Synthesis and Structure-Activity Relationships of Naphthalene-Substituted Derivatives of the Allylamine Antimycotic Terbinafine

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Derivatives of the allylamine antimycotic terbinafine (1) with varied substitution at the naphthalene ring system have been prepared, and their antifungal activity has been evaluated. In general, the potency is strongly dependent on the bulkiness of the substituent. Only hydrogen or in some cases fluorine are tolerated as substituents at positions 2-4 and 6-8 of the naphthalene moiety, whereas 5-substituents may be larger in size (F, Cl, Br, Me). Derivatives with fluorine at positions 3, 5, and 7 or chlorine at position 5 showed enhanced activity against yeasts relative to 1. This increase in sensitivity could be intensified by simultaneous introduction of two fluoro substituents at positions 5 and 7. Compound **7q** demonstrated 8- to 16-fold improved potency against *Aspergillus fumigatus*, *Candida albicans*, and *Candida parapsilosis*.

Introduction

The allylamine derivatives, a class of synthetic antifungal agents which selectively inhibit fungal squalene epoxidase,[1] have been gaining increasing importance in the therapy of mycoses during the last few years. In addition to the topical antimycotic naftifine (Exoderil), terbinafine (1, Figure 1; Lamisil) has recently entered the market for both oral and topical treatment of mycoses.[2] The discovery of terbinafine resulted from intensive studies on structure-activity relationships (SAR) within the allylamines,[3] particularly concentrating on modification of the allylamine side chain.[4]

Subsequent SAR studies revealed that high activity was retained when the naphthalene moiety in 1 was replaced by benzo[*b*]thiophenes with the allyl side chain at position 3, 4, or 7.[5,6] Furthermore, additional substitution at position 3 of the 7-benzo[*b*]thienylallylamines led to significantly enhanced efficacy against *Candida albicans*. The 3-chloro-7-benzo[*b*]thiophene derivative, SDZ 87-469 (2, Figure 1),[7-9] was identified as the most potent allylamine antimycotic in vitro at that time. SDZ 87-469 exhibited a considerable increase in in vitro potency against yeasts, in comparison with terbinafine.

These findings stimulated further studies designed to investigate whether the 3-substituted thiophene structural element was essential for high activity against Candida species. Consequently, analogues with varied substitution of the original naphthalene ring system were prepared to mimic the physicochemical properties of the 3-halobenzo[*b*]thiophenes and their antifungal activities (especially against yeasts) evaluated. In this paper, we report on the SAR of selected naphthalene derivatives and demonstrate that high efficacy against yeasts can also be attained by appropriately substituted naphthalene allylamine derivatives.

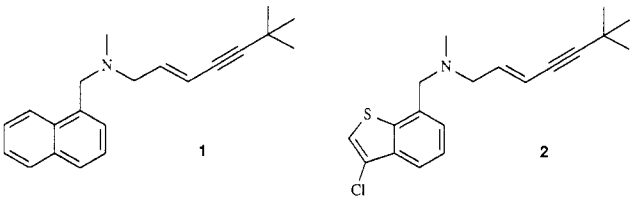
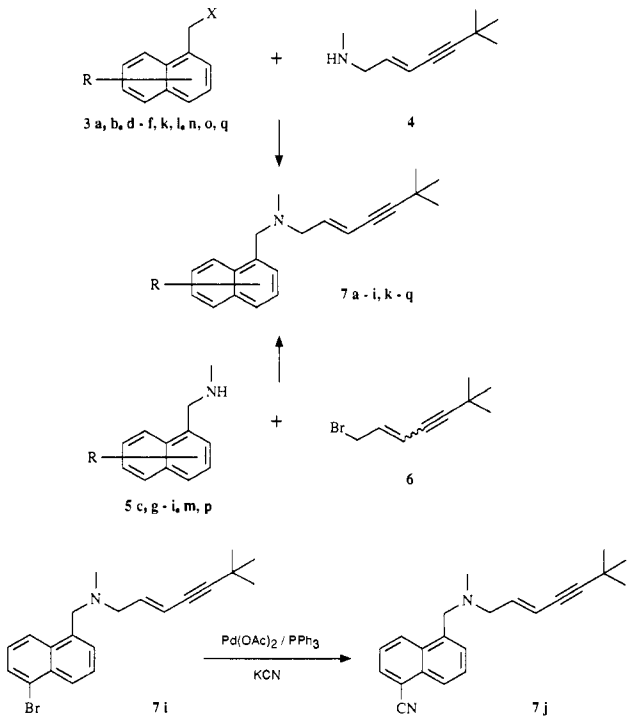


Figure 1. Terbinafine (1) and SDZ 87-469 (2).

Scheme I. Synthesis of Naphthalene-Substituted Allylamines 7



Chemistry

Several general routes for the synthesis of terbinafine-related allylamine derivatives, which contain the (*E*)-1,3-enyne structural element, have been developed.[4,10] The general strategy for the preparation of the naphthalene-substituted allylamines 7 is summarized in Scheme I. N-Alkylation was applied as the final step to produce the title compounds, either by reacting (halomethyl)naphthalenes 3 with pure (*E*)-side chain amine 4[5,11] or allylic bromide 6[3] with secondary amines 5. In the latter case the pure *E* isomers of 7 were isolated by chromatography or selective crystallization of their hydrochloride salts. The 5-cyano derivative 7j was synthesized from the 5-bromo derivative 7i by palladium catalysis.[12]

Some of the substituted naphthalene intermediates (3, 5) were novel, or only laborious multistep procedures for

