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Original article

Design, synthesis and evaluation of galanthamine derivatives as acetylcholinesterase inhibitors

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Abstract

A new series of galanthamine derivatives have been designed, synthesized and evaluated as acetylcholinesterase inhibitors. All of the new compounds prepared showed high AChE inhibitory activities, with compound **3e** that has an *N*-hexyl-benzyl piperidine substituent on the nitrogen atom reaching the best inhibitory activity for AChE ($IC_{50} = 5.62$ nM). The docking study performed with AutoDock demonstrated that **3e** was nicely accommodated by AChE.

Keywords: Galanthamine derivative; Synthesis; Cholinesterase inhibitor

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder of the central nervous system, characterized by loss of cognitive ability and severe behavior abnormalities, which ultimately results in degradation of intellectual and mental activities [1]. Studies of brain tissue indicate that intracellular neurofibrillary tangles and extracellular senile plaques accompany AD [2]. Despite an enormous amount of work, many aspects of both the etiology and physiological pathways of the disease still remain unclear. To date, the majority of current drug therapeutic approaches to AD follow the cholinergic hypothesis [3–5]. These approaches are aimed at elevating the transient levels of acetylcholine in the brain by inhibiting AChE with reversible AChE inhibitors, such as tacrine (Cognex®) [6], donepezil (Aricept®) [7,8], rivastigmine (Exelon®) [9], galanthamine (Reminyl®,**1**) [10] and other drugs currently in clinical trials [11]. Moreover, some recent evidences suggest that AChE plays also a noncholinergic role in the development of AD [12], such as accelerating β-amyloid peptide deposition, and promoting the assembly of Aβ into insoluble fibril [13]. In addition, it has been speculated that the peripheral binding site may be responsible for the aggregation-promoting action of AChE [14]. Thus, it implies that compounds which are able to simultaneously bind to the catalytic and peripheral sites of AChE would display advantages over molecules that act on a single site.

Among all the AChE inhibitors in clinic, galanthamine exhibits unique dual mechanism on cholinergic system, not only inhibiting AChE activity, but also allosterically modulates nicotinic acetylcholine receptor (nAChR), which would promote the release of acetylcholine (Ach). Moreover, it exhibits less toxicity than tacrine, rivastigmine, and donepezil. During the past few years, various galanthamine derivatives have been synthesized and tested for anticholinesterase activities [15–21], structure–activity relationship (SAR) studies reveal that substitution on the nitrogen atom of galanthamine is favorable for AChE inhibitory activity, maybe the substituents display interaction with the peripheral anionic site (PAS) [22,23].

Abbreviations: AD, Alzheimer's disease; AChE, acetylcholinesterase; nAChR, nicotinic acetylcholine receptor; Ach, acetylcholine; PAS, peripheral anionic site; Tc, Torpedo California; BChE, butyrylcholinesterase.

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The aim of our study is to develop a new series of galanthamine derivatives that are capable of interacting with both the active and peripheral sites of AChE. Examples of such bis-interacting ligands have been provided by recent studies from our and other laboratories [24]. It is worth noting that some benzyl amino groups stand out as very potent and promising pharmacophoric moieties for the AChE inhibitory activity in our previous experiments [25]. On the basis of these observations, we are interested to design *N*-substituted galanthamine derivatives by selecting benzyl amino groups and modified benzyl amino moieties (such as amide group) as pharmacophoric units and incorporating them into the galanthamine molecule for better AChE inhibitory activity. Besides, different length of the alkyl chain between galanthamine and benzyl amino moieties was also explored. Therefore, a series of galanthamine derivatives **3a–s** were synthesized and screened for their AChE and BChE inhibitory activities. Molecular docking studies are also performed for two selected molecules to understand the ligand–protein interactions in detail.

2. Chemistry

2.1. Preparation of *4a–m*

Reductive amination of 4-hydroxybenzaldehyde **8** with a secondary amine (piperidine, diethyl amine or morpholine) in the presence of KBH_4 led to **9**, followed by *O*-alkylation with commercially available (1,*n*)-dibromoalkanes to afford **4a–m**, respectively.

2.2. Preparation of *5a, b*

Reaction of morpholine with 1-(1-chloroethyl)-3-methoxybenzene **10** provided **11**, followed by *O*-demethylation with 48% hydrobromide acid to provide **12**. Subsequent *O*-alkylation of **12** with (1,*n*)-dibromoalkanes afforded **5a**, **b**, respectively.

2.3. Preparation of *6a, b*

4-Hydroxybenzoic acid **13** was acylated with Ac_2O to produce 4-acetoxybenzoic acid, which was then refluxed with $SOCl_2$ in CH_2Cl_2 to afford **14**. Sequentially, **14** was treated, in turn, with pyrrolidine, aq. NaOH and neutralized with aq. HCl to afford **15**. Compounds **6a**, **b** were finally obtained by refluxing **15** and (1,*n*)-dibromoalkanes in acetonitrile in the presence of K_2CO_3.

2.4. Preparation of *7a, b*

1-Benzylpiperidin-4-one **16** was prepared as reported in the literature [26]. Reduction of the carbonyl group of **16** with KBH_4 afforded the racemic mixture **17**, and subsequent treatment of **17** with (1,*n*)-dibromoalkanes provided compounds **7a**, **b** in satisfactory yield.

2.5. Preparation of *3a–s*

N-Demethylation of galanthamine hydrobromide **1** afforded norgalanthamine **2** via a non-classical Polonovski reaction [27], without treatment of the salt, in advance, to liberate the free base galanthamine and dryness for the subsequent *N*-oxidation and demethylation steps. Alkylation of norgalanthamine **2** with compounds **4a–m** (or **5a**, **b**, **6a**, **b**, **7a**, **b**) afforded the target compounds **3a–s**, respectively.

3. Biological activity

To determine AChE and BChE inhibitory activities, compounds **3a–s** were measured in vitro according to the modified Ellman method [28,29] using rat cortex homogenate (AChE) and rat serum (BChE). Galanthamine was measured as a standard for the comparative purpose. The results are summarized in Table 1.

4. Results and discussion

4.1. AChE and BChE inhibitory activities

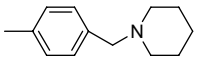
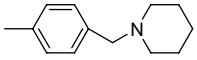
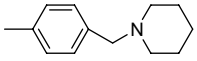
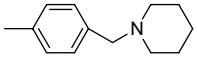
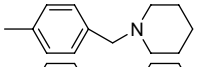
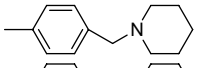
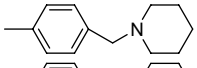
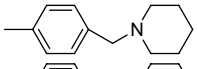
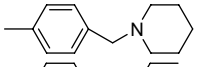
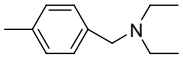
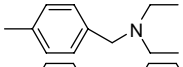
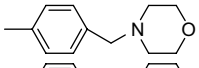
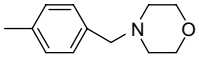
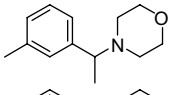
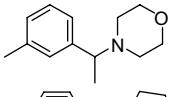
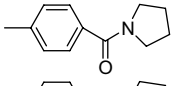
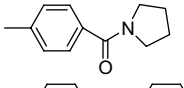
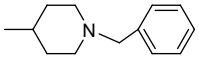
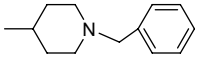
As shown in Table 1, most of the compounds showed high activities and selectivity for AChE inhibition. The potency of AChE inhibition was mainly influenced by the function at the end of the linker, as well as the length of the alkyl chain. For the same length of alkyl chain, in some cases, variation of the function at the end of the linker led to a great change in AChE inhibitory potency (i.e., **3e**, **q**). The benzyl piperidine moiety was found to be the most potent group for the PAS domain. It binds better to the peripheral site of AChE than the other moieties as illustrated in the modeling section (Figs. 1 and 2).

Changing the length of the alkyl chain could affect the ability of the molecule to interact with the peripheral and active sites simultaneously and thereby influence the AChE inhibitory potency. A length of six methylene units was optimal in the benzyl piperidine series (i.e., **3c**, **e**). And, in the diethyl benzylamine series (i.e., **3j**, **k**) and the benzylpiperidin-4-ol series (i.e., **3r**, **s**), compounds having six methylenes were also more potent than those having four methylenes. However, the same trend was not found in the morpholine-containing series (i.e., **3l–o**) or amide-containing (i.e., **3p**, **q**) series.

Replacement of the terminal piperidine group in the benzyl piperidine series (i.e., **3c**, **e**) with a dialkyl amine group led to a slight drop in AChE inhibition for the same length of alkyl linker (i.e., **3j**, **k**). The moiety of diethyl amine is a ring open analog of piperidine, which was designed to probe the available space around the nitrogen atom. The enhanced potency of **3c** (or **3e**) relative to **3j** (or **3k**) may be due to a decrease in conformational flexibility associated with the closing of the six-member ring, suggesting that the space around the nitrogen atom is limited.

Replacement of the terminal piperidine group in the benzyl piperidine series (i.e., **3c**, **e**) with a morpholine group (i.e., **3l**, **m**) resulted in drop in AChE inhibitory potency. Besides,

Table 1
IC_{50} values and selectivity of tested compounds for AChE and BChE inhibition

Compound	R	n[a]	AChE[b] inhibition (nM)	BChE[b] inhibition (10^3 nM)	Selectivity BChE/ AChE
3a		2	24.5	21.0	857
3b		3	18.0	24.0	1333
3c		4	12.4	28.0	2258
3d		5	6.52	29.0	4448
3e		6	5.62	33.0	5872
3f		8	34.7	53.0	1527
3g		9	88.1	64.0	726
3h		10	61.2	93.0	1520
3i		12	58.1	1.20	20.7
3j		4	14.6	34.0	2329
3k		6	8.86	41.0	4628
3l		4	99.1	3.30	33.3
3m		6	113	3.90	34.5
3n		4	94.1	7.10	75.5
3o		6	154	5.80	37.3
3p		4	53.8	5.60	104
3q		6	122	9.40	77.0
3r		4	306	4.30	14.1
3s		6	222	5.50	24.8
Galanthamine			1165	5.90	5.06

[a] n represents the number of methylenes in **3**.
[b] IC_{50} values are means of three different experiments.

shifting the morpholine group from the *para*- to *meta*-position and introduction of a methyl group (i.e., **3n**, **o**), aimed at emulating the binding mode of *para*-position substituted benzyl amino group in rivastigmine, didn't contribute to the AChE inhibitory activity. The significant loss in potency (8–20-fold and 8–27-fold, respectively) observed in the *para*- and *meta*-position substituted morpholine series (i.e., **3l**, **m**, and **3n**, **o**) as compared to the benzyl piperidine series (i.e., **3c**, **e**) suggested that there was a hydrophobic region for this domain. It was unfavorable to introduce a hydrophilic atom at the terminal position.

Introduction of an amide group led to a significant loss in inhibitory potency for AChE (i.e., **3p**, **q**) compared to the benzyl piperidine series. The 4–22-fold loss in potency (i.e., **3p**, **q**) as compared to the corresponding data of the benzyl piperidine series (i.e., **3c**, **e**) suggested that the presence of a free amine group at the terminal position is important for potency. Since they might form hydrogen bonds with the aromatic residues lining the gorge, while the nitrogen of the amide group has no such possibility.

Overturn of the terminal benzyl and piperidine groups (i.e., **3r**, **s**) showed significant loss in AChE inhibitory potency (25–40-fold) as compared to the corresponding data in the benzyl piperidine series (i.e., **3c**, **e**).

4.2. Docking studies

As the synthesized compounds were supposed to be bifunctional ligands, in order to investigate their interactions with AChE in detail, especially the peripheral residues of AChE,

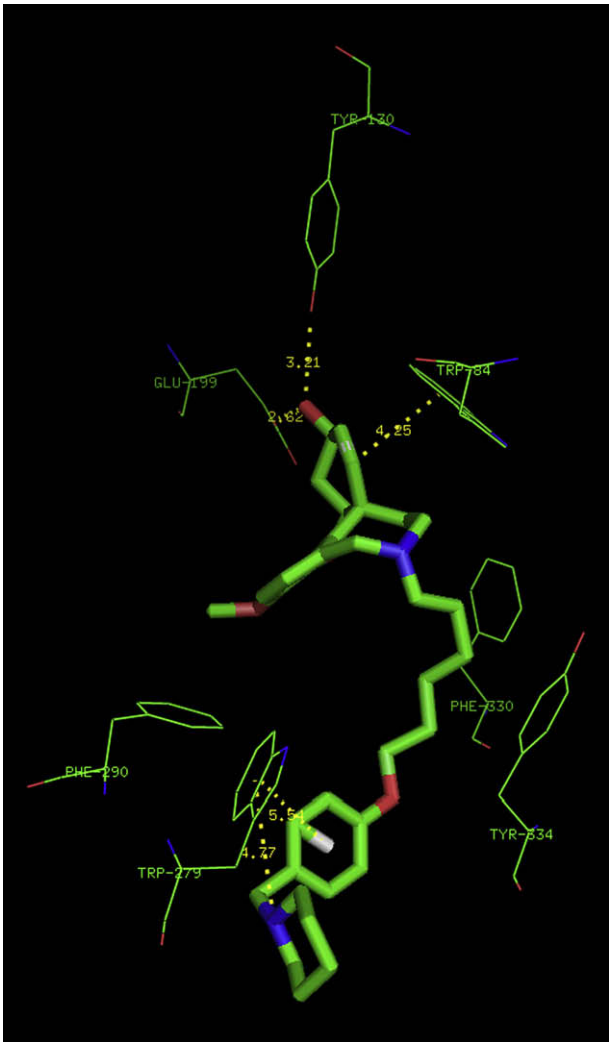


Fig. 1. Docking model of **3e** within the AChE gorge.

