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Design, Synthesis and Structure–Activity Relationships of Dual Inhibitors of Acetylcholinesterase and Serotonin Transporter as Potential Agents for Alzheimer's Disease

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Abstract—We have designed and synthesized a dual inhibitor of acetylcholinesterase (AChE) and serotonin transporter (SERT) as a novel class of treatment drugs for Alzheimer's disease on the basis of a hypothetical model of the AChE active site. Dual inhibitions of AChE and SERT would bring about greater therapeutic effects than AChE inhibition alone and avoid adverse peripheral effects caused by excessive AChE inhibition. Compound (*S*)-**6j** exhibited potent inhibitory activities against AChE (IC_{50} = 101 nM) and SERT (IC_{50} = 42 nM). Furthermore, (*S*)-**6j** showed inhibitory activities of both AChE and SERT in mice brain following oral administration.

Introduction

Alzheimer's disease (AD), a neurodegenerative disorder characterized by a progressive deterioration of memory and cognition, has been one of the most severe health problems of the aged.[1] A deficiency in the cholinergic neurotransmission is considered to play an important role in the learning and memory impairments of AD patients. Enhancement of the cholinergic function by inhibiting acetylcholinesterase (AChE), which terminates nerve impulse transmission at cholinergic synapses by catalyzing the hydrolysis of acetylcholine, is the only clinically effective method for a palliative treatment of AD.[2] At present, several AChE inhibitors have successfully reached the market, for example, tacrine,[3] donepezil[4] and rivastigmine[5] (Fig. 1). However, the usefulness of AChE inhibitors in the clinical setting is limited mainly due to their adverse effects on peripheral organs.[6] Furthermore, AD patients often suffer from psychiatric disorder-related symptoms, such as irritability, anxiety and depression.[7] Depression in AD patients has been treated with serotonin transporter (SERT) inhibitors[8] such as fluoxetine[9] and paroxetine[10] which have no anticholinergic side effect (Fig. 2). Thus, combined SERT and AChE inhibition is considered to bring about greater therapeutic benefits than AChE inhibition alone since further improvement of cognitive deficits could be achieved and dose-related adverse effects caused by excessive AChE inhibition could be avoided. These AChE–SERT dual inhibitors would be a novel

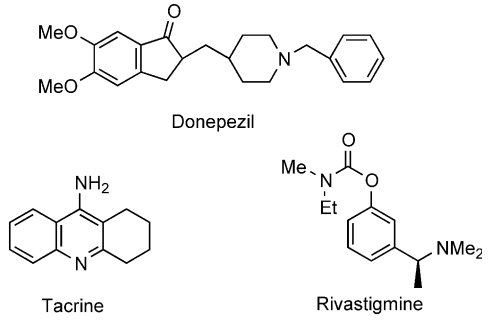

Figure 1. Examples of AChE inhibitors.

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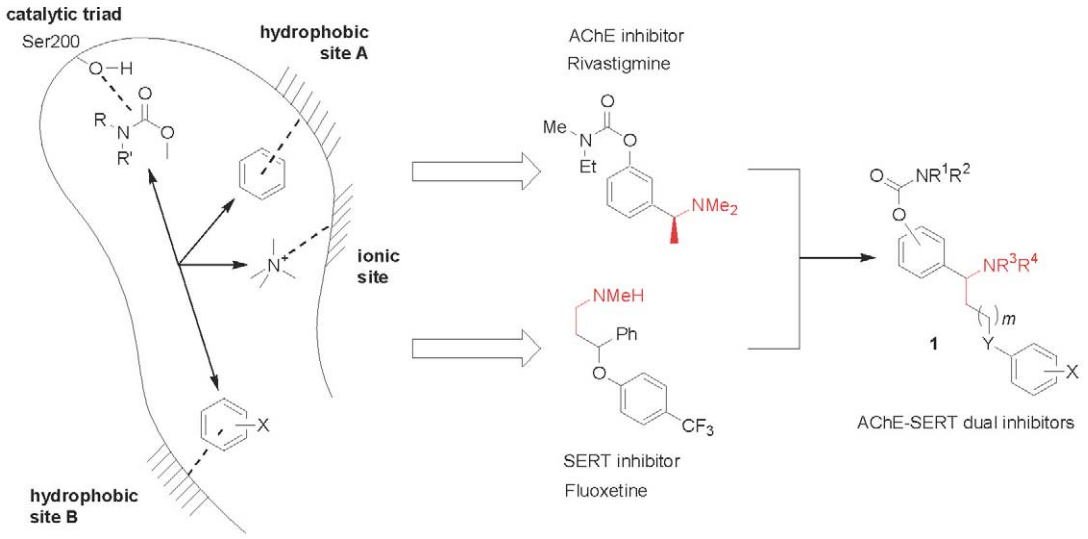


Scheme 1. Design of AChE–SERT dual inhibitors based on hypothetical model of AChE active site with proposed pharmacophore.

class of anti-AD drugs more effective in alleviating the symptoms of AD than known AChE inhibitors. To date, only two groups have studied AChE inhibitors that possess SERT inhibitory activity.[11] The reported compounds showed potent AChE inhibitory activities and moderate SERT inhibitory activities in vitro. However, the extent of inhibition against each was imbalanced for in vivo dual inhibitions. Consequently, the antidepressive effect resulting from SERT inhibition was not observed due to the dominant effect of increased cholinergic transmission. Herein, we report the design and synthesis of novel dual inhibitors of AChE and SERT as a new class of anti-AD drugs.

In an attempt to design a new type of AChE–SERT dual inhibitors, we proposed a hypothetical model of the AChE active site on the basis of the crystal structure of AChE with donepezil[12] and molecular modeling studies[13] (Scheme 1). Our hypothetical model consists of four enzyme-binding sites and corresponding binding elements. We selected rivastigmine, one of the marketed AChE inhibitors, as a lead compound because rivastigmine possesses three binding elements: a carbamate moiety at the catalytic triad site; an aromatic ring at the hydrophobic site A; and an amine moiety at the ionic site. Focusing on the fourth binding site of our model, we selected fluoxetine as a pharmacophoric element corresponding to the hydrophobic site B. Fluoxetine has potent SERT inhibitory activity and possesses an ethylamine moiety that could be overlapped with that of rivastigmine.

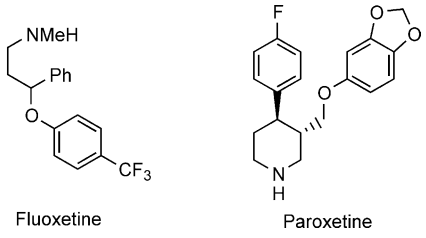
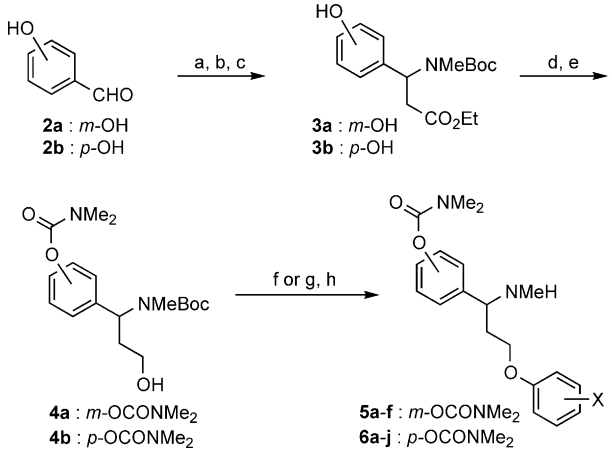


Figure 2. Examples of SERT inhibitors.

Therefore, we designed compound **1** by the hybridization of these two compounds at the common ethylamine moiety. Our designed compound **1** was anticipated to be a dual inhibitor of AChE and SERT.

Chemistry

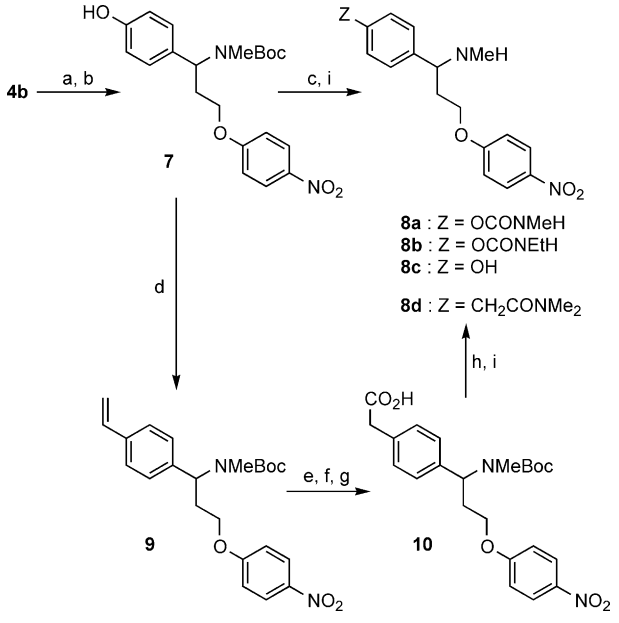
Preparation of *meta*-carbamate derivatives **5a–f** and *para*-carbamate derivatives **6a–j** is shown in Scheme 2. One-pot condensation[14] of hydroxybenzaldehyde **2**, malonic acid and methylamine, followed by esterification of the carboxylic acid catalyzed by sulfuric acid and the Boc protection of methylamine provided compound **3**. Compound **3** was treated with dimethylcarbamyl chloride, followed by reduction of the ester group with $LiAlH_4$ to furnish primary alcohol **4**. Primary alcohol **4** was etherified with various phenols, followed by deprotection of the *N*-Boc group with 2 N HCl in ethyl acetate to give compounds **5a–f** and **6a–j**.



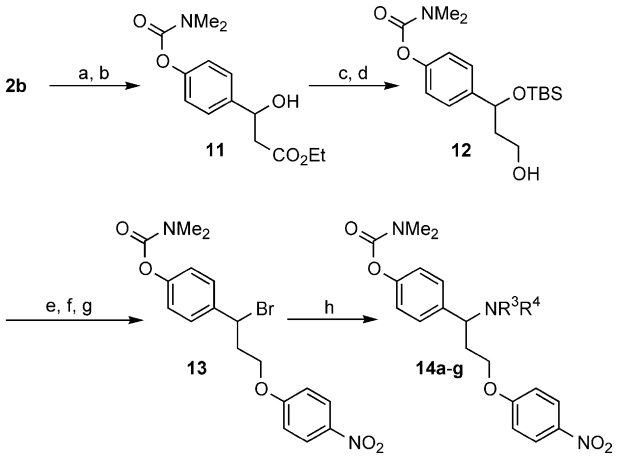
Scheme 2. Reagents and conditions: (a) $CH_2(CO_2H)_2$, MeH_3NOAc, EtOH, reflux; (b) H_2SO_4, EtOH, reflux; (c) Boc_2O, THF, rt; (d) Me_2NCOCl, K_2CO_3, DMF, rt; (e) $LiAlH_4$, THF, −20 °C; (f) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C; (ii) phenol, NaH, DMF, 0 °C to rt; (g) phenol, DEAD, PPh_3, THF, rt; (h) 2 N HCl–AcOEt, rt.

The syntheses of carbamate derivatives **8a–c** and amide derivative **8d** via common intermediate **7** are shown in Scheme 3. Intermediate **7** was synthesized by etherification of **4b** with *p*-nitrophenol under Mitsunobu reaction conditions, followed by hydrolysis of the dimethylcarbamate moiety. Deprotection of the Boc group gave derivative **8c**. Derivatives **8a**,**b** were prepared by treatment with the corresponding isocyanate and Boc deprotection. Amide derivative **8d** was prepared by the following method. Compound **7** was converted to the aryl triflate by treatment with trifluoromethanesulfonic anhydride. The resulting triflate was reacted with tributylvinylstannane by the Stille reaction[15] to give styrene compound **9**. Sequential oxidations of **9** by hydroboration/H_2O_2, sulfur trioxide pyridine complex and sodium chlorite afforded carboxylic acid **10**. Amide formation using 1,1′-carbonyldiimidazole followed by deprotection of the Boc group provided amide derivative **8d**.

Scheme 4 shows the synthesis of amino derivatives **14a–g**. *p*-Hydroxybenzaldehyde (**2b**) was treated with dimethylcarbamyl chloride, followed by aldol reaction with ethyl acetate to give **11**. Protection of benzyl alcohol **11** with a TBS group and reduction of the ethyl ester with $LiBH_4$ provided the primary alcohol **12**. Primary alcohol was etherified with *p*-nitrophenol under Mitsunobu reaction conditions, followed by deprotection of the TBS group with concentrated HCl to afford benzyl alcohol. Bromination using carbon tetrabromide and triphenylphosphine furnished benzyl bromide **13**. Compounds **14a–g** were prepared by treatment of benzyl bromide **13** with the corresponding amines in acetonitrile.



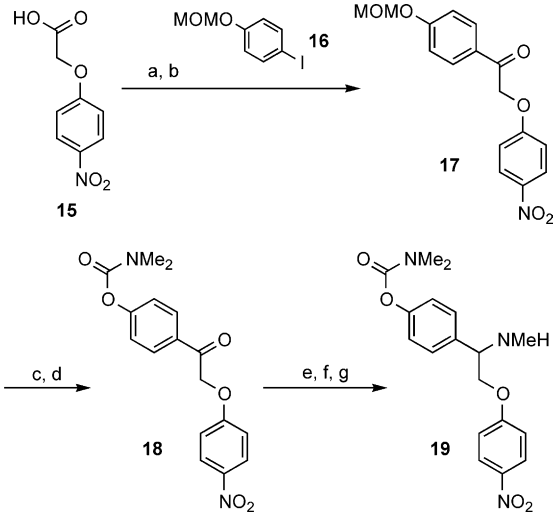
Scheme 3. Reagents and conditions: (a) *p*-nitrophenol, DEAD, PPh_3, THF, rt; (b) aq NaOH, MeOH, 65 °C, 54% (two steps); (c) MeN=C=O or EtN=C=O, Et_3N, CH_2Cl_2, rt; (d) (i) Tf_2O, py, CH_2Cl_2, 0 °C; (ii) $(CH_2{=}CH)(n\text{-}Bu)_3Sn$, LiCl, $Pd_2(dba)_3$, Ph_3As, NMP, rt, 38% (two steps); (e) 9-BBN, H_2O_2, NaOH, THF, rt, 52%; (f) SO_3·py, Et_3N, DMSO, rt, 36%; (g) $NaClO_2$, H_2O_2, NaH_2PO_4, CH_3CN–H_2O, rt, 20%; (h) Me_2NH·HCl, CDI, THF, rt, 55%; (i) 2 N HCl–AcOEt, rt.



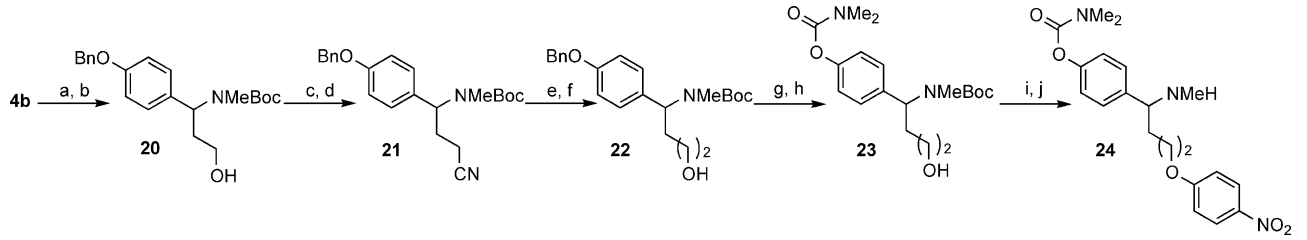
Scheme 4. Reagents and conditions: (a) Me_2NCOCl, K_2CO_3, DMF, rt, 99%; (b) EtOAc, LDA, THF, 0 °C, 92%; (c) *t*-$BuMe_2SiCl$, imidazole, DMF, 0 °C, 90%; (d) $LiBH_4$, THF, 60 °C, 67%; (e) *p*-nitrophenol, DEAD, PPh_3, THF, 90%; (f) concd HCl, MeOH, rt, 78%; (g) CBr_4, PPh_3, CH_2Cl_2, rt, 91%; (h) amine, CH_3CN, rt.

The compounds **19** ($m=0$, Y = O), **24** ($m=2$, Y = O) and **28** ($m=1$, Y = none) were synthesized by the method illustrated in Schemes 5–7. Compounds **29** (Y = NH), **30** (Y = NAc) in which the oxygen was replaced with nitrogen and **31** (Y = S) in which the oxygen was replaced with sulfur, were synthesized using the same method described in Scheme 2.

