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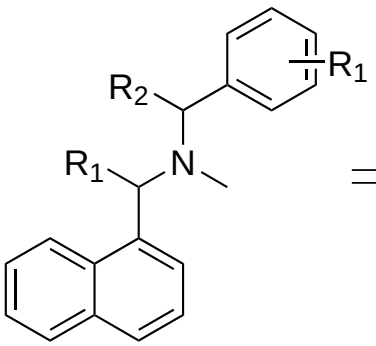
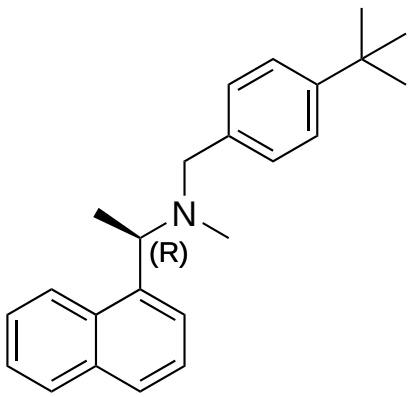
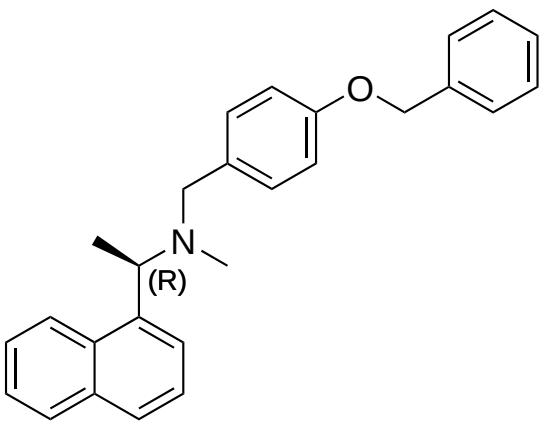


31 examples



T. mentagrophytes/
T. rubrum MIC_{50}: 0.06 μg/mL



T. mentagrophytes/
T. rubrum MIC_{50}: 0.125 μg/mL

Research highlights

- Chiral benzylamines tested for *in vitro* antifungal activity (31 examples)
- (*R*)-*N*-(4-*Tert*-butylbenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine highly active
- Benzyloxy derivative identified as a promising lead compound
- Fluorinated derivatives possessed low activity

Chiral *N*-benzyl-*N*-methyl-1-(naphthalen-1-yl)ethanamines and their *in vitro* antifungal activity against *C. neoformans*, *T.mentagrophytes* and *T. rubrum*

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Abstract

In the search for new antifungal compounds and to explore structure activity relationships, a series of 24 chiral benzyl amine type antifungals was synthesised and characterised. *In vitro* testing against the human pathogen *Cryptococcus neoformans* revealed that several derivatives had MIC_{50} values similar to that of the commercial drug Butenafine. All of these contained a bulky group in the *para* position of the benzyl fragment. Eighteen compounds were also tested for activity against the dermatophytes *Trichophyton mentagrophytes* and *Trichophyton rubrum*. Of these (*R*)-*N*-(4-*tert*-butylbenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine (MIC_{50}: 0.06 μg/mL) and a *para*-benzyloxy substituted derivative (MIC_{50}: 0.125 μg/mL) possessed high activity. Testing of derivatives with a stereocentre at the benzylic carbon, revealed that (*S*)-stereochemistry was required for potency: a MIC_{50} value of 1 μg/mL was obtained for (*S*)-1-(4-*tert*-butylphenyl)-*N*-methyl-*N*-(naphthalen-1-ylmethyl)ethanamine. Preparation of the corresponding fluoromethyl compound was achieved employing lipase B from *Candida antarctica* as catalyst in the key step. A low antifungal activity was observed for the fluorinated derivative indicating the importance of the amine basicity for the antifungal potency of these compounds.

Keywords: Antifungal agents; Squalene epoxidase; *Cryptococcus neoformans*; *Trichophyton mentagrophytes; Trichophyton rubrum;* Lipase B from *Candida antarctica;*

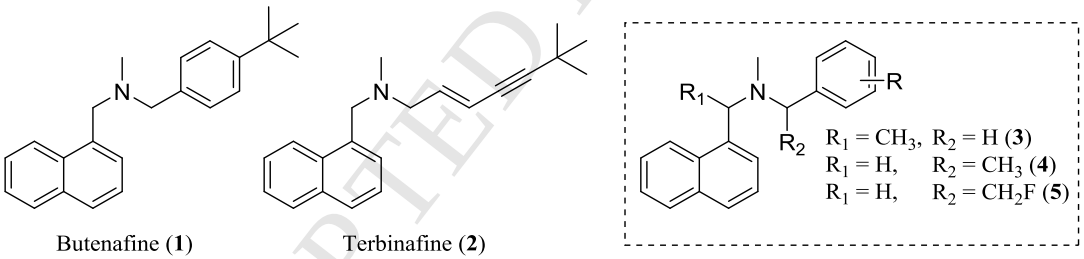
1. Introduction

Even though fungal infections are a world-wide problem, particularly for immunocompromised patients,[1, 2] the development of new therapeutic agents has stagnated. Common strategies include targeting enzymes in the ergosterol pathway, interfering with cell membrane function or maintenance, and inhibiting fungal DNA or protein synthesis.[3, 4]

The benzylamine/allylamine class of antifungals inhibit the enzyme squalene epoxidase in the ergosterol pathway. This enzyme is 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. In addition, squalene accumulation plays an essential role in the fungicidal action of these inhibitors.[5]

Butenafine[6] (**1**, Figure 1) is a well-established antimycotic agent used among others in topical treatment of dermatophyte infections of skin and nails. It is known to be very active towards *Trichophyton mentagrophytes*, *Trichophyton rubrum* and *Microsporum canis* which cause tinea infections.[6-8] Besides squalene epoxidase inhibition, it has also been suggested that the action of Butenafine (**1**) can be due to permeabilisation of the fungal cell wall.[9] The activity of some other non-chiral Butenafine derivatives towards selected fungi was reported by Nussenbaumer *et al.*[10] Also, information on the activity of a number of Naftifine and Terbinafine (**2**, Figure 1) analogues is available.[7, 10-13] Although squalene epoxidase is a validated drug target, no X-ray structures have been obtained for this enzyme. However, homology modelling, mutation data and docking studies have identified a putative binding site for Terbinafine (**2**) in the yeast squalene epoxidase.[14] Terbinafine (**2**) affinity is proposed to be due to lipophilic CH-π interactions, but also hydrogen bonding from a tyrosine residue to the central nitrogen atom is implicated.

Cryptococcus neoformans is a fungal pathogen that can cause pneumonia and meningitis in immunocompromised individuals. Fluconazole and Amphotericin B are among the agents commonly used in treatment of infections by this species. In our laboratory we recently investigated the antifungal activity of a series of chiral fluorinated and non-fluorinated Butenafine and Terbinafine derivatives.[15] While bulky and electron withdrawing groups at the stereocentre reduced the activity towards *C. neoformans*, one chiral derivative, (*R*)-**3a** (Figure 1, R = *t*-Bu), was found to be four times more potent than Butenafine (**1**). The aim of this study was to investigate how the aromatic substitution pattern in combination with stereocenters at two sites affected the antifungal activity towards *C. neoformans*, and the dermatophytes *T. mentagrophytes* and *T. rubrum*.



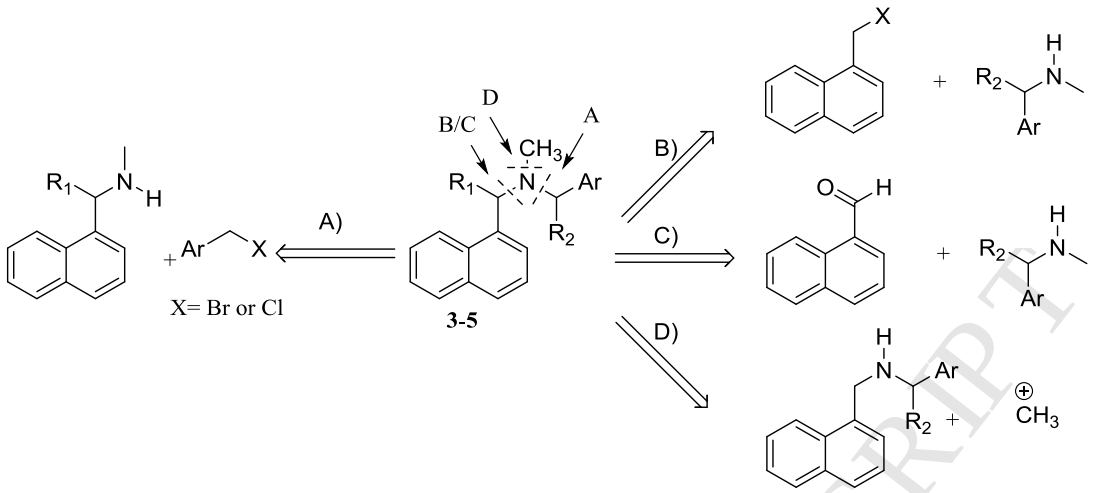
Butenafine (**1**) Terbinafine (**2**)

Figure 1. The structures Butenafine (**1**), Terbinafine (**2**), and the investigated compounds **3**-**5**.

2. Results and discussion

2.1. Synthesis

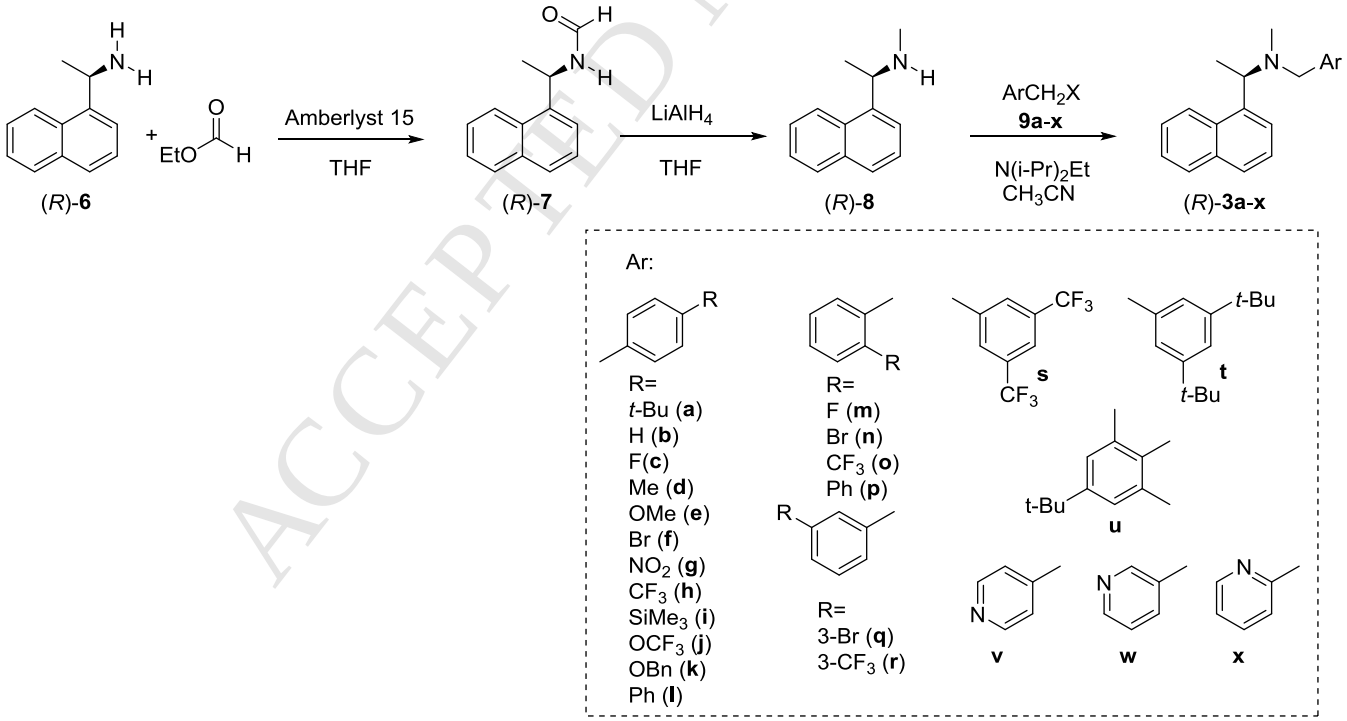
The target compounds **3**-**5** contained stereocentres either in the α–position to the naphthalene ring or at the benzylic carbon. Depending on the site of chirality the molecules can be constructed in different ways,[16] some of which are shown as disconnections A-D in Scheme 1. Paths A or B are preferred due to more divergent routes, and since nucleophilic substitution chemistry can be performed under mild conditions, avoiding any racemisation issues.[15]



Scheme 1. Tactics for preparing the antifungal compounds **3**-**5**.

2.1.1. Chirality α to the naphthalene

Utilising disconnection A in Scheme 1, a series of *N*-benzyl derivatives was targeted (Scheme 2). The secondary methyl amine **8** was prepared by formylation of (*R*)-1-(naphthalen-1-yl)ethanamine ((*R*)-**6**) with ethyl formate to give (*R*)-**7**, followed by reduction. In our hands the best yield and purity was obtained when using 3.5 equivalents of $LiAlH_4$. Purification was done by crystallisation as its hydrochloride salt. Alkylation of the secondary amine (*R*)-**8** was performed with the benzyl halides **9a**-**x** using Hünig's base (*N*,*N*-diisopropylethylamine) in acetonitrile.



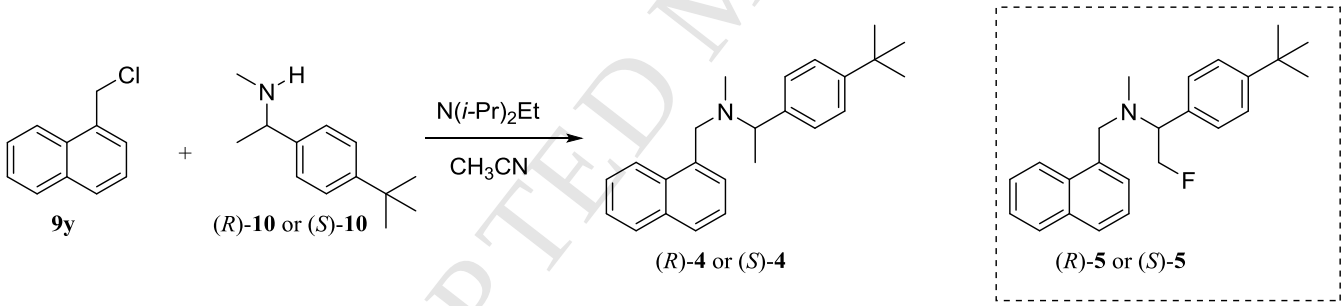
Scheme 2. Synthesis of the potential antifungal compounds **3a**-**x**.

The benzyl bromides or chlorides **9** were mainly purchased. However, the benzyloxy substituted **9k** was prepared by bromination of the corresponding benzylic alcohol using *N*-bromosuccinimide (NBS), and the silyl containing compound **9i** was made by a radical type bromination of trimethyl(*p*-tolyl)silane. Due to local restrictions on use of carbon tetrachloride and AIBN, the latter transformation was performed using trifluoromethyl toluene as solvent and 1,1'-azobis(cyclohexancarbamide) (ABCN) as radical initiator.

