H), 1.85 (t, J = 6.5 Hz, 1H), 1.2 (s, 9H).

The following compounds were prepared using the same procedure as described for **9a**, starting from the appropriately substituted alkynes **12a–d** and ethylene oxides **13a–b**.

5,5-Dimethyl-3-heptyn-1-ol (9b): bp 82–84 °C (24 mbar); NMR δ 3.67 (qua, J = 6.3 Hz, 2H), 2.44 (t, J = 6.3 Hz, 2H), 2.13 (t, J = 6.3 Hz, 1H), 0.84–1.58 (m, 5H), 1.15 (s, 6H).

5,5-Dimethyl-3-octyn-1-ol (9c): 60-MHz NMR δ 3.63 (br t, J = 7 Hz, 2H), 3.30 (br s, 1H), 2.41 (t, J = 7 Hz, 2H), 1.20–1.55 (m, 4H), 1.15 (s, 6H), 0.92 (t, J = 6 Hz, 3H).

5-Methyl-5-phenyl-3-hexyn-1-ol (9d): bp 120 °C (0.13 mbar); NMR δ 7.15–7.66 (m, 5H), 3.74 (qua, J = 6.3 Hz, 2H), 2.52 (t, J = 6.3 Hz, 2H), 1.83 (t, J = 6.3 Hz, 1H), 1.57 (s, 6H).

6,6-Dimethyl-4-heptyn-2-ol (9e): bp 80–85 °C (20 mbar) (Kugelrohr distillation); NMR δ 3.75–4.12 (m, 1H), 2.26–2.37 (dd, 2H), 2.01 (d, J = 5 Hz, 1H), 1.25 (d, J = 6.5 Hz, 3H), 1.22 (s, 9H).

6,6-Dimethyl-4-heptyn-1-ol (14a). Under an atmosphere of argon was added n-butyllithium (46.9 mL of 1.6 M solution in hexane, 75 mmol) to a solution of 3,3-dimethyl-1-butyne (**12a**; 6.16 g, 75 mmol) in hexamethylphosphoric triamide (50 mL, dried over 4-Å molecular sieves) at 0 °C. After the mixture was stirred for 30 min at about 5 °C, 1-bromo-3-[(*tert*-butyldimethylsilyl)-oxy]propane (19.9 g, 75 mmol) was added and stirring continued overnight at room temperature. The mixture was diluted with water and extracted with pentane. The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by chromatography on silica gel (toluene/hexane, 9/1) to yield 6,6-dimethyl-1-[(*tert*-butyldimethylsilyl)oxy]-4-heptyne (10.5 g, 41 mmol; 55%), which was dissolved in dry tetrahydrofuran and treated with tetrabutylammonium fluoride (82 mL of 1M solution in THF, 82 mmol). The mixture was stirred for 2 h at room temperature, poured onto brine, and extracted with ether. The organic layers were combined, dried over magnesium sulfate, and concentrated in vacuo. Pure **14a** (3.22 g, 56%; 31% overall yield) was obtained after chromatography on silica gel (toluene/ethyl acetate, 4/1) as colorless oil: NMR δ 3.78 (br qua, J = 6 Hz, 2H), 2.28 (t, J = 6.5 Hz, 2H), 1.58–1.92 (m, 3H), 1.21 (s, 9H).

7,7-Dimethyl-5-octyn-1-ol (14b) was prepared in the same way as described for **14a**, starting from **12a** and 1-bromo-4-[(*tert*-butyldimethylsilyl)oxy]butane in 63% overall yield: NMR δ 3.57–3.79 (br m, 2H), 2.19 (t, J = 6.5 Hz, 2H), 1.45–1.77 (m, 5H), 1.20 (s, 9H).

