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FULL PAPER

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Synthesis of novel benzylamine antimycotics and evaluation of their antimycotic potency

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Abstract

A series of 23 novel benzylamines was synthesized by reductive amination from halogen-substituted 3- and 4-benzyloxybenzaldehyde derivatives and 6-methylhept-2-yl amine or *n*-octylamine. The antimycotic activity of the resulting amines was evaluated in a microdilution assay against the apathogenic yeast *Yarrowia lipolytica* as test microorganism. Promising compounds were also tested against human pathogenic *Candida* species. The influence of halogen substituents at the benzyl ether side chain was studied in this screening, as well as the influence of the branched side chain of (±)-6-methylhept-2-yl amine in comparison with the *n*-octyl side chain.

KEYWORDS
antimycotics, benzylamine, reductive amination, synthesis, yeast

1 | INTRODUCTION

The benzylamine core is an interesting lead structure for the development of novel antimycotics for more than 30 years. It takes part in the prominent class of the allyl amines as naftifine and terbinafine, as well as in the related antimycotic butenafine (Figure 1).[1–5] Allyl amines and butenafine are potent inhibitors of squalene epoxidase in ergosterol biosynthesis.[6,7] Recently, similar to other drug classes like azoles, resistance rates have increased. Especially for terbinafine, the most prominent member of the allyl amines and at the moment the only systemically available allyl amine drug in human therapy, emerging resistance has been reported in India, so there is an enormous need of novel antimycotics that are effective against dermatophytes and yeasts.[8,9] Furthermore, hospital-acquired infections of *Candida auris*, first isolated in 2006 from a Japanese patient, are a serious problem, because this yeast is resistant against fluconazole and can develop resistance against echinocandins. This species might account for an increasing number of infections and may even replace *Candida albicans* or *Candida glabrata* in future.[10,11]

In continuation of our research on novel antimycotic structures,[12–14] we could identify the benzylamines **1** and **2** (Figure 2) with interesting activity against yeasts.[15] In the present work, we evaluated the influence of halogen substituents bromo, fluoro, and chloro atoms at the benzyl ether side chain on their activity and the difference between branched side chain and *n*-octyl side chain at the benzylamine core.

Halogen substituents, especially chloro and fluoro atoms, often show a remarkable increase in activity in biological systems. A lot of prominent examples of anti-infectives could be found in medical chemistry: the azole antimycotics fluconazole, miconazole and clotrimazole, the fluoroquinolones ciprofloxacin or moxifloxacin, the antimalarial drugs chloroquine or mefloquine. Also, in other drug classes like diuretics such as hydrochlorothiazide and furosemide halogen substituents were found. Halogen atoms in drug target complexes influence on several processes in biological systems such as steric aspects and the formation

Dedicated to Prof. Dr. F. Bracher on occasion of his 65th birthday.

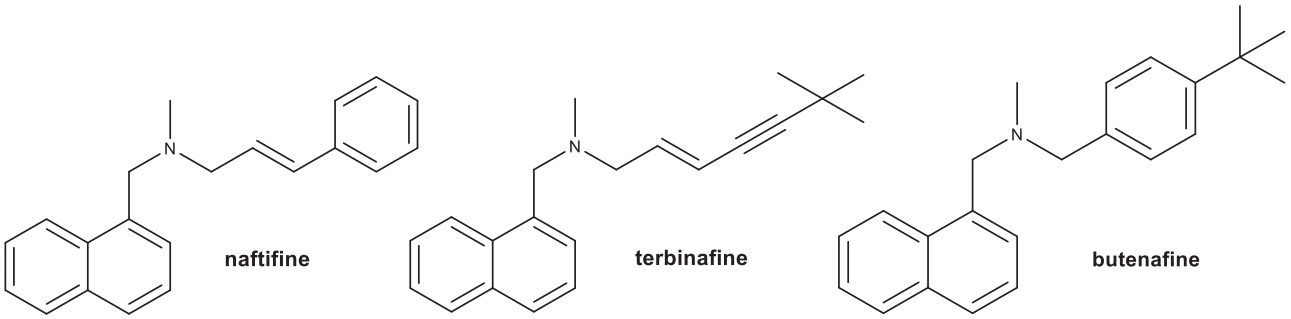


FIGURE 1 Therapeutically used allyl amine and benzylamine antimycotics.

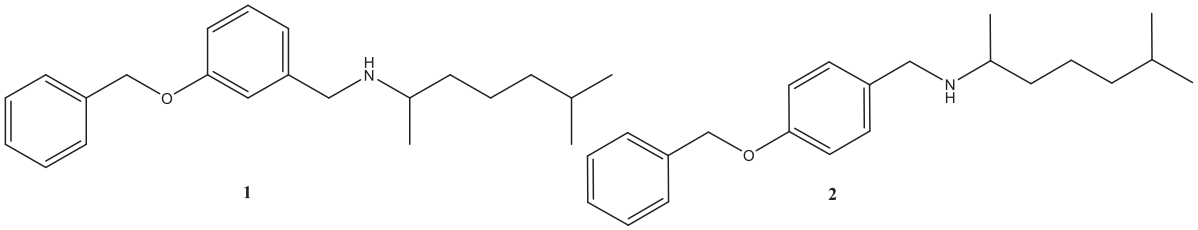


FIGURE 2 Benzylamine lead structures.[15]

of halogen bonds in ligand-target complexes.[16–20] Furthermore, halogen substituents often increase metabolic stability of the compounds against cytochrome P450 enzymes.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

A library of 23 benzylamines was synthesized by the following route (Scheme 1): In a Williamson ether synthesis, 3- and 4-hydroxybenzaldehydes **4a** and **4b** were reacted with several halogen-substituted benzyl halogenides **3a–i** to give the benzyl ethers **5a–o**.[15] By using a Finkelstein exchange with NaI, the yields of the products in the Williamson ether synthesis could increase. Using a reductive amination with $Na(B(OAc)_3H)$ and (±)−6-methylhept-2-yl amine or *n*-octylamine, the ethers **5a–o** were converted into the benzylamines amines **6a–k** and **8a–i**.[21,22] In some reactions, a small amount of the imines was collected as side products **7a** and **7b**. All benzylamines could be precipitated with HCl (freshly prepared from methanol and acetyl chloride) in diethyl ether as their corresponding hydrochlorides. To compare the halogen-substituted derivatives with methoxy- and *tert*. butyl substituents, compounds **8j** and **8k** were synthesized in the same way from 4-methoxybenzyl chloride and 4-*tert*-butylbenzyl chloride.

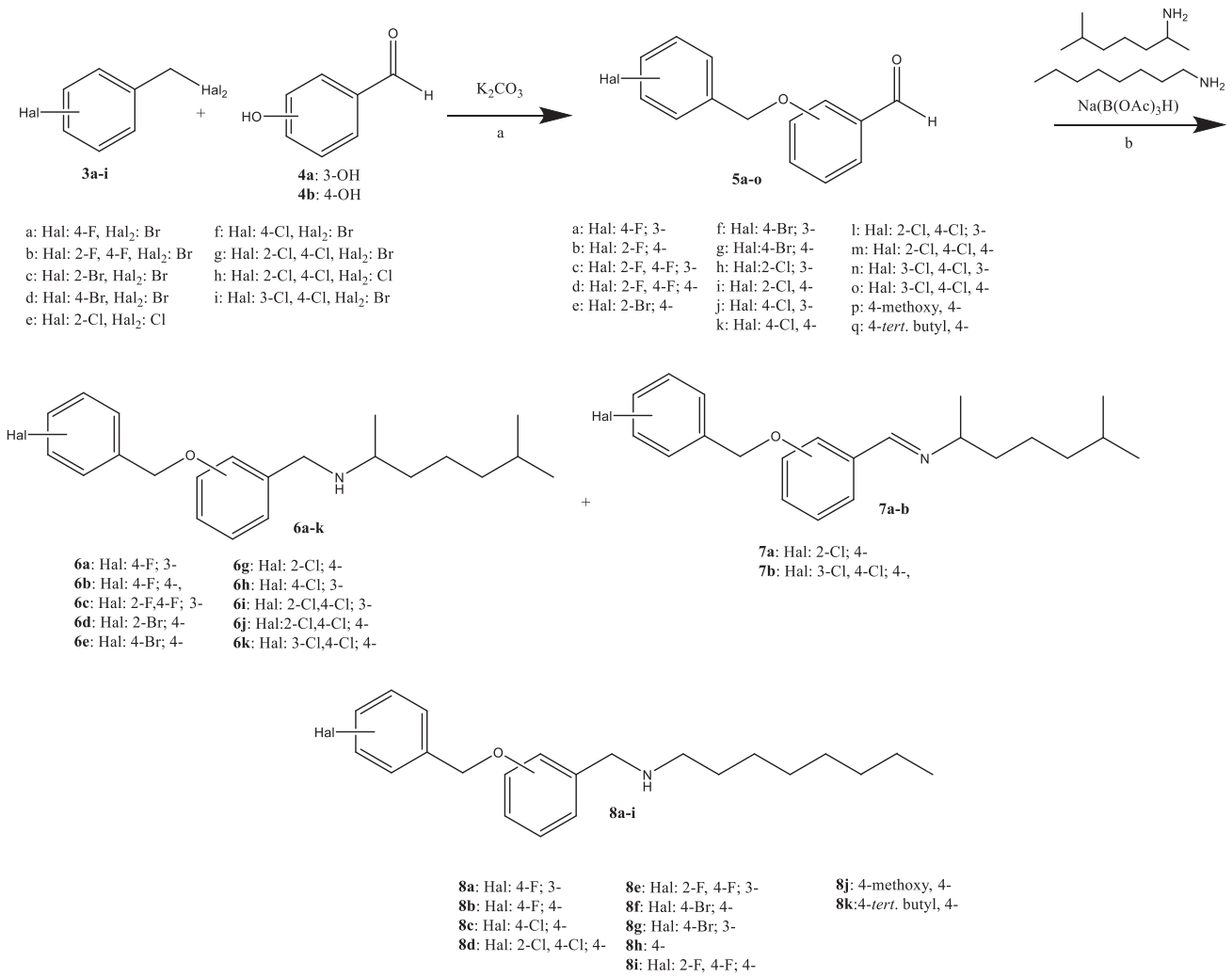
2.2 | Biology

The antimycotic activity of the resulting benzylamines was evaluated in a microdilution assay against *Yarrowia lipolytica* as a test microorganism (Table 1). *Y. lipolytica* was chosen because it is an apathogenic yeast[24–26] and in earlier work, we could find a good correlation between growth inhibition of *Y. lipolytica* and pathogenic *Candida* species.[12] The activity of the benzylamines against *Y. lipolytica* was compared with terbinafine and clotrimazole. Exemplarily the stability of **6g** and **7a** was checked by stirring both compounds for 5 days in all culture agar (AC-agar). **6g** showed no degradation products, 50% of **7a** were hydrolyzed to the corresponding aldehyde **5i** after 5 days.

Sixteen of the 23 test compounds showed antimycotic activity against our test strain *Y. lipolytica*. Eleven of these compounds showed a lower minimal inhibitory concentration (MIC) than the commonly used antimycotic terbinafine and showed MIC values in the same range as clotrimazole. Overall, against *Y. lipolytica* compounds with *n*-octyl side chain are more active than the compounds with the branched side chain. Nevertheless, we could not determine a clear correlation between antimycotic activity and the halogen substitution pattern. All active compounds with *n*-octyl side chain showed similar MIC values independent of their halogen substitution pattern.

In contrast to earlier work,[12] the activity against *Y. lipolytica* showed not for all compounds a clear correlation to the activity of the pathogenic *Candida* strains. Compound **8i** with high activity against *Yarrowia* showed no activity against *Candida* species and, on the other hand, compound **6d** showed only low activity against *Yarrowia* but high activity against *Candida* strains. Differences in outcome are most likely attributed to different test conditions, like growth media and temperature, between *Yarrowia* and the *Candida* species.

Exemplarily, the antimycotic activity of several compounds was evaluated against the opportunistic pathogenic yeast species *C. albicans*, *C. glabrata*, *Candida krusei*, and *Candida tropicalis*, following a



SCHEME 1 Synthesis of the benzylamine series **6a–k** and **8a–i**. (a) NaI, K_2CO_3, acetone, reflux; (b) Tetrahydrofuran, room temperature.

standardized protocol from European Commitee of Antimicrobial Susceptibility Testing (EUCAST).[27]

Seventeen compounds were tested against three strains of the respective *Candida* species. *C. albicans* and *C. glabrata* are the most commonly occurring yeasts in the clinical setting, followed by *C. krusei* and *C. tropicalis*. These two species are associated with more difficulties in treatment with commonly used antifungal agents. Antifungal properties were variable depending on the drug and the yeast species. Of the 17 substances, two, **6g** and **8i** showed no growth inhibitory effects on any of the 12 yeast strains at the concentrations tested (max. concentration tested = 32 µg/mL) (Table 2). The most promising candidates, exhibiting growth inhibition of 100% at a MIC comparable to terbinafine or other antifungals, at least against three of the four test species, are **6d**, **6e**, **6j**, **8g**, and **8h**. For the other substances, MICs varied within the three strains per species, or in-between species, pointing to a strain-specific activity profile. To investigate that more precisely, a lot more strains are necessary to be tested for each species.