2-(4-Nitrophenoxy)acetic acid (**15**) was converted to the Weinreb amide by 1,1′-carbonyldiimidazole (Scheme 5). This Weinreb amide was reacted with aryl lithium reagent derived from aryl iodide **16** to give ketone **17**. Deprotection of the MOM group by adding concentrated HCl in THF–MeOH, followed by treatment with dimethylcarbamyl chloride, provided compound **18**. Reduction of the ketone with $NaBH_4$ and bromination using carbon tetrabromide and triphenylphosphine



Scheme 5. Reagents and conditions: (a) Me(MeO)NH·HCl, Et_3N, CDI, CH_2Cl_2, rt, 59%; (b) **16**, *n*-BuLi, THF, −78 °C, 18%; (c) concd HCl, THF–MeOH, rt; (d) Me_2NCOCl, K_2CO_3, DMF, rt, 66% (two steps); (e) $NaBH_4$, THF–MeOH, 0 °C, 84%; (f) CBr_4, PPh_3, CH_2Cl_2, rt; (g) $MeNH_2$, MeOH, rt, 15% (two steps).

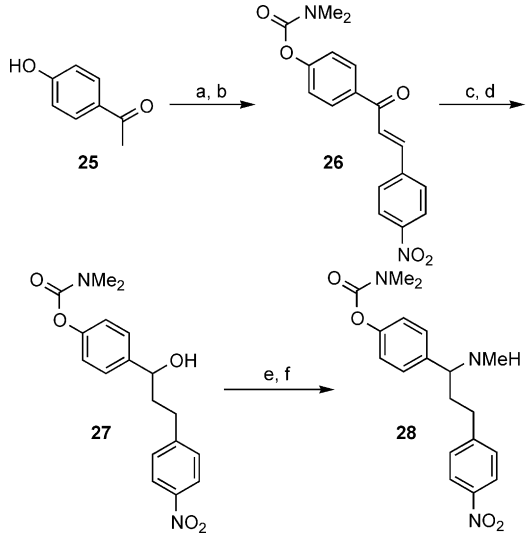


Scheme 6. Reagents and conditions: (a) aq NaOH, MeOH, 50 °C; (b) BnBr, K_2CO_3, acetone, reflux, 73% (two steps); (c) MsCl, Et_3N, THF, 0 °C to rt; (d) NaCN, 15-crown-5, DMF, rt, 79% (two steps); (e) DIBAL, CH_2Cl_2, −78 °C to rt; (f) $NaBH_4$, MeOH, rt, 22% (two steps); (g) H_2, 5% Pd/C, MeOH, rt; (h) Me_2NCOCl, K_2CO_3, DMF, rt, 77% (two steps); (i) *p*-nitrophenol, DEAD, PPh_3, THF, rt; (j) 2 N HCl–AcOEt, rt, 63% (two steps).

gave benzyl bromide. The resulting bromide was treated with methylamine in MeOH, followed by treatment with HCl in MeOH to afford compound **19**.

Compound **24** ($m=2$) which possesses a tether one carbon longer than **6j** ($m=1$) was prepared from intermediate **4b** using the one-carbon homologation method (Scheme 6). The carbamate **4b** was converted to benzyl ether **20** in order to avoid a reduction of the dimethylcarbamate moiety in the following reaction. Primary alcohol **20** was treated with methanesulfonyl chloride. This was followed by a reaction with sodium cyanide in the presence of 15-crown-5 to furnish compound **21**. Reduction of **21** by diisobutylaluminium hydride and $NaBH_4$ provided primary alcohol **22**. The resulting benzyl ether **22** was reverted to the dimethylcarbamate **23** by hydrogenation of the benzyl moiety and treatment with dimethylcarbamyl chloride. Compound **23** was converted to **24** by the method shown in Scheme 2.

Scheme 7 shows the synthesis of compound **28** in which the ethereal oxygen was removed from **6j**. 4′-Hydroxyacetophenone (**25**) was treated with dimethylcarbamyl chloride. This was followed by aldol condensation with *p*-nitrobenzaldehyde to afford α,β-unsaturated ketone **26**. Selective 1,2-reduction using $NaBH_4$ provided an allyl alcohol. Hydrogenation of the remaining double bond using Wilkinson's catalyst gave benzyl alcohol **27**.



Scheme 7. Reagents and conditions: (a) Me_2NCOCl, K_2CO_3, DMF, rt, 77%; (b) *p*-nitrobenzaldehyde, KOH, EtOH, rt, 97%; (c) $NaBH_4$, MeOH, rt, 56%; (d) H_2, $Rh(PPh_3)_3Cl$, THF, rt, 80%; (e) CBr_4, PPh_3, CH_2Cl_2, rt, 80%; (f) $MeNH_2$, CH_3CN, rt, 58%.

The nitro group still remained after this reaction.[16] Preparation of **28** from **27** was accomplished according to the method described in Scheme 4.

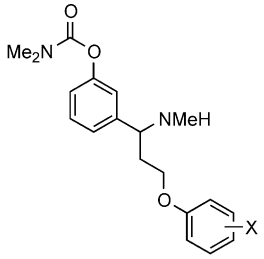
The synthesis of both enantiomers of **6j** was reported in the previous paper.[17]

Results and Discussion

All final compounds were tested for in vitro inhibitions of AChE from mouse brain and SERT from rat synaptosome. The protocols used here are described in the Experimental.

Table 1 summarizes the inhibitory activities of compounds **5a–f** ($m=1$, $Y=O$, $R^1=R^2=R^3=Me$, $R^4=H$) which possess the dimethylcarbamate at the *meta* position similarly to rivastigmine. For comparison, the assay data of rivastigmine, donepezil and fluoxetine are also included. Effect of the electron-donating (**5a**,**b**) and electron-withdrawing (**5c–f**) substituents X at the 4-position of the phenyl ether moiety was examined. Nearly all of the 4-substituted derivatives **5a–e** exhibited

Table 1. In vitro ihibition of AChE and SERT for *meta*-carbamate derivatives



Compd[a]	X	IC_{50} (nM)	
		AChE[b]	SERT[c]
Rivastigmine		11,000	>1000
Donepezil		10	>1000
Fluoxetine		>10,000	180
5a	4-OMe	>1000	38
5b	4-Me	>1000	49
5c	4-Cl	870	81
5d	4-F	870	16
5e	4-CF_3	>1000	13
5f	4-NO_2	221	52

[a]Compounds were tested as their hydrocloride salts.
[b]From mouse brain.
[c]From rat synaptosome.

potential inhibitory activity against SERT ($IC_{50} = < 50$ nM) but much lower activity against AChE ($IC_{50} = > 1000$ nM). However, only the 4-nitro-substituted derivative **5f** was found to be a potential dual inhibitor of AChE ($IC_{50} = 221$ nM) and SERT ($IC_{50} = 52$ nM).

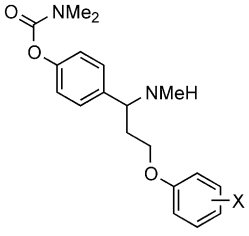
Changing the location of the dimethylcarbamate from the *meta* position to the *para* position mostly increased the potency against AChE, but decreased the potency against SERT (Table 2). Among the compounds **6a–j**, the 4-nitro-substituted derivative **6j** was revealed to possess good potencies against both AChE ($IC_{50} = 125$ nM) and SERT ($IC_{50} = 44$ nM), inhibiting them both to a suitable extent.

The effect of the carbamate moiety in **6j** was examined (Table 3). The carbamate derivatives **8a**,**b** had good anti-SERT activity but moderate anti-AChE activity. The dimethylamide derivative **8d** no longer exhibited an inhibitory effect against AChE, whereas its anti-SERT activity was maintained. The removal of the dimetylcarbamyl moiety from **6j** led to a loss of the inhibitory activities against both AChE and SERT (**8c**). These results suggest that the dimethylcarbamate moiety is essential for anti-AChE activity.

The optimization of the methylamine moiety in **6j** is shown in Table 4. The dimethylamine derivative **14a** was found to be less potent than **6j**. Increasing the size of the amine (**14c–g**) resulted in a sharp decline of inhibitory potencies against both AChE and SERT. Ammonium derivative **14b** was found to have lost its inhibitory activities against AChE ($IC_{50} = > 1000$ nM), whereas the potency against SERT was maintained ($IC_{50} = 44$ nM). In general, it seems that a small amine like methylamine is particularly favorable for dual inhibition of AChE and SERT.[18]

As shown in Table 5, the effects of the tether length and the replacement of the hetero atom were examined. Compound **19** ($m = 0$, Y = O) possessing a shorter tether length exhibited much less activity toward both AChE and SERT than **6j** ($m = 1$, Y = O). However, compound **24** possessing longer tether length ($m = 2$, Y = O) displayed stronger activity against AChE ($IC_{50} = 77$ nM) than **6j** ($IC_{50} = 125$ nM) but lower potency against SERT ($IC_{50} = > 1000$ nM). It seems that nitrophenoxy

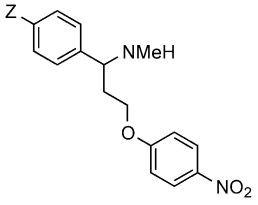
Table 2. In vitro inhibition of AChE and SERT for *para*-carbamate derivatives



Compd[a]	X	IC_{50} (nM)	
		AchE[b]	SERT[c]
6a	4-OMe	220	310
6b	4-Me	726	230
6c	H	341	> 1000
6d	4-Cl	493	210
6e	4-F	594	790
6f	4-CF_3	572	130
6g	4-CN	330	500
6h	2-NO_2	52	> 1000
6i	3-NO_2	14	175
6j	4-NO_2	125	44

[a]Compounds were tested as their hydrocloride salts.
[b]From mouse brain.
[c]From rat synaptosome.

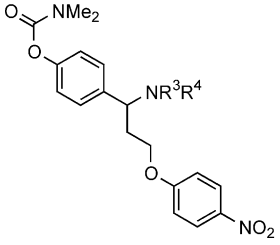
Table 3. In vitro inhibition of AChE and SERT for derivatives with different carbamates



Compd[a]	Z	IC_{50} (nM)	
		AChE[b]	SERT[c]
6j	–$OCONMe_2$	125	44
8a	–OCONMeH	497	32
8b	–OCONEtH	> 1000	46
8d	–CH_2CONMe_2	> 1000	60
8c	–OH	> 1000	> 1000

[a]Except for **8c**, compounds were tested as their hydrocloride salts.
[b]From mouse brain.
[c]From rat synaptosome.

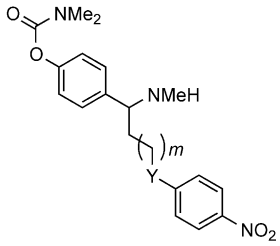
Table 4. In vitro inhibition of AChE and SERT for derivatives with various amines



Compd[a]	NR^3R^4	IC_{50} (nM)	
		AChE[b]	SERT[c]
6j	NMeH	125	44
14a	NMe_2	319	87
14b	N^+Me_3	> 1000	44
14c	NEtH	326	> 1000
14d	NMeEt	378	980
14e		852	> 1000
14f		> 1000	500
14g		> 1000	> 1000

[a]Compounds were tested as their hydrocloride salts.
[b]From mouse brain.
[c]From rat synaptosome.

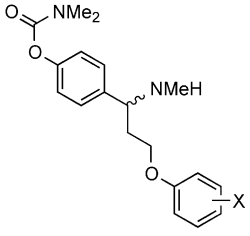
Table 5. In vitro inhibition of AChE and SERT for derivatives with different tethers and replaced heteroatoms



Compd[a]	*m*	Y	IC_{50} (nM)	
			AChE[b]	SERT[c]
19	0	O	>1000	>1000
6j	1	O	125	44
24	2	O	77	>1000
29	1	NH	36	>1000
30	1	NAc	>1000	>1000
31	1	S	61	680
28	1	None	524	670

[a]Compounds were tested as their hydrocloride salts.
[b]From mouse brain.
[c]From rat synaptosome.

Table 6. In vitro inhibition of AChE and SERT for enantiomers of **6j** and **6d**



Compd[a]	X	IC_{50} (nM)	
		AChE[b]	SERT[c]
rac-**6j**	4-NO_2	125	44
(*R*)-**6j**	4-NO_2	143	135
(*S*)-**6j**	4-NO_2	101	42
rac-**6d**	4-Cl	493	210
(*R*)-**6d**	4-Cl	343	270
(*S*)-**6d**	4-Cl	377	83

[a]Compounds were tested as their hydrocloride salts.
[b]From mouse brain.
[c]From rat synaptosome.

moiety of compound **24** interacted more efficiently with the hydrophobic site B in our hypothetical model of the AChE active site than compounds **6j** and **19**. The replacement of oxygen by nitrogen (**29** and **30**, Y = NH and NAc, respectively) or sulfur (**31**, Y = S) resulted in a reduction of inhibitory potency particularly against SERT. Compound **28** in which the ethereal oxygen was removed from **6j**, was found to be a moderate dual inhibitor of AChE (IC_{50} = 524 nM) and SERT (IC_{50} = 670 nM). These replacement studies revealed that the ethereal oxygen was crucial for the inhibition of both AChE and SERT.

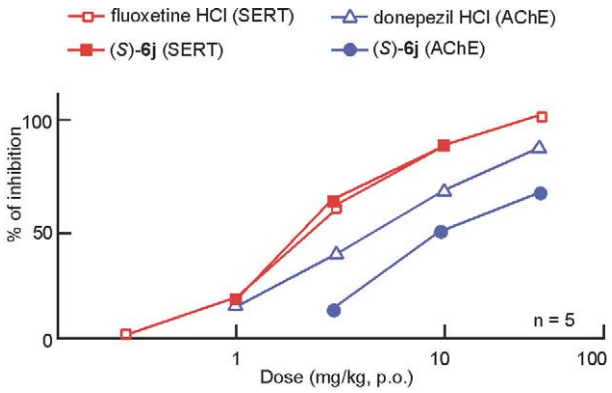


Figure 3. Inhibition of AChE and SERT in the brain following oral administration in mice (ex vivo assay).

Since we described that racemic **6j** was the best dual inhibitor of AChE and SERT, both enantiomers of **6j** were evaluated. Compound (*S*)-**6j** showed potent inhibitory potencies against both AChE (IC_{50} = 101 nM) and SERT (IC_{50} = 42 nM).[19] There was little difference in AChE inhibitory activity between the stereoisomers of **6j**. However, SERT inhibition of (*S*)-**6j** was 3-fold more potent than that of (*R*)-**6j**. This difference in inhibitory activity due to stereochemistry was also observed in the enantiomers of **6d**. Both enantiomers of **6d** showed similar anti-AChE activities, and (*S*)-**6d** exhibited a 3-fold higher inhibitory activity than (*R*)-**6d** (Table 6).

The result of the ex vivo inhibitory effects on AChE and SERT of (*S*)-**6j** is shown in Figure 3. The inhibition results of donepezil and fluoxetine are also included for comparison. After oral administration, compound (*S*)-**6j** inhibited both AChE and SERT in mice brain to the same extent as that of donepezil and fluoxetine, respectively. Compound (*S*)-**6j** is the first compound that can facilitate both cholinergic and serotonergic transmissionin in the brain following oral administration. This biological study demonstrated that compound (*S*)-**6j** could be a new type of drug to treat Alzheimer's disease.

Conclusion

On the basis of a hypothetical model of the AChE active site, we have designed and synthesized dual inhibitors of AChE and SERT as drugs to treat Alzheimer's disease. After identifying the optimum substituent on the ethereal aromatic ring, various modifications to the carbamate group, the amine moiety, the length of the tether and a substitution of the ethereal oxygen have been investigated. Among the series of compounds obtained, compound (*S*)-**6j** exhibited potent anti-AChE and anti-SERT activities. Furthermore, (*S*)-**6j** showed inhibitory activities against both AChE and SERT in mice brain following oral administration. Further pharmacological study of (*S*)-**6j** targeting Alzheimer's disease will be reported in due course.

Experimental

Chemistry

General information. Unless otherwise noted, all reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. All other dry solvents were purchased from Aldrich in SureSeal™ containers. All other commercially obtained reagents were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 or 500 spectrometer. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened. Infrared spectra were recorded on a JASCO FT-IR-8900 spectrometer. Mass spectra were obtained on a JEOL HX-100, a SX-102A or a JMS-AX-505H mass spectrometer. Optical rotations were measured on a JASCO P-1030 polarimeter. Analytical TLC was performed on 0.25 mm pre-coated Merck silica gel 60 F_{254} plates. Column chromatography was performed on Merck silica gel 60 (230–400 mesh).

3-(*tert*-Butoxycarbonylmethylamino)-3-(3-hydroxyphenyl)-propionic acid ethyl ester (3a). To a solution of 40% dimethylamine in MeOH solution (14.5 g, 187 mmol) was acetic acid (7.14 mL, 125 mmol) dropwise at 0 °C. The mixture was stirred for 1 h at 0 °C. The solvent was removed in vacuo to give methylammonium acetate (12.0 g) as a colorless solid. To a solution of **2a** (7.5 g, 61.4 mmol) and malonic acid (7.65 g, 73.5 mmol) in EtOH (30 mL), methylammonium acetate prepared beforehand was added at room temperature. The mixture was stirred for 2 h at 90 °C. The precipitate was filtered and washed with EtOH and ether to provide amino acid (6.94 g, 58%) as a colorless solid. Mp 219–221 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 2.23 (s, 3H), 2.30 (dd, 1H, J = 5.0, 16.5 Hz), 2.45 (dd, 1H, J = 10.0, 16.5 Hz), 3.90 (dd, 1H, J = 5.0, 10.0 Hz), 6.70 (dd, 1H, J = 2.0, 7.5 Hz), 6.78 (s, 1H), 6.80 (d, 1H, J = 7.5 Hz), 7.15 (t, 1H, J = 7.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 31.4, 40.3, 60.4, 114.1, 114.6, 117.7, 129.4, 141.0, 157.4, 172.5; IR (KBr) cm^{-1}: 2728, 1644, 1461, 1398, 1274, 792; HRMS calcd for $C_{10}H_{13}NO_3$ $(M)^+$ 195.0895, found 195.0892. Anal. calcd for $C_{10}H_{13}NO_3 \cdot 0.1H_2O$: C, 60.96; H, 6.75; N, 7.11. Found: C, 60.86; H, 6.39; N, 7.12.