2,5,5-Trimethyl-3-hexyn-1-ol (17). (a) **1,2-Epoxy-2,5,5-trimethyl-3-hexyne (15).** To a solution of 3,3-dimethyl-1-butyne (**12a**; 7.5 g, 91 mmol) in dry tetrahydrofuran was added n-butyllithium (60 mL of 1.6 M solution in hexane, 96 mmol) at −30 °C under argon atmosphere. After 30 min the mixture was cooled to −70 °C and treated with bromo-2-propanone (12.8 g, 93 mmol). Stirring was continued for 30 min under cooling and for 16 h at room temperature. The mixture was poured onto ice/aqueous ammonium chloride solution and extracted with ether. The organic layer was washed with brine and then fractionated in vacuo to yield **15** (6.91 g, 55%) as colorless oil: bp 54–60 °C (21 mbar); NMR δ 2.65/2.89 (AB, J_{AB} = 6 Hz, 2H), 1.54 (s, 3H), 1.23 (s, 9H).

(b) **2,5,5-Trimethyl-3-hexyn-1-ol (17).** A stream of argon was passed through a flask charged with diisobutylaluminum hydride (11 mL of 1 M solution in hexane, 11 mmol) to evaporate the solvent under gentle warming and stirring for 30 min. Then the flask was evacuated and charged again with argon twice to completely remove the hexane. Dry tetrahydrofuran (12 mL) was introduced via a septum to dissolve the neat aluminum hydride and the solution cooled to −30 °C. **15** (1.38 g, 10 mmol) dissolved in dry tetrahydrofuran (3 mL) was added, and stirring continued for 30 min at −20 °C and 10 min at 0 °C. After aqueous ammonium chloride solution was carefully added at this temperature, the mixture was extracted five times with ether. The combined organic layers were dried over magnesium sulfate, and the solvent was distilled off in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate, 95/5). The first fraction (120 mg, 9%) consisted of 2,5,5-trimethyl-2,3-hexadienal [NMR δ 9.51 (s, 1H), 5.70 (qua, J = 2.7 Hz, 1H), 1.78 (d, J = 2.7 Hz, 3H), 1.12 (s, 9H)], followed by a mixed fraction [177 mg, 13%; composed of 86% of **17** and 14% of 2,5,5-trimethyl-2,3-hexadien-1-ol: NMR δ 5.31 (sex, J = 2.7 Hz, 1H), 3.91–4.08 (m, 2H), 1.71 (d, J = 2.7 Hz, 3H), 1.82 (br s, 1H), 1.04 (s, 9H)] and pure **17** (939 mg, 67%) as a colorless oil: NMR δ 3.37–3.60 (m, 2H), 2.63 (sex, J = 7 Hz, 1H), 1.75 (dd, 1H), 1.20 (s, 9H), 1.12 (d, J = 7 Hz, 3H).

5,5-Dimethyl-2-methylene-3-hexyn-1-ol (16). At −20 °C n-butyllithium (4.75 mL of 1.6 M solution in hexane, 7.6 mmol) was added to a solution of diisopropylamine (770 mg, 7.6 mmol) in hexane under an argon atmosphere. After 30 min **15** (420 mg, 3 mmol) was added and stirring continued for 1 h at 0 °C. The mixture was poured onto ice/water and extracted with ether. The combined organic layers were washed with 1 N hydrochloric acid and water, dried over magnesium sulfate, and evaporated carefully in vacuo. The residue was subjected to Kugelrohr distillation (100–105 °C (25 mbar)) to give **16** (175 mg, 42%) as colorless oil: NMR δ 5.31–5.50 (m, 2H), 4.09 (br s, 2H), 1.89 (br s, 1H), 1.25 (s, 9H).

References

(1) Mieth, H. In Vitro and In Vivo Activities of Naftifine. In *Cutaneous Antifungal Agents*; Rippon, J. W., Fromtling, R. A., Eds.; Marcel Dekker, Inc.: New York, 1993; pp 81–88.

(2) For recent reviews, see: (a) Stütz, A. Synthesis and Structure-Activity Correlations within Allylamine Antimycotics. Antifungal Drugs. *Ann. N.Y. Acad. Sci.* **1988**, *544*, 46–62. (b) Ryder, N. S. Mechanism of Action and Biochemical Selectivity of Allylamine Agents. *Ibid.* **1988**, *544*, 208–220. (c) Stütz, A. Allylamine Derivatives. In *Molecular Aspects of Chemotherapy*; Borowski, E., Shugar, D., Eds.; Pergamon Press: New York, 1990; pp 205–213.