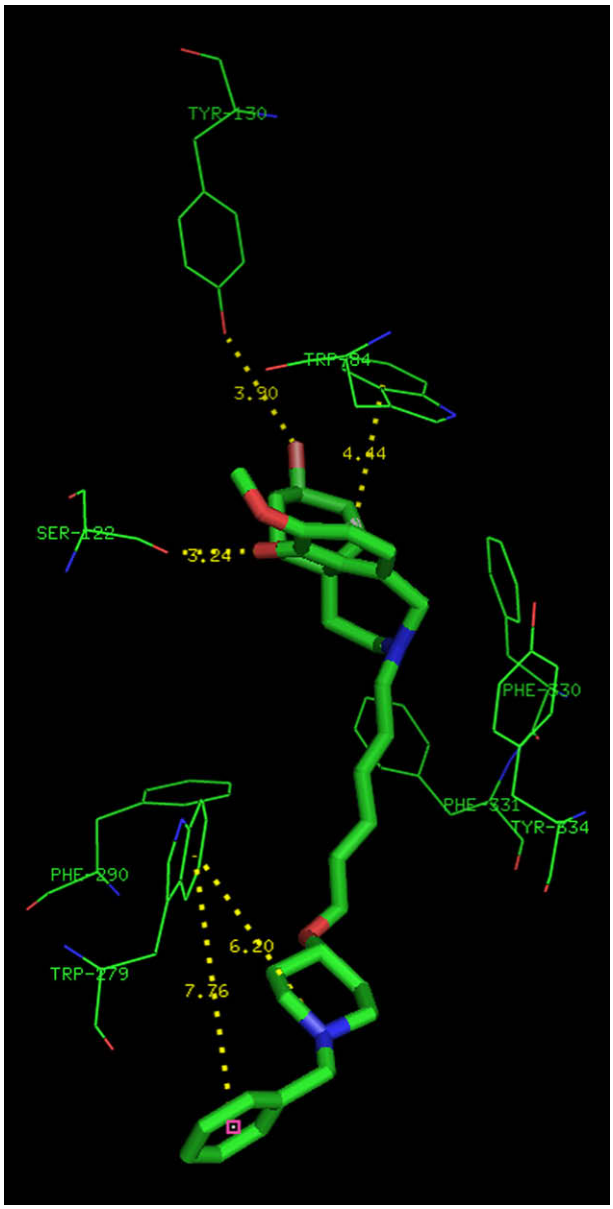


Fig. 2. Docking model of **3s** within the AChE gorge.

AutoDock 3.0.3 was used for the molecular modeling study [30–32]. The high AChE inhibitory activity of compound **3e** and the low AChE inhibitory activity of compound **3s** were chosen to understand the ligand–protein interactions in detail. Therefore, the crystal structure of a *Tc*AChE complex (PDB identification code 1W4L) [23] was used as a template to construct the complex models and the studied compounds were placed automatically in the active site cleft of the enzyme models by docking procedure of AutoDock (Figs. 1 and 2). For each compound, the conformation with the lowest binding energy in *Tc*AChE binding site was chosen for further analysis and comparison.

As seen in Fig. 1, compound **3e** interacted principally along the enzyme active site gorge. Near the bottom of the gorge, the hydroxyl oxygen of **3e** participated in hydrogen bonding with both the oxygen of Tyr130 and the oxygen of Glu199, with the distance of 3.21 and 2.62 Å, respectively. The double bond in the cyclohexene ring stacked against the π-system of Trp84, through a favorable π–π interaction, the distance was 4.25 Å from the midpoint of the double bond to the centroid of the indole ring. In the middle of the gorge, the attached alkyl chain snaked up the gorge, and the methylenes displayed hydrophobic interactions with three major residues: Phe290, Phe330 and Tyr334. At the top of the gorge, the phenyl ring of the phenoxy group stacked against the indole ring of Trp279 through π–π interaction, with the ring to ring distance of 5.54 Å. Furthermore, the charged nitrogen of piperidine formed a cation–π interaction, and the distance was 4.77 Å.

As for **3s** (Fig. 2), the docked lowest energy structure showed an unexpected orientation within the active site gorge compared to those of **3e** and galanthamine, which suggested that long chain modification could change the binding of galanthamine moiety. Near the bottom of the gorge, the hydroxyl oxygen made a strong hydrogen bond with the oxygen atom of Tyr130, with the distance of 3.90 Å. The double bond in the cyclohexene ring stacked against the π-system of the indole group of Trp84, with the distance of 4.44 Å from the midpoint of the double bond to the centroid of the indole group. Furthermore, the oxygen atom in the dihydrofuran ring made a strong hydrogen bond with the oxygen atom of Ser122, with the distance of 3.24 Å. In the middle of the gorge, the attached alkyl chain displayed hydrophobic interactions with four major residues: Phe290, Phe330, Phe331 and Tyr334, different from that of **3e**. At the top of the gorge, the protonated piperidine nitrogen didn't interact with Trp279, the distance from the piperidine nitrogen to the centroid of the indole moiety of Trp279 was 6.20 Å. Furthermore, no interaction occurred between the terminal phenyl ring and the indole group of Trp279, with the ring to ring distance of 7.76 Å.

It is obvious that compounds **3e** and **3s** bound in the active site gorge in quite different modes. The decreased affinity of **3s** may be due to this different binding mode, which showed fewer interactions of **3s** at the peripheral site of AChE.

5. Conclusion

In summary, a series of bivalent galanthamine derivatives were designed, synthesized and evaluated as AChE inhibitors. Structure–activity studies showed that the potency of AChE inhibition was mainly influenced by the function at the end of the chain, as well as the length of the connecting units. Especially, the incorporation of a phenyl ring between the alkyl chain and the terminal nitrogen-containing moieties provided additional sites of interactions between the inhibitor and the enzyme, which constitutes a key element for enhanced affinity. The results suggested that the benzyl piperidine moiety might be a potent segment for fishing the peripheral site, which could be used in the development of novel bivalent ligands, with the structure motifs of other classical AChE inhibitor as scaffold for connecting the active site of AChE. The modeling study of the most potent compound **3e** indicated that it was nicely accommodated by AChE. The results provided a foundation

for future design and development of bivalent AChE inhibitors using structure-based or 3D-QSAR methods.

6. Experimental

6.1. Chemistry

Melting points were obtained on a B-540 Büchi melting point apparatus. IR spectra were recorded on a Bruker VECTOR 22 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker AM-400 MHz spectrometer. Chemical shifts are expressed in parts per million (ppm), relative to tetramethylsilane (TMS) as an internal standard. Coupling constants (J values) are in Hertz. Multiplicities are designated as singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet (m), or broad (br). Mass spectra (MS), ESI (positive) were recorded on an Esquire-LC-00075 spectrometer.

6.1.1. General procedure for **9**

To a solution of 4-hydroxybenzaldehyde **8** (2.44 g, 0.02 mol) in methanol (5 mL), was added dropwise at about 25 °C a solution of the amine (piperidine, diethyl amine or morpholine) (2 equiv) in methanol (5 mL). To the mixture thus obtained was added portionwise potassium borohydride (0.54 g, 0.01 mol) under stirring within about 90 min. Then the mixture was stirred at room temperature for 90 min, thereafter cooled in an ice bath, and acidified with 2 mol/L hydrochloric acid up to pH 2. After removing the solvent under vacuum, the residue was taken up with ice and acidified with 2 mol/L hydrochloric acid (30 mL). After the acid solution was washed twice with 30 mL of ethyl acetate, concd. ammonium hydroxide was added up to pH 10 approximately. The mixture was extracted three times with 30 mL of ethyl acetate, and thereafter the organic phase was combined, washed with brine and dried over anhydrous Na_2SO_4. Concentration of the solvent afforded the crude product, which was recrystallized using the solvent mixture of EtOH–H_2O to afford the pure product of **9**.

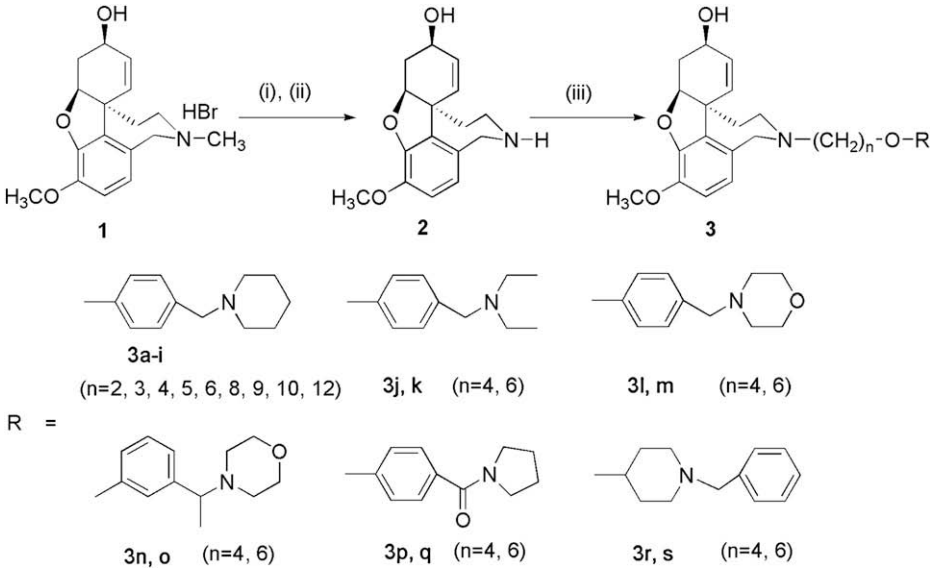
*6.1.1.1. 4-(Piperidin-1-ylmethyl)phenol (**9a**).* Yield: 89.50%, m.p. 133–135 °C (EtOH–H_2O). IR (KBr) ν (cm^{-1}): 3042, 2937, 2815, 1614, 1594, 1514, 1251, 825. ^{1}H NMR (δ, $CDCl_3$): 7.05 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 6.53 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 3.39 (2H, s, CH_2Ph), 2.51–2.44 (4H, m, H_{pip}-2,6), 1.64–1.58 (4H, m, H_{pip}-3,5), 1.45–1.44 (2H, m, H_{pip}-4). ESI-MS m/z: 192.2 $[M + H]^+$.

*6.1.1.2. 4-((Diethylamino)methyl)phenol (**9b**).* Yield: 74.1%, m.p. 93–94 °C (EtOH–H_2O). IR ($CHCl_3$) ν (cm^{-1}): 3042, 2973, 2826, 1612, 1590, 1517, 1231, 840. ^{1}H NMR (δ, $CDCl_3$): 7.10 (2H, d, $J = 7.6$ Hz, H_{phenyl}-3,5), 6.61 (2H, d, $J = 7.6$ Hz, H_{phenyl}-2,6), 3.52 (2H, s, CH_2Ph), 2.59 (4H, q, $J = 7.2$ Hz, NCH_2CH_3), 1.07 (6H, t, $J = 7.2$ Hz, NCH_2CH_3). ESI-MS m/z: 180.2 $[M + H]^+$.

*6.1.1.3. 4-(Morpholinomethyl)phenol (**9c**).* Yield: 85.2%, m.p. 118–120 °C (EtOH–H_2O). IR (KBr) ν (cm^{-1}): 3039, 2960, 2862, 1614, 1594, 1516, 1253, 1113, 835. ^{1}H NMR (δ, $CDCl_3$): 7.13 (2H, d, $J = 8.4$ Hz, H_{phenyl}-3,5), 6.67 (2H, d, $J = 8.4$ Hz, H_{phenyl}-2,6), 3.73 (4H, t, $J = 4.4$ Hz, H_{mor}-2,6), 3.45 (2H, s, CH_2Ph), 2.50–2.47 (4H, m, H_{mor}-3,5). ESI-MS m/z: 194.2 $[M + H]^+$.

