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Potent Acetylcholinesterase Inhibitors: Design, Synthesis, and Structure–Activity Relationships of Bis-interacting Ligands in the Galanthamine Series

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Abstract—New galanthamine derivatives, especially bis-interacting ligands **3**–**5** and **7**–**9** were prepared in order to interact with the catalytic and the peripheral sites of acetylcholinesterase (AChE). The synthesis, the anticholinesterase activities, and the structure–activity relationships of bis-interacting ligands are reported. Compounds **4d**–**e** were found to be more potent than galanthamine and tacrine in inhibiting AChE. © 1998 Elsevier Science Ltd. All rights reserved.

Introduction

The cholinergic hypothesis postulates that memory impairments in patients with Alzheimer's disease (AD) result from a deficit of cholinergic function in the brain.[1] The most important changes observed in the brain of AD patients are a decrease in hippocampal and cortical levels of neurotransmitter acetylcholine and associated enzymes (choline transferase and acetylcholinesterase). One possible approach to treating this disease is to restore the level of acetylcholine by inhibiting acetylcholinesterase with reversible inhibitors. Clinical trials indicate that AChE inhibitors such as tacrine and physostigmine effectively improve memory in some patients. Other cholinesterase inhibitors such as galanthamine **1**[2] have received recent attention. This compound is less potent, but also less toxic than tacrine and physostigmine. Galanthamine, a centrally acting competitive and reversible inhibitor, has been shown to produce significant improvement of cognitive performances in AD patients.[3] Moreover, Nivalin® (galanthamine hydrobromide) has recently received its first approval for the treatment of AD in Austria. A variety of synthetic galanthamine derivatives have been previously described including C-ring derivatives,[4] quaternary ammonium derivatives,[4] or esters and carbamates of 6-*O*-demethylgalanthamine **6**[5] (Scheme 1).

In this paper, we report the synthesis and biological activities of neutral or cationic bis-interacting ligands **3**–**5** and **7**–**9**.[6] Our bis-ligand strategy is based on the crystallographic structure of AChE from *Torpedo californica*.[7] The AChE active site contains a catalytic triad (Ser200, His440, Glu327) located at the bottom of a deep and narrow gorge, $\sim$ 20 Å long, lined with aromatic residues and a subsite, including Trp 84, located near the bottom of the cavity. Trp 84 has been identified as the binding site of the quaternary group of acetylcholine, decamethonium, and edrophonium.[8] In addition, Trp 279 at the peripheral site, located at the opening of the gorge, is involved in the binding of the second quaternary group of decamethonium. The distance between these two tryptophan residues (84 and 279) is 12 Å. We therefore presume that the bis-ligands could simultaneously interact with the active and the peripheral sites (Trp 84 and 279) and thereby optimize the inhibiting potency. Recently, alkyl linked bis-tacrine derivatives have been described to be highly potent inhibitors of acetylcholinesterase.[9]

In order to synthesize bis-interacting ligands **3**–**5** and **7**–**9**, different alkyl linkers $(CH_2)n$ with a terminal ammonium or phthalimido group were connected to the nitrogen of *N*-demethylgalanthamine (norgalanthamine) **2**[10] and to the oxygen of 6-*O*-demethylgalanthamine (sanguinine) **6**. Both these modifications were considered because the binding mode of galanthamine to the active site of AChE has not been elucidated.

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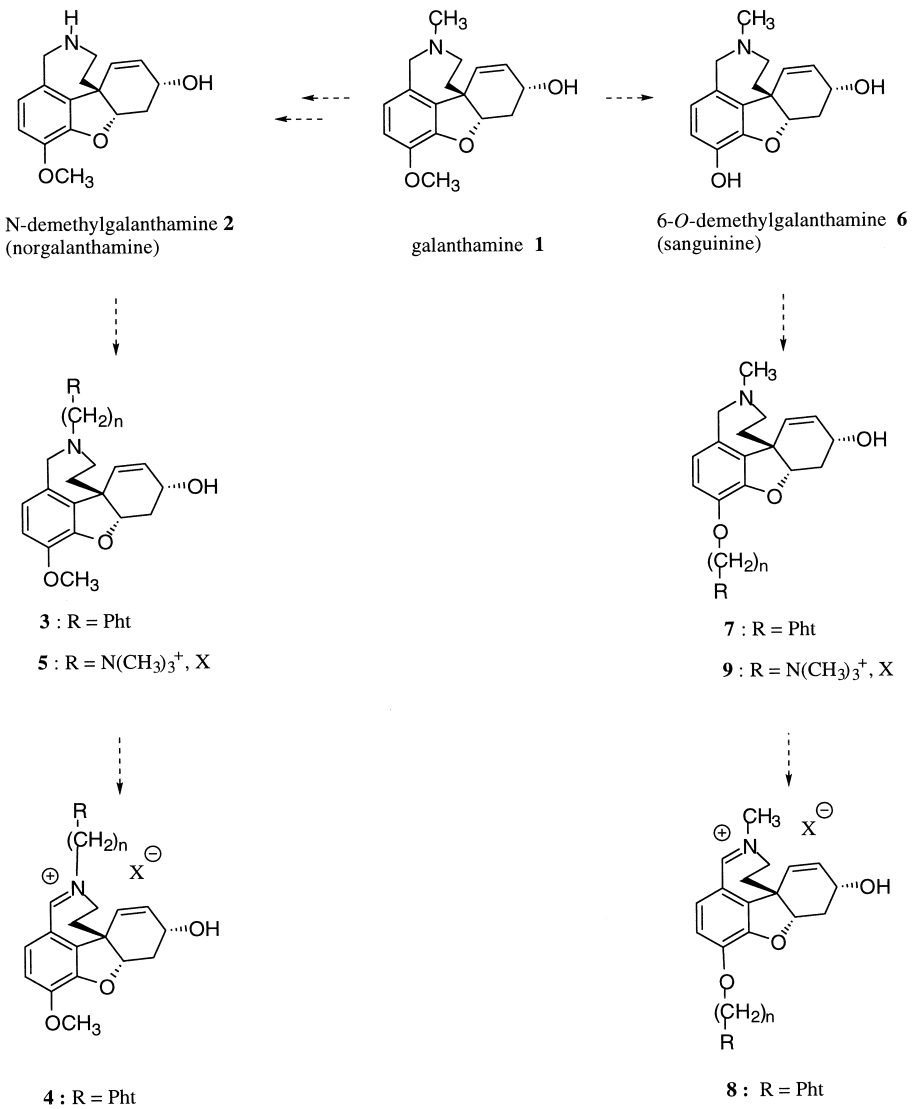
Compounds **3** and **7** were also transformed into their corresponding iminium salts **4** and **8** (Scheme 1). It was hoped that this modification could improve the anticholinesterase activity of the galanthamine moiety of bis-ligands **4** and **8**, since the presence of a permanent positive charge would favor interaction with Trp 84, which is the binding site of the quaternary group of acetylcholine. The greater inhibitory activity of galanthamine methiodide is consistent with this hypothesis.[4]

Chemical Results

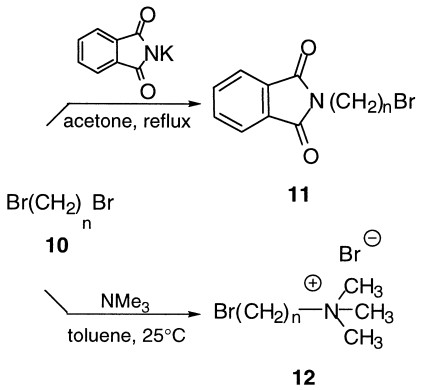
Preparation of phthalimido linkers 11 and ammonium linkers 12. (Scheme 2 and Table 1) Reaction of alkyl bromides **10** with potassium phthalimide or with trimethylamine afforded phthalimido linkers **11** and ammonium linkers **12**, respectively.

Preparation of *N*-substituted derivatives 3–5. (Scheme 3 and Table 2) Preparation of *N*-substituted galanthamine derivatives **3**–**5** requires an efficient *N*-selective demethylation of galanthamine **1** to norgalanthamine **2**. We have recently found that this transformation can be selectively accomplished by a nonclassical Polonovski reaction using iron salts.[10]

Alkylation of norgalanthamine **2** with the phthalimido linkers **11** or with the ammonium linkers **12** afforded the bis-ligands **3** and **5**, respectively, in satisfactory yields.



Scheme 1.



Scheme 2.

The iminium salts **4b–c** were obtained in two steps from the corresponding amino compounds **3b–c** under Polonovski–Potier conditions.[11] Thus, compounds **3b–c** were first converted into their corresponding *N*-oxides **3b′–c′** by reaction with *m*-chloroperbenzoic acid, and subsequent treatment with trifluoroacetic anhydride in dichloromethane at 0 °C afforded the iminium salts **4b–c** (Method A).

The iminium salts **4d–e** were obtained in one step from compounds **3d–e** by reaction of *N*-bromosuccinimide in carbon tetrachloride at room temperature (Method B). The iminium salt **4f** was prepared by reaction of iodine with **3f** (Method C).[12]

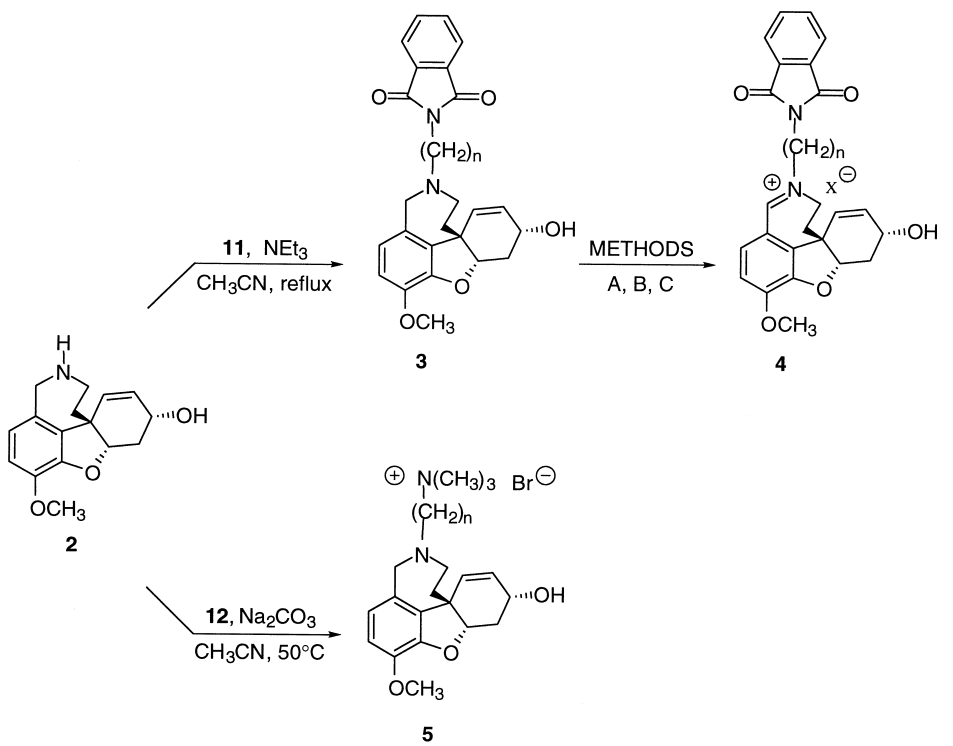
Table 1.

n	Products (yield %)	
3		**12a** (35)
4	**11b***	
6	**11c** (64)	**12c** (14)
8	**11d** (60)	**12d** (30)
10	**11e** (61)	**12e** (22)
12	**11f** (61)	**12f** (24)

*__11b__ ($n=4$) commercially available.

Preparation of *O*-substituted derivatives 7–9. (Scheme 4 and Table 3.) 6-Demethylgalanthamine **6** was used as the precursor of the *O*-substituted derivatives **7–9**. Compound **6** was prepared in high yield (95%) by reaction of galanthamine with L-selectride. This transformation has been previously achieved in presence of NaSEt in 80% yield.[13]

Alkylation of 6-*O*-demethylgalanthamine **6** with phthalimido linkers **11** or with ammonium linkers **12** in dimethylformamide in the presence of cesium carbonate



Scheme 3. Method A for **4b–c**: (i) m-CPBA 1.1 equiv, CH_2Cl_2, 20 °C, 1.5 h; (ii) $(CF_3CO)_2O$, CH_2Cl_2, 0 °C, 6 h. Method B for **4d–e**: NBS-AIBN, CCl_4, 20 °C. Method C for **4f**: (i) I_2, NaOAc, EtOH, reflux, 1 h; (ii) HBr, 0.5% solution in water.

Table 2.

n	Products (yield %)		
3			**5a** (76)
4	**3b** (88)	**4b** (38)*	
6	**3c** (80)	**4c** (49)*	**5c** (71)
8	**3d** (86)	**4d** (52)	**5d** (65)
10	**3e** (84)	**4e** (45)	**5e** (55)
12	**3f** (81)	**4f** (28)	**5f** (63)

*Overall yield for the two steps: **3b–c**→**3b′–c′**→**4b–c**.