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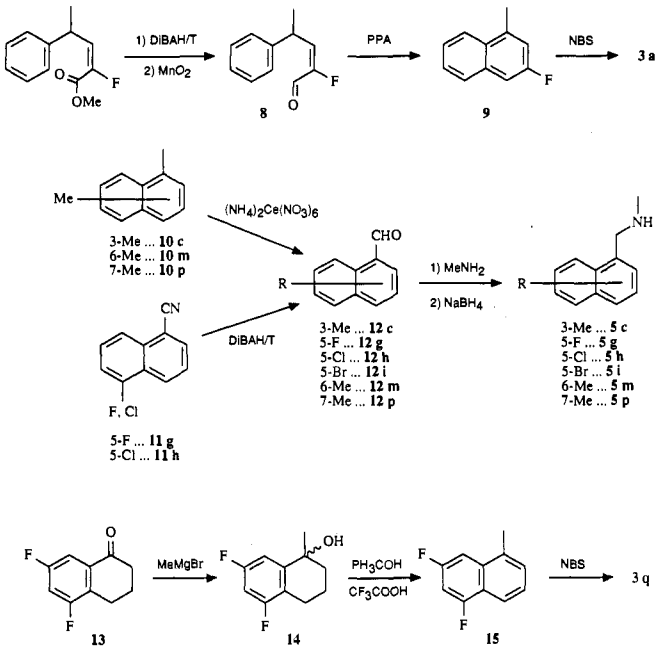
Scheme II. Key Steps in the Synthesis of Substituted Naphthalene Intermediates **3** and **5**



their preparations had been reported previously. The key steps used in the synthesis of these intermediates are shown in Scheme II. (*E*)-2-Fluoro-4-phenyl-2-pentenoic acid methyl ester[13] was converted into the aldehyde **8** by DIBAH-reduction, followed by oxidation with manganese dioxide. The carbon skeleton in **8** had already the *Z*-geometry preformed for cyclization to **9**, which was accomplished using polyphosphoric acid. The substituted naphthalenemethanamines **5** were prepared from the corresponding aldehydes **12** via Schiff base formation with methylamine and subsequent reduction with sodium borohydride in methanol. 3-, 6-, and 7-methyl-1-naphthaldehydes (**12c,m,p**) were accessible by selective oxidation of the 1-methyl groups of the corresponding dimethylnaphthalenes **10** using cerium(IV) ammonium nitrate.[14] 5-Fluoro- and 5-chloro-1-naphthaldehyde (**12g,h**) were obtained in high yields by treatment of naphthonitriles **11g,h** with DIBAH in toluene subsequently followed by acidic hydrolysis. 5,7-Difluoro-1-tetralone (**13**) was prepared starting from the commercially available 1,3-difluorobenzene following a standard procedure for the synthesis of tetralones. Friedel–Crafts acylation of 1,3-difluorobenzene with succinic acid anhydride produced the corresponding 4-oxobutanoic acid, which was converted into 4-(2,4-difluorophenyl)butanoic acid. The usually applied Clemmensen–Martin reduction[15] reproducibly yielded the corresponding 3-butenoic acid as main product. Therefore, the crude reaction product was hydrogenated over palladium to obtain the desired compound in good yield. The methyl group at position 1 was introduced by a Grignard reaction to yield **14**, which was treated with triphenylmethanol in trifluoroacetic acid[16] to achieve concomitant dehydratization and aromatization to **15** in one step. For conversions on larger scales 1 equiv of trifluoroacetic acid anhydride was usually added to bind the water generated during the reaction.

Mycology

The in vitro antifungal activity of the allylamine derivatives was investigated against isolates of *Trichophyton mentagrophytes*, *Microsporum canis*, *Sporothrix schenckii*, *Aspergillus fumigatus*, *C. 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 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 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 and Discussion

In comparison with terbinafine (**1**), enhanced activity against *C. albicans* was reported for 3-substituted 7-benzo[*b*]thienylallylamines, in particular for 3-halogen-substituted derivatives.[5] This finding raised the question of whether high efficacy against *C. albicans* was limited to 3-substituted benzo[*b*]thiophene derivatives or might be also attained by appropriately substituted naphthalene equivalents. In principle, the thiophene moiety itself (by differences in physicochemical properties, e.g., electronic, steric, and lipophilic factors), as well as the appropriate substituents (by changes in electronic density distribution and/or steric requirement), might contribute to the enhancement of biological activity.

Consequently, derivatives of **1** with substituents at positions 3–7 of the naphthalene ring system were synthesized. Substitution at positions 2 and 8 was not envisaged in this study, since this would potentially cause a conformational change of the allylamine side chain.[19] The following set of substituents was used to get an overview on the physicochemical requirements for the optimum substituent at each position: fluorine (electron-withdrawing, little influence on steric parameters), the cyano function (electron-withdrawing, increase in steric requirement), and the methyl group (weak electron-donator, increase in steric bulkiness). On the basis of the negative results obtained with the 3-, 4-, and 5-CN derivatives, further substitution by cyano at positions 6 and 7 was omitted.