6.1.2. 3-(1-Morpholinoethyl)phenol (**12**)

The general synthetic method of **12** has been reported before by our group [18], as shown in Scheme 1. 3-(1-Morpholinoethyl)phenol (**12**) has the following properties: m.p. 119–121 °C, IR (KBr) ν (cm^{-1}): 3024, 2974, 2858, 1612, 1580, 1479, 1113, 1046. ^{1}H NMR (δ, $CDCl_3$): 7.16 (1H, t, $J = 7.6$ Hz, H_{phenyl}-5), 6.84 (1H, d, $J = 7.6$ Hz, H_{phenyl}-6), 6.81 (1H, s, H_{phenyl}-2), 6.70 (1H, dd, $J = 7.6$, 2.0 Hz, H_{phenyl}-4), 3.70 (4H, t, $J = 4.6$ Hz, H_{mor}-2,6), 3.25 (1H, q,



Scheme 1. Synthesis of **3**: (i) $NaHCO_3$, *m*-CPBA, CH_2Cl_2, 0 °C, 30 min; (ii) $FeSO_4 \cdot 7H_2O$, methanol, −10 to 0 °C, 3 h; (iii) **4** (or **5**, **6**, **7**), K_2CO_3, acetonitrile, 60 °C, 24 h.

$J = 6.6$ Hz, $CHCH_3$), 2.50–2.53 (2H, m, H_{mor}-3α, H_{mor}-5α), 2.36–2.42 (2H, m, H_{mor}-3β, H_{mor}-5β), 1.34 (3H, d, $J = 6.6$ Hz, $CHCH_3$). ESI-MS *m/z*: 208.3 $[M + H]^+$.

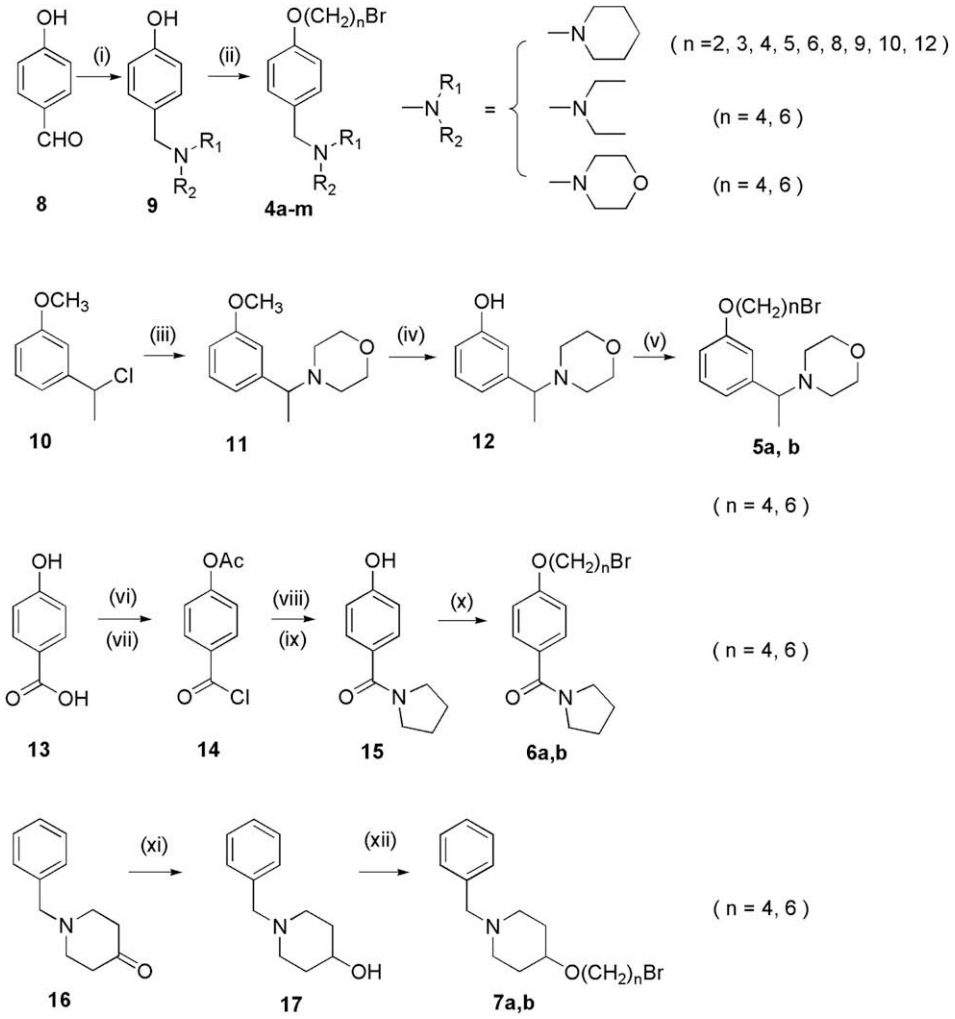
*6.1.3. General procedure for **4a–m**, **5a**, **b***

To a solution of **9** (or **12**) (1 mmol) in 5 mL of dichloromethane, were added 1 mol/L NaOH solution (2 mL), cetyltrimethylammonium bromide (36.46 mg, 0.10 mmol), and (1,*n*)-dibromide (5 equiv). After stirring at 40 °C for 6 h, the mixture was poured into water (10 mL), and extracted with ethyl acetate (3 × 10 mL), washed with brine and dried over anhydrous Na_2SO_4. After removing the solvent under vacuum, the residue was purified by silica gel chromatography using ethyl acetate:petroleum ether (1:4) as eluant to afford **4a–m** (or **5a**, **b**), respectively (Scheme 2).

*6.1.3.1. 1-(4-(2-Bromoethoxy)benzyl)piperidine (**4a**).* Yield: 90.9%, colorless oil. ^{1}H NMR (δ, $CDCl_3$): 7.23 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 6.85 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 4.28 (2H, t, $J = 6.4$ Hz, OCH_2), 3.63 (2H, t, $J = 6.4$ Hz, CH_2Br), 3.41 (2H, s, CH_2Ph), 2.38–2.31 (4H, m, H_{pip}-2,6), 1.59–1.53 (4H, m, H_{pip}-3,5), 1.45–1.42 (2H, m, H_{pip}-4). ESI-MS *m/z*: 298.2 $[M + H]^+$.

*6.1.3.2. 1-(4-(3-Bromopropoxy)benzyl)piperidine (**4b**).* Yield: 87.8%, colorless oil. ^{1}H NMR (δ, $CDCl_3$): 7.22 (2H, d, $J =$ 8.8 Hz, H_{phenyl}-2,6), 6.84 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 4.08 (2H, t, $J = 6.0$ Hz, OCH_2), 3.60 (2H, t, $J = 6.0$ Hz, CH_2Br), 3.41 (2H, s, CH_2Ph), 2.39–2.27 (6H, m, H_{pip}-2,6, H2′), 1.59–1.53 (4H, m, H_{pip}-3,5), 1.43–1.41 (2H, m, H_{pip}-4). ESI-MS *m/z*: 312.2 $[M + H]^+$.

*6.1.3.3. 1-(4-(4-Bromobutoxy)benzyl)piperidine (**4c**).* Yield: 87.8%, colorless oil. ^{1}H NMR (δ, $CDCl_3$): 7.22 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 6.84 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 3.98 (2H, t, $J = 6.0$ Hz, OCH_2), 3.49 (2H, t, $J = 6.0$ Hz, CH_2Br), 3.41 (2H, s, CH_2Ph), 2.38–2.32 (4H, m, H_{pip}-2,6), 2.10–2.02 (2H, m, H3′), 1.97–1.90 (2H, m, H2′), 1.59–1.53 (4H, m,



Scheme 2. Synthesis of **4–7**: (i) piperidine (or morpholine, diethyl amine) (2 equiv), KBH_4 (0.5 equiv), methanol, rt, 3 h; (ii) $Br(CH_2)_nBr$ (5 equiv), NaOH, cetyltrimethylammonium bromide (0.1 equiv), CH_2Cl_2–H_2O, reflux, 6 h; (iii) morpholine (1.5 equiv), Et_3N, rt, 3 h; (iv) 48% HBr, reflux, 4 h; (v) $Br(CH_2)_nBr$ (5 equiv), NaOH, cetyltrimethylammonium bromide (0.1 equiv), CH_2Cl_2–H_2O, reflux, 6 h; (vi) Ac_2O (2 equiv), reflux, 6 h; (vii) $SOCl_2$, CH_2Cl_2, 40 °C, 10 h; (viii) pyrrolidine (2.1 equiv), H_2O, 2 h; then aq. NaOH (2 mol/L), 2 h; (ix) aq. HCl (1 mol/L), rt, 2 h; (x) $Br(CH_2)_nBr$ (5 equiv), K_2CO_3 (1.5 equiv), acetonitrile, reflux, 5 h; (xi) KBH_4 (1 equiv), ethanol, rt, 3 h; (xii) $Br(CH_2)_nBr$ (5 equiv), NaH (1.1 equiv), DMF, 50 °C, 5 h.

H_{pip}-3,5), 1.44–1.41 (2H, m, H_{pip}-4). ESI-MS *m/z*: 326.3 $[M+H]^+$.

*6.1.3.4. 1-(4-(5-Bromopentyloxy)benzyl)piperidine (**4d**).* Yield: 86.7%, colorless oil. ^1H NMR (δ, $CDCl_3$): 7.24 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 6.83 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 3.95 (2H, t, $J = 6.4$ Hz, OCH_2), 3.47 (2H, t, $J = 6.4$ Hz, CH_2Br), 3.43 (2H, s, CH_2Ph), 2.45–2.38 (4H, m, H_{pip}-2,6), 1.93–1.90 (2H, m, H2′), 1.82–1.77 (2H, m, H4′), 1.64–1.57 (6H, m, H3′, H_{pip}-3,5), 1.47–1.40 (2H, m, H_{pip}-4). ESI-MS *m/z*: 340.2 $[M+H]^+$.

*6.1.3.5. 1-(4-(6-Bromohexyloxy)benzyl)piperidine (**4e**).* Yield: 88.2%, colorless oil. ^1H NMR (δ, $CDCl_3$): 7.20 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 6.83 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 3.94 (2H, t, $J = 6.8$ Hz, OCH_2), 3.42 (2H, t, $J = 7.2$ Hz, CH_2Br), 3.41 (2H, s, CH_2Ph), 2.38–2.32 (4H, m, H_{pip}-2,6), 1.91–1.87 (2H, m, H2′), 1.80–1.76 (2H, m, H5′), 1.59–1.53 (4H, m, H_{pip}-3,5), 1.52–1.48 (4H, m, H3′, H4′), 1.44–1.41 (2H, m, H_{pip}-4). ESI-MS *m/z*: 354.3 $[M+H]^+$.

*6.1.3.6. 1-(4-(8-Bromooctyloxy)benzyl)piperidine (**4f**).* Yield: 90.3%, colorless oil. ^1H NMR (δ, $CDCl_3$): 7.20 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 6.83 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 3.93 (2H, t, $J = 6.8$ Hz, OCH_2), 3.41 (2H, s, CH_2Ph), 3.40 (2H, t, $J = 7.2$ Hz, CH_2Br), 2.38–2.32 (4H, m, H_{pip}-2,6), 1.90–1.88 (2H, m, H2′), 1.79–1.75 (2H, m, H7′), 1.59–1.53 (4H, m, H_{pip}-3,5), 1.50–1.46 (6H, m, H3′, H6′, H_{pip}-4), 1.40–1.32 (4H, m, H4′, H5′). ESI-MS *m/z*: 382.3 $[M+H]^+$.

*6.1.3.7. 1-(4-(9-Bromononyloxy)benzyl)piperidine (**4g**).* Yield: 87.8%, colorless oil. ^1H NMR (δ, $CDCl_3$): 7.20 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 6.83 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 3.93 (2H, t, $J = 6.8$ Hz, OCH_2), 3.41 (2H, s, CH_2Ph), 3.40 (2H, t, $J = 7.2$ Hz, CH_2Br), 2.38–2.32 (4H, m, H_{pip}-2,6), 1.90–1.86 (2H, m, H2′), 1.79–1.74 (2H, m, H8′), 1.59–1.53 (4H, m, H_{pip}-3,5), 1.48–1.44 (6H, m, H3′, H7′, H_{pip}-4), 1.38–1.32 (6H, m, H4′, H6′, H5′). ESI-MS *m/z*: 396.4 $[M+H]^+$.

*6.1.3.8. 1-(4-(10-Bromodecyloxy)benzyl)piperidine (**4h**).* Yield: 85.8%, colorless oil. ^1H NMR (δ, $CDCl_3$): 7.20 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 6.83 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 3.93 (2H, t, $J = 6.4$ Hz, OCH_2), 3.41 (2H, s, CH_2Ph), 3.40 (2H, t, $J = 7.2$ Hz, CH_2Br), 2.38–2.33 (4H, m, H_{pip}-2,6), 1.89–1.81 (2H, m, H2′), 1.78–1.74 (2H, m, H9′), 1.59–1.53 (4H, m, H_{pip}-3,5), 1.46–1.39 (6H, m, H3′, H8′, H_{pip}-4), 1.36–1.30 (8H, m, H4′, H7′, H5′, H6′). ESI-MS *m/z*: 410.3 $[M+H]^+$.