Table 3.

n	Products (yield %)		
4	**7b** (70)	**8b** (60)	
8	**7d** (45)	**8d** (57)	**9d** (59)
10	**7e** (48)	**8e** (56)	**9e** (51)
12	**7f** (67)	**8f** (54)	**9f** (50)

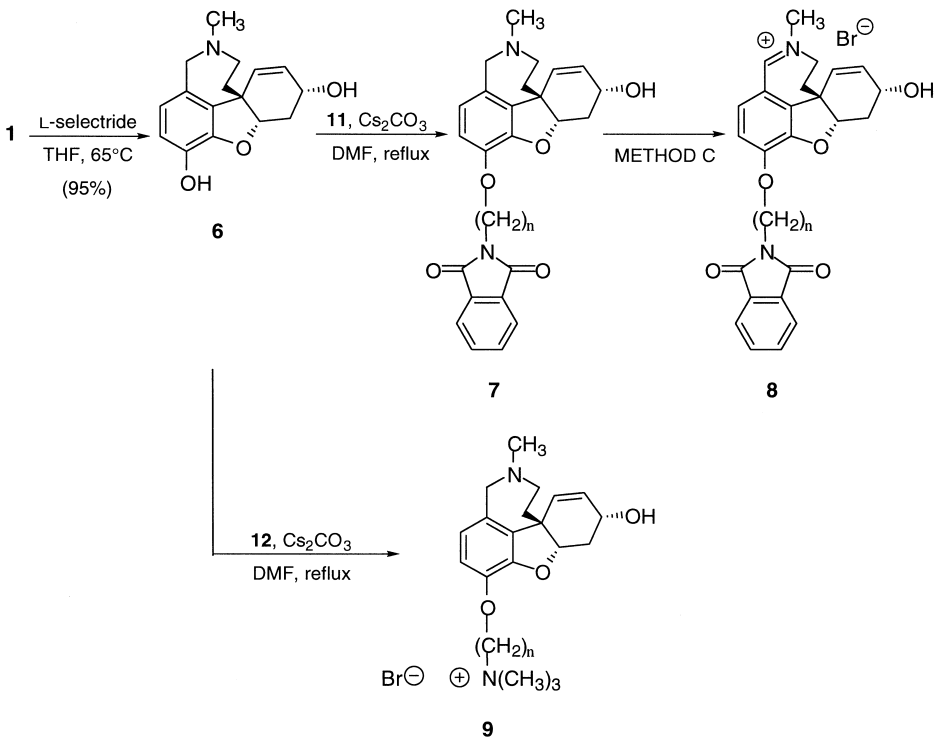
afforded compounds **7** and **9**, respectively. Subsequent treatment of *O*-substituted derivatives **7** with iodine and sodium acetate in refluxing ethanol provided the corresponding iminium salts **8** (Method C).

The bis-functional derivatives **13** which possess a phthalimido group at one end and a quaternary ammonium function at the other were also prepared in order to confirm that the galanthamine moiety present in bis-ligands **3–5** and **7–9** is essential for anticholinesterase activity. Thus, reaction of phthalimido bromides **11** with trimethylamine in toluene afforded the bis-functional linkers **13** in practically quantitative yields (Scheme 5 and Table 4).

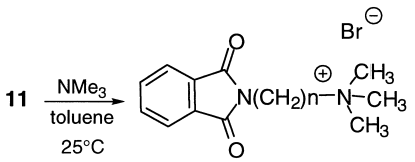
Biological Results and Discussion

In vitro acetylcholinesterase inhibition was determined using the spectroscopic method of Ellman et al.[14] The results are summarized in Table 5 as IC_{50} values. The IC_{50} values of tacrine and galanthamine were determined to be $0.5 \pm 0.04 \times 10^{-7}$ M and $3.6 \pm 0.1 \times 10^{-7}$ M, respectively.

As expected, the length of the alkyl linkers is a key feature for enhancing inhibitory potency. But the best inhibitory activities, for the same length of alkyl chain, depends on the function at the end of the linker as well as on its locality. Thus, the inhibitory activities of the *N*- and *O*-phthalimidoalkyl bis-interacting ligands were optimal in compounds **3d** and **7d** with an eight methylene linker ($n=8$) and decrease when the alkyl chain is further elongated, as in compounds **3e–f** and **7e–f**



Scheme 4.



13

Scheme 5.

Table 4.

n	Products (yield %)
8	**13d** (98)
10	**13e** (96)
12	**13f** (97)

($n=10$ or 12). In comparison, the best inhibiting activities of the *N*- and *O*-alkylammonium bis-interacting ligands were reached in compounds **5f** and **9f** with a twelve methylene linker ($n=12$). We thus presume that when the alkyl chain is of suitable length (from 8 to 12 CH_2), the bis-interacting ligands are able to interact with tryptophan residues Trp 84 and Trp 279. When the alkyl chain is shorter (compounds **5a**, $n=3$, **3b**, **7b**, $n=4$) the phthalimido or the ammonium group probably hinder the optimal fit of the molecule in the narrow gorge, thereby negatively affecting the inhibitory activities of these compounds.

N-Phthalimido compounds **3d** ($n=8$) and **3e** ($n=10$) show an inhibitory activity comparable to galanthamine, whereas *N*-alkylammonium compounds **5d–f** ($n=8$, 10 and 12) are more potent. The inhibiting activities of the *O*-bis-interacting derivatives **7b–f** and **9d–f** are lower than those of galanthamine and their corresponding *N*-bis-interacting derivatives **3b–f** and **5d–f**. These results reveal that linkage is more favorable on the nitrogen atom, suggesting a different binding mode for the *N* and *O*-bis-interacting ligands to AChE (Fig. 1(A): **3** versus **7**). It is also interesting to note that a quaternary ammonium function is more important in determining potency than the phthalimido group (Fig. 1(B): **5** versus **3**). It seems likely that the ammonium group makes close Van der Waals contact with the 'hydrophobic aromatic gorge'. Indeed, theoretical studies have shown that quaternary nitrogens interact preferentially with the π-electrons of aromatic residues, especially Trp.[7,15]

Considering the good inhibitory activities of *N*-alkyl compounds **3** and **5**, the bis-functional linkers **13** were needed to establish the influence of the galanthamine moiety. Thus, compounds **13d–f** were found to be less active than the bis-interacting ligands **3d–f**, **5d–f**, having the same number of methylenes. These results strongly suggest that the galanthamine moiety is essential for the anticholinesterase activity.

Table 5. In vitro AChE inhibition

Compd	*n*	$IC_{50} \pm SD$ (10^{-7} M)
3b	4	20 ± 1.6
3c	6	9.9 ± 2.0
3d	8	$\mathbf{2.8 \pm 0.4}$
3e	10	$\mathbf{3.3 \pm 0.2}$
3f	12	14 ± 0.9
4b	4	4.7 ± 0.4
4c	6	0.4 ± 0.01
4d	8	$\mathbf{0.1 \pm 0.02}$
4e	10	$\mathbf{0.2 \pm 0.01}$
4f	12	1.3 ± 0.09
5a	3	124 ± 6.4
5c	6	17 ± 2.7
5d	8	3.1 ± 0.2
5e	10	1.2 ± 0.5
5f	12	$\mathbf{0.8 \pm 0.1}$
7b	4	161 ± 14
7d	8	25 ± 1.5
7e	10	40 ± 2.1
7f	12	46 ± 8.3
8b	4	23 ± 3.5
8d	8	$\mathbf{0.7 \pm 0.1}$
8e	10	$\mathbf{0.5 \pm 0.09}$
8f	12	3.2 ± 0.1
9d	8	97 ± 11
9e	10	41 ± 0.9
9f	12	13 ± 1.1
13d	8	9.0 ± 3.4
13e	10	52.7 ± 3.1
13f	12	30.3 ± 3.9
14[16]	-	1.4 ± 0.2
Galanthamine		3.6 ± 0.1
Tacrine		0.5 ± 0.04

Concerning the iminium function, we have previously observed that, incorporated on galanthamine itself (i.e. compound **14**),[16] a significant enhancement of enzyme inhibition is obtained. Analogously, introducing this cationic function on the neutral phthalimidoalkyl compounds **3** and **7** conferred on them a substantial gain in inhibitory activity. Thus, compounds **4** and **8** are more active than their neutral parent compounds **3** and **7**. The effect of the length of the alkyl linker is similar to that observed in the series of compounds **3** and **7**. This permanent positive charge on the galanthamine nitrogen atom constitutes the major factor in determining AChE inhibition potency since for compounds **8**, the less favorable linkage to the oxygen atom is largely offset by the presence of the iminium function (Fig. 1(C): **8** versus **7**).

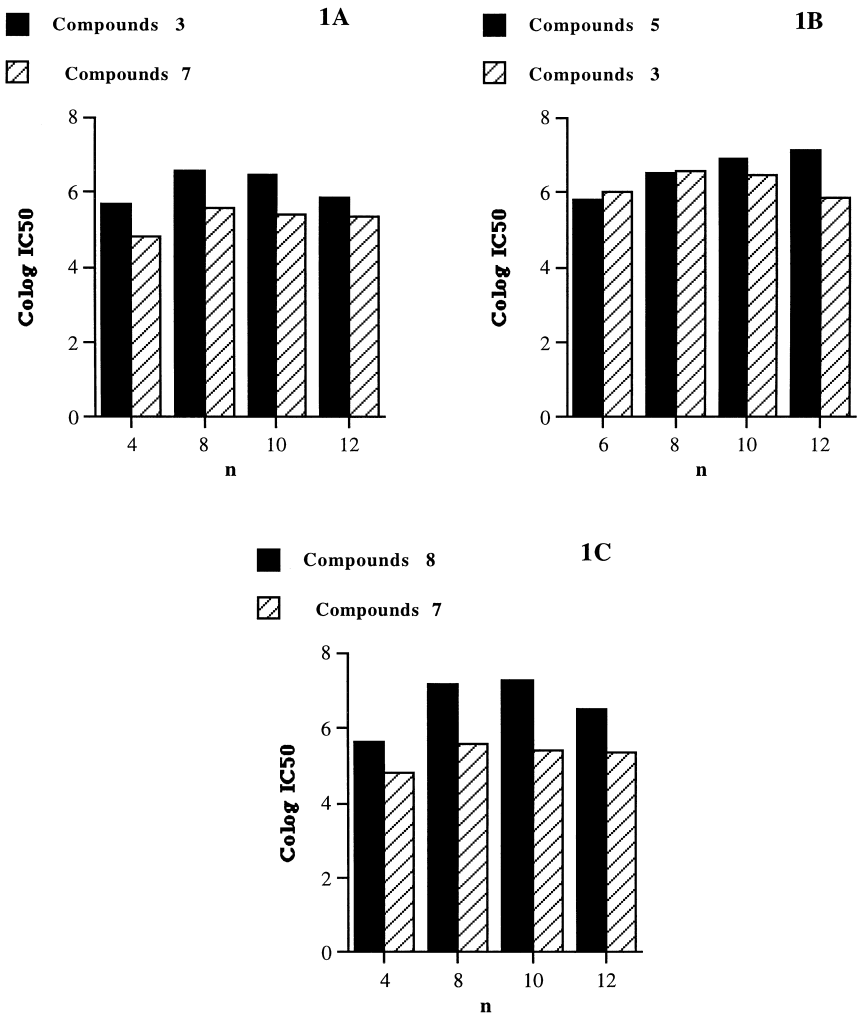


Figure 1. Influence of different parameters on the AChE inhibition as colog IC_{50} (i.e. -log IC_{50}) versus chain length (n). (A) Linkage effect: *N*-phthalimido compounds **3** versus *O*-phthalimido compounds **7**. (B) Terminal group effect: *N*-alkylammonium derivatives **5** versus *N*-phthalimido derivatives **3**. (C) Iminium function effect: charged *O*-phthalimido compounds **8** versus neutral parent compounds **7**.

The charged *N*-bis-interacting derivatives **4d** and **4e** are more potent than galanthamine (36- and 18-fold, respectively) and tacrine (5- and 2.5-fold, respectively), whereas the charged *O*-bis-interacting derivatives **8d** and **8e** are nearly equipotent with tacrine.

Conclusion

New *O*- and *N*-substituted galanthamine derivatives, especially bis-interacting ligands, have been synthesized. These compounds possess an alkyl side chain bearing a terminal phthalimido or ammonium group allowing them to interact simultaneously with the catalytic site and the peripheral site of acetylcholinesterase. Two compounds, **4d** and **4e**, were found to be more potent than both galanthamine and tacrine. These results confirm that introduction of an iminium function and *N*-alkylation of the nitrogen of the galanthamine moiety with a phthalimido alkyl linker ($n=8$ or 10) enhances enzyme inhibition. Such bis-interacting ligands in the galanthamine series constitute a possible new class of potent therapeutic agents for Alzheimer's disease.

Experimental

General

IR spectra were recorded on a Nicolet FT-IR spectrometer. ^{1}H NMR spectra were recorded at 200, 250, and 300 MHz and ^{13}C NMR spectra at 50.3, 62.9, and

75.4 MHz. Chemicals 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), multiplet (m), or broad (br). All purifications were carried out under flash chromatographic conditions on Merck silica gel 60 (70–230 mesh) at medium pressure (200 mbar). TLC was performed on Merck silica gel plates (60 F_{254}) with a fluorescent indicator. Elemental analyses were performed at the ICSN (CNRS, Gif-sur-Yvette). HRMS spectra were recorded with a KRATOS MS-80 instrument. Mass spectra were recorded with a KRATOS MS-80 (FAB), or AEI MS-9 (CI), or AEI MS-50 (EI) instrument. Chemical ionization mass spectra were recorded in the presence of isobutane gas. THF was distilled from sodium/benzophenone complex. CH_3CN was distilled from CaH_2, CH_2Cl_2 from P_2O_5 and NEt_3 from KOH. Organic extracts were washed with brine and dried with anhydrous Na_2SO_4.

Biological assays: in vitro inhibition of acetylcholinesterase

The method of Ellman et al. was followed. The assay solution consisted of a 0.1 M sodium phosphate buffer (pH 8.0), with 100 µL 5,5′-dithiobis-2-nitrobenzoic acid (DTNB, 10 mM), 200 µL acetylthiocholine iodide (7.5 mM), 2 µL AChE (Sigma C 2888 from *electrophorus electricus*) purified on sephadex and 3.3 µL of the tested compound. The final assay volume was 3.305 mL. Enzyme and drugs were added prior to substrate addition. Absorbance changes at 412 nm were monitored for 120 s with a Roucaire Shimadzu UV160 spectrophotometer immediately after mixing at 25 °C. Each drug was evaluated at several concentrations (generally between 10^{-4} M and 10^{-9} M). Values for percent inhibition were calculated relative to a control sample, and the IC_{50} values (concentration required to inhibit control activity by 50%) were determined by log-probit analysis and represent the mean ± standard deviation for three assays.

Chemistry

General Procedure for (3b–f). To a solution of norgalanthamine **2** in acetonitrile was added *N*-(bromoalkyl)-phthalimide **11** (1.2 equiv) and NEt_3 (2 equiv). The reaction mixture was refluxed for 24 h. Evaporation of the solvent gave a residue which was diluted with a saturated aqueous solution of sodium carbonate and extracted with CH_2Cl_2. After a general work up, the combined organic extracts were evaporated. Flash chromatography (elution with CH_2Cl_2/MeOH, 90/10) of the residue gave the corresponding *N*-alkylated compounds.