For all substances, highest MIC values, indicating lowest antifungal activity, were produced for *C. tropicalis*, resulting in an overall MIC range from 8 to 32 µg/mL. Against the three other test species, lower MIC values were obtained, but even here with a strong variability within the three test strains, or the replicates. This could either point to strain-specific susceptibility or diminishing stability of the newly synthesized compounds that was caused by multiple freeze-thawing events. For many isolates, we obtained MIC values as low as 1 µg/mL which is comparable to what is published for terbinafine and *C. albicans*,[28] using the same EUCAST protocol. Another study that evaluated 30 *Candida* isolates obtained MIC values between 1 and 8 µg/mL, or no MIC up to the highest test concentration of 8 µg/mL. This study employed the Clinical and Laboratory Standards Institute protocol, which is slightly different in the medium composition and the inoculum size, but does provide comparable results. Also here, a variability in the MICs of strains belonging to the same species was seen.[29] Interestingly, in a third study comparing efficacy of terbinafine and fluconazole against various *Candida* isolates, a lot higher MICs were seen, for *C. albicans* from 1 to 4 µg/mL, which is consistent with other studies, and also comparable to the MICs we obtained with the novel substances. On the other hand, MICs for *C. glabrata*, *C. krusei*, and *C. tropicalis* exceeded the test range and no MIC was detected at concentrations up to 128 µg/mL, which is a fivefold higher MIC that we have obtained with the new substances. Again, one

TABLE 1 Structures of newly synthesized drugs and MIC causing 100% growth inhibition of *Yarrowia lipolytica* cultures.

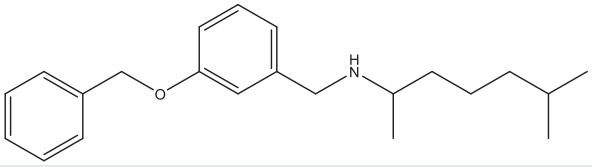
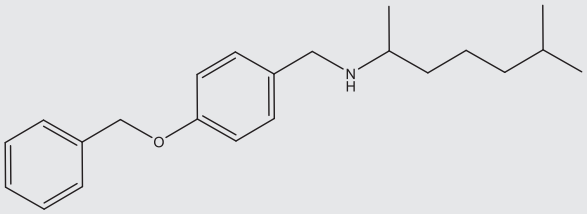
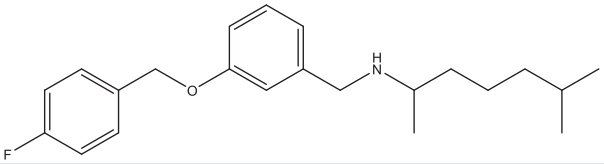
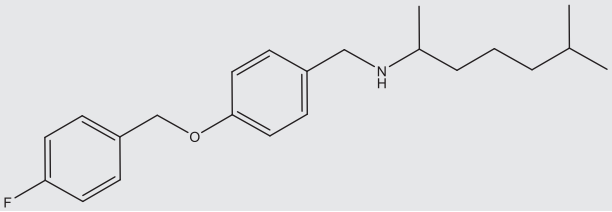
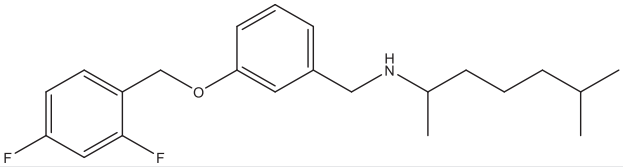
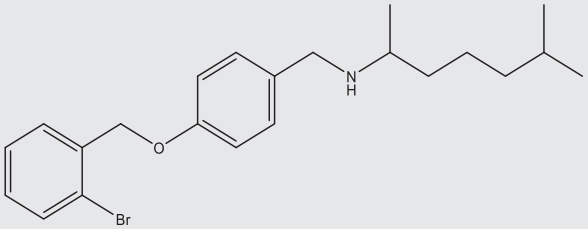
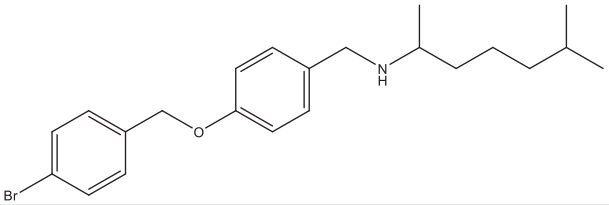
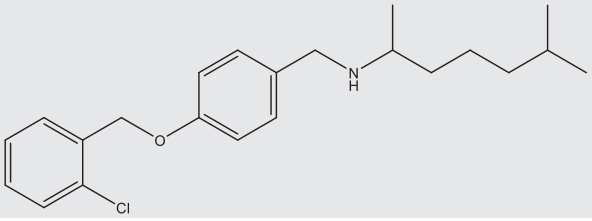
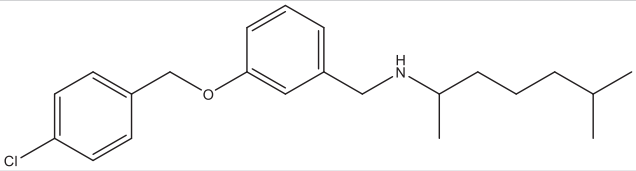
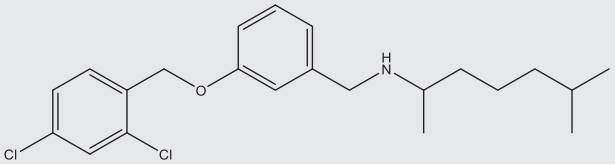
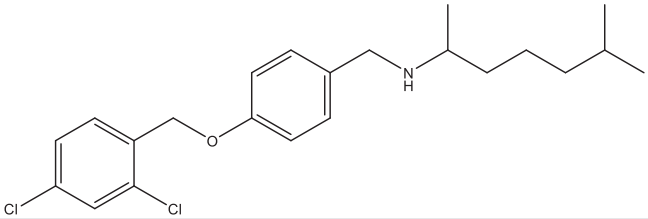
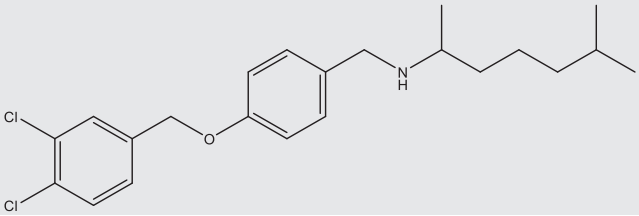
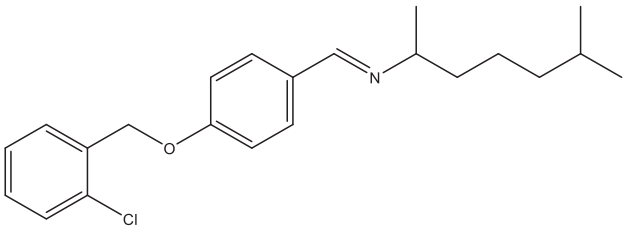
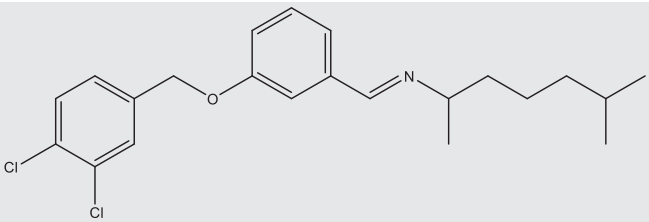
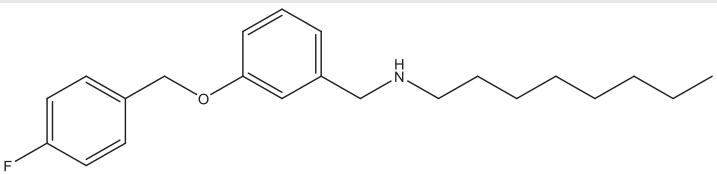
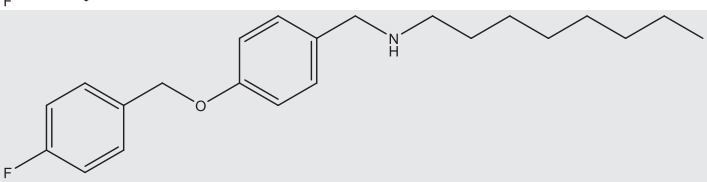
No	compound	Molecular weight	TPSA [Å^2] (calcd.)[23]	log *P* (calcd.)[23]	MIC_{100} [µg/mL]
1		325.47	21.26	5.2	25
2		325.24	21.26	5.22	6.3
6a		343.49	21.26	5.41	9.4
6b		343.23	21.26	5.51	50
6c		361.48	21.26	5.84	6.3
6d		404.39	21.26	5.80	50
6e		404.39	21.26	5.82	12.5
6g		359.94	21.26	5.72	50

TABLE 1 (Continued)

No	compound	Molecular weight	TPSA [Å^2] (calcd.)[23]	log *P* (calcd.)[23]	MIC_{100} [μg/mL]
6h		359.94	21.26	5.65	>100
6i		394.38	21.26	6.26	4.7
6j		394.38	21.26	6.21	25
6k		394.38	21.26	6.23	25
7a		357.92	21.59	6.00	=100
7b		392.36	21.59	6.53	>100
8a		343.49	21.26	5.70	6.0
8b		343.49	21.26	5.73	1.5

(Continues)

TABLE 1 (Continued)

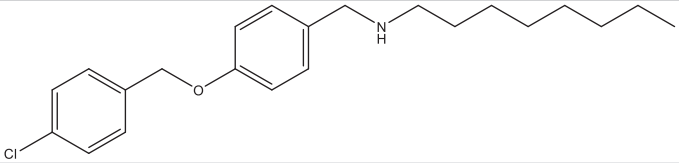
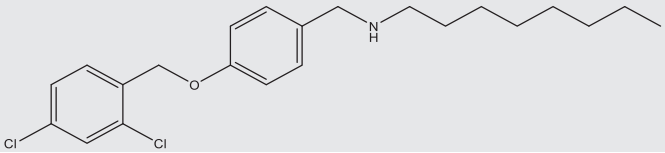
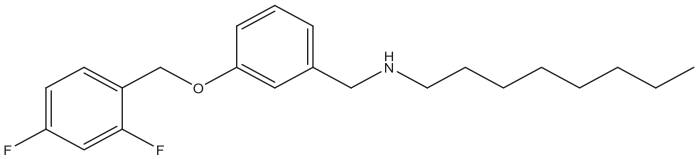
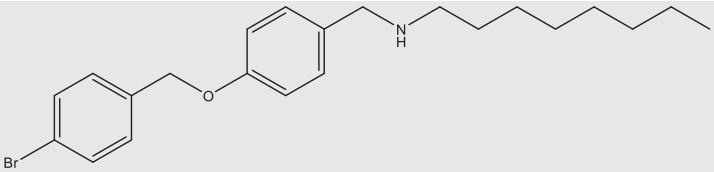
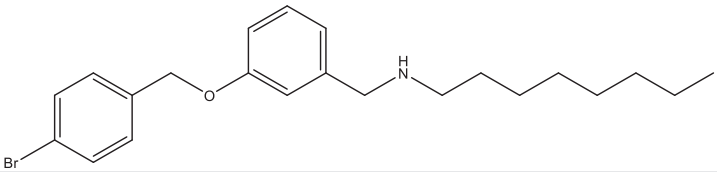
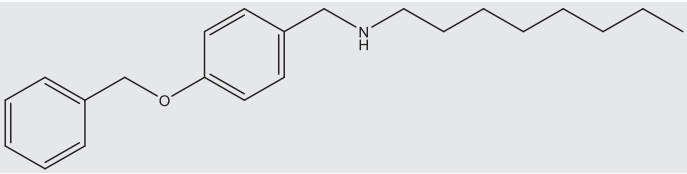
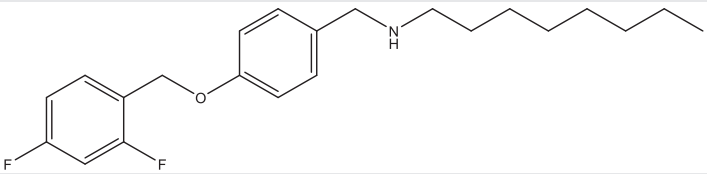
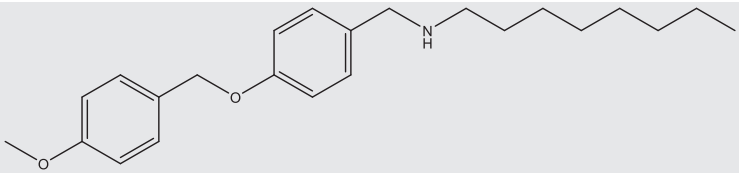
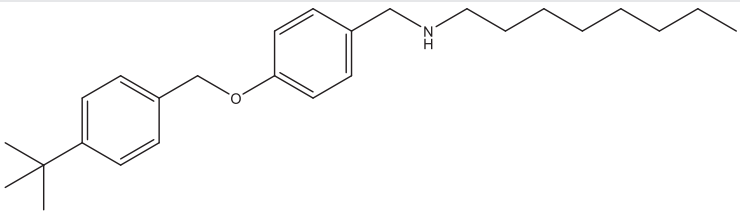
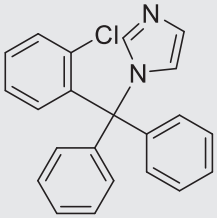
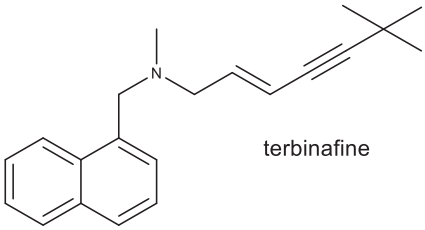
No	compound	Molecular weight	TPSA [Å^2] (calcd.)[23]	log *P* (calcd.)[23]	MIC_{100} [μg/mL]
8c		359.94	21.26	5.95	3.0
8d		394.38	21.26	6.42	6.0
8e		361.48	21.26	5.99	1.2
8f		404.39	21.26	6.02	1.5
8g		404.39	21.26	6.01	1.5
8h		325.50	21.26	5.39	0.8
8i		361.48	21.26	6.00	1.5
8j		355.52	30.49	5.37	3.1
8k		381.60	21.26	6.62	3.1

TABLE 1 (Continued)

No	compound	Molecular weight	TPSA [Å^2] (calcd.)[23]	log *P* (calcd.)[23]	MIC_{100} [µg/mL]
	 clotrimazole	344.84	15.6	5.19	0.8
	 terbinafine	291.44	3.24	4.92	12.5

Note: All substances were dissolved in methanol. All assays were carried out twice.
Abbreviations: MIC, minimal inhibitory concentration; TPSA, topological polar surface area.

could argue that is due to the slightly different test format, but in conclusion, we can say that the newly synthesized drugs do have antifungal properties that are at least comparable to the existing terbinafine. To get a more detailed picture, many more strains per species have to be tested in the near future.