The results obtained for the naphthalene-substituted terbinafine derivatives **7** are listed within Table I. The physicochemical properties of fluorine (**7a**) appeared to be optimum for this position, as 4- to 8-fold improved activities against the three Candida species (MIC = 0.2–6.25 mg/L) relative to **1** were observed. Increase in size of the substituent (3-CN, **7b**; 3-Me, **7c**) generally led to diminished activities. For **7b**, the sensitivity of dermatophytes was slightly reduced and complete loss of activity was determined against *A. fumigatus*, *S. schenckii*, and *C. albicans*. In contrast, a small increase in activity against *C. parapsilosis* was observed for **7b**. These strongly divergent findings indicated that the structural, electronic,

Table I. In Vitro Activity (MIC, mg/L) of Naphthalene-Substituted Allylamines 7

		organisms[a]						
	substit pattern	T. ment.	M. canis	A. fum.	Sp. sch.	C. a. 124	C. a. 9	C. par. 39
1	terbinafine	0.003	0.006	0.8	0.4	25	6.25	0.8
2	SDZ 87-469	0.0015	0.003	0.1	0.2	0.8	0.4	0.1
7a	3-F	0.006	0.006	0.8	0.2	6.25	0.8	0.2
7b	3-CN	0.05	0.05	>200	>200	>200	>200	0.4
7c	3-Me	0.01	0.02	3.13	0.2	50	50	1.56
7d	4-F	0.01	0.01	3.13	0.4	25	12.5	0.8
7e	4-CN	0.2	0.1	>200	>200	>200	>200	12.5
7f	4-Me	0.02	0.05	>200	0.8	50	25	3.13
7g	5-F	0.006	0.006	0.1	0.2	3.13	1.56	0.2
7h	5-Cl	0.003	0.006	0.1	0.4	1.56	0.8	0.2
7i	5-Br	0.006	0.01	1.56	0.1	3.13	1.56	0.8
7j	5-CN	0.2	0.4	>200	6.25	>200	>200	3.13
7k	5-Me	0.006	0.02	0.8	0.4	12.5	6.25	1.56
7l	6-F	0.006	0.006	6.25	0.8	25	6.25	1.56
7m	6-Me	0.01	0.05	>200	0.4	25	12.5	0.8
7n	7-F	0.006	0.006	0.4	0.4	12.5	3.13	0.4
7o	7-Cl	0.02	0.02	1.56	0.4	12.5	3.13	0.4
7p	7-Me	0.01	0.05	1.56	0.4	50	25	0.8
7q	5,7-diF	0.003	0.003	0.1	0.1	1.56	0.8	0.1

[a] 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.

and lipophilic requirements for potent growth inhibition might vary considerably for different fungi. It is also in agreement with the results of a QSAR-study within the allylamine antimycotics.[19] The differences in sensitivity between dermatophytes, *C. albicans*, and *C. parapsilosis* to terbinafine and related derivatives have been discussed previously, from the biochemical point of view.[20]

Reduction of the antifungal potencies was obtained with all 4-substituted derivatives (**7d,e,f**), in comparison with the unsubstituted terbinafine. These findings, as well as others discussed below, did not correlate with the results of the mentioned QSAR study.[19] The main reason might be that the 4-substituted compounds **7d,e,f** were not yet available for the QSAR calculations, which have to be corrected by the new data.

Derivatives with halogen substituents at position 5 of the naphthalene moiety (**7g–i**) exhibited very high in vitro activities. The results obtained with **7h** (5-Cl) and **7i** (5-Br) demonstrated that this position is rather insensitive to steric parameters. Even introduction of bromine (**7i**) caused no reduction of the antifungal potencies. The 5-fluoro (**7g**) and 5-chloro derivative (**7h**) showed a 4- to 16-fold increase in activity against *C. albicans* (MIC = 0.8–3.13 mg/L), *A. fumigatus* (MIC = 0.1 mg/L), and *C. parapsilosis* (MIC = 0.2 mg/L) relative to **1**. Thus, we have demonstrated that within the allylamine antimycotics high efficacy against yeasts is not restricted to the 3-substituted benzo[*b*]thienylallylamines but also can be attained by appropriately substituted naphthalene derivatives. The 5-methyl analogue (**5k**) was almost as active as the unsubstituted parent compound **1**, whereas introduction of the cyano group (**7j**) at position 5 caused a drastic decrease in activities. These results suggested that, at least within the 5-substituted derivatives, lipophilic factors of the substituents were much more important for increased sensitivities of the fungi (in particular of *C. albicans*) than electronic density distribution and/or steric requirement. Positions 6 and 7 of the naphthalene (**7l–p**) seemed to be very sensitive to the bulkiness of the substituents. Whereas substitution at position 6 by fluorine (**7l**) caused no change in the antifungal profile, slight improvement of activities against yeasts (MIC = 0.4–12.5 mg/L) relative to **1** was observed for the 7-fluoro derivative (**7n**). Increase in size of the substituents (6-Me, **7m**; 7-Cl, **7o**; 7-Me, **7p**) resulted in reduction of the potencies against dermatophytes and for **7m** also against *A. fumigatus*.

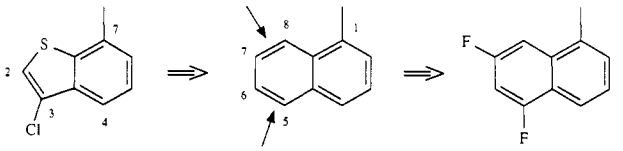


Figure 2. Consideration of the 3-chloro-7-benzo[*b*]thienyl moiety of SDZ 87–469 (**2**) as a dual-modified naphthalene equivalent.