To a solution of the above amino acid (6.87 g, 35.2 mmol) in EtOH (60 mL) was added sulfuric acid (6 mL) dropwise at room temperature. The mixture was stirred for 6 h at 80 °C. The solvent was removed in vacuo. The residue was neutralized with aq saturated $NaHCO_3$, and then extracted with AcOEt (50 mL×2). The combined organic extracts were washed with 1 N NaOH (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and evaporated to give ethyl ester (6.04 g) as a colorless solid. Mp 119–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.20 (t, 3H, J = 7.2 Hz), 2.30 (s, 3H), 2.63 (dd, 1H, J = 5.0, 16.0 Hz), 2.76 (dd, 1H, J = 8.0, 16.0 Hz), 3.94 (dd, 1H, J = 5.0, 8.0 Hz), 4.10 (q, 2H, J = 7.2 Hz), 6.75 (dd, 1H, J = 3.0, 8.0 Hz), 6.84 (d, 1H, J = 7.2 Hz), 6.86 (d, 1H, J = 3.0 Hz), 7.18 (dd, 1H, J = 7.2, 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 14.0, 33.6, 41.4, 60.6, 61.1, 113.8, 115.4, 119.2, 129.7, 142.3, 157.2, 171.8; IR (KBr) cm^{-1}: 3274, 2616, 1737, 1587, 1488, 1326, 1287, 829; HRMS calcd for $C_{12}H_{17}NO_3$ $(M)^+$ 223.1208, found 223.1205. Anal. calcd for $C_{12}H_{17}NO_3 \cdot 0.2H_2O$: C, 63.53; H, 7.73; N, 6.17. Found: C, 63.72; H, 7.56; N, 6.01.

To a solution of the above ethyl ester (5.89 g, 26.4 mmol) in THF (50 mL), Boc_2O (5.87 g, 26.9 mmol) was added dropwise at room temperature. The mixture was stirred for 12 h at room temperature. The solvent was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt 10:1 to 1:2) to give **3a** (8.53 g, 75% for two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.23 (br s, 3H), 1.47 (s, 9H), 2.63 (br s, 3H), 2.84–2.95 (m, 2H), 4.13 (br s, 2H), 5.61 (br s, 0.5H), 5.81 (br s, 0.5H), 6.73–6.80 (m, 2H), 7.16 (t, 1H, J = 8.0 Hz), 7.34 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 14.0, 28.3, 29.1, 29.7, 36.0, 36.6, 54.2, 55.6, 60.8, 80.2, 113.7, 114.4, 114.9, 118.2, 129.5, 140.3, 156.0, 156.7, 171.0; IR ($CHCl_3$) cm^{-1}: 3595, 3345, 2981, 1730, 1682, 1393, 1156, 909; HRMS calcd for $C_{17}H_{26}NO_5$ $(M+H)^+$ 324.1811, found 324.1806.

3-(*tert*-Butoxycarbonylmethylamino)-3-(4-hydroxyphenyl)-propionic acid ethyl ester (3b). This was prepared as described for the synthesis of **3a**.

Amino acid. Mp 202–203 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 2.23 (s, 3H), 2.25 (dd, 1H, J = 4.5, 15.5 Hz), 2.47 (dd, 1H, J = 10.5, 15.5 Hz), 3.94 (dd, 1H, J = 4.5, 10.5 Hz), 6.75 (d, 2H, J = 9.0 Hz), 7.20 (d, 2H, J = 9.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 30.6, 39.0, 59.9, 115.4, 128.5, 128.9, 257.4, 172.8; IR (KBr) cm^{-1}: 3001, 1593, 1398, 1269, 831; HRMS calcd for $C_{10}H_{13}NO_3$ $(M)^+$ 195.0895, found 195.0888. Anal. calcd for $C_{10}H_{13}NO_3 \cdot 0.2H_2O$: C, 60.41; H, 6.79; N, 7.04. Found: C, 60.78; H, 6.42; N, 7.19.

Ethyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.19 (t, 3H, J = 7.0 Hz), 2.28 (s, 3H), 2.63 (dd, 1H, J = 6.0, 15.6 Hz), 2.80 (dd, 1H, J = 8.0, 15.6 Hz), 3.92 (dd, 1H, J = 6.0, 8.0 Hz), 4.09 (q, 2H, J = 7.0 Hz), 4.57 (br s, 2H), 6.72 (d, 2H, J = 8.0 Hz), 7.14 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.2, 33.9, 41.8, 60.6, 60.8, 115.5, 115.6, 128.3, 132.1, 155.8, 171.8; IR ($CHCl_3$) cm^{-1}: 2983, 1725, 1614, 1514, 1257, 1171; HRMS calcd for $C_{12}H_{18}NO_3$ $(M+H)^+$ 224.1287, found 224.1288.

3b. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.22 (t, 3H, J = 6.8 Hz), 1.47 (s, 9H), 2.61 (br s, 3H), 2.87–2.90 (m, 2H), 4.09–4.15 (m, 2H), 5.24 (br s, 1H), 6.78 (d, 2H, J = 8.0 Hz), 7.12 (d, 2H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 14.0, 28.4, 29.0, 36.5, 55.0, 60.7, 80.2, 115.4, 128.2, 130.6, 155.5, 155.8, 171.0; IR ($CHCl_3$) cm^{-1}: 3596, 2982, 1730, 1682, 1258, 1159; HRMS calcd for $C_{17}H_{25}NO_5Na$ $(M+Na)^+$ 346.1631, found 346.1629.

[1-(3-Dimethylcarbamoyloxyphenyl)-3-hydroxypropyl]-methylcarbamic acid *tert*-butyl ester (4a). To a solution of **3a** (8.53 g, 26.4 mmol) and K_2CO_3 (4.74 g, 34.3

mmol) in DMF (30 mL) was added Me_2NCOCl (2.91 mL, 31.6 mmol) at room temperature. The reaction mixture was stirred for 3 h at room temperature. After dilution with water (30 mL), the mixture was extracted with AcOEt (30 mL×2), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel column chromatography (hexane–AcOEt 5:1 to 1:2) to give carbamate (9.19 g, 88%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.23 (t, 3H, J = 7.5 Hz), 1.47 (s, 9H), 2.67 (br s, 3H), 2.90–2.96 (m, 2H), 3.00 (s, 3H), 3.09 (s, 3H), 4.13 (q, 2H, J = 7.5 Hz), 5.65 (br s, 0.5H), 5.86 (br s, 0.5H), 6.99 (br s, 1H), 7.05 (dd, 1H, J = 2.0, 8.0 Hz), 7.09 (br s, 1H), 7.32 (d, 1H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 14.0, 28.2, 28.8, 29.4, 36.3, 36.5, 54.1, 55.4, 60.6, 80.0, 120.3, 120.9, 123.3, 129.1, 140.7, 151.6, 154.6, 155.4, 170.5; IR ($CHCl_3$) cm^{-1}: 2981, 1722, 1684, 1391, 1173; HRMS calcd for $C_{20}H_{31}N_2O_6$ $(M+H)^+$ 395.2182, found 395.2177.

To a solution of the carbamate (9.13 g, 23.1 mmol) in THF (60 mL) was added $LiAlH_4$ (878 mg, 23.1 mmol) at −20 °C. The reaction mixture was stirred for 10 min at −20 to −10 °C. To the reaction mixture was added water (0.8 mL), 15% of aq NaOH (0.8 mL), water (2.4 mL), and $MgSO_4$ successively. After filtration, organic solvent was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt 1:1 to AcOEt) to provide compound **4a** (4.94 g, 61%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.50 (s, 9H), 1.90–2.00 (m, 1H), 2.13–2.20 (m, 1H), 2.46 (br s, 3H), 3.01 (s, 3H), 3.10 (s, 3H), 3.51 (br s, 1H), 3.62 (br s, 1H), 3.72 (br s, 1H), 5.57 (br d, 1H, J = 10.0 Hz), 7.04 (d, 2H, J = 6.5 Hz), 7.13 (br d, 1H, J = 6.5 Hz), 7.33 (t, 1H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 28.3, 28.7, 31.7, 36.3, 36.6, 52.8, 58.4, 80.3, 120.8, 121.1, 124.6, 129.1, 140.9, 151.6, 154.7, 157.6; IR ($CHCl_3$) cm^{-1}: 2980, 1717, 1662, 1392, 1174, 1152; HRMS calcd for $C_{18}H_{29}N_2O_5$ $(M+H)^+$ 353.2076, found 353.2068.

[1-(4-Dimethylcarbamoyloxyphenyl)-3-hydroxypropyl]-methylcarbamic acid *tert*-butyl ester (4b). This was prepared as described in the synthesis of **4a**.

Carbamate. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.23 (t, 3H, J = 6.5 Hz), 1.47 (s, 9H), 2.63 (br s, 3H), 2.88–2.96 (m, 2H), 3.00 (s, 3H), 3.09 (s, 3H), 4.11–4.14 (m, 2H), 5.76 (br s, 1H), 7.09 (d, 2H, J = 8.0 Hz), 7.25 (br d, 2H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 14.0, 28.3, 29.2, 36.3, 36.6, 53.9, 55.1, 60.6, 79.8, 121.6, 127.7, 136.0, 150.7, 154.6, 170.6; IR ($CHCl_3$) cm^{-1}: 2981, 1722, 1391, 1175; HRMS calcd for $C_{20}H_{30}N_2O_6Na$ $(M+Na)^+$ 417.2001, found 417.2040.

4b. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.50 (s, 9H), 1.90–2.00 (m, 1H), 2.14–2.20 (m, 1H), 2.43 (br s, 3H), 3.01 (s, 3H), 3.10 (s, 3H), 3.51 (br s, 1H), 3.74 (br s, 1H), 5.58 (br d, 1H, J = 10.0 Hz), 7.09 (d, 2H, J = 9.0 Hz), 7.27 (br d, 2H, J = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 28.3, 28.6, 31.8, 36.3, 36.6, 52.6, 58.5, 80.3, 121.6, 128.5, 136.2, 150.6, 154.7, 157.6; IR ($CHCl_3$) cm^{-1}: 2980, 1714, 1657, 1391, 1152, 909; HRMS calcd for $C_{18}H_{28}N_2O_5Na$ $(M+Na)^+$ 375.1896, found 375.1911.

Dimethylcarbamic acid 3-[3-(4-methoxyphenoxy)-1-methylaminopropyl]phenyl ester hydrochloride salt (5a·HCl). To a solution of **4a** (327 mg, 0.928 mmol) and Et_3N (259 μL, 1.86 mmol) in CH_2Cl_2 (5 mL) was added MsCl (93 μL, 1.21 mmol) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C, quenched with water (10 mL), and extracted with CH_2Cl_2 (10 mL×2). The extracts were washed with 1 N HCl (10 mL), brine (10 mL) and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to give the mesylate. To a solution of *p*-methoxyphenol (115 mg, 0.93 mmol) in DMF (10 mL) was added a portion of 55% NaH (53 mg, 1.2 mmol) at 0 °C. The reaction mixture was stirred for 30 min at room temperature. To the reaction mixture was added the mesylate at room temperature. The reaction mixture was stirred for 2 h at room temperature. After addition of water (20 mL), the aqueous solution was extracted with AcOEt (30 mL×2). The combined extracts were washed with water (30 mL), brine (30 mL), dried over Na_2SO_4, filtered and evaporated in vacuo. Purification by silica gel column chromatography (hexane–AcOEt 1:1) gave *N*-Boc protected **5a**. The *N*-Boc protected **5a** was treated with 2 N HCl in AcOEt (6 mL). After stirring for 12 h at room temperature, the reaction mixture was neutralized with aq saturated $NaHCO_3$ and extracted with AcOEt (20 mL×2). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (AcOEt to AcOEt–MeOH 5:1) yielded **5a** (135 mg, 52% for two steps) as a colorless oil.

5a. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.92–2.00 (m, 1H), 2.12–2.20 (m, 1H), 2.24 (s, 3H), 2.30 (br s, 1H), 2.95 (s, 3H), 3.03 (s, 3H), 3.67–3.77 (m, 2H), 3.69 (s, 3H), 3.86 (dt, 1H, J = 6.0, 9.6 Hz), 6.74 (s, 4H), 6.98 (dd, 1H, J = 3.2, 8.0 Hz), 7.03 (s, 1H), 7.07 (d, 1H, J = 8.0 Hz), 7.25 (t, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 34.3, 36.4, 36.6, 37.2, 55.6, 62.1, 65.8, 114.3, 115.3, 120.1, 120.4, 123.9, 128.9, 144.3, 151.5, 152.6, 153.5, 154.5; IR ($CHCl_3$) cm^{-1}: 2939, 1714, 1509, 1391, 1179, 1041; HRMS calcd for $C_{20}H_{27}N_2O_4$ $(M+H)^+$ 359.1971, found 359.1978.

5a·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.46–2.53 (m, 1H), 2.50 (s, 3H), 2.86–2.93 (m, 1H), 2.98 (s, 3H), 3.07 (s, 3H), 3.59 (dt, 1H, J = 4.5, 10.5 Hz), 3.71 (s, 3H), 3.91 (quint, 1H, J = 4.5 Hz), 4.32 (dd, 1H, J = 4.5, 10.5 Hz), 6.71–6.77 (m, 4H), 7.16 (dd, 1H, J = 2.0, 7.5 Hz), 7.33 (s, 1H), 7.42 (t, 1H, J = 7.5 Hz), 7.46 (d, 1H, J = 7.5 Hz), 8.44 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 31.2, 33.8, 36.3, 36.5, 55.5, 61.4, 64.0, 114.4, 115.4, 121.7, 122.8, 124.9, 130.1, 135.2, 151.9, 152.4, 153.8, 154.3; IR ($CHCl_3$) cm^{-1}: 2962, 2715, 1721, 1509, 1391, 1242, 1179, 1038; HRMS calcd for $C_{20}H_{27}N_2O_4$ $(M+H)^+$ 359.1971, found 359.1960.

Dimethylcarbamic acid 4-[1-methylamino-3-(4-nitrophenoxy)propyl]phenyl ester hydrochloride salt (5f·HCl). To a solution of **4a** (236 mg, 0.670 mmol), 4-nitrophenol

(102 mg, 0.737 mmol), and Ph_3P (263 mg, 1.00 mmol) in THF (10 mL) was added 40% diethyl azodicarboxylic acid toluene solution (263 mg, 1.00 mmol) dropwise at 0 °C. The reaction mixture was stirred for 1 h at room temperature and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt 2:1 to AcOEt) to give *N*-Boc protected **5f**. Compound **5f** was obtained by the method used for **5a**.

5f. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.05–2.14 (m, 1H), 2.14 (br s, 1H), 2.23–2.30 (m, 1H), 2.30 (s, 3H), 3.00 (s, 3H), 3.08 (s, 3H), 3.74–3.77 (m, 1H), 3.91–3.96 (m, 1H), 4.03–4.09 (m, 1H), 6.89 (d, 2H, J = 10.0 Hz), 7.04 (dd, 1H, J = 3.0, 8.0 Hz), 7.07 (s, 1H), 7.11 (d, 1H, J = 8.0 Hz), 7.28–7.33 (m, 1H), 8.15 (d, 2H, J = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 34.1, 36.3, 36.5, 61.6, 65.8, 114.4, 120.2, 120.7, 123.8, 125.7, 129.2, 141.2, 143.9, 151.8, 154.6, 163.8; IR ($CHCl_3$) cm^{-1}: 2941, 1715, 1593, 1513, 1342, 1262, 1173; HRMS calcd for $C_{19}H_{24}N_3O_5$ $(M+H)^+$ 374.1716, found 374.1739.

5f·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.54 (s, 3H), 2.63–2.68 (m, 1H), 2.97 (s, 3H), 3.00–3.07 (m, 1H), 3.07 (s, 3H), 3.80 (dt, 1H, J = 3.5, 8.5 Hz), 4.11 (quint, 1H, J = 4.5 Hz), 4.34 (br s, 1H), 6.86 (d, 2H, J = 9.0 Hz), 7.18 (d, 1H, J = 8.0 Hz), 7.33 (s, 1H), 7.44 (t, 1H, J = 8.0 Hz), 7.49 (d, 1H, J = 8.0 Hz), 8.13 (d, 2H, J = 9.0 Hz), 9.98 (br s, 1H), 10.30 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 30.9, 33.1, 36.3, 36.5, 61.2, 64.2, 114.4, 122.0, 123.3, 124.7, 125.6, 130.5, 134.0, 141.5, 152.1, 154.2, 163.0; IR ($CHCl_3$) cm^{-1}: 2978, 2710, 1721, 1594, 1516, 1343, 1258, 1173; HRMS calcd for $C_{19}H_{24}N_3O_5$ $(M+H)^+$ 374.1716, found 374.1737.