Next, based on the low MICs obtained against *Y. lipolytica*, the cytotoxicity of compounds **6c**, **8g**, **8i**, **8e**, and **8h** was evaluated in an MTT assay against a human leukemia cell line (HL-60)[30] (Table 3).

The compounds showed a moderate cytotoxicity against HL-60 cells. Compounds **6c** and **8e** showed the highest cytotoxicity with IC_{50}-values from 2 to 5 µM, but these values are in the same range as we found for systemically used posaconazole (5 µM).[12] So, the antimycotic activity might not be an unspecific cytotoxic effect but of course it needs to be evaluated in more detail, adding comparable information with terbinafine and other antifungals. The benzylamines might show a selective effect on fungi and show a mechanism of action as reported for butenafine or terbinafine, but further studies should evaluate this hypothesis. Furthermore, it should be tested if the compounds showed a fungicidal or fungistatic effect against yeasts. All compounds showed a high theoretical log *P* value, so according to the Lipinski rules of five they should be used for topical mycosis or their hydrochlorides should be used for systemic test settings.[23,31] Potentially, the novel drugs could serve as combinatorial therapy options with other antifungals, which need to be evaluated in checkerboard assays for example.

3 | CONCLUSION

A library of 23 novel benzylamine compounds was prepared by William ether synthesis and following reductive amination with octan-1-amine or (±)−6-methylhept-2-yl amine. The ether side chain of the benzylamines showed several halogen substitution patterns.

The screening on our model yeast *Y. lipolytica* showed an antimycotic activity of mostly all compounds. In comparison to the lead structures, the halide-substituted compounds showed no significant increase of activity. So, the screening allowed no clear correlation of the antimycotic activity and the halogen substitution pattern. According to the "Topliss tree,"[32] we also synthesized the methoxy and the *tert*-butyl substituted derivates **8j** and **8k** and evaluated their antimycotic potency against *Y. lipolytica* but they showed no significant increase of activity compared to the halogen-substituted ones.

On the other hand, the *n*-octyl side chain led to an increase of activity in comparison with the branched alkyl side chain. Against our test microorganism *Y. lipolytica* **8a–e** and **8g–l** showed MIC values between 0.8 and 6 µg/mL in the same range as clotrimazole (MIC value 0.8 µg/mL) and clearly higher activity than terbinafine (12.5 µg/mL).

Against pathogenic *Candida* species **6d** and **8g** showed the highest activity against all *Candida* species. The most active compounds showed no higher toxicity against HL-60 cells than what was reported for the commonly used antifungal drug posaconazole (IC_{50}: 5 µM).

Benzyloxybenzylamines with *n*-octly side chain have been identified as an interesting lead structure for development of novel antifungals. Due to the short and easy synthesis and the cheap build blocks further testing as agrofungicides against phytopathogenic fungi or fungicides in dye industry might be interesting as well.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General remarks

All solvents used were of high performance liquid chromatography (HPLC) grade or p.a. grade and/or purified according to standard

TABLE 2 Minimal inhibitory concentration (MIC) causing 90% growth inhibition of yeast cultures.

Species	MIC_{90} (µg/mL), 24 h															
	6b	6c	6d	6e	6 g	6 h	6i	6j	6k	8a	8b	8c	8d	8f	8g	8h	8i
Candida albicans (*n* = 3)	32	4–8	4–8	8–16	>32	32	8–16	4–8	4–16	16–32	8	32	>32	8–6	4	4–8	>32
Candida glabrata (*n* = 3)	8	8/>32	2–8	1–8	>32	8	2–16	2–4	1–8	2–32	8/>32	2–4	1–8	8	4	2–4	>32
Candida krusei (*n* = 3)	2–4	>32	2–8	2–8	>32	2–4	2–16	2–16	2–16	2–32	8/>32	4	4-32	8	4	4–32	>32
Candida tropicalis (*n* = 3)	32	>32	16–32	16–32	>32	>32	>32	8–16	16–32	32	8–16	16/>32	>32	16–32	32/>32	8–16	>32

Note: All substances were dissolved in DMSO and diluted in RPMI 1640 medium, containing 2% glucose. Three strains per species were tested twice against each compound.

TABLE 3 Cytotoxicity against HL-60 cell line (substances were tested in triplicate).

Compound	IC_{50} [µM]	Compound	IC_{50} [µM]
6c	5	**8e**	2
8g	24	**8h**	13
8i	17	Posaconazole	5

procedures. Chemical reagents were purchased from Sigma Aldrich and Acros. IR-spectra: Jasco FT/IR 4600 series (KBr pellet method); mass spectrometry (MS): Hewlett Packard MS-Engine, electron ionization (EI) 70 eV, chemical ionization with CH_4 (300 eV); MS spectra: Thermo Q Exactive GC Orbitrap or Finnigan MAT 95 spectrometer, high resolution mass spectrometry (HR-MS): Thermo Finnigan LTQ FT. NMR: Avance III HD 400 MHz Bruker BioSpin (^{1}H: 400 MHz, ^{13}C: 100 MHz); 500 MHz Avance III HD 500 MHz Bruker BioSpin (^{1}H: 500 MHz, ^{13}C: 125 MHz); melting points: Büchi Melting Point B-540 (not corrected); flash column chromatography (FCC): silica gel 60 (230–400 mesh, E. Merck); Compound purities were determined by HPLC (Table 4). HPLC conditions: System: Shimadzu LC 20, with UV-detector, 220 nm, Column: Waters, ODS-2, 3 µm, 4.6 mm × 12.5 mm, 40°C. Mobile phase: 85% MeOH/water pH 7. Mode: Isocratic system, Flow rate: 1 mL/min, concentration: 0.5–1.5 mg/mL, injection: 5 µL.

The spectra as well as the InChI codes of the investigated compounds, together with some biological activity data, are provided as Supporting Information.

4.1.2 | General procedure 1

Six millimole of the alkyl halogenide were dissolved in 50 mL dry acetone, 1.5 g (10.0 mmol) of NaI were added and the solution was stirred for 30 min. 5.0 mmol of the phenols **5a** or **5b** and 2.48 g (15.0 mmol) K_2CO_3 were added and the suspension was refluxed for 5 h. The solvent was evaporated and the residue was dissolved in 50 mL of ethyl acetate/2 M aqueous HCl (1:1). The aqueous layer was again extracted with ethyl acetate (2 × 25 mL). The combined organic layers were extracted with 50 mL 10% aqueous $Na_2S_2O_3$ solution and the organic layer was dried over Na_2SO_4. The solvent was evaporated and the residue was purified by FCC (isohexane/ethyl acetate 4:1).

4.1.3 | General procedure 2

4.5 mmol of the aldehyde and 6.4 mmol of (±)−6-methylheptan-2-amine or octan-1-amine were dissolved in 40 mL dry tetrahydrofuran and 2.76 g (13.0 mmol) sodium triacetoxyborhydride were added. The suspension was stirred under N_2 atmosphere for 12 h. Then it was quenched with 30 mL saturated aqueous $NaHCO_3$ solution and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by FCC (isohexane/ethyl acetate/trimethylamine 2:1:0.1).

TABLE 4 Purity of tested compounds determined by HPLC.

Compounds	Purity (area %)
2	99.9
6a	n.t.
6b	88.8
6c	99.8
6d	98.5
6e	97.4
6g	94.6
6i	97.9
6j	96.6
6k	99.9
8a	92.1
8b	96.5
8c	99.6
8d	99.5
8e	95.2
8f	97.5
8g	95.0
8h	99.9
8i	98.1
8j	96.2
8k	95.0

Abbreviation: n.t., not tested.

4.1.4 | General procedure 3

Two millimole of the amine were solved in 20 mL dry diethyl ether and 5.0 mL of a 2 M hydrochloric acid solution in diethyl ether (freshly prepared from 3.84 g methanol and 7.75 acetyl chloride in 50 mL diethyl ether) were added. The mixture was stored for 5 h at 4°C and the precipitate was collected, washed with diethyl ether, and dried in vacuo.

4.1.5 | Compound characterization

3-[(4-Fluorobenzyl)oxy]benzaldehyde (**5a**): The compound was prepared according to general procedure 1 from 1.04 g (5.5 mmol) 4-fluorobenzyl bromide and 617 mg (5.0 mmol) 3-hydroxy benzaldehyde to give 756 mg (66%) of **5a** as pale yellow oil. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.90 (s, 1H, CHO), 7.41–7.37 (m, 3H, 3 arom. CH), 7.38–7.30 (m, 3H, 3 arom. CH), 7.20–7.13 (m, 1H, arom. CH), 7.05–6.96 (m, 2H, 2 arom. CH), 5.00 (s, 2H, CH_2). ^{13}C NMR (126 MHz, chloroform-*d*) δ 192.00 (CHO), 162.62 (d, J = 243.8 Hz, quat. C), 159.14 (arom. CH), 137.85 (quat. C), 132.07 (d, J = 3.2 Hz, quat C), 130.17 (arom. CH), 129.43 (d, J = 8.2 Hz, 2 arom. CH), 123.94 (arom. CH), 122.22 (arom. CH), 115.63 (d, J = 21.7 Hz, 2 arom. CH), 113.04 (arom. CH), 69.57 (CH_2). GC-MS: 230 (M^+, 10), 109 (100). MS (EI) m/z = 230 (M^+, 2.4), 109 (100). HR-MS (EI) calcd. for $C_{14}H_{10}FO_2$ (M^+-H): 229.0665. Found: 229.0659.

4-[(4-Fluorobenzyl)oxy]benzaldehyde (**5b**): The compound was prepared according to general procedure 1 from 1.04 g (5.5 mmol) 4-fluorobenzyl bromide and 611 mg (5.0 mmol) 4-hydroxy benzaldehyde (**4b**) to give 1.15 g (99%) of **5b** as a pale brown solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.89 (s, 1H, CHO), 7.85 (d, J = 8.8 Hz, 2H, 2 arom. CH), 7.44–7.37 (m, 2H, 2 arom. CH), 7.13–7.03 (m, 2H, 2 arom. CH), 7.07 (d, J = 8.8 Hz, 2H, 2 arom. CH), 5.11 (s, 2H, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 186.03 (CHO), 158.80 (quat. C), 157.95 (d, J = 247.1 Hz, quat. C), 127.28 (2 arom. CH), 126.98 (d, J = 3.3 Hz, quat. C), 125.51 (quat. C), 124.68 (d, J = 8.3 Hz, 2 arom. CH), 110.96 (d, J = 21.7 Hz, 2 arom. CH, 110.37 (2 arom. CH), 64.85 (CH_2). MS (EI) m/z = 229 (M^+-H, 18), 109 (100). HR-MS (EI) calcd. for $C_{14}H_{10}FO_2$ (M^+-H): 229.0665. Found: 229.0660.

3-[(2,4-Difluorobenzyl)oxy]benzaldehyde (**5c**): The compound was prepared according to general procedure 1 from 1.24 g (6.0 mmol) 2,4-difluorobenzyl bromide and 617 mg (5.0 mmol) 3-hydroxy benzaldehyde (**4a**) to give 988 mg (80%) of **5c** as a white solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.99 (s, 1H, CHO), 7.54–7.42 (m, 4H, 4 arom. CH), 7.26–7.22 (m, 1H, arom. CH), 6.98–6.81 (m, 2H, 2 arom. CH), 5.13 (s, 2H, CH_2). ^{13}C NMR (101 MHz, chloroform-*d*) δ 191.94 (CHO), 163.11 (dd, J = 226.3, 12.1 Hz, quat. C), 160.62 (dd, J = 226.9, 12.0 Hz, quat. C). 158.97 (quat. C), 137.89 (quat. C), 130.88 (dd, J = 9.9, 5.3 Hz, arom. CH), 130.23 (arom. CH), 124.02 (arom. CH), 122.06 (arom. CH), 119.52 (dd, J = 14.7, 3.8 Hz, quat. C), 113.20 (arom. CH), 111.56 (dd, J = 21.2, 3.8 Hz, arom. CH), 104.05 (t, J = 25.3 Hz, arom. CH), 63.55 (CH_2). MS (EI) m/z = 247 (M^+-H, 2), 127 (100), 101 (11). HR-MS (EI) calcd. for $C_{14}H_9F_2O_2$ (M^+-H): 247.0571. Found: 247.0561.