Whereas alkylation using benzyl bromides proceeded readily at room temperature, reactions with benzyl chlorides required more time or refluxing. Free basing of (*R*)-**8**·HCl was initially done prior to alkylation. However, the process could be simplified by using the hydrochloride salt of **8** directly in the reaction, provided sufficient base was added. Purification of the products was done by silica-gel column chromatography, or they were precipitated as HCl salts. Preparative HPLC was used for the purification of compound **3i**. The yield ranged from 29-92%. The purity of the synthesised materials was evaluated by HPLC, typically 95 to >99%, while the enantiomeric excess was evaluated in the case of **3a** showing >99% ee. Thus, no racemisation occurred under these conditions.

2.1.2. Chirality at the benzylic carbon

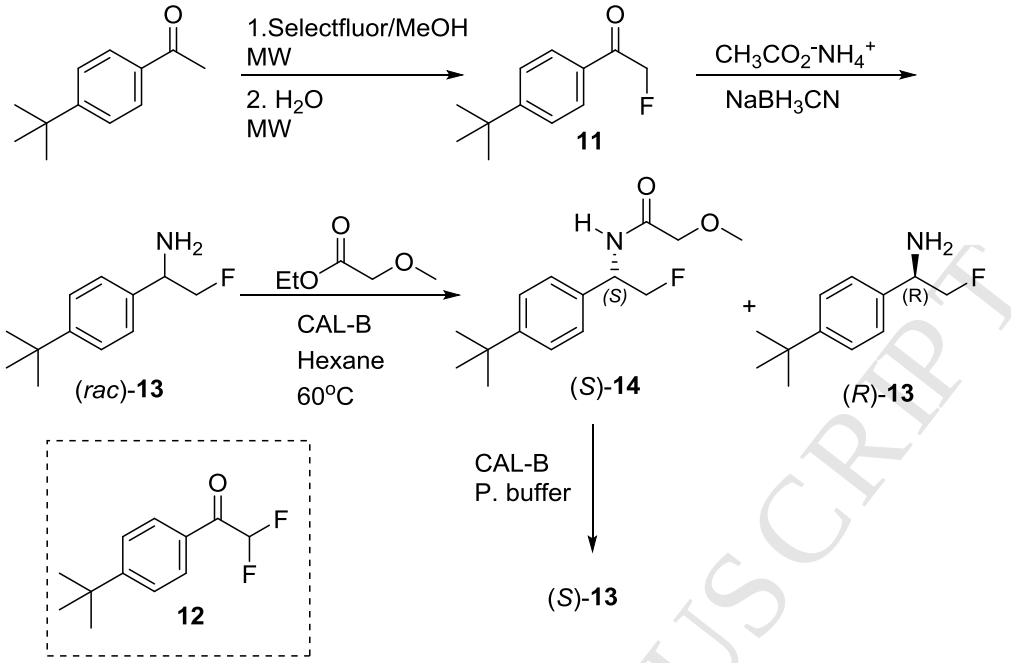
To investigate how a benzylic defined stereocenter, and the amine basicity affected the antifungal activity, two more pairs of enantiomers were targeted, namely **4** and **5**. The enantiomers of **4** were prepared starting with the secondary amine **10** and 1-(chloromethyl)naphthalene (**9y**), see Scheme 3.



Scheme 3. Synthesis of the potential antifungal compounds (*R*)- and (*S*)-**4** and the structure of the fluoro containing derivative **5**.

The reactions were performed at 50 °C, and the crude products were subjected to acid-base extraction, silica-gel column chromatography, and finally isolated as their HCl-salt in 55-57% yield. The ee of the products were measured using a chiral Phenomenex Lux Cellulose-1 HPLC column, and were >99% for both enantiomers.

Preparation of the fluorinated analogue **5** could not benefit from commercial available building blocks. Therefore, the primary amines (*S*)- and (*R*)-**13** were chosen as a starting point, see Scheme 4. The racemic amine **13** was made in two steps from 1-(4-*tert*-butylphenyl)ethanone. A microwave aided fluorination using Selectfluor,[17] gave the α-fluoroketone **11**. Although the method is very easy in terms of handling, a mediocre 64% yield was obtained due to over fluorination giving the corresponding α,α-difluoroketone **12**.

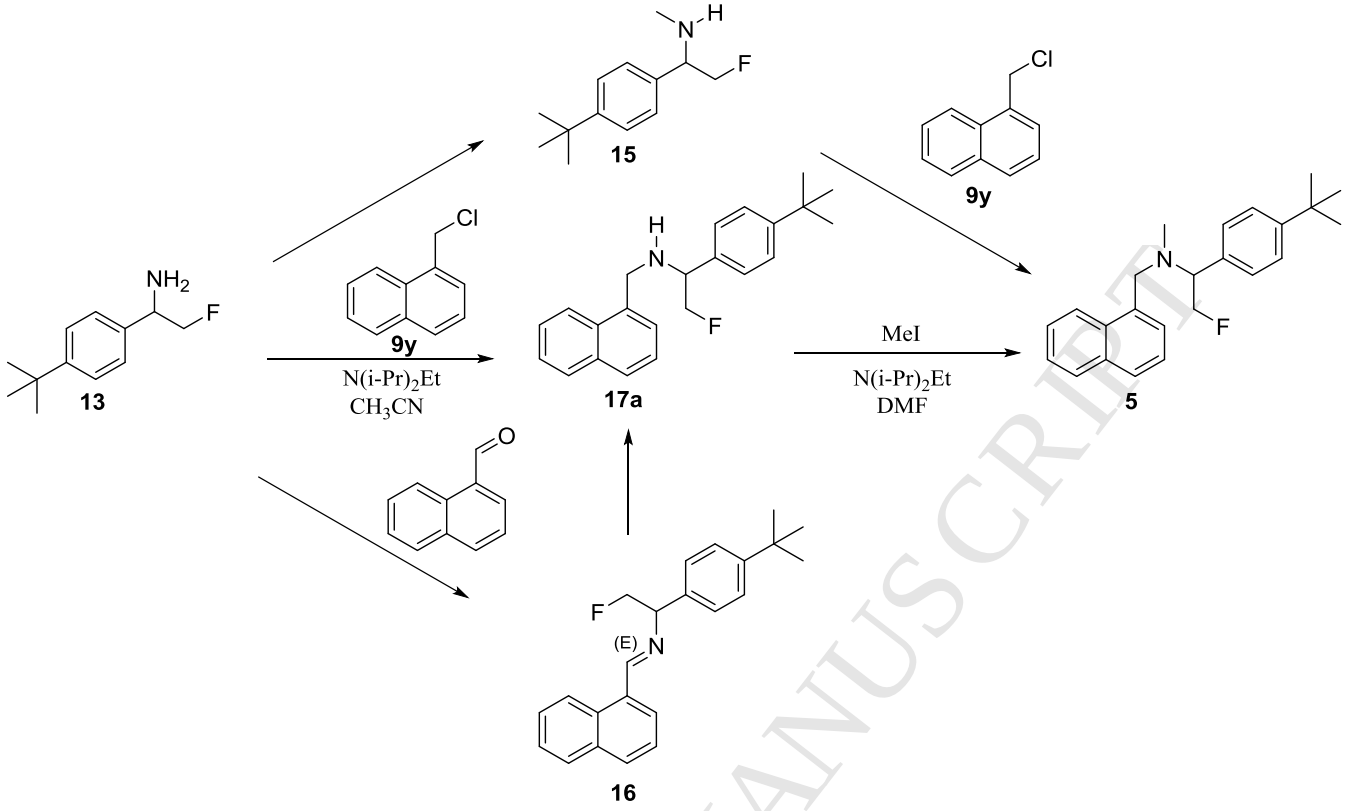


Scheme 4. Synthesis of (*R*)- and (*S*)-**13** via a lipase catalysed kinetic resolution and lipase catalysed amide hydrolysis.

Synthesis of the amine **13** from the fluoroketone **11** was achieved using the reductive amination procedure as described by Borch *et al.*[18] Following the reaction, the product amine could be isolated as its HCl salt, which is convenient in terms of storage, as the free base of **13** was discoloured within days at 4 °C. The (*R*)- and (*S*)-enantiomers of **13** were resolved by a kinetic resolution using Lipase B from *Candida antarctica* (CALB-Novozyme 435) as catalyst. Ethyl 2-methoxyacetate was used as acyl donor and hexane as solvent at 60 °C. The resolution, which proceeded with excellent E-value (>200), was completed in 20 h and gave 99% ee of both the amine (*R*)-**13** and the 2-methoxyacetamide product (*S*)-**14**.

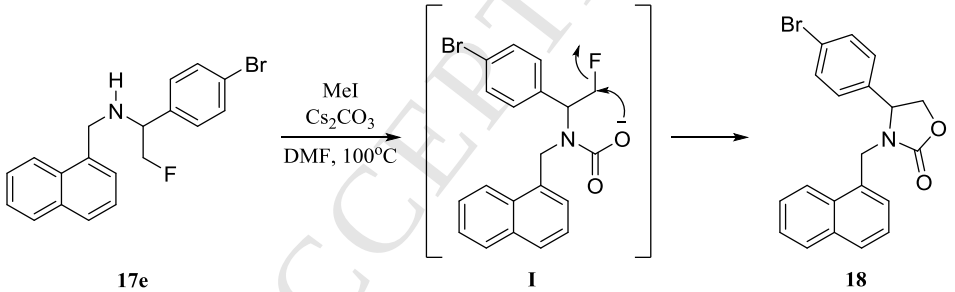
Whereas the amine **13** was somewhat unstable at higher temperatures, the amide **14** was surprisingly inert. As hydrolysis using several different previously reported approaches was found to be inefficient,[19-21] we attempted lipase catalysed amide hydrolysis.[22] Using CAL-B-Novozyme 435 as catalyst at 60°C, full conversion was obtained in 48 h, allowing for isolation of the fluoroamine (*S*)-**13** in 77% yield.

The transformations of the amines (*R*)-**13** and (*S*)-**13** to the target products (*R*)-**5** and (*S*)-**5** were especially challenging, and the routes shown in Scheme 5 were attempted. We concluded the most efficient method to be a direct alkylation of the primary amine **13** with 1-(chloromethyl)naphthalene (**9y**). In this transformation dialkylation did not occur, possibly due to the lowered nucleophilicity caused by the fluoro atom, and the steric bulk of the product. This allowed for the isolation of the secondary amines (*S*)- and (*R*)-**17a** in 58 and 66% yield, respectively. Methylation of **17a** with methyl iodide also proceeded with difficulties and a low rate in THF and *tert*-butyl methyl ether was seen. By performing the substitution in *N*,*N*-dimethylformamide at 100 °C, and under somewhat dilute conditions, (*S*)-**5** was obtained in 79% yield (98% ee), while (*R*)-**5** was isolated in 65% yield (97% ee). Apparently, the reaction took place with 1-2% racemisation.



Scheme 5. Strategies undertaken in conversion of **13** to compounds **17a** and **5**.

Interestingly, by performing methylation on the model compound **17e** using caesium carbonate as base at high temperature, the cyclic carbamate **18** was formed as the main product, Scheme 6. Possibly, the amine **17e** reacts with the carbonate base to form the carbamate intermediate **I**, before expelling fluorine to form the cyclic carbamate **18**.



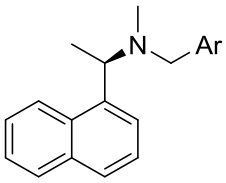
Scheme 6. The formation of the cyclic carbamate **18** from the secondary amine **17e** by Cs_2CO_3.

2.2. *In vitro* antifungal activity

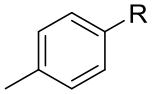
2.2.1. Activity towards *C. neoformans*

First the antifungal properties of the *para* substituted derivatives **3a-l** were determined using the broth microdilution method. Substituents were varied to identify any differences in activity springing from size, polarisability and hydrophobicity of the groups. The results given as MIC values are shown Table 1. Amphotericin B and Butenafine (**1**) were used as positive controls.

Table 1. Antifungal activity (MIC) of Amphotericin B, Butenafine (**1**) and **3a-l** against *C. neoformans.*



3a-l



Ar:

R=
t-Bu (**a**), H (**b**), F(**c**), Me (**d**), OMe (**e**), Br (**f**), NO_2 (**g**) CF_3 (**h**), $SiMe_3$ (**i**), OCF_3 (**j**), OBn (**k**), Ph (**l**).

Entry	**Comp.**	**R**	**MIC_{50} (μg/mL)**	**MIC_{80} (μg/mL)**
1	Amphotericin B		0.25	<0.5
2	Butenafine (**1**)	*t*-Bu	0.5	1.0
3	*(R)*-**3a**	*t*-Bu	[a]	0.25
4	*(S)*-**3a**	*t*-Bu	1	2
5	*(R)*-**3b**	H	16	>16
6	*(R)*-**3c**	F	4	8
7	*(R)*-**3d**	Me	0.5	1
8	*(R)*-**3e**	OMe	2	4
9	*(R)*-**3f**	Br	0.5	1
10	*(R)*-**3g**	NO_2	2	>16
11	*(R)*-**3h**	CF_3	0.5	1
12	*(R)*-**3i**	$Si(CH_3)_3$	0.5	1
13	*(R)*-**3j**	OCF_3	2	4
14	*(R)*-**3k**	OBn	0.5	1
15	*(R)*-**3l**	Ph	>16	>32[b]

[a] No MIC_{50} value obtained as the 0.125 μg/mL dilution showed more than 50% growth.

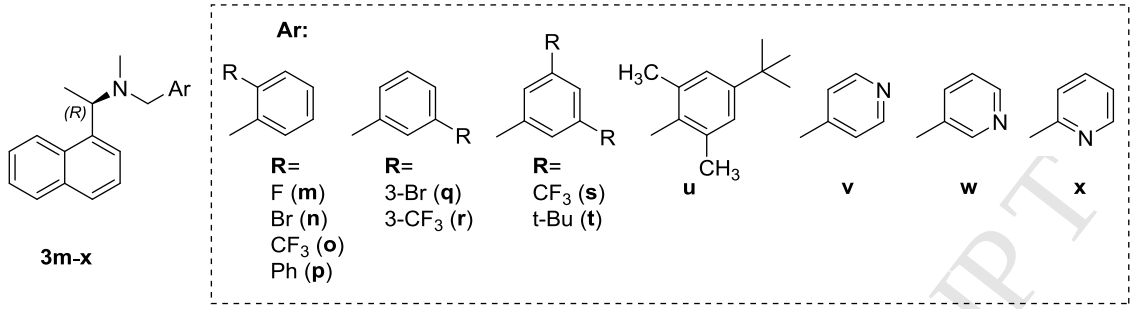
[b] Some growth inhibition at higher concentrations.

In addition to (*R*)-**3a**,[15] several of the newly synthesised compounds had a MIC_{50} value similar to that of Butenafine (**1**). These included the *para* substituted derivatives with a methyl (entry 7), bromo (entry 9), trifluoromethyl (entry 11) or a trimethylsilyl (entry 12) group. This is possibly owing to favourable van der Waals type contacts not applicable with compounds with smaller substituents (entry 5 and 6).

