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Chiral derivatives of Butenafine and Terbinafine: synthesis and antifungal activity

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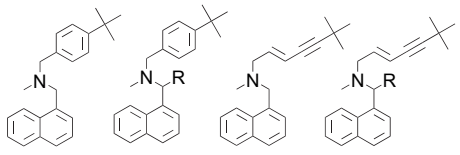
ABSTRACT

Two series of allylamines/benzylamines have been synthesised and evaluated for their antifungal activity towards *Cryptococcus neoformans*. All compounds are chiral derivatives of Butenafine and Terbinafine, having additional substituents at the carbon connected to the central nitrogen atom. In both series, the antifungal activity was strongly dependent on both the steric bulk and the electronic nature of the substituents. Compared to the parent compounds (Butenafine and Terbinafine), the activity was maintained when the hydrogen was replaced with a methyl group. Lower activity was observed for ethyl, whereas introduction of $-CH_2F$, $-CHF_2$, $-CF_3$ or –CN substituents removed all antifungal activity. Testing of (*R*)- and (*S*)-*N*-(4-*tert*-butylbenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine against *C. neoformans*, *Cryptococcus diffluens* and *Trichosporon cutaneum* revealed that most of the activity resides in the (*R*)-enantiomer. The (*R*)-enantiomer performed as well as, or better (lower MIC values) than Butenafine against each test strain, suggesting that antimycotics based on this compound might be an improvement of existing Butenafine-based formulations.

1. Introduction

Treatment of an increasing number of infections associated with immuno-compromised patients[1] is causing a marked increase in the number of fungal strains showing resistance to presently available antimycotic agents.[2–4] Among others, *Cryptococcosis*, caused by members of the *Cryptococcus neoformans* species, is a serious and potentially fatal fungal disease afflicting a large number of AIDS patients.[5–7] *C. neoformans* has also become the most common cause of meningitis in the developing world.[8,9] *Cryptococcus diffluens* is less commonly associated with disease, but has been frequently isolated from the skin of patients with atopic dermatitis.[10] *Trichosporon* species are usually found in soil and fresh water and are known to cause white piedra and hypersensitive pneumonia. Invasive infections due to *Trichosporon* are rare, but can be fatal to immuno-compromised patients, and have been observed with growing frequency.[11] Butenafine (**1a**) and Terbinafine (**2a**) (Fig. 1) are well established antimycotic agents used among others in topical treatment of dermatocytes invading skin and nails. Their mode of action is by inhibiting the enzyme squalene epoxidase in the ergosterol pathway responsible for converting squalene into squalene 2,3-epoxide, which is subsequently converted into lanosterol and ergosterol. Inhibition results in deficiency of the essential membrane component ergosterol and also squalene accumulation plays an essential role in the fungicidal action of these inhibitors.[12] It has also been indicated that the action of Butenafine (**1a**) can be partly due to permeabilisation of the fungal cell wall.[13] Structure–activity studies on Butenafine (**1a**) and Terbinafine (**2a**) analogues have been performed.[14–20] However, investigations of derivatives containing a stereocentre in the vicinity of the central nitrogen atom, are substantially less studied. The racemic derivatives *rac*-**1b**,[21,22] and *rac*-**2b**,[23] (Fig. 1) have previously been shown to have antifungal activity, while the usefulness of (*R*)-**2b** has been indicated by comparative molecular field analysis.[21,24]



Butenafine (**1a**) **1b-g** Terbinafine (**2a**) **2b-g**

Figure 1. The structures Butenafine (**1a**), Terbinafine (**2a**), and the studied compounds **1b–g** and **2b–g**, R=Me, Et, CH_2F, CHF_2, CF_3, CN.

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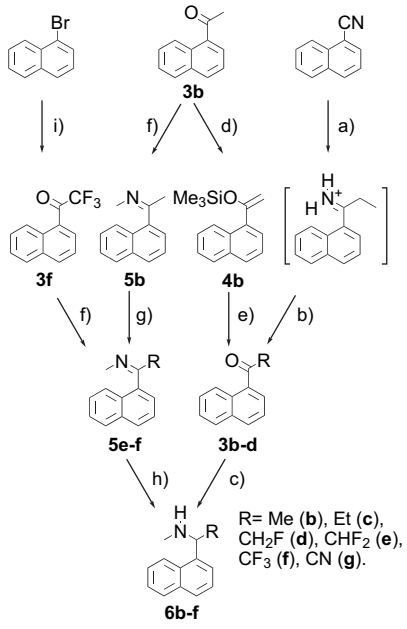
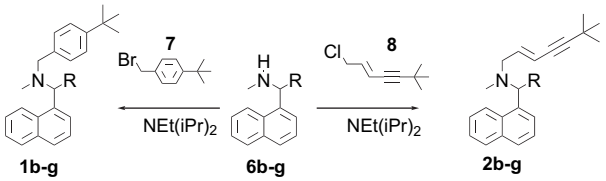
2. Results and discussion

2.1. Synthesis of potential antifungal compounds

The synthesis of the target compounds **1b–g** and **2b–g** was performed as shown in Schemes 1 and 2. Key intermediates were the secondary methyl amines **6b–f**. The amines, **6b–d**, were made from the corresponding ketones **3b–d** by reductive amination in methanol/acetic acid using $NaBH_3CN$ as reducing agent (53–76% yield). The moderate yields were mainly due to background reduction of the ketones giving the corresponding secondary alcohols.



Scheme 1. Synthetic methods for preparation of **6b–f**: (a) EtMgBr/THF; (b) H^+/H_2O;(c) NH_2Me, AcOH, $NaBH_3CN$; (d) LiHMDS, TMS–Cl; (e) F-TEDA-BF_4; (f) NH_2Me, $TiCl_4$; (g) NFSI, mol. sieve, K_2CO_3; (h) $NaBH_3CN$, AcOH; (i) ethyl trifluoroacetate; (j) $NaBH_3CN$/AcOH.



Scheme 2. Synthesis of *rac*-**1b–g** and *rac*-**2b–g**.

1-(Naphthalen-1-yl)propan-1-one (**3c**) was obtained by ethylation of 1-cyanonaphthalene followed by hydrolysis,[25] while **3d** was synthesised by fluorination of the corresponding trimethylsilyl enol ether **4b** using Selectfluor™ (F-TEDA-BF_4).[26] The preparation of α-fluoroketone **3d** was also attempted from **3c** by using F-TEDA-BF_4 in refluxing methanol.[26,27] This method gave the desired product, however two other structurally related α-fluoroketones were also formed, resulting in a troublesome purification. ^{19}F NMR spectroscopic analysis of the crude product suggested that additional ring fluorination had taken place.

The amine **6e** was most conveniently prepared by difluorination of the imine **5b** using *N*-fluorodibenzenesulfonimide (NFSI) yielding the difluoroimine **5e**. Reduction of **5e** using $NaBH_3CN$ in glacial acetic acid gave **6e** in 73% overall yield from **3b**. The use of F-TEDA-BF_4 as a fluorinating agent was also investigated in the formation of **5e**. However, this led to decomposition of the imine, yielding mainly the α,α-difluoroketone **3e**. The trifluorinated amine, **6f**, was obtained from 2,2,2-trifluoro-1-(naphthalen-1-yl)ethanone (**3f**), which in turn was synthesised from 1-bromonaphthalene and ethyl trifluoroacetate. Treatment of **3f** with $NaBH_3CN$/methylamine in methanol did not give the desired product. However, high conversion towards **5f** was obtained when adding titanium tetrachloride to a preformed mixture of **3f** and methylamine. Reduction of the imine **5f** using $NaBH_3CN$ in glacial acetic acid yielded the amine **6f** in 63% from **3f**.