Dimethylcarbamic acid 3-(1-methylamino-3-*p*-tolyloxypropyl)phenyl ester hydrochloride salt (5b·HCl). This was prepared by the method used for **5a**. **5b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.98–2.05 (m, 1H), 2.10 (br s, 1H), 2.18–2.23 (m, 1H), 2.26 (s, 3H), 2.29 (s, 3H), 2.99 (s, 3H), 3.07 (s, 3H), 3.76 (t, 1H, J = 7.0 Hz), 3.79–3.83 (m, 1H), 3.93 (dt, 1H, J = 5.5, 10.0 Hz), 6.75 (d, 2H, J = 8.5 Hz), 7.02 (d, 1H, J = 8.0 Hz), 7.04 (d, 2H, J = 8.5 Hz), 7.08 (s, 1H), 7.12 (d, 1H, J = 8.0 Hz), 7.29 (t, 1H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 20.3, 34.3, 36.3, 36.5, 37.1, 62.2, 65.2, 114.3, 120.2, 120.5, 124.1, 129.1, 129.7, 144.6, 151.7, 154.7, 156.6; IR ($CHCl_3$) cm^{-1}: 2947, 1714, 1511, 1391, 1245, 1176; HRMS calcd for $C_{20}H_{27}N_2O_3$ $(M+H)^+$ 343.2022, found 343.2034.

5b·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.23 (s, 3H), 2.48–2.60 (m, 1H), 2.52 (t, 3H, J = 5.5 Hz), 2.90–3.01 (m, 1H), 2.98 (s, 3H), 3.06 (s, 3H), 3.58 (dt, 1H, J = 4.0, 10.0 Hz), 3.92 (quint, 1H, J = 4.0 Hz), 4.32–4.39 (m, 1H), 6.68 (d, 2H, J = 9.0 Hz), 7.00 (d, 2H, J = 9.0 Hz), 7.17 (d, 1H, J = 7.5 Hz), 7.35 (s, 1H), 7.40 (t, 1H, J = 7.5 Hz), 7.47 (d, 1H, J = 7.5 Hz), 9.93 (br s, 1H), 10.28 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 20.2, 31.0, 33.5, 36.3, 36.5, 61.4, 63.2, 114.3, 121.8, 123.0, 125.0, 129.6, 130.0, 130.2, 134.5, 151.9, 154.2, 156.1; IR ($CHCl_3$) cm^{-1}: 2975, 2714, 1721, 1511, 1391, 1244, 1177; HRMS calcd for $C_{20}H_{27}N_2O_3$ $(M+H)^+$ 343.2022, found 343.2037.

Dimethylcarbamic acid 3-[3-(4-chlorophenoxy)-1-methylaminopropyl]phenyl ester hydrochloride salt (5c·HCl). This was prepared by the method used for **5f**.

5c. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.91 (br s, 1H), 1.98–2.05 (m, 1H), 2.17–2.23 (m, 1H), 2.29 (s, 3H), 3.00 (s, 3H), 3.08 (s, 3H), 3.74 (t, 1H, J = 6.0 Hz), 3.77–3.82 (m, 1H), 3.92 (dt, 1H, J = 6.0, 9.0 Hz), 6.76 (d, 2H, J = 9.0 Hz), 7.02 (d, 1H, J = 8.0 Hz), 7.06 (s, 1H), 7.10 (d, 1H, J = 8.0 Hz), 7.19 (d, 2H, J = 9.0 Hz), 7.30 (t, 1H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 34.3, 36.3, 36.5, 36.9, 61.9, 65.3, 115.7, 120.2, 120.5, 123.9, 125.3, 129.1, 144.3, 151.7, 154.7, 157.3; IR ($CHCl_3$) cm^{-1}: 2942, 1715, 1492, 1391, 1245, 1171; HRMS calcd for $C_{19}H_{24}N_2O_3Cl$ $(M+H)^+$ 363.1475, found 363.1482.

5c·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.52 (t, 3H, J = 6.0 Hz), 2.54–2.61 (m, 1H), 2.93–2.99 (m, 1H), 2.98 (s, 3H), 3.07 (s, 3H), 3.60 (dt, 1H, J = 4.0, 9.5 Hz), 3.93 (quint, 1H, J = 5.0 Hz), 4.10–4.38 (m, 1H), 6.71 (d, 2H, J = 9.0 Hz), 7.15 (d, 2H, J = 8.0 Hz), 7.17 (d, 1H, J = 8.0 Hz), 7.31 (s, 1H), 7.42 (t, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 8.0 Hz), 9.94 (br s, 1H), 10.30 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 31.0, 33.4, 36.3, 36.5, 61.3, 63.6, 115.7, 121.9, 123.1, 124.8, 125.7, 129.1, 130.3, 134.3, 152.0, 154.2, 156.7; IR ($CHCl_3$) cm^{-1}: 2976, 2713, 1721, 1492, 1391, 1244, 1171; HRMS calcd for $C_{19}H_{24}N_2O_3Cl$ $(M+H)^+$ 363.1475, found 363.1476.

Dimethylcarbamic acid 3-[3-(4-fluorophenoxy)-1-methylaminopropyl]phenyl ester hydrochloride salt (5d·HCl). This was prepared by the method used for **5a**.

5d. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.91 (br s, 1H), 1.98–2.05 (m, 1H), 2.17–2.25 (m, 1H), 2.29 (s, 3H), 2.99 (s, 3H), 3.08 (s, 3H), 3.76 (t, 1H, J = 6.0 Hz), 3.77–3.83 (m, 1H), 3.92 (dt, 1H, J = 6.0, 9.0 Hz), 6.75–6.80 (m, 2H), 6.90–6.95 (m, 2H), 7.02 (dd, 1H, J = 2.0, 8.0 Hz), 7.07 (s, 1H), 7.11 (d, 1H, J = 8.0 Hz), 7.30 (t, 1H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 34.3, 36.3, 36.5, 37.0, 62.0, 65.8, 115.4, 115.5, 115.7, 120.2, 120.5, 124.0, 129.1, 144.5, 151.8, 154.7, 154.8, 156.1, 158.0; IR ($CHCl_3$) cm^{-1}: 2948, 1715, 1506, 1391, 1178; HRMS calcd for $C_{19}H_{24}N_2O_3F$ $(M+H)^+$ 347.1771, found 347.1788.

5d·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.51 (s, 3H), 2.51–2.58 (m, 1H), 2.90–2.96 (m, 1H), 2.98 (s, 3H), 3.07 (s, 3H), 3.61 (dt, 1H, J = 5.0, 10.0 Hz), 3.93 (quint, 1H, J = 5.0 Hz), 4.32 (dd, 1H, J = 5.0, 10.0 Hz), 6.70–6.74 (m, 2H), 6.87–6.91 (m, 2H), 7.17 (dd, 1H, J = 2.0, 8.0 Hz), 7.32 (s, 1H), 7.42 (t, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 31.1, 33.6, 36.3, 36.5, 61.4, 64.0, 115.5, 115.6, 115.7, 121.9, 123.0, 124.8, 130.3, 134.8, 152.0, 154.2, 154.3, 156.3, 158.2; IR ($CHCl_3$) cm^{-1}: 2975, 2713, 1721, 1507, 1391, 1245, 1172; HRMS calcd for $C_{19}H_{24}N_2O_3F$ $(M+H)^+$ 347.1771, found 347.1798.

Dimethylcarbamic acid 3-[1-methylamino-3-(4-trifluoromethylphenoxy)propyl]phenyl ester hydrochloride salt (5e·HCl). This was prepared by the method used for **5f**.

5e. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.90 (br s, 1H), 2.01–2.08 (m, 1H), 2.20–2.27 (m, 1H), 2.30 (s, 3H), 2.99 (s, 3H), 3.07 (s, 3H), 3.75 (t, 1H, J = 6.0 Hz), 3.85–3.90 (m, 1H), 4.00 (dt, 1H, J = 6.0, 9.5 Hz), 6.89 (d, 2H, J = 9.0 Hz), 7.03 (d, 1H, J = 8.0 Hz), 7.07 (s, 1H), 7.11 (d, 1H, J = 8.0 Hz), 7.30 (t, 1H, J = 8.0 Hz), 7.50 (d, 2H, J = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 34.3, 36.2, 36.5, 36.8, 61.8, 65.3, 114.4, 120.2, 120.6, 122.5, 123.3, 123.9, 125.4, 126.6, 126.7, 129.2, 144.3, 151.8, 154.7, 161.2; IR ($CHCl_3$) cm^{-1}: 2941, 1715, 1391, 1329, 1255, 1177, 1113; HRMS calcd for $C_{20}H_{24}N_2O_3F_3$ $(M+H)^+$ 397.1739, found 397.1727.

5e·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.54 (t, 3H, J = 6.0 Hz), 2.58–2.65 (m, 1H), 2.97 (s, 3H), 2.99–3.03 (m, 1H), 3.05 (s, 3H), 3.70 (dt, 1H, J = 5.0, 10.0 Hz), 4.02 (quint, 1H, J = 5.0 Hz), 4.34–4.40 (m, 1H), 6.85 (d, 2H, J = 9.0 Hz), 7.18 (d, 1H, J = 7.5 Hz), 7.33 (s, 1H), 7.43 (t, 1H, J = 7.5 Hz), 7.47 (d, 2H, J = 9.0 Hz), 7.50 (d, 1H, J = 7.5 Hz), 9.99 (br s, 1H), 10.34 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 30.9, 33.2, 36.2, 36.4, 61.2, 63.5, 114.3, 121.9, 122.8, 123.0, 123.1, 124.7, 125.2, 126.6, 130.3, 134.2, 152.0, 154.1, 160.5; IR ($CHCl_3$) cm^{-1}: 2977, 2711, 1722, 1329, 1252, 1177; HRMS calcd for $C_{20}H_{24}N_2O_3F_3$ $(M+H)^+$ 397.1739, found 397.1733.

Compounds **6a–j** were prepared by the method used for **5a–f** from the corresponding alcohol **4b**.

Dimethylcarbamic acid 4-[3-(4-methoxyphenoxy)-1-methylaminopropyl]phenyl ester hydrochloride salt (6a·HCl). 6a. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.94–2.02 (m, 1H), 2.03 (br s, 1H), 2.16–2.23 (m, 1H), 2.26 (s, 3H), 2.98 (s, 3H), 3.07 (s, 3H), 3.72–3.78 (m, 2H), 3.72 (s, 3H), 3.88 (dt, 1H, J = 6.0, 8.5 Hz), 6.76–6.81 (m, 4H), 7.07 (d, 2H, J = 9.0 Hz), 7.28 (d, 2H, J = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 34.1, 36.2, 36.4, 37.2, 55.5, 61.8, 65.7, 114.4, 115.3, 121.5, 127.8, 139.6, 150.4, 152.8, 153.6, 154.7; IR ($CHCl_3$) cm^{-1}: 2939, 1713, 1509, 1391, 1175, 1041; HRMS calcd for $C_{20}H_{27}N_2O_4$ $(M+H)^+$ 359.1971, found 359.1972.

6a·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.50 (s, 3H), 2.51–2.58 (m, 1H), 2.90–2.98 (m, 1H), 2.99 (s, 3H), 3.08 (s, 3H), 3.53 (dt, 1H, J = 4.0, 9.5 Hz), 3.71 (d, 3H, J = 4.0 Hz), 3.86–3.92 (m, 1H), 4.37 (dd, 1H, J = 5.0, 11.0 Hz), 6.70–6.76 (m, 4H), 7.17 (d, 2H, J = 8.0 Hz), 7.62 (d, 2H, J = 8.0 Hz), 10.03 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 30.9, 33.6, 36.3, 36.5, 55.5, 61.3, 63.8, 114.4, 115.3, 122.6, 129.5, 129.9, 152.2, 152.3, 153.8, 154.2; IR ($CHCl_3$) cm^{-1}: 2962, 1722, 1509, 1391, 1177, 1038, 909; HRMS calcd for $C_{20}H_{27}N_2O_4$ $(M+H)^+$ 359.1971, found 359.1981.

Dimethylcarbamic acid 4-(1-methylamino-3-*p*-tolyloxypropyl)phenyl ester hydrochloride salt (6b·HCl). 6b. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.96–2.02 (m, 1H), 2.13–2.24 (m, 1H), 2.26 (s, 3H), 2.27 (s, 3H), 2.99 (s, 3H), 3.07 (s, 3H), 3.74–3.81 (m, 2H), 3.91 (dt, 1H, J = 6.0, 9.5 Hz), 6.74 (d, 2H, J = 8.5 Hz), 7.04 (d, 2H, J = 8.5 Hz), 7.07 (d, 2H, J = 8.5 Hz), 7.28 (d, 2H, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 20.3, 34.2, 36.2, 36.5, 37.2, 61.8, 65.1, 114.2, 121.5, 127.8, 129.7, 139.6, 150.4, 154.7, 156.5; IR ($CHCl_3$) cm^{-1}: 2941, 1713, 1511, 1391, 1244, 1175; HRMS calcd for $C_{20}H_{27}N_2O_3$ $(M+H)^+$ 343.2022, found 343.2032.

6b·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.23 (s, 3H), 2.50 (s, 3H), 2.52–2.59 (m, 1H), 2.90–2.98 (m, 1H), 2.99 (s, 3H), 3.07 (s, 3H), 3.54 (dt, 1H, J = 4.0, 9.5 Hz), 3.89–3.92 (m, 1H), 4.35–4.39 (m, 1H), 6.67 (d, 2H, J = 8.5 Hz), 7.00 (d, 2H, J = 8.5 Hz), 7.17 (d, 2H, J = 8.5 Hz), 7.61 (d, 2H, J = 8.5 Hz), 9.89 (br s, 1H), 10.19 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 20.2, 30.9, 33.5, 36.2, 36.5, 61.2, 63.1, 114.1, 122.6, 129.4, 129.6, 129.9, 130.0, 152.1, 154.1, 156.0; IR ($CHCl_3$) cm^{-1}: 2974, 2714, 1722, 1511, 1391, 1242, 1177; HRMS calcd for $C_{20}H_{27}N_2O_3$ $(M+H)^+$ 343.2022, found 343.2048.

Dimethylcarbamic acid 4-(1-methylamino-3-phenoxypropyl)phenyl ester hydrochloride salt (6c·HCl). 6c. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.97–2.03 (m, 1H), 2.08 (br s, 1H), 2.19–2.26 (m, 1H), 2.28 (s, 3H), 2.99 (s, 3H), 3.07 (s, 3H), 3.76 (t, 1H, J = 7.0 Hz), 3.79–3.84 (m, 1H), 3.94 (dt, 1H, J = 6.0, 8.5 Hz), 6.84 (d, 2H, J = 8.0 Hz), 6.91 (d, 1H, J = 8.0 Hz), 7.08 (d, 2H, J = 8.0 Hz), 7.30 (t, 2H, J = 8.0 Hz), 7.28 (d, 2H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 34.2, 36.2, 36.5, 37.2, 61.8, 64.9, 114.4, 120.5, 121.6, 127.8, 129.2, 139.6, 150.4, 154.7, 158.6; IR ($CHCl_3$) cm^{-1}: 2942, 1713, 1497, 1391, 1245, 1174; HRMS calcd for $C_{19}H_{25}N_2O_3$ $(M+H)^+$ 329.1865, found 329.1860.

6c·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.47–2.52 (m, 1H), 2.47 (s, 3H), 2.84–2.91 (m, 1H), 2.99 (s, 3H), 3.07 (s, 3H), 3.60 (dt, 1H, J = 4.0, 9.5 Hz), 3.91–3.96 (m, 1H), 4.31 (dd, 1H, J = 4.0, 10.0 Hz), 6.78 (d, 2H, J = 8.0 Hz), 7.16 (d, 2H, J = 8.0 Hz), 7.19–7.22 (m, 3H), 7.58 (d, 2H, J = 8.0 Hz), 8.40 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 31.2, 33.8, 36.2, 36.5, 61.2, 63.2, 114.3, 120.7, 122.5, 129.2, 129.3, 130.9, 151.9, 154.2, 158.1; IR ($CHCl_3$) cm^{-1}: 2971, 2713, 1721, 1497, 1391, 1244, 1176; HRMS calcd for $C_{19}H_{25}N_2O_3$ $(M+H)^+$ 329.1865, found 329.1883.

