A New Class of Diamine-Based Human Histamine H_3 Receptor Antagonists: 4-(Aminoalkoxy)benzylamines

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4-(Aminoalkoxy)benzylamines were prepared and screened for in vitro activity at the human histamine H_3 receptor. Some members of this series exhibited subnanomolar binding affinities. Analogues in which one nitrogen atom was replaced with a methine group showed greatly reduced binding affinities. Six members of this series were found to be antagonists in a cell-based model of human histamine H_3 receptor activation. One member of this series, 1-[4-(3-piperidin-1-ylpropoxy)benzyl]piperidine (**7b**), was found to be a selective and potent human H_3 receptor antagonist.

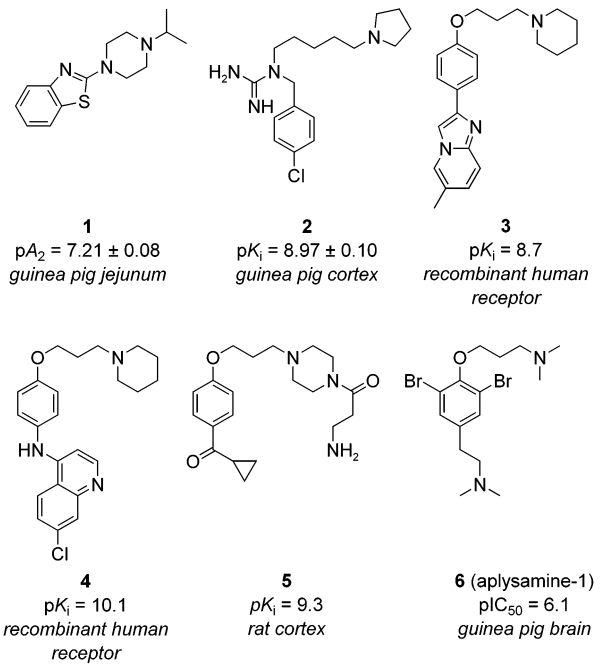
Introduction

Histamine elicits a variety of physiological responses that are mediated by four G-protein coupled receptors (H_1, H_2, H_3, and H_4).[1] In the central nervous system (CNS), the synthesis and release of histamine are regulated by presynaptic H_3 receptors as part of a negative-feedback mechanism.[2] In its capacity as a heteroreceptor, the H_3 receptor also mediates the release of several other neurotransmitters.[3] Antagonists of the H_3 receptor have been proposed as potential treatments for conditions involving sleep, cognition, and memory disorders.[4] Other uses have been suggested for both agonists and antagonists because of the occurrence of H_3 receptors outside of the CNS.[5] Despite the development of numerous drugs that target the H_1 and H_2 receptors, few H_3 receptor ligands have advanced into human clinical development.[6]

Although the existence of H_3 receptors in human tissue was confirmed in 1988,[7] the human receptor has until recently rarely been used in ligand development work. Reports of contrasting ligand binding affinities between rat and human H_3 receptors highlight the potential for significant and unpredictable species-specific receptor behavior.[8] The recent cloning of the human H_3 receptor cDNA has simplified the development of ligands specifically targeting the human receptor.[9,10]

The discovery of non-imidazole H_3 ligands in the past 5 years marked an important breakthrough in the field (Chart 1). Prior ligand designs exploited the well-known affinity of 4(5)-substituted imidazoles for the H_3 receptor,[11] despite the potential pharmacological liabilities associated with such functionality.[6b] Representative examples of newer non-imidazole ligand families include benzthiazole **1**,[12] aminoalkylguanidine **2**,[13] imidazopyridine **3**,[14] quinoline **4**,[15] and piperazine amide **5**.[16] Isolated examples of weakly binding non-imidazole H_3 ligands have also been reported, including clozapine,[17] phencyclidine,[18] and aplysamine-1 (**6**).[19] Strategies for developing new non-imidazole H_3 receptor ligand families include the replacement of the imidazole ring of known H_3 receptor ligands with a saturated nitrogen heterocycle[20] and the incorporation of phenoxyalkylamine functionality.[21]

Chart 1. Representative Non-Imidazole Histamine H_3 Receptor Ligands



Our ligand design began with an attempt to develop a model to account for the activity of the structurally diverse non-imidazole H_3 ligands that had been reported and some of those that we found in our own compound collection. Despite the apparent heterogeneity of these compounds, three structural motifs were remarkably prevalent: (1) a basic nitrogen atom, (2) an aromatic ring, and (3) two basic functional groups flanking a lipophilic core. In this context, the weakly active marine natural product aplysamine-1 (**6**) was particularly intriguing because it unambiguously contained each of the three features we identified.[19] Encouraged by this report, we reasoned that a readily accessed chemical

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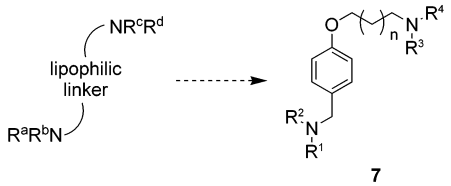
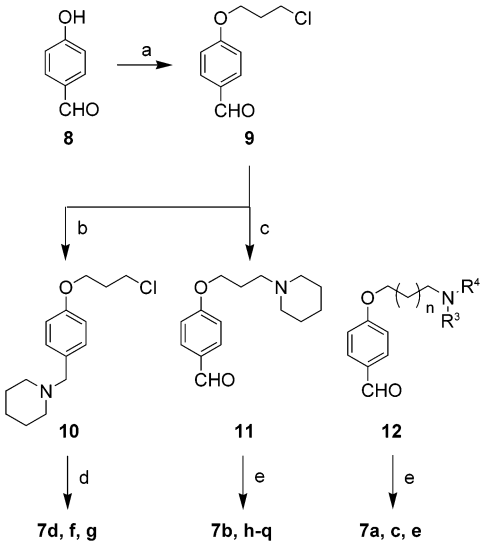


Figure 1. Design of 4-(aminoalkoxy)benzylamines (**7**).