To separate a possible size effect from an electronic effect in interpretation of antifungal activity data, the cyano containing compounds **1g** and **2g** (Fig. 1) were synthesised, starting with the commercial available cyano derivative **6g**. In terms of electronic properties the cyano substituent mimics a CF_2H or CF_3 group, while it occupies a smaller space than a methyl group.[28]

The potential antifungal agents **1b–g** and **2b–g** were obtained by reacting the secondary amines **6b–g** with the commercially available 1-*tert*-butyl-4-(bromomethyl)benzene (**7**) and (*E*)-1-chloro-6,6-dimethylhept-2-en-4-yne (**8**), respectively. All reactions were performed in refluxing acetonitrile using *N*,*N*-diisopropylethylamine as base, see Scheme 2.

As expected, the reaction rate depended on the electronic properties of the R-group of the amine, and on the alkylating agent. Compounds **6b–c** reacted with **7** to full conversion within 2 h, while reactions using **6f–g** and **8** took several days. Isolated yields were in the range of 60–90% for **1b–g**, while for **2b–g** 40–63% were experienced. The moderate yield of **2b–g** can in part be explained by the presence of 4% of the *Z*-isomer of **8**, which led to a structurally related product and a consequent loss in yield during purification. Moreover, in the synthesis of **1g** and **2g**, ^1H NMR spectroscopy indicated that some hydrolysis of the nitrile group had taken place.

To evaluate the effect of stereochemistry on the antifungal activity, the (*R*)- and (*S*)-enantiomers of *N*-(4-*tert*-butylbenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine, (*R*)-**1b** and (*S*)-**1b**, were synthesised from (*R*)-**6b** and (*S*)-**6b** with the same procedure as outlined in Scheme 2.

2.2. Antifungal activity

The antifungal activity of compounds **1a–g** and **2a–g** was initially tested towards *C. neoformans* by the semisolid antifungal susceptibility test (SAAS).[29] The MIC values along with the calculated pK_a's for the compounds, and the steric bulk (Charton volume) of the substituents are shown in Table 1 (**2a–g**) and Table 2 (**1a–g**).

Testing of Terbinafine (**2a**) towards *C. neoformans* gave a MIC_{50} value of 0.25 μg/mL, while compound **2b** was a less efficient inhibitor (MIC_{50}: 0.5 μg/mL). Modifying the structure with an ethyl substituent (entry 3), reduced the antifungal properties further,

Table 1
Antifungal activities (MIC) of **2a–g** towards *C. neoformans*

Entry	Comp.	R	Calcd pK_a[a]	Rel size[b]	MIC_{50} (μg/mL)	MIC_{75} (μg/mL)
1	**2a**	H	8.9	0	0.25	0.5
2	*rac*-**2b**	Me	9.2	0.52	0.5	1.0
3	*rac*-**2c**	Et	9.5	0.56	2–8[c]	16
4	*rac*-**2d**	CH_2F	7.6	0.62	>16	>16
5	*rac*-**2e**	CHF_2	5.8	0.68	>16	>16
6	*rac*-**2f**	CF_3	2.9	0.91	>16	>16
7	*rac*-**2g**	CN	5.1	0.40	>16	>16

[a] The pK_a values were estimated using the Marvin program suite.
[b] Charton volume is from tabulated values.[28]
[c] Trailing growth complicated assignment of MIC values.

Table 2
Antifungal activity (MIC) of **1a–g** towards *C. neoformans*

Entry	Comp.	R	Calcd pK_a[a]	Rel size[b]	MIC_{50} (μg/mL)	MIC_{75} (μg/mL)
1	**1a**	H	9.2	0	0.125	0.25
2	*rac*-**1b**	Me	9.5	0.52	0.125	0.25
3	(*R*)-**1b**	Me	9.5	0.52	<0.031	0.031
4	(*S*)-**1b**	Me	9.5	0.52	0.5[c]	1–8[c]
5	*rac*-**1c**	Et	9.8	0.56	0.25–4[c]	8
6	*rac*-**1d**	CH_2F	7.9	0.62	>16	>16
7	*rac*-**1e**	CHF_2	6.1	0.68	>16	>16
8	*rac*-**1f**	CF_3	3.2	0.91	>16	>16
9	*rac*-**1g**	CN	5.4	0.40	>16	>16

[a] The pK_a values were estimated using the Marvin program suite.
[b] Charton volume is from tabulated values.[28]
[c] Trailing growth complicated assignment of MIC values.

whereas the compounds containing fluorines or a cyano group (entries 4–7), had no activity towards *C. neoformans* in the concentration ranges tested.

Testing of the derivatives **1a–g** (Table 2) showed that Butenafine (**1a**) was more active than Terbinafine (**2a**). Moreover, *rac*-**1b** proved to have the same activity as **1a** (MIC_{50} 0.125 μg/mL). Synthesis and antifungal activity testing of (*S*)-**1b** and (*R*)-**1b** revealed that the activity of the racemate mainly relies on the activity of the (*R*)-enantiomer (MIC_{50}<0.031 μg/mL), and it was found to be significantly more potent than Butenafine (**1a**). Compound (*S*)-**1b** also inhibited fungal growth, and the MIC values were comparable with that of **1c**. However, trailing growth typical of a fungistatic activity, complicated the analysis of the test results in both cases, making endpoint assignments more difficult. Compounds **1d–g** had no activity towards *C. neoformans* within the concentration range tested. As observed in testing of **2d**, introduction of one fluorine atom depleted the antifungal activity of the compound.

Assuming that the antifungal activity of these compounds is mainly due to inhibition of squalene epoxidase, the results suggest that both steric and electronic effects are of importance for the antifungal properties of these compounds. A drop in activity was seen going from the methyl substituted analogues, **1b** and **2b**, to inhibitors having the more bulky ethyl substituents, **1c** and **2c**. However, the cyano group occupies a smaller volume than a methyl substituent, and the activity observed for **1g** and **2g** (MIC_{50}>16), indicates that electronic effects are of equal importance. The lack of activity in testing of compounds **1d–f** and **2d–f** is therefore likely to be due to both the unfavourable size and the electron withdrawing nature of fluoro-containing substituents. As structural information of squalene epoxidases is unavailable, the effects can currently not be explained at the molecular level.

When dealing with fungistatic agents and testing fungal species for which there exist limited published data regarding antibiotic susceptibilities, it seemed pertinent to include results from alternative test regimes. To verify the main results, the MIC values of Butenafine (**1a**), (*rac*)-**1**, (*R*)-**1b** and (*S*)-**1b** were also measured using the broth microdilution method.[30] Two other fungal strains representing two other species were included in the testing (*C. diffluens* and *T. cutaneum*) to investigate the usefulness of (*R*)-**1a** as an antifungal agent. The results are summarised in Table 3. The SAAS and the broth microdilution method were in general agreement with respect to the relative activity of the compounds tested against *C. neoformans*. However, MIC values obtained using the two methods differed in some instances by more than a single doubling dilution. When (*R*)-**1b** and Butenafine (**1a**) were tested against *C. neoformans* using the broth microdilution method, MIC_{50} values of 0.125 and 0.5 μg/mL were obtained, respectively.