*6.1.3.9. 1-(4-(12-Bromododecyloxy)benzyl)piperidine (**4i**).* Yield: 82.1%, colorless oil. ^1H NMR (δ, $CDCl_3$): 7.19 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 6.81 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 3.91 (2H, t, $J = 6.8$ Hz, OCH_2), 3.40 (2H, s, CH_2Ph), 3.37 (2H, t, $J = 7.2$ Hz, CH_2Br), 2.36–2.32 (4H, m, H_{pip}-2,6), 1.87–1.79 (2H, m, H2′), 1.78–1.72 (2H, m, H11′), 1.57–1.52 (4H, m, H_{pip}-3,5), 1.46–1.38 (6H, m, H3′, H10′, H_{pip}-4), 1.34–1.27 (12H, m, H4′, H9′, H5′, H8′, H6′, H7′). ESI-MS *m/z*: 438.4 $[M+H]^+$.

*6.1.3.10. N-(4-(4-Bromobutoxy)benzyl)-N-ethylethanamine (**4j**).* Yield: 76.8%, colorless oil. ^1H NMR (δ, $CDCl_3$): 7.23 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 6.83 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 3.98 (2H, t, $J = 6.0$ Hz, OCH_2), 3.52 (2H, s, CH_2Ph), 3.49 (2H, t, $J = 6.4$ Hz, CH_2Br), 2.52 (4H, q, $J = 7.2$ Hz, NCH_2CH_3), 2.09–2.04 (2H, m, H3′), 1.96–1.91 (2H, m, H2′), 1.04 (6H, t, $J = 7.2$ Hz, NCH_2CH_3). ESI-MS *m/z*: 314.3 $[M+H]^+$.

*6.1.3.11. N-(4-(6-Bromohexyloxy)benzyl)-N-ethylethanamine (**4k**).* Yield: 87.6%, colorless oil. ^1H NMR (δ, $CDCl_3$): 7.23 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 6.83 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 3.94 (2H, t, $J = 6.0$ Hz, OCH_2), 3.52 (2H, s, CH_2Ph), 3.42 (2H, t, $J = 6.4$ Hz, CH_2Br), 2.52 (4H, q, $J = 7.2$ Hz, NCH_2CH_3), 1.91–1.88 (2H, m, H2′), 1.80–1.76 (2H, m, H5′), 1.52–1.48 (4H, m, H3′, H4′), 1.04 (6H, t, $J = 7.2$ Hz, NCH_2CH_3). ESI-MS *m/z*: 342.3 $[M+H]^+$.

*6.1.3.12. 4-(4-(4-Bromobutoxy)benzyl)morpholine (**4l**).* Yield: 78.6%, colorless oil. ^1H NMR (δ, $CDCl_3$): 7.21 (2H, d, $J = 8.4$ Hz, H_{phenyl}-2,6), 6.83 (2H, d, $J = 8.4$ Hz, H_{phenyl}-3,5), 3.96 (2H, d, $J = 6.2$ Hz, OCH_2), 3.68 (4H, t, $J = 4.4$ Hz, H_{mor}-2,6), 3.47 (2H, t, $J = 6.6$ Hz, CH_2Br), 3.42 (2H, s, CH_2Ph), 2.41 (4H, br t, $J = 4.4$ Hz, H_{mor}-3,5), 2.08–2.01 (2H, m, H3′), 1.95–1.88 (2H, m, H2′). ESI-MS *m/z*: 328.2 $[M+H]^+$.

*6.1.3.13. 4-(4-(6-Bromohexyloxy)benzyl)morpholine (**4m**).* Yield: 73.8%, colorless oil. ^1H NMR (δ, $CDCl_3$): 7.21 (2H, d, $J = 8.2$ Hz, H_{phenyl}-2,6), 6.83 (2H, d, $J = 8.2$ Hz, H_{phenyl}-3,5), 3.94 (2H, t, $J = 6.4$ Hz, OCH_2), 3.69 (4H, t, $J = 4.4$ Hz, H_{mor}-2,6), 3.42 (2H, s, CH_2Ph), 3.41 (2H, t, $J = 7.2$ Hz, CH_2Br), 2.41 (4H, br t, $J = 4.4$ Hz, H_{mor}-3,5), 1.91–1.84 (2H, m, H2′), 1.81–1.75 (2H, m, H5′), 1.50–1.48 (4H, m, H3′, H4′). ESI-MS *m/z*: 356.3 $[M+H]^+$.

*6.1.3.14. 4-(1-(3-(4-Bromobutoxy)phenyl)ethyl)morpholine (**5a**).* Yield: 89.2%, colorless oil. ^1H NMR (δ, $CDCl_3$): 7.19 (1H, t, $J = 8.0$ Hz, H_{phenyl}-5), 6.95 (1H, s, H_{phenyl}-2), 6.89 (1H, d, $J = 8.0$ Hz, H_{phenyl}-4), 6.76 (1H, dd, $J = 8.0$, 2.0 Hz, H_{phenyl}-6), 3.98 (2H, t, $J = 6.0$ Hz, CH_2O), 3.78–3.74 (4H, m, H_{mor}-2,6), 3.46–3.40 (3H, m, CH_2Br, $CHCH_3$), 2.68–2.57 (2H, m, H_{mor}-3α, H_{mor}-5α), 2.52–2.46 (2H, m, H_{mor}-3β, H_{mor}-5β), 2.07–2.01 (2H, m, H3′), 1.93–1.86 (2H, m, H2′), 1.43 (3H, d, $J = 7.2$ Hz, $CHCH_3$). ESI-MS *m/z*: 342.2 $[M+H]^+$.

*6.1.3.15. 4-(1-(3-(6-Bromohexyloxy)phenyl)ethyl)morpholine (**5b**).* Yield: 76.6%, colorless oil. ^1H NMR (δ, $CDCl_3$): 7.19 (1H, t, $J = 8.0$ Hz, H_{phenyl}-5), 6.95 (1H, s, H_{phenyl}-2), 6.89 (1H, d, $J = 8.0$ Hz, H_{phenyl}-4), 6.76 (1H, dd, $J = 8.0$, 2.0 Hz, H_{phenyl}-6), 3.96 (2H, t, $J = 6.0$ Hz, CH_2O), 3.78–3.74 (4H, m, H_{mor}-2,6), 3.41–3.40 (3H, m, $CHCH_3$, CH_2Br), 2.68–2.57 (2H, m, H_{mor}-3α, H_{mor}-5α), 2.53–2.44 (2H, m, H_{mor}-3β, H_{mor}-5β), 1.91–1.85 (2H, m, H2′), 1.80–1.77 (2H, m, H5′),

1.50–1.49 (4H, m, H3′, H4′), 1.43 (3H, d, $J = 7.2$ Hz, $CHCH_3$). ESI-MS *m/z*: 370.3 $[M + H]^+$.

*6.1.4. (4-Hydroxyphenyl)(pyrrolidin-1-yl)methanone (**15**)*

4-Hydroxybenzoic acid **13** (4.14 g, 0.03 mol) was heated with Ac_2O (5.67 mL) under reflux for 6 h. After removing the excess Ac_2O, the residue was washed with Et_2O, and then filtered to provide 4-acetoxybenzoic acid as a white solid (4.43 g, 82%), m.p. 189 °C (lit. [33], m.p. 189 °C). A mixture of 4-acetoxybenzoic acid (3.60 g, 0.02 mmol) with $SOCl_2$ (36 mL) in CH_2Cl_2 was stirred at 40 °C for 10 h. The solvent and excess $SOCl_2$ were then removed, and the residue was dried in vacuo and washed with dry Et_2O to give 4-acetoxybenzoyl chloride **14** (3.14 g, 79%). Without further purification, it was put into the next reaction.

To a solution of pyrrolidine (1.49 g, 21 mmol) in water (6 mL), was added 4-acetoxybenzoyl chloride **14** (1.98 g, 10 mmol) at room temperature. The reaction mixture was stirred for 1 h, treated with 2 mol/L NaOH (45 mL), stirred for 1 h, acidified at 0 °C with diluted HCl and stirred for 2 h. After filtering the mixture, the cake was washed with water (15 × 3 mL) and recrystallized with the solvent mixture of CH_3OH–H_2O to give (4-hydroxyphenyl)(pyrrolidin-1-yl)methanone **15** as a white crystal (1.52 g, 79.8%), m.p. 170–171 °C. IR (KBr) ν (cm^{-1}): 3435, 3081, 2969, 2885, 1613, 1591, 1567, 1483, 1448, 1382, 1279, 1247, 1173. ^{1}H NMR (δ, $CDCl_3$): 7.39 (2H, d, $J = 9.0$ Hz, H_{phenyl}-3,5), 6.77 (2H, d, $J = 9.0$ Hz, H_{phenyl}-2,6), 3.43 (4H, t, $J = 6.6$ Hz, $H_{pyrrolidine}$-2,5), 1.88–1.75 (4H, m, $H_{pyrrolidine}$-3,4). ESI-MS *m/z*: 192.2 $[M + H]^+$.

*6.1.5. General procedure for **6a**, **b***

To a solution of (4-hydroxyphenyl)(pyrrolidin-1-yl)methanone **15** (191.24 mg, 1 mmol) in 2 mL of absolute acetonitrile, was added K_2CO_3 (138.21 mg, 1.5 mmol) and (1,*n*)-dibromide (5 equiv). The mixture was refluxed for 5 h. Then the solvent was removed under reduced pressure. The residue was poured into water (40 mL), and extracted with dichloromethane (3 × 15 mL), then washed with brine and dried over anhydrous Na_2SO_4. Concentration of the solvent and purification by silica gel chromatography using ethyl acetate:petroleum ether (1:3) as eluant afforded the desired products **6** (Scheme 2).

*6.1.5.1. (4-(4-Bromobutoxy)phenyl)(pyrrolidin-1-yl)methanone (**6a**).* Yield: 85.8%, a colorless foam. ^{1}H NMR (δ, $CDCl_3$): 7.51 (2H, d, $J = 8.6$ Hz, H_{phenyl}-2,6), 6.88 (2H, d, $J = 8.6$ Hz, H_{phenyl}-3,5), 4.02 (2H, t, $J = 6.0$ Hz, OCH_2), 3.63 (2H, t, $J = 6.6$ Hz, CH_2Br), 3.51–3.46 (4H, m, $H_{pyrrolidine}$-2,5), 2.11–2.03 (2H, m, H3′), 1.98–1.93 (4H, m, $H_{pyrrolidine}$-3,4), 1.89–1.85 (2H, m, H2′). ESI-MS *m/z*: 326.2 $[M + H]^+$.

*6.1.5.2. (4-(6-Bromohexyloxy)phenyl)(pyrrolidin-1-yl)methanone (**6b**).* Yield: 86.9%, a colorless foam. ^{1}H NMR (δ, $CDCl_3$): 7.50 (2H, d, $J = 8.4$ Hz, H_{phenyl}-2,6), 6.88 (2H, d, $J = 8.4$ Hz, H_{phenyl}-3,5), 3.98 (2H, t, $J = 6.4$ Hz, OCH_2), 3.63–3.61 (2H, m, $H_{pyrrolidine}$-2α, $H_{pyrrolidine}$-5α), 3.49–3.46 (2H, m, $H_{pyrrolidine}$-2β, $H_{pyrrolidine}$-5β), 3.42 (2H, t, $J = 6.8$ Hz, CH_2Br), 1.95–1.85 (6H, m, H2′, H5′, $H_{pyrrolidine}$-3α, $H_{pyrrolidine}$-5α), 1.81–1.79 (2H, m, $H_{pyrrolidine}$-3β, $H_{pyrrolidine}$-5β), 1.51–1.48 (4H, m, H3′, H4′). ESI-MS *m/z*: 354.3 $[M + H]^+$.

*6.1.6. 1-Benzyl-4-piperidinol (**17**)*

To a solution of 1-benzylpiperidin-4-one **16** (1 g, 5.28 mmol) in ethanol (50 mL), was added KBH_4 (285 mg, 5.28 mmol) portionwise during 30 min at room temperature. The mixture was stirred for 3 h and then the solvent was removed on a rotary evaporator. The residue was poured into water (30 mL), and extracted with ethyl acetate (3 × 20 mL). After the solvent is evaporated off, the residue was purified by silica gel chromatography using ethyl acetate as eluant to afford the product **17** (0.97 g, 95.9%), m.p. 61–62 °C (EtOAc). IR ($CHCl_3$) ν (cm^{-1}): 3166, 3066, 2942, 2835, 1496, 1454, 1134, 1055. ^{1}H NMR (δ, $CDCl_3$): 7.32–7.23 (5H, m, H_{phenyl}), 3.72–3.67 (1H, m, H_{pip}-4), 3.50 (2H, s, CH_2Ph), 2.78–2.74 (2H, m, H_{pip}-2α, H_{pip}-6α), 2.17–2.11 (2H, m, H_{pip}-2β, H_{pip}-6β), 1.90–1.86 (2H, m, H_{pip}-3α, H_{pip}-5α), 1.63–1.54 (2H, m, H_{pip}-3β, H_{pip}-5β). ESI-MS *m/z*: 192.3 $[M + H]^+$.