4-[(2,4-Difluorobenzyl)oxy]benzaldehyde (**5d**): The compound was prepared according general procedure 1 from 1.24 g (6.0 mmol) 2,4-difluorobenzyl bromide and 611 mg (5.0 mmol) 4-hydroxy benzaldehyde (**4b**) to give 757 mg (61%) of **5d** as a white-yellow solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.90 (s, 1H, CHO), 7.86 (d, J = 8.9 Hz, 2H, 2 arom. CH), 7.47 (td, J = 8.5, 6.3 Hz, 1H, arom. CH), 7.08 (d, J = 8.8 Hz, 2H, 2 arom. CH), 6.99–6.80 (m, 2H, 2 arom. CH), 5.16 (s, 2H, CH_2). ^{13}C NMR (101 MHz, chloroform-*d*) δ 190.74 (CHO), 163.28 (quat. C), 163.12 (dd, J = 237.7 Hz, J = 12.3 Hz, quat. C), 160.64 (dd, J = 237.9, 12.0 Hz, quat. C), 132.04 (2 arom. CH), 130.88 (dd, J = 9.8, 5.6 Hz, arom. CH), 130.42 (quat. C), 119.18 (dd, J = 14.3 Hz, J = 3.8 Hz, quat. C), 115.03 (2 arom. CH), 111.67 (dd, J = 21.1, 3.8 Hz, arom. CH), 104.09 (t, J = 25.2 Hz, arom. CH), 63.50 (d, J = 3.8 Hz, CH_2). MS (EI) m/z = 247 (M^+, 4), 127 (100). HR-MS (EI) calcd. for $C_{14}H_{10}F_2O$ (M^+): 248.0649. Found: 248.0647.

4-[(2-Bromobenzyl)oxy]benzaldehyde (**5e**): The compound was prepared according to general procedure 1 from 1.55 g (6.0 mmol) 2-bromobenzyl bromide and 611 mg (5.0 mmol) 4-hydroxy benzaldehyde (**4b**) to give 1.21 g (83%) of **5e** as a white solid. ^{1}H NMR (500 MHz, chloroform-*d*) δ 9.90 (s, 1H, CHO), 7.86 (d, J = 8.6 Hz, 2H,

2 arom. CH), 7.61 (d, *J* = 8.0 Hz, 1H, arom. CH), 7.51 (d, *J* = 7.7 Hz, 1H, arom. CH), 7.35 (t, *J* = 7.5 Hz, 1H, arom. CH), 7.22 (t, *J* = 7.7 Hz, 1H, arom. CH), 7.09 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 5.22 (s, 2H, CH_2). ^{13}C NMR (100 MHz, chloroform-*d*) *δ* 190.79 (CHO), 159.65 (quat. C), 135.94 (quat. C), 133.37 (arom. CH), 132.82 (2 arom. CH), 130.09 (quat. C), 129.13 (arom. CH), 128.91 (arom. CH), 127.64 (arom. CH), 122.17 (quat. C), 114.61 (2 arom. CH), 69.65 (CH_2). MS (EI) *m/z* = 291 (M^++H, 0.03), 172 (7), 171 (100), 90 (19). HR-MS (EI) calcd. for $C_{14}H_{12}BrO_2$ (M^++H): 291.0021. Found: 291.0012.

3-[(4-Bromobenzyl)oxy]benzaldehyde (**5f**): The compound was prepared according to general procedure 1 from 1.37 g (5.5 mmol) 4-bromobenzyl bromide and 617 mg (5.0 mmol) 3-hydroxy benzaldehyde (**4a**) to give 440 mg (30%) of **5f**. ^1H NMR (400 MHz, chloroform-*d*) *δ* 9.98 (s, 1H, CHO), 7.53 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 7.51–7.42 (m, 3H, 3 arom. CH), 7.32 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 7.23 (ddd, *J* = 7.5, 2.7, 1.8 Hz, 1H, arom. CH), 5.08 (s, 2H, CH_2). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 191.96 (CHO), 159.05 (quat. C), 137.87 (quat. C), 135.34 (quat. C), 131.83 (2 arom. CH), 130.20 (arom. CH), 129.12 (2 arom. CH), 124.01 (arom. CH), 122.18 (arom. CH), 122.15 (quat. C), 69.06 (CH_2). MS (EI) *m/z* = 290 (M^+, 5), 171 (100), 90 (94), 63 (58). HR-MS (EI) calcd. for $C_{14}H_{11}BrO_2$ (M^+): 289.9942. Found: 289.9926.

4-[(4-Bromobenzyl)oxy]benzaldehyde (**5g**): The compound was prepared according to general procedure 1 from 1.50 g (6.0 mmol) 4-bromobenzyl bromide and 611 mg (5.0 mmol) 4-hydroxy benzaldehyde to give 1.0 g (69%) of **5g** as a white solid. ^1H NMR (400 MHz, chloroform-*d*) *δ* 9.89 (s, 1H, CHO), 7.84 (d, *J* = 8.8 Hz, 2H, 2 arom. CH), 7.53 (d, *J* = 8.4 Hz, 2H, arom. CH), 7.31 (d, *J* = 8.4 Hz, 2H, 2 arom. CH), 7.06 (d, *J* = 8.8 Hz, 2H, 2 arom. CH), 5.10 (s, 2H, CH_2). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 190.72 (CHO), 163.40 (quat. C), 134.97 (quat. C), 132.01 (2 arom. CH), 131.89 (2 arom. CH), 130.32 (quat. C), 129.07 (2 arom. CH), 122.30 (quat. C), 115.11 (2 arom. CH), 69.48 (CH_2). MS (EI) *m/z* = 290 (M^+, 5), 171 (100), 90 (28). HR-MS (EI) calcd. for $C_{14}H_{11}BrO_2$ (M^+): 289.9942. Found: 289.9922.

3-[(2-Chlorobenzyl)oxy]benzaldehyde (**5h**): The compound was prepared according to general procedure 1 from 960 mg (6.0 mmol) 2-chlorobenzyl chloride and 610 mg (5.0 mmol) 3-hydroxy benzaldehyde to give 763 mg (62%) of **5h**. ^1H NMR (400 MHz, chloroform-*d*) *δ* 9.99 (s, 1H, CHO), 7.58–7.38 (m, 5H, 5 arom. CH), 7.34–7.26 (m, 3H, 3 arom. CH), 5.23 (s, 2H, CH_2). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 192.03 (CHO), 159.11 (quat. C), 137.91 (quat. C), 134.07 (quat. C), 132.83 (quat. C), 130.22 (arom. CH), 129.54 (arom. CH), 129.29 (arom. CH), 128.89 (arom. CH), 127.04 (arom. CH), 123.82 (arom. CH), 122.02 (arom. CH), 113.56 (arom. CH), 67.42 (CH_2). MS (EI) *m/z* = 246 (M^+, 4), 207 (11), 125 (100). HR-MS calcd. for $C_{14}H_{11}ClO_2$ [M^+]: 246.0448. Found: 246.0446.

4-[(2-Chlorobenzyl)oxy])benzaldehyde (**5i**): The compound was prepared according to general procedure 1 from 966 mg (6.0 mmol) 2-chlorobenzyl chloride and 611 mg (5.0 mmol) 4-hydroxy benzaldehyde to give 983 mg (80%) of **5i** as pale yellow oil. ^1H NMR (400 MHz, chloroform-*d*) *δ* 9.90 (s, 1H, CHO), 7.86 (d, *J* = 8.8 Hz, 2H, 2 arom. CH), 7.56–7.51 (m, 1H, arom. CH), 7.47–7.39 (m, 1H, arom. CH), 7.33–7.27 (m, 2H, 2 arom. CH), 7.10 (d, *J* = 8.8 Hz, 2H, 2 arom. CH), 5.26 (s, 2H, CH_2). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 190.77 (CHO), 163.43 (quat. C), 133.70 (quat. C), 132.74 (quat. C), 132.05 (2 arom. CH), 130.37 (quat. C), 129.57 (arom. CH), 129.40 (arom. CH), 128.80 (arom. CH), 127.10 (arom. CH), 115.15 (2 arom. CH), 67.38 (CH_2). MS (EI) *m/z* = 246 (M^+, 4), 207 (1), 177 (27), 125 (100). HR-MS calcd. for $C_{14}H_{11}ClO_2$ [M^+]: 246.0448. Found: 246.0444.

3-[(4-Chlorobenzyl)oxy]benzaldehyde (**5j**): The compound was prepared according to general procedure 1 from 886 mg (5.5 mmol) 4-chlorobenzyl bromide and 610 mg (5.0 mmol) 3-hydroxy benzaldehyde to give mg of **5j**. ^1H NMR (400 MHz, chloroform-*d*) *δ* 9.98 (s, 1H, CHO), 7.51–7.44 (m, 3H, 3 arom. CH), 7.38 (s, 4H, 4 arom. CH), 7.24 (dt, *J* = 7.3, 2.5 Hz, 1H, arom. CH), 5.10 (s, 2H, CH_2). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 191.98 (CO), 159.08 (quat. C), 137.87 (quat. C), 134.82 (quat. C), 134.06 (quat. C), 130.21 (arom. CH), 128.89 (2 arom. CH), 128.84 (2 arom. CH), 124.01 (arom. CH), 122.20 (arom. CH), 113.06 (arom. CH), 69.44 (CH_2). IR (KBr) ν (cm^{-1}) 2823, 2736, 1696, 1598, 1493, 1387, 1261, 1166, 1014, 862, 807, 776, 762, 677. MS (EI) *m/z* = 245 (M^+−1, 5), 125 (100). HR-MS calcd. for $C_{14}H_{10}ClO_2$ [M^+−1]: 245.0369. Found: 245.0363.

4-[(4-Chlorobenzyl)oxy]benzaldehyde (**5k**): The compound was prepared according to general procedure 1 from 886 mg (5.5 mmol) 4-chlorobenzyl bromide and 610 mg (5.0 mmol) 3-hydroxy benzaldehyde to give 641 mg (52%) mg of **5k**. ^1H NMR (400 MHz, chloroform-*d*) *δ* 9.89 (s, 1H, CH=), 7.84 (d, *J* = 8.8 Hz, 2H, 2 arom. CH), 7.37 (s, 4H, 4 arom. CH), 7.06 (d, *J* = 8.8 Hz, 2H, 2 arom. CH), 5.12 (s, 2H, CH_2). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 190.80 (CHO), 163.45 (quat. C), 134.45 (quat. C), 134.21 (quat. C), 132.04 (2 arom. CH), 130.30 (quat. C), 128.94 (2 arom. CH), 128.81 (2 arom. CH), 115.13 (2 arom. CH), 69.47 (CH_2). MS (EI) *m/z* = 246 (M^+, 6), 127 (66), 125 (100). HR-MS calcd. for $C_{14}H_{10}ClO_2$ [M^+−1]: 246.0448. Found: 246.0442.

3-[(2,4-Dichlorobenzyl)oxy]benzaldehyde (**5l**): The compound was prepared according to general procedure 1 from 1.44 g (6.0 mmol) 2,4-dichlorobenzyl bromide and 610 mg (5.0 mmol) 3-hydroxy benzaldehyde to give 885 mg (63%) of **5l**. ^1H NMR (400 MHz, chloroform-*d*) *δ* 9.99 (s, 1H, CHO), 7.54–7.43 (m, 5H, 5 arom. CH), 7.31–7.24 (m, 3H, 3 arom. CH), 5.18 (s, 2H, CH_2). ^{13}C NMR (100 MHz, chloroform-*d*) *δ* 191.92 (CHO), 158.87 (quat. C), 137.93 (quat. C), 134.47 (quat. C), 133.40 (quat. C), 132.74 (quat. C), 130.28 (arom. CH), 129.68 (arom. CH), 129.38 (arom. CH), 127.38 (arom. CH), 124.12 (arom. CH), 122.00 (arom. CH), 113.30 (arom. CH), 66.84 (CH_2). MS (EI) *m/z* = 280 (M^+−1, 4), 159 (100). HR-MS calcd. for $C_{14}H_{10}Cl_2O_2$ [M^+]: 280.0058. Found: 280.0055.

4-[(2,4-Dichlorobenzyl)oxy]benzaldehyde (**5m**): The compound was prepared according to general procedure 1 from 1.17 g (6.0 mmol) 2,4-dichlorobenzyl chloride and 610 mg (5.0 mmol) 4-hydroxy benzaldehyde to give 1.21 g (71%) of **5m** as ^1H NMR (500 MHz, chloroform-d) *δ* 9.90 (s, 1H, CHO), 7.86 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 7.47 (d, *J* = 8.3 Hz, 1H, arom. CH), 7.45 (d, *J* = 2.0 Hz, 1H, arom. CH), 7.29 (dd, *J* = 8.3, 2.0 Hz, 1H, arom. CH), 7.08 (d, *J* = 8.6 Hz, 2H, arom. CH), 5.21 (s, 2H, CH_2). ^{13}C NMR (100 MHz, chloroform-*d*) *δ* 190.71 (CHO), 163.13 (quat. C), 134.62 (quat. C), 133.33 (quat. C), 132.37 (quat. C), 132.06 (2 arom. CH), 130.52 (quat. C), 129.63 (arom. CH), 129.42 (arom. CH), 127.46 (arom. CH), 115.11 (2 arom.

CH), 66.80 (CH_2). MS (EI) *m/z* = 282 (M^+, 5), 281 (M^+, 2), 280 (M^+, 8), 159 (100). HR-MS calcd. for $C_{14}H_{10}Cl_2O_2$ [M^+]: 280.0058. Found: 280.0048.