Although endpoints in general were easier to assign with the broth microdilution method, trailing growth complicated testing towards *C. diffluens*. However, the results suggest that (*R*)-**1b** (MIC_{50} 0.25 μg/mL) was more active than Butenafine (**1a**). All compounds tested towards *T. cutaneum* were active. Butenafine (**1a**), (*rac*)-**1b** and (*R*)-**1b** all gave a MIC_{50} value of 0.5 μg/mL. The relatively high activity of (*S*)-**1b** towards *T. cutaneum* shows that the stereochemistry of the inhibitor is less important than was the case for *C. neoformans* and *C. diffluens*. This could indicate a wider or more flexible binding pocket for the inhibitors.

3. Conclusions

Two groups of chiral amines structurally related to Butenafine (**1a**) and Terbinafine (**2a**) have been synthesised and tested as potential antifungal agents. The activity towards *C. neoformans* depended on both the steric bulk and electronic character of the substituents. Racemic *N*-(4-*tert*-butylbenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine (**1b**) was found to have the same activity as Butenafine (**1a**) towards *C. neoformans*. Assessment of antifungal activity using the SAAS method of the (*R*)- and (*S*)-enantiomers concluded that most of the activity is due to (*R*)-**1b**, giving a MIC_{50} value of <0.031 μg/mL (MIC_{50} **1a**: 0.25 μg/mL). Compounds containing electron withdrawing groups at the stereogenic centre were not active towards *C. neoformans*. Surprisingly, the insertion of one fluorine atom was sufficient to remove all antifungal activity. This could indicate that the nitrogen basicity is important for binding of the compounds to the squalene epoxidase. Antifungal testing using the broth microdilution method confirmed that (*R*)-**1b** performed as well as or better than Butenafine (**1a**) against *C. neoformans*, *C. diffluens* and *T. cutaneum*, suggesting that antimycotics based on this compound might be an improvement of existing Butenafine-based formulations.

4. Experimental

4.1. General

1-Acetonaphthone (**3b**) was purchased from Fluka. LiHMDS, Selectfluor (F-TEDA-BF_4), 1-*tert*-butyl-4-(bromomethyl)benzene, 1-naphthonitrile, 1-bromonaphthalene, (*R*)- and (*S*)-*N*-methyl-1-(naphthalen-1-yl)ethanamine ((*R*)-**6b** and (*S*)-**6b**), *N*-fluorodibenzenesulfonimide (NFSI) and trimethylsilyl chloride were from Aldrich. 2-(Methylamino)-2-(naphthalen-1-yl)acetonitrile (**6g**) was from UkrOrgSynthesis Building Blocks (Ukraine). (*E*)-1-Chloro-6,6-dimethylhept-2-en-4-yne (*trans*-**8**, 94% pure) was from Waterstone Technology. Terbinafine·HCl was from Sigma, while Butenafine·HCl was from AK Scientific Inc. Column

Table 3
Antifungal activities (MIC) of **1a**, (*rac*)-**1b**, (*R*)-**1b** and (*S*)-**1b** towards *C. neoformans*, *C. diffluens* and *T. cutaneum* by the broth microdilution method

Comp.	*C. neoformans*		*C. diffluens*		*T. cutaneum*	
	MIC_{50} (μg/mL)	MIC_{75} (μg/mL)	MIC_{50} (μg/mL)	MIC_{75} (μg/mL)	MIC_{50} (μg/mL)	MIC_{75} (μg/mL)
1a	0.5	1.0	0.5[a]	4.0[a]	0.5	1.0
rac-**1b**	0.25	0.5	0.5[a]	2.0[a]	0.5	1.0
(*R*)-**1b**	0.125	0.25	0.25[a]	1.0[a]	0.5	1.0
(*S*)-**1b**	1.0[a]	2.0[a]	4.0[a]	>16[a]	1.0[a]	2.0[a]

[a] Trailing growth complicated assignment of MIC values.

chromatography was performed using silica gel 60A from Fluka, pore size 40–63 μm.

4.2. Analyses

NMR spectra were recorded with Bruker Avance DPX 400 operating at 400 MHz for ^{1}H, 375 MHz for ^{19}F and 100 MHz for ^{13}C. For ^{1}H and ^{13}C NMR chemical shifts are in parts per million relative to TMS, while for ^{19}F NMR the shift values are relative to hexafluorobenzene. Coupling constants are in hertz. MS (EI/70 eV) Finnigan MAT 95 XL, MS (ESI) Waters QTOF II and MS (CI): Waters Prospec Q. FTIR spectra were recorded on a Thermo Nicolet Avatar 330 infrared spectrophotometer. Optical rotations were measured using sodium D line at 589 nm on a Perkin–Elmer 243 B polarimeter. HPLC was performed using an Agilent 1100 series system equipped with a Bruker DAD detector. The enantiomeric excess of (*R*)-**1b** and (*S*)-**1b** was determined by an Astec CHIROBIOTIC V2 column, 5 μm, 4.6×250 mm (Supelco, Pennsylvania, USA) eluting with MeOH/water cont. 20 mM aq ammonium acetate, 60/40. Flow rate: 0.8 mL/min, detection at 220 nm, retention times (*S*)-**1b**: 24.2 min and (*R*)-**1b**: 28.4 min. HPLC analysis of **1b**–**g** and **2b**–**g** was performed using the same HPLC system equipped with a Symmetry C8 3.5 μm, 4.6×150 mm column. Mobile phase: water/acetonitrile 30/70 containing 0.1% diethyl amine, flow rate: 1.0 mL/min and detection at 220 nm. Retention times (min): **1b**: 37.2, **1c**: 64.6, **1d**: 34.4, **1e**: 32.3, **1f**: 37.0, **1g**: 19.0, **2b**: 23.9, **2c**: 29.5, **2d**: 17.9, **2e**: 17.0, **2f**: 27.0, **2g**: 14.5.

4.3. Microbiology

4.3.1. Fungal isolates. Cultures of two quality control strains (*C. neoformans* DSM 11959; *Trichosporon cutaneum* DSM 70698) and a strain of *Cryptococcus diffluens* isolated from drinking water were grown for 18–24 h at 35 °C on Sabouraud's dextrose agar (Oxoid, Basingstoke, UK). Well-isolated colonies were used to make the inoculum in each of the methods used for the determination of minimum inhibitory concentrations (MICs).

4.3.2. Semisolid agar antifungal susceptibility test (SAAS). The test was performed essentially as previously described.[29] Five-millilitre aliquots of semisolid heart infusion broth (Difco Laboratories, Detroit, MI) containing 0.5% agar (Bacto Agar; Difco Laboratories) at a pH of approximately 7.4 (without dextrose, buffer, or indicator) were prepared with and without an antifungal drug in 16- by 125-mm glass tubes. Analytical grade powders of Amphotericin B (Sigma–Aldrich, St. Louis, MO) and the agents to be tested were prepared as stock solutions in DMSO (Sigma–Aldrich) at 1.6 mg/mL. The concentration range tested was 0.031–16 μg/mL and was obtained by adding agent from 100-times stocks in DMSO into tubes held molten at 50 °C. A suspension equivalent to a 0.5 McFarland standard (determined photometrically) was prepared by suspending the selected yeast in sterile water. The homogeneous suspension was used for inoculation. A standard platinum loopful (~0.001 mL) of the inoculum suspension was inserted deep into each tube of medium containing a known concentration of drug, as well as a drug-free control, by a centred down–up motion to form a two dimensional inoculum. The tubes were tightly capped. A loopful of the inoculum suspension was streaked onto SAB agar to check the purity and viability of the inoculum. All cultures were incubated for 72 h at 35 °C. The growth in all tubes was compared by visual inspection with that of the drug-free control in order to determine the degree of growth inhibition. Growth was scored in the following manner: 4+, growth comparable to that of the drug-free control; 3+, growth approximately 75% that of the control; 2+, growth approximately 50% that of the control (MIC_{50}); 1+, growth 25% or less that of the control (MIC_{75}); and 0, no visible growth.