*6.1.7. General procedure for **7a**, **b***

To a cold suspension of sodium hydride (52.8 mg, 50%, 1.1 mmol) in dry DMF (2 mL), was added 1-benzyl-4-piperidinol **17** and, after 10 min, (1,*n*)-dibromide was added . After stirring at 50 °C for 3 h, the mixture was poured into water (100 mL), stirred for 5 min and then extracted with dichloromethane (3 × 40 mL). The extract was washed with water, brine, and dried over anhydrous Na_2SO_4. After removing the solvent in vacuo, the residue was purified by silica gel chromatography using ethyl acetate:petroleum ether (1:3) as eluant. The desired fraction was combined and evaporated to afford colorless oil **7** (Scheme 2).

*6.1.7.1. 1-Benzyl-4-(4-bromobutoxy)piperidine (**7a**).* Yield: 62.7%, colorless oil. ^{1}H NMR (δ, $CDCl_3$): 7.32–7.23 (5H, m, H_{phenyl}), 3.50 (2H, s, CH_2Ph), 3.47–3.43 (4H, m, H1′, H4′), 3.31–3.26 (1H, m, H_{pip}-4), 2.75–2.72 (2H, m, H_{pip}-2α, H_{pip}-6α), 2.17–2.12 (2H, m, H_{pip}-2β, H_{pip}-6β), 1.98–1.91 (2H, m, H3′), 1.88–1.85 (2H, m, H_{pip}-3α, H_{pip}-5α), 1.74–1.67 (2H, m, H2′), 1.64–1.56 (2H, m, H_{pip}-3β, H_{pip}-5β). ESI-MS *m/z*: 326.3 $[M + H]^+$.

*6.1.7.2. 1-Benzyl-4-(6-bromohexyloxy)piperidine (**7b**).* Yield: 63.4%, colorless oil. ^{1}H NMR (δ, $CDCl_3$): 7.32–7.23 (5H, m, H_{phenyl}), 3.51 (2H, s, CH_2Ph), 3.43–3.39 (4H, m, H1′, H6′), 3.31–3.25 (1H, m, H_{pip}-4), 2.76–2.73 (2H, m, H_{pip}-2α, H_{pip}-6α), 2.17–2.13 (2H, m, H_{pip}-2β, H_{pip}-6β), 1.89–1.82 (4H, m, H_{pip}-3α, H_{pip}-5α, H3′), 1.64–1.52 (4H, m, H5′, H_{pip}-3β, H_{pip}-5β), 1.49–1.42 (2H, m, H2′), 1.41–1.33 (2H, m, H4′). ESI-MS *m/z*: 354.3 $[M + H]^+$.

*6.1.8. Norgalanthamine (**2**)*

To a suspension of galanthamine hydrobromide **1** (176.64 mg, 0.48 mmol) in dichloromethane was added

1 mol/L $NaHCO_3$ solution (0.48 mL, 0.48 mol) and the mixture stirred until the entire solid had dissolved. The solution was cooled to 0 °C and treated with *m*-chloroperbenzoic acid (207 mg, 50%, 0.48 mmol) in several portions, followed by the addition of methanol (20 mL) and iron(II) sulfate heptahydrate (266.88 mg, 0.96 mmol). After stirring at −10 to 0 °C for 3 h, the mixture was treated with a solution of 5 mol/L hydrochloric acid (10 mL) and the dichloromethane was removed under reduced pressure. The aqueous residue was extracted twice with methyl *tert*-butyl ether to remove *m*-chlorobenzoic acid, basified with concd. ammonium hydroxide, and then extracted three times with dichloromethane. The extract was combined, washed with brine, and dried over anhydrous Na_2SO_4. After removing the solvent under vacuum, the residue was purified by column chromatography on silica gel using chloroform:methanol (80:20) as eluant to afford the product norgalanthamine **2** (95 mg, 72.6%). IR (KBr) ν (cm^{-1}): 3420, 3316, 2918, 2847, 1626, 1511, 1439, 1275, 1207, 1168, 1056. ^1H NMR (δ, CD_3OD): 6.71 (1H, d, $J = 8.0$ Hz, H7), 6.63 (1H, d, $J = 8.0$ Hz, H8), 6.12 (1H, d, $J = 10.4$ Hz, H1), 5.91 (1H, dd, $J = 10.4$ Hz, 4.8 Hz, H2), 4.53 (1H, br s, H4a), 4.14 (1H, br t, $J = 4.8$ Hz, H3), 4.06 (1H, d, $J = 15.2$ Hz, H9α), 3.89 (1H, d, $J = 15.2$ Hz, H9β), 3.79 (3H, s, OCH_3), 3.25 (2H, m, H11), 2.49 (1H, dm, $J = 16.0$ Hz, H4α), 2.24 (1H, ddd, $J = 16.0$ Hz, 4.8 Hz, 2.4 Hz, H4β), 1.84 (2H, m, H12). ESI-MS *m/z*: 274.1 $[M + H]^+$.

6.1.9. General procedure for *3a–s*

To a solution of norgalanthamine **2** (27.3 mg, 0.1 mmol) in anhydrous acetonitrile (2 mL), were added **4** (or **5**, **6**, **7**) (1 equiv) and anhydrous K_2CO_3 (3 equiv) under nitrogen atmosphere. After stirring at 60 °C for 24 h, the solvent was removed in vacuo. The residue was diluted with dichloromethane, washed with water, saturated NaCl solution and dried over anhydrous Na_2SO_4. Subsequently, concentration of the solvent and purification by silica gel chromatography using methanol: chloroform (1:4) as eluant afforded the desired product **3**.

*6.1.9.1. 10-N-Demethyl-10-N-(2-(4-(piperidin-1-ylmethyl)phenoxy)ethan-1-yl)-galanthamine (**3a**).* Compound **3a** was obtained as a colorless oil in 55.0% yield. IR ($CHCl_3$) ν (cm^{-1}): 3551, 3027, 2931, 2852, 1612, 1508, 1437, 1286, 1238, 1053. ^1H NMR (δ, $CDCl_3$): 7.23 (2H, d, $J = 8.0$ Hz, H_{phenyl}-3,5), 6.85 (2H, d, $J = 8.0$ Hz, H_{phenyl}-2,6), 6.67 (1H, d, $J = 8.0$ Hz, H7), 6.63 (1H, d, $J = 8.0$ Hz, H8), 6.10 (1H, d, $J = 10.0$ Hz, H1), 6.03 (1H, dd, $J = 10.0$, 4.7 Hz, H2), 4.62 (1H, br s, H4a), 4.25 (1H, d, $J = 15.6$ Hz, H9α), 4.14 (1H, t, $J = 4.7$ Hz, H3), 4.07 (2H, td, $J = 5.7$, 2.8 Hz, H2′), 3.91 (1H, d, $J = 15.6$ Hz, H9β), 3.84 (3H, s, OCH_3), 3.48 (1H, br t, $J = 14.8$, 13.6 Hz, H11α), 3.47 (2H, s, CH_2Ph), 3.28 (1H, br d, $J = 14.8$ Hz, H11β), 2.95 (2H, td, $J = 5.7$, 2.8 Hz, H1′), 2.70 (1H, dt, $J = 15.6$, 1.6 Hz, H4α), 2.43–2.36 (4H, m, H_{pip}-2,6), 2.10 (1H, m, H12α), 2.04–1.97 (1H, m, H4β), 1.62–1.53 (5H, m, H_{pip}-3,5, H12β), 1.44–1.43 (2H, m, H_{pip}-4). ^{13}C NMR (δ, $CDCl_3$): 158.02 (C_{phenyl}-1), 145.86 (C5a), 144.16 (C6), 133.09 (C_{phenyl}-4), 130.68 (C_{phenyl}-3,5), 129.31 (C8b), 127.60 (C2, C8a), 126.76 (C1), 122.06 (C8), 114.15 (C_{phenyl}-2,6), 111.18 (C7), 88.62 (C4a), 66.23 (C2′), 62.67 (CH_2Ph), 61.94 (C3, C1′), 58.07 (C9), 55.81 (OCH_3), 53.94 (C_{pip}-2,6), 52.02 (C11), 48.37 (C4b), 33.05 (C12), 29.59 (C4), 25.30 (C_{pip}-3,5), 23.95 (C_{pip}-4). ESI-MS *m/z*: 491.4 $[M + H]^+$.

*6.1.9.2. 10-N-Demethyl-10-N-(3-(4-(piperidin-1-ylmethyl)phenoxy)propan-1-yl)-galanthamine (**3b**).* Compound **3b** was obtained as a colorless oil in 65.0% yield. IR ($CHCl_3$) ν (cm^{-1}): 3552, 3027, 2932, 2854, 1612, 1508, 1437, 1267, 1239, 1058. ^1H NMR (δ, $CDCl_3$): 7.21 (2H, d, $J = 8.0$ Hz, H_{phenyl}-3,5), 6.82 (2H, d, $J = 8.0$ Hz, H_{phenyl}-2,6), 6.66 (1H, d, $J = 8.0$ Hz, H7), 6.61 (1H, d, $J = 8.0$ Hz, H8), 6.10 (1H, d, $J = 10.4$ Hz, H1), 6.00 (1H, dd, $J = 10.4$, 4.8 Hz, H2), 4.61 (1H, br s, H4a), 4.16 (1H, d, $J = 15.2$ Hz, H9α), 4.13 (1H, t, $J = 4.8$ Hz, H3), 3.96 (2H, t, $J = 6.0$ Hz, H3′), 3.83 (3H, s, OCH_3), 3.82 (1H, d, $J = 15.2$ Hz, H9β), 3.43 (2H, s, CH_2Ph), 3.37 (1H, br t, $J = 14.8$, 13.6 Hz, H11α), 3.18 (1H, br d, $J = 14.8$ Hz, H11β), 2.71–2.66 (3H, m, H4α, H1′), 2.40–2.35 (4H, m, H_{pip}-2,6), 2.04 (1H, m, H12α), 2.03–1.98 (1H, m, H4β), 1.95–1.90 (2H, m, H2′), 1.61–1.55 (4H, m, H_{pip}-3,5), 1.52 (1H, d, $J = 15.0$ Hz, H12β), 1.43–1.42 (2H, m, H_{pip}-4). ESI-MS *m/z*: 505.5 $[M + H]^+$.

*6.1.9.3. 10-N-Demethyl-10-N-(4-(4-(piperidin-1-ylmethyl)phenoxy)butan-1-yl)-galanthamine (**3c**).* Compound **3c** was obtained as a colorless oil in 53.2% yield. IR ($CHCl_3$) ν (cm^{-1}): 3552, 3026, 2930, 2835, 1612, 1508, 1437, 1267, 1243, 1057. ^1H NMR (δ, $CDCl_3$): 7.23 (2H, d, $J = 8.0$ Hz, H_{phenyl}-3,5), 6.82 (2H, d, $J = 8.0$ Hz, H_{phenyl}-2,6), 6.65 (1H, d, $J = 8.0$ Hz, H7), 6.61 (1H, d, $J = 8.0$ Hz, H8), 6.09 (1H, d, $J = 10.4$ Hz, H1), 6.00 (1H, dd, $J = 10.4$, 4.8 Hz, H2), 4.60 (1H, br s, H4a), 4.14 (1H, t, $J = 4.8$ Hz, H3), 4.12 (1H, d, $J = 15.2$ Hz, H9α), 3.94 (2H, t, $J = 6.4$ Hz, H4′), 3.83 (3H, s, OCH_3), 3.81 (1H, d, $J = 15.2$ Hz, H9β), 3.46 (2H, s, CH_2Ph), 3.36 (1H, br t, $J = 14.8$, 13.2 Hz, H11α), 3.17 (1H, br d, $J = 14.8$ Hz, H11β), 2.69 (1H, dt, $J = 15.6$, 1.6 Hz, H4α), 2.60–2.49 (2H, m, H1′), 2.41–2.40 (4H, m, H_{pip}-2,6), 2.06 (1H, m, H12α), 2.04–1.97 (1H, m, H4β), 1.80–1.73 (2H, m, H3′), 1.67–1.63 (2H, m, H2′), 1.63–1.57 (4H, m, H_{pip}-3,5), 1.51 (1H, d, $J = 14.0$ Hz, H12β), 1.45–1.43 (2H, m, H_{pip}-4). ESI-MS *m/z*: 519.5 $[M + H]^+$.