3-[(3,4-Dichlorobenzyl)oxy])benzaldehyde (**5n**): The compound was prepared according to general procedure 1 from 1.43 g (6.0 mmol) 3,4-dichlorobenzyl bromide and 610 mg (5.0 mmol) 3-hydroxy benzaldehyde to give 1.08 g (72%) of **5n**. ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 9.98 (s, 1H, CHO), 7.56 (d, *J* = 1.8 Hz, 1H, arom. CH), 7.53–7.41 (m, 5H, 5 arom. CH), 7.30–7.20 (m, 2H, arom. CH), 5.08 (s, 2H, CH_2). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 191.89 (CHO), 158.84 (quat. C), 137.90 (quat. C), 136.57 (quat. C), 130.67 (arom. CH), 130.51 (quat. C), 130.29 (arom. CH), 129.28 (arom. CH), 127.81 (quat. C), 126.55 (arom. CH), 124.26 (arom. CH), 122.15 (arom. CH), 112.91 (arom. CH), 68.72 (CH_2). MS (EI) *m/z* = 280 (M^+, 3), 161 (72), 159 (100). HR-MS: Calcd. for $C_{14}H_{10}Cl_2O_2$: 280.0058. Found: 280.0076.

4-[(3,4-Dichlorobenzyl)oxy]benzaldehyde (**5o**): The compound was prepared according to general procedure 1 from 1.43 g (6.0 mmol) 3,4-dichlorobenzyl bromide and 610 mg (5.0 mmol) 3-hydroxy benzaldehyde to give 927 mg (66%) of **5o**. ^{1}H NMR (500 MHz, chloroform-*d*) *δ* 9.90 (s, 1H, CHO), 7.86 (d, *J* = 8.7 Hz, 2H, 2 arom. CH), 7.55 (d, *J* = 1.8 Hz, 1H, arom. CH), 7.48 (d, *J* = 8.2 Hz, 1H, arom. CH), 7.27 (dd, *J* = 1.8 Hz, *J* = 8.2 Hz, 1H, arom. CH), 7.06 (d, *J* = 8.7 Hz, 2H, 2 arom. CH), 5.10 (s, 2H, CH_2O). ^{13}C NMR (100 MHz, chloroform-*d*) δ 190.69 (CHO), 163.11 (quat. C), 136.18 (quat. C), 132.95 (quat. C), 132.41 (quat. C), 132.04 (2 arom. CH), 130.73 (arom. CH), 130.49 (quat. C), 129.26 (arom. CH), 126.52 (arom. CH), 115.08 (2 arom. CH), 68.74 (CH_2). MS (EI): *m/z* = 280 (M^+, 3), 161 (68), 159 (100). HR-MS: Calcd. for $C_{14}H_{10}Cl_2O_2$: 280.0058. Found: 280.0033.

4-[(4-Methoxybenzyl)oxy])benzaldehyde (**5p**): The compound was prepared according to general procedure 1 from 940 mg (6.0 mmol) 4-methoxybenzylbromide and 610 mg (5.0 mmol) 4-hydroxy benzaldehyde to give 1.06 g (88%) of **5o**. ^{1}H NMR (500 MHz, chloroform-*d*) *δ* ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 9.88 (s, 1H, CHO), 7.83 (d, *J* = 8.8 Hz, 2H, 2 arom. CH), 7.36 (d, *J* = 8.8 Hz, 2H, 2 arom. CH), 7.07 (d, *J* = 8.8 Hz, 2H, 2 arom. CH), 6.93 (d, *J* = 8.8 Hz, 2H, 2 arom. CH), 5.07 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 190.85 (CHO), 163.86 (quat. C), 159.75 (quat. C), 132.02 (2 arom. CH), 130.05 (quat. C), 129.34 (2 arom. CH), 127.94 (quat. C), 115.16 (2 arom. CH), 114.16 (2 arom. CH), 70.13 (CH_2), 55.27 (OCH_3). MS (EI): *m/z* = 242 (M^+, 0.6), 161 (68), 121 (100), 91 (6). HR-MS: Calcd. for $C_{15}H_{14}O_3$: 242.0943. Found: 242.0936.

4-[(4-*tert*-Butylbenzyl)oxy]benzaldehyde (**5q**): The compound was prepared according to general procedure 1 from 1.36 g (6.0 mmol) 4-*tert*-butylobenzylbromide and 623 mg (5.0 mmol) 4-hydroxy benzaldehyde to give 856 mg (64%) of **5o**. ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 9.89 (s, 1H, CHO), 7.84 (d, *J* = 8.9 Hz, 2H, 2 arom. CH), 7.43 (d, *J* = 8.5 Hz, 2H, 2 arom. CH), 7.37 (d, *J* = 8.9 Hz, 2H, 2 arom. CH), 7.08 (d, *J* = 8.5 Hz, 2H, 2 arom. CH), 5.12 (s, 2H, CH_2), 1.33 (s, 9H, 3 CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 190.83 (CHO), 163.90 (quat. C), 151.51 (quat. C), 132.87 (quat. C), 132.02 (2 arom. CH), 130.07 (quat. C), 127.50 (2 arom. CH), 125.71 (2 arom. CH), 115.14 (2 arom. CH), 70.21 (CH_2), 34.66 (quat. C), 31.33 (3 CH_3). MS (EI): *m/z* = 268 (M^+, 0.06), 147 (100), 126 (2), 119 (6), 105 (6), 91 (7). HR-MS: Calcd. for $C_{18}H_{20}O_2$: 268.1463. Found: 268.1458.

(±)-*N*-{3-[(4-Fluorobenzyl)oxy]benzyl}−6-methylheptan-2-amine (**6a**): The compound was prepared according to general procedure 2 from 375 mg (1.63 mmol) 3-(4-fluorobenzyloxy)benzaldehyde (**5a**) and 280 mg (2.17 mmol) 6-methylheptan-2-amine to give 524 mg (98%) of **6a**. ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.40 (dd, *J* = 8.6, 5.4 Hz, 2H, arom. CH), 7.23 (t, *J* = 7.9 Hz, 1H, arom. CH), 7.07 (t, *J* = 8.7 Hz, 2H, 2 arom. CH), 6.96 (t, *J* = 2.1 Hz, 1H, arom. CH, 2-H), 6.92 (d, *J* = 7.9 Hz, 1H, arom. CH), 6.84 (dd, *J* = 7.9, 2.3 Hz, 1H, arom. CH), 5.02 (s, 2H, CH_2), 3.81 (d, *J* = 13.1 Hz, 1H, CH_2), 3.72 (d, *J* = 13.1 Hz, 1H, CH_2), 2.66 (p, *J* = 6.2 Hz, 1H, CH), 1.63–1.46 (m, 3H, CH_2, CH), 1.36–1.22 (m, 2H, CH_2), 1.19–1.10 (m, 2H, CH_2), 1.07 (d, *J* = 6.2 Hz, 3H, CH_3), 0.86 (d, *J* = 6.6 Hz, 6H, 2CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 162.24 (quat. C), 158.80 (quat. C), 142.68 (arom. CH), 132.86 (d, *J* = 3.5 Hz, quat. C), 129.37 (d, *J* = 6.0 Hz, 2 arom. CH), 129.30 (arom. CH), 120.86 (arom. CH), 115.47 (d, *J* = 21.3 Hz, 2 arom. CH), 114.62 (arom. CH), 113.17 (arom. CH), 69.26 (CH_2), 52.48 (CH), 51.29 (CH_2), 39.17 (CH_2), 37.32 (CH_2), 27.96 (CH), 23.74 (CH_2), 22.67 (CH_3), 22.59 (CH_3), 20.31 (CH_3). MS (EI) *m/z* = 284 (3), 244 (26), 215 (100), 187 (11), 128 (23). HR-MS (EI, M^++H) calcd. for $C_{22}H_{31}FNO_2$ (M^++H): 344.2390. Found: 344.2382.

(±)-*N*-{4-[(4-Fluorobenzyl)oxy])benzyl}−6-methylheptan-2-amine (**6b**): The compound was prepared according to general procedure 2 from 375 mg (1.63 mmol) of **5b** and 280 mg (2.17 mmol) 6-methyl-2-heptylamine to give 252 mg (45%) of **6b** as pale yellow oil. ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.40 (dd, *J* = 8.5, 5.6 Hz, 2H, 2 arom. CH), 7.24 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 7.06 (t, *J* = 8.7 Hz, 2H, 2 arom. CH), 6.91 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 5.01 (s, 2H, CH_2), 3.76 (d, *J* = 12.7 Hz, 1H, CH_2), 3.67 (d, *J* = 12.8 Hz, 1H, CH_2), 2.66 (h, *J* = 6.3 Hz, 1H, CH), 1.53 (tt, *J* = 12.2, 6.0 Hz, 1H, CH), 1.48–1.11 (m, 6H, 3CH_2), 1.07 (d, *J* = 6.2 Hz, 3H, CH_3), 0.87 (d, *J* = 6.6 Hz, 6H, 2CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 162.49 (d, *J* = 246.2 Hz, quat. C), 157.56 (quat. C), 133.62 (quat. C), 132.88 (d, *J* = 3.1 Hz, quat. C).129.32 (2 arom. CH), 129.30 (d, *J* = 8.2 Hz, 2 arom. CH), 115.47 (d, *J* = 21.6 Hz, 2 arom. CH), 114.73 (2 arom. CH), 69.39 (CH_2), 52.49 (CH), 50.84 (CH_2), 39.18 (CH_2), 37.36 (CH_2), 27.96 (CH), 23.74 (CH_2), 22.68 (CH_3), 22.59 (CH_3), 20.38 (CH_3). MS (EI): *m/z* = 342 (M^+-H, 1), 298 (6), 258 (12), 215 (38, $C_{14}H_{12}FO^•$), 109 (100, $C_7H_6F^•$). HR-MS: calcd. for $C_{22}H_{29}FNO$ (M^+-H): 342.2233. Found: 342.2218.

(±)-*N*-{3-[(2,4-Difluorobenzyl)oxy]benzyl}−6-methylheptan-2-amine (**6c**): The compound was prepared according to general procedure 2 from 397 mg (1.6 mmol) of **5c** and 289 mg (2.24 mmol) of 6-methyl-2-heptylamine to give 482 mg (83%) of **6c** as colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.58–7.41 (m, 1H, arom. CH), 7.28–7.21 (m, 1H, arom. CH), 6.99 (t, *J* = 2.1 Hz, 1H, arom. CH), 6.94 (d, *J* = 7.8 Hz, 1H, arom. CH), 6.92–6.80 (m, 3H, 3 arom. CH), 5.07 (s, 2H, CH_2), 3.82 (d, *J* = 13.2 Hz, 1H, CH_2), 3.73 (d, *J* = 13.2 Hz, 1H, CH_2), 2.73–2.60 (m, 1H, CH), 1.59–1.42 (m, 3H, CH, CH_2), 1.38–1.26 (m, 2H, CH_2), 1.21–1.11 (m, 2H, CH_2), 1.08 (d, *J* = 6.3 Hz, 3H, CH_3), 0.86 (d, *J* = 6.6 Hz, 6H, 2CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 162.92 (dd, *J* = 218.6,

11.9 Hz, quat. C), 160.44 (dd, *J* = 219.4, 12.0 Hz, quat. C), 158.58 (quat. C), 142.50 (quat. C), 130.79 (dd, *J* = 9.8, 5.6 Hz, arom. CH), 129.47 (arom. CH), 121.10 (arom. CH), 120.27 (dd, *J* = 14.6, 3.8 Hz, quat. C), 114.60 (arom. CH), 113.17 (arom. CH), 111.40 (dd, *J* = 21.1, 3.7 Hz, arom. CH), 103.82 (t, *J* = 25.4 Hz, arom. CH), 63.18 (CH_2), 52.47 (CH), 51.16 (CH_2), 39.15 (CH_2), 37.21 (CH_2), 27.88 (CH), 23.56 (CH_2), 22.65 (CH_3), 22.57 (CH_3), 20.19 (CH_3). MS (EI) *m/z* = 346 (M^+-CH_3, 12), 276 (M^+-C_6H_{13}, 100), 233 (M^+-$C_8H_{18}N$, 60), 127 (72). HR-MS (ESI) calcd. for $C_{22}H_{30}F_2NO$ (M^++H): 362.2296. Found 362.2299.

(±)-*N*-{4-[(2-Bromobenzyl)oxy])benzyl}−6-methylheptan-2-amine (**6d**): The compound was prepared according to general procedure 2 from 582 mg (2.0 mmol) of **5e** and 362 mg (2.8 mmol) 6-methyl-2-heptylamine to give 500 mg (62%) of **6d**. ^{1}H NMR (500 MHz, methylene chloride-d_2) *δ* 7.58 (dd, *J* = 8.0, 1.2 Hz, 1H, arom. CH), 7.54 (dd, *J* = 7.8, 1.7 Hz, 1H, arom. CH), 7.32 (td, *J* = 7.6, 1.3 Hz, 1H, arom. CH), 7.27 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 7.18 (td, *J* = 7.7, 1.8 Hz, 1H, arom. CH), 6.94 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 5.11 (s, 2H, CH_2), 3.78 (d, *J* = 12.8 Hz, 1H, CH_2), 3.69 (d, *J* = 12.8 Hz, 1H, CH_2), 2.75–2.63 (m, 1H, CH), 1.53–1.44 (m, 1H, CH_2), 1.52 (hept, *J* = 6.6 Hz, 1H, CH), 1.40–1.24 (m, 3H, $2CH_2$), 1.19–1.11 (m, 2H, CH_2), 1.10 (d, *J* = 6.3 Hz, 3H, CH_3), 0.86 (d, *J* = 6.7 Hz, 6H, $2CH_3$). ^{13}C NMR (100 MHz, chloroform-*d*) *δ* 157.56 (quat. C), 136.38 (quat. C), 132.60 (arom. CH), 129.58 (quat. C), 129.58 (arom. CH), 129.18 (arom. CH), 128.86 (2 arom CH), 127.53 (arom. CH), 122.25 (quat. C), 114.85 (2 arom. CH), 69.45 (CH_2), 52.45 (CH), 50.49 (CH2), 39.10 (CH_2), 36.93 (CH_2), 27.94 (CH), 23.71 (CH_2), 22.67 (CH_3), 22.58 (CH_3). MS (EI) *m/z* = 403 (M^+, 2), 318 (20), 275 (60), 169 (100). HR-MS: Calcd. for $C_{22}H_{30}BrNO$: 403.1511. Found: 403.1511.