Whereas the phenyl derivative **3l** was inactive, the benzyloxy derivative **3k** had a MIC_{50} value of 0.5 μg/mL (entry 14). The reason for the higher potency of **3k** as compared to the methoxy and trifluoromethoxy derivatives, **3e** and **3j**, might be that the *para*-benzyloxy substitutent is flexible enough to avoid steric interferance, and penetrates deeper into the squalene epoxidase binding site allowing for other binding interactions to be utilised. Alternatively, the antifugal activity of **3k** could reside in a different mode of action.

In order to further investigate the effect of substrate structure on activity, a series of *ortho*- and *meta*-, di and trisubstituted analogues and pyridine derivatives, were tested, see Table 2.

Table 2. Antifingal activity (MIC) of *ortho*- and *meta*-, di and trisubstituted derivatives and pyridine derivatives **3m-x** towards *C. neoformans*.



Entry	Comp.	Substituent (R or Ar)	MIC_{50} (μg/mL)	MIC_{80} (μg/mL)
1	**3m**	*o*-F	>32	>32[a]
2	**3n**	*o*-Br	>32	>32[b]
3	**3o**	*o*-CF_3	>32	>32[b]
4	**3p**	*o*-Ph	>32	>32[b]
5	**3q**	*m*-Br	4	8
6	**3r**	*m*-CF_3	4	8
7	**3s**	3,5-di-CF_3	>32	>32[b]
8	**3t**	3,5-di-*t*-Bu	32	>32
9	**3u**	2,6-di-Me-4-*t*-Bu	1	32
10	**3v**	4-pyridine	16	>32
11	**3w**	3-pyridine	>32	>32[a]
12	**3x**	2-pyridine	>32	>32[a]

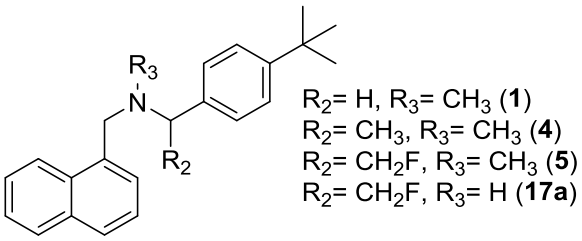
[a] Some growth inhibition at higher concentrations

[b] No sign of growth inhibition.

Compounds with substituents in the *ortho* position had no inhibitory effect on *C. neoformans* in the concentration range tested (Table 2, entry 1-4). This is possibly in part due to a conformational effect, but also the absence of a large substituent in the *para* position, as indicated by the activity of trisubstituted derivative **3u**. A mediocre activity was seen for the *meta* bromo and trifluoromethyl substituted compounds **3q** and **3r**. The di-trifluoromethyl derivative **3s**, the di-*tert*-butyl derivative **3t**, and the pyridine substituted compounds **3w-x** were all inactive, whereas a modest activity was seen for **3v**. For **3s-t** the abolished potency might be due to size limitations, whereas the pyridines **3v-x** suffer from the absence of properly sized substituent in the *meta* or *para* position, and possibly also causing an unfavourable electronic effect.

We then turned our attention to analogues having stereocenteres at the benzylic carbon. As the synthesis of these compounds was more time consuming, the R_2 group was varied only with a methyl and a fluoromethyl group, and the *tert*-butyl substituent was kept constant. The secondary amines (*S*)- and (*R*)-**17a** were also included in the testing. The results of activity testing are summarised in Table 3.

Table 3. Antifungal activities (MIC) of **1**, **4**, **5** and **17a** against *C. neoformans*.



Entry	Comp.	R_2	R_3	MIC_{50} (μg/mL)	MIC_{80} (μg/mL)
1	Butenafine (**1**)	H	CH_3	0.5	1.0
2	(*R*)-**4**	CH_3	CH_3	>32	>32[a)]
3	(*S*)-**4**	CH_3	CH_3	2.0	4.0
4	(*R*)-**17a**	CH_2F	H	>32	>32[b)]
5	(*S*)-**17a**	CH_2F	H	>32	>32[b)]
6	(*R*)-**5**	CH_2F	CH_3	>32	>32[b)]
7	(*S*)-**5**	CH_2F	CH_3	>32	>32[b)]

[a)] Some growth inhibition at higher concentrations

[b)] No sign of growth inhibition.

Compound (*R*)-**4** with a stereo centre at the benzylic carbon had a MIC_{50} of >32 μg/mL (Table 3, entry 2). Evidently, all activity resides in the (*S*)-enantiomer (entry 3). The fluoro containing derivatives **17a** and **5** also failed to show any growth inhibition, as was previously seen when placing fluoromethyl or cyano groups α to the naphthalene ring.[15] Figure 3 summarises the structure activity relationships seen for this substrate class towards *C. neoformans*. Included is also our previous data on testing of compounds having the *tert*-butylbenzylamine fragment combined with chiral naphthalene units containing the cyano, ethyl and fluoromethyl groups at the stereogenic centre.[15]

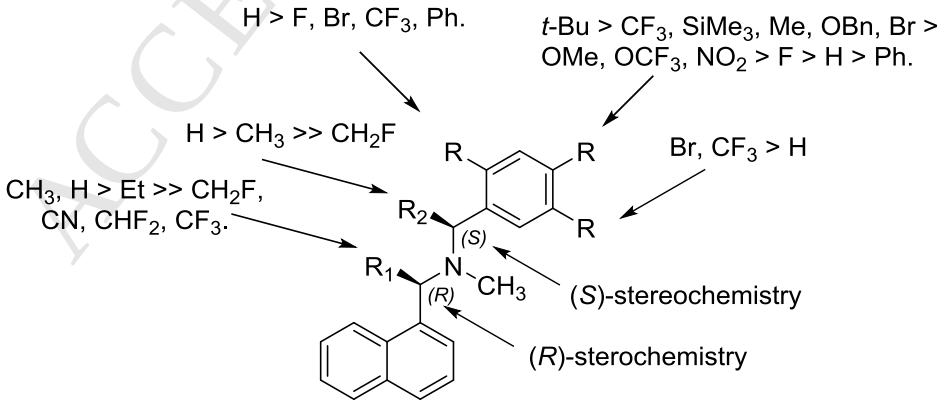


Figure 2. Structure activity relationships observed for the benzylamines towards *C. neoformans*.

It is apparent that the electronic character of the central amine is of utmost importance for the potency of these compounds. ^{13}C NMR spectroscopy shows that the N-CH_3 carbon is shifted from 38.2 to 38.9 depending on the aromatic substituent. This indicates long range electronic effects. Higher basicity of the amine function gives more active compounds, which could indicate the involvement of hydrogen bonding with the protein target as suggested by homology modelling.[14] Unfortunately, no X-ray data is available to support these indications. Assuming squalene epoxidase is the only target, a *para tert*-butyl group seems to have a perfect size for matching lipophilic surfaces in the protein, while at the same time maintaining a basic nitrogen atom.

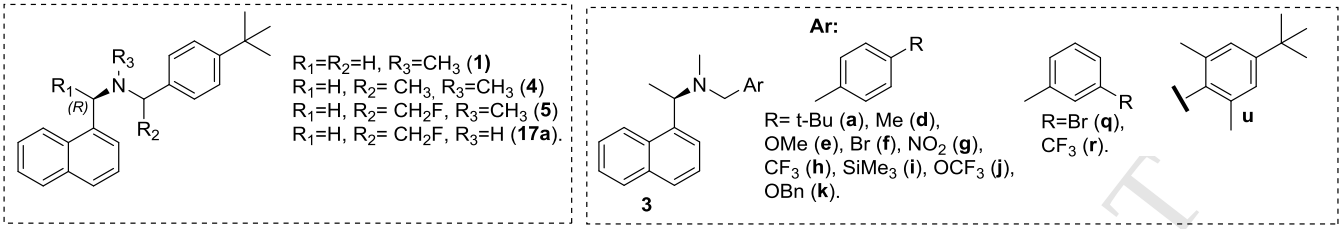
2.2.2. Activity towards dermatophytes

Compounds having MIC_{50} values of 2 μg/mL or better towards *C. neoformans*, and the enantiomers of **4**, **5** and **17a** were also tested for their activity towards the dermatophytes *T. mentagrophytes* and *T. rubrum*. Both Amphotercin B and Butenafine (**1**) were included as positive controls. The results are summarised in Table 4.

Generally, the compounds had higher activity towards *T.mentagrophytes* and *T. rubrum* than towards *C. neoformans.* Compound (*R*)-**3a** was found to be equipotent with Butenafine (**1**) towards *T.mentagrophytes*, and also had a low MIC_{50} value with *T. rubrum* (0.06 μg/mL). Of the other derivatives tested, the *para* benzyloxy compound **3k** was most active, showing a MIC_{50} value of 0.125 μg/mL. The activity was highly dependent on the aromatic substitution pattern, and the *meta* substituted derivatives showed a modest potency (entry 12-13)

The activities of the compounds with a stereocentre at the benzylic carbon were found to depend on the absolute configuration. Whereas (*S*)-**4** showed a MIC_{50} of 0.5 μg/mL against *T. rubrum* and *T.mentagrophytes*, the antipode (*R*)-**4** was inactive. For the fluoro containing derivatives **5** and **17a** (entries 17-20), the stereochemical notation changes due to the higher priority of the CH_2F as compared to the methyl group. By introduction of an electron withdrawing group, the antifungal activity for compounds **5** and **17a** dropped. Surprisingly, the secondary amine derivative (*R*)-**17a** had a higher activity than the methylated analogue (*R*)-**5**. This could be due to steric constraints in the squalene binding site, or that the molecule has a more favourable rotameric conformation for binding.

Table 4. Antifungal activities (MIC) of selected compounds against *T.mentagrophytes* and *T. rubrum*.



Entry		R	R_1	R_2	R_3	*T.mentagrophytes* MIC_{50} (μg/mL)	*T.mentagrophytes* MIC_{80} (μg/mL)	*T. rubrum*. MIC_{50} (μg/mL)	*T. rubrum*. MIC_{80} (μg/mL)
1	Amphotericin B					0.50	<1.0	>0.25	<0.50
2	Butenafine (**1**)	*p*-*t*-Bu	H	H	CH_3	0.06	0.125	0.03	0.06
3	(*R*)-**3a**	*p*-*t*-Bu	CH_3	H	CH_3	0.06	0.125	0.06	0.125
4	(*R*)-**3d**	*p*-Me	CH_3	H	CH_3	0.25	0.50	0.25	0.5
5	(*R*)-**3e**	*p*-OMe	CH_3	H	CH_3	1.0	2.0	1.0	2.0
6	(*R*)-**3f**	*p*-Br	CH_3	H	CH_3	0.25	0.50	0.125	0.25
7	(*R*)-**3g**	*p*-NO_2	CH_3	H	CH_3	1.0	2.0	0.25	0.5
8	(*R*)-**3h**	*p*-CF_3	CH_3	H	CH_3	0.25	0.5	0.25	0.5
9	(*R*)-**3i**	*p*-$SiMe_3$	CH_3	H	CH_3	[b]	0.50	[b]	0.5
10	(*R*)-**3j**	*p*-OCF_3	CH_3	H	CH_3	[b]	0.50	0.5	1.0
11	(*R*)-**3k**	*p*-OBn	CH_3	H	CH_3	0.125	0.25	0.125	0.25
12	(*R*)-**3q**	*m*-Br	CH_3	H	CH_3	2.0	4.0	1.0	2.0
13	(*R*)-**3r**	*m*-CF_3	CH_3	H	CH_3	4.0	>32	2.0	4.0
14	(*R*)-**3u**	[a]	CH_3	H	CH_3	>32	>32[c]	>32	>32[c]
15	(*S*)-**4**	*t*-Bu	H	CH_3	CH_3	0.50	1.0	0.5	1.0
16	(*R*)-**4**	*t*-Bu	H	CH_3	CH_3	>32	>32[d]	>32	>32[d]
17	(*R*)-**17a**	*t*-Bu	H	CH_2F	H	2.0	4.0	2.0	4.0
18	(*S*)-**17a**	*t*-Bu	H	CH_2F	H	>32	>32[d]	>32	>32[d]
19	(*R*)-**5**	*t*-Bu	H	CH_2F	CH_3	>32	>32[d]	>32	>32[d]
20	(*S*)-**5**	*t*-Bu	H	CH_2F	CH_3	>32	>32[c]	>32	>32[c]

[a] See Table Scheme above

[b] No MIC_{50} value obtained as the 0.25 μg/mL dilution showed more than 50% growth.

[c] No sign of growth inhibition

[d] Some growth inhibition at higher concentrations.

3. Conclusion

New chiral benzylamine based compounds have been investigated as antifungals agents using the medically important *C. neoformans*, *T.mentagrophytes* and *T. rubrum* as test organisms. Standard substitution methodology could be used for preparation of most of the compounds. However, synthesis of the fluoroamine derivatives used as a mechanistic probe

required the development of an enzyme catalysed kinetic resolution, an enzyme catalysed amide hydrolysis, and a change in synthetic strategy.

Generally, the effect of the aromatic substitution pattern on potency was similar for the three fungi. A high antifungal activity was seen when having a *tert*-butyl group situated in the *para* position, although other groups of similar size also show good potency. It is assumed that this is due to favourable lipophilic interactions and size limitations in this part of the protein binding pocket. The amine basicity is also likely to play a role, which is supported by the low activity observed for the fluoro containing analogues. Insertion of a methyl group at the benzylic carbon, revealed that the potency only resides in the (*S*)-enantiomer. However, the activity was lower than that seen with Butenafine (**1**) and (*R*)-*N*-(4-*tert*-butylbenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine (**3a**).

The dermatophytes were generally more sensitive to the antifungal compounds than *C. neoformans*. (*R*)-*N*-(4-*Tert*-butylbenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine (**3a**) was highly active against all three test fungi. (*R*)-*N*-(4-(Benzyloxy)benzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine (**3k**) was also efficient against *T.mentagrophytes* and *T. rubrum*, and possibly represents a new lead compound, allowing for other binding interactions to be utilised.

4. Experimental

4.1. General

Compounds (*R*)-**3a** and (*S*)-**3a** were synthesised as described previously.[15] The benzyl halides **9a-h**, **9j**, **9l-y**, (4-(benzyloxy)phenyl)methanol, trimethyl(*p*-tolyl)silane, α,α,α-trifluorotoluene, (*R*)-1-(naphthalen-1-yl)ethanamine ((*R*)-**6**), 1-(4-*tert*-butylphenyl)ethanone, SelectFluor™, ethyl 2-methoxyacetate, methyl iodide, lithium aluminium hydride, *N*-bromosuccinimide, 1,1'-azobis(cyclohexanecarbonitril) (ABCN), *N,N*-diisopropylethylamine (Hünigs base), Butenafine hydrochloride, Amphotericin B, DMSO, RPMI-1640 medium, 4-morpholinepropanesulfonic acid (MOPS), lipase A from *Candida antarctica* (CAL-A) immobilised on CLEA, lipase B from *Candida antarctica* (CAL-B) immobilised on immobead 150 and Novozyme 435, and Ace Pressure tubes (15 mL) were bought from Sigma Aldrich. (*R*)-1-(4-*Tert*-butylphenyl)-*N*-methylethanamine *((R)*-**10**) and (*S*)-1-(4-*tert*-butylphenyl)-*N*-methylethanamine ((*S*)-**10**) were obtained from Alpha Aesar. Column chromatography was performed using silica gel 60A (pore size 40 - 63 μm) from Fluka. Amberlyst 15 was from Janssen Chimica, and ammonium acetate was from Merck. All chemicals were used as supplied with one exception; 1-(chloromethyl)naphthalene (**9y**) was purified by silica-gel column chromatography (pentane : EtOAc, 8 : 2) to remove small amounts of 2-(chloromethyl)naphthalene.