Scheme 1[a]



[a] Reagents and conditions: (a) $Br(CH_2)_3Cl$, K_2CO_3, acetone, reflux; (b) piperidine, $NaBH(OAc)_3$, DCE, room temp; (c) piperidine, Na_2CO_3, KI, 1-butanol, 105 °C; (d) HNR^3R^4, Na_2CO_3, KI, 1-butanol, 105 °C; (e) HNR^1R^2, $NaBH(OAc)_3$, (HOAc), DCE, room temp.

series that incorporated similar structural features could furnish a viable platform for the development of non-imidazole H_3 receptor ligands.[22]

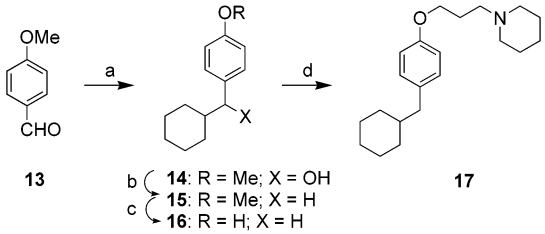
To test this idea, a chemical template containing a lipophilic core flanked by two alkylamine groups was sought (Figure 1). Candidates were limited to those enabled by concise, modular syntheses utilizing only carbon−heteroatom bond connections.[23] This analysis resulted in the selection of 4-(aminoalkoxy)benzylamines (**7**). Herein we report the synthesis and human histamine H_3 receptor binding affinities and functional activities of several members of this series.

Chemistry

The synthesis of 4-(aminoalkyloxy)benzylamines **7a**−**q** utilized three complementary routes (Scheme 1). Two of these routes proceeded through 4-(3-chloropropoxy)-benzaldehyde (**9**). The orthogonal reactivity of this intermediate was exploited to reductively aminate the aldehyde functionality[24] or nucleophilically displace the alkyl halide functionality[25] via intermediate **10** or intermediate **11**. The third route proceeded via reductive amination of commercially available 4-aminoalkoxybenzaldehydes **12**.

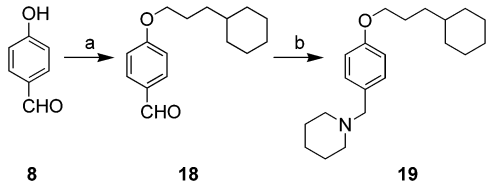
Benzylcyclohexane **17** was prepared as shown in Scheme 2. Treatment of 4-methoxybenzaldehyde (**13**) with cyclohexylmagnesium chloride gave alcohol **14**. Reduction of this alcohol with TFA−Et_3SiH gave benzylcyclohexane **15**. Demethylation with boron tribromide gave phenol **16**, which was etherified under modified Mitsunobu conditions[26] to give **17**.

Scheme 2[a]



[a] Reagents and conditions: (a) *c*-$C_6H_{11}MgCl$, THF, 0 °C to room temp; (b) triethylsilane, TFA, DCE, room temp; (c) BBr_3, DCM, 0 °C to room temp; (d) 3-piperidinyl-1-ol, polymer-supported triphenylphosphine, di-*tert*-butylazodicarboxylate, DCM, room temp.

Scheme 3[a]



[a] Reagents and conditions: (a) *c*-$C_6H_{11}(CH_2)_3OH$, PPh_3, di-*tert*-butylazodicarboxylate, THF, 0 °C to room temp; (b) piperidine, $NaBH(OAc)_3$, DCE, room temp.

Propylcyclohexane **19** was prepared from 4-hydroxybenzaldehyde (**8**) as shown in Scheme 3. Mitsunobu etherification of phenol **8** with 3-cyclohexylpropanol gave aldehyde **18**. Reductive amination of this aldehyde with piperidine gave propylcyclohexane **19**.

Results and Discussion

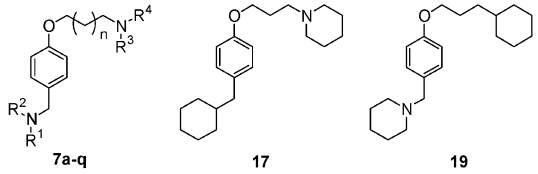
The human H_3 receptor affinities of a series of 4-(aminoalkoxy)benzylamines (**7a**−**q**) and related compounds (**17** and **19**) were determined (Table 1). The structures of these compounds reflect an effort to probe three regions: (1) the alkyl linker ($-CH_2(CH_2)_nCH_2-$), (2) the alkylamine group ($-NR^3R^4$), and (3) the benzylamine group ($-NR^1R^2$). Most compounds exhibited a high level of H_3 receptor affinity, with the largest changes in activity resulting from modification of alkyl linker length and the alkylamine group ($-NR^3R^4$).

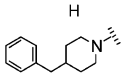
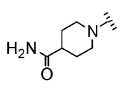
Variation of the alkyl linker length revealed propylene-linked diamines to be more active than their ethylene-linked counterparts. This difference was 15-fold in piperidines **7a** and **7b** and 40-fold in diethylamines **7c** and **7d**. This trend may reflect orientational constraints either between the aryl ring and the ($-NR^3R^4$) group or between the two amino groups.

Compounds bearing cyclic and lipophilic $-NR^3R^4$ groups showed the highest binding affinity. Thus, activity increased nearly 10-fold across the series dimethylamino- (**7e**), diethylamino- (**7d**), and piperidino- (**7b**). Similarly, piperidine **7b** was 5-fold more active than its morpholine analogue **7f** and 30-fold more active than its *N*-methylpiperazine analogue **7g**.