Dimethylcarbamic acid 4-[3-(4-chlorophenoxy)-1-methylaminopropyl]phenyl ester hydrochloride salt (6d·HCl). 6d. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.94–2.03 (m, 1H), 2.18–2.26 (m, 1H), 2.28 (s, 3H), 3.00 (s, 3H), 3.08 (s, 3H), 3.73–3.80 (m, 2H), 3.91 (dt, 1H, J = 6.0, 9.6 Hz), 6.76 (d, 2H, J = 8.8 Hz), 7.08 (d, 2H, J = 8.0 Hz), 7.19 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 34.2, 36.3, 36.5, 37.0, 61.7, 65.4, 115.7, 121.7, 125.4, 127.8, 129.1, 139.4, 150.6, 154.8, 157.3; IR ($CHCl_3$) cm^{-1}: 2941, 1714, 1492, 1391, 1246, 1173; HRMS calcd for $C_{19}H_{24}N_2O_3Cl$ $(M+H)^+$ 363.1475, found 363.1477.

6d·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.50 (t, 3H, J = 6.0 Hz), 2.53–2.58 (m, 1H), 2.93–2.98 (m, 1H), 2.99 (s, 3H), 3.08 (s, 3H), 3.58 (dt, 1H, J = 4.5, 9.5 Hz), 3.91 (dt, 1H, J = 4.5, 9.5 Hz), 4.32–4.39 (m, 1H), 6.70 (d, 2H, J = 8.5 Hz), 7.15 (d, 2H, J = 8.5 Hz), 7.17 (d, 2H, J = 8.5 Hz), 7.60 (d, 2H, J = 8.5 Hz), 9.90 (br s, 1H), 10.21 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm:

31.0, 33.4, 36.3, 36.6, 115.6, 122.7, 125.8, 129.1, 129.4, 129.7, 152.3, 154.2, 156.8; IR ($CHCl_3$) cm^{-1}: 2974, 2712, 1723, 1492, 1391, 1244, 1176; HRMS calcd for $C_{19}H_{24}N_2O_3Cl$ $(M+H)^+$ 363.1475, found 363.1470.

Dimethylcarbamic acid 4-[3-(4-fluorophenoxy)-1-methylaminopropyl]phenyl ester hydrochloride salt (6e·HCl). **6e**. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.96–2.03 (m, 2H), 2.18–2.25 (m, 1H), 2.28 (s, 3H), 3.00 (s, 3H), 3.08 (s, 3H), 3.74–3.80 (m, 2H), 3.90 (dt, 1H, $J=6.0$, 8.5 Hz), 6.75–6.78 (m, 2H), 6.91–6.94 (m, 2H), 7.08 (d, 2H, $J=8.5$ Hz), 7.28 (d, 2H, $J=8.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 34.2, 36.3, 36.5, 37.1, 61.8, 65.7, 115.3, 115.4, 115.5, 115.7, 121.6, 127.8, 139.5, 150.5, 154.8, 154.9, 156.1, 158.0; IR ($CHCl_3$) cm^{-1}: 2947, 1714, 1506, 1391, 1175; HRMS calcd for $C_{19}H_{24}N_2O_3F$ $(M+H)^+$ 347.1771, found 347.1784.

6e·HCl. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.52 (s, 3H), 2.53–2.62 (m, 1H), 2.92–3.02 (m, 1H), 3.00 (s, 3H), 3.08 (s, 3H), 3.54–3.62 (m, 1H), 3.88–3.96 (m, 1H), 4.38 (br s, 1H), 6.69–6.74 (m, 2H), 6.87–6.92 (m, 2H), 7.17–7.21 (m, 2H), 7.61–7.64 (m, 2H), 9.90 (br s, 1H), 10.21 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 30.9, 33.4, 36.2, 61.1, 63.8, 115.3, 115.4, 115.5, 115.6, 122.6, 129.4, 129.7, 152.2, 154.1, 154.2, 156.2, 158.1; IR ($CHCl_3$) cm^{-1}: 2975, 2713, 1722, 1507, 1392, 1177; HRMS calcd for $C_{19}H_{24}N_2O_3F$ $(M+H)^+$ 347.1771, found 347.1784.

Dimethylcarbamic acid 4-[1-methylamino-3-(4-trifluoromethylphenoxy)propyl]phenyl ester hydrochloride salt (6f·HCl). **6f**. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.00 (br s, 1H), 2.00–2.07 (m, 1H), 2.21–2.29 (m, 1H), 2.29 (s, 3H), 3.00 (s, 3H), 3.09 (s, 3H), 3.76 (t, 1H, $J=6.0$ Hz), 3.83–3.88 (m, 1H), 3.91 (dt, 1H, $J=5.0$, 9.5 Hz), 6.89 (d, 2H, $J=8.0$ Hz), 7.09 (d, 2H, $J=9.0$ Hz), 7.28 (d, 2H, $J=9.0$ Hz), 7.50 (d, 2H, $J=8.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 34.2, 36.3, 36.5, 36.9, 61.6, 65.3, 114.3, 121.7, 126.7, 126.8, 127.8, 139.4, 150.6, 154.8, 161.2; IR ($CHCl_3$) cm^{-1}: 2941, 1714, 1392, 1328, 1256, 1174, 1122; HRMS calcd for $C_{20}H_{24}N_2O_3F_3$ $(M+H)^+$ 397.1739, found 397.1712.

6f·HCl. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.52 (t, 3H, $J=5.5$ Hz), 2.53–2.64 (m, 1H), 2.98–3.03 (m, 1H), 2.99 (s, 3H), 3.08 (s, 3H), 3.65 (dt, 1H, $J=4.0$, 10.0 Hz), 4.00 (quint, 1H, $J=5.0$ Hz), 4.34–4.42 (m, 1H), 6.83 (d, 2H, $J=8.5$ Hz), 7.18 (d, 2H, $J=8.5$ Hz), 7.46 (d, 2H, $J=8.5$ Hz), 7.62 (d, 2H, $J=8.5$ Hz), 9.94 (br s, 1H), 10.26 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 30.9, 33.3, 36.2, 36.5, 61.1, 63.5, 114.2, 122.8, 126.7, 126.5, 129.4, 129.6, 152.3, 154.1, 160.5; IR ($CHCl_3$) cm^{-1}: 2975, 2712, 1723, 1329, 1253, 1176, 1124; HRMS calcd for $C_{20}H_{24}N_2O_3F_3$ $(M+H)^+$ 397.1739, found 397.1735.

Dimethylcarbamic acid 4-[3-(4-cyanophenoxy)-1-methylaminopropyl]phenyl ester hydrochloride salt (6g·HCl). **6g**: ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.85 (br s, 1H), 2.00–2.09 (m, 1H), 2.21–2.26 (m, 1H), 2.29 (s, 3H), 3.01 (s, 3H), 3.09 (s, 3H), 3.74 (dd, 1H, $J=6.0$, 8.0 Hz), 3.83–3.89 (m, 1H), 4.00 (dt, 1H, $J=6.0$, 9.6 Hz), 6.87 (d, 2H, $J=8.8$ Hz), 7.09 (d, 2H, $J=8.8$ Hz), 7.27 (d, 2H, $J=8.8$ Hz), 7.54 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 34.3, 34.4, 36.5, 36.7, 36.8, 61.6, 65.5, 103.7, 114.9, 115.1, 119.0, 121.7, 127.6, 133.7, 139.0, 150.5, 154.5, 161.8; IR ($CHCl_3$) cm^{-1}: 2942, 1714, 1606, 1509, 1392, 1258, 1172; HRMS calcd for $C_{20}H_{24}N_3O_3$ $(M+H)^+$ 354.1818, found 354.1836.

6g·HCl. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.51 (s, 3H), 2.58–2.66 (m, 1H), 2.94–3.04 (m, 1H), 3.00 (s, 3H), 3.09 (s, 3H), 3.66–3.73 (m, 1H), 4.00–4.07 (m, 1H), 4.35 (br s, 1H), 6.84 (d, 2H, $J=9.0$ Hz), 7.19 (d, 2H, $J=8.0$ Hz), 7.52 (d, 2H, $J=8.0$ Hz), 7.61 (d, 2H, $J=9.0$ Hz), 9.92 (br s, 1H), 10.25 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 30.9, 33.1, 36.3, 36.5, 61.0, 63.7, 104.2, 115.0, 118.8, 122.8, 129.3, 129.4, 133.8, 152.3, 154.1, 161.3; IR ($CHCl_3$) cm^{-1}: 2976, 2711, 1723, 1606, 1509, 1392, 1255, 1174; HRMS calcd for $C_{20}H_{24}N_3O_3$ $(M+H)^+$ 354.1818, found 354.1824.

Dimethylcarbamic acid 4-[1-methylamino-3-(2-nitrophenoxy)propyl]phenyl ester hydrochloride salt (6h·HCl). **6h**. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.03–2.10 (m, 1H), 2.24–2.34 (m, 1H), 2.30 (s, 3H), 3.00 (s, 3H), 3.09 (s, 3H), 3.86 (t, 1H, $J=6.0$ Hz), 3.91 (dt, 1H, $J=5.0$, 9.0 Hz), 4.13 (dt, 1H, $J=5.0$, 10.0 Hz), 6.96 (d, 1H, $J=7.5$ Hz), 6.99 (t, 1H, $J=8.0$ Hz), 7.08 (d, 2H, $J=8.0$ Hz), 7.32 (d, 2H, $J=8.0$ Hz), 7.46 (t, 1H, $J=8.0$ Hz), 7.83 (d, 1H, $J=7.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 34.2, 36.3, 36.5, 36.6, 61.4, 66.6, 114.2, 120.1, 121.7, 125.5, 127.9, 134.0, 139.1, 139.6, 150.6, 152.1, 154.8; IR ($CHCl_3$) cm^{-1}: 2942, 1714, 1526, 1392, 1175; HRMS calcd for $C_{19}H_{24}N_3O_5$ $(M+H)^+$ 374.1716, found 374.1742.

6h·HCl. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.54 (s, 3H), 2.63 (br t, 1H, $J=10.0$ Hz), 2.96–3.04 (m, 1H), 2.99 (s, 3H), 3.08 (s, 3H), 3.74 (br t, 1H, $J=9.0$ Hz), 4.28–4.34 (m, 1H), 4.45–4.52 (m, 1H), 6.95 (d, 1H, $J=8.0$ Hz), 7.00 (t, 1H, $J=8.0$ Hz), 7.16 (d, 2H, $J=9.0$ Hz), 7.46 (t, 1H, $J=8.0$ Hz), 7.71 (d, 2H, $J=9.0$ Hz), 7.84 (d, 1H, $J=8.0$ Hz), 9.87 (br s, 1H), 10.16 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 31.1, 32.9, 36.3, 36.6, 60.9, 64.7, 114.4, 120.6, 122.7, 125.6, 129.6, 129.8, 134.3, 139.3, 151.5, 152.3, 154.3; IR ($CHCl_3$) cm^{-1}: 2975, 2713, 1723, 1492, 1445, 1244, 1176; HRMS calcd for $C_{19}H_{24}N_3O_5$ $(M+H)^+$ 374.1716, found 374.1730.

Dimethylcarbamic acid 4-[1-methylamino-3-(3-nitrophenoxy)propyl]phenyl ester hydrochloride salt (6i·HCl). **6i**. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.92 (br s, 1H), 2.04–2.12 (m, 1H), 2.24–2.29 (m, 1H), 2.29 (s, 3H), 3.00 (s, 3H), 3.09 (s, 3H), 3.77 (t, 1H, $J=6.4$ Hz), 3.90 (q, 1H, $J=8.0$ Hz), 4.01–4.07 (m, 1H), 7.09 (d, 2H, $J=8.8$ Hz), 7.15 (dd, 1H, $J=2.4$, 8.0 Hz), 7.29 (d, 2H, $J=8.8$ Hz), 7.36–7.41 (m, 1H), 7.66 (t, 1H, $J=2.4$ Hz), 7.78 (dd, 1H, $J=2.4$, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 34.3, 36.4, 36.6, 36.8, 61.5, 65.8, 108.7, 115.4, 121.1, 121.6, 127.6, 129.6, 139.1, 148.8, 150.4, 154.5, 159.0; IR ($CHCl_3$) cm^{-1}: 2940, 1714, 1531, 1392, 1352, 1246, 1174; HRMS calcd for $C_{19}H_{24}N_3O_5$ $(M+H)^+$ 374.1716, found 374.1746.

6i·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.53 (t, 3H, J = 6.0 Hz), 2.62–2.67 (m, 1H), 2.99 (s, 3H), 2.99–3.06 (m, 1H), 3.09 (s, 3H), 3.73 (dt, 1H, J = 5.0, 10.0 Hz), 4.08 (quint, 1H, J = 5.0 Hz), 4.36–4.40 (m, 1H), 7.14 (dd, 1H, J = 2.0, 8.0 Hz), 7.20 (d, 2H, J = 8.0 Hz), 7.37 (t, 1H, J = 8.0 Hz), 7.57 (s, 1H), 7.63 (d, 2H, J = 8.0 Hz), 7.77 (t, 1H, J = 8.0 Hz), 9.96 (br s, 1H), 10.29 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 30.9, 33.2, 36.3, 36.5, 61.1, 64.0, 108.8, 115.9, 121.2, 122.8, 129.4, 129.5, 129.9, 148.9, 152.4, 154.1, 158.6; IR ($CHCl_3$) cm^{-1}: 2975, 2710, 1723, 1532, 1392, 1352, 1246, 1176; HRMS calcd for $C_{19}H_{24}N_3O_5$ $(M+H)^+$ 374.1716, found 374.1733.

Dimethylcarbamic acid 4-[1-methylamino-3-(4-nitrophenoxy)propyl]phenyl ester hydrochloride salt (6j·HCl). **6j**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.02–2.10 (m, 1H), 2.22–2.31 (m, 1H), 2.29 (s, 3H), 2.96 (s, 3H), 3.05 (s, 3H), 3.75 (dd, 1H, J = 5.6, 7.2 Hz), 3.88–3.94 (m, 1H), 4.05 (dt, 1H, J = 5.6, 9.6 Hz), 6.83 (d, 2H, J = 8.8 Hz), 7.04 (d, 2H, J = 8.0 Hz), 7.22 (d, 2H, J = 8.0 Hz), 8.12 (d, 2H, J = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 34.2, 36.3, 36.6, 36.7, 61.5, 65.9, 114.3, 121.8, 125.8, 127.8, 139.1, 141.3, 150.7, 154.8, 163.8; IR ($CHCl_3$) cm^{-1}: 2941, 1714, 1593, 1512, 1498, 1392, 1342, 1263, 1173, 1112, 1017, 861, 846; HRMS calcd for $C_{19}H_{24}N_3O_5$ $(M+H)^+$ 374.1716, found 374.1732.

6j·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.47 (t, 3H, J = 5.6 Hz), 2.57–2.63 (m, 1H), 2.93–3.02 (m, 1H), 2.96 (s, 3H), 3.04 (s, 3H), 3.69 (dt, 1H, J = 4.0, 10.0 Hz), 4.04 (quint, 1H, J = 4.8 Hz), 4.23–4.32 (m, 1H), 6.81 (d, 2H, J = 9.2 Hz), 7.14 (d, 2H, J = 8.4 Hz), 7.54 (d, 2H, J = 8.4 Hz), 8.10 (d, 2H, J = 9.2 Hz), 9.94 (br s, 1H), 10.30 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 31.1, 33.3, 36.5, 36.8, 61.2, 64.2, 114.3, 122.9, 125.7, 129.2, 129.3, 141.5, 152.3, 154.0, 162.8; IR ($CHCl_3$) cm^{-1}: 2975, 2710, 1723, 1594, 1515, 1498, 1392, 1343, 1258, 1175, 1112, 1031, 846; HRMS calcd for $C_{19}H_{24}N_3O_5$ $(M+H)^+$ 374.1716, found 374.1723.

[1-(4-Hydroxyphenyl)-3-(4-nitrophenoxy)propyl]methylcarbamic acid *tert*-butyl ester (7). To a solution of **4b** (1.32 g, 3.75 mmol), 4-nitrophenol (573 mg, 4.12 mmol), and Ph_3P (1.47 g, 5.60 mmol) in THF (15 mL) was added 40% diethyl azodicarboxylic acid toluene solution (2.44 g, 5.60 mmol) dropwise at 0 °C. The reaction mixture was stirred for 1 h at room temperature, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt 2:1 to 1:1) to give a crude product.

To a solution of this crude compound in MeOH (20 mL) was added 15% of aq NaOH (5.0 mL) at room temperature. The reaction mixture was stirred for 30 min at 65 °C, and then concentrated in vacuo. The residue was neutralized with 1 N HCl, and then extracted with AcOEt (30 mL×2). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 5:1 to 1:1) provided phenol **7** (820 mg, 54% for two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.41 (s, 9H), 2.33–2.45 (m, 2H), 2.58 (s, 3H), 4.11 (br t, 2H, J = 5.5 Hz), 5.53 (br, 1H), 6.85 (d, 2H, J = 8.0 Hz), 6.94 (d, 2H, J = 9.0 Hz), 7.14 (d, 2H, J = 8.0 Hz), 8.16 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 28.3, 39.4, 54.4, 65.6, 80.3, 114.3, 115.4, 125.8, 128.5, 130.5, 141.4, 155.8, 156.4, 163.8; IR ($CHCl_3$) cm^{-1}: 3595, 2980, 1680, 1594, 1513, 1342, 1263, 1172, 1148, 1112, 845; HRMS calcd for $C_{21}H_{26}N_2O_6Na$ $(M+Na)^+$ 425.1688, found 425.1682.