4.2. Analyses

^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance DPX 400 operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. ^{19}F NMR was recorded with a Bruker Avance DPX 600 operating at 564 MHz. For ^{1}H and ^{13}C NMR chemical shifts are in ppm rel. to TMS, while for ^{19}F NMR the shift values are relative to hexafluorobenzene. Coupling constants are in hertz. Resonance multiplicities were abbreviated as follows: s=singlet, d = doublet, t = triplet, q = quartet, ap d: appeared as a doublet (although more complicated splitting could be expected), d_{AB}= doublet in AB system; m=multiplet, br=broad, dm=

doublet of multiplet. MS (EI/70eV) 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. GC was performed using Varian 3380 GC using a CP-8410 Auto injector, and a FID detector. The enantiomeric excess of (*R*)-**13**, (*S*)-**13** and (*S*)-**14** were determined by using a Varian CP-Chirasil-Dex CB (25m, I.D. 0.25 mm, 0.25 μm, part no: CP7502) chiral column. The amines (*R*)-**13** and (*S*)-**13** had to be derivatized prior to GC analysis. This was done by mixing the amine with acetic anhydride and pyridine in CH_2Cl_2 for 5 minutes, followed by a simple wash with water and drying over Na_2SO_4, yielding the corresponding acetamide. Analysis by GC was done by isothermal elution at 160°C (pressure: 10 psi); retention times: (*R*)-**13**-acetamide: 18.8 min, (*S*)-**13**-acetamide: 19.5 min, (*R*)-**14**: 27.7 min, and (*S*)-**14**: 28.5 min. HPLC was performed using an Agilent 1100 series system equipped with an Agilent 1200 DAD detector. The enantiomeric excess of (*R*)-**4**, (*S*)-**4**, (*R*)-**5**, (*S*)-**5**, (*R*)-**17a** and (*S*)-**17a** were determined by using a Phenomenex Lux 5u Cellulose-1 4.6 × 250 mm chiral column (part no. 00G-4459-E0). Eluting with hexane (cont. 0.2% triethylamine) : *i*-propanol, 95 : 5, flow rate: 1 mL/min; detection at 230 nm; the retention times: (*S*)-**5**: 7.1 min and (*R*)-**5**: 8.6 min. Eluting with hexane (cont. 0.2% diethylamine):2-propanol, 97:3; flow rate: 1 mL/min; detection at 230 nm; retention times: (*R*)-**4**: 4.3 min, (*S*)-**4**: 4.8 min, (*S*)-**17a**: 6.7 min, and (*R*)-**17a**: 8.0 min. Purity analysis of **3a-x**, **4**, **5** and **17a** was performed using a Agilent Poroshell EC-C18, 4.6 × 100 mm, 2.7 micron HPLC column (part no. 695975-902) running a gradient of water and acetonitrile starting with 90% water, going to 100% acetonitrile over 40 min.

4.3. Microbiology

4.3.1. Fungal strains

The following strains were included in the study: *Cryptococcus neoformans* (DSM 11959), *Trichophyton mentagrophytes* (ATCC 9533) and *Trichophyton rubrum* (ATCC 28188).

4.3.2. In vitro susceptibility testing by the broth microdilution method

For all strains the tests were performed in sterile round-bottomed 96-well microplates. The test antimicrobials were prepared as stock solutions at 3200 μg/mL in DMSO, and diluted following the schemes given in the respective standard methods (see below). Doubling dilutions in MOPS-buffered RPMI-1640 with glucose (hence, growth medium) in the range 64 – 0.06 μg/mL were made. These double-strength dilutions were pipetted (0.1 mL) into each of two parallel wells. Upon addition of 0.1 mL inoculum (see below) the final drug concentration range for testing, 32 – 0.03 μg/mL, was achieved. MIC-testing of *T. mentagrophytes* and *T. rubrum* was performed according to the CLSI M38-A standard for the susceptibility testing of dermatophytes.[23] Isolates were subcultured onto potato dextrose agar (Oxoid, Basingstoke, UK) and incubated at 28 °C for 7-10 days. Conidia were harvested in 5-10 mL sterile saline (0.85% NaCl) by probing the plate surface with a swab, and the suspension was allowed to settle in a 50 mL sterile tube for 10- 15 min. The upper layer was adjusted to an OD_{530} = 0.14 - 0.15, and this was diluted in growth medium (~ 1/50) producing the 2× inoculum concentration of ~$0.4 – 5 \times 10^4$ CFU/mL. The inoculum size was checked by plating onto Sabouraud dextrose agar (Oxoid) as described in the method protocol.[23] For testing of *C. neoformans* the following applied: after 36-48 h growth on Sabouraud dextrose agar at 35°C, colonies were suspended in 5 mL of sterile distilled water and vortexed. The OD_{530} was adjusted to a McFarland standard of 0.5 with sterile distilled water. The suspension was then diluted in growth medium according to the CLSI M27-A3 protocol,[24] to produce

the 2× inoculum. For testing, 0.1 mL of the 2× inoculum was added to wells with double-strength drug concentrations as described above. For dermatophytes, plates were incubated for 7 days at 28 °C before determining MIC values, whereas *C. neoformans* plates were incubated for 72 h at 35 °C. After incubation, plates were scored visually. For Amphotericin B, the MIC value was taken as the lowest drug concentration that prevented any discernible growth. For all other substances tested, turbidity was compared with a drug free control and scored as two values: (i) MIC_{80}; the lowest concentration showing about 80% or more growth inhibition relative to the control (ii) MIC_{50}; the lowest concentration showing a prominent (~50%) reduction in turbidity relative to the control.

4.4. Synthesis of building blocks

4.4.1. (*R*)-*N*-(1-(Naphthalen-1-yl)ethyl)formamide (7).[25]

(*R*)-1-(Naftalen-1-yl)etanamine (**6**) (28.61 g, 0.167 mol) and Amberlyst 15 (1.25 g) were mixed with THF (80 mL) at 50 °C. Ethyl formate (60 mL, 0.73 mol) was then added and the mixture was refluxed for 24 h. After cooling to ambient temperature, diethyl ether (30 mL) was added and the catalyst was removed by filtration. Upon evaporation of the solvent this gave 32.12 g, (161 mmol, 97%) of a white solid; mp. 129-131 °C; $[\alpha]_D^{20}$ = +120.03 (c 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.68 (d, *J*=6.7 Hz, 3H), 5.89 (br s, 1H, NH), 5.98 (q, *J*=6.8 Hz, 1H), 7.42-7.56 (m, 4H), 7,79 (d, *J*=8.2 Hz, 1H), 7.86 (d, *J*=9.5 Hz, 1H), 8.08 (d, *J*=8.4 Hz, 1H), 8.12 (s, 1H).

4.4.2. (*R*)-*N*-Methyl-1-(naphthalen-1-yl)ethanamine (8).[16]

A solution of $LiAlH_4$ in THF (2M, 44 mL) was heated to 65 °C, and (*R*)-*N*-(1-(naphthalen-1-yl)ethyl)formamide (**2**) (5.02 g, 25 mmol) dissolved in THF (20 mL) was added over 5 min. The mixture was refluxed for 3.5 h. After cooling to 0-5 °C, water (3.5 mL) was added drop wise. The mixture was further treated with an aq. NaOH-solution (1M, 7 mL), and water (11 mL). After stirring for 15 min, a celite filtration was performed followed by an additional celite wash with diethyl ether (50 mL). The phases were separated and the organic fraction was dried over Na_2SO_4. The crude oil obtained after concentration was diluted with diethyl ether (40 mL) and HCl sat. diethyl ether (4 mL) was added drop wise. The precipitated material was isolated by filtration and subjected to a re-crystallisation from EtOH. After drying this gave 4.95 g (22 mmol, 89%) of a white solid; mp. 210-212 °C; $[\alpha]_D^{20}$ = +31.5 (c 1.0, MeOH); purity >97% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) δ: 1.49 (d, *J*=6.6 Hz, 3H), 1.62 (br s, 1H, NH), 2.41 (s, 3H), 4.52 (q, *J*=6.6 Hz, 1H), 7.44-7.52 (m, 3H), 7.62 (d, *J*=7.1 Hz, 1H), 7.74 (d, *J*=8.2 Hz, 1H), 7.86 (d, *J*=9.4 Hz, 1H), 8.18 (d, *J*=8.4 Hz, 1H).

4.4.3. (4-(Bromomethyl)phenyl)trimethylsilane (9i). [26]

N-Bromosuccinimide (NBS) (1.07 g, 6.00 mmol) was added to a solution of trimethyl(p-tolyl)silane (986 mg, 6.00 mmol) in α,α,α-trifluorotoluene (40 mL). 1,1'-Azobis(cyclohexanecarbonitril) (ABCN) (15 mg, 0.06 mmol) was added, and the reaction was stirred at 120 °C for 5.5 h. After cooling to room temperature, the mixture was washed with water (2×20 mL). The water phases were back-extracted with diethyl ether (3×15 mL). The combined organic phases were dried over Na_2SO_4. Evaporation of the solvent gave 1.53 g of the crude product, which was purified by silica-gel column chromatography (hexane, R_f = 0.23). This gave 943 mg (3.88 mmol, 65%) of clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.26 (s, 9H), 4.49 (s, 2H), 7.36-7.39 (m, 2H), 7.48-7.52 (m, 2H). ^{1}H NMR confirmed with that reported previously.[26]

4.4.4. 1-(Benzyloxy)-4-(bromomethyl)benzene (9k).[27]

To a solution of *N*-bromosuccinimide (NBS) (42 mg, 2.38 mmol) in CH_2Cl_2 (75 mL) at 0 °C, dimethylsulfide (0.2 mL, 2.7 mmol) was added over 10 min. The mixture was kept at 0 °C for 10 min after addition was complete. The mixture was further cooled to -20 °C and 4-(benzyloxy)phenyl)methanol (417 mg, 1.94 mmol) dissolved in CH_2Cl_2 (10mL) was added, then the mixture was allowed to warm to ambient temperature and stirring continuously for 22 h. The mixture was poured onto brine (6 mL), and extracted with hexane : diethyl ether (4:1) (3×10 mL). The combined organic phases were washed with brine (3×15 mL), and dried over Na_2SO_4. Evaporation of the solvent gave 436 mg (1.57 mmol, 80%) as a white solid; mp. 84-86 °C (lit.[27] 85-86 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.50 (s, 2H), 5.07 (s, 2H), 6.94 (m, 2H), 7.31-7.42 (m, 7H). ^{1}H NMR confirmed with that reported previously.[27]

4.4.5. 1-(4-*Tert*-butylphenyl)-2-fluoroethanone (11)

1-(4-*Tert*-butylphenyl)ethanone (6.17 g , 35 mmol), SelectFluor™ (24.8 g , 70 mmol) and methanol (75 mL) was distributed evenly over five polytetrafluoroethylene tubes (as of Anton Paar 3000 microwave). Each tube was heated separately at 70 W for 60 min. Water (15 mL) was added to the tube, and the reaction was heated again at 70 W for 30 min. The reaction mixtures were combined, water (300 mL) was added, and the mixture was extracted with CH_2Cl_2 (5× 100 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuum*. The product was isolated by silica-gel column chromatography (CH_2Cl_2 : pentane, 1 : 1, R_f = 0.27). This yielded 4.33 g (21.00 mmol, 60%) of white crystal flakes, mp. 37-38 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.35 (s, 9H), 5.51 (d, J=47.0 Hz, 2H), 7.49-7.53 (m, 2H), 7.82-7.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 31.0 (3C), 35.3, 83.5 (d, J=182.2 Hz), 125.9 (2C), 127.8 (d, J=3.0 Hz, 2C), 131.2, 158.1, 193.0 (d, J=15.2 Hz); ^{19}F NMR ($CDCl_3$, 564 MHz) *δ*: -233.9 (t, J=47.3 Hz); IR (neat, cm^{-1}): 2966, 2909, 1694, 1600, 1409, 1238, 1087, 970, 835, 582; HRMS (ESI): 179.0863 (calcd. 179.0865, $[M^*\text{-}CH3]^+$).

4.4.6. 1-(4-*Tert*-butylphenyl)-2,2-difluoroethanone (12)

Following the reaction and purification described in Section 4.5.5, 1-(4-*tert*-butylphenyl)-2,2-difluoroethanone (**12**) was isolated by silica-gel column chromatography (CH_2Cl_2 : pentane, 1 : 1, R_f = 0.67) as a clear oil in 1.91 g (9.00 mmol, 26%) yield; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.36 (s, 9H), 6.28 (t, J=53.6 Hz, 1H), 7.52-7.57 (m, 2H), 8.00-8.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 30.9 (3C), 35.4, 111.3 (t, J=253.4 Hz), 126.0 (2C), 128.9 (t, J=1.5 Hz), 129.6 (t, J=2.2 Hz, 2C), 159.0, 187.2 (t, J=24.8 Hz); ^{19}F NMR ($CDCl_3$, 564 MHz) *δ*: -125.1 (d, J=53.3 Hz); IR (neat, cm^{-1}): 2966, 2871, 1696, 1605, 1140, 1108, 1059, 876, 670, 556; HRMS (ESI): 197.0771 (calcd. 197.0770, $[M^*\text{-}CH3]^+$). The product contained trace amounts of what appeared to be 1-(4-*tert*-butylphenyl)-2-chloro-2-fluoroethanone.

4.4.7. 1-(4-Tert-butylphenyl)-2-fluoroethanamine (13)

The reaction was performed by adding 1-(4-*tert*-butylphenyl)-2-fluoroethanone (**11**) (971 mg, 5.00 mmol) to a solution of ammonium acetate (3854 mg, 50.00 mmol) in dry methanol (20 mL). Sodium cyanoborohydride (319 mg, 5.00 mmol) was added, and the reaction was stirred at 50 °C for 24 hours. After cooling to room temperature, methanol was evaporated in vacuum, and $CHCl_3$ (20 mL) was added. The mixture was washed with water (4×20 mL), and the water phases were back-extracted with $CHCl_3$ (2×20 mL). The combined organic phases were washed with sat. sodium hydrogen carbonate (20 mL), dried over Na_2SO_4, filtered, and evaporated. This gave 836 mg (4.28 mmol, 86%) of a clear oil; ^{1}H NMR ($CDCl_3$, 400 MHz,

free base) δ: 1.32 (s, 9H), 4.25-4.58 (m, 3H), 7.31 (d, J=8.4 Hz, 2H), 7.38 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) δ: 31.5 (3C), 34.7, 55.5 (d, J=19.5 Hz), 88.4 (d, J=174.0 Hz), 125.7 (2C), 126.8 (2C), 137.3 (d, J=8.1 Hz), 151.0; ^{19}F NMR ($CDCl_3$, 564 MHz, free base) δ: -222.2 (dt, J=47.5 Hz, 15.4); IR (neat, cm^{-1}): 2961, 2903, 2868, 1510, 1462, 1363, 1263, 1269, 1000, 909, 830, 731, 573; HRMS (ESI): 195.1414 (calcd 195.1416, $[M+H]^+$).