Modification of the benzylamine group ($-NR^1R^2$) in a series of piperidinylpropanes resulted in relatively little change in binding affinity. Increasing the size of this group as in the series dimethylamino- (**7h**), piperidino- (**7b**), 4-benzylpiperidino- (**7l**), and tetrahydroisoquinolino (**7q**) resulted in a 3-fold variation in activity. Incorporation of polar substituents as in morpholine **7i**, *N*-methylpiperazine **7m**, carboxamidopiperidine **7n**, and hydroxypiperidine **7o** led to less than a 3-fold reduction

Table 1. In Vitro Human H_3 Receptor Binding Affinities[a]



compd	n	NR^1R^2	NR^3R^4	$pK_i \pm SEM$[b]
7a	0			8.05 ± 0.11
7b	1			9.24 ± 0.12
7c	0			7.30 ± 0.11
7d	1			8.91 ± 0.13
7e	1			8.41 ± 0.08
7f	1			8.64 ± 0.07
7g	1			7.87 ± 0.15
7h	1			9.03 ± 0.03
7i	1			9.06 ± 0.04
7j	1			9.29 ± 0.12
7k	1			8.08 ± 0.06
7l	1			8.82 ± 0.07
7m	1			8.87 ± 0.06
7n	1			9.02 ± 0.02
7o	1			9.13 ± 0.09
7p	1			9.08 ± 0.06
7q	1			8.77 ± 0.08
17				7.30 ± 0.08
19				6.20 ± 0.10

[a] Displacement of *N*-[^{3}H]-methylhistamine from human H_3 receptors expressed in SK-N-MC cells. [b] Values reported as the mean of three or four determinations.

in activity compared to piperidine **7b**. Cyclohexylamine **7j** and aminoindane **7p** were nearly equipotent with piperidine **7b**, indicating little preference for tertiary over secondary amine functionality. The 16-fold higher activity of cyclohexylamine **7j** relative to aniline **7k** may be due to the comparatively weak basicity of the aniline.

These results raise the question of whether both nitrogen atoms in 4-(aminoalkoxy)benzylamines participate in ligand binding to the human H_3 receptor. To address this issue, the affinity of bispiperidine **7b** was compared with the affinities of analogues **17** and **19**, in which one of the piperidine rings was replaced with a cyclohexyl ring. These modifications led to reductions in activity of 100-fold for benzylcyclohexane **17** and 1300-fold for propylcyclohexane **19**. These findings are consistent with the existence of attractive interactions between both nitrogen atoms of 4-(aminoalkoxy)benzylamines and the human H_3 receptor.

Table 2. In Vitro Human H_3 Receptor Functional Activities of Selected Compounds[a]

compd	$pA_2 \pm SEM$[b]	compd	$pA_2 \pm SEM$[b]
7a	8.05 ± 0.08	**7i**	9.27 ± 0.09
7b	9.84 ± 0.07	**7j**	9.71 ± 0.05
7e	7.98 ± 0.06	**7o**	9.64 ± 0.03

[a] pA_2 values are derived from Schild regression analysis of the compound-induced rightward shifts in dose−response curves of histamine-induced inhibition of forskolin-stimulated cAMP accumulation in SK-N-MC cells overexpressing the human histamine H_3 receptor. [b] Values are reported as the mean of three or four determinations.

Six compounds were selected for evaluation in a cell-based model of human H_3 receptor activation (Table 2). All were found to be antagonists, with good agreement between the observed binding affinities and functional activities.

One of the most active compounds in this series, bispiperidine **7b**, was selected for further in vitro characterization. This compound exhibited selectivity for the H_3 receptor of at least 1000-fold over 50 other receptors and ion channels, as determined in a commercial screening package (Cerep, ExpresSProfile). Significantly, **7b** exhibited greater than 1000-fold selectivity over the histamine H_1, H_2, and H_4 receptors. Activity at the rat histamine H_3 receptor ($pK_i = 9.34 \pm 0.07$, $n = 3$, rat cortex) was comparable to activity at the human receptor. Compound **7b** possessed good Caco-2 permeability (Papp $= 2.34 \times 10^{-6}$ cm/s), high human liver microsomal stability ($t_{1/2} > 24$ h), and moderate human plasma protein binding (54%), indicative of a compound with a promising pharmacokinetic profile.

In addition to their potency at the human H_3 receptor, the diamine-based ligands described in this study are noteworthy for their structural simplicity and ease of synthesis. All were prepared in three synthetic steps or fewer, and the requisite synthetic inputs (primary and secondary amines, hydroxybenzaldehydes, and dihaloalkanes or halogenated alcohols) are commercially available in a variety of functionalized forms. These features make 4-(aminoalkoxy)benzylamines attractive targets for further elaboration of structure−activity relationships and the development of compounds with desirable biological properties.

Elucidation of the binding interactions between these non-imidazole ligands and the H_3 receptor will require further investigation. The results presented here indicate a ligand binding domain in which two amine binding sites play critical roles. It remains to be determined if models of H_3 receptor binding to imidazole-based ligands are relevant to the non-imidazole ligands discussed here.[27]

Conclusions

Analysis of the structural features common to non-imidazole H_3 receptor ligands led to the design and

synthesis of a series of diamine-based ligands **7a**−**q**. These compounds exhibited generally high affinities for the human histamine H_3 receptor. Structure−activity trends are consistent with the existence of attractive interactions between both nitrogen atoms and the H_3 receptor. One member of the series, bispiperidine **7b**, was found to be a selective and potent human H_3 receptor antagonist.

Experimental Section

Human and Rat Histamine H_3 Binding Assays. Binding of compounds to the cloned human H_3 receptor, stably expressed in SK-N-MC cells, was performed as described earlier.[8d] For determination of the binding to the rat receptor, the same procedure was employed except frozen rat cortical hemispheres were used instead of cell pellets.