(3) Petranyi, G.; Ryder, N. S.; Stütz, A. Allylamine Derivatives: New Class of Synthetic Antifungal Agents Inhibiting Fungal Squalene Epoxidase. *Science* **1984**, *224*, 1239–1241.

(4) Stütz, A.; Petranyi, G. Synthesis and Antifungal Activity of (E)-N-(6,6-Dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine (SF 86-327) and Related Allylamine Derivatives with Enhanced Oral Activity. *J. Med. Chem.* **1984**, *27*, 1539–1543.

(5) Stütz, A. Allylamine Derivatives - a New Class of Active Substances in Antifungal Chemotherapy. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 320–328.

(6) Stütz, A. The Discovery and Chemistry of Terbinafine. In *Cutaneous Antifungal Agents*; Rippon, J. W., Fromtling, R. A., Eds.; Marcel Dekker, Inc.: New York, 1993; pp 117–126.
(7) Mieth, H. In Vitro and In Vivo Activities of Terbinafine. In *Cutaneous Antifungal Agents*; Rippon, J. W., Fromtling, R. A., Eds.; Marcel Dekker, Inc.: New York, 1993; pp 137–149.
(8) For the therapeutic potential of terbinafine, see: (a) Goodfield, M. J. D. Short-duration Therapy with Terbinafine for Dermatophyte Onychomycosis. *Br. J. Dermatol.* **1992**, *126*, Suppl. 39, 33–35. (b) Baudraz-Rosselet, F.; Rakosi, T.; Willi, P. B.; Kenzelmann, R. Treatment of Onychomycosis with Terbinafine. *Ibid.* **1992**, *126*, Suppl. 39, 40–46. (c) Haroon, T. S.; Hussain, I.; Mahmood, A.; Nagl, A. H.; Ahmad, I.; Zahid, M. An Open Clinical Pilot Study of the Efficacy and Safety of Oral Terbinafine in Dry Non-inflammatory Tinea Capitis. *Ibid.* **1992**, *126*, Suppl. 39, 47–50. (d) Hull, P. R.; Vismer, H. F. Treatment of Cutaneous Sporotrichosis with Terbinafine. *Ibid.* **1992**, *126*, Suppl. 39, 51–55. (e) Villars, V. V.; Jones, T. C. Special Featurs of the Clinical Use of Oral Terbinafine in the Treatment of Fungal Diseases. *Ibid.* **1992**, *126*, Suppl. 39, 61–69. (f) Mieth, H.; Villars, V. Terbinafine: Clinical Efficacy and Development. In *Recent Progress in Antifungal Chemotherapy*; Yamaguchi, H., Kobayashi, G. S., Takahashi, H., Eds.; Marcel Dekker, Inc.: New York, 1991; pp 135–146. (g) Villars, V. V.; Jones, T. C. Clinical Use of Oral and Topical Terbinafine in the Treatment of Fungal Diseases. In *Cutaneous Antifungal Agents*; Rippon, J. W., Fromtling, R. A., Eds.; Marcel Dekker, Inc.: New York, 1993; pp 151–168.
(9) Nussbaumer, P.; Petranyi, G.; Stütz, A. Synthesis and Structure-Activity Relationships of Benzo[b]thienylallylamine Antimycotics. *J. Med. Chem.* **1991**, *34*, 65–73.
(10) Nussbaumer, P.; Ryder, N. S.; Stütz, A. Allylamine Antimycotics: Recent Trends in Structure-Activity Relationships and Syntheses. *Pestic. Sci.* **1991**, *31*, 437–455.
(11) Stütz, A.; Nussbaumer, P. Synthesis and Structure-Activity Relationships of Novel Benzo[b]thienylallylamine Antimycotics. *Revista Ibérica de Micolgía* **1988**, *5*, Suppl. 1, 89 (Proceedings of the Xth Congress of the International Society for Human and Animal Mycology 1988 in Barcelona).