10-*N*-Demethyl-10-*N*-(4′-phthalimidobutyl)-galanthamine (3b). Reactants: **2** (760 mg, 2.8 mmol) in CH_3CN (50 mL), **11b** (942 mg, 3.3 mmol), and NEt_3 (776 µL, 5.6 mmol) yielded **3b** (1.17 g, 88%). IR ($CHCl_3$) ν: 3650, 3032, 2935, 1771, 1708 cm^{-1}; EIMS 474 ($M^{+\cdot}$) 286, 272; ^1H NMR (300 MHz, CD_3OD, δ) 7.83–7.72 (4H, m, phthalimido), 6.61 (1H, d, $J=8$, H7), 6.54 (1H, d, $J=8.0$, H8), 6.14 (1H, d, $J=10.5$, H1), 5.91 (1H, dd, $J_1=10.5$, $J_2=4.7$, H2), 4.53 (1H, br s, H4a), 4.15 (1H, d, $J=15.0$, H9α), 4.13 (1H, br t, $J=4.7$, H3), 3.77 (1H, d, $J=15.0$, H9β), 3.75 (3H, s, OCH_3), 3.65 (2H, t, $J=8.2$, H4′), 3.34 (1H, br t, $J=13.0$, H11α), 3.14 (1H, dm, $J=13.0$, H11β), 2.57–2.44 (3H, m, H1′, H4α), 2.14–2.01 (2H, m, H12α, H4β), 1.63 (2H, m, H2′), 1.59–1.48 (3H, m, H3′, H12β); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.0 (CO), 146.9 (C6), 144.7 (C5a), 134.5 (CHar meta), 133.6 (C8b), 132.5 (Car), 128.6 (C8a), 127.9 (C2), 127.5 (C1), 123.2 (CHar ortho), 122.1 (C8), 112.2 (C7), 88.2 (C4a), 61.8 (C3), 57.5 (C9), 55.8 (OCH_3), 51.9 (C11), 51.4 (C1′), 47.8 (C4b), 37.8 (C4′), 33.5 (C12), 30.7 (C4), 26.5 (C3′), 24.4 (C2′); Anal. calcd for $C_{28}H_{30}N_2O_5 \cdot 1/2H_2O$: C, 69.57; H, 6.42; N, 5.80. Found: C, 69.51; H, 6.52; N 5.62.

10-*N*-Demethyl-10-*N*-(6′-phthalimidohexyl)-galanthamine (3c). Reactants: **2** (1.17 g, 4.3 mmol) in CH_3CN (40 mL), **11c** (1.40 g, 4.5 mmol), and NEt_3 (1.2 mL, 8.6 mmol) produced **3c** (1.73 g, 80%). IR ($CHCl_3$) ν: 3556, 3431, 3031, 2937, 2862, 1769, 1712, 1619, 1508, 1398, 1220 cm^{-1}; EIMS 502 ($M^{+\cdot}$), 485 $(M\text{-}OH)^+$, 286, 272; ^1H NMR (300 MHz, $CDCl_3$, δ) 7.83 (2H, m, Har ortho), 7.71 (2H, m, Har meta), 6.66 (1H, d, $J=8.3$, H7), 6.61 (1H, d, $J=8.3$, H8), 6.09 (1H, d, $J=10.0$, H1), 6.00 (1H, dd, $J_1=10.0$, $J_2=4.8$, H2), 4.61 (1H, br s, H4a), 4.14 (1H, br t, $J=4.8$, H3), 4.12 (1H, d, $J=15.5$, H9α), 3.83 (3H, s, OCH_3), 3.80 (1H, d, $J=15.5$, H9β), 3.66 (2H, t, $J=7.3$, H6′), 3.35 (1H, br t, $J_1=15.0$, $J_2=13.0$, H11α), 3.16 (1H, br d, $J=15.0$, H11β), 2.68 (1H, dm, $J=16.0$, H4α), 2.52–2.39 (2H, m, H1′), 2.10–1.96 (2H, m, H12α, H4β), 1.72–1.60 (2H, m, H5′), 1.54–1.41 (3H, m, H12β, H2′), 1.38–1.29 (4H, m, H4′, H3′); ^{13}C NMR (75.4 MHz, $CDCl_3$, δ) 169.2 (CO), 146.5 (C6), 144.8 (C5a), 134.6 (CHar meta), 133.9 (C8b), 132.9 (Car), 130.1 (C8a), 128.3 (C2), 127.7 (C1), 123.9 (CHar ortho), 122.8 (C8), 111.9 (C7), 89.4 (C4a), 62.8 (C3), 58.4 (C9), 56.6 (OCH_3), 52.2 (C11), 51.6 (C1′), 49.2 (C4b), 38.7 (C6′), 33.7 (C12), 30.7 (C4), 29.3 (C5′), 27.9 (C2′), 27.6 (C4′), 27.5 (C3′); HMRS calcd for $C_{30}H_{34}N_2O_5$, 502.2467; found, 502.2485.

10-*N*-Demethyl-10-*N*-(8′-phthalimidooctyl)-galanthamine (3d). Reactants: **2** (250 mg, 0.9 mmol) in CH_3CN (35 mL), **11d** (403 mg, 1.19 mmol), and NEt_3 (255 µL, 1.55 mmol) yielded **3d** (420 mg, 86%). IR ($CHCl_3$) ν: 3556, 3463, 3014, 2934, 2858, 1772, 1711 cm^{-1}; CIMS 531 $(MH)^+$, 513 $(M\text{-}H_2O)^+$; ^1H NMR (300 MHz,

$CDCl_3$, δ) 7.84 (2H, m, Har ortho), 7.71 (2H, m, Har meta), 6.66 (1H, d, $J=8.0$, H7), 6.61 (1H, d, $J=8.0$, H8), 6.08 (1H, d, $J=10.0$, H1), 6.00 (1H, dd, $J_1=10.0$, $J_2=4.5$, H2), 4.61 (1H, br s, H4a), 4.14 (1H, br t, $J=4.5$, H3), 4.13 (1H, d, $J=15.0$, H9α), 3.83 (3H, s, OCH_3), 3.80 (1H, d, $J=15.0$, H9β), 3.66 (2H, t, $J=7.0$, H8′), 3.35 (1H, br t, $J_1=14.5$, $J_2=13.0$, H11α), 3.17 (1H, br d, $J=14.5$, H11β), 2.68 (1H, dm, $J=15.5$, H4α), 2.46 (2H, m, H1′), 2.40 (1H, br s, OH), 2.08–1.97 (2H, m, H12α, H4β), 1.65 (2H, m, H7′), 1.54–1.43 (3H, m, H12β, H2′), 1.31 (4H, br s, H6′, H3′), 1.26 (4H, m, H4′, H5′); ^{13}C NMR (75.4 MHz, $CDCl_3$, δ) 168.2 (CO), 145.6 (C6), 143.8 (C5a), 133.6 (CHar meta), 132.9 (C8b), 131.9 (Car), 129.2 (C8a), 127.4 (C2), 126.8 (C1), 122.9 (CHar ortho), 121.8 (C8), 111.0 (C7), 88.5 (C4a), 61.9 (C3), 57.5 (C9), 55.7 (OCH_3), 51.3 (C1′, C11), 48.2 (C4b), 37.8 (C8′), 32.7 (C12), 29.8 (C4), 29.1 (C4′), 28.9 (C3′), 28.3 (C7′), 27.1 (C2′), 27.0 (C5′), 26.6 (C6′); Anal. calcd for $C_{32}H_{38}N_2O_5$: C, 72.43; H, 7.22; N, 5.28. Found: C, 72.09; H, 7.66; N, 4.91.

10-*N*-Demethyl-10-*N*-(10′-phthalimidodecyl)-galanthamine (3e). Reactants: **2** (103 mg, 0.38 mmol) in CH_3CN (15 mL), **11e** (166 mg, 0.45 mmol), and NEt_3 (105 μL, 0.75 mmol) produced **3e** (177 mg, 84%). IR ($CHCl_3$) ν: 3557, 3464, 3012, 2932, 2857, 1771, 1712 cm^{-1}; CIMS 559 $(MH)^+$, 541 $(M\text{-}H_2O)^+$; ^1H NMR (300 MHz, $CDCl_3$, δ) 7.82 (2H, m, Har ortho), 7.70 (2H, m, Har meta), 6.66 (1H, d, $J=8.0$, H7), 6.61 (1H, d, $J=8.0$, H8), 6.09 (1H, d, $J=10.0$, H1), 5.99 (1H, dd, $J_1=10.0$, $J_2=5.0$, H2), 4.61 (1H, br s, H4a), 4.14 (1H, br s, H3), 4.13 (1H, d, $J=15.0$, H9α), 3.82 (3H, s, OCH_3), 3.81 (1H, d, $J=15.0$, H9β), 3.66 (2H, t, $J=7.0$, H10′), 3.35 (1H, br t, $J_1=15.0$, $J_2=13.5$, H11α), 3.17 (1H, br d, $J=15.0$, H11β), 2.67 (1H, dm, $J=14.0$, H4α), 2.47 (2H, m, H1′), 2.07 (1H, m, H12α), 2.01 (1H, ddd, $J_1=14.0$, $J_2=5.0$, $J_3=2.5$, H4β), 1.66 (2H, m, H9′), 1.51 (1H, dm, $J=15.0$, H12β), 1.46 (2H, m, H2′), 1.31 (2H, m, H8′), 1.25 (10H, br s, H3′, H4′, H5′, H6′, H7′); ^{13}C NMR (75.4 MHz, $CDCl_3$, δ) 168.9 (CO), 146.3 (C6), 144.5 (C5a), 134.3 (CHar meta), 133.6 (Car), 132.6 (C8b), 129.9 (C8a), 128.1 (C2), 127.5 (C1), 123.6 (CHar ortho), 122.5 (C8), 111.7 (C7), 89.2 (C4a), 62.5 (C3), 58.2 (C9), 56.4 (OCH_3), 52.1–52.0 (C1′, C11), 48.9 (C4b), 38.5 (C10′), 33.4 (C12), 30.5 (C4), 30.0–29.6 (C3′, C4′, C5′, C6′, C7′), 29.0 (C9′), 27.8 (C2′), 27.3 (C8′); HRMS calcd for $C_{34}H_{43}N_2O_5$ $(MH)^+$, 559.3161; found, 559.3170.

10-*N*-Demethyl-10-*N*-(12′-phthalimidododecyl)-galanthamine (3f). Reactants: **2** (102 mg, 0.37 mmol) in CH_3CN (15 mL), **11f** (177 mg, 0.45 mmol), and NEt_3 (104 μL, 0.75 mmol) yielded **3f** (177 mg, 81%). IR ($CHCl_3$) ν: 3563, 3032, 2932, 1772, 1709, 1588, 1055 cm^{-1}; CIMS: 587 $(MH)^+$, 569 $(M\text{-}H_2O)^+$; ^1H NMR (300 MHz, $CDCl_3$, δ) 7.84 (2H, m, Har ortho), 7.70 (2H, m, Har meta), 6.66 (1H, d, $J=8.0$, H7), 6.61 (1H, d, $J=8.0$, H8), 6.09 (1H, d, $J=10.0$, H1), 6.00 (1H, dd, $J_1=10.0$, $J_2=5.0$, H2), 4.61 (1H, br s, H4a), 4.14 (1H, br t, $J=4.5$, H3), 4.13 (1H, d, $J=15.0$, H9α), 3.83 (3H, s, OCH_3), 3.82 (1H, d, $J=15.0$, H9β), 3.67 (2H, t, $J=7.0$, H12′), 3.36 (1H, br t, $J_1=15.0$, $J_2=13.0$, H11α), 3.18 (1H, br d, $J=15.0$, H11β), 2.68 (1H, dm, $J=15.5$, H4α), 2.46 (3H, m, OH, H1′), 2.07 (1H, m, H12α), 2.00 (1H, ddd, $J_1=15.5$, $J_2=5.0$, $J_3=2.5$, H4β), 1.66 (2H, m, H11′), 1.54–1.45 (3H, m, H12β, H2′), 1.31 (2H, m, H10′), 1.24 (14H, br s, H3′, H4′, H5′, H6′, H7′, H8′, H9′); ^{13}C NMR (75.4 MHz, $CDCl_3$, δ) 167.9 (CO), 145.3 (C6), 143.5 (C5a), 133.3 (CHar meta), 132.6 (C8b), 131.7 (Car), 128.8 (C8a), 127.1 (C2), 126.5 (C1), 122.6 (CHar ortho), 121.5 (C8), 110.7 (C7), 88.2 (C4a), 61.5 (C3), 57.2 (C9), 55.4 (OCH_3), 51.1–51.0 (C1′, C11), 47.9 (C4b), 37.5 (C12′), 32.5 (C12), 29.5 (C4), 29.0 (C4′, C5′, C6′, C7′, C8′, C9′), 28.6 (C3′), 28.1 (C11′), 26.9 (C2′), 26.3 (C10′); HRMS calcd for $C_{36}H_{47}N_2O_5$, 587.3473; found, 587.3498.

General procedure for (4b–c). To a solution of **3b** or **3c** in dry CH_2Cl_2 was added m-CPBA (1.1 equiv). The reaction mixture was stirred at room temperature for 1.5 h and evaporated. Flash chromatography (elution with CH_2Cl_2/MeOH, 90/10; then CH_2Cl_2/MeOH/NH_3, 90/9/1) of the residue afforded the corresponding N-oxide as a white powder after trituration with ether.

10-*N*-Demethyl-10-*N*-(4′-phthalimidobutyl)-galanthamine N-oxide (3b′). Reactants: **3b** (203 mg, 0.43 mmol) in CH_2Cl_2 (10 mL) and m-CPBA (116 mg, 0.67 mmol) yielded **3b′** (180 mg, 86%). IR ($CHCl_3$) ν: 3406, 3031, 2937, 1775, 1712, 1219 cm^{-1}; EIMS: 490 $(M^{+\cdot})$, 474 (M-O), 286, 272; ^1H NMR (300 MHz, $CDCl_3$, δ) 7.80 (2H, m, Har ortho), 7.72 (2H, m, Har meta), 6.63 (2H, m, H8, H7), 6.08 (2H, br s, H2, H1), 4.84 (1H, br d, $J=14.0$, H9a), 4.69 (1H, br s, H4a), 4,41 (1H, d, $J=14.0$, H9β), 4.18 (1H, br t, $J=5.0$, H3), 4.06 (1H, m, H11α), 3.82 (3H, s, OCH_3), 3.71–3.62 (3H, m, H11β, H4′), 3.11 (2H, m, H1′), 2.71 (1H, dm, $J=15.0$, H4α), 2.08–1.90 (5H, m, H12, H4β, H2′), 1.67 (2H, m, H3′); ^{13}C NMR (75.4 MHz, $CDCl_3$, δ) 168.3 (CO), 146.3 (C6, C5a), 134.0 (CHar meta), 131.9 (C8b), 129.9 (C2, C1), 124.4 (Car), 123.7 (C8), 123.2 (CHar ortho), 119.3 (C8a), 112.0 (C7), 88.7 (C4a), 73.5 (C9), 67.6 (C11), 61.4 (C3), 55.9 (OCH_3), 50.1 (C1′), 46.3 (C4b), 37.3 (C4′), 33.9 (C12), 30.1 (C4), 25.8 (C2′), 19.1 (C3′); HRMS calcd for $C_{28}H_{31}N_2O_6$ $(MH)^+$, 491.2174; found, 491.2147.