4.3.3. Broth microdilution method. Testing was performed according to the guidelines of the NCCLS document M27-A.[30] Analytical grade powders of Amphotericin B (Sigma–Aldrich, St. Louis, MO) and the agents to be tested were prepared as described above. Stock solutions were diluted with RPMI 1640 medium (with L-glutamine but without bicarbonate; Sigma–Aldrich) buffered to pH 7.0 with 0.176 M morpholinopropanesulfonic acid (MOPS, Sigma–Aldrich). The final concentration range tested was 0.031–16 μg/mL. Testing was performed in 96-well microtitration plates (Nalge Nunc International, Denmark). Yeast inocula were prepared in sterile 0.85% saline and were diluted in RPMI 1640 medium to give a final inoculum concentration in wells of 5×10^{2}–2.5×10^{3} colony forming units (CFU)/mL. The plates were lidded, and incubated at 35 °C. Endpoints were read visually at 72 h. Growth was scored as for the SAAS method.

4.4. Synthesis of intermediates

*4.4.1. 1-(Naphthalen-1-yl)propan-1-one (**3c**)*[25,31]. 1-(Naphthalen-1-yl)propan-1-one (**3c**) was prepared from 1-naphthonitrile (10.00 g, 65.28 mmol) as described by Kloetzel et al.[25] Distillation at 98–100 °C (4×10^{-3} mbar) gave 10.60 g (57.53 mmol, 88%) of a colourless oil. ^{1}H NMR spectroscopy corresponded with that reported.[31]

*4.4.2. 2-Fluoro-1-(naphthalen-1-yl)ethanone (**3d**)*[32]. Compound **3d** was synthesised from **3b** (3.43 g, 20.15 mmol) via the trimethylsilyl enol ether as described by Fuglseth et al.[26] The product was purified by silica-gel column chromatography (dichloromethane) giving an oil. A following crystallisation (EtOAc/pentane) yielded 1.10 g (5.84 mmol, 29%) of a white solid, mp 44–45 °C (lit.[33] 82–84 °C). The ^{1}H, ^{13}C and ^{19}F NMR data corresponded with that reported.[32] ^{1}H NMR ($CDCl_3$) δ: 5.60 (d, J=47.2, 2H), 7.50–7.61 (m, 2H), 7.65 (m, 1H), 7.80 (m, 1H), 7.89 (m, 1H), 8.05 (d, J=8.3, 1H), 8.71 (m, 1H).

*4.4.3. 2,2,2-Trifluoro-1-(naphthalen-1-yl)ethanone (**3f**)*[34]. 2,2,2-Trifluoro-1-(naphthalen-1-yl)ethanone was prepared as described by Konno et al. starting with 1-bromonaphthalene (4.15 g, 20.04 mmol).[34] Purification by silica-gel column chromatography (EtOAc/pentane, 1/20) yielded 2.99 g (13.34 mmol, 67%) of a coloured oil. ^{1}H, ^{13}C and ^{19}F NMR spectroscopy were in accordance with that reported.[34] ^{1}H NMR ($CDCl_3$) δ: 7.55–7.64 (m, 2H), 7.70 (m, 1H), 7.90–7.95 (m, 1H), 8.10–8.20 (m, 1H), 8.18–8.22 (m, 1H), 8.82 (m, 1H).

*4.4.4. N-Methyl-1-(naphthalen-1-yl)ethanamine (**6b**)*[35]. To a mixture of methylamine in MeOH (30 mL, 2 M) were added acetic acid (1.23 g, 20.48 mmol), 1-acetonaphthone (**3b**) (1.70 g, 9.99 mmol) and $NaBH_3CN$ (0.38 g, 6.05 mmol). The reaction was stirred at room temperature for 70 h. The pH was adjusted to <2 using concd HCl. After removal of MeOH the reaction mixture was diluted with water (10 mL) and the mixture was extracted using *tert*-butyl methyl ether (3×20 mL). The pH of the water phase was then adjusted to pH>10 using KOH. The water phase was saturated with NaCl and extracted with *tert*-butyl methyl ether (5×15 mL). The organic fraction was dried over Na_2SO_4, and the solvent was removed under reduced pressure. This gave a 1.40 g (7.76 mmol, 76%) of **6b** as colourless oil, which was sufficiently pure for subsequent step. ^{1}H NMR ($CDCl_3$) δ: 1.50 (d, J=6.6, 3H), 2.07 (br s, 1H), 2.42 (s, 3H), 4.53 (q, J=6.6, 1H), 7.55–7.43 (m, 3H), 7.61 (d, J=7.0, 1H), 7.75 (d, J=8.1, 1H), 7.88 (m, 1H), 8.18 (d, J=8.1, 1H). ^{13}C NMR ($CDCl_3$) δ: 23.0, 34.5, 55.4, 122.7, 122.8, 125.3, 125.7, 125.8, 127.3, 129.0, 131.4,

134.0, 141.1. HRMS (ESI): 186.1283 (calcd $C_{13}H_{16}N^+$, M+H$^+$, 186.1277). IR (neat, cm^{-1}): 3061, 2972, 1678, 1136, 800, 770, 691.

*4.4.5. N-Methyl-1-(naphthalen-1-yl)propaneamine (**6c**)*[35]. Compound **6c** was prepared as described for **6b** starting with **3c** (1.84 g, 9.99 mmol). This gave after silica-gel column chromatography (MeOH) 1.28 g (6.42 mmol, 64%) of a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 0.87 (t, J=7.4, 3H), 1.49 (br s, 1H), 1.88 (m, 2H), 2.34 (s, 3H), 4.34 (t, J=6.4, 1H), 7.44–7.52 (m, 3H), 7.56–7.58 (m, 1H), 7.75 (d, J=8.1, 1H), 7.86–7.88 (m, 1H), 8.24 (d, J=8.3, 1H). ^{13}C NMR ($CDCl_3$) δ: 10.8, 30.0, 34.8, 62.0, 123.2, 123.6, 125.2, 125.6, 125.7, 127.2, 128.9, 132.1, 134.0, 139.5. HRMS (ESI): 200.1437 (calcd $C_{14}H_{18}N^+$, M+H$^+$, 200.1434). IR (neat, cm^{-1}): 2962, 1590, 1449, 1377, 1082, 775.

*4.4.6. 2-Fluoro-N-methyl-1-(naphthalen-1-yl)ethanamine (**6d**).* Compound **6d** was synthesised as described for **6b** starting with **3d** (1.00 g, 5.31 mmol) giving 0.57 g (2.80 mmol, 53%) of **6d** as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.71 (br s, 1H), 2.42 (s, 3H), 4.47 (dt, J=48.9, 9.3, 1H), 4.62 (ddd, J=47.0, 9.3, 3.4, 1H), 4.81 (m, 1H), 7.47–7.58 (m, 3H), 7.73 (d, J=7.0, 1H), 7.81 (d, J=8.3, 1H), 7.89 (m, 1H), 8.22 (d, J=8.5, 1H). ^{13}C NMR ($CDCl_3$) δ: 34.5, 60.0 (d, J=19.0), 86.5 (d, J=175.0), 122.4, 124.91, 124.93, 125.57, 125.62, 126.3, 128.3, 129.1, 131.8, 134.0. ^{19}F NMR ($CDCl_3$) δ: −217.7 (dt, J=47.8, 14.2). IR (neat, cm^{-1}): 3060, 2948, 1589, 1144, 998, 800, 780, 691.