The 3-chloro-7-benzo[*b*]thienyl moiety of SDZ 87–469 (**2**) may be considered as a dual-modified naphthalene equivalent (Figure 2). On the basis of the observation that both **7g** (5-F) and **7n** (7-F) showed increased activities against yeasts, the 5,7-difluoro derivative **7q** was synthesized and tested. **7q** exhibited a significantly improved antimycotic profile in comparison to **1** (MIC = 0.003–1.56 mg/L). The most pronounced (8- to 16-fold) enhancement in potency was determined against *C. albicans* (MIC = 0.8–1.56 mg/L), *A. fumigatus* (MIC = 0.1 mg/L), and *C. parapsilosis* (MIC = 0.1 mg/L). With regard to the spectrum and intensity of activity, **7q** (SDZ 880–540) demonstrated equivalent antifungal properties to the 3-chloro-7-benzo[*b*]thienylallylamine SDZ 87–469 (**2**) in vitro. **7q** has also been shown to be highly effective in vivo.[17] In the guinea pig trichophytosis model[18] (treatment once daily for 9 days starting on the day of inoculation) **7q** proved to be significantly superior to griseofulvin and ketoconazole by a factor of 20 and 25, respectively, after oral application: ED_{50} [mg/kg/day] = 1.9 (**7q**), 40.7 (griseofulvin), 50.8 (ketoconazole). With **7q**, 100% mycological cure was already achieved at a dose of 4 mg/kg/day. These results suggest that 5,7-difluoronaphthalene and 3-chlorobenzo[*b*]thiophene have very similar physicochemical properties which are relevant for biological efficiency and therefore constitute bioequivalents within the allylamine antimycotics.

In conclusion, high in vitro activity of allylamine antimycotics against yeasts, most notably *C. albicans*, is not restricted to 3-substituted benzo[*b*]thiophene derivatives but can also be attained by appropriately substituted naphthalene analogues, e.g., the 5-fluoro (**7g**), the 5-chloro