*6.1.9.4. 10-N-Demethyl-10-N-(5-(4-(piperidin-1-ylmethyl)phenoxy)pentan-1-yl)-galanthamine (**3d**).* Compound **3d** was obtained as a colorless oil in 50.3% yield. IR ($CHCl_3$) ν (cm^{-1}): 3556, 3027, 2931, 2852, 1612, 1508, 1437, 1286, 1238, 1053. ^1H NMR (δ, $CDCl_3$): 7.23 (2H, d, $J = 8.0$ Hz, H_{phenyl}-3,5), 6.82 (2H, d, $J = 8.0$ Hz, H_{phenyl}-2,6), 6.66 (1H, d, $J = 8.0$ Hz, H7), 6.61 (1H, d, $J = 8.0$ Hz, H8), 6.09 (1H, d, $J = 10.0$ Hz, H1), 6.01 (1H, dd, $J = 10.0$, 4.8 Hz, H2), 4.61 (1H, br s, H4a), 4.14 (1H, t, $J = 4.8$ Hz, H3), 4.13 (1H, d, $J = 15.2$ Hz, H9α), 3.93 (2H, t, $J = 6.6$ Hz, H5′), 3.84 (3H, s, OCH_3), 3.81 (1H, d, $J = 15.2$ Hz, H9β), 3.48 (2H, s, CH_2Ph), 3.36 (1H, br t, $J = 15.0$, 13.2 Hz), 3.18 (1H, br d, $J = 15.0$ Hz), 2.69 (1H, dt, $J = 15.4$, 1.6 Hz, H4α),

2.58–2.46 (2H, m, H1′), 2.45–2.38 (4H, m, H_{pip}-2,6), 2.07 (1H, m, H12α), 2.04–1.98 (1H, m, H4β), 1.81–1.74 (2H, m, H4′), 1.64–1.58 (4H, m, H_{pip}-3,5), 1.56–1.49 (3H, m, H2′, H12β), 1.48–1.41 (4H, m, H3′, H_{pip}-4). ESI-MS *m/z*: 533.5 $[M+H]^+$.

*6.1.9.5. 10-N-Demethyl-10-N-(6-(4-(piperidin-1-ylmethyl)phenoxy)hexan-1-yl)-galanthamine (**3e**).* Compound **3e** was obtained as a colorless oil in 52.3% yield. IR ($CHCl_3$) ν (cm^{-1}): 3556, 3027, 2932, 2854, 1612, 1508, 1437, 1267, 1239, 1058. ^1H NMR (δ, $CDCl_3$): 7.20 (2H, d, $J=8.8$ Hz, H_{phenyl}-3,5), 6.82 (2H, d, $J=8.8$ Hz, H_{phenyl}-2,6), 6.65 (1H, d, $J=8.0$ Hz, H7), 6.61 (1H, d, $J=8.0$ Hz, H8), 6.09 (1H, d, $J=10.0$ Hz, H1), 6.00 (1H, dd, $J=10.0$, 4.8 Hz, H2), 4.60 (1H, br s, H4a), 4.13 (1H, t, $J=4.8$ Hz, H3), 4.12 (1H, d, $J=14.8$ Hz, H9α), 3.92 (2H, t, $J=6.8$ Hz, H6′), 3.82 (3H, s, OCH_3), 3.80 (1H, d, $J=14.8$ Hz, H9β), 3.41 (2H, s, CH_2Ph), 3.35 (1H, br t, $J=15.0$, 13.6 Hz, H11α), 3.17 (1H, br d, $J=15.0$ Hz, H11β), 2.68 (1H, dt, $J=15.6$, 1.6 Hz, H4α), 2.55–2.43 (2H, m, H1′), 2.40–2.32(4H, m, H_{pip}-2,6), 2.06 (1H, m, H12α), 2.03–1.97 (1H, m, H4β), 1.79–1.72 (2H, m, H5′), 1.59–1.54 (4H, m, H_{pip}-3,5), 1.52–1.42 (7H, m, H12β, H2′, H3′, H4′), 1.35–1.31 (2H, m, H_{pip}-4). ^{13}C NMR (δ, $CDCl_3$): 158.19 (C_{phenyl}-1), 145.70 (C5a), 143.94 (C6), 133.08 (C_{phenyl}-4), 130.53 (C_{phenyl}-3,5), 129.36 (C8b), 127.48 (C2,C8a), 126.91 (C1), 121.90 (C8), 114.01 (C_{phenyl}-2,6), 111.05 (C7), 88.62 (C4a), 67.72 (C6′), 62.91 (CH_2Ph), 61.98 (C3), 57.68 (C9), 55.78 (OCH_3), 54.06 (C_{pip}-2,6), 53.35 (C1′), 51.44 (C11), 48.34 (C4b), 32.86 (C12), 29.59 (C4), 29.16 (C5′), 27.29 (C3′), 27.05 (C2′), 25.94 (C4′), 25.26 (C_{pip}-3,5), 24.12 (C_{pip}-4). ESI-MS *m/z*: 547.5 $[M+H]^+$.

*6.1.9.6. 10-N-Demethyl-10-N-(8-(4-(piperidin-1-ylmethyl)phenoxy)octan-1-yl)-galanthamine (**3f**).* Compound **3f** was obtained as a colorless oil in 53.4% yield. IR ($CHCl_3$) ν (cm^{-1}): 3554, 3026, 2930, 2835, 1612, 1508, 1437, 1267, 1243, 1057. ^1H NMR (δ, $CDCl_3$): 7.21 (2H, d, $J=8.8$ Hz, H_{phenyl}-3,5), 6.83 (2H, d, $J=8.8$ Hz, H_{phenyl}-2,6), 6.65 (1H, d, $J=8.0$ Hz, H7), 6.61 (1H, d, $J=8.0$ Hz, H8), 6.09 (1H, d, $J=10.0$ Hz, H1), 5.99 (1H, dd, $J=10.0$, 4.8 Hz, H2), 4.60 (1H, br s, H4a), 4.14 (1H, t, $J=4.8$ Hz, H3), 4.11 (1H, d, $J=15.2$ Hz, H9α), 3.92 (2H, t, $J=6.6$ Hz, H8′), 3.83 (3H, s, OCH_3), 3.80 (1H, d, $J=15.2$ Hz, H9β), 3.44 (2H, s, CH_2Ph), 3.34 (1H, br t, $J=14.8$, 13.2 Hz, H11α), 3.17 (1H, br d, $J=13.2$ Hz, H11β), 2.68 (1H, d m, $J=15.6$ Hz, H4α), 2.52–2.43 (2H, m, H1′), 2.40–2.35 (4H, m, H_{pip}-2,6), 2.07 (1H, m, H12α), 2.03–1.97 (1H, m, H4β), 1.79–1.72 (2H, m, H7′), 1.61–1.56 (4H, m, H_{pip}-3,5), 1.54–1.42 (7H, m, H12β, H2′, H3′, H6′), 1.35–1.25 (6H, m, H_{pip}-4, H4′, H5′). ESI-MS *m/z*: 575.6 $[M+H]^+$.

*6.1.9.7. 10-N-Demethyl-10-N-(9-(4-(piperidin-1-ylmethyl)phenoxy)nonan-1-yl)-galanthamine (**3g**).* Compound **3g** was obtained as a colorless oil in 53.5% yield. IR ($CHCl_3$) ν (cm^{-1}): 3553, 3027, 2932, 2854, 1612, 1508, 1437, 1267, 1239, 1058. ^1H NMR (δ, $CDCl_3$): 7.21 (2H, d, $J=8.4$ Hz, H_{phenyl}-3,5), 6.83 (2H, d, $J=8.4$ Hz, H_{phenyl}-2,6), 6.66 (1H, d, $J=8.0$ Hz, H7), 6.61 (1H, d, $J=8.0$ Hz, H8), 6.09 (1H, d, $J=10.0$ Hz, H1), 6.00 (1H, dd, $J=10.0$, 4.8 Hz, H2), 4.65 (1H, br s, H4a), 4.14 (1H, t, $J=4.8$ Hz, H3), 4.12 (1H, d, $J=15.2$ Hz, H9α), 3.93 (2H, t, $J=6.8$ Hz, H9′), 3.83 (3H, s, OCH_3), 3.81 (1H, d, $J=15.2$ Hz, H9β), 3.44 (2H, s, CH_2Ph), 3.35 (1H, br t, $J=14.8$, 13.2 Hz, H11α), 3.17 (1H, d, $J=14.8$ Hz, H11β), 2.69 (1H, dm, $J=15.6$ Hz, H4α), 2.52–2.42 (2H, m, H1′), 2.41–2.35 (4H, m, H_{pip}-2,6), 2.07 (1H, m, H12α), 2.03–1.97 (1H, m, H4β), 1.79–1.72 (2H, m, H8′), 1.61–1.56 (4H, m, H_{pip}-3,5), 1.54–1.39 (7H, m, H12β, H2, H3′, H7′), 1.36–1.25 (8H, m, H_{pip}-4, H4′, H5′, H6′). ESI-MS *m/z*: 589.5 $[M+H]^+$.

*6.1.9.8. 10-N-Demethyl-10-N-(10-(4-(piperidin-1-ylmethyl)-phenoxy)decan-1-yl)-galanthamine (**3h**).* Compound **3h** was obtained as a colorless oil in 48.9% yield. IR ($CHCl_3$) ν (cm^{-1}): 3558, 3026, 2930, 2835, 1612, 1508, 1437, 1267, 1243, 1057. ^1H NMR (δ, $CDCl_3$): 7.29 (2H, d, $J=8.0$ Hz, H_{phenyl}-3,5), 6.85 (2H, d, $J=8.0$ Hz, H_{phenyl}-2,6), 6.66 (1H, d, $J=8.0$ Hz, H7), 6.61 (1H, d, $J=8.0$ Hz, H8), 6.08 (1H, d, $J=10.0$ Hz, H1), 6.00 (1H, dd, $J=10.0$, 4.8 Hz, H2), 4.61 (1H, br s, H4a), 4.14 (1H, t, $J=4.8$ Hz, H3), 4.13 (1H, d, $J=15.6$ Hz, H9α), 3.94 (2H, d, $J=6.8$ Hz, H10′), 3.83 (3H, s, OCH_3), 3.81 (1H, d, $J=15.6$ Hz, H9β), 3.61 (2H, s, CH_2Ph), 3.35 (1H, br t, $J=14.0$, 13.2 Hz, H11α), 3.17 (1H, br d, $J=13.2$ Hz, H11β), 2.67 (1H, dm, $J=15.6$ Hz, H4α), 2.59–2.52 (4H, m, H_{pip}-2,6), 2.51–2.43 (2H, m, H1′), 2.07 (1H, m, H12α), 2.03–1.97 (1H, m, H4β), 1.81–1.68 (6H, m, H9′, H_{pip}-3,5), 1.55–1.40 (7H, m, H2′, H3′ H8′), 1.35–1.21 (10H, m, H_{pip}-4, H4′, H5′, H6′, H7′). ESI-MS *m/z*: 603.6 $[M+H]^+$.

*6.1.9.9. 10-N-Demethyl-10-N-(12-(4-(piperidin-1-ylmethyl)-phenoxy)dodecan-1-yl)-galanthamine (**3i**).* Compound **3i** was obtained as a colorless oil in 51.3% yield. IR ($CHCl_3$) ν (cm^{-1}): 3558, 3027, 2926, 2853, 1611, 1509, 1437, 1267, 1239, 1058. ^1H NMR (δ, $CDCl_3$): 7.33 (2H, d, $J=8.4$ Hz, H_{phenyl}-3,5), 6.86 (2H, d, $J=8.4$ Hz, H_{phenyl}-2,6), 6.66 (1H, d, $J=8.0$ Hz, H7), 6.62 (1H, d, $J=8.0$ Hz, H8), 6.09 (1H, d, $J=10.4$ Hz, H1), 5.99 (1H, dd, $J=10.4$, 4.8 Hz, H2), 4.61 (1H, br s, H4a), 4.16–4.12 (2H, m, H3, H9α), 3.94 (2H, t, $J=6.4$ Hz, H12′), 3.85–3.81 (4H, m, OCH_3, H9β), 3.67 (2H, s, CH_2Ph), 3.36 (1H, br t, $J=14.0$, 13.2 Hz, H11α), 3.18 (1H, br d, $J=14.0$ Hz, H11β), 2.68 (1H, d, $J=15.6$ Hz, H4α), 2.64–2.56 (4H, m, H_{pip}-2,6), 2.54–2.44 (2H, m, H1′), 2.09–1.99 (2H, m, H12α, H4β), 1.78–1.73 (6H, m, H11′, H_{pip}-3,5), 1.54–1.41 (7H, m, H12β, H2′, H3′, H10′), 1.36–1.26 (14H, m, H_{pip}-4, H4′, H5′, H6′, H7′, H8′, H9′). ESI-MS *m/z*: 631.7 $[M+H]^+$.