4.4.8. Lipase catalysed resolution to (*R*)-1-(4-*tert*-butylphenyl)-2-fluoroethanamine ((*R*)-13)

The reaction was performed by adding a solution of racemic 1-(4-*tert*-butylphenyl)-2-fluoroethanamine (**13**) (293 mg, 1.50 mmol) in hexane (15 mL) to an Ace Pressure tube (15 mL). Ethyl 2-methoxyacetate (177 mg, 1.50 mmol) and CAL-B (293 mg) were added. The reaction was shaken in an incubator (300 rpm) at 60 °C. After 18 hours, the conversion was shown by GC to be 50%. After cooling, the enzyme was filtered off, and the hexane was evaporated in vacuum. The residue was diluted in $CHCl_3$ (20 mL), and the mixture was extracted with aq. HCl (4×15 mL, 1M), and the combined water phase was washed with $CHCl_3$ (2×15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated. This gave a slightly brown oil of the corresponding 2-methoxyacetamide ((*S*)-**14**), Section 4.4.9. The combined aq. acid phases were saturated with NaCl, and the pH was adjusted to 12, followed by extraction with $CHCl_3$ (5×15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated. This gave 135 mg (0.69 mmol, 46%) of a clear oil, ee: 99%; $[\alpha]_D^{20}$ = -32.0 (c 1.05, $CHCl_3$); the spectroscopic data corresponded to that of the racemic amine.

4.4.9. (*S*)-*N*-(1-(4-*Tert*-butylphenyl)-2-fluoroethyl)-2-methoxyacetamide ((*S*)-14)

The reaction was performed as described in Section 4.4.8. This gave a brownish oil which was purified by silica- gel column chromatography (pentane : EtOAc, 8 : 2, R_f = 0.16) and the mobile phase was made more polar by adding more EtOAc towards the end. This gave 191 mg (0.71 mmol, 47%) of a white solid; mp. 48-49°C; ee: 99%; $[\alpha]_D^{20}$ = +68.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.31 (s, 9H), 3.43 (s, 3H), 3.93 (d_{AB}, J=15.1 Hz, 1H), 3.96 (d_{AB}, J=15.1 Hz, 1H), 4.66 (ddd_{AB}, J=47.2 Hz, 9.6 Hz, 4.9 Hz, 1H), 4.70 (ddd_{AB}, J= 47.2 Hz, 9.6 Hz, 4.4 Hz, 1H), 5.25-5.36 (dm, J=23.8 Hz, 1H), 7.28 (d, J=8.3 Hz, 2H), 7.39 (d, J=8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.4 (3C), 34.7, 52.2 (d, J=19.9 Hz), 59.4, 72.1, 84.9 (d, J=175.9 Hz), 126.0 (2C), 126.8 (2C), 134.6, 151.3, 169.3. ^{19}F NMR ($CDCl_3$, 564 MHz) δ: -229.6 (dt, J=47.5 Hz, 24.1 Hz); IR (neat, cm^{-1}): 3296, 2960, 2359, 2341, 1662, 1520, 1113, 1011, 830, 570; HRMS (ESI): 247.1567 (calcd 247.1567, $[M+H]^+$).

4.4.10. Lipase catalysed hydrolysis to (*S*)-1-(4-*tert*-butylphenyl)-2-fluoroethanamine ((*S*)-13)

The reaction was performed by adding (*S*)-*N*-(1-(4-*tert*-butylphenyl)-2-fluoroethyl)-2-methoxyacetamide (**14**) (150 mg, 0.561 mmol) and phosphate buffer (15 mL, pH 7.0) to an Ace Pressure tube (15 mL). CAL-B (300 mg) was added, and the reaction was shaken in an incubator (300 rpm) at 50 °C. The reaction was monitored by GC, and after 48 h full conversion was obtained. The mixture was then cooled down to room temperature, the enzyme was filtered off, and the tube and the enzyme were rinsed with $CHCl_3$ in portions (in total 30 mL). Following phase separation, the water phase was extracted with $CHCl_3$ (15×4 mL). The combined organic phases was dried over Na_2SO_4, filtered, and evaporated. This gave 84 mg (0.431 mmol, 77%) of a clear oil, ee: 99%; $[\alpha]_D^{20}$ = +32.2 (c 1.05, $CHCl_3$). The spectroscopic data corresponded to that of the racemic amine.

4.5. Synthesis of potential anti-fungicidal agents

4.5.1. General procedure for preparation of 3a-x

N-Methyl-1-(naphthalen-1-yl)ethanamine (**8**) (0.37 g, 2.00 mmol), *N*,*N*-diisopropylethylamine (0.39 g, 3.02 mmol), 1-(bromomethyl)-4-*tert*-butylbenzene (0.50 g, 2.20 mmol) and acetonitrile (5 mL) were mixed and stirred at reflux under an N_2-atmosphere for 2 hours. The solvent was then removed at reduced pressure and CH_2Cl_2 (5 mL) was added. The dichloromethane phase was washed with water (5 mL) and the water phase was back extracted with CH_2Cl_2 (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. Alternatively, the purification was done by filtration through a short silica gel column (pentane : EtOAc, 9 : 1), followed by precipitation as it hydrochloride salt by addition of HCl saturated ether. The solid material was washed with cold pentane. Alternatively, using **8**·HCl the reaction was run similarly, but employing a 3-fold excess of *N*,*N*-diisopropylethylamine .

4.5.2. (*R*)-*N*-Benzyl-*N*-methyl-1-(naphthalen-1-yl)ethanamine (3b)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (203 mg, 1.10 mmol), *N*,*N*-diisopropylethylamine (211 mg, 1.63 mmol), (bromomethyl)-benzene (209 mg, 1.22 mmol) and acetonitrile (5 mL). Purification was done by silica-gel column chromatography (pentane : EtOAc, 9 : 1, R_f = 0.34). This yielded 233 mg (0.85 mmol, 77%) of clear oil; $[\alpha]_D^{20}$ = -68.6 (*c* 1.00, MeOH); purity >99% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) δ: 1.56 (d, J=6.8 Hz, 3H), 2.20 (s, 3H), 3.42 (d_{AB}, J=13.3 Hz, 1H), 3.65 (d_{AB}, J=13.3 Hz, 1H), 4.38 (q, J=6.8 Hz, 1H), 7.14-7.27 (m, 5H), 7.41-7.55 (m, 3H), 7.65 (ap d, J=7.3 Hz, 1H), 7.75 (ap d, J= 8.1 Hz, 1H), 7.85 (m, 1H), 8.46 (ap d, J=8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) δ: 16.7, 38.4, 59.1, 60.6, 124.5, 124.6, 125.26, 125.33, 125.5, 125.6, 127.5, 128.1 (2C), 128.67 (2 C), 128.73, 131.8, 134.1, 140.1, 140.7; IR (neat, cm^{-1}): 2970, 2787, 1229, 796, 776, 736, 697; HRMS (ESI): 276.1755 (calcd 276.1752, $[M+H]^+$).

4.5.3. (*R*)-*N*-(4-Fluorobenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine (3c)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (215 mg, 1.16 mmol), *N*,*N*-diisopropylethylamine (225 mg, 1.74 mmol), 1-(bromomethyl)-4-fluorobenzene (250 mg, 1.32 mmol) and acetonitrile (5 mL). Purification was done by silica-gel column chromatography (pentane : EtOAc, 9 : 1, R_f = 0.38). This gave 208 mg (0.71 mmol, 61%) of a white solid; mp. 46-47 °C; $[\alpha]_D^{20}$ = -80.3 (c 1.00, MeOH); purity >99% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) δ: 1.56 (d, J= 6.7 Hz, 3H), 2.20 (s, 3H), 3.38 (d_{AB}, J= 13.4 Hz, 1H), 3.59 (d_{AB}, J= 13.4 Hz, 1H), 4.39 (q, J= 6.7 Hz, 1H), 6.93 (m, 2H), 7.19 (m, 2H), 7.42-7.56 (m, 3H), 7.65 (ap d, J= 7.7 Hz, 1H), 7.77 (ap d, J= 8.1 Hz, 1H), 7.87 (m, 1H), 8.45 (ap d, J= 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) δ: 16.6, 38.3, 58.2, 60.6, 114.8 (d, J= 20.8 Hz, 2C), 124.48, 124.52, 125.3, 125.4, 125.5, 127.5, 128.7, 130.1 (d, J=7.7 Hz, 2C), 131.8, 134.2, 135.8 (d, J=3.2 Hz), 140.5, 161.8 (d, J=244.1 Hz); ^{19}F NMR ($CDCl_3$, 564 MHz) δ: -119.8 (s); IR (neat, cm^{-1}): 2973, 2784, 1506, 1218, 1153, 776; HRMS (ESI): 294.1665 (calcd 294.1653, $[M+H]^+$).

4.5.4. (*R*)-*N*-Methyl-*N*-(4-methylbenzyl)-1-(naphthalen-1-yl)ethanamine hydrochloride (3d)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (421 mg, 2.27 mmol), *N*,*N*-diisopropylethylamine (880 mg, 6.81 mmol), 1-(bromomethyl)-4-methylbenzene (463 mg, 2.50 mmol) and acetonitrile (5 mL). Purification was done by filtration using silica-gel column chromatography (pentane : EtOAc, 9 : 1), followed by isolation as its hydrochloric salt. This yielded 324 mg (1.00 mmol, 44%) of a white solid; mp. 195-197 °C; $[\alpha]_D^{20}$ = −53.1 (*c* 1.00, MeOH); purity > 98% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.54 (d, *J*=6.7 Hz, 3H), 2.18 (s, 3H), 2.29 (s, 3H) 3.51 (d_{AB}, J=12.9 Hz, 1H), 3.73 (d_{AB}, J=12.9 Hz, 1H), 4.36 (q, *J*=6.6 Hz, 1H), 7.06 (d, *J*=7.9 Hz, 2H), 7.13 (d, *J*=8.0 Hz, 2H), 7.41-7.53 (m, 3H), 7.65 (d, *J*=6.7 Hz, 1H), 7.73 (d, *J*=8.2 Hz, 1H), 7.84 (m, 1H), 8.44 (d, *J*=8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 16.8, 21.1, 38.3, 58.9, 60.5, 124.5, 124.6, 125.3, 125.3, 125.4, 127.4, 128.6, 128.7 (2C), 128.8 (2C), 131.9, 134.1, 136.1, 137.0, 140.8; IR (neat, cm^{-1}): 2973, 2787, 776, 754; HRMS (EI): found 289.1828 (calcd 289.1830, M^+).

4.5.5. (*R*)-*N*-(4-Methoxybenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine hydrochloride (3e)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (111 mg, 0.500 mmol), *N*,*N*-diisopropylethylamine (195 mg, 1.500 mmol), 1-(bromomethyl)-4-methoxybenzene (82 mg, 0.525 mmol) and acetonitrile (10 mL). Purification was done by filtration through a silica-gel column (pentane : EtOAc, 7 : 3), followed by isolation of the product as its hydrochloride salt. This gave 100 mg (0.33 mmol, 65%) of a white solid, mp. 179-181 °C; $[\alpha]_D^{20}$ = -62.3 (*c* 1.00, MeOH); purity >98% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.54 (d, J=6.6 Hz, 3H), 2.18 (s, 3H), 3.35 (d_{AB}, J=13.1 Hz, 1H), 3.58 (d_{AB}, J=13.1 Hz, 1H), 3.77 (s, 3H), 4.36 (q, J=6.6 Hz, 1H), 6.80 (d, J=8.7 Hz, 2H), 7.34 (d, J=7.8 Hz, 2H), 7.42-7.54 (m, 3H), 7.65 (d, J=7.4 Hz, 1H), 7.75 (d, J=8.1 Hz, 1H), 7.85 (d, J=8.1 Hz, 1H), 8.43 (d, J=8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 16.8, 38.3, 55.4, 58.6, 60.5, 113.6 (2C), 124.6, 124.7, 125.4, 125.5, 125.6, 127.6, 128.8, 130.0 (2C), 132.0, 132.3, 134.3, 140.9, 158.6; IR (neat, cm^{-1}): 2957, 2487, 1610, 1514, 1248, 1180, 1029, 802, 579; HRMS (ESI): 306.1805 (calcd 306.1852, $[M+H]^+$).

4.5.6. (*R*)-*N*-(4-Bromobenzyl)-N-methyl-1-(naphthalen-1-yl)ethanamine (3f)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (222 mg, 1.198 mmol), *N*,*N*-diisopropylethylamine (290 mg, 2.24 mmol), 1-(bromomethyl)-4-bromobenzene (3.27 mg, 1.765 mmol) and acetonitrile (5 mL). Purification was done by silica-gel column chromatography (CH_2Cl_2 : EtOAc, 40 : 1, R_f = 0.46). This gave 347 mg (0.979 mmol, 82%) of an oil; $[\alpha]_D^{20}$ = -67.8 (*c* 1.00, $CHCl_3$); purity >99% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.57 (d, *J*=6.7 Hz, 3H), 2.21 (s, 3H), 3.38 (d_{AB}, *J*=13.5 Hz, 1H), 3.58 (d_{AB}, *J*=13.5 Hz, 1H), 4.40 (q, *J*=6.7 Hz, 1H), 7.12 (d, *J*=8.1 Hz, 2H), 7.38 (d, *J*=8.3 Hz, 2H), 7.45-7.56 (m, 3H), 7.65 (d, *J*=7.0 Hz, 1H), 7.77 (d, *J*=8.1 Hz, 1H), 7.88 (m, *J*=7.9 Hz, 1H), 8.45 (d, *J*=8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 16.6, 38.5, 58.3, 60.6, 120.3, 124.46, 124.5, 125.3, 125.4, 125.5, 127.6, 128.7, 130.3 (2C), 131.2 (2C), 131.8, 134.1, 139.3, 140.4; IR (neat, cm^{-1}): 2972, 2787, 1485, 1068, 1010, 798, 777, 731; HRMS (ESI): 354.0855 (calcd 354.0852, $[M+H]^+$).

4.5.7. (*R*)-*N*-Methyl-1-(naphthalen-1-yl)-*N*-(4-nitrobenzyl)ethanamine hydrochloride (3g)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (441 mg, 2.380 mmol), *N*,*N*-diisopropylethylamine (460 mg, 3.559 mmol), 1-(bromomethyl)-4-nitrobenzene (575 mg, 2.662 mmol) and acetonitrile (10 mL). Purification of the compound was by precipitation as its hydrochloride salt. This yielded 608 mg (1.898 mmol, 79%) of a yellowish solid; mp. 122-124 °C; $[\alpha]_D^{20}$ = -101.1 (*c* 1.00, MeOH); purity > 98% (HPLC, 280 nm); Free base: mp. 74.5-75.5 °C; $[\alpha]_D^{20}$ = -118.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.58 (d, *J*=6.7 Hz, 3H), 2.24 (s, 3H), 3.50 (d_{AB}, *J*=14.3 Hz, 1H), 3.67 (d_{AB}, *J*=14.3 Hz, 1H), 4.44 (q, *J*=6.7 Hz, 1H), 7.36 (d, *J*=8.7 Hz, 2H), 7.43-7.57 (m, 3H), 7.63 (d, *J*=7.0 Hz, 1H), 7.77 (d, *J*=8.2 Hz, 1H), 7.87 (d, *J*=9.3 Hz, 1H), 8.08 (d, *J*=8.8 Hz, 2H), 8.44 (d, *J*=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 16.4, 38.9, 58.0, 60.9, 123.4 (2C), 124.3, 124.7, 125.3, 125.5, 125.6, 127.8, 128.8, 129.0 (2C), 131.7, 134.2, 140.0, 146.9, 148.4; IR (neat, cm^{-1}): 2972, 2786, 1515, 1341, 777, 738; HRMS (EI): found 320.1524 (calcd 320.1525, M^+).