Table II. Physicochemical Properties of Naphthalene-Substituted Allylamines 7

no.	morphology, mp, °C	NMR ($CDCl_3$) δ	yield,[a] (%)	Anal.
7a	oil (HCl), 181–185	8.15–8.24 (m, 1H), 7.73–7.81 (m, 1H), 7.40–7.53 (m, 2H), 7.36 (dd, J = 9 + 2.5 Hz, 1H), 7.30 (dd, J = 9 + 2.5 Hz, 1H), 6.14 (dt, J = 16 + 6.5 Hz, 1H), 5.69 (dt, J = 16 + 1.5 Hz, 1H), 3.88 (s, 2H), 3.13 (dd, J = 6.5 + 1.5 Hz, 2H), 2.24 (s, 3H), 1.24 (s, 9H)	68	$C_{21}H_{24}FN$·HCl (345.89): C, H, Cl, F, N
7b	yellowish crystals, 72–73	8.30 (dd, J = 8 + 1.5 Hz, 1H), 8.16 (s, 1H), 7.90 (dd, J = 8 + 1.5 Hz, 1H), 7.56–7.70 (m, 3H), 6.13 (dt, J = 16 + 6.5 Hz, 1H), 5.70 (dt, J = 16 + 1.5 Hz, 1H), 3.90 (s, 2H), 3.15 (dd, J = 6.5 + 1.5 Hz, 2H), 2.24 (s, 3H), 1.25 (s, 9H)	57	$C_{22}H_{24}N_2$ (316.45): C, H, N
7c	oil	8.16–8.24 (m, 1H), 7.71–7.79 (m, 1H), 7.54 (br s, 1H), 7.39–7.48 (m, 2H), 7.28 (br s, 1H), 6.15 (dt, J = 16 + 6 Hz, 1H), 5.68 (dt, J = 16 + 1.5 Hz, 1H), 3.86 (s, 2H), 3.13 (dd, J = 6 + 1.5 Hz, 2H), 2.49 (s, 3H), 2.22 (s, 3H), 1.24 (s, 9H)	49[b]	$C_{22}H_{27}N$ (305.46): C, H, N
7d	oil	8.02–8.39 (m, 2H), 7.48–7.66 (m, 2H), 7.34 (dd, J = 8 + 5.5 Hz, 1H), 7.05 (dd, J = 10 + 8 Hz, 1H), 6.15 (dt, J = 16 + 6.5 Hz, 1H), 5.66 (dt, J = 16 + 1.5 Hz, 1H), 3.83 (s, 2H), 3.10 (dd, J = 6.5 + 1.5 Hz, 2H), 2.20 (s, 3H), 1.24 (s, 9H)	71	$C_{21}H_{24}FN$ (309.42): C, H, N
7e	colorless crystals, 78–80	8.12–8.18 (m, 1H), 8.03–8.10 (m, 1H), 7.87 (d, J = 7.2 Hz, 1H), 7.60–7.74 (m, 2H), 7.55 (d, J = 7.2 Hz, 1H), 6.12 (dt, J = 16 + 6.3 Hz, 1H), 5.64 (dt, J = 16 + 1.5 Hz, 1H), 3.94 (s, 2H), 3.13 (dd, J = 6.3 + 1.5 Hz, 2H), 2.24 (s, 3H), 1.24 (s, 9H)	80	$C_{22}H_{24}N_2$ (316.45): C, H, N
7f	colorless crystals, 40–45	8.26–8.34 (m, 1H), 7.97–8.06 (m, 1H), 7.48–7.57 (m, 2H), 7.31 (d, J = 7 Hz, 1H), 7.24 (d, J = 7 Hz, 1H), 6.15 (dt, J = 16 + 6.5 Hz, 1H), 5.67 (dt, J = 16 + 1.5 Hz, 1H), 3.87 (s, 2H), 3.12 (dd, J = 6.5 + 1.5 Hz, 2H), 2.69 (s, 3H), 2.22 (s, 3H), 1.24 (s, 9H)	79	$C_{22}H_{27}N$ (305.46): C, H, N
7g	colorless crystals, 62–64, (HCl) 209–210	7.95–8.20 (m, 2H), 7.30–7.60 (m, 3H), 7.16 (ddd, J = 10.5 + 8 + 1 Hz, 1H), 6.17 (dt, J = 16 + 6.3 Hz, 1H), 5.67 (dt, J = 16 + 1.3 Hz, 1H), 3.88 (s, 2H), 3.12 (dd, J = 6.3 + 1.3 Hz, 2H), 2.22 (s, 3H), 1.24 (s, 9H)	57[b]	$C_{21}H_{24}FN$·HCl (345.89): C, H, N
7h	colorless crystals, 64–68	8.18–8.28 (m, 2H), 7.58 (dd, J = 7.5 + 1 Hz, 1H), 7.37–7.56 (m, 3H), 6.13 (dt, J = 16 + 6.5 Hz, 1H), 5.67 (dt, J = 16 + 1.5 Hz, 1H), 3.88 (s, 2H), 3.12 (dd, J = 6.5 + 1.5 Hz, 2H), 2.21 (s, 3H), 1.25 (s, 9H)	51[b]	$C_{21}H_{24}ClN$ (325.88): C, H, Cl, N
7i	colorless crystals, 78–80	8.28 (dt, J = 8 + 1 Hz, 1H), 8.21 (dd, J = 7.5 + 2 Hz, 1H), 7.79 (dd, J = 7.5 + 1 Hz, 1H), 7.44–7.56 (m, 2H), 7.35 (dd, J = 7.5 + 8 Hz, 1H), 6.13 (dt, J = 16 + 7 Hz, 1H), 5.67 (dt, J = 16 + 1 Hz, 1H), 3.88 (s, 2H), 3.10 (dd, J = 7 + 1 Hz, 2H), 2.20 (s, 3H), 1.24 (s, 9H)	65[b]	$C_{21}H_{24}BrN$ (370.34): C, H, Br, N
7j	colorless crystals, 105–107	8.61 (dt, J = 8 + 1 Hz, 1H), 8.16–8.25 (m, 1H), 7.93 (dd, J = 8 + 1 Hz, 1H), 7.50–7.66 (m, 3H), 6.12 (dt, J = 16 + 7 Hz, 1H), 5.68 (dt, J = 16 + 1.5 Hz, 1H), 3.91 (s, 2H), 3.12 (dd, J = 7 + 1.5 Hz, 2H), 2.21 (s, 3H), 1.25 (s, 9H)	72	$C_{22}H_{24}N_2$ (316.45): C, H, N
7k	colorless crystals, 54–56	8.11–8.19 (m, 1H), 7.92–8.00 (m, 1H), 7.29–7.59 (m, 4H), 6.15 (dt, J = 16 + 6 Hz, 1H), 5.68 (dt, J = 16 + 1.5 Hz, 1H), 3.90 (s, 2H), 3.13 (dd, J = 6 + 1.5 Hz, 2H), 2.71 (s, 3H), 2.23 (s, 3H), 1.24 (s, 9H)	77	$C_{22}H_{27}N$ (305.46): C, H, N
7l	oil, (HCl) 216–218	(HCl) 8.20 (dd, J = 9.5 + 5 Hz, 1H), 7.99 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.54 (dd, J = 8.7 + 2.5 Hz, 1H), 7.39–7.50 (m, 1H), 6.35 (dt, J = 16 + 7 Hz, 1H), 5.87 (d, J = 16 Hz, 1H), 4.68 (br d, 2H), 3.77 (br d, 2H), 2.65 (s, 3H), 1.25 (s, 9H)	69	$C_{21}H_{24}FN$·HCl (345.89): C, H, N
7m	colorless crystals, 47–49	8.16 (d, J = 8.7 Hz, 1H), 7.63–7.72 (m, 1H), 7.60 (s, 1H), 7.31–7.40 (m, 3H), 6.15 (dt, J = 16 + 6.5 Hz, 1H), 5.67 (dt, J = 16 + 1.5 Hz, 1H), 3.86 (s, 2H), 3.10 (dd, J = 6.5 + 1.5 Hz, 2H), 2.50 (s, 3H), 2.20 (s, 3H), 1.24 (s, 9H)	52[b]	$C_{22}H_{27}N$ (305.46): C, H, N
7n	oil, (HCl) 205–208	7.65–8.10 (m, 3H), 7.10–7.55 (m, 3H), 6.17 (dt, J = 16 + 6.3 Hz, 1H), 5.67 (dt, J = 16 + 1.3 Hz, 1H), 3.83 (s, 2H), 3.12 (dd, J = 6.3 + 1.3 Hz, 2H), 2.22 (s, 3H), 1.24 (s, 9H)	73	$C_{21}H_{24}FN$·HCl (345.89): C, H, N
7o	oil	8.32 (d, J = 2 Hz, 1H), 7.64–7.88 (m, 2H), 7.33–7.52 (m, 3H), 6.19 (dt, J = 16 + 6.5 Hz, 1H), 5.68 (dt, J = 16 + 1.5 Hz, 1H), 3.83 (s, 2H), 3.12 (dd, J = 6.5 + 1.5 Hz, 2H), 2.21 (s, 3H), 1.23 (s, 9H)	63	$C_{21}H_{24}ClN$ (325.88): C, H, Cl, N
7p	oil	7.98 (br s, 1H), 7.65–7.75 (m, 2H), 7.26–7.40 (m, 3H), 6.18 (dt, J = 16.5 + 6.5 Hz, 1H), 5.69 (dt, J = 16.5 + 1.5 Hz, 1H), 3.82 (s, 2H), 3.12 (dd, J = 6.5 + 1.5 Hz, 2H), 2.53 (s, 3H), 2.21 (s, 3H), 1.24 (s, 9H)	56[b]	$C_{22}H_{27}N$ (305.46): C, H, N
7q	colorless crystals, 36–38, (HCl) 213–217	7.90–8.15 (m, 1H), 7.60–7.90 (m, 1H), 7.25–7.60 (m, 2H), 6.98 (ddd, J = 10.5 + 8.5 + 2.5 Hz, 1H), 6.16 (dt, J = 16 + 6.3 Hz, 1H), 5.66 (dt, J = 16 + 1.3 Hz, 1H), 3.81 (s, 2H), 3.11 (dd, J = 6.3 + 1.3 Hz, 2H), 2.20 (s, 3H), 1.24 (s, 9H)	79	$C_{21}H_{23}F_2N$·HCl (363.87): C, H, Cl, F, N

[a] Yields (not optimized) of isolated, analytically pure products. [b] The reactions were carried out with an *E*/*Z* mixture (≃3/1) of **6**; the yield given refers to pure *E*-isomer only.