*6.1.9.10. 10-N-Demethyl-10-N-(4-(4-((diethylamino)methyl)-phenoxy)butan-1-yl)-galanthamine (**3j**).* Compound **3j** was obtained as a colorless oil in 54.3% yield. IR ($CHCl_3$) ν (cm^{-1}): 3558, 3026, 2929, 2855, 1612, 1509, 1437, 1286, 1265, 1242, 1059. ^1H NMR (δ, $CDCl_3$): 7.26 (2H, d, $J=8.8$ Hz, H_{phenyl}-3,5), 6.83 (2H, d, $J=8.8$ Hz, H_{phenyl}-2,6), 6.65 (1H, d, $J=8.0$ Hz, H7), 6.61 (1H, d, $J=8.0$ Hz, H8), 6.09 (1H,

d, $J = 10.0$ Hz, H1), 6.00 (1H, dd, $J = 10.0$, 4.8 Hz, H2), 4.61 (1H, br s, H4a), 4.14 (1H, t, $J = 4.8$ Hz, H3), 4.13 (1H, d, $J = 15.2$ Hz, H9α), 3.93 (2H, t, $J = 6.4$ Hz, H4′), 3.83 (3H, s, OCH_3), 3.81 (1H, d, $J = 15.2$ Hz, H9β), 3.57 (2H, s, CH_2Ph), 3.35 (1H, br t, $J = 15.6$, 13.2 Hz, H11α), 3.17 (1H, br d, $J = 15.6$ Hz, H11β), 2.68 (1H, dm, $J = 15.2$ Hz, H4α), 2.57 (4H, q, $J = 6.8$ Hz, NCH_2CH_3), 2.52–2.45(2H, m, H1′), 2.06 (1H, m, H12α), 2.03–1.98 (1H, m, H4β), 1.80–1.73 (2H, m, H3′), 1.68–1.62 (2H, m, H2′), 1.51 (1H, d, $J = 13.6$ Hz, H12β), 1.08 (6H, t, $J = 6.8$ Hz, NCH_2CH_3). ESI-MS *m/z*: 507.5 $[M + H]^+$.

*6.1.9.11. 10-N-Demethyl-10-N-(6-(4-((diethylamino)methyl)-phenoxy)hexan-1-yl)-galanthamine (**3k**).* Compound **3k** was obtained as a colorless oil in 49.9% yield. IR ($CHCl_3$) ν (cm^{-1}): 3556, 3026, 2929, 2855, 1611, 1509, 1437, 1286, 1265, 1242, 1059. ^1H NMR (δ, $CDCl_3$): 7.26 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 6.83 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 6.65 (1H, d, $J = 8.0$ Hz, H7), 6.61 (1H, d, $J = 8.0$ Hz, H8), 6.09 (1H, d, $J = 10.0$ Hz, H1), 6.00 (1H, dd, $J = 10.0$, 4.8 Hz, H2), 4.61 (1H, br s, H4a), 4.14 (1H, t, $J = 4.8$ Hz, H3), 4.13 (1H, d, $J = 15.2$ Hz, H9α), 3.93 (2H, t, $J = 6.4$ Hz, H6′), 3.83 (3H, s, OCH_3), 3.81 (1H, d, $J = 15.2$ Hz, H9β), 3.57 (2H, s, CH_2Ph), 3.35 (1H, br t, $J = 15.6$, 13.2 Hz, H11α), 3.17 (1H, br d, $J = 15.6$ Hz, H11β), 2.68 (1H, dt, $J = 15.2$, 1.6 Hz, H4α), 2.57 (4H, q, $J = 6.8$ Hz, NCH_2CH_3), 2.52–2.45 (2H, m, H1′), 2.06 (1H, dd, $J = 13.6$, 3.0 Hz, H12α), 2.03–1.98 (1H, m, H4β), 1.80–1.73 (2H, m, H5′), 1.53–1.44 (5H, m, H12β, H2′, H4′), 1.38–1.33 (2H, m, H3′), 1.08 (6H, t, $J = 6.8$ Hz, NCH_2CH_3). ^{13}C NMR (δ, $CDCl_3$): 158.01 (C_{phenyl}-1), 145.68 (C5a), 143.95 (C6), 133.06 (C_{phenyl}-4), 130.10 (C_{phenyl}-3,5), 129.43 (C8b), 127.47 (C8a, C2), 126.81 (C1), 121.91 (C8), 114.03 (C_{phenyl}-2,6), 111.06 (C7), 88.62 (C4a), 67.72 (C6′), 62.00 (CH_2Ph, C3), 57.69 (C9), 56.56 (OCH_3), 55.78 (C1′), 51.44 (C11), 48.34 (C4b), 46.29 (2 NCH_2CH_3), 32.84 (C12), 29.62 (C4), 29.18 (C5′), 27.31 (C3′), 27.06 (C2′), 25.95 (C4′), 11.35 (2 NCH_2CH_3). ESI-MS *m/z*: 535.5 $[M + H]^+$.

*6.1.9.12. 10-N-Demethyl-10-N-(4-(4-(morpholinomethyl)phenoxy)butan-1-yl)-galanthamine (**3l**).* Compound **3l** was obtained as a colorless oil in 62.5% yield. IR ($CHCl_3$) ν (cm^{-1}): 3554, 3027, 2930, 2853, 1612, 1509, 1437, 1286, 1264, 1243, 1116, 1058. ^1H NMR (δ, $CDCl_3$): 7.21 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 6.81 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 6.65 (1H, d, $J = 8.0$ Hz, H7), 6.62 (1H, d, $J = 8.0$ Hz, H8), 6.07 (1H, d, $J = 10.4$ Hz, H1), 6.01 (1H, dd, $J = 10.4$, 4.8 Hz, H2), 4.60 (1H, br s, H4a), 4.18 (1H, d, $J = 15.6$ Hz, H9α), 4.14 (1H, t, $J = 4.8$ Hz, H3), 3.94 (2H, t, $J = 6.4$ Hz, H4′), 3.86 (1H, d, $J = 15.6$ Hz, H9β), 3.82 (3H, s, OCH_3), 3.70 (4H, t, $J = 4.8$ Hz, NCH_2CH_2O), 3.45 (2H, s, CH_2Ph), 3.40 (1H, br t, $J = 15.2$, 13.2 Hz, H11α), 3.21 (1H, br d, $J = 15.2$ Hz, H11β), 2.68 (1H, dm, $J = 15.6$ Hz, H4α), 2.64–2.55 (2H, m, H1′), 2.47–2.41 (4H, m, NCH_2CH_2O), 2.07 (1H, m, H12α), 2.03–1.98 (1H, m, H4β), 1.80–1.75 (2H, m, H3′), 1.73–1.67 (2H, m, H2′), 1.56 (1H, d, $J = 13.2$ Hz, H12β). ESI-MS *m/z*: 521.4 $[M + H]^+$.

*6.1.9.13. 10-N-Demethyl-10-N-(6-(4-(morpholinomethyl)phenoxy)hexan-1-yl)-galanthamine (**3m**).* Compound **3m** was obtained as a colorless oil in 47.1% yield. IR ($CHCl_3$) ν (cm^{-1}): 3553, 3026, 2930, 2855, 1612, 1509, 1437, 1285, 1265, 1243, 1116, 1058. ^1H NMR (δ, $CDCl_3$): 7.21 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 6.83 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 6.65 (1H, d, $J = 8.0$ Hz, H7), 6.61 (1H, d, $J = 8.0$ Hz, H8), 6.09 (1H, d, $J = 10.0$ Hz, H1), 6.00 (1H, dd, $J = 10.0$, 4.8 Hz, H2), 4.60 (1H, br s, H4a), 4.14 (1H, t, $J = 4.8$ Hz, H3), 4.13 (1H, d, $J = 15.6$ Hz, H9α), 3.92 (2H, t, $J = 6.4$ Hz, H6′), 3.83 (3H, s, OCH_3), 3.81 (1H, d, $J = 15.6$ Hz, H9β), 3.69 (4H, t, $J = 4.8$ Hz, NCH_2CH_2O), 3.42 (2H, s, CH_2Ph), 3.35 (1H, br t, $J = 15.2$, 13.8 Hz, H11α), 3.17 (1H, br d, $J = 15.2$ Hz, H11β), 2.68 (1H, dt, $J = 15.6$, 1.6 Hz, H4α), 2.55–2.44 (2H, m, H1′), 2.43–2.41 (4H, m, NCH_2CH_2O), 2.06 (1H, m, H12α), 2.03–1.97 (1H, m, H4β), 1.80–1.73 (2H, m, H5′), 1.54–1.44 (5H, m, H12β, H2′, H4′), 1.38–1.32 (2H, m, H3′). ^{13}C NMR (δ, $CDCl_3$): 158.22 (C_{phenyl}-1), 145.76 (C5a), 144.02 (C6), 133.06 (C_{phenyl}-4), 130.26 (C_{phenyl}-3,5), 129.37 (C8b), 127.55 (C8a, C2), 126.80 (C1), 121.93 (C8), 114.10 (C_{phenyl}-2,6), 111.16 (C7), 88.59 (C4a), 67.74 (C6′), 66.86 (C_{mor}-2,6), 62.72 (C3), 61.93 (CH_2Ph), 59.41 (C9), 57.58 (C1′), 55.80 (OCH_3), 53.39 (C_{mor}-3,5), 51.41 (C11), 48.27 (C4b), 32.79 (C12), 31.13 (C4), 29.13 (C5′), 27.15 (C3′), 27.00 (C2′), 25.90 (C4′). ESI-MS *m/z*: 549.5 $[M + H]^+$.

*6.1.9.14. 10-N-Demethyl-10-N-(4-(3-(1-morpholinoethyl)phenoxy)butan-1-yl)-galanthamine (**3n**).* Compound **3n** was obtained as a colorless oil in 48.3% yield. IR ($CHCl_3$) ν (cm^{-1}): 3554, 3026, 2930, 2855, 1589, 1506, 1437, 1265, 1118, 1059. ^1H NMR (δ, $CDCl_3$): 7.20 (1H, t, $J = 7.8$ Hz, H_{phenyl}-5), 6.88–6.86 (2H, m, H_{phenyl}-6, H_{phenyl}-2), 6.74 (1H, d, $J = 7.8$ Hz, H_{phenyl}-4), 6.65 (1H, d, $J = 8.0$ Hz, H7), 6.61 (1H, d, $J = 8.0$ Hz, H8), 6.09 (1H, d, $J = 10.4$ Hz, H1), 6.00 (1H, dd, $J = 10.4$, 4.8 Hz, H2), 4.61 (1H, br s, H4a), 4.17–4.13 (2H, m, H9α, H3), 3.95 (2H, t, $J = 6.4$ Hz, H4′), 3.84 (1H, d, $J = 15.2$ Hz, H9β), 3.82 (3H, s, OCH_3), 3.68 (4H, t, $J = 4.8$ Hz, NCH_2CH_2O), 3.38 (1H, br t, $J = 14.8$, 13.6 Hz, H11α), 3.26 (1H, q, $J = 6.5$ Hz, $CHCH_3$), 3.19 (1H, br d, $J = 14.8$ Hz, H11β), 2.68 (1H, dm, $J = 15.6$ Hz, H4α), 2.64–2.53 (2H, m, H1′), 2.51–2.47 (2H, m, H_{mor}-3α, H_{mor}-5α), 2.39–2.34 (2H, m, H_{mor}-3β, H_{mor}-5β), 2.09–2.05 (1H, m, H12α), 2.03–1.97 (1H, m, H4β), 1.81–1.76 (2H, m, H3′), 1.71–1.66 (2H, m, H2′), 1.53 (1H, d, $J = 13.8$ Hz, H12β), 1.32 (3H, d, $J = 6.8$ Hz). ESI-MS *m/z*: 535.5 $[M + H]^+$.

*6.1.9.15. 10-N-Demethyl-10-N-(6-(3-(1-morpholinoethyl)phenoxy)hexan-1-yl)-galanthamine (**3o**).* Compound **3o** was obtained as a colorless oil in 45.8% yield. IR ($CHCl_3$) ν (cm^{-1}): 3556, 3026, 2930, 2855, 1585, 1506, 1437, 1265, 1118, 1058. ^1H NMR (δ, $CDCl_3$): 7.20 (1H, t, $J = 8.0$ Hz, H_{phenyl}-5), 6.88–6.87 (2H, m, H_{phenyl}-6, H_{phenyl}-2), 6.75 (1H, d, $J = 8.0$ Hz, H_{phenyl}-4), 6.66 (1H, d, $J = 8.0$ Hz, H7), 6.62 (1H, d, $J = 8.0$ Hz, H8), 6.09 (1H, d, $J = 10.0$ Hz, H1), 6.00 (1H, dd, $J = 10.0$, 4.8 Hz, H2), 4.60 (1H, br s, H4a), 4.14 (1H, d, $J = 15.6$ Hz, H9α), 4.13 (1H, t, $J = 4.8$ Hz, H3),

3.93 (2H, t, $J = 6.4$ Hz, H6′), 3.83 (1H, d, $J = 15.6$ Hz, H9β), 3.82 (3H, s, OCH_3), 3.68 (4H, t, $J = 4.8$ Hz, H_{mor}-2, H_{mor}-6), 3.36 (1H, br t, $J = 14.4$, 13.2 Hz, H11α), 3.25 (1H, q, $J = 6.8$ Hz, $CHCH_3$), 3.18 (1H, br d, $J = 14.4$ Hz, H11β), 2.68 (2H, dm, $J = 15.6$ Hz, H4α), 2.57–2.45 (4H, m, H1′, H_{mor}-3α, H_{mor}-5α), 2.38–2.34 (2H, m, H_{mor}-3β, H_{mor}-5β), 2.08–2.04 (1H, m, H12α), 2.03–1.98 (1H, m, H4β), 1.81–1.74 (2H, m, H5′), 1.56–1.44 (5H, m, H12β, H2′, H4′), 1.38–1.35 (2H, m, H4′), 1.33 (3H, d, $J = 6.8$ Hz, $CHCH_3$). ^{13}C NMR (δ, $CDCl_3$): 159.07 (C_{phenyl}-1), 145.62 (C5a), 143.94 (C6), 133.06 (C8b), 129.41 (C8a), 129.11 (C_{phenyl}-5), 127.47 (C_{phenyl}-3, C2), 126.88 (C1), 121.89 (C8), 119.80 (C_{phenyl}-4), 113.71 (C_{phenyl}-6), 112.55 (C_{phenyl}-2), 111.10 (C7), 88.64 (C4a), 67.66 (C6′), 67.13 (C_{mor}-2,6), 65.34 ($CHCH_3$), 61.98 (C3), 57.68 (C9), 55.78 (OCH_3), 53.36 (C1′), 51.44 (C11), 51.25 (C_{mor}-3,5), 48.33 (C4b), 32.83 (C12), 29.86 (C4), 29.21 (C5′), 27.33 (C3′), 27.10 (C2′), 25.98 (C4′), 19.83 ($CHCH_3$). ESI-MS *m/z*: 563.5 $[M + H]^+$.