10-*N*-Demethyl-10-*N*-(6′-phthalimidohexyl)-galanthamine N-oxide (3c′). Reactants: **3c** (55 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) and m-CPBA (30 mg, 0.17 mmol) produced **3c′** (48 mg, 85%). EIMS 518 $(M^{+\cdot})$, 502 (M-O), 286, 272; ^1H NMR (200 MHz, CD_3OD, δ) 7.85–7.75 (4H, m, phthalimido), 6.82 (2H, m, H8, H7), 6.23 (1H,

br d, $J=10.0$, H1), 6.03 (1H, dd, $J_1=10.0$, $J_2=4.0$, H2), 4.71 (1H, br d, $J=14.3$, H9α), 4.66 (1H, br s, H4a), 4.38 (1H, br d, $J=14.3$, H9β), 4.19 (1H, br s, H3), 3.98 (1H, m, H11α), 3.79 (3H, s, OCH_3), 3.76 (1H, m, H11β), 3.60 (2H, br t, $J=7.0$, H6′), 3.06 (2H, m, H1′), 2.54 (1H, dm, $J=15.5$, H4α), 2.14 (1H, ddd, $J_1=15.5$, $J_2=5.5$, $J_3=3.5$, H4β), 2.02–1.76 (4H, m, H12, H5′), 1.61 (2H, m, H2′), 1.29 (4H, br s, H4′, H3′).

To a solution of *N*-oxide **3b′** or **3c′** in CH_2Cl_2 was added freshly distilled trifluoroacetic anhydride. The mixture was stirred at 0 °C for 6 h then allowed to come to room temperature. Evaporation of the solvent gave a residue which was purified by flash chromatography (elution with CH_2Cl_2/MeOH/NH_3, 95/5/1) to provide the corresponding iminium salts.

9-Dehydro-10-*N*-demethyl-10-*N*-(4′-phthalimidobutyl)-galanthaminium trifluoroacetate (4b). Reactants: **3b′** (178 mg, 0.36 mmol) in CH_2Cl_2 (10 mL) and $(CF_3CO)_2O$ (154 μL, 1.09 mmol) yielded **4b** (79 mg, 44%). IR ($CHCl_3$) ν: 3408, 3021, 2931, 2856, 1775, 1712, 1609, 1394, 1225, 1141 cm^{-1}; EIMS 473 $(M)^+$, 454 $(M\text{-}H_2O)^+$; ^1H NMR (250 MHz, $CDCl_3+CF_3COOH$, δ) 8.77 (1H, s, H9), 7.83 (2H, m, Har ortho), 7.74 (2H, m, Har meta), 7.59 (1H, d, $J=8.7$, H8), 7.02 (1H, d, $J=8.7$, H7), 6.14 (1H, dd, $J_1=10.0$, $J_2=4.7$, H2), 5.62 (1H, d, $J=10.0$, H1), 4.81 (1H, br s, H4a), 4.38 (1H, br t, $J=4.7$, H3), 4.14 (2H, m, H11), 3.98 (3H, s, OCH_3), 3.77 (2H, br t, $J=6.7$, H4′), 2.78 (1H, dm, $J=16.0$, H4α), 2.26 (2H, m, H1′), 2.18–2.09 (2H, m, H12α, H4β), 2.00 (2H, m, H2′), 1.88–1.66 (3H, m, H3′, H12β). ^{13}C NMR (62.9 MHz, $CDCl_3+CF_3COOH$, δ) 169.0 (CO), 168.0 (C9), 160.3 ($COCF_3$), 153.5 (C6), 146.7 (C5a), 136.2 (C8), 134.5 (CHar meta), 134.4 (C8b), 131.8 (Car), 129.4 (C2), 126.8 (C1), 123.6 (CHar ortho), 114.5 (C8a), 113.3 (C7), 88.7 (C4a), 64.5 (C1′), 61.5 (C3), 56.9 (OCH_3), 52.5 (C11), 50.5 (C4b), 36.5 (C4′), 31.7 (C12), 28.9 (C4), 25.6 (C2′), 25.2 (C3′); HRMS calcd for $C_{28}H_{29}N_2O_5$, 473.2069; found, 473.2061.

9-Dehydro-10-*N*-demethyl-10-*N*-(6′-phthalimidohexyl)-galanthaminium trifluoroacetate (4c). Reactants: **3c′** (48 mg, 0.09 mmol) in CH_2Cl_2 (5 mL), $(CF_3CO)_2O$ (52 μL, 0.37 mmol). **4c** (28 mg, 58%). IR ($CHCl_3$) ν: 3462, 3022, 2937, 2862, 1775, 1712, 1609, 1512, 1398, 1225 cm^{-1}; FABMS 501 $(M)^+$; ^1H NMR (300 MHz, $CDCl_3+CF_3COOH$, δ) 8.95 (1H, s, H9), 7.85 (2H, m, Har ortho), 7.78 (2H, m, Har meta), 7.69 (1H, d, $J=8.5$, H8), 7.02 (1H, d, $J=8.5$, H7), 6.15 (1H, dd, $J_1=10.0$, $J_2=5.0$, H2), 5.60 (1H, d, $J=10.0$, H1), 4.78 (1H, br s, H4a), 4.25 (1H, br t, H3), 4.11 (2H, m, H11), 3.98 (3H, s, OCH_3), 3.66 (2H, t, $J=7.0$, H6′), 2.77 (1H, dm, $J=16.0$, H4α), 2.25 (2H, m, H1′), 2.12 (1H, dm, $J=16.0$, H4β), 1.95 (2H, m, H5′), 1.78–1.63 (3H, m, H12α, H2′), 1.52–1.35 (5H, m, H12β, H4′, H3′); ^{13}C NMR (75.4 MHz, $CDCl_3$, δ) 168.5 (CO), 168.3 (C9), 162.9 ($COCF_3$), 153.2 (C6), 146.5 (C5a), 137.0 (C8b), 136.0 (C8), 134.0 (CHar meta), 132.0 (Car), 130.3 (C2), 126.0 (C1), 123.2 (CHar ortho), 114.7 (C8a), 113.0 (C7), 88.9 (C4a), 65.3 (C1′), 61.0 (C3), 56.7 (OCH_3), 52.2 (C11), 46.8 (C4b), 37.3 (C6′), 31.8 (C12), 29.7 (C4), 28.2 (C5′), 28.0 (C2′), 25.9 (C4′), 25.4 (C3′).

General procedure for compounds (4d–e). To a solution of compound **3** in CCl_4 shielded from light was added *N*-bromosuccinimide (1.3 equiv) and 5% AIBN at room temperature. After 24 h, water was added and was extracted with CH_2Cl_2. After general workup, the combined organic extracts were evaporated. Purification by preparative TLC (elution with CH_2Cl_2/MeOH/0.5% HBr, 91/9/0.1) of the residue provided the corresponding iminium salts.

9-Dehydro-10-*N*-demethyl-10-*N*-(8′-phthalimidooctyl)-galanthaminium bromide (4d). Reactants: **3d** (72 mg, 0.13 mmol) in CCl_4 (2 mL) with NBS (32 mg, 0.18 mmol) and AIBN (1 mg, 0.007 mmol) yielded **4d** (43 mg, 52%). IR ($CHCl_3$) ν: 3450, 3020, 2937, 2856, 1710, 1609, 1137, 1117 cm^{-1}; FABMS 529 $(M)^+$; ^1H NMR (300 MHz, $CDCl_3$, δ) 10.09 (1H, s, H9), 8.03 (1H, d, $J=8.5$, H8), 7.83 (2H, m, Har ortho), 7.71 (2H, m, Har meta), 6.90 (1H, d, $J=8.5$, H7), 6.19 (1H, dd, $J_1=10.0$, $J_2=5.0$, H2), 5.85 (1H, d, $J=10.0$, H1), 4.78 (1H, br s, H4a), 4.44–4.34 (3H, m, H1′, H11α), 4.23 (1H, br t, $J=4.5$, H3), 4.15 (1H, dm, $J_1=17.0$, $J_2=4.0$, H11β), 3.95 (s, 3H, OCH_3), 3.65 (2H, t, $J=7.0$, H8′), 2.74 (1H, dm, $J=16.0$, H4α), 2.23 (2H, m, H12), 2.09 (1H, dm, $J_1=16.0$, $J_2=5.0$, $J_3=2.0$, H4β), 1.92 (2H, m, H2′), 1.65 (2H, m, H7′), 1.42 (2H, m, H3′), 1.33 (6H, m, H4′, H5′ H6′); ^{13}C NMR (75.4 MHz, $CDCl_3$, δ) 168.9 (CO, C9), 153.0 (C6), 146.7 (C5a), 137.4 (C8b), 136.6 (C8), 134.5 (CHar meta), 132.6 (Car), 130.7 (C2), 127.1 (C1), 123.7 (CHar ortho), 115.8 (C8a), 111.8 (C7), 89.3 (C4a), 65.4 (C1′), 61.5 (C3), 57.3 (OCH_3), 53.0 (C11), 47.4 (C4b), 38.4 (C8′), 32.5 (C12), 30.0 (C4), 29.5–29.3 (C4′, C5′), 29.1–29.0 (C2′, C7′), 27.1 (C6′), 26.7 (C3′); HRMS calcd for $C_{32}H_{37}N_2O_5$, 529.2702; found, 529.2699.

9-Dehydro-10-*N*-demethyl-10-*N*-(10′-phthalimidodecyl)-galanthaminium bromide (4e). Reactants: **3e** (89 mg, 0.16 mmol) in CCl_4 (2.5 mL), NBS (37 mg, 0.21 mmol), AIBN (1 mg, 0.008 mmol). **4e** (46 mg, 45%). IR ($CHCl_3$) ν: 3408, 3020, 2935, 2865, 1710, 1609, 1137, 1116 cm^{-1}; FABMS 557 $(M)^+$; ^1H NMR (300 MHz, $CDCl_3$, δ) 10.7 (1H, s, H9), 8.06 (1H, d, $J=8.5$, H8), 7.83 (2H, m, Har ortho), 7.71 (2H, m, Har meta), 6.91 (1H, d, $J=8.5$, H7), 6.19 (1H, dd, $J_1=10.0$, $J_2=5.0$, H2), 5.81 (1H, d, $J=10.0$, H1), 4.78 (1H, br s, H4a), 4.45–4.33 (3H, m, H1′, H11α), 4.23 (1H, br s, H3), 4.13 (1H, dm, $J=17.0$, H11β), 3.97 (3H, s, OCH_3), 3.66 (2H, t, $J=7.0$, H10′), 2.75 (1H, dm, $J=16.0$, H4α), 2.23 (2H, m, H12), 2.09

(1H, dm, $J_1 = 16.0$, $J_2 = 5.0$, $J_3 = 2.0$, H4β), 1.91 (2H, m, H2′), 1.65 (2H, m, H9′), 1.41 (2H, m, H3′), 1.30–1.26 (10H, m, H4′, H5′, H6′, H7′, H8′); ^{13}C NMR (75.4 MHz, $CDCl_3$, δ) 169.2 (CO), 169.0 (C9), 153.2 (C6), 146.8 (C5a), 137.5 (C8b), 136.8 (C8), 134.6 (CHar meta), 132.8 (Car), 130.8 (C2), 127.3 (C1), 123.8 (CHar ortho), 116.0 (C8a), 113.3 (C7), 89.5 (C4a), 65.6 (C1′), 61.7 (C3), 57.4 (OCH_3), 53.2 (C11), 47.6 (C4b), 38.7 (C10′), 32.7 (C12), 30.2 (C4), 30.0–29.7 (C4′, C5′, C6′, C7′), 29.3–29.2 (C2′, C9′), 27.4 (C8′), 26.9 (C3′); HRMS calcd for $C_{34}H_{41}N_2O_5$, 557.3015; found, 557.3024.

9-Dehydro-10-*N*-demethyl-10-*N*-(12′-phthalimidododecyl)-galanthaminium bromide (4f). To a solution of **3f** (73 mg, 0.12 mmol) in EtOH (5 mL) was added sodium acetate (13 mg, 0.16 mmol) and iodine (63 mg, 0.25 mmol). The reaction mixture was refluxed for 1 h, then cooled to room temperature. A 10% aq solution of sodium bisulfite was added. The solvents were removed in vacuo. Saturated solution of sodium carbonate was added to the residue and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with a 0.5% aq solution of HBr. After a general workup, the combined organic extracts were evaporated. Flash chromatography (elution with CH_2Cl_2/MeOH/1% HBr, 80/19/1) of the residue afforded **4f** (23 mg, 28%) as a yellow oil. IR ($CHCl_3$) ν: 3575, 3025, 2933, 1711, 1609 cm^{-1}; FABMS 585 $(M)^+$, 567 $(M\text{-}H_2O)^+$, 515; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 10.03 (1H, s, H9), 8.03 (1H, d, $J = 8.5$, H8), 7.83 (2H, m, Har ortho), 7.71 (2H, m, Har meta), 6.90 (1H, d, $J = 8.5$, H7), 6.18 (1H, dd, $J_1 = 10.0$, $J_2 = 5.0$, H2), 5.86 (1H, d, $J = 10.0$, H1), 4.78 (1H, br s, H4a), 4.47–4.34 (3H, m, H1′, H11α), 4.22 (1H, br s, H3), 4.18 (1H, dm, $J = 17.0$, H11β), 3.96 (3H, s, OCH_3), 3.66 (2H, t, $J = 7.0$, H12′), 2.74 (1H, dm, $J = 16.0$, H4α), 2.39 (1H, br s, OH), 2.23 (2H, m, H12), 2.10 (1H, dm, $J_1 = 16.0$, $J_2 = 5.0$, $J_3 = 2.0$, H4β), 1.91 (2H, m, H2′), 1.66 (2H, m, H11′), 1.40–1.30 (4H, m, H3′, H10′), 1.23 (12H, br s, H4′, H5′, H6′, H7′, H8′, H9′); ^{13}C NMR (75.4 MHz, $CDCl_3$, δ) 168.3 (CO), 168.1 (C9), 152.3 (C6), 145.9 (C5a), 136.6 (C8b), 136.1 (C8), 133.7 (CHar meta), 132.0 (Car), 130.0 (C2), 126.4 (C1), 123.0 (CHar ortho), 115.1 (C8a), 112.5 (C7), 88.7 (C4a), 64.8 (C1′), 60.9 (C3), 56.5 (OCH_3), 52.3 (C11), 46.7 (C4b), 37.9 (C12′), 31.8 (C12), 29.2 (C4), 29.1–29.0 (C4′, C5′, C6′, C7′, C8′), 28.5 (C11′, C2′), 26.6 (C9′), 26.1 (C3′); HRMS calcd for $C_{36}H_{45}N_2O_5$, 585.3328; found, 585.3328.