(±)-*N*-{4-[(4-Bromobenzyl)oxy]benzyl}−6-methylheptan-2-amine (**6e**): The compound was prepared according to general procedure 2 from 408 mg (1.4 mmol) **5g** and 252 mg (1.96 mmol) 6-methyl-2-heptylamine to give 320 mg (41%) of **6g**. ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.50 (d, *J* = 8.5 Hz, 2H, 2 arom. CH), 7.30 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 7.23 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 6.90 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 5.00 (s, 2H, CH_2), 3.76 (d, *J* = 12.7 Hz, 1H, CH_2), 3.67 (d, *J* = 12.8 Hz, 1H, CH_2), 2.66 (p, *J* = 5.9 Hz, 1H, CH), 1.62–1.45 (m, 1H, CH), 1.33–1.11 (m, 5H, $2CH_2$), 1.21–1.10 (m, 1H, CH_2), 1.07 (d, *J* = 6.3 Hz, 3H, CH_3), 0.86 (d, *J* = 6.6 Hz, 6H, $2CH_3$). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 157.44 (quat. C), 136.19 (quat. C), 133.67 (quat. C), 131.68 (2 arom. CH), 129.33 (2 arom. CH), 129.04 (2 arom. CH), 121.79 (quat. C), 114.75 (2 arom. CH), 69.28 (CH_2), 52.48 (CH), 50.81 (CH_2), 39.17 (CH_2), 37.34 (CH_2), 27.95 (CH), 23.73 (CH_2), 22.67 (CH_3), 22.59 (CH_3), 20.35 (CH_3). MS (EI) *m/z* = 360 (6), 318 (14), 275 (34), 171 (100), 169 (96). HR-MS (EI) calcd. for $C_{22}H_{30}BrN$ (M^+): 403.1511. Found: 403.1468.

(±)-*N*-{4-[(2-Chlorobenzyl)oxy]benzyl}−6-methylheptan-2-amine (**6g**): The compound was prepared according to general procedure 2 from 246 mg (1.0 mmol) **5i** and 181 mg (1.4 mmol) 6-methyl-2-heptylamine to give 202 mg (56%) of **6g** as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.30–7.25 (m, 4H, 4 arom. CH), 7.24 (d, *J* = 8.7 Hz, 2H, 2 arom. CH), 6.94 (d, *J* = 8.7 Hz, 2H, 2 arom. CH), 5.16 (s, 2H, CH_2), 3.77 (d, *J* = 12.8 Hz, 1H, CH_2), 3.67 (d, *J* = 12.8 Hz, 1H, CH_2), 2.66 (h, *J* = 6.2 Hz, 1H, CH), 1.57–1.49 (m, 1H, CH), 1.35–1.24 (m, 4H, $2CH_2$), 1.18–1.11 (m, 2H, CH_2), 1.07 (d, *J* = 6.2 Hz, 3H, CH_3), 0.86 (d, *J* = 7.3 Hz, 6H, $2CH_3$). MS (EI) *m/z* = 358 (M^+-H, 0.7), 344 (0.9), 274 (26), 233 (29), 231 (100), 127 (26), 125 (87). HR-MS (EI) calcd. for $C_{22}H_{29}ClNO$ (M^+-H): 358.1938. Found: 358.1925. According to general procedure 3 the compound could be precipitated as hydrochloride in quantitative yield. ^{1}H NMR (400 MHz, Methanol-d_4) *δ* 7.58–7.51 (m, 1H, arom. CH), 7.48–7.41 (m, 1H, arom. CH), 7.44 (d, *J* = 8.8 Hz, 2H, 2 arom. CH), 7.36–7.30 (m, 2H, 2 arom. CH), 7.09 (d, *J* = 8.8 Hz, 2H, 2 arom. CH), 5.21 (s, 2H, CH_2), 4.22–4.08 (m, 2H, CH_2), 3.29–3.20 (m, 1H, CH), 1.86–1.75 (m, 1H, CH_2), 1.64–1.48 (m, 2H, CH, CH_2), 1.47–1.33 (m, 2H, CH_2), 1.37 (d, *J* = 6.6 Hz, 3H, CH_3), 1.27–1.20 (m, 2H, CH_2), 0.91 (d, *J* = 6.6 Hz, 6H, $2CH_3$).^{13}C NMR (101 MHz, methanol-d_4) *δ* 159.52 (quat. C), 134.33 (quat. C), 132.82 (quat. C), 131.18 (2 arom. CH), 129.23 (arom. CH), 129.18 (arom. CH), 129.15 (arom. CH), 126.82 (arom. CH), 123.74 (quat. C), 115.18 (2 arom. CH), 67.00 (CH_2), 54.10 (CH), 47.65 (CH_2), 38.28 (CH_2), 32.82 (CH_2), 27.59 (CH), 22.89 (CH_2), 21.56 (CH_3), 21.39 (CH_3), 14.93 (CH_3).

(±)-*N*-{3-[(4-Chlorobenzyl)oxy]benzyl}−6-methylheptan-2-amine (**6h**): The compound was prepared according to general procedure 2 from 370 mg (1.5 mmol) of **5j** and 271 mg (2.1 mmol) 6-methyl-2-heptylamine to give 425 mg (72%) of **6h**. ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.29 (m, 4H, 4 arom. CH), 7.20 (t, *J* = 7.9 Hz, 1H, arom. CH), 6.93 (t, *J* = 2.1 Hz, 1H, arom. CH), 6.89 (d, *J* = 7.6 Hz, 1H, arom. CH, CH), 6.81 (dd, *J* = 8.3, 2.6 Hz, 1H, arom. CH), 4.97 (s, 2H, CH_2), 4.61 (s, 2H, CH_2), 3.89 (dq, *J* = 8.6, 6.6 Hz, 1H), 1.44 (dq, *J* = 12.1, 6.1, 5.7 Hz, 1H, CH), 1.37–1.07 (m, 6H, $3CH_2$), 1.05 (d, *J* = 6.6 Hz, 3H, CH_3), 0.79 (d, *J* = 6.6 Hz, 6H, $2CH_3$). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 158.45 (quat. C), 141.69 (quat. C), 134.48 (quat. C), 132.73 (quat. C), 128.66 (arom. CH), 127.74 (4 arom. CH), 118.53 (arom. CH), 113.04 (arom. CH), 112.19 (arom. CH), 68.15 (CH_2), 64.56 (CH_2), 44.32 (CH), 37.76 (CH_2), 36.18 (CH_2), 26.86 (CH), 22.75 (CH_2), 21.56 (CH_3), 21.53 (CH_3), 19.96 (CH_3). MS (EI) *m/z* = 231 (2, M^+ −$C_8H_{18}N^•$), 127 (33), 125 (100). HR-MS (EI) calcd. for $C_{13}H_{10}OCl$ [M^+-$C_9H_{20}N$]: 217.0420. Found: 217.0412.

(±)-*N*-{3-[(2,4-Dichlorobenzyl)oxy]benzyl}−6-methylheptan-2-amine (**6i**): The compound was prepared according to general procedure 2 from 562 mg (2.0 mmol) of **5l** and 362 mg (2.8 mmol) 6-methyl-2-heptylamine to give 568 mg (72%) of **6i** as colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.44 (d, *J* = 8.3 Hz, 1H, arom. CH), 7.35 (d, *J* = 2.2 Hz, 1H, arom. CH), 7.23–7.14 (m, 2H, 2 arom. CH), 6.93–6.87 (m, 1H, arom. CH), 6.87 (d, *J* = 7.6 Hz, 1H, arom. CH), 6.77 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H, arom. CH), 5.05 (s, 2H, CH_2), 3.74 (d, *J* = 13.2 Hz, 1H, CH_2), 3.65 (d, *J* = 13.2 Hz, 1H, CH_2), 2.59 (h, *J* = 5.9 Hz, 1H, CH), 1.53–1.40 (m, 1H, CH), 1.39–1.21 (m, 4H, $2CH_2$), 1.13–1.03 (m, 2H, $2CH_2$), 1.00 (d, *J* = 6.3 Hz, 3H, CH_3), 0.79 (d, *J* = 6.7 Hz, 6H, $2CH_3$). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 158.42 (quat. C), 142.85 (quat. C), 134.03 (quat. C), 133.56 (quat. C), 133.12 (quat. C), 129.62 (arom. CH), 129.50 (arom. CH), 129.17 (arom. CH), 127.30 (arom. CH), 121.15 (arom. CH), 114.63 (arom. CH), 113.06 (arom. CH), 66.42 (CH_2), 52.51 (CH), 51.27 (CH_2), 39.16 (CH_2), 37.33 (CH_2), 27.95 (CH), 23.73 (CH_2), 22.67 (CH_3), 22.59 (CH_3), 20.33 (CH_3). MS (EI) *m/z* = 394 (M^+, 6), 347 (10), 265 (65), 308 (80), 265 (50), 159 (100). HR-MS: Calcd. for $C_{22}H_{30}Cl_2NO$ [M^++H]: 394.1704. Found: 394.1679.

(±)-*N*-{4-[(2,4-Dichlorobenzyl)oxy]benzyl}−6-methylheptan-2-amine (**6j**): The compound was prepared according general procedure 2 from 562 mg (2.0 mmol) of **5l** and 362 mg (2.8 mmol) 6-methyl-2-heptylamine to give 568 mg (72%) of **6i** as a pale yellow oil. ^{1}H NMR (400 MHz, chloroform-d) δ 7.49 (d, J = 8.4 Hz, 1H, arom. CH, 5″-H), 7.42 (d, J = 2.1 Hz, 1H, arom. CH, 3″-H), 7.26 (dd, J = 2.1 Hz, J = 8.4 Hz, 1H, arom. CH, 6″-H), 7.25 (d, J = 8.7 Hz, 2H, arom. CH, 1′-H, 6′-H), 6.92 (d, J = 8.7 Hz, 2H, 2 arom. CH, 3′-H, 5′-H), 5.11 (s, 2H, CH_2), 3.77 (d, J = 12.8 Hz, 1H, CH_2), 3.67 (d, J = 12.8 Hz, 1H, CH_2), 2.66 (h, J = 6.0 Hz, 1H, CH), 1.60–1.24 (m, 6H, $3CH_2$), 1.07 (d, J = 6.3 Hz, 3H, CH_3), 0.86 (d, J = 6.6 Hz, 6H, $2CH_3$). ^{13}C NMR (100 MHz, chloroform-d) 157.23 (quat. C), 134.04 (quat. C), 133.76 (quat. C), 133.55 (quat. C), 133.10 (quat. C), 129.59 (arom. CH), 129.43 (2 arom. CH), 129.18 (arom (CH), 127.29 (arom. CH), 114.76 (2 arom. CH), 66.64 (CH_2), 52.51 (CH), 50.76 (CH_2), 39.15 (CH_2), 37.21 (CH_2), 27.89 (CH), 23.74 (CH_2), 22.67 (CH_3), 22.59 (CH_3), 20.28 (CH_3). MS (EI) m/z = 393 (M^+, 1), 265 (65), 160 (100). HR-MS: Calcd. for $C_{22}H_{29}Cl_2NO$: 393.1626. Found: 393.1639.

(±)-*N*-{4-[(3,4-Dichlorobenzyl)oxy]benzyl}−6-methylheptan-2-amine (**6k**): The compound was prepared according to general procedure 2 from 562 mg (2.0 mmol) of **5o** and 362 mg (2.8 mmol) 6-methyl-2-heptylamine to give 411 mg (52%) of **6i** as a pale yellow oil. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.24 (s, 1H, arom. CH), 7.90–7.84 (m, 1H), 7.70 (d, 2H, 2 arom. CH), 7.65–7.59 (m, 1H, arom. CH), 7.54–7.50 (m, 1H, arom. CH), 7.06 (d, J = 8.9 Hz, 2H, 2 arom. CH), 5.18 (s, 1H, NH), 5.12 (s, 2H, CH_2), 4.85 (s, 2H, CH_2), 3.37–3.27 (m, 1H, CH), 1.60–1.46 (m, 1H, CH), 1.22 (d, J = 3.3 Hz, 3H, CH_3), 1.30–1.08 (m, 7 H, $3CH_2$, CH), 0.85 (d, J = 6.6 Hz, 6H, $2CH_3$). ^{13}C NMR (100 MHz, chloroform-d) δ 157.24 (quat. C), 137.45 (quat. C), 133.77 (quat. C), 131.95 (quat. C), 131.87 (quat. C), 129.21 (arom. CH), 129.43 (2 arom. CH), 130.58 (arom. CH), 126.50 (arom. CH), 114.75 (2 arom. CH), 68.59 (CH_2), 52.51 (CH), 50.74 (CH_2), 39.16 (CH_2), 37.28 (CH_2), 27.95 (CH), 22.67 (CH_2), 22.67 (CH_3), 22.59 (CH_3), 20.30 (CH_3). HR-MS: Calcd. for $C_{22}H_{29}Cl_2NO$: 393.1626. Found: 393.1639.