Methylcarbamic acid 4-[1-methylamino-3-(4-nitrophenoxy)propyl]phenyl ester hydrochloride salt (8a·HCl). To a solution of **7** (123 mg, 0.306 mmol) and Et_3N (128 μL, 0.918 mmol) in CH_2Cl_2 (2 mL) was added methyl isocyanate (30 μL, 0.46 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature, quenched with water (5 mL), and extracted with AcOEt (5 mL×2). The extracts were washed with brine (5 mL) and dried over Na_2SO_4. Purification by silica gel column chromatography (hexane–AcOEt 9:1 to 1:9) gave the corresponding carbamate (135 mg, 96%) as a colorless oil. Compound **8a** was obtained by the method used for **5a**.

8a. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.98–2.06 (m, 1H), 2.18–2.23 (m, 1H), 2.26 (s, 3H), 2.86 (d, 3H, J = 5.1 Hz), 2.93 (br, 1H), 3.71 (t, 1H, J = 6.9 Hz), 3.85–3.90 (m, 1H), 4.02 (dt, 1H, J = 5.9, 9.6 Hz), 4.92 (br, 1H), 6.83 (d, 2H, J = 9.5 Hz), 7.06 (d, 2H, J = 8.8 Hz), 7.23 (d, 2H, J = 8.8 Hz), 8.12 (d, 2H, J = 9.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 27.5, 34.1, 36.6, 61.4, 65.9, 114.3, 121.5, 125.7, 127.7, 139.2, 141.2, 150.2, 155.1, 163.7; IR (film) cm^{-1}: 3329, 2944, 1733, 1592, 1506, 1341, 1263, 1214, 1110, 846, 753; HRMS calcd for $C_{18}H_{21}N_3O_5Na$ $(M+Na)^+$ 382.1379, found 382.1378.

8a·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.47 (s, 3H), 2.56-2.63 (m, 1H), 2.86 (d, 3H, J = 4.4 Hz), 2.96–3.02 (m, 1H), 3.71 (dt, 1H, J = 4.4, 9.5 Hz), 4.03–4.09 (m, 1H), 4.26 (dd, 1H, J = 4.4, 10.2 Hz), 4.95 (d, 1H, J = 5.1 Hz), 6.81 (d, 2H, J = 9.5 Hz), 7.16 (d, 2H, J = 8.8 Hz), 7.54 (d, 2H, J = 8.8 Hz), 8.11 (d, 2H, J = 9.5 Hz); IR (KBr) cm^{-1}: 3306, 2944, 1739, 1592, 1508, 1342, 1260, 1218, 1175, 1110, 848; HRMS calcd for $C_{18}H_{21}N_3O_5Na$ $(M+Na)^+$ 382.1379, found 382.1378.

Ethylcarbamic acid 4-[1-methylamino-3-(4-nitrophenoxy)-propyl]phenyl ester hydrochloride salt (8b·HCl). This was prepared using a method similar to that used for **8a**.

8b. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.18 (t, 3H, J = 7.3 Hz), 1.98–2.06 (m, 1H), 2.18–2.23 (m, 1H), 2.25 (s, 3H), 3.24–3.31 (m, 2H), 3.70 (t, 1H, J = 7.3 Hz), 3.85–3.90 (m, 1H), 4.01 (dt, 1H, J = 5.9, 9.5 Hz), 4.94 (br, 1H), 6.84 (d, 2H, J = 9.5 Hz), 7.06 (d, 2H, J = 8.8 Hz), 7.22 (d, 2H, J = 8.8 Hz), 8.13 (d, 2H, J = 9.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 15.0, 34.2, 36.0, 36.7, 61.5, 65.9, 114.3, 121.7, 125.7, 127.8, 139.2, 141.3, 150.2, 154.4, 163.7; IR (film) cm^{-1}: 3324, 2937, 1730, 1592, 1499, 1340, 1263, 1212, 1110, 845, 753; HRMS calcd for $C_{19}H_{24}N_3O_5$ $(M+H)^+$ 374.1716, found 374.1712.

8b·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.18 (t, 3H, J = 7.3 Hz), 2.46 (s, 3H), 2.58 (br, 1H), 2.96 (br, 1H), 3.24–3.31 (m, 2H), 3.68–3.73 (m, 1H), 4.04–4.09 (m, 1H), 4.24 (dd, 1H, J = 4.4, 10.3 Hz), 4.97 (t, 1H, J = 5.9 Hz), 6.81 (d, 2H, J = 9.6 Hz), 7.17 (d, 2H, J = 8.8 Hz), 7.53 (d, 2H, J = 8.8 Hz), 8.11 (d, 2H, J = 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 15.0, 31.1, 33.2, 36.1, 61.1, 64.2, 114.2, 122.6, 122.7, 125.6, 129.3, 141.4, 151.8, 153.6, 162.8; IR (KBr) cm^{-1}: 3302, 2939, 1736, 1592, 1509, 1342, 1260, 1215, 1175, 1110, 848; HRMS calcd for $C_{19}H_{24}N_3O_5$ $(M+H)^+$ 374.1716, found 374.1708.

4-[1-Methylamino-3-(4-nitrophenoxy)propyl]phenol (8c). This was prepared from **7** by deprotection as described for **5a**. ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 2.16–2.36 (m, 2H), 2.77 (s, 3H), 3.50–3.70 (m, 2H), 5.38–5.48 (m, 1H), 6.75 (d, 2H, J = 8.4 Hz), 6.96 (d, 2H, J = 9.5 Hz), 7.12 (d, 2H, J = 8.4 Hz), 8.10 (d, 2H, J = 9.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 31.8, 33.9, 56.3, 57.4, 111.0, 115.7, 125.7, 128.1, 129.8, 135.5, 154.6, 156.5; IR (KBr) cm^{-1}: 3434, 3192, 1595, 1317, 1210, 1122; HRMS calcd for $C_{16}H_{18}N_2O_4$ $(M)^+$ 302.1266, found 302.1272. Anal. calcd for $C_{16}H_{18}N_2O_4·0.3H_2O$: C, 62.45; H, 6.09; N, 9.10. Found: C, 62.42; H, 5.95; N, 9.04.

Methyl-[3-(4-nitrophenoxy)-1-(4-vinylphenyl)propyl]-carbamic acid *tert*-butyl ester (9). To a solution of **7** (820 mg, 2.04 mmol) and pyridine (330 μL, 4.07 mmol) in CH_2Cl_2 (10 mL) was added trifluoromethanesulfonic anhydride (411 μL, 2.44 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, quenched with water (10 mL) and extracted with CH_2Cl_2 (10 mL×2). The extracts were washed with 1 N HCl (10 mL), brine (10 mL) and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to give the triflate (838 mg). To a solution of the triflate (838 mg) in 1-methyl-2-pyrrolidinone (20 mL) were added $Pd_2(dba)_3·CHCl_3$ (16 mg, 0.015 mmol), triphenylarsine (19.0 mg, 0.062 mmol), LiCl (200 mg, 4.70 mmol) and $(CH_2{=}CH)(n\text{-}Bu)_3Sn$ (550 μL, 1.88 mmol). The reaction mixture was stirred for 2 h at room temperature. After adding aq saturated KF (10 mL), the product was extracted with AcOEt (20 mL×2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt 5:1 to 2:1) to give styrene compound **9** (323 mg, 38% for two steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.41 (s, 9H), 2.38–2.50 (m, 2H), 2.60 (br s, 3H), 4.13 (br t, 2H, J = 6.0 Hz), 5.25 (d, 1H, J = 10.5 Hz), 5.60 (br, 1H), 5.75 (d, 1H, J = 17.5 Hz), 6.71 (dd, 1H, J = 10.5, 17.5 Hz), 6.95 (d, 2H, J = 8.5 Hz), 7.27 (d, 2H, J = 8.5 Hz), 7.40 (d, 2H, J = 8.5 Hz), 8.19 (d, 2H, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 28.2, 29.3, 53.9, 65.6, 79.8, 114.0, 114.3, 125.7, 126.3, 127.4, 136.1, 136.8, 138.9, 141.4, 155.9, 163.7; IR ($CHCl_3$) cm^{-1}: 2977, 1681, 1593, 1513, 1498, 1393, 1342, 1263, 1142, 1112, 845; HRMS calcd for $C_{23}H_{28}N_2O_5Na$ $(M+Na)^+$ 435.1896, found 435.1901.

[4-[1-(*tert*-Butoxycarbonylmethylamino)-3-(4-nitrophenoxy)propyl]phenyl]acetic acid (10). To a solution of **9** (389 mg, 0.94 mmol) in THF (5 mL) was added 9-BBN in THF (4.0 mL, 0.5 M) dropwise at 0 °C. The reaction mixture was stirred for 3 h at room temperature. After adding 3 N NaOH (5 mL) and 30% of aq H_2O_2 (5 mL) at 0 °C, the mixture was stirred for 30 min at room temperature. The product was extracted with AcOEt (20 mL×2) and the organic solution was washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 10:1 to 2:1) gave an alcohol (212 mg, 52%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.51 (s, 9H), 2.30–2.45 (m, 2H), 2.55 (br s, 3H), 2.84 (t, 2H, J = 6.6 Hz), 3.83 (q, 2H, J = 6.6 Hz), 4.08 (q, 2H, J = 6.6 Hz), 5.55 (br, 1H), 6.91 (d, 2H, J = 9.6 Hz), 7.21 (d, 4H, J = 9.6 Hz), 8.16 (d, 2H, J = 9.6 Hz); IR ($CHCl_3$) cm^{-1}: 3609, 2931, 1680, 1594, 1512, 1393, 1342, 1263, 1144, 1045, 909; HRMS calcd for $C_{23}H_{30}N_2O_6Na$ $(M+Na)^+$ 453.2001, found 453.2018.

To a solution of the alcohol (86 mg, 0.20 mmol) and Et_3N (150 μL, 0.60 mmol) in DMSO (3 mL) was added a portion of SO_3·py (83 mg, 0.30 mmol) at room temperature. The mixture was stirred for 2 h at room temperature. The reaction was quenched with water (10 mL) and extracted with AcOEt (15 mL×2). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 5:1 to 1:1) gave the corresponding aldehyde (30 mg, 36%) as a colorless oil. To a solution of aldehyde (25 mg, 0.046 mmol), 30% of aq H_2O_2 (0.30 mL) and NaH_2PO_4 (3 mg) in CH_3CN (0.5 mL) was added a solution of $NaClO_2$ (20 mg, 0.22 mmol) in water (0.2 mL) at room temperature. The mixture was stirred for 2 h at room temperature. The reaction was quenched with aq saturated Na_2SO_3 (5 mL) and extracted with AcOEt (10 mL×2). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated. Purification by preparative TLC (hexane–AcOEt 1:1) gave the carboxylic acid **10** (5.4 mg, 20%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.39 (s, 9H), 2.35–2.52 (m, 2H), 2.59 (br s, 3H), 3.66 (s, 2H), 4.10–4.14 (m, 2H), 5.59 (br, 1H), 6.94 (d, 2H, J = 9.0 Hz), 7.27 (d, 4H, J = 9.0 Hz), 8.19 (d, 2H, J = 9.0 Hz); IR ($CHCl_3$) cm^{-1}: 3690, 2978, 2934, 1681, 1594, 1514, 1342, 1263, 1148; HRMS calcd for $C_{23}H_{28}N_2O_7Na$ $(M+Na)^+$ 467.1794, found 467.1797.

***N*,*N*-Dimethyl-2-[4-[1-methylamino-3-(4-nitrophenoxy)-propyl]phenyl]acetamide hydrochloride salt (8d·HCl).** To a solution of the carboxylic acid **10** (5.0 mg, 0.011 mmol) in THF (2 mL) was added 1,1′-carbonyldiimidazole (9.0 mg, 0.055 mmol) at room temperature. The mixture was stirred for 1 h at room temperature. $Me_2NH·HCl$ (6.4 mg, 0.077 mmol) was added to the reaction mixture at room temperature and stirred for 3 h at this temperature. After addition of water (5 mL), the aqueous solution was extracted with AcOEt (5 mL×2). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered and evaporated. Purification by preparative TLC (AcOEt) gave *N*-Boc protected **8d** (3 mg, 55%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.39 (s, 9H), 2.34–2.48 (m, 2H), 2.59 (br s, 3H), 3.97 (s, 3H), 3.02 (s, 3H), 3.70

(s, 2H), 4.10–4.14 (m, 2H), 5.57 (br, 1H), 6.94 (d, 2H, $J=9.0$ Hz), 7.26 (s, 4H), 8.20 (d, 2H, $J=9.0$ Hz); HRMS calcd for $C_{25}H_{33}N_3O_6Na$ $(M+Na)^+$ 494.2267, found 494.2273.

Compound **8d** was prepared after deprotection as carried out for **5a**.

8d. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.98–2.05 (m, 1H), 2.19–2.26 (m, 1H), 2.29 (s, 3H), 2.97 (s, 3H), 3.01 (s, 3H), 3.70 (s, 2H), 3.77–3.80 (m, 2H), 3.88–3.93 (m, 1H), 6.87 (d, 2H, $J=9.0$ Hz), 7.26 (s, 4H), 8.16 (d, 2H, $J=9.0$ Hz); IR ($CHCl_3$) cm^{-1}: 2940, 1638, 1593, 1512, 1342, 1263, 1112, 1021, 909, 846; HRMS calcd for $C_{20}H_{26}N_3O_4$ $(M+H)^+$ 372.1924, found 372.1928.

8d·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.53 (t, 3H, $J=6.5$ Hz), 2.60–2.70 (m, 1H), 2.95–3.05 (m, 1H), 3.06 (s, 6H), 3.73 (dt, 1H, $J=4.4$, 9.6 Hz), 3.79 (s, 2H), 4.06–4.12 (m, 1H), 4.25–4.34 (m, 1H), 6.86 (d, 2H, $J=9.2$ Hz), 7.33 (d, 2H, $J=8.0$ Hz), 7.55 (d, 2H, $J=8.0$ Hz), 8.16 (d, 2H, $J=9.2$ Hz), 9.87 (br, 1H), 10.30 (br, 1H).

3-(4-Dimethylcarbamoyloxyphenyl)-3-hydroxypropionic acid ethyl ester (11). To a solution of **2b** (5.00 g, 40.9 mmol) and K_2CO_3 (6.90 g, 50.0 mmol) in DMF (20 mL) was added Me_2NCOCl (4.60 mL, 50.0 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature. After dilution with water (30 mL), the mixture was extracted with AcOEt (30 mL×2), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated to give a carbamate (7.88 g, 99%) as a colorless oil. This compound was used in the following reaction without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.03 (s, 3H), 3.12 (s, 3H), 7.30 (d, 2H, $J=8.6$ Hz), 7.90 (d, 2H, $J=8.6$ Hz), 9.98 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 36.4, 36.6, 122.1, 130.9, 133.2, 153.7, 156.2, 190.9; IR (film) cm^{-1}: 3103, 1726, 1601, 1388, 1216, 1159, 860; HRMS calcd for $C_{10}H_{11}NO_3$ $(M)^+$ 193.0739, found 193.0731.

To a solution of *i*-Pr_2NH (5.05 g, 50.0 mmol) in THF (80 mL) was added *n*-BuLi in hexane (33.8 mL, 1.6 M) dropwise at −20 °C. After stirring for 20 min at −20 °C, AcOEt (3.96 g, 45.0 mmol) was added to the reaction mixture at −78 °C. After stirring for 15 min at −78 °C, a solution of the above aldehyde (7.88 g, 40.7 mmol) in THF was added to the reaction mixture at −78 °C. The mixture was stirred for 1 h at −78 °C and quenched with aq saturated NH_4Cl (50 mL). The product was extracted with AcOEt (100 mL×2) and the organic solution was washed with water (80 mL), and brine (80 mL), dried over Na_2SO_4, filtered and evaporated to provide **11** (10.5 g, 92%) as a colorless oil. This crude **11** was used in the next reaction without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.28 (t, 3H, $J=7.2$ Hz), 2.68–2.78 (m, 2H), 3.02 (s, 3H), 3.10 (s, 3H), 3.29 (d, 1H, $J=3.2$ Hz), 4.19 (q, 2H, $J=7.2$ Hz), 5.12–5.16 (m, 1H), 7.11 (d, 2H, $J=8.8$ Hz), 7.38 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 14.0, 36.3, 36.6, 43.3, 60.8, 69.8, 121.7, 126.5, 139.4, 150.9, 154.8, 172.2; IR ($CHCl_3$) cm^{-1}: 2985, 1714, 1392, 1173, 1017, 869; HRMS calcd for $C_{14}H_{19}NO_5Na$ $(M+Na)^+$ 304.1161, found 304.1168.