4.5.8. (*R*)-*N*-methyl-1-(naphthalen-1-yl)-*N*-(4-(trifluoromethyl)benzyl)ethanamine hydrochloride (3h)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (113 mg, 0.510 mmol), *N*,*N*-diisopropylethylamine (195 mg, 1.500 mmol), 1-(bromomethyl)-4-(trifluoromethyl)benzene (126 mg, 0.525 mmol) and acetonitrile (10 mL). The crude product was purified twice by silica-gel column chromatography using pentane : EtOAc (9:1) and then CH_2Cl_2 : MeOH (200:1). This gave 108 mg (0.134 mmol, 29%) of a clear oil which crystallised on storage at rt; mp. 47.5-48.0 °C; $[\alpha]_D^{20}$ = -77.9 (*c* 1.10, MeOH), purity > 99% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.55 (d, J= 6.8 Hz, 3H), 2.20 (s, 3H), 3.44 (d_{AB}, J= 13.8 Hz, 1H), 3.63 (d_{AB}, J= 13.8 Hz, 1H), 4.39 (q, J=6.8 Hz, 1H), 7.31 (ap d, J= 7.8 Hz, 2H), 7.38-7.59 (m, 5H), 7.62 (ap d, J=6.8 Hz, 1H), 7.74 (ap d, J=8.3 Hz, 1H), 7.84 (m, 1H), 8.44 (ap d, J=8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 16.5, 38.4, 58.4, 60.8, 124.3 (q, J=270.0 Hz), 124.47, 124.51, 125.0 (q, J=3.9 Hz, 2C), 125.3, 125.5, 125.6, 127.7, 128.7 (2C), 128.8, 128.9 (q, J=32.5 Hz), 131.8, 134.2, 140.3, 144.5 (q, J=1.4 Hz); ^{19}F NMR ($CDCl_3$, 564 MHz, free base) *δ*: -65.5 (s); IR (neat, cm^{-1}): 2978, 2792, 1618, 1509, 1322, 1158, 1104, 797, 777; HRMS (EI): found 344.1634 (calcd 344.1621, $[M+H]^+$).

4.5.9. (*R*)-*N*-methyl-1-(naphthalen-1-yl)-*N*-(4-(trimethylsilyl)benzyl)ethanamine hydrochloride (3i)

The reaction was performed as described in Section 4.5.1 with *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (111 mg, 0.500 mmol), *N*,*N*-diisopropylethylamine (195 mg, 1.500 mmol), (4-(bromomethyl)phenyl)trimethylsilane (128 mg, 0.525 mmol) and acetonitrile (10 mL). and (4-(bromomethyl)phenyl)trimethylsilane as alkylating agent. Purification was done by filtration through a silica-gel column (pentane : EtOAc, 9 : 1), followed by isolation of the product as its hydrochloride salt. The product was further purified by preparative HPLC (Poroshell, 100×21.5 mm) with gradient elution starting with 0.1% TFA in water/acetonitrile (65/35) with an increase in acetonitrile amount of 1.14%/min, R_t = 10.0 min. This gave 103 mg (0.27 mmol, 54%) of a white solid; mp. 200-202 °C; $[\alpha]_D^{20}$ = -44.1 (c 1.00, MeOH); purity: 98% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 0.23 (s, 9H), 1.56 (d, J=6.3 Hz, 3H), 2.21 (s, 3H), 3.42 (d_{AB}, J=13.4 Hz, 1H), 3.63 (d_{AB}, J=13.4 Hz, 1H), 4.39 (q, J=6.6 Hz, 1H), 7.22-7.25 (m, 2H), 7.39-7.54 (m, 5H), 7.65 (d, J=7.2 Hz, 1H), 7.74 (d, J=8.4 Hz, 1H), 7.85 (d, J=7.9 Hz, 1H), 8.46 (d, J=8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: -0.9 (3C), 16.7, 38.6, 59.2,

60.8, 124.6, 124.8, 125.4, 125.5, 125.6, 127.6, 128.2 (2C), 128.8, 132.0, 133.3 (2C), 134.3, 138.6, 140.8, 141.0; IR (neat, cm^{-1}): 2953, 2839, 2789, 1598, 1508, 1393, 1246, 1107, 834, 669; HRMS (EI): found 347.2062 (calcd. 347.2064, M^+).

4.5.10. (*R*)-*N*-Methyl-1-(naphthalen-1-yl)-*N*-(4-(trifluoromethoxy)benzyl)ethanamine (3j)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (111 mg, 0.500 mmol), *N*,*N*-diisopropylethylamine (195 mg, 1.500 mmol), 1-(bromomethyl)-4-(trifluoromethoxy)benzene (134 mg, 0.525 mmol) and acetonitrile (10 mL). Purification was done by filtration through silica-gel column (pentane : EtOAc, 9 : 1), followed by isolation as its hydrochloric salt. This gave 157 mg (0.44 mmol, 88%) of white solid, mp. 156-158 °C; $[\alpha]_D^{20}$ = -68.3 (*c* 1.00, MeOH); purity > 99% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.56 (d, J=6.5 Hz, 3H), 2.21 (s, 3H), 3.40 (d_{AB}, J=13.5 Hz, 1H), 3.60 (d_{AB}, J=13.5 Hz, 1H), 4.39 (q, J=6.5 Hz, 1H), 7.08 (d, J=8.2 Hz, 2H), 7.23 (d, J=8.2 Hz, 2H), 7.42-7.56 (m, 3H), 7.63 (d, J=7.1 Hz, 1H), 7.76 (d, J=8.2 Hz, 1H), 7.86 (d, J=7.8 Hz, 1H), 8.43 (d, J=8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 16.7, 38.7, 58.3, 60.8, 119.4, 120.8 (2C), 124.62, 124.64, 125.4, 125.6, 125.7, 127.8, 128.9, 130.0 (2C), 132.0, 134.3, 139.2, 140.5, 148.1 (m); ^{19}F NMR ($CDCl_3$, 564 MHz, free base) *δ*: -61.1 (s); IR (neat, cm^{-1}): 2960, 2490, 1598, 1511, 1457, 1255, 1157, 1063, 880, 800, 620; HRMS (ESI): 360.1572 (calcd 360.1570, $[M+H]^+$).

4.5.11. (*R*)-*N*-(4-(Benzyloxy)benzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine hydrochloride (3k)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (415 mg, 2.239 mmol), *N*,*N*-diisopropylethylamine (868 mg, 6.717 mmol), 1-(benzyloxy)-4-(bromomethyl)benzene (683 mg, 2.463 mmol) and acetonitrile (5 mL). Purification was by precipitation as its hydrochloride salt, which yielded 626 mg (1.500 mmol, 67%) of a white solid; mp. 184-186 °C; $[\alpha]_D^{20}$ = -42.3 (*c* 0.99, MeOH); purity: 94% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) δ: 1.56 (d, J=6.6 Hz, 3H), 2.20 (s, 3H), 3.38 (d_{AB}, J=13.1 Hz, 1H), 3.60 (d_{AB}, J=13.1 Hz, 1H), 4.38 (q, J=6.6 Hz, 1H), 5.04 (s, 2H), 6.89 (d, J=8.7 Hz, 2H), 7.17 (d, J=8.6 Hz, 2H), 7.30-7.55 (m, 8H), 7.67 (d, J=6.8 Hz, 1H), 7.76 (m, 1H), 7.87 (d, J=9.4 Hz, 1H), 8.46 (d, J=8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) δ: 16.7, 38.2, 58.5, 60.4, 70.0, 114.5 (2C), 124.5, 124.6, 125.2, 125.3, 125.4, 127.4 (3C), 127.9, 128.5 (2C), 128.7, 129.9 (2C), 131.8, 132.4, 134.1, 137.2, 140.7, 157.7; IR (neat, cm^{-1}): 2972, 2781, 1508, 1234, 777; HRMS (EI): found 381.2094 (calcd 381.2087, M^+).

4.5.12. (*R*)-*N*-(Biphenyl-4-ylmethyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine (3l)

The reaction was performed as described in Section 4.5.1 using *N*-Methyl-1-(naphthalen-1-yl)ethanamine (**8**) (309 mg, 1.668 mmol), *N*,*N*-diisopropylethylamine (340 mg, 2.63 mmol), 4-(chloromethyl)biphenyl (355 mg, 1.752 mmol) and acetonitrile (5 mL), but refluxing for 3 h. Purification was done by silica-gel column chromatography (CH_2Cl_2 : MeOH, 40 : 1, R_f = 0.51), which yielded 383 mg (1.090 mmol, 65%) of an off-white solid; mp. 88-89 °C; $[\alpha]_D^{20}$ = -81.7 (*c* 0.97, $CHCl_3$); purity > 99% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.55 (d, J= 6.6 Hz, 3H), 2.22 (s, 3H), 3.44 (d_{AB}, J=13.6 Hz, 1H), 3.66 (d_{AB}, J=13.6 Hz, 1H), 4.37 (q, J=6.6 Hz, 1H), 7.25-7.32 (m, 3H), 7.35-7.58 (m, 9 H), 7.65 (ap d, J=7.1 Hz, 1H), 7.73 (ap d, J=8.1 Hz, 1H), 7.84 (ap d, J=8.1 Hz, 1H), 8.47 ap d, J=8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 16.7, 38.4, 58.7, 60.6, 124.5, 124.6, 125.2, 125.3,125.5, 126.8 (2C), 126.97 (2C), 127.0, 127.5, 128.65 (2C), 128.7, 129.1 (2C), 131.8, 134.1, 139.3, 139.6, 140.6, 141.1; IR (neat, cm^{-1}): 3028, 2975, 2847, 1596, 1053, 804, 792, 777, 723; HRMS (EI): found 351.1979 (calcd 351.1982, M^+).

4.5.13. (*R*)-*N*-(2-Fluorobenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine hydrochloride (3m)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (111 mg, 0.500 mmol), *N*,*N*-diisopropylethylamine (195 mg, 1.500 mmol), 1-(bromomethyl)-2-fluorobenzene (99 mg, 0.525 mmol) and acetonitrile (10 mL). Purification was done by filtration through a silica-gel column (pentane : EtOAc, 9 : 1), followed by isolation as its hydrochloride salt. This gave 117 mg (0.40 mmol, 80%) of white solid; mp. 178-180 °C; $[\alpha]_D^{20}$ = -97.1 (*c* 1.00, MeOH); purity >99% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.57 (d, J=6.6 Hz, 3H), 2.21 (s, 3H), 3.55 (d_{AB}, J=13.7 Hz, 1H), 3.68 (d_{AB}, J=13.7 Hz, 1H), 4.42 (q, J=6.5 Hz, 1H), 6.93-7.07 (m, 2H), 7.13-7.20 (m, 1H), 7.30-7.36 (m, 1H), 7.42-7.53 (m, 3H), 7.65 (d, J=7.0 Hz, 1H), 7.75 (d, J=8.3 Hz, 1H), 7.85 (d, J=8.5 Hz, 1H), 8.42 (d, J=8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 16.8, 38.4, 51.7 (d, J=2.2 Hz), 60.6, 115.2 (d, J=22.1 Hz), 124.0 (d, J=3.2 Hz), 124.6 (2C), 125.4, 125.5, 125.7, 126.8 (d, J=13.9 Hz), 127.7, 128.3 (d, J=8.5 Hz), 128.8, 131.3 (d, J=4.6 Hz), 132.0, 134.2, 140.6. 161.5 (d, J=245 Hz); ^{19}F NMR ($CDCl_3$, 564 MHz, free base) *δ*: -121.4 (m); IR (neat, cm^{-1}): 2989, 2452, 1586, 1454, 1367, 1236, 1004, 802, 762, 619; HRMS (ESI): 294.1649 (calcd 294.1653, $[M+H]^+$).

4.5.14. (*R*)-*N*-(2-Bromobenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine hydrochloride (3n)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (111 mg, 0.500 mmol), *N*,*N*-diisopropylethylamine (195 mg, 1.500 mmol), 1-(bromomethyl)-2-bromobenzene (131 mg, 0.525 mmol) and acetonitrile (10 mL). Purification was done by filtration through a silica-gel column (pentane : EtOAc, 9 : 1), followed by isolation as its hydrochloride salt. This gave 162 mg (0.46 mmol, 92%) of a white solid; mp. 178-180 °C; $[\alpha]_D^{20}$ = -52.1 (*c* 1.00, MeOH); purity > 99% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.60 (d, J=6.7 Hz, 3H), 2.22 (s, 3H), 3.67 (d_{AB}, J=14.6 Hz, 1H), 3.71 (d_{AB}, J=14.6 Hz, 1H), 4.49 (q, J=6.7 Hz, 1H), 7.01-7.08 (m, 1H), 7.19-7.25 (m, 1H), 7.41-7.53 (m, 5H), 7.64 (d, J=7.1 Hz, 1H), 7.75 (d, J=8.1 Hz, 1H), 7.83-7.87 (m, 1H), 8.43 (d, J=8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 16.5, 38.7, 58.3, 60.7, 124.4, 124.6, 124.7, 125.4, 125.5 (2C), 125.6, 127.4, 127.7, 128.1, 128.8, 130.8, 132.0, 132.6, 139.2, 140.5; IR (neat, cm^{-1}): 3019, 2455, 2378, 1595, 1439, 1384, 1238, 1126, 1026, 806, 657; HRMS (ESI): 354.0851 (calcd 354.0852, $[M+H]^+$).

4.5.15. (*R*)-*N*-Methyl-1-(naphthalen-1-yl)-*N*-(2-(trifluoromethyl)benzyl)ethanamine (3o)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (111 mg, 0.500 mmol), *N*,*N*-diisopropylethylamine (195 mg, 1.500 mmol), 1-(bromomethyl)-2-(trifluoromethyl)benzene (126 mg, 0.525 mmol) and acetonitrile (10 mL). Purification was done by filtration through a silica-gel column (pentane : EtOAc, 9 : 1), followed by isolation as its hydrochloride salt. This gave 104 mg (0.27 mmol, 54%) of a white solid; mp. 169-170 °C; $[\alpha]_D^{20}$ = -133.4 (*c* 1.00, MeOH); purity > 99% (HPLC 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.58 (d, J=6.7 Hz, 3H), 2.20 (s, 3H), 3.73 (s, 2H), 4.41 (q, J=6.7 Hz, 1H), 7.21-7.27 (m, 1H), 7.39-7.57 (m, 5H), 7.65 (d, J=7.1 Hz, 1H), 7.72-7.77 (m, 2H), 7.86 (d, J=8.1 Hz, 1H), 8.47 (d, J=8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 16.4, 38.7, 54.0 (m), 60.9, 124.4, 124.5 (q, J=274.6 Hz), 124.6, 125.3, 125.3 (q, J=6.0 Hz), 125.4, 125.5, 126.3, 127.6, 128.2 (q, J=30.0 Hz), 128.7, 130.1, 131.7 (m), 131.8, 134.1, 139.6 (q, J=1.4 Hz), 140.4; ^{19}F NMR ($CDCl_3$, 564 MHz, free base) *δ*: -65.7 (s); IR (neat, cm^{-1}): 3024, 2459, 2382, 1606, 1482, 1310, 1163, 1124, 1038, 889, 807, 770; HRMS (ESI): 344.1617 (calcd 344.1621, $[M+H]^+$).