*4.4.7. 2,2-Difluoro-N-methyl-1-(naphthalen-1-yl)ethanamine (**6e**).*

*4.4.7.1. Compound **5b**.* Methylamine (0.90 g, 28.98 mmol) was dissolved in pentane (20 mL) and cooled to 0 °C. $TiCl_4$ (0.4 mL, 0.69 g, 3.64 mmol) was added dropwise over 5 min under rigorous stirring. 1-Acetonaphthone (**3b**) (0.83 g, 4.90 mmol) was then added in one portion and the reaction mixture was stirred for 1 h allowing the temperature to rise to ambient temperature. Diethyl ether (30 mL) was added and the suspension was filtered, followed by washing of the inorganic residue with additional ether (4×10 mL). The combined ether fractions were concentrated under reduced pressure giving 0.82 g (89%) of *N*-(1-(naphthalen-1-yl)ethylidene)methanamine (**5b**). The product was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ: 2.40 (q, J=1.5, 3H), 2.92 (q, J=1.5, 3H), 7.19 (dd, J=7.0, 1.3, 1H), 7.50 (m, 4H), 7.86 (m, 2H).

*4.4.7.2. Compound **5e**.* A mixture of *N*-fluorodibenzenesulfonimide (NFSI, 4.75 g, 15.06 mmol), K_2CO_3 (1.43 g, 10.35 mmol), 3 Å molecular sieve (3.00 g) and acetonitrile (30 mL) was stirred for 15 min at room temperature. Then *N*-(1-(naphthalen-1-yl)ethylidene)methanamine (**5b**) (0.64 g) in acetonitrile (20 mL) was added dropwise and the mixture was stirred at room temperature for 18 h, followed by quenching with triethylamine (2.0 mL). The resulting mixture was filtered through Celite and the Celite was washed with diethyl ether (3×15 mL). The filtrate was then washed with NaOH (0.5 M, 20 mL) and the aqueous layer was back extracted with ether (4×30 mL). The combined organic fractions were dried over Na_2SO_4, and the solvents were evaporated under reduced pressure. The oily product was used in the next step without purification. ^{1}H NMR ($CDCl_3$) δ: 3.09 (t, J=2.8, 3H), 6.32 (t, J=55.6, 1H), 7.36 (d, J=7.2, 1H), 7.54 (m, 4H), 7.93 (m, 2H).

*4.4.7.3. Compound **6e**.* Crude *N*-(2,2-difluoro-1-(naphthalen-1-yl)ethylidene)methanamine (**5e**) (0.77 g, ~3.5 mmol) was dissolved in absolute MeOH (35 mL). $NaBH_3CN$ (0.35 g, 5.40 mmol) and glacial acetic acid (0.41 g, 6.90 mmol) were added and the mixture was stirred at room temperature overnight. The solvents were evaporated under reduced pressure and the crude product was directly purified by silica-gel column chromatography (EtOAc/pentane, 1/2) yielding a colourless oil 0.56 g (2.53 mmol, 73% yield from **3c**). ^{1}H NMR ($CDCl_3$) δ: 1.75 (br s, 1H), 2.42 (s, 3H), 4.73 (td, J=10.7, 4.9, 1H), 6.00 (dt, J=56.3, 4.9, 1H), 7.55–7.50 (m, 2H), 7.57 (m, 1H), 7.77 (d, J=8.5, 1H), 7.86 (d, J=8.0, 1H), 7.91 (m, 1H), 8.24 (d, J=7.2, 1H). ^{13}C NMR ($CDCl_3$) δ: 34.5, 62.3 (t, J=21.9), 117.2 (t, J=245.8), 122.9, 125.5, 125.7, 126.4 (2C), 128.9, 129.0, 131.6, 132.3, 134.0. ^{19}F NMR ($CDCl_3$) δ: −122.6 (dd, J=279.9, 57.4), −124.2 (ddd, J=279.9, 57.4, 11.5). HRMS (ESI): 222.1093 (calcd $C_{13}H_{14}F_2N^+$, M+H$^+$, 222.1089). IR (neat, cm^{-1}): 3353, 3053, 2972, 2851, 2795.

*4.4.8. 2,2,2-Trifluoro-N-methyl-1-(naphthalen-1-yl)ethanamine (**6f**).*

*4.4.8.1. Compound **5f**.* 2,2,2-Trifluoro-1-(naphthalen-1-yl)ethanone (**3f**) (2.21 g, 9.86 mmol) and methylamine (2.60 g, 83.72 mmol) were dissolved in *n*-hexane (150 mL) and cooled to 0 °C. $TiCl_4$ (0.80 mL, 1.39 g, 7.33 mmol) in *n*-hexane (5 mL) was added dropwise under vigorous stirring. The orange suspension was slowly warmed to room temperature and stirred for 2 h. Diethyl ether (100 mL) was then added and the suspension was filtered, before the inorganic residue was washed with additional ether (3×25 mL). The solvents were removed under reduced pressure and the crude product (2.14 g, 91%) was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ: 3.15 (q, J=1.9, 3H), 7.39 (d, J=7.0, 1H), 7.56 (m, 4H), 7.93 (m, 1H), 7.98 (dd, J=8.3, 0.8, 1H).

*4.4.8.2. Compound **6f**.* Crude *N*-(2,2,2-trifluoro-1-(naphthalen-1-yl)ethylidene)methanamine (**5f**) (2.14 g, 9.02 mmol) was dissolved in dry MeOH. $NaBH_3CN$ (1.01 g, 15.58 mmol) and glacial acetic acid (0.97 g, 16.10 mmol) were added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by addition of satd $NaHCO_3$ (100 mL). A white precipitate was filtered off and the aqueous layer was extracted with diethyl ether (5×75 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvents evaporated under reduced pressure. The product was purified by silica-gel column chromatography (pentane/EtOAc, 9/1) yielding 1.49 g (6.23 mmol, 63% from **3f**) of **6f**. ^{1}H NMR ($CDCl_3$) δ: 1.75 (br s, 1H), 2.46 (s, 3H), 4.98 (q, J=7.2, 1H), 7.50–7.60 (m, 3H), 7.74 (d, J=7.1, 1H), 7.90 (m, 2H), 8.14 (d, J=8.5, 1H). ^{13}C NMR ($CDCl_3$) δ: 34.8, 61.3 (q, J=29.5), 122.7, 123.3, 125.3, 125.6, 125.8, 125.9 (q, J=281.2), 126.7, 129.0, 129.5, 130.2, 134.0. ^{19}F NMR ($CDCl_3$) δ: −76.0 (d, J=6.9). HRMS (ESI): 240.0998 (calcd $C_{13}H_{13}F_3N^+$, M+H$^+$, 240.0995). IR (neat, cm^{-1}): 3353, 3053, 2972, 2867, 2802.