Dimethylcarbamic acid 4-[1-(*tert*-butyldimethylsilanyloxy)-3-hydroxypropyl]phenyl ester (12). To a solution of **11** (10.5 g, 37.4 mmol) and imidazole (3.26 g, 48.0 mmol) in DMF (50 mL) was added *t*-butyldimethylsilyl chloride (7.23 g, 48.0 mmol) at room temperature. The mixture was stirred for 12 h at room temperature. After addition of water (50 mL), the aqueous solution was extracted with AcOEt (50 mL×2). The combined organic extracts were washed with water (50 mL), and brine (50 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 5:1 to 4:1) provided a TBS-protected compound (13.4 g, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: −0.17 (s, 3H), 0.11 (s, 3H), 0.84 (s, 9H), 1.25 (t, 3H, $J=7.2$ Hz), 2.51 (dd, 1H, $J=3.6$, 14.6 Hz), 2.69 (dd, 1H, $J=9.6$, 14.6 Hz), 3.00 (s, 3H), 3.09 (s, 3H), 4.05–4.17 (m, 2H), 5.14 (dd, 1H, $J=3.6$, 9.6 Hz), 7.06 s (d, 2H, $J=8.8$ Hz), 7.32 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: −5.3, −4.7, 14.1, 17.9, 25.6, 36.3, 36.6, 46.4, 60.4, 71.6, 121.4, 126.6, 140.9, 150.7, 154.8, 171.0; IR ($CHCl_3$) cm^{-1}: 2931, 1721, 1391, 1258, 1171, 1089, 837; HRMS calcd for $C_{20}H_{33}NO_5SiNa$ $(M+Na)^+$ 418.2026, found 418.2017.

To a solution of the TBS-protected compound (6.46 g, 16.3 mmol) in THF (40 mL) was added $LiBH_4$ (370 mg, 17.0 mmol) at 60 °C. The reaction mixture was stirred for 2 h at 60 °C. The reaction mixture was quenched with water (20 mL) and aq saturated $NaHCO_3$ (30 mL). The product was extracted with AcOEt (60 mL×2) and the organic solution was washed with water (50 mL), and then brine (50 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 5:1 to 2:1) provided primary alcohol **12** (3.86 g, 67%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: −0.15 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.86–1.97 (m, 2H), 2.36 (t, 1H, $J=5.0$ Hz), 3.00 (s, 3H), 3.09 (s, 3H), 3.66–3.78 (m, 2H), 4.95 (dd, 1H, $J=3.5$, 6.5 Hz), 7.07 (d, 2H, $J=8.5$ Hz), 7.30 (d, 2H, $J=8.5$ Hz);^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: −5.2, −4.6, 18.0, 25.7, 36.3, 36.6, 42.2, 60.1, 73.8, 121.4, 126.5, 141.3, 150.5, 154.8; IR ($CHCl_3$) cm^{-1}: 3522, 2931, 1713, 1472, 1391, 1258, 1173, 1090, 1064, 909, 838; HRMS calcd for $C_{18}H_{31}NO_4SiNa$ $(M+Na)^+$ 376.1920, found 376.1914.

Dimethylcarbamic acid 4-[1-bromo-3-(4-nitrophenoxy)-propyl]phenyl ester (13). To a solution of **12** (3.86 g, 10.9 mmol), 4-nitrophenol (1.53 g, 11.0 mmol), and Ph_3P (3.67 g, 14.0 mmol) in THF (20 mL) was added 40% diethyl azodicaboxylic acid toluene solution (6.09 g, 14.0 mmol) dropwise at 0 °C. The reaction mixture was stirred for 1 h at room temperature, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt 5:1 to 4:1) to give a 4-nitrophenoxy ether derivative (4.64 g, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: −0.16 (s, 3H), −0.05 (s, 3H), 0.85 (s, 9H), 2.11 (q, 2H,

J=7.0 Hz), 3.01 (s, 3H), 3.10 (s, 3H), 4.02 (dt, 1H, J=5.0, 9.5 Hz), 4.22 (dt, 1H, J=5.0, 9.5 Hz), 4.94 (t, 1H, J=6.5 Hz), 6.93 (d, 2H, J=9.0 Hz), 7.08 (d, 2H, J=8.0 Hz), 7.31 (d, 2H, J=8.0 Hz), 8.19 (d, 2H, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: −5.2, −4.6, 18.0, 25.7, 36.4, 36.6, 39.8, 65.0, 70.7, 114.3, 121.5, 125.9, 126.4, 141.4, 141.5, 150.6, 154.9, 163.9; IR ($CHCl_3$) cm^{-1}: 2955, 2931, 1713, 1593, 1512, 1498, 1391, 1342, 1264, 1172, 1111, 1016, 908, 837; HRMS calcd for $C_{24}H_{34}N_2O_6SiNa$ $(M+Na)^+$ 497.2084, found 497.2095.

To a solution of the 4-nitrophenoxy ether derivative (4.64 g, 9.77 mmol) in MeOH (21 mL) was added concentrated HCl (8 mL) at room temperature. The reaction mixture was stirred for 6 h at room temperature. The solvent was concentrated in vacuo. After addition of water (50 mL), the aqueous solution was extracted with AcOEt (50 mL×2). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated. Recrystallization from hexane–AcOEt gave benzyl alcohol (2.74 g, 78%) as a colorless crystal. Mp 110–112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.10 (d, 1H, J=3.0 Hz), 2.16–2.31 (m, 2H), 3.01 (s, 3H), 3.10 (s, 3H), 4.11 (dt, 1H, J=6.0, 9.0 Hz), 4.25–4.29 (m, 1H), 4.99 (quint, 1H, J=4.0 Hz), 6.95 (d, 2H, J=9.5 Hz), 7.11 (d, 2H, J=8.5 Hz), 7.37 (d, 2H, J=8.5 Hz), 8.20 (d, 2H, J=9.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 36.4, 36.6, 38.0, 65.7, 70.7, 114.4, 121.9, 125.8, 126.5, 140.7, 141.5, 151.0, 154.8, 163.8; IR (KBr) cm^{-1}: 3378, 2887, 1715, 1592, 1509, 1391, 1342, 1261, 1220, 1175, 1110, 1037, 862, 847, 750; HRMS calcd for $C_{18}H_{20}N_2O_6Na$ $(M+Na)^+$ 383.1219, found 383.1222. Anal. calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.90; H, 5.67; N, 7.74.

To a solution of the benzyl alcohol (3.77 g, 10.5 mmol) and CBr_4 (4.16 g, 12.6 mmol) in CH_2Cl_2 (20 mL) was added Ph_3P (3.29 g, 12.6 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt 5:1 to 2:1) to provide benzyl bromide **13** (4.04 g, 91%) as a colorless solid. Mp 98–100 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.55–2.62 (m, 1H), 2.69–2.76 (m, 1H), 3.01 (s, 3H), 3.10 (s, 3H), 4.11 (dt, 1H, J=6.0, 9.5 Hz), 4.22–4.27 (m, 1H), 5.25 (dd, 1H, J=6.0, 9.5 Hz), 6.95 (d, 2H, J=8.5 Hz), 7.11 (d, 2H, J=8.5 Hz), 7.42 (d, 2H, J=8.5 Hz), 8.20 (d, 2H, J=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 36.4, 36.7, 39.2, 50.2, 66.3, 114.4, 122.1, 125.9, 128.2, 137.8, 141.7, 151.5, 154.5, 163.5; IR (KBr) cm^{-1}: 1716, 1593, 1511, 1347, 1268, 1221, 1175; HRMS calcd for $C_{18}H_{20}N_2O_5Br$ $(M+H)^+$ 423.0563, found 423.0549. Anal. calcd for $C_{18}H_{19}BrN_2O_7$: C, 51.08; H, 4.52; N, 6.62. Found: C, 51.47; H, 4.33; N, 6.59.

Dimethylcarbamic acid 4-[1-morpholin-4-yl-3-(4-nitrophenoxy)propyl]phenyl ester hydrochloride salt (14g·HCl). To a solution of benzyl bromide **13** (111 mg, 0.260 mmol) in CH_3CN (10 mL) was added morpholine (100 mg, 1.15 mmol) at room temperature. The reaction mixture was stirred for 5 h at room temperature. The solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (AcOEt to AcOEt–MeOH 10:1) to give **14g** (94 mg, 84%) as a colorless oil.

14g. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.04–2.14 (m, 1H), 2.41–2.54 (m, 5H), 3.01 (s, 3H), 3.10 (s, 3H), 3.52 (dd, 1H, J=6.4, 9.2 Hz), 3.68 (t, 4H, J=4.4 Hz), 3.83 (q, 1H, J=9.2 Hz), 3.99 (dt, 1H, J=6.4, 9.2 Hz), 6.85 (d, 2H, J=8.8 Hz), 7.09 (d, 2H, J=8.0 Hz), 7.23 (d, 2H, J=8.0 Hz), 8.16 (d, 2H, J=8.8 Hz); IR ($CHCl_3$) cm^{-1}: 2963, 1714, 1593, 1512, 1498, 1392, 1343, 1264, 1173, 1113; HRMS calcd for $C_{22}H_{28}N_3O_6$ $(M+H)^+$ 430.1978, found 430.1987.

14g·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.69 (br q, 1H, J=7.2 Hz), 2.92 (br s, 2H), 3.01 (s, 3H), 3.10 (s, 3H), 3.64 (br t, 1H, J=8.0 Hz), 3.79 (d, 1H, J=12.0 Hz), 3.88 (d, 1H, J=12.0 Hz), 4.01 (d, 1H, J=12.0 Hz), 4.07–4.10 (m, 1H), 4.19 (br s, 1H), 4.26 (t, 1H, J=12.0 Hz), 4.52 (t, 1H, J=12.0 Hz), 6.80 (d, 2H, J=9.0 Hz), 7.22 (d, 2H, J=9.0 Hz), 7.65 (br s, 2H), 8.15 (d, 2H, J=9.0 Hz); IR ($CHCl_3$) cm^{-1}: 2974, 2316, 1725, 1594, 1514, 1498, 1392, 1344, 1260, 1174; HRMS calcd for $C_{22}H_{28}N_3O_6$ $(M+H)^+$ 430.1978, found 430.1989.

Preparation of compounds **14c**,**e**,**f** was carried out by a method similar to that used for **14g**.

Dimethylcarbamic acid 4-[1-ethylamino-3-(4-nitrophenoxy)propyl]phenyl ester hydrochloride salt (14c·HCl).
14c. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.06 (t, 3H, J=7.0 Hz), 2.03–2.10 (m, 1H), 2.23–2.30 (m, 1H), 2.50 (q, 2H, J=7.0 Hz), 3.00 (s, 3H), 3.09 (s, 3H), 3.86–3.93 (m, 2H), 4.03–4.12 (m, 1H), 6.88 (d, 2H, J=9.5 Hz), 7.08 (d, 2H, J=8.0 Hz), 7.28 (d, 2H, J=8.0 Hz), 8.16 (d, 2H, J=9.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 15.2, 36.3, 36.6, 37.0, 41.7, 59.5, 65.9, 114.3, 121.8, 125.8, 127.7, 139.7, 141.3, 150.6, 154.8, 163.8; IR ($CHCl_3$) cm^{-1}: 2962, 1714, 1593, 1513, 1342, 1263, 1173; HRMS calcd for $C_{20}H_{26}N_3O_5$ $(M+H)^+$ 388.1872, found 388.1864.

14c·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.45 (t, 3H, J=8.0 Hz), 2.69–2.75 (m, 1H), 2.82–2.90 (m, 2H), 3.01 (s, 3H), 3.09 (s, 3H), 3.09–3.17 (m, 1H), 3.71 (dt, 1H, J=5.0, 9.5 Hz), 4.04 (quint, 1H, J=5.0 Hz), 4.42 (br t, 1H, J=10.5 Hz), 6.82 (d, 2H, J=9.0 Hz), 7.19 (d, 2H, J=9.0 Hz), 7.65 (d, 2H, J=9.0 Hz), 8.12 (d, 2H, J=9.0 Hz), 9.97 (br s, 1H), 10.3 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 11.1, 33.1, 36.3, 36.6, 41.0, 59.4, 64.3, 114.3, 122.9, 125.7, 129.4, 129.7, 141.6, 152.4, 154.2, 163.0; IR ($CHCl_3$) cm^{-1}: 2977, 1723, 1594, 1515, 1343, 1260, 1175; HRMS calcd for $C_{20}H_{26}N_3O_5$ $(M+H)^+$ 388.1872, found 388.1855.

Dimethylcarbamic acid 4-[3-(4-nitrophenoxy)-1-pyrrolidin-1-yl-propyl]phenyl ester hydrochloride salt (14e·HCl).
14e. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.78 (br s, 4H), 2.19 (br s, 1H), 2.47 (br s, 2H), 2.49–2.55 (m, 1H), 2.61 (br s, 2H), 3.01 (s, 3H), 3.10 (s, 3H), 3.42 (br s, 1H), 3.74 (q, 1H, J=9.0 Hz), 3.90–3.94 (m, 1H), 6.82 (d, 2H, J=8.5 Hz), 7.07 (d, 2H, J=8.0 Hz), 7.31 (d, 2H, J=8.0

Hz), 8.14 (d, 2H, $J=8.5$ Hz); IR ($CHCl_3$) cm^{-1}: 2968, 1713, 1593, 1512, 1392, 1342, 1264, 1173; HRMS calcd for $C_{22}H_{28}N_3O_5$ $(M+H)^+$ 414.2029, found 414.2027.

14e·HCl. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.97 (br s, 1H), 2.03–2.24 (m, 2H), 2.35 (br s, 1H), 2.66 (br s, 1H), 2.81 (br s, 1H), 2.88–3.04 (m, 2H), 3.01 (s, 3H), 3.10 (s, 3H), 3.30 (br s, 1H), 3.57 (br t, 1H, $J=9.2$ Hz), 4.06 (br d, 1H, $J=7.2$ Hz), 4.08–4.22 (m, 2H), 6.83 (d, 2H, $J=8.8$ Hz), 7.18 (d, 2H, $J=7.2$ Hz), 7.70 (d, 2H, $J=7.2$ Hz), 8.16 (d, 2H, $J=8.8$ Hz); IR ($CHCl_3$) cm^{-1}: 2970, 2419, 1724, 1594, 1514, 1343, 1258, 1175; HRMS calcd for $C_{22}H_{28}N_3O_5$ $(M+H)^+$ 414.2029, found 414.2021.

Dimethylcarbamic acid 4-[3-(4-nitrophenoxy)-1-piperazin-1-yl-propyl]phenyl ester hydrochloride salt (14f·HCl). **14f**: ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.10–2.17 (m, 1H), 2.44–2.53 (m, 1H), 2.46 (br s, 4H), 2.90 (br s, 4H), 3.02 (s, 3H), 3.11 (s, 3H), 3.58 (dd, 1H, $J=6.0$, 8.5 Hz), 3.87 (dt, 1H, $J=7.0$, 9.0 Hz), 4.03 (dt, 1H, $J=6.5$, 8.5 Hz), 6.86 (d, 2H, $J=9.0$ Hz), 7.09 (d, 2H, $J=8.5$ Hz), 7.22 (d, 2H, $J=8.5$ Hz), 8.17 (d, 2H, $J=9.0$ Hz); IR ($CHCl_3$) cm^{-1}: 2943, 1723, 1593, 1342, 1263, 1173; HRMS calcd for $C_{22}H_{29}N_4O_5$ $(M+H)^+$ 429.2138., found 429.2105.

14f·HCl. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.72 (br s, 1H), 2.92 (s, 3H), 3.03 (br s, 1H), 3.04 (s, 3H), 3.03–4.15 (m, 9H), 4.29 (br s, 1H), 4.80 (br s, 1H), 6.80 (br s, 2H), 7.14 (br s, 2H), 7.70 (br s, 2H), 8.06 (d, 2H, $J=7.6$ Hz); IR ($CHCl_3$) cm^{-1}: 3416, 2963, 2658, 2452, 1720, 1593, 1513, 1392, 1343, 1175, 1111, 1018; HRMS calcd for $C_{22}H_{29}N_4O_5$ $(M+H)^+$ 429.2138, found 429.2118.

Dimethylcarbamic acid 4-[1-dimethylamino-3-(4-nitrophenoxy)propyl]phenyl ester hydrochloride salt (14a·HCl). Compound **6j** (250 mg, 0.669 mmol) was dissolved in a mixture of HCO_2H (2.5 mL) and 37% of aq HCHO (2.5 mL) and stirred for 3 h at 80 °C. After cooling to room temperature, satd aq $NaHCO_3$ (10 mL) was added and extracted with AcOEt (20 mL×2). The extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated in vacuo. Purification by silica gel flash column chromatography (AcOEt to AcOEt–MeOH 5:1) gave **14a** (215 mg, 83%) as a colorless oil.

14a. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.59–2.68 (m, 1H), 2.65 (s, 6H), 2.88–2.97 (m, 1H), 3.02 (s, 3H), 3.10 (s, 3H), 3.73 (dt, 1H, $J=5.2$, 9.6 Hz), 4.07 (quint, 1H, $J=4.8$ Hz), 4.18 (dd, 1H, $J=3.6$, 10.8 Hz), 6.81 (d, 2H, $J=9.6$ Hz), 7.21 (d, 2H, $J=8.0$ Hz), 7.48 (d, 2H, $J=8.0$ Hz), 8.15 (d, 2H, $J=9.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 32.4, 36.2, 36.5, 42.2, 42.3, 66.1, 66.2, 114.0, 114.2, 121.1, 125.3, 125.5, 128.7, 135.1, 140.9, 150.4, 154.3, 163.5; IR ($CHCl_3$) cm^{-1}: 2940, 1714, 1593, 1512, 1342, 1263, 1173, 909; HRMS calcd for $C_{20}H_{25}N_3O_5$ $(M)^+$ 387.1794, found 387.1795.