(±)−1-{4-[(2-Chlorobenzyl)oxy]phenyl}-*N*-(6-methylheptan-2-yl) methanimine (**7a**): The compound was collected as by-product of **6g** in a small amount. **7a** was also synthesized: 493 mg (2.0 mmol) of aldehyde **5i** were dissolved in 30 mL dry methanol and 388 mg (3.0 mmol) of 6-methyl-2-heptylamine were added. The solution was stirred for 24 h and the solvent was evaporated. The residue was purified by FCC (isohexane/triethylamine 20:3) to 580 mg (80%) of **7a** as a colorless oil. ^{1}H NMR (400 MHz, chloroform-d) δ 8.20 (s, 1H, CH═N), 7.68 (d, J = 8.9 Hz, 2H, 2 arom. CH), 7.56–7.52 (m, 1H, arom. CH), 7.43–7.38 (m, 1H, arom. CH), 7.30–7.26 (m, 2H, 2 arom. CH), 7.00 (d, J = 8.8 Hz, 2H, 2 arom. CH), 5.21 (s, 2H, CH_2), 3.26 (dq, J = 8.2, 5.3 Hz, 1H, CH), 1.58–1.45 (m, 3H, CH_2, CH), 1.28–1.12 (m, 4H, $2CH_2$), 1.23 (d, J = 6.28 Hz, 3H, CH_3), 0.84 (d, J = 6.67 Hz, 3H, CH_3), 0.84 (d, J = 6.60 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, chloroform-d) δ 160.23 (quat. C), 157.93 (CH), 134.41 (quat. C), 132.60 (quat. C), 129.95 (quat. C), 129.65 (2 arom. CH), 129.42 (arom. CH), 129.08 (arom. CH), 128.75 (arom. CH), 127.00 (arom. CH), 67.14 (CH_2), 66.68 (CH), 38.89 (CH_2), 38.13 (CH_2), 27.91 (CH), 24.37 (CH_2), 22.73 (CH_3), 22.69 (CH_3), 22.60 (CH_3). MS (EI): m/z = 358 (M^++H, 0.15), 342 (0.63), 314 (16), 243 (10), 232 (19), 148 (26), 127 (33), 125 (100). HR-MS calcd. for $C_{22}H_{29}ClNO$• [M^++ H]: 358.1931. Found: 358.1938.

(±)−1-{4-[(3,4-Dichlorobenzyl)oxy]phenyl}-*N*-(6-methylheptan-2-yl)methanimine (**7b**): The compound was collected as by-product of **6k** in a small amount. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.19 (s, 1H, CH), 7.68 (d, J = 8.8 Hz, 2H, 2 arom. CH), 7.54 (d, J = 2.0 Hz, 1H, arom. CH), 7.45 (d, J = 8.3 Hz, 1H, arom. CH), 7.26 (dd, J = 8.3, 2.0 Hz, 1H, arom. CH), 6.96 (d, J = 8.8 Hz, 2H, 2 arom. CH), 5.05 (s, 2H, CH_2), 3.26 (tq, J = 6.6, 6.3 Hz, 1H, CH), 1.67–1.57 (m, 3H, CH_2, CH), 1.57–1.46 (m, 2H, CH_2), 1.33–1.09 (m, 2H, CH_2), 1.23 (d, J = 6.4 Hz, 3H, CH_3), 0.84 (d, J = 6.6 Hz, 3H, CH_3), 0.84 (d, J = 6.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, chloroform-*d*) δ 159.94 (quat. C), 157.82 (CH), 136.96 (quat. C), 132.81 (quat. C), 132.06 (quat. C), 130.75, 130.61 (arom. CH), 130.13 (quat. C), 129.67 (2 arom. CH), 129.22 (arom. CH), 126.50 (arom. CH), 114.78 (2 arom. CH), 68.53 (CH_2), 66.67 (CH), 38.88 (CH_2), 38.11 (CH_2), 27.90 (CH), 24.35 (CH_2), 22.70 (CH_3), 22.68 (CH_3), 22.59 (CH_3). MS (EI): m/z = 392 (M^+ + H), 348 (50, $C_{19}H_{20}Cl_2NO^•$), 305 (20), 232 (30, $C_{15}H_{22}NO^•$), 158 (100, $C_7H_5Cl_2^•$). HR-MS calcd. for $C_{19}H_{20}Cl_2NO^•$ [M^+-C_3H_7]: 348.0922. Found: 348.0908.

N-{3-[(4-Fluorobenzyl)oxy]benzyl}octan-1-amine (**8a**): The compound was prepared according general procedure 2 from 375 mg (1.63 mmol) of **5a** and 280 mg (2.17 mmol) of *n*-octylamine to give 515 mg (97%) of **8a** as a pale yellow oil. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.44–7.37 (m, 2H, 2 arom. CH), 7.29–7.21 (m, 1H, arom. CH), 7.10–7.03 (m, 2H, 2 arom. CH), 6.97 (t, J = 2.1 Hz, 1H, arom. CH), 6.92 (d, J = 8.0 Hz, 1H, arom. CH), 6.85 (dd, J = 8.4, 2.4 Hz, 1H, arom. CH), 5.02 (s, 2H, CH_2), 3.77 (s, 2H, CH_2), 2.61 (t, J = 7.2 Hz, 2H, CH_2), 1.56–1.40 (m, 2H, CH_2), 1.36–1.19 (m, 10H, 5 CH_2), 0.87 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) δ 162.47 (d, J = 244.9 Hz quat. C), 158.80 (quat. C), 142.22 (quat. C), 132.85 (d, J = 3.4 Hz, quat. C), 129.40 (d, J = 5.7 Hz, 2 arom. CH), 129.29 (arom. CH), 128.86 (arom. CH), 115.45 (d, J = 23.6 Hz, 2 arom. CH), 114.52 (arom. CH), 113.30 (arom. CH), 69.27 (CH_2), 53.93 (CH_2), 49.45 (CH_2), 31.84 (CH_2), 30.06 (CH_2), 29.54 (CH_2), 29.28 (CH_2), 27.37 (CH_2), 22.67 (CH_2), 14.11 (CH_3). MS (EI) m/z = 298 (M^+-C_4H_{10}, 8), 259 (13), 258 (76), 215 (100), 187 (15), 159 (22). HR-MS (EI) calcd. for $C_{22}H_{31}FNO$ (M^++H): 344.2390. Found: 344.2382. The compound could be precipitated as hydrochloride according to general procedure 3. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.49–7.43 (m, 2H, 2 arom. CH), 7.35 (t, J = 8.0 Hz, 1H, arom. CH), 7.24–7.21 (m, 1H, arom. CH), 7.13–7.03 (m, 4H, 4 arom. CH), 5.09 (s, 2H, CH_2), 4.16 (s, 2H, CH_2), 3.03–2.95 (m, 2H, CH_2), 1.71 (dq, J = 16.3, 8.0 Hz, 2H, CH_2), 1.42–1.21 (m, 10H, 5 CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3).

N-{4-[(4-Fluorobenzyl)oxy]benzyl}octan-1-amine (**8b**): The compound was prepared according to general procedure 2 from 460 mg (2.0 mmol) of **5b** and 362 mg (2.8 mmol) *n*-octylamine to give 653 mg (95%) of **8a** as a pale yellow solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.42–7.35 (m, 2H, 2 arom. CH), 7.23 (d, J = 8.6 Hz, 2H, 2 arom. CH), 7.06 (t, J = 8.7 Hz, 2H, 2 arom. CH), 6.91 (d, J = 8.7 Hz, 2H, 2 arom. CH), 5.00 (s, 2H, CH_2), 3.72 (s, 2H, CH_2), 2.60 (t, J = 7.2 Hz, 2H, CH_2), 1.49 (p, J = 7.2 Hz, 2H, CH_2), 1.36–1.20 (m, 10H, 5 CH_2), 0.87 (t, J = 6.6 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) δ 162.60 (d,

J = 248, 0 Hz, quat. C), 158.38 (quat. C), 132.97 (quat. C), 132.85 (d, *J* = 3.3 Hz, quat. C), 129.40 (2 arom. CH), 129.30 (d, *J* = 8.3 Hz, 2 arom. CH), 115.47 (d, *J* = 21.5 Hz, 2 arom. CH), 114.74 (2 arom. CH), 69.37 (CH_2), 53.38 (CH_2), 49.38 (CH_2), 31.83 (CH_2), 29.99 (CH_2), 29.53 (CH_2), 29.27 (CH_2), 27.38 (CH_2), 22.66 (CH_2), 14.10 (CH_3). MS (EI) *m/z* = 343 (M^+, 0.05), 342 (0.2), 230 (3), 215 (21), 109 (100). HR-MS (EI) calcd. for $C_{22}H_{31}FNO$ (M^++H): 344.2390. Found: 344.2383.

N-{4-[(4-Chlorobenzyl)oxy]benzyl}octan-1-amine (**8c**): The compound was prepared according to general procedure 2 from 247 mg (1.0 mmol) **5k** and 181 mg (1.4 mmol) *n*-octylamine to give 317 mg (63%) of **8c** as a pale brown solid. ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.39–7.31 (m, 4H, 4 arom. CH), 7.23 (d, *J* = 8.7 Hz, 2H, 2 arom. CH), 6.90 (d, *J* = 8.7 Hz, 2H, arom. CH), 5.02 (s, 2H, CH_2), 3.72 (s, 2H, CH_2), 2.66–2.56 (t, *J* = 7.2 Hz, 2H, CH_2), 1.49 (p, *J* = 7.2 Hz, 2H, CH_2), 1.39–1.16 (m, 10H, 5 CH_2), 0.87 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 157.52 (quat. C), 135.66 (quat. C), 133.70 (quat. C), 133.31 (quat. C), 129.36 (2 arom. CH), 128.75 (4 arom. CH), 114.73 (2 arom. CH), 69.26 (CH_2), 53.49 (CH_2), 49.50 (CH_2), 31.85 (CH_2), 30.12 (CH_2), 29.55 (CH_2), 29.29 (CH_2), 27.40 (CH_2), 22.68 (CH_2), 14.12 (CH_3). MS (EI) *m/z* = 358 (M^+-H, 3), 233, (14), 231 (39), 127 (26), 125 (100), 89 (13). HR-MS (EI) calcd. for $C_{22}H_{29}ClNO$ (M^+-H): 358.1938. Found: 358.1934.

N-{4-[(2,4-Dichlorobenzyl)oxy]benzyl}octan-1-amine (**8d**): The compound was prepared according to general procedure 2 from 560 mg (2.0 mmol) **5 m** and 362 mg (2.8 mmol) *n*-octylamine to give 623 mg (79%) of **8d** as a pale brown solid. ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.50 (d, *J* = 8.3 Hz, 1H, arom. CH), 7.41 (d, *J* = 2.1 Hz, 1H, arom. CH), 7.31–7.26 (m, 1H, arom. CH), 7.23 (d, *J* = 8.5 Hz, 2H, 2 arom. CH), 6.92 (d, *J* = 8.5 Hz, 2H, 2 arom. CH), 5.11 (s, 2H, CH_2), 3.72 (s, 2H, CH_2), 2.61 (t, *J* = 7.2 Hz, 2H, CH_2), 1.56–1.45 (m, 2H, CH_2), 1.39–1.14 (m, 10H, 5 CH_2), 0.87 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 157.25 (quat. C), 134.03 (quat. C), 133.55 (quat. C), 133.16 (quat. C), 133.10 (quat. C), 129.58 (arom. CH), 129.40 (2 arom. CH), 127.29 (arom. CH), 129.17 (arom. CH), 114.72 (2 arom. CH), 66.63 (CH_2), 62.11 (CH_2), 53.47 (CH_2), 49.51 (CH_2), 31.84 (CH_2), 30.10 (CH_2), 29.54 (CH_2), 29.28 (CH_2), 27.39 (CH_2), 22.66 (CH_2), 14.10 (CH_3). MS (EI) *m/z* = 392 (M^+-H, 1), 281 (11), 267, (27), 265 (52), 161 (65), 159 (100), 89 (13). HR-MS (EI) calcd. for $C_{22}H_{29}Cl_2NO$ (M^+-H): 393.1626. Found: 393.1623. The compound could be precipitated according to general procedure 3 as hydrochlorid to give a white solid in quantitative yield.

N-{3-[(2,4-Difluorobenzyl)oxy]benzyl}octan-1-amine (**8e**): The compound was prepared according to general procedure 2 from 397 mg (1.6 mmol) of **5c** and 290 mg (1.4 mmol) *n*-octylamine to give 315 mg (55%) of **8e** as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.52–7.44 (m, 1H, arom. CH), 7.24 (t, *J* = 7.9 Hz, 1H, arom. CH), 6.99–6.95 (m, 1H, arom. CH), 6.95–6.92 (m, 1H, arom. CH), 6.92–6.87 (m, 1H, arom. CH), 6.87–6.83 (m, 2H, 2 arom. CH), 5.08 (s, 2H, CH_2), 3.77 (s, 2H, CH_2), 2.61 (t, *J* = 7.2 Hz, 2H, CH_2), 1.50 (p, *J* = 7.5 Hz, 2H, CH_2), 1.39–1.19 (m, 10H, 5 CH_2), 0.87 (t, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 162.92 (dd, *J* = 219.7, 11.9 Hz, quat. C), 160.38 (dd, *J* = 220.2 Hz, *J* = 12.2 Hz, quat. C), 158.57 (quat. C), 142.52 (quat. C), 130.77 (dd, *J* = 9.8, 5.6 Hz, arom. CH), 129.45 (arom. CH), 121.02 (arom. CH), 120.26 (dd, *J* = 14.7, 3.8 Hz, quat. C), 114.45 (arom. CH), 113.17 (arom. CH), 111.42 (dd, *J* = 21.2, 3.8 Hz, arom. CH), 103.84 (t, *J* = 25.4 Hz, arom. CH), 63.17 (d, *J* = 3.8 Hz, CH_2), 54.01 (CH_2), 49.55 (CH_2), 31.85 (CH_2), 30.16 (CH_2), 29.56 (CH_2), 29.29 (CH_2), 27.38 (CH_2), 22.67 (CH_2), 14.10 (CH_3). MS (EI) *m/z* = 360 (M^+, 2), 262 (76), 233 (100), 127 (78). HR-MS (EI) calcd. for $C_{22}H_{28}F_2NO$ (M^+-H): 360.2139. Found: 360.2128.