(**7h**), and above all the 5,7-difluoro (**7q**) derivatives. With regard to the optimal substituent of each single position at the naphthalene moiety, the results can be summarized as follows: Positions 2–4 and 6–8 seem to be very sensitive to steric parameters, so that only hydrogen or in some cases fluorine (positions 3, 6, and 7) are tolerated as substituent. 5-Substituents may be larger in size (even the bromo derivative shows high activity), with fluorine and chlorine as the most preferred ones. In general, it seems that electronegative, lipophilicity-increasing sub-

stituents at positions 5 and 7 of the naphthalene ring system are required for high activity against yeasts.

Experimental Section

1-(Bromomethyl)-3-cyanonaphthalene,[21] 3-methyl-1-naphthaldehyde,[14] 1-(chloromethyl)-4-fluoronaphthalene,[22] 1-(bromomethyl)-4-cyanonaphthalene,[21] 1-(bromomethyl)-4-methylnaphthalene,[23] 5-fluoro-1-naphthonitrile,[24] 5-chloro-1-naphthonitrile,[25] 5-bromo-1-naphthaldehyde,[26] 1-(bromomethyl)-5-methylnaphthalene,[23] 1-(bromomethyl)-6-fluoronaphthalene,[27] 6-methyl-1-naphthaldehyde,[14] 1-(bromomethyl)-7-fluoronaphthalene,[27] 7-chloro-1-(chloromethyl)naphthalene,[28] and 7-methyl-1-naphthaldehyde[14] were prepared according to published procedures.

Melting points were determined on a Reichert Thermovar microscope and are not corrected. The temperature is given in °C. The purity of the compounds was determined by GLC (Siemens Sichromat 1) using quartz columns (stat. 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) visualizing with UV or iodine vapor. 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 Allylamines 7. 1. N-Alkylation. General Procedure. In a typical experiment, 1-(bromomethyl)-5,7-difluoronaphthalene (**3q**; 1.4 g, 5.4 mmol) was dissolved in dry dimethylformamide (10 mL) and added slowly to a mixture of (*E*)-*N*,6,6-trimethyl-2-hepten-4-yn-1-amine[5,11] (**4**; 0.82 g, 5.4 mmol) and potassium carbonate (900 mg, 6.5 mmol) in dry dimethylformamide at 0 °C. After the mixture was stirred 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 (hexane/ethyl acetate (95/5)) to give **7q** (1.41 g, 79%) as a colorless oil.

2. Synthesis of (*E*)-*N*-(6,6-Dimethyl-2-hepten-4-ynyl)-*N*-methyl-5-cyano-1-naphthalenemethanamine (7j). **7i** (80 mg, 0.22 mmol), potassium cyanide (21.5 mg, 0.33 mmol), palladium diacetate (7.4 mg, 0.033 mmol), triphenylphosphine (17.3 mg, 0.066 mmol), calcium hydroxide (16 mg, 0.22 mmol), and dry dimethylformamide (1 mL) were mixed, flushed with argon, and heated to 160 °C for 1 h. On cooling, the mixture was poured onto aqueous sodium bicarbonate solution and extracted with ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. Purification by column chromatography (hexane/ethyl acetate (9/1)) gave **7j** (49 mg, 72%) as colorless crystals: mp 105–107 °C.

Synthesis of Starting Materials. 1. Synthesis of (Bromomethyl)naphthalenes (3). 1-(Bromomethyl)-3-fluoronaphthalene (3a). (a) (*E*)-2-Fluoro-4-phenyl-2-penten-1-ol. Diisobutylaluminum hydride (8 mL, 9.6 mmol, 1.2 M solution in toluene) was added to (*E*)-2-fluoro-4-phenyl-2-pentenoic acid methyl ester[13] (915 mg, 4.4 mmol) in dry toluene (20 mL) under argon at −40 °C. After being stirred for 0.75 h the mixture was poured onto saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give the title compound as colorless oil (640 mg, 81%): NMR δ 7.14–7.36 (m, 5H), 5.39 (dd, *J* = 20.5 + 10 Hz, 1H), 4.24 (d, *J* = 20.5 Hz, 2H), 3.52–3.68 (m, 1H), 2.23 (br s, 1H), 1.38 (d, *J* = 7 Hz, 3H).

(b) 3-Fluoro-1-methylnaphthalene (9). Manganese dioxide (3 g, 35 mmol) was added to a solution of (*E*)-2-fluoro-4-phenyl-2-penten-1-ol (615 mg, 3.4 mmol) in dry dichloromethane (25 mL) and the mixture stirred for 16 h at room temperature. The mixture was filtered over Celite and the solvent distilled off. The crude aldehyde (**8**; 610 mg) was added to polyphosphoric acid (6 g) preheated to 65 °C. After mechanical stirring for 20 min at this temperature, the mixture was poured onto ice and extracted with pentane. The crude product obtained from the evaporated pentane layer was purified by chromatography (hexane) to give **9** as a colorless oil (303 mg, 55%): NMR δ 7.89–8.00 (m, 1H), 7.74–7.82 (m, 1H), 7.42–7.54 (m, 2H), 7.30 (dd, *J* = 10 + 3 Hz, 1H), 7.07–7.16 (m, 1H), 2.68 (s, 3H).