4.5.16. (*R*)-*N*-(Biphenyl-2-ylmethyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine (3p)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (111 mg, 0.500 mmol), *N*,*N*-diisopropylethylamine (195 mg, 1.500 mmol), 2-(bromomethyl)biphenyl (130 mg, 0.525 mmol) and acetonitrile (10 mL). Purification was done by filtration through a silica gel column (pentane : EtOAc, 9:1), followed by isolation of the product as its hydrochloride salt. This gave 151 mg (0.43 mmol, 86%) of a white solid; mp. 191-192 °C; $[\alpha]_D^{20}$ = +2.2 (*c* 1.00, MeOH); purity > 99% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) δ: 1.38 (d, J=6.7 Hz, 3H), 2.05 (s, 3H), 3.56 (d_{AB}, J=14.0 Hz, 1H), 3.54 (d_{AB}, J=14.0 Hz, 1H), 4.27 (q, J=6.68 Hz, 1H), 7.17-7.49 (m, 12H), 7.55 (d, 1H, J=7.3 Hz), 7.60 (d, J=7.7 Hz, 1H), 7.72 (d, J=8.2 Hz, 1H), 7.81-7.86 (m, 1H), 8.25-8.30 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) δ: 16.6, 38.4, 55.8, 60.3, 124.4, 124.5, 125.3 (2C), 125.4, 126.3, 126.7, 127.3, 127.3, 127.9 (2C), 128.6, 129.4 (2C), 129.6, 129.8, 131.8, 134.1, 137.4, 140.8, 141.6, 142.2; IR (neat, cm^{-1}): 3044, 2434, 2374, 1480, 1238, 1077, 890, 808, 759; HRMS (ESI): 352.2060 (calcd 352.2060, $[M+H]^+$).

4.5.17. (*R*)-*N*-(3-Bromobenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine hydrochloride (3q)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (111 mg, 0.500 mmol), *N*,*N*-diisopropylethylamine (195 mg, 1.500 mmol), 1-(bromomethyl)-3-bromobenzene (131 mg, 0.525 mmol) and acetonitrile (10 mL). Purification was done by filtration employing silica-gel column chromatography (pentane : EtOAc, 9 : 1), followed by isolation as its hydrochloride salt. This gave 153 mg (0.43 mmol, 86%) of white solid; mp. 169-170 °C; $[\alpha]_D^{20}$ = -97.4 (*c* 1.00, MeOH); purity > 99% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) δ: 1.55 (d, J=6.7 Hz, 3H), 2.21 (s, 3H), 3.37 (d_{AB}, J=13.7 Hz, 1H), 3.58 (d_{AB}, J=13.7 Hz, 1H), 4.38 (q, J=6.7 Hz, 1H), 7.07-7.16 (m, 2H), 7.31 (d, J=7.7 Hz, 1H), 7.38-7.57 (m, 4H), 7.63 (d, J=7.1 Hz, 1H), 7.76 (d, J=8.2 Hz, 1H), 7.86 (d, J=8.2 Hz, 1H), 8.43 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) δ: 16.8, 38.7, 58.6, 60.7, 122.5, 124.63, 124.65, 125.4, 125.6, 125.7, 127.4, 127.8, 128.9, 129.8, 129.9, 131.8, 131.9, 134.3, 140.5, 142.9; IR (neat, cm^{-1}): 3020, 2361, 1569, 1457, 1252, 1113, 1074, 858, 695; HRMS (ESI): 354.0851 (calcd 354.0852, $[M+H]^+$).

4.5.18. (*R*)-*N*-Methyl-1-(naphthalen-1-yl)-*N*-(3-(trifluoromethyl)benzyl)ethanamine hydrochloride (3r)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (111 mg, 0.500 mmol), *N*,*N*-diisopropylethylamine (195 mg, 1.500 mmol), 1-(bromomethyl)-3-(trifluoromethyl)benzene (126 mg, 0.525 mmol) and acetonitrile (10 mL). Purification was done by filtration through a silica-gel column (pentane : EtOAc, 9 : 1), followed by isolation as its hydrochloride salt. This gave 96 mg (0.28 mmol, 56%) of white solid; mp. 101-103 °C; $[\alpha]_D^{20}$ = -81.6 (*c* 1.00, MeOH); purity > 99% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) δ: 1.57 (d, J=6.7 Hz, 3H), 2.22 (s, 3H), 3.46 (d_{AB}, J=13.1 Hz, 1H), 3.64 (d_{AB}, J=13.1 Hz, 1H), 4.41 (q, J=6.7 Hz, 1H), 7.30-7.67 (m, 8H), 7.76 (d, J=8.2 Hz, 1H), 7.86 (d, J=8.2 Hz, 1H), 8.46 (d, J=8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, free base) δ: 16.4, 38.6, 58.4, 60.7, 123.5 (q, J=3.7 Hz), 124.3 (q, J=272.4 Hz), 124.5, 124.6, 125.2, 125.3 (q, J=3.8 Hz), 125.5, 125.6, 127.7, 128.5, 128.7, 130.4 (q, J=32.6 Hz), 131.8, 131.9, 134.2, 140.2, 141.3; ^{19}F NMR (CDCl3, 564 MHz, free base) δ: -65.7 (s); IR (neat, cm^{-1}): 2918, 2473, 1598, 1455, 1327, 1149, 1075, 799, 701; HRMS (ESI): 344.1621 (calcd 344.1621, $[M+H]^+$).

4.5.19. (*R*)-*N*-(3,5-Bis(trifluoromethyl)benzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine hydrochloride (3s)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (111 mg, 0.500 mmol), *N*,*N*-diisopropylethylamine (195 mg, 1.500 mmol), 1-(bromomethyl)-3,5-bis(trifluoromethyl)benzene (161 mg, 0.525 mmol) and acetonitrile (10 mL). Purification was done by filtration through a silica-gel column (pentane : EtOAc, 9 : 1), followed by isolation as its hydrochloride salt. This gave 175 mg (0.43 mmol, 86%) of a white solid; mp 102-104 °C; $[\alpha]_D^{20}$ = -111.6 (*c* 1.00, MeOH); purity > 97% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.60 (d, J=6.7 Hz, 3H), 2.28 (s, 3H), 3.53 (d_{AB}, , J=14.2 Hz, 1H), 3.65 (d_{AB}, J=14.2 Hz, 1H), 4.48 (q, J=6.7 Hz, 1H), 7.42-7.67 (m, 7H), 7.77 (d, J=8.2 Hz, 1H), 7.86 (d, J=8.2 Hz, 1H), 8.44 (d, J=8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 16.1, 39.0, 57.6, 60.9, 120.8 (m), 123.5 (q, J=272.4 Hz, 2C), 124.6, 124.7, 125.3, 125.8, 125.9, 128.2, 128.7 (m, 2C), 128.9, 131.4 (q, J=33.7 Hz, 2C), 131.8, 134.3, 139.6, 143.1; ^{19}F NMR ($CDCl_3$, 564 MHz, free base) *δ*: -66.0 (s); IR (neat, cm^{-1}): 2960, 2473, 1630, 1460, 1276, 1170, 1125, 905, 705, 619; HRMS (ESI): 412.1492 (calcd 412.1492, $[M+H]^+$).

4.5.20. (*R*)-*N*-(3,5-Di-*tert*-butylbenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine hydrochloride (3t)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (131 mg, 0.707 mmol), *N*,*N*-diisopropylethylamine (274 mg, 2.121 mmol), 1-(bromomethyl)-3,5-di-*tert*-butylbenzene (220 mg, 0.778 mmol) and acetonitrile (5 mL). Purification was by precipitation of the product as its hydrochloride salt. The yield was 122 mg (0.29 mmol, 41%) of a white solid; mp. 115-118 °C; $[\alpha]_D^{20}$ = -48.6 (*c* 0.80, MeOH); purity > 95% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.29 (s, 18H), 1.60 (d, *J*=6.6 Hz, 3H), 2.27 (s, 3H), 3.50 (d_{AB}, *J*=13.4 Hz, 1H), 3.62 (d_{AB}, *J*=13.4 Hz, 1H), 4.46 (q, *J*=6.6 Hz, 1H), 7.09 (m, 2H), 7.26 (m, 1H), 7.43-7.54 (m, 3H), 7.62 (d, *J*=7.1 Hz, 1H), 7.76 (d, *J*=8.1 Hz, 1H), 7.86 (m, 1H), 8.56 (d, *J*=8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 15.3, 31.5 (6C), 34.7 (2C), 38.4, 59.1, 60.4, 120.5, 122.8 (2C), 124.6, 125.1, 125.2, 125.3, 125.4, 127.8, 128.8, 132.1, 134.3, 139.2, 140.7, 150.4 (2C); IR (neat, cm^{-1}): 2962, 2866, 1361, 777, 714; HRMS (EI): found 388.3001 (calcd 388.2999, $[M+H]^+$).

4.5.21. (*R*)-*N*-(4-*Tert*-butyl-2,6-dimethylbenzyl)-*N*-methyl-1-(naphthalen-1-yl)ethanamine hydrochloride (3u)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (130 mg, 0.702 mmol), *N*,*N*-diisopropylethylamine (272 mg, 2.106 mmol), 2-(bromomethyl)-5-*tert*-butyl-1,3-dimethylbenzene (197 mg, 0.772 mmol) and acetonitrile (5 mL). Purification was by precipitation of the product as its hydrochloride salt. The yield was 130 mg (0.33 mmol, 47%) of a white solid; mp. 164-166 °C; $[\alpha]_D^{20}$ = -55.3 (*c* 0.99, MeOH); purity: 95% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.32 (s, 9H), 1.63 (d, *J*=6.7 Hz, 3H), 2.11 (s, 3H), 2.33 (s, 6H), 3.61 (d_{AB}, *J*=12.4 Hz, 1H), 3.72 (d_{AB}, *J*=12.4 Hz, 1H), 4.41 (q, *J*=6.7 Hz, 1H), 7.03 (s, 2H), 7.34 (d, *J*=7.2 Hz, 1H), 7.41 (m, 2H), 7.62 (d, *J*=7.0 Hz, 1H), 7,75 (d, *J*=8.2 Hz, 1H), 7.83 (d, *J*=8.0 Hz, 1H), 8.06 (d, *J*=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 14.9, 20.6 (2C), 31.4 (3C), 34.2, 37.8, 51.5, 59.0, 124.4, 124.5, 125.0, 125.17 (2C), 125.2, 125.3, 127.4, 128.5, 132.1, 132.7, 134.0, 137.9 (2C), 140.4, 149.5; IR (neat, cm^{-1}): 2962, 1361, 1233, 800, 777, 730; HRMS (ESI): found 360.2684 (calcd 360.2686, $[M+H]^+$).

4.5.22. (*R*)-*N*-Methyl-1-(naphthalen-1-yl)-*N*-(pyridin-4-ylmethyl)ethanamine hydrochloride (3v)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (111 mg, 0.500 mmol), *N*,*N*-diisopropylethylamine (259 mg, 2.000 mmol), 4-(bromomethyl)pyridine hydrochloride (133 mg, 0.525 mmol)

and acetonitrile (10 mL). Purification was done by filtration through a silica-gel column (pentane : EtOAc, 9 : 1), followed by isolation as its hydrochloride salt. This gave 97 mg (0.35 mmol, 70%) of a white solid, which decomposed upon melting; $[\alpha]_D^{20}$ = -93.8 (*c* 1.00, MeOH); purity > 98% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.57 (d, J=6.7 Hz, 3H), 2.24 (s, 3H), 3.42 (d_{AB}, J=14.7 Hz, 1H), 3.60 (d_{AB}, J=14.7 Hz, 1H), 4.42 (q, J=6.7 Hz, 1H), 7.16 (d, J=5.2 Hz, 2H), 7.42-7.58 (m, 3H), 7.63 (d, J=7.1 Hz, 1H), 7.76 (d, J=8.4 Hz, 1H), 7.87 (d, J=7.9 Hz, 1H), 8.45 (d, J=7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 16.7, 39.1, 57.9, 61.0, 123.7, 124.5, 124.6, 125.4 (2C), 125.6 (2C), 125.8 (2C), 127.9, 128.9, 131.9, 134.3, 149.7 (2C); IR (neat, cm^{-1}): 3053, 2357, 2095, 1638, 1511, 1459, 1248, 1002, 800, 606; HRMS (ESI): 276.1625 (calcd 276.1626, M^+).

4.5.23. (*R*)-*N*-Methyl-1-(naphthalen-1-yl)-*N*-(pyridin-3-ylmethyl)ethanamine hydrochloride (3w)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (111 mg, 0.500 mmol), *N*,*N*-diisopropylethylamine (259 mg, 2.000 mmol), 3-(bromomethyl)pyridine hydrochloride (133 mg, 0.525 mmol) and acetonitrile (10 mL). Purification was done by filtration through a silica-gel column (pentane : EtOAc, 9 : 1), followed by isolation of the product as its hydrochloric salt. This gave 85 mg (0.31 mmol, 62%) of a white solid; mp. 170-172°C; $[\alpha]_D^{20}$ = -109.4 (c=1.00, MeOH); purity: >99% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.57 (d, J=6.7 Hz, 3H), 2.22 (s, 3H), 3.41 (d_{AB}, J=13.6 Hz, 1H), 3.60 (d_{AB}, J=13.6 Hz, 1H), 4.40 (q, J=6.7 Hz, 1H), 7.13-7.18 (m, 1H), 7.43-7.57 (m, 4H), 7.64 (d, J=7.0 Hz, 1H), 7.76 (d, J=8.4 Hz, 1H), 7.86 (d, J=7.9 Hz, 1H), 8.44-8.45 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 16.7, 38.7, 56.2, 61.0, 123.4, 124.6, 124.7, 125.4, 125.6, 125.8, 127.9, 128.9, 131.9, 134.3, 135.6, 136.5, 140.4, 148.3, 150.3; IR (neat, cm^{-1}): 2959, 2490, 1598, 1511, 1457, 1204, 1157, 1064, 800, 621; HRMS (ESI): 277.1695 (calcd 277.1699, $[M+H]^+$).

4.5.24. (*R*)-*N*-Methyl-1-(naphthalen-1-yl)-*N*-(pyridin-2-ylmethyl)ethanamine hydrochloride (3x)

The reaction was performed as described in Section 4.5.1 using *N*-methyl-1-(naphthalen-1-yl)ethanamine (**8**) (111 mg, 0.500 mmol), *N*,*N*-diisopropylethylamine (259 mg, 2.000 mmol), 2-(bromomethyl)pyridine hydrochloride (133 mg, 0.525 mmol) and acetonitrile (10 mL). Purification was done by filtration through a silica-gel column (pentane : EtOAc, 9 : 1), followed by isolation of the product as its hydrochloride salt. This gave 92 mg (0.33 mmol, 66%) of a white solid; mp. 163-165 °C; $[\alpha]_D^{20}$ = -85.8 (*c* 1.00, MeOH); purity > 98% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) *δ*: 1.58 (d, J=6.6 Hz, 3H), 2.27 (s, 3H), 3.67 (d_{AB}, J=14.3 Hz, 1H), 3.79 (d_{AB}, J=14.3 Hz, 1H), 4.48 (q, J=6.6 Hz, 1H), 7.06-7.11 (m, 1H), 7.34 (d, J=7.8 Hz, 1H), 7.42-7.59 (m, 4H), 7.65 (d, J=7.2 Hz, 1H), 7.75 (d, J=8.1 Hz, 1H), 7.85 (d, J=7.8 Hz, 1H), 8.43-8.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) *δ*: 16.4, 39.1, 60.7, 60.8, 121.8, 122.9, 124.65, 124.67, 125.4, 125.5, 125.7, 127.7, 128.8, 132.0, 134.3, 136.5, 140.4, 148.8, 160.8; IR (neat, cm^{-1}): 3408, 3008, 2360, 2063, 1999, 1616, 1469, 1391, 1231, 1002, 890, 609; HRMS (ESI): 277.1694 (calcd 277.1699, $[M+H]^+$).