General procedure for bromoalkyl trimethylammonium bromide (5a) and (5c–e). To a solution of norgalanthamine **2** in acetonitrile was added Na_2CO_3 (2.5 equiv) and *N*-(bromoalkyl)-trimethylammonium bromide **12** (1.1 equiv). After stirring at 50 °C for 20 h, the reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated to dryness. Purification of the residue by preparative TLC (elution with CH_2Cl_2/MeOH/H_2O, 50/40/10) provided the corresponding alkylated compound as a white solid.

10-*N*-Demethyl-10-*N*-(3′-trimethylammoniumpropyl) galanthamine bromide (5a). Reactants: **2** (39 mg, 0.14 mmol) in CH_3CN (5 mL) and Na_2CO_3 (38 mg, 0.36 mmol) with **12a** (41 mg, 0.16 mmol) yielded **5a** (49 mg, 76%). IR ν: 3396, 3031, 2938, 2837, 1622, 1508, 1224 cm^{-1}; FABMS 373 $(M)^+$, 314 $(M\text{-}N(CH_3)_3)^+$; ^{1}H NMR (250 MHz, CD_3OD, δ) 6.78 (2H, s, H8, H7), 6.19 (1H, d, $J = 10.0$, H1), 5.95 (1H, dd, $J_1 = 10.0$, $J_2 = 4.5$, H2), 4.59 (1H, br s, H4a), 4.42 (1H, d, $J = 15.0$, H9α), 4.17 (1H, br s, H3), 4.06 (1H, d, $J = 15.0$, H9β), 3.81 (3H, s, OCH_3), 3.57–3.37 (4H, m, H11, H3′), 3.18 (9H, s, $N(CH_3)_3$), 2.82 (2H, br t, $J = 7.0$, H1′), 2.49 (1H, dm, $J = 16.0$, H4α), 2.20–2.03 (4H, m, H12α, H4β, H2′), 1.71 (1H, dm, $J = 14.5$, H12β); ^{13}C NMR (62.9 MHz, CD_3OD, δ) 147.8 (C6), 145.5 (C5a), 134.4 (C8b), 130.1 (C8a), 128.7 (C2), 128.3 (C1), 122.9 (C8), 113.1 (C7), 89.1 (C4a), 66.3 (C3′), 62.5 (C3), 58.2 (C9), 56.7 (OCH_3), 53.7 ($N(CH_3)_3$), 53.6 (C1′), 52.9 (C11), 49.1 (C4b), 34.7 (C12), 31.6 (C4), 21.7 (C2′); HRMS calcd for $C_{22}H_{33}N_2O_5$, 373.2491; found, 373.2491.

10-*N*-Demethyl-10-*N*-(6′-trimethylammoniumhexyl) galanthamine bromide (5c). Reactants: **2** (39 mg, 0.14 mmol) in CH_3CN (5 mL), Na_2CO_3 (38 mg, 0.36 mmol), and **12c** (48 mg, 0.16 mmol) produced **5c** (50 mg, 71%). IR ν: 3394, 3022, 2937, 2856, 1626, 1224 cm^{-1}; FABMS: 415 $(M)^+$; ^{1}H NMR (250 MHz, CD_3OD, δ) 6.80 (1H, d, $J = 8.5$, H7), 6.75 (1H, d, $J = 8.5$, H8), 6.18 (1H, d, $J = 10.5$, H1), 5.97 (1H, dd, $J_1 = 10.5$, $J_2 = 4.5$, H2), 4.61 (1H, br s, H4a), 4.45 (1H, d, $J = 15.0$, H9α), 4.17 (1H, br t, $J = 4.5$, H3), 4.11 (1H, d, $J = 15.0$, H9β), 3.81 (3H, s, OCH_3), 3.59 (1H, br t, $J = 13.0$, H11α), 3.46–3.36 (3H, m, H11β, H6′), 3.13 (9H, s, $N(CH_3)_3$), 2.84 (2H, m, H1′), 2.49 (1H, dm, $J = 16.0$, H4α), 2.24–2.08 (2H, m, H12α, H4β), 1.84–1.63 (5H, m, H12β, H5′, H2′), 1.28 (4H, br s, H3′, H4′); ^{13}C NMR (62.9 MHz, $CDCl_3$, δ) 147.9 (C6), 146.2 (C5a), 134.4 (C8b), 129.8 (C8a), 128.9 (C2), 128.0 (C1), 123.6 (C8), 113.3 (C7), 88.9 (C4a), 67.6 (C6′), 62.3 (C3), 58.3 (C9), 56.7 (OCH_3), 53.7 (C1′), 53.6 ($N(CH_3)_3$), 53.1 (C11), 49.7 (C4b), 34.1 (C12), 31.5 (C4), 27.5 and 26.8 (C3′, C4′), 26.5 (C2′), 23.7 (C5′); HRMS calcd for $C_{25}H_{39}N_2O_5$, 415.2961; found, 415.2956.

10-*N*-Demethyl-10-*N*-(8′-trimethylammoniumoctyl) galanthamine bromide (5d). Reactants: **2** (41 mg, 0.15 mmol) in CH_3CN (5 mL), Na_2CO_3 (40 mg, 0.37 mmol), and **12d** (55 mg, 0.16 mmol) produced **5d** (51 mg, 65%). IR ν: 3385, 3031, 2938, 2837, 1626, 1509, 1223 cm^{-1}; FABMS: 443 $(M)^+$; ^{1}H NMR (250 MHz, CD_3OD, δ) 6.80 (1H, d, $J = 8.3$, H7), 6.74 (1H, d, $J = 8.3$, H8), 6.19 (1H, d, $J = 10.5$, H1), 5.96 (1H, dd, $J_1 = 10.5$, $J_2 = 5.0$, H2), 4.61 (1H, br s, H4a), 4.39 (1H, d, $J = 15.0$, H9α), 4.18 (1H,

br t, $J=5.0$, H3), 4.07 (1H, d, $J=15.0$, H9β), 3.82 (3H, s, OCH_3), 3.55 (1H, br t, $J_1=15.0$, $J_2=12.8$, H11α), 3.42–3.36 (3H, m, H11β, H8′), 3.15 (9H, s, $N(CH_3)_3$), 2.77 (2H, m, H1′), 2.49 (1H, dm, $J=16.0$, H4α), 2.22–2.10 (2H, m, H12α, H4β), 1.85–1.70 (3H, m, H7′, H12β), 1.64 (2H, m, H2′), 1.38 (8H, m, H3′, H4′, H5′, H6′); ^{13}C NMR (62.9 MHz, $CDCl_3$, δ) 147.9 (C6), 146.3 (C5a), 134.4 (C8b), 129.1 (C2), 127.9 (C1), 125.2 (C8a), 123.8 (C8), 113.4 (C7), 88.9 (C4a), 67.8 (C8′), 62.2 (C3), 58.3 (C9), 56.7 (OCH_3), 54.1 (C1′), 53.6 ($N(CH_3)_3$), 53.2 (C11), 48.9 (C4b), 34.1 (C12), 31.5 (C4), 30.0, 29.9, 27.9 and 27.1 (C3′, C4′, C5′, C6′), 26.6 (C2′), 23.8 (C7′); HRMS calcd for $C_{27}H_{43}N_2O_3$, 443.3274; found, 443.3279.

10-*N*-Demethyl-10-*N*-(10′-trimethylammoniumdecyl) galanthamine bromide (5e). Reactants: **2** (43 mg, 0.16 mmol) in CH_3CN (5 mL), Na_2CO_3 (42 mg, 0.39 mmol), and **12e** (62 mg, 0.17 mmol) yielded **5e** (48 mg, 55%). IR ($CHCl_3$) ν: 3423, 3025, 2934, 2858, 1168, 1133, 1110, 1055 cm^{-1}; FABMS 471 $(M)^+$; ^1H NMR (250 MHz, CD_3OD, δ) 6.79 (1H, d, $J=8.3$, H7), 6.72 (1H, d, $J=8.3$, H8), 6.18 (1H, d, $J=10.3$, H1), 5.96 (1H, dd, $J_1=10.2$, $J_2=4.5$, H2), 4.60 (1H, br t, H4a), 4.37 (1H, d, $J=14.8$, H9α), 4.17 (1H, br t, $J=4.5$, H3), 4.03 (1H, d, $J=14.8$, H9β), 3.82 (3H, s, OCH_3), 3.53 (1H, br t, $J_1=15.0$, $J_2=3.0$, H11α), 3.39–3.33 (3H, m, H11β, H10′), 3.14 (9H, s, $N(CH_3)_3$), 2.75–2.69 (2H, m, H1′), 2.49 (1H, dm, $J=16.0$, H4α), 2.20–2.09 (2H, m, H12α, H4β), 1.84–1.70 (3H, m, H9′, H12β), 1.61 (2H, m, H2′), 1.37 (4H, br s, H8′, H3′), 1.32 (8H, m, H4′, H5′, H6′, H7′); ^{13}C NMR (75.4 MHz, CD_3OD, δ) 148.8 (C6), 147.0 (C5a), 135.4 (C8b), 129.9 (C2), 129.1 (C1), 127.2 (C8a), 124.6 (C8), 114.3 (C7), 89.9 (C4a), 68.8 (C10′), 63.3 (C3), 59.2 (C9), 57.7 (OCH_3), 54.9 (C1′), 54.6 ($N(CH_3)_3$), 54.1 (C11), 49.1 (C4b), 35.1 (C12), 32.5 (C4), 31.3 and 31.0 (C4′, C5′, C6′, C7′), 29.0 (C3′), 28.2 (C8′), 27.8 (C2′), 24.9 (C9′); HRMS calcd for $C_{29}H_{47}N_2O_3$, 471.3587; found, 471.3587.

10-*N*-Demethyl-10-*N*-(12′-trimethylammoniumdodecyl) galanthamine bromide (5f). Reactants: **2** (50 mg, 0.18 mmol) in CH_3CN (5 mL), Na_2CO_3 (49 mg, 0.46 mmol), and **12f** (78 mg, 0.20 mmol) produced **5f** (67 mg, 63%). IR ν: 3392, 3021, 2933, 2857, 1626, 1509, 1225 cm^{-1}; FABMS 499 $(M)^+$; ^1H NMR (300 MHz, CD_3OD, δ) 6.76 (1H, d, $J=8.3$, H7), 6.67 (1H, d, $J=8.3$, H8), 6.17 (1H, d, $J=10.3$, H1), 5.93 (1H, dd, $J_1=10.3$, $J_2=4.8$, H2), 4.56 (1H, br s, H4a), 4.24 (1H, d, $J=15.8$, H9α), 4.17 (1H, br t, $J=4.8$, H3), 3.89 (1H, d, $J=15.8$, H9β), 3.81 (3H, s, OCH_3), 3.46–3.24 (4H, m, H11, H12′), 3.15 (9H, s, $N(CH_3)_3$), 2.56 (2H, m, H1′), 2.48 (1H, dm, $J=16.0$, H4α), 2.18–2.02 (2H, m, H12α, H4β), 1.77 (2H, m, H11′), 1.63 (1H, dm, $J=14.5$, H12β), 1.52 (2H, m, H2′), 1.38 (4H, br s, H3′, H10′), 1.27 (12H, m, H4′, H5′, H6′, H7′, H8′, H9′); ^{13}C NMR (75.4 MHz, CD_3OD, δ) 147.8 (C6), 145.9 (C5a), 134.4 (C8b), 128.7 (C2), 128.3 (C1), 127.2 (C8a), 123.4 (C8), 113.2 (C7), 89.0 (C4a), 67.8 (C12′), 62.3 (C3), 58.3 (C9), 56.6 (OCH_3), 53.7 (C1′), 53.6 ($N(CH_3)_3$), 53.0 (C11), 49.1 (C4b), 34.2 (C12), 31.5 (C4), 30.5–30.4 and 30.2 (C4′, C5′, C6′, C7′, C8′, C9′), 28.2 (C3′), 27.3 (C2′), 27.2 (C10′), 24.9 (C11′); HRMS calcd for $C_{31}H_{51}N_2O_3$, 499.3900; found, 499.3872.

6-*O*-Demethylgalanthamine (6). To a solution of galanthamine **1** (507 mg, 1.77 mmol) in THF (20 mL) was added L-selectride® (1 M solution in tetrahydrofuran 8 mL, 7.95 mmol) at room temperature. The reaction mixture was refluxed for 20 h, then diluted with AcOEt at 0 °C and quenched slowly with water. Evaporation of the combined aq layers afforded a residue, which was purified by flash chromatography (elution with CH_2Cl_2/MeOH/NH_3, 90/9/1) and crystallized in acetone to provide 6-*O*-demethylgalanthamine **6** (460 mg, 95%). Mp 228–230 °C; CIMS 274 $(MH)^+$; ^1H NMR (250 MHz, CD_3OD, δ) 6.57 (1H, d, $J=8.0$, H8), 6.52 (1H, d, $J=8.0$, H7), 6.11 (1H, d, $J=10.5$, H1), 5.91 (1H, dd, $J_1=10.5$, $J_2=5.0$, H2), 4.52 (1H, br s, H4a), 4.15 (1H, br t, $J=4.5$, H3), 4.06 (1H, d, $J=15.0$, H9α), 3.64 (1H, d, $J=15.0$, H9β), 3.22 (1H, br t, $J=12.5$, H11α), 3.01 (1H, dm, $J=14.5$, H11β), 2.49 (1H, dm, $J=16.0$, H4α), 2.38 (3H, s, NCH_3), 2.10 (1H, ddd, $J_1=16.0$, $J_2=5.0$, $J_3=3.0$, H4β), 2.05 (1H, m, H12α), 1.65 (1H, dm, $J=14.5$, H12β); ^{13}C NMR (75.4 MHz, CD_3OD, δ) 146.8 (C6), 142.6 (C5a), 134.2 (C8b), 128.6 (C2), 128.1 (C1), 128.0 (C8a), 123.1 (C8), 116.7 (C7), 88.8 (C4a), 62.6 (C3), 61.6 (C9), 55.2 (C11), 47.9 (C4b), 43.1 (NCH_3), 35.5 (C12), 31.3 (C4); Anal. calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.39; H, 7.01; N, 4.86.