Human Histamine H_3 Functional Assay. Sublines of SK-N-MC cells were created that expressed a reporter construct and the human H_3 receptor. The reporter gene was β-galactosidase under the control of multiple cyclic AMP responsive elements. In 96-well plates, compounds were added directly to the cell media followed 5 min later by an addition of forskolin (5 μM final concentration). After a 6 h incubation at 37 °C, the media was aspirated and the cells were washed with 200 μL of phosphate-buffered saline followed by a second aspiration. Cells were lysed with 25 μL of 0.1× assay buffer (10 mM Na phosphate, pH 8, 0.2 mM $MgSO_4$, 0.01 mM $MnCl_2$) and incubated at room temperature for 10 min. Cells were then incubated for 10 min with 100 μL of 1× assay buffer containing 0.5% Triton and 40 mM β-mercaptoethanol. Color was developed using 25 mL of 1 mg/mL substrate solution (cholorphenol red β-D-galactopyranoside; Roche Molecular Biochemicals, Indianapolis, IN). Color was quantitated on a microplate reader at absorbance 570 nm. The pA_2 values were calculated by Schild regression analysis of the EC_{50} values.

Additional In Vitro Data. Human liver microsomal stability, human plasma protein binding, and Caco-2 permeability were determined by Absorption Systems, Exton, PA.

General Procedures for the Synthesis of Reported Compounds. Reagents were purchased from commercial suppliers and were used without purification unless otherwise noted. The following aldehydes were obtained from commercial suppliers: 4-(2-piperidin-1-ylethoxy)benzaldehyde (D&O), 4-(3-(dimethylamino)propoxy)benzaldehyde (Aldrich), and 4-(2-diethylaminoethoxy)benzaldehyde (Aldrich). Polymer-supported triphenylphosphine was purchased from Aldrich. Anhydrous tetrahydrofuran was obtained from a GlassContour solvent-dispensing system. Chromatography was performed using prepacked ISCO RediSep silica cartridges. ^{1}H (400 MHz) and ^{13}C (101 MHz) NMR spectra were recorded on a Bruker 400. Chemical shifts are reported in parts per million downfield from an internal Me_4Si standard. Melting points are uncorrected and were obtained on a MelTemp apparatus. Mass spectra were recorded on a Hewlet Packard 1100MSD using electrospray ionization (ESI). Combustion analyses were performed by Desert Analytics.

4-(3-Chloropropoxy)benzaldehyde (9).[28] A suspension of 4-hydroxybenzaldehyde (40.0 g, 328 mmol, 1.0 equiv), 1-bromo-3-chloropropane (63 mL, 658 mmol, 2.0 equiv), and potassium carbonate (136 g, 984 mmol, 3.0 equiv) in acetone (920 mL) was heated to reflux temperature for 16 h. The resulting mixture was filtered, and the residue was evaporated. Kugelrohr distillation of the residue (0.5 mmHg, 220 °C) gave the title compound as pale-yellow oil (46 g, 70%).

1-[4-(3-Chloropropoxy)benzyl]piperidine (10).[29] To a solution of aldehyde **9** (2.50 g, 12.6 mmol, 1.0 equiv) and piperidine (1.4 mL, 14 mmol, 1.1 equiv) in dichloroethane (50 mL) was added sodium triacetoxyborohydride (3.73 g, 17.7 mmol, 1.4 equiv). After 15 h, the resulting mixture was treated with 10% aqueous sodium hydroxide (50 mL). The aqueous phase was extracted with DCM (2 × 50 mL), and the combined organic phases were dried ($MgSO_4$) and evaporated, giving the title compound as a colorless oil that was used without further purification (3.05 g, 90%): ^{1}H NMR ($CDCl_3$) δ 7.22 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.10 (t, J = 5.9 Hz, 2H), 3.74 (t, J = 6.3 Hz, 2H), 3.41 (s, 2H), 2.40−2.30 (br s, 4H), 2.26−2.19 (m, 2H), 1.59−1.52 (m, 4H), 1.46−1.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.6, 130.8, 130.4, 114.0, 64.2, 63.2, 54.3, 41.5, 32.3, 25.9, 24.4.

4-(3-Piperidin-1-ylpropoxy)benzaldehyde (11). A suspension of chloropropane **9** (5.00 g, 25.2 mmol, 1.0 equiv), piperidine (3.8 mL, 38 mmol, 1.5 equiv), sodium carbonate (4.05 g, 38.2 mmol, 1.5 equiv), and potassium iodide (211 mg, 1.27 mmol, 5.0×10^{-2} equiv) in 1-butanol (30 mL) was heated in a 105 °C bath for 20 h. The resulting mixture was treated with water (25 mL) and extracted with DCM (3 × 25 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Chromatography of the residue (0−6% 2 M methanolic ammonia/dichloromethane) gave the title compound as a yellow oil (3.49 g, 56%): ^{1}H NMR ($CDCl_3$) δ 9.88 (s, 1H), 7.82 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.6 Hz, 2H), 4.10 (t, J = 6.5 Hz, 2H), 2.50−2.34 (m, 6H), 2.05−1.96 (m, 2H), 1.63−1.55 (m, 4H), 1.48−1.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 190.8, 164.1, 131.9, 129.8, 114.7, 66.9, 55.7, 54.6, 26.6, 26.0, 24.4.