*6.1.9.16. 10-N-Demethyl-10-N-(4-(4-(pyrrolidine-1-carbonyl)-phenoxy)butan-1-yl)-galanthamine (**3p**).* Compound **3p** was obtained as a colorless foam in 54.3% yield. IR ($CHCl_3$) ν (cm^{-1}): 3558, 2928, 2855, 1613, 1607, 1508, 1427, 1249, 1202, 1171, 1057. ^{1}H NMR (δ, $CDCl_3$):7.49 (2H, d, $J = 8.0$ Hz, H_{phenyl}-3,5), 6.85 (2H, d, $J = 8.0$ Hz, H_{phenyl}-2,6), 6.66 (1H, d, $J = 8.0$ Hz, H7), 6.62 (1H, d, $J = 8.0$ Hz, H8), 6.08 (1H, d, $J = 10.4$ Hz, H1), 6.01 (1H, dd, $J = 10.4$, 4.6 Hz, H2), 4.61 (1H, br s, H4a), 4.19 (1H, d, $J = 15.6$ Hz, H9α), 4.14 (1H, t, $J = 4.6$ Hz, H3), 3.98 (2H, t, $J = 6.0$ Hz, H4′), 3.88 (1H, d, $J = 15.6$ Hz, H9β), 3.83 (3H, s, OCH_3), 3.63 (2H, m, $H_{pyrrolidine}$-2α, $H_{pyrrolidine}$-5α), 3.49–3.48 (2H, m, $H_{pyrrolidine}$-2β, $H_{pyrrolidine}$-5β), 3.45 (1H, br t, $J = 14.8$, 13.2 Hz, H11α), 3.21 (1H, br d, $J = 14.8$ Hz, H11β), 2.68 (1H, dm, $J = 15.8$ Hz, H4α), 2.64–2.56 (2H, m, H1′), 2.10–2.05 (1H, m, H12α), 2.03–1.99 (1H, m, H4β), 1.97–1.91 (2H, m, $H_{pyrrolidine}$-3α, $H_{pyrrolidine}$-4α), 1.90–1.85 (2H, m, $H_{pyrrolidine}$-3β, $H_{pyrrolidine}$-4β), 1.81–1.76 (2H, m, H3′), 1.74–1.67 (2H, m, H2′), 1.58 (1H, d, $J = 13.6$ Hz, H12β). ESI-MS *m/z*: 519.4 $[M + H]^+$.

*6.1.9.17. 10-N-Demethyl-10-N-(6-(4-(pyrrolidine-1-carbonyl)-phenoxy)hexan-1-yl)-galanthamine (**3q**).* Compound **3q** was obtained as a colorless foam in 43.6% yield. IR ($CHCl_3$) ν (cm^{-1}): 3558, 2928, 2857, 1613, 1608, 1508, 1427, 1249, 1203, 1171, 1055. ^{1}H NMR (δ, $CDCl_3$): 7.50 (2H, d, $J = 8.8$ Hz, H_{phenyl}-3,5), 6.87 (2H, d, $J = 8.8$ Hz, H_{phenyl}-2,6), 6.67 (1H, d, $J = 8.0$ Hz, H7), 6.63 (1H, d, $J = 8.0$ Hz, H8), 6.08 (1H, d, $J = 10.4$ Hz, H1), 6.01 (1H, dd, $J = 10.4$, 4.8 Hz, H2), 4.61 (1H, br s, H4a), 4.17–4.13 (2H, m, H3, H9α), 3.96 (2H, t, $J = 6.6$ Hz, H6′), 3.86 (1H, d, $J = 15.6$ Hz, H9β), 3.83 (3H, s, OCH3), 3.63 (2H, t, $J = 6.8$ Hz, $H_{pyrrolidine}$-2α, $H_{pyrrolidine}$-5α), 3.48 (2H, t, $J = 6.8$ Hz, $H_{pyrrolidine}$-2β, $H_{pyrrolidine}$-5β), 3.39 (1H, br t, $J = 13.6$, 13.2 Hz, H11α), 3.21 (1H, br d, $J = 13.6$ Hz, H11β), 2.68 (1H, dm, $J = 15.2$ Hz, H4α), 2.59–2.47 (2H, m, H1′), 2.09–2.05 (1H, m, H12α), 2.04–1.98 (1H, m, H4β), 1.97–1.92 (2H, m, $H_{pyrrolidine}$-3α, $H_{pyrrolidine}$-4α), 1.89–1.85 (2H, m, $H_{pyrrolidine}$-3β, $H_{pyrrolidine}$-4β), 1.81–1.74 (2H, m, H5′), 1.58–1.53 (3H, m, H2′, H12β), 1.49–1.43 (2H, m, H4′), 1.39–1.32 (2H, m, H3′). ^{13}C NMR (δ, $CDCl_3$): 169.42 (C(O)), 160.28 (C_{phenyl}-1), 145.82 (C5a), 144.05 (C6), 133.16 (C8b), 129.21 (C_{phenyl}-4), 129.10 (C_{phenyl}-3,5), 127.56 (C2, C8a), 126.95 (C1), 121.94 (C8), 113.89 (C_{phenyl}-2,6), 111.12 (C7), 88.70 (C4a), 67.91 (C6′), 62.05 (C3), 57.75 (C9), 55.87 (OCH_3), 51.53 (C1′), 49.75 (C11), 48.39 ($C_{pyrrolidine}$-2,5), 46.27 (C4b), 32.98 (C12), 29.93 (C4), 29.08 (C5′), 27.34 (C3′), 27.07 (C2′), 26.47 (C4′), 25.94 ($C_{pyrrolidine}$-3,4). ESI-MS *m/z*: 547.5 $[M + H]^+$.

*6.1.9.18. 10-N-Demethyl-10-N-(4-(1-benzylpiperidin-4-yloxy)-butan-1-yl)-galanthamine (**3r**).* Compound **3r** was obtained as a colorless oil in 45.8% yield. IR ($CHCl_3$) ν (cm^{-1}): 3554, 3206, 2934, 2856, 1623, 1509, 1436, 1266, 1058. ^{1}H NMR (δ, $CDCl_3$): 7.31–7.23 (5H, m, H_{phenyl}), 6.64 (1H, d, $J = 8.4$ Hz, H7), 6.60 (1H, d, $J = 8.4$ Hz, H8), 6.09 (1H, d, $J = 10.4$ Hz, H1), 5.99 (1H, dd, $J = 10.4$, 4.8 Hz, H2), 4.60 (1H, br s, H4a), 4.14–4.10 (2H, m, H3, H9α), 3.82 (3H, s, OCH_3), 3.81 (1H, d, $J = 15.8$ Hz, H9β), 3.48 (2H, s, CH_2Ph), 3.43–3.40 (2H, m, H4′), 3.34 (1H, br t, $J = 15.2$, 13.2 Hz, H11α), 3.26–3.24 (1H, m, H_{pip}-4), 3.16 (2H, br d, $J = 15.2$ Hz, H11β), 2.74–2.66 (3H, m, H_{pip}-2α, H_{pip}-6α, H4α), 2.51–2.46 (2H, m, H1′), 2.13–2.07 (2H, m, H_{pip}-2β, H_{pip}-6β), 2.07–2.04 (1H, m, H12α), 2.03–1.97 (1H, m, H4β), 1.86–1.82 (2H, m, H_{pip}-3α, H_{pip}-5α), 1.62–1.48 (7H, m, H_{pip}-3β, H_{pip}-5β, H12β, H2′, H3′). ^{13}C NMR (δ, $CDCl_3$): 145.72 (C5a), 143.96 (C6), 138.44 (C_{phenyl}-1), 133.10 (C8b), 129.51 (C8a), 129.02 (C_{phenyl}-2,6,4), 128.09 (C_{phenyl}-3,5), 127.47 (C2), 126.87 (C1), 121.89 (C8), 111.04 (C7), 88.65 (C4a), 74.96 (C_{pip}-4), 67.49 (C4′), 62.94 (CH_2Ph), 62.01 (C3), 57.65 (C9), 55.81 (C1′, OCH3), 51.51 (C11), 51.15 (C4b), 48.35 (C_{pip}-2,6), 32.95 (C12), 31.30 (C_{pip}-3,5), 29.89 (C4), 27.77 (C3′), 24.15 (C2′). ESI-MS *m/z*: 519.5 $[M + H]^+$.

*6.1.9.19. 10-N-Demethyl-10-N-(6-(1-benzylpiperidin-4-yloxy)-hexan-1-yl)-galanthamine (**3s**).* Compound **3s** was obtained as a colorless oil in 46.8% yield. IR ($CHCl_3$) ν (cm^{-1}): 3557, 3026, 2931, 2855, 1623, 1506, 1436, 1266, 1058. ^{1}H NMR (δ, $CDCl_3$): 7.31–7.23 (5H, m, H_{phenyl}), 6.65 (1H, d, $J = 8.4$ Hz, H7), 6.60 (1H, d, $J = 8.4$ Hz, H8), 6.09 (1H, d, $J = 10.4$ Hz, H1), 5.99 (1H, dd, $J = 10.4$, 4.8 Hz, H2), 4.60 (1H, br s, H4a), 4.14–4.10 (2H, m, H3, H9α), 3.82 (3H, s, OCH_3), 3.80 (1H, d, $J = 15.6$ Hz, H9β), 3.48 (2H, s, CH_2Ph), 3.40 (2H, t, $J = 6.4$ Hz, H6′), 3.34 (1H, br t, $J = 15.2$, 13.2 Hz, H11α), 3.28–3.23 (1H, m, H_{pip}-4), 3.16 (1H, br d, $J = 15.2$ Hz, H11β), 2.75–2.71 (2H, m, H_{pip}-2α, H_{pip}-6α), 2.68 (1H, dm, $J = 15.6$ Hz, H4α), 2.51–2.41 (2H, m, H1′), 2.13–2.08 (2H, m, H_{pip}-2β, H_{pip}-6β), 2.05–1.97 (2H, m, H12α, H4β), 1.88–1.84 (2H, m, H_{pip}-3α, H_{pip}-5α), 1.61–1.45 (7H, m, H_{pip}-3β, H_{pip}-5β, H5′, H2′, H12β), 1.35–1.26 (4H, m, H4′, H3′). ESI-MS *m/z*: 547.5 $[M + H]^+$.

6.2. Pharmacology

AChE and BChE activities were measured through Ellman's colorimetric method with a slight modification

[28,29]. AChE was prepared from rat cortex homogenate, while BChE from rat serum. In assays, a reaction mixture, with 200 μL containing acetylthiocholine iodide 0.3 mmol/L or butyrylthiocholine iodide 0.4 mmol/L, sodium phosphate buffer (0.1 mmol/L, pH 7.4) 100 μL, cortex homogenate or serum 20 μL, and different concentrations of test compounds 20 μL, was incubated at 37 °C for 15 min. The reaction was terminated by adding 50 μL 3% sodium lauryl sulfate, and then 50 μL 0.2% 5,5′-dithio-bis(2-nitrobenzoic acid) (DTNB) was added to produce the yellow anion of 5-thio-2-nitro-benzoic acid. The rate of color production was measured spectrophotometrically at 450 nm. All assays were performed with at least 7 concentrations of compounds and IC_{50} (nM drug concentration that inhibits 50% cholinesterase activity) was calculated according to the inhibition curve. Galanthamine was applied as a positive drug. All samples were assayed in duplicate.

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