General procedure for compounds (7b) and (7d–f). To a solution of 6-*O*-demethylgalanthamine **6** in dimethylformamide was added Cs_2CO_3 (1 equiv) and *N*-(bromoalkyl)-phthalimide **11** (1 equiv). The reaction mixture was refluxed for 24 h. Evaporation of the solvent gave a residue which was taken up with a saturated aqueous solution of sodium carbonate and extracted with CH_2Cl_2. After a general workup, the combined organic extracts were evaporated. Flash chromatography (elution with CH_2Cl_2/MeOH, 90/10) of the residue afforded the corresponding *O*-alkylated compounds in good yields.

6-*O*-Demethyl-6-*O*-(4′-phthalimidobutyl)-galanthamine (7b). Reactants: **6** (79 mg, 0.29 mmol) in DMF (3 mL), Cs_2CO_3 (94 mg, 0.29 mmol), and **11b** (82 mg, 0.29 mmol) afforded **7b** (95 mg, 70%). IR ($CHCl_3$) ν: 3427, 3037, 2944, 1775, 1712, 1609, 1227 cm^{-1}; EIMS 474 $(M^{+\cdot})$, 456 $(M\text{-}H_2O)^+$, 272 $(M\text{-}(CH_2)_4Pht)^+$, 202, 160; ^1H NMR (300 MHz, $CDCl_3$, δ) 7.84 (2H, m, Har ortho),

7.72 (2H, m, Har meta), 6.72 (1H, d, $J=8.3$, H7), 6.67 (1H, d, $J=8.3$, H8), 6.10 (1H, dd, $J_1=10.0$, $J_2=5.0$, H2), 5.93 (1H, d, $J=10.0$, H1), 4.65 (1H, br s, H4a), 4.17 (1H, br s, H3), 4.08 (1H, br d, $J=15.0$, H9α), 4.06 (2H, m, H1′), 4.01 (1H, d, $J=15.0$, H9β), 3.70 (2H, t, $J=7.0$, H4′), 3.62 (1H, br t, $J_1=15.0$, $J_2=13.0$, H11α), 3.33 (1H, m, $J=15.0$, H11β), 2.72 (1H, dm, $J=16.0$, H4α), 2.59 (3H, s, NCH_3), 2.13 (1H, dm, $J=13.5$, H12α), 2.01 (1H, ddd, $J_1=16.0$, $J_2=5.0$, $J_3=2.5$, H4β), 1.86 (1H, m, H12β), 1.79 (2H, m, H2′), 1.59 (2H, m, H3′); ^{13}C NMR (62.9 MHz, $CDCl_3$, δ) 168.7 (CO), 146.3 (C6), 143.7 (C5a), 137.1 (C8b), 134.2 (CHar meta), 133.9 (Car), 132.4 (C8a), 128.0 (C2), 127.1 (C1), 123.5 (CHar ortho), 122.4 (C8), 113.5 (C7), 88.8 (C4a), 68.6 (C1′), 62.3 (C3), 60.8 (C9), 54.0 (C11), 48.4 (C4b), 42.2 (NCH_3), 37.8 (C4′), 33.9 (C12), 30.1 (C4), 26.8 (C2′), 25.3 (C3′).

6-*O*-Demethyl-6-*O*-(8′-phthalimidooctyl)-galanthamine (7d). Reactants: **6** (110 mg, 0.40 mmol) in DMF (4 mL), Cs_2CO_3 (132 mg, 0.40 mmol), and **11d** (137 mg, 0.40 mmol) afforded **7d** (97 mg, 45%). IR ($CHCl_3$) ν: 3535, 3033, 2930, 2857, 1771, 1711, 1268, 1234 cm^{-1}; CIMS 531 $(MH)^+$, 513 $(MH\text{-}H_2O)^+$; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.83 (2H, m, Har ortho), 7.70 (2H, m, Har meta), 6.65 (1H, d, $J=8.0$, H7), 6.58 (1H, d, $J=8.0$, H8), 6.05 (1H, d, $J=10.5$, H1), 5.99 (1H, m, H2), 4.59 (1H, br s, H4a), 4.12 (1H, br t, H3), 4.08 (1H, d, $J=15.0$, H9α), 3.95 (2H, m, H1′), 3.67 (1H, d, $J=15.0$, H9β), 3.66 (2H, t, $J=6.5$, H8′), 3.26 (1H, br t, $J_1=15.0$, $J_2=13.0$, H11α), 3.04 (1H, br d, $J=14.5$, H11β), 2.83 (1H, br s, OH), 2.68 (1H, dm, $J=15.5$, H4β), 2.39 (3H, s, NCH_3), 2.11 (1H, dm, $J=13.5$, H12α), 1.99 (1H, dm, $J=15.5$, H4α), 1.83 (5H, m, H2′, H7′, H12β), 1.42 (2H, m, H3′), 1.33 (6H, br s, H4′, H5′, H6′); ^{13}C NMR (75.4 MHz, $CDCl_3$, δ) 168.9 (CO), 146.7 (C6), 144.0 (C5a), 134.3 (CHar meta), 133.6 (Car), 132.6 (C8b), 129.5 (C8a), 128.1 (C2), 127.3 (C1), 123.6 (CHar ortho), 122.5 (C8), 113.4 (C7), 89.0 (C4a), 69.6 (C1′), 62.6 (C3), 61.0 (C9), 54.3 (C11), 48.6 (C4b), 42.5 (NCH_3), 38.5 (C8′), 34.2 (C12), 30.4 (C4), 29.6 (C2′), 29.5 (C6′, C5′), 29.0 (C7′), 27.3 (C4′), 26.3 (C3′); HRMS calcd for $C_{32}H_{39}N_2O_5$, 531.2849; found, 531.2846.

6-*O*-Demethyl-6-*O*-(10′-phthalimidodecyl)-galanthamine (7e). Reactants: **6** (110 mg, 0.40 mmol) in DMF (4 mL), Cs_2CO_3 (131 mg, 0.40 mmol), and **11e** (148 mg, 0.40 mmol) yielded **7e** (108 mg, 48%). IR ($CHCl_3$) ν: 3556, 3031, 2932, 2858, 1772, 1712, 1616, 1509, 1398, 1225 cm^{-1}; CIMS 559 $(MH)^+$, 541 $(MH\text{-}H_2O)^+$; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.84 (2H, m, Har ortho), 7.70 (2H, m, Har meta), 6.66 (1H, d, $J=8.0$, H7), 6.60 (1H, d, $J=8.0$, H8), 6.06 (1H, d, $J=10.3$, H1), 6.00 (1H, dd, $J_1=10.3$, $J_2=4.5$, H2), 4.60 (1H, br s, H4a), 4.12 (1H, br t, H3), 4.10 (1H, br d, $J=14.5$, H9α), 3.97 (2H, m, H1′), 3.69 (1H, d, $J=14.5$, H9β), 3.67 (2H, t, $J=7.0$, H10′), 3.32 (1H, br t, $J_1=15.0$, $J_2=13.0$, H11α), 3.06 (1H, br d, $J=14.5$, H11β), 2.68 (1H, dm, $J=15.5$, H4α), 2.48 (1H, br s, OH), 2.41 (3H, s, NCH_3), 2.11 (1H, dm, $J=13.5$, H12α), 2.00 (1H, ddd, $J_1=15.5$, $J_2=5.0$, $J_3=2.3$, H4β), 1.75 (2H, m, $J=7.0$, H2′), 1.70–1.53 (3H, m, H9′, H12β), 1.39 (2H, m, H3′), 1.28 (10H, br s, H4′, H5′, H6′, H7′, H8′); ^{13}C NMR (75.4 MHz, $CDCl_3$, δ) 167.9 (CO), 145.7 (C6), 143.1 (C5a), 133.3 (CHar meta), 132.6 (Car), 131.7 (C8b), 116.6 (C8a), 127.2 (C2), 126.3 (C1), 122.7 (CHar ortho), 121.6 (C8), 112.4 (C7), 88.0 (C4a), 68.6 (C1′), 61.6 (C3), 60.0 (C9), 53.3 (C11), 47.7 (C4b), 41.5 (NCH_3), 37.5 (C10′), 33.2 (C12), 29.4 (C4), 28.9 (C2′), 28.8–28.7 and 28.6 (C5′, C6′, C7′, C8′), 28.1 (C9′), 26.3 (C4′), 25.3 (C3′); HRMS calcd for $C_{34}H_{43}N_2O_5$, 559.3161; found, 559.3155.

6-*O*-Demethyl-6-*O*-(12′-phthalimidododecyl)-galanthamine (7f). Reactants: **6** (55 mg, 0.20 mmol) in DMF (3 mL), Cs_2CO_3 (66 mg, 0.20 mmol), **11f** (79 mg, 0.20 mmol). **7f** (79 mg, 67%). IR ($CHCl_3$) ν: 3027, 2930, 2856, 1775, 1711, 1612, 1398, 1225 cm^{-1}; CIMS 587 $(MH)^+$, 569 $(MH\text{-}H_2O)^+$; ^{1}H NMR (200 MHz, $CDCl_3$, δ) 7.84 (2H, m, Har ortho), 7.70 (2H, m, Har meta), 6.67 (1H, d, $J=8.3$, H7), 6.60 (1H, d, $J=8.3$, H8), 6.06 (1H, d, $J=10.5$, H1), 5.98 (1H, m, H2), 4.61 (1H, br s, H4a), 4.14 (1H, br s, H3), 4.12 (1H, d, $J=15.0$, H9α), 3.97 (2H, m, H1′), 3.71 (1H, d, $J=15.0$, H9β), 3.67 (2H, t, $J=7.0$, H12′), 3.30 (1H, br t, $J_1=14.5$, $J_2=13.0$, H11α), 3.07 (1H, br d, $J=14.5$, H11β), 2.76 (1H, dm, $J=16.0$, H4α), 2.54 (1H, br s, OH), 2.42 (3H, s, NCH_3), 2.12 (1H, dm, $J=13.5$, H12α), 2.00 (1H, ddd, $J_1=16.0$, $J_2=5.0$, $J_3=2.3$, H4β), 1.75 (2H, m, $J=7.0$, H2′), 1.61 (3H, m, H11′, H12β), 1.31 (2H, m, H3′), 1.26 (14H, br s, H4′, H5′, H6′, H7′, H8′, H9′, H10′); HRMS calcd for $C_{36}H_{47}N_2O_5$, 587.3473; found, 587.3460.

General procedure for compounds (8b) and (8d–f). To a solution of compound **7** in absolute ethanol was added iodine (2 equiv) and NaOAc (1.3 equiv). The reaction mixture was refluxed for 1 h, then cooled to room temperature. A 10% aqueous solution of sodium thiosulphate was added dropwise. The solvents were removed in vacuo. The residue was taken up with water and extracted with CH_2Cl_2. The organic layers were washed successively with a saturated aqueous solution of sodium carbonate and with a 0.5% aqueous solution of HBr. After a general work up, the combined organic layers were evaporated. Purification of the residue by preparative TLC (elution with CH_2Cl_2/EtOH/0.5% HBr, 90/10/0.1) provided the corresponding iminium salt as a yellow solid.

9-Dehydro-6-*O*-demethyl-6-*O*-(4′-phthalimidobutyl)-galanthaminium bromide (8b). Reactants: **7b** (80 mg, 0.17 mmol) in EtOH (8 mL), I_2 (86 mg, 0.34 mmol), and NaOAc (18 mg, 0.22 mmol) produced **8b** (56 mg, 60%).

FABMS 473 $(M)^+$, 456 $(M\text{-}OH)^+$; ^1H NMR (300 MHz, $CDCl_3$ with two drops of CD_3OD, δ) 9.40 (1H, s, H9), 7.83 (2H, m, Har ortho), 7.74 (2H, m, Har meta), 6.97 (2H, s, H7, H8), 6.20 (1H, dd, $J_1=10.0$, $J_2=4.5$, H2), 5.78 (1H, d, $J=10.0$, H1), 4.80 (1H, br s, H4a), 4.30 (1H, br t, $J=13.0$, H11α), 4.23 (1H, br s, H3), 4.14–4.05 (3H, m, H1′, H11β), 4.02 (3H, s, NCH_3), 3.77 (2H, t, $J=7.0$, H4′), 2.75 (1H, dm, $J=16.0$, H4α), 2.28 (1H, m, H12α), 2.19 (1H, m, H12β), 2.07 (1H, dm, $J=16.0$, H4β), 1.88 (4H, br s, H2′, H3′).