(c) 1-(Bromomethyl)-3-fluoronaphthalene (3a) was prepared from **9** and *N*-bromosuccinimide following the procedure described for **3q** and used in the following alkylation procedure without purification.

1-(Bromomethyl)-5,7-difluoronaphthalene (3q). (a) 4-(2,4-Difluorophenyl)-4-oxobutanoic Acid. A mixture of aluminum chloride (28 g, 0.21 mol) and 1,3-difluorobenzene (50 mL) was treated with succinic anhydride (10 g, 0.1 mol) in small portions at 40–50 °C. The mixture was stirred for 6 h at 65 °C, cooled, and poured onto ice/4 N hydrochloric acid (250 mL). After vigorous stirring the organic layer was diluted with dichloromethane, separated, and extracted with 2 N NaOH. The aqueous alkaline solution was washed with ether and acidified with hydrochloric acid to precipitate the crude product, which was washed with water and dried (17.9 g, 84%): mp 113–115 °C; NMR δ 7.98 (dt, *J* = 9 + 6.5 Hz, 1H), 6.80–7.10 (m, 2H), 5.80–6.80 (br s, 1H), 3.20–3.40 (m, 2H), 2.80 (t, *J* = 6.5 Hz, 2H).

(b) 4-(2,4-Difluorophenyl)butanoic Acid. Zinc (50 g), mercuric chloride (5 g), concentrated hydrochloric acid (2.5 mL), and water (75 mL) were mixed and stirred vigorously for 10 min. The liquid was decanted and the amalgamated zinc treated subsequently with water (30 mL), concentrated hydrochloric acid (75 mL), acetic acid (3 mL), and a solution of 4-(2,4-difluorophenyl)-4-oxobutanoic acid (16 g, 75 mmol) in toluene (40 mL). The mixture was heated to reflux for 8 h under mechanical stirring; meanwhile, additional portions of concentrated hydrochloric acid (10 mL) were added every 2 h. After cooling, the organic layer was separated, washed with water, dried over magnesium sulfate, and evaporated. The residue was dissolved in 1 N NaOH (100 mL) and hydrogenated over palladium (200 mg, 10% on charcoal) for 36 h at room temperature and atmospheric pressure. The mixture was filtered, acidified, and extracted with ether to give the crude product (12.3 g, 83%), which was used in the following cyclization procedure without purification.

Kugelrohr distillation (120 °C/0.15 mbar) of a sample of the crude product for analytical reasons yielded the title compound as colorless crystals (mp 45–47 °C): NMR δ 7.15 (dt, *J* = 8 + 7 Hz, 1H), 6.70–6.90 (m, 2H), 2.68 (t, *J* = 7 Hz, 2H), 2.38 (t, *J* = 7 Hz, 2H), 1.75–2.10 (m, 2H).

(c) 5,7-Difluoro-1-tetralone (13). Crude 4-(2,4-difluorophenyl)butanoic acid (11.5 g, 57 mmol) was cautiously mixed with thionyl chloride (50 mL) and stirred for 1 h at 55 °C. Excess thionyl chloride was distilled off and the residue dissolved in dichloroethane (130 mL). This solution was added slowly at 0 °C to a stirred suspension of aluminum chloride (11.1 g, 83 mmol) in dichloroethane (85 mL). After the addition the mixture was stirred for 1 h at room temperature followed by 0.5 h at 60 °C, poured onto ice/6 N hydrochloric acid (150 mL), and extracted with dichloromethane. The combined organic layers were washed subsequently with water, 1 N NaOH, and water, dried over magnesium sulfate, and concentrated under reduced pressure. Purification was achieved either by chromatography (hexane/ethyl acetate (4/1)) or by vacuum sublimation (100 °C/1 mbar) to yield **13** as colorless crystals (7.95 g, 76%): mp 89–91 °C; NMR δ 7.57 (ddd, *J* = 9 + 2.5 + 1.5 Hz, 1H), 7.02 (ddd, *J* = 9 + 8 + 2.5 Hz, 1H), 2.93 (t, *J* = 6.5 Hz, 2H), 2.7 (t, *J* = 6.5 Hz, 2H), 2.00–2.50 (m, 2H).

(d) 5,7-Difluoro-1-methyl-1-tetralol (14). **13** (11.6 g, 64 mmol) was dissolved in dry ether and added at room temperature to the Grignard reagent freshly prepared from magnesium (2 g, 83 mmol) and iodomethane (11.7 g, 83 mmol) in dry ether. The mixture was heated to reflux for 2.5 h and after cooling poured onto saturated aqueous ammonium chloride solution. Extraction with ether afforded crude product, which could be used in the following reaction or purified by chromatography (hexane/ethyl acetate (6/1)) to obtain **14** (11.5 g, 91%) as colorless crystals: mp 73–74 °C; NMR δ 7.12 (dd, *J* = 9 + 2.5 Hz, 1H), 6.86 (ddd, *J* = 9 + 8 + 2.5 Hz, 1H), 2.63–2.71 (m, 2H), 1.96 (s, 1H), 1.70–2.00 (m, 4H), 1.51 (s, 3H).