4.5. Potential anti-fungicidal compounds

*4.5.1. N-(4-tert-Butylbenzyl)-N-methyl-1-(naphthalen-1-yl)ethanamine (**1b**).* *N*-Methyl-1-(naphthalen-1-yl)ethanamine (**6b**) (370 mg, 2.00 mmol), *N*,*N*-diisopropylethylamine (391 mg, 3.03 mmol), 1-(bromomethyl)-4-*tert*-butylbenzene (500 mg, 2.20 mmol) and acetonitrile (5 mL) were mixed and stirred at reflux under a N_2 atmosphere for 2 h. The solvent was removed at reduced pressure and dichloromethane (5 mL) was added. The dichloromethane phase was washed with water (5 mL) and the water phase was back extracted with dichloromethane (3×5 mL). The combined organic fractions were dried over Na_2SO_4, and concentrated in vacuum. The crude product was purified by silica-gel column chromatography (pentane/EtOAc, 9/1). This gave 540 mg (1.63 mmol, 82%) of colourless oil. ^{1}H NMR ($CDCl_3$) δ: 1.29 (9H, s), 1.55 (3H, d, J=6.7), 2.20 (3H, s), 3.39 (1H, d, J=13.5), 3.62 (1H, d, J=13.5), 4.38 (1H, q, J=6.7), 7.18 (2H, m), 7.28 (2H, m), 7.35–7.56 (3H, m), 7.65 (m, 1H), 7.74 (1H, d, J=8.5), 7.85 (1H, m), 8.45 (1H, d, J=7.8). ^{13}C NMR ($CDCl_3$) δ: 16.5, 34.4, 38.4, 58.7, 60.4, 124.5, 124.7, 125.0 (2C), 125.2, 125.3, 125.4, 127.4, 128.4 (2C), 128.6, 131.9, 31.4 (3C), 134.1, 137.1, 140.7, 149.5. HRMS (ESI): 332.2378 (calcd for $C_{24}H_{30}N^+$, M+H$^+$, 332.2373). IR (neat, cm^{-1}): 3045, 2948, 1516, 1249, 800 and 772.

*4.5.2. N-(4-tert-Butylbenzyl)-N-methyl-1-(naphthalen-1-yl)ethanamine ((R)-**1b**).* Compound (*R*)-**1b** was synthesised as described for

1b starting with (*R*)-**6b** (370 mg, 2.00 mmol) from Aldrich, giving 403 mg (1.22 mmol, 61%) of (*R*)-**1b** as a colourless oil. ^{1}H and ^{13}C NMR were identical with that of *rac*-**1b**, ee: 99.5% (CHIROBIOTIC V2), $[\alpha]_D^{25}$ −56.1 (*c* 1.0, MeOH).

*4.5.3. N-(4-tert-Butylbenzyl)-N-methyl-1-(naphthalen-1-yl)ethanamine ((S)-**1b**).* Compound (*S*)-**1b** was synthesised as described for **1b** starting with (*S*)-**6b** (370 mg, 2.00 mmol) from Aldrich, giving 467 mg (1.41 mmol, 70%) of (*R*)-**1b** as a colourless oil. ^{1}H and ^{13}C NMR spectra were identical with that of *rac*-**1b**, ee: 98.5% (CHIROBIOTIC V2), $[\alpha]_D^{25}$ 54.3 (*c* 1.0, MeOH).

*4.5.4. N-(4-tert-Butylbenzyl)-N-methyl-1-(naphthalen-1-yl)propan-1-amine (**1c**).* Compound **1c** was synthesised as described for **1b** starting with **6c** (390 mg, 1.99 mmol). Purification by silica-gel column chromatography (pentane/EtOAc, 9/1) gave 562 mg (1.63 mmol, 82%) of **1c** as a colourless oil. ^{1}H NMR ($CDCl_3$) δ: 0.78 (t, *J*=7.3, 3H), 1.29 (s, 9H), 2.10 (m, 2H), 2.22 (s, 3H), 3.37 (d, *J*=13.1, 1H), 3.60 (d, *J*=13.1, 1H), 4.12 (m, 1H), 7.16–7.18 (m, 2H), 7.24–7.29 (m, 2H), 7.43–7.51 (m, 3H), 7.58 (d, *J*=6.8, 1H), 7.74 (d, *J*=8.4, 1H), 7.83–7.84 (m, 1H), 8.41 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 11.1, 23.5, 31.4 (3C), 34.4, 38.8, 59.0, 65.9, 124.6, 124.9 (2C), 125.0, 125.2, 125.4, 125.6, 127.4, 128.4 (2C), 128.7, 132.6, 134.2, 137.2, 137.9, 149.5. HRMS (ESI): 346.2520 (calcd $C_{25}H_{32}N^+$, M+H$^+$, 346.2529). IR (neat, cm^{-1}): 2960, 2871, 2783, 1510, 1361, 1267, 776.

*4.5.5. N-(4-tert-Butylbenzyl)-2-fluoro-N-methyl-1-(naphthalen-1-yl)ethanamine (**1d**).* *N*-(4-*tert*-Butylbenzyl)-2-fluoro-*N*-methyl-1-(naphthalen-1-yl)ethanamine (**1d**) was prepared as described for **1b** starting with **6d** (200 mg, 0.98 mmol). The product was purified by silica-gel column chromatography using pentane/EtOAc (20/1) as eluent. This gave 294 mg (0.84 mmol, 86%) of an oil. ^{1}H NMR ($CDCl_3$) δ: 1.29 (s, 9H), 2.33 (d, *J*=1.9, 3H), 3.53 (d, *J*=13.4, 1H), 3.71 (d, *J*=13.4, 1H), 4.56 (ddd, *J*=21.0, 6.8, 3.4, 1H), 4.79 (ddd, *J*=47.8, 10.0, 3.4, 1H), 5.03 (ddd, *J*=47.6, 10.0, 6.8, 1H), 7.18–7.24 (m, 2H), 7.28–7.35 (m, 2H), 7.43–7.60 (m, 3H), 7.69 (d, *J*=7.0, 1H), 7.81 (d, *J*=8.2, 1H), 7.88 (m, 1H), 8.35 (d, *J*=8.3, 1H). ^{13}C NMR ($CDCl_3$) δ: 31.4 (3C), 34.4, 39.2, 59.3 (d, *J*=1.8), 65.3 (d, *J*=18.7), 84.9 (d, *J*=175.6), 123.9, 125.1 (2C), 125.3, 125.6, 125.7, 126.0, 128.3 (2C), 128.4, 128.9, 131.8, 134.2, 135.1 (d, *J*=7.8), 136.5, 149.7. ^{19}F NMR ($CDCl_3$) δ: −213.3 (dt, *J*=47.0, 20.3). HRMS (ESI): 350.2284 (calcd for $C_{24}H_{29}FN^+$, M+H$^+$, 350.2279). IR (neat, cm^{-1}): 3045, 2964, 1508, 1197, 812 and 776.