Cyclohexyl(4-methoxyphenyl)methanol (14).[30] A solution of 4-methoxybenzaldehyde (1.5 mL, 12 mmol, 1.0 equiv) in THF (50 mL) was cooled in an ice bath and treated with a solution of cyclohexylmagnesium chloride (9.2 mL of a 2 M solution in ether, 19 mmol, 1.5 equiv). The bath was removed, and after 3 h water (1.5 mL) was added. The resulting suspension was dried ($MgSO_4$) and filtered. Removal of solvent gave a white solid that was recrystallized from hot hexane, giving the title compound as a white crystalline solid (1.59 g, 59%): mp 76−77 °C (lit.[30] 81−82 °C).

4-Cyclohexylmethylphenol (16).[31] A solution of alcohol **14** (1.50 g, 6.81 mmol, 1.0 equiv) in DCE (30 mL) was treated sequentially with TFA (1.05 mL, 13.6 mmol, 2.0 equiv) and triethylsilane (2.2 mL, 14 mmol, 2.0 equiv). After 16 h, solid sodium carbonate (2.0 g) was slowly added with stirring. After 30 min, the resulting mixture was filtered and the filtrate was evaporated. Chromatography of the residue (0−5% ethyl acetate−hexane) gave an oil that contained a mixture of benzylcyclohexane **15** and hexaethylsiloxane in a 3:1 molar ratio by ^{1}H NMR (1.01 g). This oil was dissolved in DCM (16 mL), cooled in an ice bath, and treated with boron tribromide (6.9 mL of a 1.0 M solution in DCM). The bath was removed after 2 h, and the resulting brown solution was again cooled in an ice bath and treated with water (10 mL) over 5 min. The organic phase was washed with saturated aqueous sodium bicarbonate (20 mL), dried ($MgSO_4$), and evaporated. Chromatography of the residue (0−20% ethyl acetate−hexane) gave the title compound as a white amorphous solid (569 mg, 44% from **14**): mp 70−71 °C; ^{1}H NMR ($CDCl_3$) δ 7.00 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 4.44 (s, 1H), 2.40 (d, J = 7.4 Hz, 2H), 1.71−1.60 (m, 5H), 1.51−1.38 (m, 1H), 1.25−1.10 (m, 3H), 0.98−0.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 153.4, 133.6, 130.2, 114.9, 43.2, 39.9, 33.1, 26.6, 26.3.

4-(3-Cyclohexylpropoxy)benzaldehyde (18). A solution of 4-hydroxybenzaldehyde (244 mg, 2.0 mmol, 1.0 equiv), 3-cyclohexyl-1-propanol (0.33 mL, 2.2 mmol, 1.1 equiv), and triphenylphosphine (577 mg, 2.2 mmol, 1.1 equiv) in THF (8 mL) was cooled in an ice bath and treated with di-*tert*-butylazodicarboxylate (506 mg, 2.2 mmol, 1.1 equiv) in portions over 5 min. The ice bath was removed, and after 2 h the resulting mixture was evaporated. Chromatography of the residue (0−20% ethyl acetate−hexane) gave the title compound as a colorless oil (270 mg, 55%): ^{1}H NMR ($CDCl_3$) δ 9.88 (s, 1H), 7.83 (d, J = 8.9 Hz, 2H), 6.99 (d, J = 8.9 Hz, 2H), 4.02 (t, J = 6.7, 2H), 1.87−1.62 (m, 7H), 1.38−1.09 (m, 6 H), 0.98−0.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 190.8, 164.3, 132.0, 129.7, 114.8, 68.8, 37.4, 33.6, 33.3, 26.6, 26.4, 26.3. Anal. ($C_{16}H_{22}O_2$) C, H.

Method A: Representative Procedure for the Preparation of 1-[2-(4-Piperidin-1-ylmethylphenoxy)ethyl]piperidine (7a). A solution of 4-(2-piperidin-1-ylethoxy)benzaldehyde (233 mg, 1.00 mmol, 1.0 equiv) and piperidine (0.11 mL, 1.1 mmol, 1.1 equiv) in DCE (4 mL) was treated with

sodium triacetoxyborohydride (296 mg, 1.40 mmol, 1.3 equiv). After 16 h, the resulting mixture was treated with 10% aqueous potassium hydroxide (4 mL). The organic phase was extracted with DCM (2 × 3 mL), and the combined organic phases were dried ($MgSO_4$) and evaporated. Chromatography of the residue (0−6% 2 M methanolic ammonia−DCM) gave the title compound as a pale-yellow oil (193 mg, 64%): ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 8.3 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.09 (t, J = 6.1 Hz, 2H), 3.40 (s, 2H), 2.76 (t, J = 6.1 Hz, 2H), 2.55−2.45 (br m, 4H), 2.40−2.29 (m, 4H), 1.64−1.52 (m, 8H), 1.48−1.37 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 157.8, 130.5, 130.3, 114.1, 65.9, 63.2, 57.9, 55.0, 54.3, 25.9, 25.8, 24.4, 24.2; MS m/z 303.2 $(M + H)^+$. Anal. ($C_{19}H_{30}N_2O$) C, H, N.

Method B: Representative Procedure for the Preparation of 4-[3-(4-Piperidin-1-ylmethylphenoxy)propyl]-morpholine (7f). A suspension of chloropropane **10** (268 mg, 1.00 mmol, 1.0 equiv), morpholine (0.11 mL, 1.3 mmol, 1.3 equiv), sodium carbonate (159 mg, 1.50 mmol, 1.5 equiv), and potassium iodide (8.3 mg, 5.0×10^{-1} mmol, 0.050 equiv) in 1-butanol (4 mL) was heated in a 105 °C bath for 16 h. Water was added (4 mL), and the aqueous phase was extracted with DCM (3 × 4 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Chromatography of the residue (0−6% 2 M methanolic ammonia−DCM) gave the title compound as a colorless oil (138 mg, 43%): ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.01 (t, J = 6.3 Hz, 2H), 3.74−3.69 (m, 4H), 3.40 (s, 2H), 2.51 (t, J = 7.3 Hz, 2H), 2.48−2.43 (m, 4H), 2.40−2.30 (br s, 4H), 2.00−1.91 (m, 2H), 1.59−1.51 (m, 4H), 1.45−1.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.9, 130.3, 114.0, 66.9, 66.0, 63.2, 55.5, 54.2, 53.7, 26.4, 25.9, 24.3; MS m/z 319.3 $(M + H)^+$. Anal. ($C_{19}H_{30}N_2O_2$) C, H, N.