(e) 5,7-Difluoro-1-methylnaphthalene (15). A mixture of 14 (10 g, 50 mmol), trifluoroacetic acid anhydride (10.5 g, 50 mmol), triphenylmethanol (14.3 g, 55 mmol), and trifluoroacetic acid (60 mL) was heated to reflux for 5 h, poured onto ice/water, and extracted with dichloromethane. The combined organic layers were washed with aqueous sodium bicarbonate solution and dried over magnesium sulfate, and the solvent was distilled off under slightly reduced pressure (Caution! The product is extremely volatile). The residue was chromatographed (hexane) to yield 15 (7.6 g of a 87% solution in hexane, i.e., 73% yield): NMR δ 7.80–8.00 (m, 1H), 7.30–7.50 (m, 3H), 6.98 (ddd, J = 10.5 + 9 + 2.5 Hz, 1H), 2.60 (s, 3H).

(f) 1-(Bromomethyl)-5,7-difluoronaphthalene (3q). 15 (4.6 g of a 87% solution in hexane, i.e., 22 mmol) and N-bromosuccinimide (4 g, 22 mmol) were refluxed in tetrachloromethane after addition of a catalytic amount of dibenzoyl peroxide for 4 h. The mixture was cooled in an ice bath, filtered, and concentrated in vacuo. The crude product was crystallized from hexane or methanol (4.6 g, 80%): mp 77–78 °C; NMR δ 7.85–8.15 (m, 1H), 7.30–7.65 (m, 3H), 6.98 (ddd, J = 10.5 + 9 + 2.5 Hz, 1H), 4.80 (s, 2H).

2. Synthesis of Secondary Amines 5. *N*-Methyl-5-fluoro-1-naphthalenemethanamine (5g). Methylamine (5 mL, 40 mmol, 8.03 M solution in ethanol) and 4-Å molecular sieve were added to a solution of **12g** (1.7 g, 9.7 mmol) in dry ether (20 mL) and stirred overnight at room temperature. The mixture was filtered and concentrated in vacuo. The residual Schiff base 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 2 N hydrochloric acid, washed with ether, made alkaline using potassium carbonate, and extracted again with ether. **5g** (1.55 g, 84%) thus obtained was used for the following alkylation procedure: mp (hydrochloride) 220–222 °C from 2-propanol/ether; NMR δ 8.00–8.16 (m, 1H), 7.85–8.00 (m, 1H), 7.35–7.6 (m, 3H), 7.17 (ddd, J = 10.5 + 8 + 1 Hz, 1H), 4.20 (s, 2H), 2.56 (s, 3H), 1.5 (s, 1H).

The following compounds were prepared in the same way as described for **5g**, starting from the appropriately substituted 1-naphthaldehydes **12**.

***N*,3-Dimethyl-1-naphthalenemethanamine (5c):** NMR δ 7.93–8.20 (m, 1H), 7.67–7.87 (m, 1H), 7.27–7.58 (m, 4H), 4.17 (s, 2H), 2.56 (s, 3H), 2.50 (s, 2H), 1.47 (br s, 1H).

***N*-Methyl-5-chloro-1-naphthalenemethanamine (5h):** NMR δ 7.95–8.30 (m, 2H), 7.32–7.65 (m, 4H), 4.18 (s, 2H), 2.52 (s, 3H), 1.37 (s, 1H).

***N*-Methyl-5-bromo-1-naphthalenemethanamine (5i):** NMR δ 8.17–8.26 (m, 1H), 8.13 (dt, J = 8.5 + 1 Hz, 1H), 7.79 (dd, J = 8.5 + 1 Hz, 1H), 7.49–7.58 (m, 2H), 7.36 (dd, J = 8.5 + 7.5 Hz, 1H), 4.19 (s, 2H), 2.54 (s, 3H), 1.43 (s, 1H).

***N*,6-Dimethyl-1-naphthalenemethanamine (5m):** NMR δ 8.04 (d, J = 8.5 Hz, 1H), 7.59–7.78 (m, 2H), 7.28–7.50 (m, 3H), 4.19 (s, 2H), 2.55 (s, 3H), 2.52 (s, 3H), 1.47 (s, 1H).

***N*,7-Dimethyl-1-naphthalenemethanamine (5p):** NMR δ 7.86 (s, 1H), 7.68–7.79 (m, 2H), 7.28–7.46 (m, 3H), 4.16 (s, 2H), 2.54 (s, 6H), 1.57 (br s, 1H).

3. Synthesis of Substituted 1-Naphthaldehydes (12). 5-Fluoro-1-naphthaldehyde (12g). Diisobutylaluminum hydride (10.4 mL, 12.5 mmol, 1.2 M solution in toluene) was added to **11g** (1.95 g, 11.4 mmol) in dry toluene (40 mL) under argon at −30 °C. After being stirred for 2 h without cooling, the mixture was poured onto 3 N hydrochloric acid (75 mL), stirred vigorously for 4 h at room temperature, and extracted with toluene. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The crude product was crystallized from ether/hexane to give **12g** (1.82 g, 92%) as colorless crystals (mp 93 °C): NMR δ 10.40 (d, J = 1 Hz, 1H), 9.03 (dt, J = 8.8 + 0.7 Hz, 1H); 8.41 (dqui, J = 7.5 + 0.7 Hz, 1H), 8.05 (dd, J = 7 + 1.3 Hz, 1H), 7.71 (dd, J = 7.5 + 7 Hz, 1H), 7.63 (ddd, J = 8.8 + 7.8 + 5.9 Hz, 1H), 7.27 (ddd, J = 10.4 + 7.8 + 1 Hz, 1H).

Following this procedure 5-chloro-1-naphthaldehyde (**12h**, 91%) was prepared starting from **11h**: mp 95–96 °C from cyclohexane; NMR δ 10.44 (s, 1H), 9.18–9.36 (m, 1H), 8.55–8.74 (m, 1H), 8.09 (dd, J = 7 + 1.8 Hz, 1H), 7.49–7.93 (m, 3H).

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