(12) Petranyi, G.; Meingassner, J. G.; Schaude, M. Experimental Chemotherapeutic Activity of SDZ 87–469, a New Allylamine Antimycotic. *Revista Ibérica de Micología* **1988**, *5*, Suppl. 1, 88 (Proceedings of the Xth Congress of the International Society for Human and Animal Mycology 1988 in Barcelona).
(13) Stütz, A.; Nussbaumer, P. SDZ 87–469. *Drugs Future* **1989**, *14* (7), 639–642.
(14) Maeda, T.; Takase, M.; Ishibashi, A.; Yamamoto, T.; Sasaki, K.; Arika, T.; Yokoo, M.; Amemiya, K. Synthesis and Antifungal Activity of Butenafine Hydrochloride (KP-363), a New Benzylamine Antifungal Agent. *Yakugaku Zasshi* **1991**, *111* (2), 126–137.
(15) Nussbaumer, P.; Dorfstätter, G.; Grassberger, M. A.; Leitner, I.; Meingassner, J. G.; Thirring, K.; Stütz, A. Synthesis and Structure-Activity Relationships of Phenyl-Substituted Benzylamine Antimycotics: A Novel Benzylbenzylamine Antifungal Agent for Systemic Treatment. *J. Med. Chem.* **1993**, *36*, 2115–2120.
(16) Perveev, F. Ya.; Gonoboblev, L. N. Isomerization of Acetylenic α-Oxides in an Alkaline Medium. *Zh. Org. Khim.* **1969**, *5* (6), 1001–1002; *Chem. Abstr.* **1969**, *71*, 61070k.
(17) Nussbaumer, P.; Stütz, A. Regioselective Ring Opening of α-Substituted α-Alkynyl Oxiranes to 2-Substituted 3-Butyn-1-ols. *Tetrahedron Lett.* **1992**, *33* (49), 7507–7508.
(18) Ryder, N. S.; Stuetz, A.; Nussbaumer, P. Squalene Epoxidase Inhibitors: Structural Determinants for Activity and Selectivity of Allylamines and Related Compounds. In *Regulation of Isopentenoid Metabolism. ACS Symposium Series 497*; Nes, W. D., Parish, E. J., Trzaskos, J. M., Eds.; American Chemical Society: Washington, DC, 1992; pp 192–204.
(19) Stütz, A.; Nussbaumer, P.; Leitner, I. Unpublished Results.
(20) Blicke, F. F.; Monroe, E. Antispasmodics. *J. Am. Chem. Soc.* **1939**, *61*, 91–93.
(21) Chapman, N. B.; James, J. W. N-Ethyl(or -Methyl or -Phenyl)-N-2-halogenoethyl-1′(or -2′)-naphthyl-methylamines. Part I. Structure and Pharmacological Activity. *J. Chem. Soc.* **1953**, 1865–1868.
(22) Bartlett, P. D.; Rosen, L. J. An Acetylenic Analog of Neopentyl Bromide; Evidence that the Hindrance to Displacement Reactions in Neopentyl Halides is Steric in Nature. *J. Am. Chem. Soc.* **1942**, *64*, 543–546.
(23) Bernadou, F.; Mesnard, D.; Miginiac, L. Selection of Methods for the Unequivocal Synthesis of Branched Alkynes. Part 1. Alkynes with One Branched Group. *J. Chem. Res., Synop.* **1978**, 106–107.
(24) Klein, J.; Brenner, S. Metalation Reactions. VIII. Evidence for the Sequence of Reactions of Dilithiophenyl-1-propyne. *J. Org. Chem.* **1971**, *36* (9), 1319–1320.
(25) Hill, S. T.; Mokotoff, M. Chlorine Migration in the Mass Spectra of *tert*-Butyldimethylsilyl Derivatives of Chloro Alcohols. *J. Org. Chem.* **1984**, *49*, 1441–1442.