*4.5.6. N-(4-tert-Butylbenzyl)-2,2-difluoro-N-methyl-1-(naphthalen-1-yl)ethanamine (**1e**).* Compound **1e** was prepared as described for **1b** starting with **6e** (448 mg, 2.02 mmol). The reaction was run for 48 h. The product was purified by silica-gel column chromatography using pentane/EtOAc (20/1) as eluent. This gave 660 mg (1.80 mmol, 90%) of an opaque oil, which solidified at 0 °C. ^{1}H NMR ($CDCl_3$) δ: 1.29 (s, 9H), 2.39 (s, 3H), 3.66 (d, *J*=13.8, 1H), 3.81 (d, *J*=13.8, 1H), 4.69 (td, *J*=12.8, 4.4, 1H), 6.69 (dt, *J*=55.3, 4.4, 1H), 7.15 (d, *J*=8.2, 2H), 7.28 (d, *J*=8.2, 2H), 7.48 (t, *J*=7.7, 1H), 7.54 (m, 2H), 7.65 (d, *J*=7.1, 1H), 7.84 (d, *J*=8.1, 1H), 7.88 (m, 1H), 8.20 (d, *J*=8.3, 1H). ^{13}C NMR ($CDCl_3$) δ: 31.3 (3C), 34.4, 38.8, 58.8, 65.6 (t, *J*=21), 117.3 (t, *J*=247.0), 124.1, 124.8, 125.1 (2C), 125.7, 126.2, 126.5, 128.3 (2C), 128.8 (2C), 131.8, 132.5, 134.1, 136.1, 149.8. ^{19}F NMR ($CDCl_3$) δ: −120.8 (ddd, *J*=285.7, 56.2, 9.2), −123.3 (dd, *J*=285.7, 56.2). HRMS (ESI): 368.2182 (calcd $C_{24}H_{28}F_2N^+$, M+H$^+$, 368.2184). IR (neat, cm^{-1}): 3053, 2956, 2859.

*4.5.7. N-(4-tert-Butylbenzyl)-2,2,2-trifluoro-N-methyl-1-(naphthalen-1-yl)ethanamine (**1f**).* Compound **1f** was prepared as described for **1b** starting with **6f** (720 mg, 3.01 mmol) and reacting for 5 days. The product **1f** was purified by silica-gel column chromatography using pentane/EtOAc (9/1) as eluent. This gave 950 mg (2.46 mmol, 82%) of an off-white solid, mp 63–65 °C. ^{1}H NMR ($CDCl_3$) δ: 1.32 (s, 9H), 2.47 (s, 3H), 3.81 (d, *J*=13.8, 1H), 3.87 (d, *J*=13.8, 1H), 5.17 (q, *J*=8.7, 1H), 7.13(d, *J*=8.2, 2H), 7.30 (d, *J*=8.2, 2H), 7.51 (t, *J*=7.7, 1H), 7.58 (m, 2H), 7.80 (d, *J*=6.9, 1H), 7.90 (d, *J*=8.2, 1H), 7.92 (m, 1H), 8.06 (d, *J*=8.5, 1H). ^{13}C NMR ($CDCl_3$) δ: 31.4 (3C), 34.4, 38.1, 58.0, 64.5 (q, *J*=26.1), 123.8, 124.8, 125.2 (2C), 125.8, 126.3, 126.5, 127.3 (q, *J*=290.7), 128.2 (2C), 129.0, 129.3, 129.6, 132.3, 134.1, 135.9, 150.0. ^{19}F NMR ($CDCl_3$) δ: −66.3 (s). HRMS (ESI): 386.2090 (calcd $C_{24}H_{27}F_3N^+$, M+H$^+$, 386.2090). IR (neat, cm^{-1}): 3037, 2964, 2859.

*4.5.8. 2-((4-tert-Butylbenzyl)(methyl)amino)-2-(naphthalen-1-yl)acetonitrile (**1g**).* Compound **1g** was prepared as described for **1b** starting with **6g** (191 mg, 0.97 mmol) and reacting for 4 h. The product was purified by silica-gel column chromatography using pentane/EtOAc (85/15) as eluent. This gave 250 mg (0.73 mmol, 75%) of white solid, mp 75–77 °C. ^{1}H NMR ($CDCl_3$) δ: 1.32 (s, 9H), 2.27 (s, 3H), 3.64 (d, *J*=12.9, 1H), 3.82 (d, *J*=12.9, 1H), 5.52 (s, 1H), 7.25–7.29 (m, 2H), 7.34–7.38 (m, 2H), 7.44–7.52 (m, 3H), 7.82–7.87 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 31.4 (3C), 34.6, 38.2, 59.0, 59.1, 115.3, 123.9, 124.7, 125.4 (2C), 126.2, 126.5, 127.0, 128.7, 129.0, 129.1 (2C), 130.0, 130.9, 134.0, 134.2, 150.9. HRMS (ESI): 343.2171 (calcd $C_{24}H_{27}N_2^+$, M+H$^+$, 343.2169). IR (neat, cm^{-1}): 2964, 2871, 1510, 1358, 1014, 778.

*4.5.9. (E)-N,6,6-Trimethyl-N-(1-(naphthalen-8-yl)ethyl)hept-2-en-4-yn-1-amine (**2b**).* *N*-Methyl-1-(naphthalen-1-yl)ethanamine (**6b**) (370 mg, 2.00 mmol), *N*,*N*-diisopropylethylamine (390 mg, 3.02 mmol) and *E*-1-chloro-6,6-dimethylhept-2-ene-4-yne (**8**) (340 mg, 2.17 mmol) were mixed in acetonitrile (5 mL), and refluxed under a N_2 atmosphere for 2 h. The solvent was removed at reduced pressure and dichloromethane (5 mL) was added. The dichloromethane phase was washed with water (5 mL). The water phase was back extracted with dichloromethane (3×5 mL). The combined organic fractions were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography using pentane/EtOAc (85/15) as eluent. This gave 370 mg (1.21 mmol, 61%) of a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.22 (s, 9H), 1.46 (d, *J*=6.7, 3H), 2.25 (s, 3H), 2.97 (dd, *J*=14.5, 6.7, 1H), 3.16 (dd, *J*=14.5, 6.2, 1H), 4.26 (q, *J*=6.7, 1H), 5.58 (d, *J*=15.9, 1H), 6.04 (dt, *J*=15.9, 6.4, 1H), 7.37–7.52 (m, 3H), 7.56 (d, *J*=7.1, 1H), 7.73 (d, *J*=8.2, 1H), 7.83 (m, 1H), 8.38 (d, *J*=8.5, 1H). ^{13}C NMR ($CDCl_3$) δ: 17.8, 27.9, 31.0, 38.9, 56.8, 60.3, 77.3, 98.1, 111.9, 124.2, 124.4, 125.3 (2C), 125.5, 127.4, 128.7, 131.7, 134.1, 140.1, 140.7. HRMS (ESI): 306.2212 (calcd $C_{22}H_{28}N^+$, M+H$^+$, 306.2216). IR (neat, cm^{-1}): 3053, 2964, 1443, 1192, 795 and 772.

*4.5.10. (E)-N-6,6-Trimethyl-N-(1-(naphthalen-1-yl)propyl)hept-2-en-4-yn-1-amine (**2c**).* Compound **2c** was prepared as described for **2b** starting with **6c** (400 mg, 2.01 mmol). The product **1f** was purified by silica-gel column chromatography using pentane/EtOAc (9/1) as eluent. This gave 350 mg (1.10 mmol, 55%) of an oil. ^{1}H NMR ($CDCl_3$) δ: 0.67 (t, *J*=7.3, 3H), 1.22 (s, 9H), 1.89–2.09 (m, 2H), 2.26 (s, 3H), 2.94 (ddd, *J*=1.3, 6.3, 14.7, 1H), 3.14 (ddd, *J*=1.3, 5.8, 14.7, 1H), 4.02 (br m, 1H), 5.55 (dt, *J*=1.3, 15.6, 1H), 6.02 (ddd, *J*=5.8, 6.3, 15.6, 1H), 7.40–7.50 (m, 4H), 7.74 (d, *J*=8.3, 1H), 7.83–7.85 (m, 1H), 8.39–8.40 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 10.8, 24.4, 27.9, 31.0 (3C), 39.3, 57.0, 66.8 (br), 77.3, 98.1, 111.9, 124.3, 125.0, 125.2, 125.5, 125.6, 127.4, 128.7, 132.5, 134.1, 137.8, 140.2. HRMS (ESI): 320.2377 (calcd $C_{23}H_{30}N^+$, M+H$^+$, 320.2373). IR (neat, cm^{-1}): 2966, 2870, 2785, 1509, 1361, 1264, 790, 776.