Method C: Representative Procedure for the Preparation of 4-[4-(3-Piperidin-1-ylpropoxy)benzyl]morpholine (7i). A solution of aldehyde **11** (207 mg, 0.837 mmol, 1.0 equiv), morpholine (74 μL, 0.85 mmol, 1.0 equiv), and acetic acid (55 μL, 0.87 mmol, 1.0 equiv) in DCE (3 mL) was treated with sodium triacetoxyborohydride (258 mg, 1.22 mmol, 1.4 equiv). After 16 h, the resulting mixture was treated with 10% aqueous potassium hydroxide (5 mL). The organic phase was extracted with DCM (3 × 10 mL), and the combined organic phases were evaporated. Chromatography of the residue (0−8% 2 M methanolic ammonia−DCM) gave the title compound as an oil (172 mg, 64%): ^{1}H NMR ($CDCl_3$) δ 7.21 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.99 (t, J = 6.4 Hz, 2H), 3.69 (t, J = 4.7 Hz, 4H), 3.42 (s, 2H), 2.48 (t, J = 7.1 Hz, 2H), 2.45−2.36 (br m, 8H), 1.97 (m, 2H), 1.63−1.56 (m, 4H), 1.44 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 158.2, 130.3, 129.6, 114.2, 67.0, 66.5, 62.8, 56.0, 54.6, 53.5, 26.8, 25.9, 24.4; MS m/z 319.3 $(M + H)^+$. Anal. ($C_{19}H_{30}N_2O_2$) C, H, N.

1-[4-(3-Piperidin-1-ylpropoxy)benzyl]piperidine (7b). 7b was prepared according to method A (41%): ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 3.99 (t, J = 6.4 Hz, 2H), 3.40 (s, 2H), 2.50−2.30 (m, 10H), 2.01−1.97 (m, 2H), 1.62−1.52 (m, 8H), 1.45−1.38 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 158.0, 130.3, 114.0, 66.4, 63.2, 56.0, 54.6, 54.3, 26.9, 26.0, 25.9, 24.5, 24.4; MS m/z 317.3 $(M + H)^+$. Anal. ($C_{20}H_{32}N_2O$) C, H, N.

Diethyl[2-(4-piperidin-1-ylmethylphenoxy)ethyl]-amine (7c). 7c was prepared according to method A (21%): ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.03 (t, J = 6.5 Hz, 2H), 3.40 (s, 2H), 2.87 (t, J = 6.5 Hz, 2H), 2.63 (q, J = 7.1 Hz, 4H), 2.40−2.29 (br s, 4H), 1.60−1.52 (m, 4H), 1.46−1.37 (m, 2H), 1.07 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 157.9, 130.5, 130.4, 114.1, 66.5, 63.3, 54.3, 51.8, 47.8, 26.0, 24.4, 11.9; MS m/z 291.3 $(M + H)^+$. Anal. ($C_{18}H_{30}N_2O$) C, H, N.

Diethyl[3-(4-piperidin-1-ylmethylphenoxy)propyl]-amine (7d). 7d was prepared according to method B from chloropropane **10** (268 mg, 1.00 mmol, 1.0 equiv), diethylamine (0.41 mL, 4.0 mmol, 4.0 equiv), sodium carbonate (159 mg, 1.50 mmol, 1.5 equiv), and potassium iodide (17 mg, 1.0×10^{-1} mmol, 0.10 equiv) to give the title compound (38%): ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 8.2 Hz, 2H), 6.84 (d, J = 8.2 Hz, 2H), 3.98 (d, J = 6.3 Hz, 2H), 3.40 (s, 2H), 2.63−2.51 (m, 6H), 2.40−2.29 (br s, 4H), 1.96−1.87 (m, 2H), 1.60−1.52 (m, 4H), 1.45−1.37 (m, 2H), 1.03 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 158.0, 130.3, 114.0, 66.3, 63.2, 54.3, 49.4, 46.9, 27.0, 25.9, 24.4, 11.7; MS m/z 305.2 $(M + H)^+$. Anal. ($C_{19}H_{32}N_2O$) C, H, N.

Dimethyl[3-(4-piperidin-1-ylmethylphenoxy)propyl]-amine (7e). 7e was prepared according to method A (43%): ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 8.2 Hz, 2H), 6.84 (d, J = 8.3 Hz, 2H), 3.99 (t, J = 6.5 Hz, 2H), 3.40 (s, 2H), 2.44 (t, J = 7.3 Hz, 2H), 2.40−2.30 (br s, 4H), 2.25 (s, 6H), 1.99−1.90 (m, 2H), 1.60−1.52 (m, 4H), 1.46−1.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 158.0, 130.4, 130.3, 114.0, 66.1, 63.2, 56.4, 54.3, 45.5, 27.6, 25.9, 24.4; MS m/z 277.3 $(M + H)^+$. Anal. ($C_{17}H_{28}N_2O$) C, H, N.

1-Methyl-4-[3-(4-piperidin-1-ylmethylphenoxy)propyl]-piperazine (7g). 7g was prepared according to method B (39%): ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 3.99 (t, J = 6.3 Hz, 2H), 3.40 (s, 2H), 2.60−2.31 (m, 14H), 2.28 (s, 3H), 2.00−1.91 (m, 2H), 1.59−1.52 (m, 4H), 1.45−1.36 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.9, 130.3, 114.0, 66.1, 63.2, 55.1, 55.1, 54.2, 53.1, 46.0, 26.8, 25.9, 24.3; MS m/z 332.3 $(M + H)^+$. Anal. ($C_{20}H_{33}N_3O$) C, H, N.