N-{4-[(4-Bromobenzyl)oxy]benzyl}octan-1-amine (**8f**): The compound was prepared according to general procedure 2 from 408 mg (1.4 mmol) of **5g** and 253 mg (1.96 mmol) *n*-octylamine to give 351 mg (62%) of **8f** as a pale brown solid. ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.50 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 7.30 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 7.23 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 6.90 (d, *J* = 8.6 Hz, 2H, 2 arom. CH), 5.00 (s, 2H, CH_2), 3.78 (s, 2H, CH_2), 2.60 (t, *J* = 7.3 Hz, 2H, CH_2), 1.48 (tt, *J* = 7.2 Hz, 2H, CH_2), 1.37–1.18 (m, 10H, 5 CH_2), 0.87 (t, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 157.48 (quat. C), 136.18 (quat. C), 133.39 (quat. C), 131.69 (2 arom. CH), 129.33 (2 arom. CH), 129.05 (2 arom. CH), 121.80 (quat. C), 114.71 (2 arom. CH), 69.27 (CH2), 53.51 (CH_2), 49.52 (CH_2), 31.84 (CH_2), 30.14 (CH_2), 29.55 (CH_2), 29.28 (CH_2), 27.40 (CH_2), 22.67 (CH_2), 14.11 (CH_3). MS (EI) *m/z* = 404 (M^+, 7), 304 (90), 275 (46), 171 (96), 169 (100). HR-MS (EI) calcd. for $C_{22}H_{31}BrNO$ (M^+ + H): 404,1584. Found: 404.1607.

N-{3-[(4-Bromobenzyl)oxy]benzyl}octan-1-amine (**8g**): The compound was prepared according to general procedure 2 from 408 mg (1.4 mmol) **5f** and 253 mg (1.96 mmol) *n*-octylamine to give 283 mg (50%) of **8g** as a pale brown solid. ^{1}H NMR (400 MHz, chloroform-*d*) *δ* 7.50 (d, *J* = 8.5 Hz, 2H, 2 arom. CH), 7.31 (d, *J* = 8.5 Hz, 2H, 2 arom. CH), 7.23 (t, *J* = 7.9 Hz, 1H, arom. CH), 6.95 (s, 1H, arom. CH), 6.92 (d, *J* = 7.6 Hz, 1H, arom. CH), 6.83 (dd, *J* = 8.1, 2.9 Hz, 1H, arom. CH), 5.02 (s, 2H, CH_2), 3.76 (s, 2H, CH_2), 2.60 (t, *J* = 7.2 Hz, 2H, CH_2), 1.49 (p, *J* = 7.2, 6.4 Hz, 2H, CH_2), 1.41–1.15 (m, 10H, 5 CH_2), 0.87 (t, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) *δ* 158.66 (quat. C), 142.38 (quat. C), 136.15 (quat. C), 131.66 (2 arom. CH), 129.40 (arom. CH), 129.04 (2 arom. CH), 121.78 (quat. C), 120.89 (arom. CH), 114.46 (arom. CH), 113.22 (arom. CH), 69.13 (CH_2), 53.95 (CH_2), 49.48 (CH_2), 31.83 (CH_2), 30.10 (CH_2), 29.53 (CH_2), 29.26 (CH_2), 27.36 (CH_2), 22.65 (CH_2), 14.09 (CH_3). MS (EI) *m/z* = 404 (M^+, 2), 304 (90), 275 (100), 169 (88), 128 (46). HR-MS (EI) calcd. for $C_{22}H_{30}BrNO$ (M^+): 403.1511. Found: 403.1529. According to general procedure 3 the compound could be precipitated as hydrochloride in quantitative yield. ^{1}H NMR (400 MHz, methylene chloride-d_2) *δ* 9.82 (s, 2H, 2 NH), 7.40 (d, *J* = 8.4 Hz, 2H, 2 arom. CH), 7.32 (t, *J* = 2.0 Hz, 1H, arom. CH), 7.24 (d, *J* = 8.4 Hz, 2H, 2 arom. CH), 7.20 (t, *J* = 7.9 Hz, 1H, arom. CH), 7.02 (d, *J* = 7.5 Hz, 1H, arom. CH), 6.86 (dd, *J* = 8.0, 2.3 Hz, 1H, arom. CH), 4.97 (s, 2H, CH_2), 3.90 (s, 2H, CH_2), 2.68–2.58 (m, 2H, CH_2), 1.72 (p, *J* = 7.9, 7.5 Hz, 2H, CH_2), 1.34–1.05 (m, 10H, 5 CH_2), 0.77 (t, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, methylene chloride-d_2) *δ* 158.88 (quat. C), 136.06 (quat. C), 132.12 (quat. C), 131.54 (2 arom. CH), 129.99 (arom. CH), 129.37 (2 arom. CH), 122.84 (arom. CH), 121.70 (quat. C), 116.26 (arom. CH), 116.05 (arom. CH), 69.23 (CH_2), 50.22 (CH_2), 45.89 (CH_2), 31.72 (CH_2), 29.09 (CH_2), 29.01 (CH_2), 26.77 (CH_2), 25.88 (CH_2), 13.83 (CH_3). HR-MS (EI) calcd. for $C_{22}H_{31}BrNO^+$ (M^+): 404.1589. Found: 404.1578.

N-[4-(Benzyloxy)benzyl]octan-1-amine (**8h**): The compound was prepared according to general procedure 2 from 1.06 g (5.0 mmol) 4-benzyloxybenzaldehyde and 905 mg (7.0 mmol) *n*-octylamine to give 1.19 g (73%) of **8h** as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.43 (d, J = 7.2 Hz, 2H, 2 arom. CH), 7.38 (t, J = 7.2 Hz, 2H, 2 arom. CH), 7.36–7.28 (m, 1H, arom. CH), 7.23 (d, J = 8.6 Hz, 2H, 2 arom. CH), 6.93 (d, J = 8.6 Hz, 2H, 2 arom. CH), 5.05 (s, 2H, CH_2), 3.72 (s, 2H, CH_2), 2.60 (t, J = 7.4 Hz, 2H, CH_2), 1.49 (p, J = 7.0 Hz, 2H, CH_2), 1.35–1.20 (m, 10H, 5 CH_2), 0.87 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) δ 157.78 (quat. C), 137.13 (quat. C), 133.13 (quat. C), 129.28 (2 arom. CH), 128.56 (2 arom. CH), 127.91 (arom. CH), 127.46 (2 arom. CH), 114.73 (2 arom. CH), 70.04 (CH_2), 53.54 (CH_2), 49.50 (CH_2), 31.84 (CH_2), 30.14 (CH_2), 29.54 (CH_2), 29.28 (CH_2), 27.40 (CH_2), 22.66 (CH_2), 14.10 (CH_3). MS (EI) m/z = 325 (M^+, 3), 197 (59), 91 (100). HR-MS (EI) calcd. for $C_{22}H_{31}NO$ (M^+): 325.2406. Found: 325.2399.

N-{4-[(2,4-Difluorobenzyl)oxy]benzyl}octan-1-amine (**8i**): The compound was prepared according general procedure 2 from 496 mg (2.0 mmol) 4-(2-4-difluorobenzyloxy)benzaldehyde and 362 mg (2.8 mmol) *n*-octylamine to give 609 mg (84%) of **8i** as a white waxy solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.46 (td, J = 8.4, 6.3 Hz, 1H, arom. CH), 7.26 (d, J = 8.7 Hz, 2H, 2 arom. CH), 6.93 (d, J = 8.7 Hz, 2H, 2 arom. CH), 6.91–6.77 (m, 2H, 2 arom. CH), 5.06 (s, 2H, CH_2), 3.75 (s, 2H, CH_2), 2.62 (t, J = 7.4 Hz, 2H, CH_2), 1.51 (q, J = 7.4 Hz, 2H, CH_2), 1.36–1.17 (m, 10H, 5 CH_2), 0.87 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) δ 163.22 (m, quat. C), 160.45 (m, quat. C), 157.64 (quat. C), 131.74 (quat. C), 130.75 (dd, J = 9.8, 5.6 Hz, arom. CH), 129.76 (2 arom. CH), 120.17 (dd, J = 14.6, 3.9 Hz, quat. C), 114.78 (2 arom. CH), 111.44 (dd, J = 21.2, 3.7 Hz, arom. CH), 103.87 (t, J = 25.4 Hz, arom. CH), 63.27 (d, J = 4.1 Hz, CH_2), 52.68 (CH_2), 48.71 (CH_2), 31.81 (CH_2), 29.44 (CH_2), 29.32 (CH_2), 29.24 (CH_2), 27.28 (CH_2), 22.65 (CH_2), 14.09 (CH_3). MS (EI) m/z = 360 (M^+, 4), 233 (64), 127 (100). HR-MS (EI) calcd. for $C_{22}H_{29}F_2NO$ (M^+): 361.2217. Found: 361.2215.

N-{4-[(4-Methoxybenzyl)oxy]benzyl}octan-1-amine (**8j**): The compound was prepared according to general procedure 2 from 730 mg (3.0 mmol) of **5p** and 554 mg (4.3 mmol) *n*-octylamine to give 660 mg (62%) of **8j** as a white solid. M.P. 60.3°C. ^{1}H NMR (400 MHz, chloroform-*d*) δ ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.35 (d, J = 8.8 Hz, 2H, 2 arom. CH), 7.22 (d, J = 8.8 Hz, 2H, 2 arom. CH), 6.95–6.88 (m, 4H, 4 arom. CH), 4.97 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.71 (s, 2H, CH_2), 2.60 (t, J = 7.0 Hz, 2H, CH_2), 1.56–1.44 (m, 2H, CH_2), 1.34–1.22 (m, 10H, 5 CH_2), 0.87 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) δ 159.44 (quat. C), 157.86 (quat. C), 132.98 (quat. C), 129.29 (2 arom. CH), 129.22 (2 arom. CH), 129.16 (quat. C), 114.75 (2 arom. CH), 114.00 (2 arom. CH), 69.84 (CH_2), 55.32 (OCH_3), 53.54 (CH_2), 49.49 (CH_2), 31.85 (CH_2), 30.13 (CH_2), 29.56 (CH_2), 29.29 (CH_2), 22.68 (CH_2), 14.12 (CH_3). MS (EI) m/z = 355 (M^+, 0.1), 121 (100). HR-MS (EI) calcd. for $C_{23}H_{33}NO_2$ (M^+): 355.2511. Found: 355.2508.

N-{4-[(4-(*tert*-Butyl)benzyl]oxy}benzyl)octan-1-amine (**8k**): The compound was prepared according to general procedure 2 from 537 mg (2.0 mmol) of **5q** and 362 mg (2.8 mmol) *n*-octylamine to give 526 mg (69%) of **8k** as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*) δ ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.44–7.33 (m, 4H, 2 arom. CH), 7.23 (d, J = 8.6 Hz, 2H, 2 arom. CH), 6.94 (d, J = 8.6 Hz, 2H, 2 arom. CH), 5.01 (s, 2H, CH_2), 3.72 (s, 2H, CH_2), 2.61 (t, H, J = 7.2 Hz, CH_2), 1.67–1.43 (m, 2H, CH_2), 1.33 (s, 9H, 3 CH_3), 1.30–1.21 (m, 10H, 5 CH_2), 0.87 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, chloroform-*d*) δ 157.94 (quat. C), 150.99 (quat. C), 134.09 (quat. C), 133.00 (quat. C), 129.29 (2 arom. CH), 127.46 (2 arom. CH), 125.54 (2 arom. CH), 114.70 (2 arom. CH), 69.92 (CH_2), 53.57 (CH_2), 49.52 (CH_2), 34.60 (quat. C), 31.86 (CH_2), 31.37 (3 CH_3), 30.16 (CH_2), 29.57 (CH_2), 29.30 (CH_2), 27.42 (CH_2), 22.69 (CH_2), 14.13 (CH_3). MS (EI) m/z = 380 (M^+, 0.11), 253 (4), 147 (100), 119 (11). HR-MS (EI) calcd. for $C_{26}H_{38}NO$ (M^+): 380.2953. Found: 380.2949.

4.2 | Pharmacological/biological assays

Determination of MICs against *Y. lipolytica* was carried out according to Krauss et al.[12] *Y. lipolytica* was cultivated in AC-agar (Sigma Aldrich). Concentration of yeast cells was determined by photometer and adjusted to a turbitity of 0.5 according to McFarland Standard at 600 nm.

Determination of MICs against *Candida* species was carried out according to the European Committee of Antifungal Susceptibility Testing.[27,33] Concentration of yeast cells was determined by photometer and adjusted to a turbitity of 0.5 according to McFarland Standard. MIC_{90} was determined by microdilution plate reader (Sunrise Tecan) at 450 nm, after 24 h incubation at 37°C. MIC_{90} was defined as the minimal concentration of chemical causing 90% growth inhibition, respectively. All substances were dissolved in DMSO and diluted in RPMI 1640 medium, containing 2% glucose. All assays were carried out twice.

4.2.1 | Cytotoxicity assays

HL-60 cells (human leukemia cells, DSM No. ACC3) were obtained from DSMZ (German Collection of Microorganisms and Cell Cultures) and cultivated in RPMI 1640 medium with 10% fetal bovine serum, both from PAA Laboratories) without the addition of antibiotics at 37°C in a humidified atmosphere containing 5% CO_2. The assay was performed according to Mosmann et al.[30]

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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