*4.5.11. (E)-N-(2-Fluoro-1-(naphthalen-1-yl)ethyl)-N-6,6-trimethylhept-2-en-4-yn-1-amine (**2d**).* Compound **2d** was prepared as described for **2b** starting with **6d** (163 mg, 0.80 mmol). The product **2d** was purified by silica-gel column chromatography using pentane/EtOAc (20/1) as eluent. This gave 102 mg (0.32 mmol, 41%) of a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.22 (s, 9H), 2.37 (s, 3H), 3.06 (dd, *J*=14.7, 6.8, 1H), 3.22 (ddd, *J*=14.7, 5.9, 1.7, 1H), 4.46 (ddd, *J*=20.9, 6.6, 3.3, 1H), 4.67 (d, 48.0, 10.1, 3.3, 1H), 4.89 (ddd, *J*=47.5, 10.1, 6.6,

1H), 5.58 (dt, *J*=15.9, 1.5, 1H), 6.02 (ddd, *J*=15.9, 6.9, 5.9, 1H), 7.60–7.40 (m, 4H), 7.79 (d, *J*=8.3, 1H), 7.86 (m, 1H), 8.29 (d, *J*=8.2, 1H). ^{13}C NMR ($CDCl_3$) δ: 27.9 (3C), 31.0, 39.6, 57.3, 65.0 (d, *J*=20.5), 77.2, 85.1 (d, *J*=175.9), 98.3, 112.4, 123.6, 125.3, 125.6, 125.8, 126.1, 128.3, 128.9, 131.7, 134.1, 134.5 (d, *J*=7.5), 139.4. ^{19}F NMR ($CDCl_3$) δ: −212.6 (dt, *J*=47.6, 20.6). HRMS (ESI): 324.2127 (calcd $C_{22}H_{27}FN^+$, M+H$^+$, 324.2122). IR (neat, cm^{-1}): 3055, 2969, 1460, 1203, 804 and 774.

*4.5.12. (E)-N-(2,2-Difluoro-1-(naphthalen-1-yl)ethyl)-N-6,6-trimethylhept-2-en-4-yn-1-amine (**2e**).* Compound **2e** was prepared as described for **2b** starting with **6e** (370 mg, 1.67 mmol) and reacting for 6 days. The product **2e** was purified by silica-gel column chromatography using pentane/EtOAc, 40/1, then 9/1 as eluent. This gave 362 mg (1.06 mmol, 63%) of an opaque oil. ^{1}H NMR ($CDCl_3$) δ: 1.22 (s, 9H), 2.39 (s, 3H), 3.13 (dd, *J*=14.8, 6.8, 1H), 3.27 (dd, *J*=14.8, 5.8, 1H), 4.55 (dt, *J*=12.9, 4.3, 1H), 5.56 (dt, *J*=16.0, 1.5, 1H), 5.96 (dt, *J*=16.0, 6.4, 1H), 6.30 (dt, *J*=55.1, 4.3, 1H), 7.40–7.57 (m, 4H), 7.78–7.87 (m, 2H), 8.20 (d, *J*=8.4, 1H). ^{13}C NMR ($CDCl_3$) δ: 27.9, 31.0 (3C), 39.3, 57.0, 65.7 (t, *J*=21.2), 77.2, 98.6, 112.7, 117.0 (t, *J*=246.9), 123.9, 124.9, 125.7, 126.3, 126.8, 128.9, 129.0, 131.6, 132.5, 134.1, 139.0. ^{19}F NMR ($CDCl_3$) δ: −120.9 (dd, *J*=285.7, 55.1), −123.3 (dd, *J*=285.7, 55.1). HRMS (ESI): 342.2042 (calcd $C_{22}H_{26}F_2N^+$, M+H$^+$, 342.2028). IR (neat, cm^{-1}): 3053, 2964, 2826.

*4.5.13. (E)-N,6,6-Trimethyl-N-(2,2,2-trifluoro-1-(naphthalen-1-yl)ethyl)hept-2-en-4-yn-1-amine (**2f**).* Compound **2f** was prepared as described for **2b** starting with **6f** (430 mg, 1.80 mmol) and reacting for 10 days. The product **2f** was purified by silica-gel column chromatography using pentane/EtOAc 40/1, then 9/1 as eluent. This gave 286 mg (0.80 mmol, 44%) of an opaque oil. ^{1}H NMR ($CDCl_3$) δ: 1.22 (s, 9H), 2.43 (s, 3H), 3.28 (dd, *J*=14.8, 6.2, 1H), 3.37 (dd, *J*=14.8, 6.6, 1H), 5.00 (q, *J*=8.7, 1H), 5.90 (dt, *J*=15.9, 6.2, 1H), 5.57 (dt, *J*=15.9, *J*=1.5, 1H), 7.44–7.59 (m, 3H), 7.67 (d, *J*=7.6, 1H), 7.85 (d, *J*=8.5, 1H), 7.88 (d, *J*=9.0, 1H), 8.05 (d, *J*=8.6, 1H). ^{13}C NMR ($CDCl_3$) δ: 27.8, 30.9, 38.3, 56.4, 64.3 (q, *J*=26.8), 77.2, 98.7, 112.6, 123.4, 124.7, 125.7, 126.3, 126.5, 127.0 (q, *J*=289.6), 129.0, 129.3, 129.4, 132.2, 134.0, 139.2. ^{19}F NMR ($CDCl_3$) δ: −67.3 (d, *J*=8.0). HRMS (ESI): 360.1936 (calcd $C_{22}H_{25}F_3N^+$, M+H$^+$, 360.1934). IR (neat, cm^{-1}): 3045, 2964, 2859.

*4.5.14. (E)-N-6,6-Trimethyl-N-(1-(naphthalen-1-yl)propyl)hept-2-en-4-yn-1-amine (**2g**).* Compound **2g** was prepared as described for **2b** starting with **6g** (200 mg, 1.02 mmol) reacting for 5 days. The product **2g** was purified by silica-gel column chromatography using pentane/EtOAc (85/15) as eluent. This gave 145 mg (0.46 mmol, 45%) of a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.23 (s, 9H), 2.24 (s, 3H), 3.20 (ddd, *J*=13.9, 7.8, 1.0, 1H), 3.31 (ddd, *J*=13.9, 5.6, 1.8, 1H), 5.56 (s, 1H), 5.77 (dt, *J*=15.9, 1.3, 1H), 6.02 (ddd, *J*=15.9, 7.8, 5.6, 1H), 7.45–7.59 (m, 3H), 7.79 (d, *J*=7.3, 1H), 7.87–7.89 (m, 2H), 8.10 (d, *J*=8.0, 1H). ^{13}C NMR ($CDCl_3$) δ: 27.9, 30.9 (3C), 38.1, 56.9, 59.6, 76.7, 99.5, 114.5, 115.1, 123.8, 124.8, 126.3, 126.7, 126.9, 128.7, 128.8, 130.2, 130.8, 134.0, 137.1. HRMS (ESI): 317.2009 (calcd $C_{22}H_{25}N_2^+$, M+H$^+$, 317.2012). IR (neat, cm^{-1}): 2966, 2870, 1511, 1361, 1263, 792, 781.

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