Dimethyl[4-(3-piperidin-1-ylpropoxy)benzyl]amine (7h). 7h was prepared according to method C using 2.5 equiv of dimethylamine hydrochloride (75%): ^{1}H NMR ($CDCl_3$) δ 7.19 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.99 (t, J = 6.5 Hz, 2H), 3.34 (s, 2H), 2.47 (t, J = 7.5 Hz, 2H), 2.42−2.36 (br, 4H), 2.21 (s, 6H), 1.99−1.94 (m, 2H), 1.61−1.56 (m, 4H), 1.47−1.40 (br, 2H); ^{13}C NMR ($CDCl_3$) δ 158.1, 130.8, 130.1, 114.2, 66.5, 63.7, 56.0, 54.6, 45.2, 26.9, 26.0, 24.4; MS m/z 277.3 $(M + H)^+$. Anal. ($C_{17}H_{28}N_2O$) C, H, N.

Cyclohexyl[4-(3-piperidin-1-ylpropoxy)benzyl]amine (7j). 7j was prepared according to method C (53%): ^{1}H NMR ($CDCl_3$) δ 7.21 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 3.99 (t, J = 6.5 Hz, 2H), 3.73 (s, 2H), 2.50−2.35 (m, 7H), 2.00−1.94 (m, 2H), 1.90 (m, 2H), 1.72 (m, 2H), 1.63−1.56 (m, 5H), 1.47−1.41 (br, 2H) 1.29−1.06 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 157.9, 129.2, 114.4, 66.5, 56.1, 56.0, 54.6, 50.4, 33.5, 26.8, 26.2, 25.9, 25.0, 24.4; MS m/z 331.3 $(M + H)^+$. Anal. ($C_{21}H_{34}N_2O$) C, H, N.

Phenyl[4-(3-piperidin-1-ylpropoxy)benzyl]amine (7k). 7k was prepared according to method C (79%): ^{1}H NMR ($CDCl_3$) δ 7.27 (d, J = 8.8 Hz, 2H), 7.17 (t, J = 7.4 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.71 (t, J = 7.4 Hz, 1H), 6.64 (d, J = 7.7 Hz, 2H), 4.24 (br, 2H), 4.00 (t, J = 6.4 Hz, 2H), 3.93 (br, 1H), 2.48 (t, J = 7.1 Hz, 2H), 2.45−2.36 (br, 4H), 2.01−1.95 (m, 2H), 1.63−1.58 (m, 4H), 1.48−1.42 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 158.3, 148.2, 131.2, 129.2, 128.7, 117.4, 114.6, 112.8, 66.5, 55.9, 54.6, 47.8, 26.8, 25.9, 24.3; MS m/z 325.3 $(M + H)^+$. Anal. ($C_{21}H_{28}N_2O$) C, H, N.

1-[4-(3-Piperidin-1-ylpropoxy)benzyl]-4-benzylpiperidine (7l). 7l was prepared according to method C (86%): ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 2H), 7.18 (m, 3H), 7.12 (m, 2H), 6.83 (d, J = 8.5 Hz, 2H), 3.98 (t, J = 6.6 Hz, 2H), 3.40 (s, 2H), 2.84 (m, 2H), 2.52 (d, J = 6.9 Hz, 2H), 2.47 (t, J = 7.4 Hz, 2H), 2.44−2.35 (br, 4H), 1.99−1.93 (m, 2H), 1.86 (t, J = 11.8 Hz, 2H), 1.62−1.56 (m, 6H), 1.54−1.47 (m, 1H), 1.46−1.41 (m, 2H), 1.34−1.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 158.0, 140.7, 130.3, 130.2, 129.0, 128.0, 125.6, 114.0, 66.4, 62.8, 56.0, 54.6, 53.6, 43.2, 37.9, 32.1, 26.8, 25.9, 24.4; MS m/z 407.3 $(M + H)^+$. Anal. ($C_{27}H_{38}N_2O$) C, H, N.

1-Methyl-4-[4-(3-piperidin-1-ylpropoxy)benzyl]piperazine (7m). 7m was prepared according to method C (86%): ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 3.98 (t, J = 6.3 Hz, 2H), 3.43 (s, 2H), 2.46 (t, J = 7.4 Hz, 2H), 2.45−2.34 (br, 12H), 2.27 (s, 3H), 1.99−1.93 (m, 2H), 1.61−1.56 (m, 4H), 1.47−1.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 158.1, 130.3, 130.0, 114.1, 66.5, 62.4, 56.0, 55.1, 54.6, 52.9, 46.0, 26.8, 25.9, 24.4; MS m/z 332.3 $(M + H)^+$. Anal. ($C_{20}H_{33}N_3O$) C, H, N.

1-[4-(3-Piperidin-1-ylpropoxy)benzyl]piperidine-4-carboxylic Acid Amide (7n). 7n was prepared according to method C (40%): ^{1}H NMR ($CDCl_3$) δ 7.19 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 5.48−5.34 (br, 2H), 3.99 (t, J = 6.3 Hz, 2H), 3.42 (s, 2H), 2.91 (m, 2H), 2.47 (t, J = 7.4 Hz, 2H), 2.43−2.34 (br, 4H), 2.17−2.10 (m, 1H), 2.00−1.93 (m, 4H),

1.88−1.82 (m, 2H), 1.77−1.68 (m, 2H), 1.61−1.56 (m, 4H), 1.46−1.40 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 177.3, 158.1, 130.1, 114.1, 66.5, 62.5, 56.0, 54.6, 52.9, 42.8, 28.9, 26.8, 25.9, 24.4; MS *m*/*z* 360.3 $(M + H)^+$. Anal. ($C_{21}H_{33}N_3O_2$): C, H, N. N: calcd, 11.69; found, 11.20.