9-Dehydro-6-*O*-demethyl-6-*O*-(8′-phthalimidooctyl)-galanthaminium bromide (8d). Reactants: **7d** (64 mg, 0.12 mmol) in EtOH (4 mL), I_2 (62 mg, 0.24 mmol), and NaOAc (13 mg, 0.16 mmol) afforded **8d** (42 mg, 57%). IR ($CHCl_3$) ν: 3556, 3011, 2931, 2858, 1772, 1709, 1619, 1266, 1235 cm^{-1}; FABMS 529 $(M)^+$, 512 $(M\text{-}OH)^+$; ^1H NMR (300 MHz, $CDCl_3$, δ) 9.40 (1H, s, H9), 7.84 (2H, m, Har ortho), 7.77 (1H, d, $J=9.0$, H8), 7.73 (2H, m, Har meta), 6.96 (1H, d, $J=9.0$, H7), 6.16 (1H, dd, $J_1=10.0$, $J_2=5.0$, H2), 5.79 (1H, d, $J=10.0$, H1), 4.77 (1H, br s, H4a), 4.32 (1H, br t, $J_1=17.0$, $J_2=13.0$, H11α), 4.22 (1H, br t, $J=5.0$, H3), 4.15–4.09 (3H, m, H1′, H11β), 4.02 (3H, s, NCH_3), 3.68 (2H, t, $J=7.0$, H8′), 2.76 (1H, dm, $J=16.0$, H4α), 2.30 (1H, tm, $J_1=15.0$, $J_2=13.0$, $J_3=3.0$, H12α), 2.16 (1H, dm, $J=15.0$, H12β), 2.10 (1H, ddd, $J_1=16.0$, $J_2=5.5$, $J_3=2.0$, H4β), 1.83 (2H, m, $J=7.0$, H2′), 1.68 (2H, m, H7′), 1.43 (2H, m, H3′), 1.36 (6H, br s, H4′, H5′, H6′); ^{13}C NMR (75.4 MHz, CD_3OD, δ) 169.2 (CO), 168.6 (C9), 153.1 (C6), 146.9 (C5a), 137.7 (C8b), 136.2 (C8), 134.6 (CHar meta), 132.5 (Car), 130.6 (C2), 126.8 (C1), 123.7 (CHar ortho), 115.1 (C8a), 114.1 (C7), 89.0 (C4a), 70.5 (C1′), 61.4 (C3), 55.0 (C11), 52.8 (NCH_3), 47.2 (C4b), 38.5 (C8′), 31.8 (C12), 29.9 (C4), 29.6–29.5 (C4′, C5′), 29.3 (C2′), 29.0 (C7′), 27.2 (C6′), 26.2 (C3′); HRMS calcd for $C_{32}H_{37}N_2O_5$, 529.2702; found, 529.2710.

9-Dehydro-6-*O*-demethyl-6-*O*-(10′-phthalimidodecyl)-galanthaminium bromide (8e). Reactants: **7e** (72 mg, 0.13 mmol) in EtOH (4 mL), I_2 (66 mg, 0.26 mmol), and NaOAc (14 mg, 0.17 mmol) afforded **8e** (46 mg, 56%). IR ($CHCl_3$) ν: 3560, 3411, 3022, 2935, 2858, 1768, 1711, 1608, 1140 cm^{-1}; FABMS 557 $(M)^+$, 540 $(M\text{-}OH)^+$, 272 $(M\text{-}Pht(CH_2)_{10})^+$; ^1H NMR (300 MHz, $CDCl_3$ with two drops of CD_3OD, δ) 9.44 (1H, s, H9), 7.84 (2H, m, Har ortho), 7.78 (1H, d, $J=8.5$, H8), 7.72 (2H, m, Har meta), 6.95 (1H, d, $J=8.5$, H7), 6.17 (1H, dd, $J_1=10.0$, $J_2=5.0$, H2), 5.80 (1H, d, $J=10.0$, H1), 4.77 (1H, br s, H4a), 4.33 (1H, br t, $J_1=17.0$, $J_2=13.0$, H11α), 4.22 (1H, br t, $J=5.0$, H3), 4.14 (2H, t, $J=6.5$, H1′), 4.12 (1H, m, H11β), 4.03 (3H, s, NCH_3), 3.67 (2H, t, $J=7.0$, H10′), 2.74 (1H, dm, $J=16.0$, H4α), 2.30 (1H, tm, $J_1=15.0$, $J_2=12.0$, $J_3=3.0$, H12α), 2.16 (1H, dm, $J=15.0$, H12β), 2.10 (1H, ddd, $J_1=16.0$, $J_2=5.0$, $J_3=2.0$, H4β), 1.83 (2H, m, $J=7.0$, H2′), 1.67 (2H, m, H9′), 1.42 (2H, m, H3′), 1.30 (10H, br s, H4′, H5′, H6′, H7′, H8′); ^{13}C NMR (75.4 MHz, CD_3OD, δ) 170.6 (CO), 170.1 (C9), 154.4 (C6), 148.2 (C5a), 139.1 (C8b), 137.7 (C8), 136.0 (CHar meta), 134.0 (Car), 132.0 (C2), 128.3 (C1), 125.1 (CHar ortho), 116.6 (C8a), 115.5 (C7), 90.5 (C4a), 72.0 (C1′), 63.0 (C3), 56.5 (C11), 54.3 (NCH_3), 48.6 (C4b), 40.0 (C10′), 33.2 (C12), 31.3 (C4), 31.1–31.0 (C4′, C5′, C6′, C7′), 30.7 (C2′), 30.5 (C9′), 28.7 (C8′), 27.6 (C3′); HRMS calcd for $C_{34}H_{41}N_2O_5$, 557.3015; found, 557.3007.

9-Dehydro-6-*O*-demethyl-6-*O*-(12′-phthalimidododecyl)-galanthaminium bromide (8f). Reactants: **7f** (65 mg, 0.11 mmol) in EtOH (4 mL), I_2 (56 mg, 0.22 mmol), and NaOAc (12 mg, 0.14 mmol) yielded **8f** (40 mg, 54%). IR ($CHCl_3$) ν: 3550, 3030, 2938, 2857, 1769, 1711, 1609, 1237 cm^{-1}; FABMS 585 $(M)^+$; ^1H NMR (200 MHz, $CDCl_3$, δ) 9.46 (1H, s, H9), 7.86 (2H, m, Har ortho), 7.77 (1H, d, $J=8.5$, H8), 7.73 (2H, m, Har meta), 6.96 (1H, d, $J=8.5$, H7), 6.18 (1H, dd, $J_1=10.0$, $J_2=5.0$, H2), 5.78 (1H, d, $J=10.0$, H1), 4.75 (1H, br s, H4a), 4.32 (1H, m, H11α), 4.22 (1H, br s, H3), 4.13 (2H, t, $J=6.5$, H1′), 4.08 (1H, m, H11β), 4.03 (3H, s, NCH_3), 3.68 (2H, t, $J=7.0$, H12′), 2.75 (1H, dm, $J=16.0$, H4α), 2.28 (1H, tm, $J_1=15.0$, $J_2=11.5$, $J_3=3.0$, H12α), 2.17 (1H, dm, $J=15.0$, H12β), 2.10 (1H, ddd, $J_1=16.0$, $J_2=4.5$, $J_3=2.0$, H4β), 1.85 (2H, m, H2′), 1.68 (2H, m, H11′), 1.42 (2H, m, H3′), 1.31 (14H, br s, H4′, H5′, H6′, H7′, H8′, H9′, H10′); HRMS calcd for $C_{36}H_{45}N_2O_5$, 585.3328; found, 585.3319.

General procedure for compounds (9d–f). A mixture of 6-*O*-demethylgalanthamine **6** and Cs_2CO_3 (1 equiv) in anhydrous DMF was stirred for 30 min at rt. Bromoalkyl-trimethylammonium bromide **12** (1.1 equiv) was added and the mixture was heated at 130 °C under argon for 2 h. The precipitate was filtered off and the filtrate was evaporated. Purification of the residue by flash chromatography (elution with H_2O/EtOH/CH_2Cl_2, 4/36/60) provided the expected product.

6-O-Demethyl-6-*O*-(8′-trimethylammoniumoctyl) galanthamine bromide (9d). Reactants: **6** (208 mg, 0.76 mmol) in DMF (6 mL), Cs_2CO_3 (248 mg, 0.76 mmol), and **12d** (277 mg, 0.84 mmol) yielded **9d** (236 mg, 59%). IR ($CHCl_3$) ν: 3392, 3012, 2937, 2861, 1625, 1506, 1174, 1125 cm^{-1}; FABMS 443 $(M)^+$; ^1H NMR (250 MHz, CD_3OD, δ) 6.74 (1H, d, $J=7.5$, H7), 6.64 (1H, d, $J=7.5$, H8), 6.13 (1H, d, $J=9.5$, H1), 5.93 (1H, dd, $J_1=9.5$, $J_2=4.2$, H2), 4.54 (1H, br s, H4a), 4.16 (1H, br t, H3), 4.13 (1H, d, $J=14.0$, H9α), 4.00 (2H, t, $J=6.0$, H1′), 3.70 (1H, d, $J=14.0$, H9β), 3.36 (2H, m, H8′), 3.27 (1H, br t, $J_1=13.5$, $J_2=12.0$, H11α), 3.14 (9H, s, $N(CH_3)_3$), 3.04 (1H, br d, $J=13.5$, H11β), 2.48 (1H, dm, $J=14.5$, H4α), 2.41 (3H, s, NCH_3), 2.15–2.05 (2H, m,

H4β, H12α), 1.80–1.65 (5H, m, H12β, H2′, H7′), 1.42 (8H, br s, H6′, H5′, H4′, H3′); ^{13}C NMR (62.9 MHz, CD_3OD, δ) 147.9 (C6), 144.8 (C5a), 134.4 (C8b), 129.0 (C8a), 128.6 (C2), 128.4 (C1), 123.2 (C8), 114.6 (C7), 88.9 (C4a), 70.2 (C1′), 67.7 (C8′), 62.4 (C3), 61.3 (C9), 55.1 (C11), 53.5 ($N(CH_3)_3$), 48.6 (C4b), 43.1 (NCH_3), 35.5 (C12), 31.5 (C4), 30.3 (C2′), 30.1 (C3′), 30.0 (C4′), 27.1 (C5′), 26.8 (C6′), 23.8 (C7′); HRMS calcd for $C_{27}H_{43}N_2O_3$, 443.3274; found, 443.3269.

6-*O*-Demethyl-6-*O*-(10′-trimethylammoniumdecyl) galanthamine bromide (9e). Reactants: **6** (27 mg, 0.10 mmol) in DMF (1 mL), Cs_2CO_3 (32 mg, 0.10 mmol), and **12e** (39 mg, 0.11 mmol) produced **9e** (28 mg, 51%). IR ($CHCl_3$) ν: 3399, 3020, 2934, 2864, 1622, 1139, 1127 cm^{-1}; FABMS 471 $(M)^+$; ^{1}H NMR (250 MHz, CD_3OD, δ) 6.77 (1H, d, J = 7.6, H7), 6.70 (1H, d, J = 7.6, H8), 6.16 (1H, d, J = 9.5, H1), 5.96 (1H, dd, J_1 = 9.5, J_2 = 4.2, H2), 4.58 (1H, br s, H4a), 4.34 (1H, d, J = 13.6, H9α), 4.18 (1H, br t, J = 4.0, H3), 4.01 (2H, t, J = 6.0, H1′), 3.89 (1H, d, J = 13.6, H9β), 3.51–3.33 (3H, m, H11α, H10′), 3.23–3.15 (10H, m + s, H11β, $N(CH_3)_3$), 2.58 (3H, s, NCH_3), 2.50 (1H, dm, J = 14.5, H4α), 2.20–2.10 (2H, m, H4β, H12α), 1.82–170 (5H, m, H9′, H2′, H12β), 1.39 (6H, br s, H8′, H7′ H6′), 1.36 (6H, br s, H5′, H4′, H3′); ^{13}C NMR (62.9 MHz, CD_3OD, δ) 148.1(C6), 145.3 (C5a), 134.4 (C8b), 128.9 (C2), 128.0 (C1), 126.7 (C8a), 123.6 (C8), 114.7 (C7), 88.8 (C4a), 70.3 (C1′), 67.8 (C10′), 62.4 (C3), 61.1 (C9), 55.3 (C11), 53.6 ($N(CH_3)_3$), 48.8 (C4b), 43.3 (NCH_3), 35.3 (C12′), 31.5 (C4), 30.3–30.1 (C2′, C3′, C4′, C5′, C6′), 27.2 (C7′), 27.0 (C8′), 23.9 (C9′); HRMS calcd for $C_{29}H_{47}N_2O_3$, 471.3587; found, 471.3596.

6-*O*-Demethyl-6-*O*-(12′-trimethylammoniumdodecyl) galanthamine bromide (9f). Reactants: **6** (104 mg, 0.38 mmol) in DMF (5 mL), with Cs_2CO_3 (124 mg, 0.38 mmol), and **12f** (162 mg, 0.42 mmol) produced **9f** (111 mg, 50%). IR ($CHCl_3$) ν: 3388, 3020, 2932, 2864, 1629, 1138, 1127 cm^{-1}; FABMS 499 $(M)^+$; ^{1}H NMR (300 MHz, CD_3OD, δ) 6.76 (1H, d, J = 8.0, H7), 6.70 (1H, d, J = 8.0, H8), 6.16 (1H, d, J = 10.0, H1), 5.96 (1H, dd, J_1 = 10.0, J_2 = 4.5, H2), 4.58 (1H, br s, H4a), 4.33 (1H, d, J = 14.6, H9α), 4.18 (1H, br t, J = 4.5, H3), 4.01 (2H, t, J = 6.5, H1′), 3.88 (1H, d, J = 14.6, H9β), 3.50–3.35 (3H, m, H11α, H12′), 3.23–3.16 (10H, m + s, H11β, $N(CH_3)_3$), 2.57 (3H, s, NCH_3), 2.50 (1H, dm, J = 15.5, H4α), 2.18–2.10 (2H, m, H4β, H12α), 1.80–1.70 (5H, m, H11′, H2′, H12β), 1.45–1.38 (8H, m, H10′, H9′, H8′, H7′), 1.33 (8H, br s, H6′, H5′, H4′, H3′); ^{13}C NMR (75.4 MHz, CD_3OD, δ) 148.0 (C6), 145.3 (C5a), 134.4 (C8b), 128.9 (C2), 128.0 (C1), 126.8 (C8a), 123.5 (C8), 114.7 (C7), 88.8 (C4a), 70.3 (C1′), 67.8 (C12′), 62.3 (C3), 61.1 (C9), 55.3 (C11), 53.6 ($N(CH_3)_3$), 49.0 (C4b), 43.3 (NCH_3), 35.3 (C12), 31.4 (C4), 30.5–30.1 (C2′, C3′, C4′, C5′, C6′, C7′, C8′), 27.3 (C9′), 27.0 (C10′), 23.9 (C11′); HRMS calcd for $C_{31}H_{51}N_2O_3$, 499.3900; found, 499.3892.