4.5.25. (*S*)-1-(4-*Tert*-butylphenyl)-*N*-methyl-*N*-(naphthalen-1-ylmethyl)ethanamine ((*S*)-4)

1-(Chloromethyl)naphthalene (**9y**) (93 mg, 0.525 mmol), (*S*)-1-(4-*tert*-butylphenyl)-*N*-methylethanamine (113 mg, 0.500 mmol) ((***S***)-**6**) and *N*-*N*-diisopropylethylamine (194 mg, 1.500 mmol) were dissolved in acetonitrile (5 mL). The reaction mixture was stirred at 50 °C for 24h. The acetonitrile was removed *in vacuo*, and $CHCl_3$ (20 mL) was added. The mixture

was washed with water (3×10 mL), and the water phases were back-extracted with $CHCl_3$ (2×10 mL). The combined organic phases were dried over Na_2SO_4. After the solvent was removed, ether (5 mL) was added and the product was isolated as its hydrochloric salt by adding a sat. solution of HCl in ether (0.3 mL) dropwise. The white solid was washed several times with pentane, and then dried in vacuum. This yielded 101 mg (0.28 mmol, 55%) of a white solid, mp. 155-157 °C; $[\alpha]_D^{20}$ = -25.0 (*c* 1.00, MeOH); purity > 98% (HPLC, 280 nm); ^{1}H NMR ($CDCl_3$, 400 MHz, free base) δ: 1.32 (s, 9H), 1.49 (d, J=6.9 Hz, 3H), 2.12 (s, 3H), 3.77 (q, J=6.9 Hz, 1H), 3.89 (d_{AB}, J=13.0 Hz, 1H), 3.93 (d_{AB}, J=13.0 Hz, 1H), 7.34-7.49 (m, 8H), 7.74 (d, J=8.2 Hz, 1H), 7.79-7.84 (m, 1H), 8.13-8.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, free base) δ: 16.7, 31.6 (3C), 34.6, 38.2, 57.4, 63.0, 124.9, 125.1 (2C), 125.3, 125.6, 125.7, 127.4, 127.72 (2C), 127.75, 128.5, 132.7, 134.0, 135.7, 140.6, 149.8; IR (neat, cm^{-1}): 3047, 2963, 2866, 2787, 2359, 1684, 1596, 1508, 1460, 1362, 1017, 836, 731; HRMS (ESI): 331.2300 (calcd. 331.2295, $[M+H]^+$).

4.5.26. (*R*)-1-(4-*Tert*-butylphenyl)-*N*-methyl-*N*-(naphthalen-1-ylmethyl)ethanamine hydrochloride ((*R*)-4)

The reaction was performed as described in Section 4.5.25, starting with (*R*)-1-(4-*tert*-butylphenyl)-*N*-methylethanamine (113 mg, 0.500 mmol) ((*R*)-**6**). The product was isolated as its hydrochloric salt, which gave 107 mg (0.29 mmol, 57%) of a white solid; mp. 156-158 °C; $[\alpha]_D^{20}$ = +27.3 (*c* 1.00, MeOH); purity >99% (HPLC, 280 nm). The spectroscopic data corresponded to that of the (*S*)-**4**.

4.5.27. (*S*)-1-(4-*Tert*-butylphenyl)-2-fluoro-*N*-(naphthalen-1-ylmethyl)ethanamine hydrochloride ((*S*)-17a)

(*S*)-1-(4-*Tert*-butylphenyl)-2-fluoroethanamine ((*S*)-**13**) (118 mg, 0,509 mmol) and 1-(chloromethyl)naphthalene (**9y**) (94 mg, 0.534 mmol) were dissolved in acetonitrile (5 mL). *N,N*-diisopropylethylamine (197 mg, 1.527 mmol) was added, and the reaction was stirred at 50 °C for 24 h. After cooling to rt, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (3×15 mL). The water phases were back-extracted with CH_2Cl_2 (2×15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and the solvent was removed. The crude product was dissolved in ether (5 mL), and the product was isolated as its hydrochloric salt by adding sat. hydrochloric acid in ether (0.5 mL) drop wise. The white solid obtained was washed several times with pentane. This yielded 109 mg (0.293 mmol, 58%) of a white solid; mp. 183-184 °C; ee: 99%; $[\alpha]_D^{20}$ = +3.8 (c 1.03, MeOH) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.34 (s, 9H), 4.06 (d_{AB}, J=13.2 Hz, 1H), 4.18 (d_{AB}, J=13.2 Hz, 1H), 4.13-4.21 (m, 1H), 4.42 (ddd_{AB}, J= 47.5 Hz, 8.9 Hz, 8.8 Hz, 1H), 4.49 (ddd_{AB}, J= 47.5 Hz, 8.9 Hz, 4.2 Hz, 1H), 7.40 (d, J=3.3 Hz, 4H), 7.42-7.52 (m. 4H), 7.76 (d, J=8.1 Hz, 1H), 7.84 (d, J=8.1 Hz, 1H), 8.02 (d, J=8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.5 (3C), 34.7, 49.4, 62.9 (d, J=19.0 Hz), 87.3 (d, J=175.2 Hz), 123.9, 125.6, 125.8 (3C), 126.2, 126.3, 127.7 (2C), 128.0, 128.8, 131.9, 134.0, 135.4 (d, J=8.4 Hz), 136.0, 151.2; ^{19}F NMR ($CDCl_3$, 564 MHz) δ: -221.1 (dt, J=48.0, 13.3 Hz); IR (neat, cm^{-1}): 2961, 1567, 1509, 1459, 1363, 1266, 1111, 996, 776, 736, 574; HRMS (EI): 315.1982 (calcd. 315.1982, $[M-CH_2F]^+$)

4.5.28. (*R*)-1-(4-*Tert*-butylphenyl)-2-fluoro-*N*-(naphthalen-1-ylmethyl)ethanamine hydrochloride ((*R*)-17a)

The reaction was performed as described in Section 4.30.1, but starting with (*R*)-1-(4-*tert*-butylphenyl)-2-fluoroethanamine ((*R*)-**13**) (98 mg, 0.500 mmol), 1-(chloromethyl)naphthalene (**9y**) (93 mg, 0.525 mmol), and *N,N*-diisopropylethylamine (258

mg, 2.000 mmol). This yielded 110 mg (0.33 mmol, 66%) of a white solid; mp. 183-184 °C; ee: 99%; $[\alpha]_D^{20}$ = -3.5 (c 1.02, MeOH). The analytical data corresponds to that of the (*S*)-**17a**.

4.5.29. 1-(4-Bromophenyl)-2-fluoro-N-(naphthalen-1-ylmethyl)ethanamine (17e)

1-(4-Bromophenyl)-2-fluoroethanamine hydrochloride (127 mg, 0.500 mmol) and 1-(chloromethyl)naphthalene (**9y**) (93 mg, 0.525 mmol) were dissolved in acetonitrile (5 mL). *N*,*N*-diisopropylethylamine (258 mg, 2.00 mmol) was added, and the reaction was stirred at reflux for 27 h. After cooling to rt, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (3×15 mL). The water phases were back-extracted with CH_2Cl_2 (2×15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and the solvent was removed. The crude product was purified by silica-gel chromatography (pentane : EtOAc, 9 : 1). This yielded 118 mg (0.329 mmol, 66%) of a clear oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.04 (d_{AB}, J=13.1 Hz, 1H), 4.13 (m, 1H), 4.16 (d_{AB}, J=13.1 Hz, 1H), 4.29-4.52 (m, 2H), 7.33-7.43 (m, 4H), 7.46-7.55 (m, 4H), 7.75-7.80 (m, 1H), 7.84-7.87 (m, 1H), 7.97-8.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 49.2, 62.4 (d, J=19.9 Hz), 86.6 (d, J=175.5 Hz), 122.0, 123.6, 125.4, 125.7, 126.1 (d, J=4.1 Hz, 2C), 128.0, 128.7, 129.7 (2C), 131.7, 131.9 (2C), 133.9, 135.5, 137.5 (d, J=7.7 Hz); ^{19}F NMR ($CDCl_3$, 564 MHz) δ: -222.0 (dt, J=47.3, 13.3 Hz); IR (neat, cm^{-1}): 3046, 2974, 2828, 2360, 2341, 1596, 1486, 1403, 1070, 1000, 776; HRMS (ESI): 358.0603 (calcd. 358.0607, $[M+H]^+$).

4.5.30. (*S*)-1-(4-*Tert*-butylphenyl)-2-fluoro-*N*-methyl-*N*-(naphthalen-1-ylmethyl)ethanamine hydrochloride ((*S*)-5)

(*S*)-1-(4-*Tert*-butylphenyl)-2-fluoro-*N*-(naphthalen-1-ylmethyl)ethanamine hydrochloride ((*S*)-**17a**) (56 mg, 0.150 mmol) and *N*,*N*-diisopropylethylamine (58 mg, 0.450 mmol) were dissolved in dry DMF (9 mL) in an Ace Pressure tube (15 mL). MeI (2M in methyl *tert*-butyl ether, 300 µL, 0.600 mmol) was added while flushing the tube with N_2. The tube was sealed and the reaction was stirred at 100 °C for 24 h. After cooling to rt, the mixture was diluted with diethyl ether (50 mL) and then washed with brine (5×25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and the solvent was removed. The crude product was purified by silica-gel column chromatography (pentane : EtOAc, 8 : 2, R_f = 0.78), by-product 1-naphthylaldehyde (R_f = 0.47). The solvent was removed, and ether (5 mL) was added before the product was precipitated by adding sat. hydrochloric acid in ether (0.5 mL) drop wise. The white solid was washed several times with pentane. This gave 46 mg (0.119 mmol, 79%) of a white solid; mp. 129-131 °C; purity > 98% (HPLC, 280 nm); ee: 97% (HPLC, Phenomenex Lux Cellulose-1); $[\alpha]_D^{20}$ = +18.1 (*c* 1.00, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.32 (s, 9H), 2.22 (s, 3H), 3.95 (ddd, J=19.3 Hz, 6.8 Hz, 4.6 Hz, 1H), 4.03 (s, 2H), 4.71-5.02 (m, 2H), 7.29-7.51 (m, 8H), 7.73-7.78 (m, 1H), 7.82-7.86 (m, 1H), 8.19-8.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.4 (3C), 34.6, 38.7 (d, J=1.4 Hz), 57.8 (d, J=1.4 Hz), 67.5 (d, J=18.3 Hz), 84.2 (d, J=174.5 Hz), 124.6, 125.2, 125.3 (2C), 125.6, 125.7, 127.3, 127.8, 128.2 (2C), 128.4, 132.4, 133.9, 134.8 (d, J=6.6 Hz), 134.9, 150.1. ^{19}F NMR ($CDCl_3$, 564 MHz) δ: -221.1 (dt, J=47.8, 19.8, Hz); IR (neat, cm^{-1}): 3048, 2961, 2867, 2360, 1691, 1509, 1363, 1269, 1004, 775, 575; HRMS (EI): 349.2200 (calcd. 349.2200, M^+)

4.5.31. (*R*)-1-(4-*Tert*-butylphenyl)-2-fluoro-*N*-methyl-*N*-(naphthalen-1-ylmethyl)ethanamine hydrochloride ((*R*)-5)

The reaction was performed as described in Section 4.5.30, but starting with (*R*)-1-(4-*tert*-butylphenyl)-2-fluoro-*N*-(naphthalen-1-ylmethyl)ethanamine hydrochloride ((*R*)-**17a**) (56 mg, 0.150 mmol). This yielded 35 mg (0.098 mmol, 65%)

of a white solid; mp. 128-130 °C; purity> 99% (HPLC, 280 nm); ee: 98% (HPLC, Phenomenex Lux Cellulose-1); $[\alpha]_D^{20}$ = -20.1 (*c* 1.00, MeOH); The analytical data corresponds to that of the (*S*)-**5a**.

4.5.32. 4-(4-Bromophenyl)-3-(naphthalen-1-ylmethyl)oxazolidin-2-one (18)

1-(4-Bromophenyl)-2-fluoro-*N*-(naphthalen-1-ylmethyl)ethanamine (**17e**) (15 mg, 0.042 mmol) and Cs_2CO_3 (27 mg, 0.084 mmol) were dissolved in DMF (3 mL) in an Ace Pressure tube. MeI (2M in TBME, 84 uL, 0.168 mmol) was added while flushing the tube with N_2. The sealed tube was stirred at 100 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL), and washed with water (4×10 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed. The crude product was purified by preparative HPLC (Poroshell, 100×21.5 mm) starting with water/acetonitrile (50/50) for 5 min, then a gradient elution with an increase in acetonitrile amount of 1.67%/min, R_t = 9.2 min. This gave 10 mg (0.026 mmol, 62%) of a white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) d: 4.04 (dd, J=8.9, 5.7 Hz, 1H), 4.15 (d, J=14.7 Hz, 1H), 4.29 (dd, J=8.9, 5.7 Hz, 1H), 4.45 (t, J=8.9 Hz, 1H), 5.37 (d, J=14.7 Hz, 1H), 6.97-7.05 (m, 3H), 7.29-7.33 (m, 1H), 7.49-7.58 (m, 4H), 7.80-83 (m, 1H), 7.86-7.89 (m, 1H), 8.07-8.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 44.4, 58.2, 70.0, 123.0, 123.8, 124.9, 126.2, 127.0, 128.3, 128.68 (2C), 128.73, 129.3, 130.5, 131.8, 132.3, 132.4 (2C), 133.3, 167.0; IR (neat, cm^{-1}): 3727, 3628, 2922, 2852, 2360, 2341, 1749, 1419, 1062, 1010, 781, 669, 650; HRMS (EI): 381.0362 (calcd. 381.0364, M^+).

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Figure 1. The structures Butenafine (**1**), Terbinafine (**2**), and the investigated compounds **3**-**5**.

Figure 2. Structure activity relationships observed for the benzylamines towards *C. neoformans*.

Scheme 1. Tactics for preparing the antifungal compounds **3**-**5**.

Scheme 2. Synthesis of the potential antifungal compounds **3a**-**x**.

Scheme 3. Synthesis of the potential antifungal compounds (*R*)- and (*S*)-**4** and the structure of the fluoro containing derivative **5**.

Scheme 4. Synthesis of (*R*)- and (*S*)-**13** via a lipase catalysed kinetic resolution and lipase catalysed amide hydrolysis

Scheme 5. Strategies undertaken in conversion of **13** to compounds **17a** and **5**.

Scheme 6. The formation of the cyclic carbamate **18** from the secondary amine **17e** by Cs_2CO_3.