1-[4-(3-Piperidin-1-ylpropoxy)benzyl]piperidin-4-ol (7o). 7o was prepared according to method C (50%): ^{1}H NMR ($CDCl_3$) δ 7.19 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.99 (t, J = 6.3 Hz, 2H), 3.68 (m, 1H), 3.43 (s, 2H), 2.76−2.70 (m, 2H), 2.46 (t, J = 7.4 Hz, 2H), 2.43−2.36 (br, 4H), 2.14−2.07 (m, 2H), 1.99−1.94 (m, 2H), 1.90−1.83 (m, 2H), 1.61−1.53 (m, 6H), 1.47−1.40 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 158.2, 130.3, 130.2, 114.1, 68.2, 66.5, 62.3, 56.0, 54.6, 50.8, 34.5, 26.8, 25.9, 24.4; MS *m*/*z* 333.3 $(M + H)^+$. Anal. ($C_{20}H_{32}N_2O_2$) C, H, N.

Indan-1-yl[4-(3-piperidin-1-ylpropoxy)benzyl]amine (7p). 7p was prepared according to method A (44%): ^{1}H NMR ($CDCl_3$) δ 7.39−7.17 (m, 6H), 6.86 (d, J = 8.3 Hz, 2H), 4.28 (dd, J = 6.6, 6.6 Hz, 1H), 4.00 (t, J = 6.3 Hz, 2H), 3.90−3.78 (m, 4H), 3.05−2.96 (m, 1H), 2.86−2.76 (m, 1H), 2.50−2.32 (m, 6H), 2.01−1.82 (m, 3H), 1.62−1.54 (m, 4H), 1.48−1.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 158.0, 145.4, 143.6, 132.6, 129.2, 127.3, 126.1, 124.7, 124.0, 114.4, 66.5, 62.6, 56.0, 54.6, 50.8, 33.6, 30.4, 26.8, 26.0, 24.4; MS *m*/*z* 365.2 $(M + H)^+$. Anal. ($C_{24}H_{32}N_2O$) C, H, N.

2-[4-(3-Piperidin-1-ylpropoxy)benzyl]-1,2,3,4-tetrahydroisoquinoline (7q). 7q was prepared according to method A (49%): ^{1}H NMR ($CDCl_3$) δ 7.27 (d, J = 8.6 Hz, 2H), 7.14−7.06 (m, 3H), 6.99−6.96 (m, 1H), 6.86 (d, J = 8.6 Hz, 2H), 4.00 (t, J = 6.5 Hz, 2H), 3.61 (s, 2H), 3.59 (s, 2H), 2.88 (t, J = 5.9 Hz, 2H), 2.72 (t, J = 5.9 Hz, 2H), 2.50−2.45 (m, 2H), 2.44−2.36 (br, 4H), 2.01−1.94 (m, 2H), 1.62−1.56 (m, 4H), 1.47−1.40 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 158.2, 135.0, 134.4, 130.2, 128.7, 126.6, 126.0, 125.5, 114.2, 66.5, 62.2, 56.0, 54.6, 50.5, 29.1, 26.9, 26.0, 24.4; MS *m*/*z* 365.2 $(M + H)^+$. Anal. ($C_{24}H_{32}N_2O$) C, H, N.

1-[3-(4-Cyclohexylmethylphenoxy)propyl]piperidine (17). A suspension of phenol **16** (190 mg, 1.00 mmol, 1.0 equiv), 3-piperidin-1-ylpropan-1-ol (158 mg, 1.10 mmol, 1.1 equiv), and polymer-supported triphenylphosphine (667 mg, 3.0 mmol/g loading, 2.0 mmol phosphorus, 2.0 equiv) in DCM (5 mL) was treated with di-*tert*-butylazodicarboxylate (345 mg, 1.50 mmol, 1.5 equiv). After 2 h, the resulting brown mixture was filtered through a pad of Celite and washed with DCM. Chromatography of the filtrate (0−4% 2 M methanolic ammonia−DCM) gave the title compound as a pale-yellow oil (110 mg, 35%): ^{1}H NMR ($CDCl_3$) δ 7.02 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 3.98 (t, J = 6.5 Hz, 2H), 2.50−2.35 (m, 8H), 2.01−1.92 (m, 2H), 1.71−1.55 (m, 9H), 1.50−1.39 (m, 3H), 1.25−1.10 (m, 3H), 0.97−0.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 157.0, 133.3, 129.9, 114.0, 66.5, 56.0, 54.6, 43.1, 39.9, 33.1, 26.9, 26.6, 26.3, 26.0, 24.4; MS *m*/*z* 316.2 $(M + H)^+$. Anal. ($C_{21}H_{33}NO$) C, H, N.

1-[4-(3-Cyclohexylpropoxy)benzyl]piperidine (19). 19 was prepared according to method A (21%): ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 3.91 (t, J = 6.6 Hz, 2H), 3.40 (s, 2H), 2.40−2.30 (br s, 4H), 1.82−1.61 (m, 7H), 1.60−1.52 (m, 4H), 1.46−1.37 (m, 2H), 1.36−1.09 (m, 6H), 0.96−0.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 158.1, 130.3, 130.2, 114.0, 68.3, 63.2, 54.3, 37.4, 33.7, 33.3, 26.6, 26.3, 25.9, 24.4; MS *m*/*z* 316.3 $(M + H)^+$. Anal. ($C_{21}H_{33}NO$) C, H, N.

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