General procedure for compounds (11c–f). To a boiling solution of alkyl dibromide **10** (2 equiv) in acetone was added potassium phthalimide in four equal portions over a 4 h period. The resulting mixture was refluxed for 24 h, then cooled to rt and filtered. The filtrate was evaporated to dryness. Purification by flash chromatography (elution with CH_2Cl_2/heptane, 90/10; then 50/50) of the residue provided the corresponding compound as a white powder.

***N*-(6-Bromohexyl)-phthalimide (11c).** Reactants: **10c** (11.2 g, 45.8 mmol) in acetone (100 mL) and PhtK (4.24 g, 22.9 mmol) produced **11c** (4.55 g, 64%). Mp 50–52 °C; IR ($CHCl_3$) ν: 3028, 3012, 2941, 2861, 1772, 1712 cm^{-1}; EIMS 311 and 309 $(M^{+\cdot})$, 230 $(M\text{-}Br)^+$; ^{1}H NMR (250 MHz, $CDCl_3$, δ) 7.85 (2H, m, Har ortho), 7.72 (2H, m, Har meta), 3.69 (2H, t, J = 7.2, H1), 3.40 (2H, t, J = 7.0, H6), 1.86 (2H, m, H5), 1.70 (2H, m, H2), 1.47 (2H, m, H4), 1.37 (2H, m, H3); ^{13}C NMR (62.9 MHz, $CDCl_3$, δ) 168.4 (CO), 133.9 (CHar meta), 132.1 (Car), 123.1 (CHar ortho), 37.8 (C1), 33.8 (C6), 28.4 (C2), 27.7 (C5), 27.3 (C4), 26.0 (C3).

***N*-(8-Bromooctyl)-phthalimide (11d).** Reactants: **10d** (5.87 g, 21.6 mmol) in acetone (80 mL), PhtK (2.00 g, 10.8 mmol). **11d** (2.55 g, 60%). Mp 52–54 °C; EIMS 339 and 337 $(M^{+\cdot})$, 258 $(M\text{-}Br)^+$; ^{1}H NMR (250 MHz, $CDCl_3$, δ) 7.86 (2H, m, Har ortho), 7.72 (2H, m, Har meta), 3.69 (2H, t, J = 7.5, H1), 3.41 (2H, t, J = 7.0, H8), 1.86 (2H, m, J = 7.0, H7), 1.69 (2H, m, J = 7.0, H2), 1.43 (2H, m, H6), 1.35 (6H, br s, H3, H4, H5); ^{13}C NMR (75.4 MHz, $CDCl_3$) 168.6 (CO), 134.0 (CHar meta), 132.3 (Car), 123.3 (CHar ortho), 38.1 (C1), 34.1 (C8), 32.8 (C2), 29.0 (C7), 28.7, 28.6, 28.2 and 26.8 (C4, C3, C5, C6).

***N*-(10-Bromodecyl)-phthalimide (11e).** Reactants: **10e** (6.48 g, 21.6 mmol) in acetone (80 mL), PhtK (2.00 g, 10.8 mmol). **11e** (2.22 g, 61%). Mp 60–61 °C; IR ($CHCl_3$) ν: 3031, 2932, 2858, 1772, 1712, 1398 cm^{-1}; EIMS 367 and 365 $(M^{+\cdot})$; ^{1}H NMR (250 MHz, $CDCl_3$, δ) 7.84 (2H, m, Har ortho), 7.71 (2H, m, Har meta), 3.68 (2H, t, J = 7.2, H1), 3.40 (2H, t, J = 7.0, H10), 1.84 (2H, m, J = 7.0, H9), 1.67 (2H, m, H2), 1.41 (2H, m, H8), 1.34–1.23 (10H, m, H3, H4, H5, H6, H7); HRMS calcd for $C_{18}H_{25}BrNO_2$ $(MH)^+$, 366.1063; found, 366.1086.

***N*-(12-Bromododecyl)-phthalimide (11f).** Reactants: **10f** (7.08 g, 21.6 mmol) in acetone (80 mL), PhtK (2.00 g, 10.8 mmol). **11f** (2.42 g, 61%). Mp 65–66 °C; IR ($CHCl_3$) ν: 3030, 2930, 2857, 1772, 1711 cm^{-1}; CIMS 396 and 394 $(MH)^+$; ^{1}H NMR (250 MHz, $CDCl_3$, δ) 7.85 (2H, m, Har ortho), 7.71 (2H, m, Har meta), 3.67

(2H, t, $J=7.5$, H1), 3.41 (2H, t, $J=7.0$, H12), 1.85 (2H, m, $J=7.0$, H11), 1.66 (2H, m, H2), 1.41 (2H, m, H10), 1.32 (2H, m, H3), 1.26 (12H, br s, H4, H5, H6, H7, H8, H9); HRMS calcd for $C_{20}H_{29}BrNO_2$, 394.1375; found, 394.1355.

General procedure for compounds (12a–e). To a solution of dihalide **10** (1.2 equiv) in toluene or ether was added dropwise Me_3N (33% in EtOH, 1 equiv) at room temperature and the reaction mixture was kept for 2 days in the dark. After precipitation of the product with ether, the precipitate was filtered and washed with Et_2O and then with dichloromethane. The crude product was taken up in acetone and the undissolved material was removed by filtration. Evaporation of the filtrate provided the corresponding bromoalkyl trimethylammonium bromide.

***N*-(3-Bromopropyl)-trimethylammonium bromide (12a).** Reactants: **10a** (1 mL, 10 mmol) in toluene (10 mL), Me_3N (2 mL of a 33% in EtOH solution). **12a** (786 mg, 35%). Mp 210–214 °C; IR ($CHCl_3$) ν: 3415, 2950, 1476, 1136, 1115 cm^{-1}; FABMS 182 and 180 $(M)^+$; ^1H NMR (250 MHz, D_2O, δ) 3.53–3.46 (4H, m, H1, H3), 3.26 (9H, s, $N(CH_3)_3$), 2.43 (2H, m, H2); ^{13}C NMR (75.4 MHz, CD_3OD, δ) 66.5 (C1), 53.8 ($N(CH_3)_3$), 29.4 (C3), 27.2 (C2); HRMS calcd for $C_6H_{15}NBr$, 180.0388; found, 180.0395.

***N*-(6-Bromohexyl)-trimethylammonium bromide (12c).** Reactants: **10c** (3 mL, 20 mmol) in Et_2O (50 mL), Me_3N (1 mL of a 33% in EtOH solution). **12c** (174 mg, 14%). Mp 110–112 °C; IR ($CHCl_3$) ν: 3390, 2946, 1488, 1478, 1237, 1132, 1117 cm^{-1}; FABMS 224 and 222 $(M)^+$; ^1H NMR (300 MHz, D_2O, δ) 3.52 (2H, t, $J=6.5$, H6), 3.32 (2H, m, H1), 3.11 (9H, s, $N(CH_3)_3$), 1.94–1.76 (4H, m, H5, $J=6.5$, H2), 1.56–1.48 (2H, m, $J=6.5$, H4), 1.45–1.35 (2H, m, H3); HRMS calcd for $C_6H_{21}NBr$, 222.0857; found, 222.0868.

***N*-(8-Bromooctyl)-trimethylammonium bromide (12d).** Reactants: **10d** (1.85 mL, 10 mmol) in toluene (20 mL), Me_3N (2 mL of a 33% in EtOH solution). **12d** (850 mg, 30%). Mp 78–80 °C; IR ($CHCl_3$) ν: 3389, 2940, 2861, 1488, 1478, 1239,1139 cm^{-1}; FABMS 252 and 250 $(M)^+$; ^1H NMR (250 MHz, $CDCl_3$, δ) 3.65 (2H, m, H1), 3.47 (9H, s, $N(CH_3)_3$), 3.42 (2H, t, $J=6.5$, H8), 1.91–1.72 (4H, m, H7, H2), 1.49–1.29 (8H, m, H3, H4, H5, H6); ^{13}C NMR (75.4 MHz, $CDCl_3$, δ) 66.7 (C1), 53.3 ($N(CH_3)_3$), 34.0 (C8), 32.5 (C2), 28.9 (C7), 28.3 (C3), 27.8 (C6), 25.9 (C4), 23.0 (C5); HRMS calcd for $C_{11}H_{25}NBr$, 250.1170; found, 250.1170.

***N*-(10-Bromodecyl)-trimethylammonium bromide (12e).** Reactants: **10e** (3 g, 10 mmol) in toluene (20 mL), Me_3N (2 mL of a 33% in EtOH solution). **12e** (680 mg, 22%). Mp 130–132 °C; IR ($CHCl_3$) ν: 3399, 3020, 2935, 2859, 1488, 1478, 1237, 1139, 1116 cm^{-1}; FABMS 280 and 278 $(M)^+$; ^1H NMR (250 MHz, $CDCl_3$, δ) 3.64 (2H, m, H1), 3.47 (9H, s, $N(CH_3)_3$), 3.42 (2H, t, $J=7.0$, H10), 1.85 (2H, m, $J=7.0$, H9), 1.80–1.70 (2H, m, H2), 1.47–1.29 (12H, m, H3, H4, H5, H6, H7, H8); ^{13}C NMR (75.4 MHz, $CDCl_3$, δ) 66.6 (C1), 53.2 ($N(CH_3)_3$), 34.0 (C10), 32.5 (C2), 29.0 (C9, C3, C8), 28.4 (C4), 27.8 (C7), 25.9 (C5), 23.0 (C6); HRMS calcd for $C_{13}H_{29}NBr$, 278.1483; found, 278.1481.

***N*-(12-Bromododecyl)-trimethylammonium bromide (12f).** Reactants: **10f** (3.28 g, 10 mmol) in toluene (20 mL), Me_3N (2 mL of a 33% in EtOH solution). **12f** (794 mg, 24%). Mp 181–183 °C; IR ($CHCl_3$) ν: 3392, 3010, 2932, 2857, 1488, 1478, 1238, 1139 cm^{-1}; FABMS 308 and 306 $(M)^+$; ^1H NMR (250 MHz, D_2O, δ) 3.53 (2H, t, $J=7.0$, H12), 3.36 (2H, m, H1), 3.15 (9H, s, $N(CH_3)_3$), 1.89 (2H, m, $J=7.0$, H11), 1.81 (2H, m, H2), 1.52–1.34 (16H, m, H3, H4, H5, H6, H7, H8, H9, H10); ^{13}C NMR (50.3 MHz, $CDCl_3$, δ) 66.9 (C1), 53.4 ($N(CH_3)_3$), 34.2 (C12), 32.8 (C2), 29.3 (C9, C3, C4, C10, C11), 28.7 (C5), 28.1 (C8), 26.2 (C6), 23.2 (C7); HRMS calcd for $C_{15}H_{33}NBr$, 306.1796; found, 306.1796.

General procedure for compounds (13d–f). To a solution of **11** (1.2 equiv) in toluene (20 mL) was added dropwise Me_3N (33% in EtOH) at room temperature and the reaction mixture was kept for 2 days in the dark. After precipitation of the product with ether, the mixture was filtered and the precipitate was washed with Et_2O and then with CH_2Cl_2. The crude product was taken up in acetone and the undissolved material was removed by filtration. Evaporation of the filtrate provided the corresponding phthalimidoalkyl trimethylammonium bromide.

8-(Phthalimidooctyl)-trimethylammonium bromide (13d). Reactants: **11d** (503 mg, 1.49 mmol) in toluene (3 mL), Me_3N (1.77 mL of a 33% in EtOH solution). **13d** (577 mg, 98%); IR ($CHCl_3$) ν: 3391, 3020, 2943, 2861, 1772, 1710, 1616, 1398 cm^{-1}; mp 168–171 °C; FABMS 317 $(M)^+$, 160 $(M\text{-}((CH_2)_7N(Me_3)_3))^+$; ^1H NMR (250 MHz, $CDCl_3$, δ) 7.82 (2H, m, Har ortho), 7.73 (2H, m, Har meta), 3.67 (2H, t, $J=7.0$, H8), 3.59 (2H, m, H1), 3.48 (9H, s, $N(CH_3)_3$), 1.77 (2H, m, H2), 1.67 (2H, m, H7), 1.36 (8H, br s, H3, H4, H5, H6); HRMS calcd for $C_{19}H_{29}N_2O_2$, 317.2229; found, 317.2247.

10-(Phthalimidodecyl)-trimethylammonium bromide (13e). Reactants: **11e** (491 mg, 1.34 mmol) in toluene (5 mL), Me_3N (6.4 mL of a 33% in EtOH solution). **13e** (545 mg, 96%). IR ($CHCl_3$) ν: 3400, 3031, 2935, 2859, 1771, 1712, 1617, 1398 cm^{-1}; mp 153–155 °C; FABMS 345 $(M)^+$; ^1H NMR (300 MHz, $CDCl_3$, δ) 7.84 (2H, m, Har ortho), 7.72 (2H, m, Har meta), 3.67 (2H, t,

$J = 7.0$, H10), 3.59 (2H, m, H1), 3.49 (9H, s, $N(CH_3)_3$), 1.76 (2H, m, H2), 1.66 (2H, m, H9), 1.31 (12H, m, H3, H4, H5, H6, H7, H8); HRMS calcd for $C_{21}H_{33}N_2O_2$, 345.2542; found, 345.2544.

12-(Phthalimidododecyl)-trimethylammonium bromide (13f). Reactants: **11f** (500 mg, 1.27 mmol) in toluene (3 mL), Me_3N (604 μL of a 33% in EtOH solution). **13f** (557 mg, 97%). IR ($CHCl_3$) ν: 3399, 3020, 2932, 2858, 1771, 1711, 1614, 1398 cm^{-1}; mp 156–157 °C; FABMS 373 $(M)^+$; ^1H NMR (300 MHz, $CDCl_3$, δ) 7.84 (2H, m, Har ortho), 7.71 (2H, m, Har meta), 3.67 (2H, t, $J = 7.0$, H12), 3.57 (2H, m, H1), 3.48 (9H, s, $N(CH_3)_3$), 1.75 (2H, m, H2), 1.67 (2H, m, H11), 1.32 (16H, m, H3, H4, H5, H6, H7, H8, H9, H10); HRMS calcd for $C_{23}H_{37}N_2O_2$, 373.2855; found, 373.2845.

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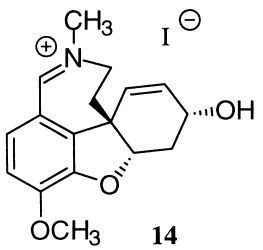
16. Compound **14** was prepared as described in reference 6.



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