14a·HCl. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.63 (br s, 3H), 2.71–2.79 (m, 1H), 2.88 (br s, 3H), 2.99–3.07 (m, 1H), 3.02 (s, 3H), 3.10 (s, 3H), 3.72 (dt, 1H, $J=4.4$, 9.6 Hz), 4.07 (quint, 1H, $J=4.4$ Hz), 4.33 (dd, 1H, $J=2.8$, 10.8 Hz), 6.81 (d, 2H, $J=9.6$ Hz), 7.23 (d, 2H, $J=8.0$ Hz), 7.55 (d, 2H, $J=8.0$ Hz), 8.14 (d, 2H, $J=9.6$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 30.6, 36.4, 36.7, 39.7, 42.7, 64.6, 68.1, 114.3, 123.1, 125.9, 127.5, 130.4, 141.9, 153.1, 154.0, 162.8; IR ($CHCl_3$) cm^{-1}: 2963, 2336, 1724, 1594, 1515, 1344, 1257, 1175; HRMS calcd for $C_{20}H_{26}N_3O_5$ $(M+H)^+$ 388.1866, found 388.1876.

[1-(4-Dimethylcarbamoyloxyphenyl)-3-(4-nitrophenoxy)-propyl]trimethylammonium iodide (14b). To a solution of **14a** (75 mg, 0.19 mmol) in acetone (20 mL) was added methyl iodide (0.12 mL, 1.93 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature, and then concentrated in vacuo. The resulting solid was recrystallized from EtOH to provide **14b** (72 mg, 72%) as a colorless crystal. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.56–2.65 (m, 1H), 2.86–2.90 (m, 1H), 2.91 (s, 3H), 2.99 (s, 3H), 3.34 (s, 9H), 3.73 (dt, 1H, $J=5.1$, 9.5 Hz), 3.92–3.97 (m, 1H), 5.56 (dd, 1H, $J=2.9$, 12.4 Hz), 6.81 (d, 2H, $J=9.5$ Hz), 7.20 (br, 2H), 7.45 (br, 1H), 7.73 (br, 1H), 8.00 (d, 2H, $J=9.5$ Hz); HRMS calcd for $C_{21}H_{28}N_3O_5$ $(M-I)^+$ 402.2029, found 402.2028, Anal. calcd for $C_{21}H_{28}N_3O_5I$: C, 47.65; H, 5.33; N, 7.94. Found: C, 47.61; H, 5.10; N, 7.83.

Dimethylcarbamic acid 4-[1-(ethylmethylamino)-3-(4-nitrophenoxy)propyl]phenyl ester hydrochloride salt (14d·HCl). This was prepared using a method similar to that for **14a**.

14d. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.03 (t, 3H, $J=7.2$ Hz), 2.12–2.20 (m, 1H), 2.18 (s, 3H), 2.27–2.36 (m, 1H), 2.42–2.52 (m, 2H), 3.01 (s, 3H), 3.10 (s, 3H), 3.74 (dd, 1H, $J=6.4$, 8.0 Hz), 3.90 (dt, 1H, $J=7.6$, 8.8 Hz), 4.05 (dt, 1H, $J=6.8$, 8.8 Hz), 6.87 (d, 2H, $J=8.8$ Hz), 7.08 (d, 2H, $J=8.8$ Hz), 7.23 (d, 2H, $J=8.8$ Hz), 8.15 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 12.3, 32.2, 36.4, 36.6, 37.5, 47.9, 63.8, 66.4, 114.4, 121.4, 125.8, 129.2, 135.6, 141.3, 150.7, 154.8, 164.0; IR ($CHCl_3$) cm^{-1}: 2970, 1714, 1593, 1513, 1342, 1264, 1173; HRMS calcd for $C_{21}H_{28}N_3O_5$ $(M+H)^+$ 402.2029, found 402.2009.

14d·HCl. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.36 (t, 1.5H, $J=7.5$ Hz), 1.53 (t, 1.5H, $J=7.5$ Hz), 1.90 (br s, 1H), 2.61 (d, 1.5H, $J=5.0$ Hz), 2.70–2.79 (m, 1H), 2.81–2.89 (m, 0.5H), 2.92 (d, 1.5H, $J=5.0$ Hz), 2.94–3.12 (m, 1.5H), 3.01 (d, 3H, $J=2.0$ Hz), 3.10 (d, 3H, $J=2.0$ Hz), 3.18–3.26 (m, 0.5H), 3.30–3.40 (m, 0.5H), 3.60–3.66 (m, 0.5H), 3.72–3.78 (m, 0.5H), 4.04–4.13 (m, 1H), 4.28–4.34 (m, 0.5H), 4.42–4.48 (m, 0.5H), 6.81 (dd, 2H, $J=2.0$, 9.0 Hz), 7.22 (t, 2H, $J=7.5$ Hz), 7.56 (d, 1H, $J=9.0$ Hz), 7.64 (d, 1H, $J=9.0$ Hz), 8.13 (dd, 2H, $J=2.0$, 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 8.5, 8.9, 30.4, 30.7, 35.7, 36.4, 36.7, 38.4, 47.9, 50.1, 64.6, 64.7, 65.3, 67.5, 144.3, 114.4, 123.0, 123.1, 125.8, 127.4, 128.2, 130.3, 130.6, 141.8, 152.8, 153.0, 154.0, 162.9; IR ($CHCl_3$) cm^{-1}: 2968, 2348, 1724, 1594, 1516, 1343, 1259, 1175; HRMS calcd for $C_{21}H_{28}N_3O_5$ $(M+H)^+$ 402.2029, found 402.2007.

1-(4-Methoxymethoxyphenyl)-2-(4-nitrophenoxy)ethanone (17). To a solution of carboxylic acid **15** (9.86 g, 50.0 mmol) in CH_2Cl_2 (50 mL) was added 1,1′-carbonyldi-

imidazole (9.73 g, 60.0 mmol) at room temperature. The mixture was stirred for 30 min at room temperature. Et_3N (9.80 mL, 70.0 mmol) and Me(MeO)NH·HCl (6.83 g, 70.0 mmol) was added to the reaction mixture at room temperature and stirred for 12 h at this temperature. After addition of water (50 mL), the aqueous solution was extracted with CH_2Cl_2 (50 mL×2). The combined organic extracts were washed with brine (80 mL), dried over Na_2SO_4, filtered and evaporated. Recrystallization from hexane–AcOEt gave the Weinreb amide (7.10 g, 59%) as a colorless crystal. Mp 95–97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 3.25 (s, 3H), 3.79 (s, 3H), 4.93 (s, 2H), 6.99 (d, 2H, J=9.0 Hz), 8.20 (d, 2H, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 61.7, 65.6, 104.7, 114.7, 125.8, 142.0, 163.1; IR (KBr) cm^{-1}: 1673, 1591, 1500, 1342, 1280, 1243, 1107, 989, 841; HRMS calcd for $C_{10}H_{12}N_2O_5$ $(M)^+$ 240.0746, found 240.0745. Anal. calcd for $C_{10}H_{12}N_2O_5·0.1H_2O$: C, 49.63; H, 5.08; N, 11.57. Found: C, 49.48; H, 4.95; N, 11.72.

To a solution of **16** (8.95 g, 33.9 mmol) in THF (50 mL) was added *n*-BuLi in hexane (21.6 mL, 1.6 M) dropwise at −78 °C. After stirring for 30 min at −78 °C, a solution of the Weinreb amide (5.43 g, 22.6 mmol) in THF (10 mL) was added to the reaction mixture at −78 °C. The mixture was stirred for 30 min at −78 °C and quenched with satd aq NH_4Cl (50 mL). The product was extracted with AcOEt (50 mL×2) and the organic solution was washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 10:1 to 1:1) gave crude **17**. This crude **17** was recrystallized from hexane–AcOEt to furnish pure **17** (1.93 g, 18%) as a colorless crystal. Mp 115–117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 3.49 (s, 3H), 5.26 (s, 2H), 5.35 (s, 2H), 6.98 (d, 2H, J=9.0 Hz), 7.13 (d, 2H, J=9.0 Hz), 7.96 (d, 2H, J=9.0 Hz), 8.20 (d, 2H, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 56.3, 70.5, 94.1, 114.8, 116.2, 125.9, 127.9, 130.3, 142.1, 162.0, 163.0, 191.3; IR (KBr) cm^{-1}: 1704, 1602, 1508, 1343, 1270, 1236, 1156, 1081, 969; HRMS calcd for $C_{16}H_{15}NO_6Na$ $(M+Na)^+$ 340.0797, found 340.0815. Anal. calcd for $C_{16}H_{15}NO_6$: C, 60.57; H, 4.77; N, 4.41. Found: C, 60.39; H, 4.73; N, 4.46.

Dimethylcarbamic acid 4-[2-(4-nitrophenoxy)acetyl]phenyl ester (18). To a solution of **17** (280 mg, 0.883 mmol) in THF (6 mL) and MeOH (6 mL) was added a concentrated HCl (3 mL) at room temperature. The reaction mixture was stirred for 12 h at room temperature. After neutralization with satd aq $NaHCO_3$, the solvent was concentrated in vacuo. The aqueous solution was extracted with AcOEt (20 mL×2). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated to provide the phenol (250 mg) as a colorless solid. Mp 229–232 °C; ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 5.55 (s, 2H), 6.89 (d, 2H, J=8.8 Hz), 7.10 (d, 2H, J=8.8 Hz), 7.95 (d, 2H, J=8.8 Hz), 8.21 (d, 2H, J=8.8 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ ppm: 71.5, 116.1, 116.6, 126.7, 127.2, 131.7, 164.9, 193.7; IR (KBr) cm^{-1}: 3378, 1676, 1598, 1509, 1334, 1252, 1175, 1109, 988, 846; HRMS calcd for $C_{14}H_{11}NO_5$ $(M)^+$ 273.0637, found 273.0632. Anal. calcd for $C_{14}H_{11}NO_5·0.5H_2O$: C, 59.58; H, 4.29; N, 4.96. Found: C, 59.95; H, 3.99; N, 4.70.

To a solution of the above phenol (250 mg) and K_2CO_3 (365 mg, 2.64 mmol) in DMF (10 mL) was added Me_2NCOCl (98 μL, 1.1 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature. After dilution with water (20 mL), the mixture was extracted with AcOEt (20 mL×2), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated. Recrystallization from hexane–AcOEt gave **18** (201 mg, 66% for 2 steps) as a colorless crystal. Mp 135–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 3.03 (s, 3H), 3.12 (s, 3H), 5.38 (s, 2H), 6.98 (d, 2H, J=9.0 Hz), 7.29 (d, 2H, J=9.0 Hz), 8.00 (d, 2H, J=9.0 Hz), 8.20 (d, 2H, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 36.5, 36.8, 70.6, 114.8, 122.2, 125.9, 129.6, 130.8, 142.1, 153.7, 156.2, 162.8, 191.6; IR (KBr) cm^{-1}: 1721, 1594, 1511, 1349, 1231, 1173, 1111, 985; HRMS calcd for $C_{17}H_{16}N_2O_6Na$ $(M+Na)^+$ 367.0906, found 367.0905. Anal. calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.10; H, 4.52; N, 8.11.

Dimethylcarbamic acid 4-[1-methylamino-2-(4-nitrophenoxy)ethyl]phenyl ester hydrochloride salt (19·HCl). To a solution of **18** (200 mg, 0.581 mmol) in THF (10 mL) and MeOH (5 mL) was added $NaBH_4$ (33 mg, 0.87 mmol) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The reaction was quenched with water and the organic solvent was concentrated in vacuo. The residue was extracted with AcOEt (15 mL×2), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated. Recrystallization from hexane–AcOEt gave benzyl alcohol (169 mg, 84%) as a colorless crystal. Mp 140–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.99 (s, 3H), 3.09 (s, 3H), 4.05–4.13 (m, 2H), 5.08 (br s, 1H), 6.93 (d, 2H, J=8.8 Hz), 7.12 (d, 2H, J=8.8 Hz), 7.41 (d, 2H, J=8.8 Hz), 8.16 (d, 2H, J=8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 36.3, 36.6, 71.7, 73.6, 114.5, 121.9, 125.8, 127.0, 136.3, 141.7, 151.3, 154.7, 163.3; IR (KBr) cm^{-1}: 3446, 1707, 1591, 1507, 1390, 1336, 1263, 1210, 1173, 1111, 1017, 877, 848, 783; HRMS calcd for $C_{17}H_{19}N_2O_6$ $(M+H)^+$ 347.1243, found 347.1264. Anal. calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.80; H, 5.13; N, 8.02.

Compound **19** was prepared using a method similar to that used for **14g** from the above alcohol.

Benzyl bromide. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 3.00 (s, 3H), 3.09 (s, 3H), 4.47 (dd, 1H, J=6.5, 9.5 Hz), 4.53 (dd, 1H, J=6.5, 9.5 Hz), 5.23 (t, 1H, J=6.5 Hz), 6.94 (d, 2H, J=10.0 Hz), 7.14 (d, 2H, J=8.0 Hz), 7.45 (d, 2H, J=8.0 Hz), 8.16 (d, 2H, J=10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 36.3, 36.5, 48.9, 72.2, 114.6, 122.0, 125.8, 128.7, 134.4, 141.8, 151.8, 154.3, 162.6; IR ($CHCl_3$) cm^{-1}: 2939, 1721, 1593, 1513, 1496, 1392, 1344, 1259, 1173, 1112, 1017, 846; HRMS calcd for $C_{17}H_{17}N_2O_5BrNa$ $(M+Na)^+$ 431.0219, found 431.0208.

19. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.36 (s, 3H), 3.02 (s, 3H), 3.10 (s, 3H), 4.00–4.05 (m, 2H), 4.07–4.12 (m, 1H), 6.94 (d, 2H, J = 9.0 Hz), 7.14 (d, 2H, J = 9.0 Hz), 7.41 (d, 2H, J = 9.0 Hz), 8.19 (d, 2H, J = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 34.3, 36.4, 36.6, 63.5, 73.2, 114.4, 122.0, 125.8, 128.4, 135.8, 141.7, 151.2, 154.8, 163.5; IR (film) cm^{-1}: 2936, 1721, 1593, 1511, 1388, 1341, 1262, 1213, 1172, 1112, 1013, 1112, 753; HRMS calcd for $C_{18}H_{22}N_3O_5$ $(M+H)^+$ 360.1559, found 360.1551.

19·HCl. Mp 233–240 °C; ^{1}H NMR (500 MHz, CD_3OD) δ ppm: 2.68 (s, 3H), 3.00 (s, 3H), 3.12 (s, 3H), 4.62 (d, 2H, J = 6.0 Hz), 4.79 (br s, 1H), 7.24 (d, 2H, J = 9.0 Hz), 7.28 (d, 2H, J = 8.0 Hz), 7.64 (d, 2H, J = 8.0 Hz), 8.26 (d, 2H, J = 9.0 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ ppm: 31.9, 36.7, 36.9, 62.8, 69.3, 116.2, 124.1, 126.9, 129.7, 130.9, 143.8, 154.3, 156.2, 163.8; IR (KBr) cm^{-1}: 2936, 2697, 1720, 1593, 1513, 1390, 1343, 1260, 1219, 1177, 1110, 1016, 862, 752; HRMS calcd for $C_{18}H_{22}N_3O_5$ $(M+H)^+$ 360.1559, found 360.1544.

[1-(4-Benzyloxyphenyl)-3-hydroxypropyl]methylcarbamic acid *tert*-butyl ester (20). To a solution of **4b** (2.46 g, 6.98 mmol) in MeOH (10 mL) was added 15% of aq NaOH (3 mmol) at room temperature. The reaction mixture was stirred for 2 h at 50 °C. The reaction mixture was neutralized with 1 N HCl, and then extracted with AcOEt (30 mL×2). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated to give a diol (2.20 g) as a colorless oil.

To a solution of the diol (1.88 g) and K_2CO_3 (1.84 g, 13.4 mmol) in acetone (30 mL) was added BnBr (0.79 mL, 6.68 mmol) at room temperature. The reaction mixture was stirred for 2 h at 50 °C. After dilution with water (80 mL), the mixture was extracted with AcOEt (50 mL×2), and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 5:1 to AcOEt) provided alcohol **20** (1.90 g, 73% for two steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.52 (s, 9H), 1.90–2.00 (m, 1H), 2.12–2.26 (m, 1H), 2.45 (br s, 3H), 3.54 (br, 1H), 3.74 (br, 2H), 5.05 (s, 2H), 5.54 (br, 1H), 6.96 (d, 2H, J = 8.5 Hz), 7.22 (d, 2H, J = 8.5 Hz), 7.30–7.44 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 28.2, 31.9, 52.5, 58.5, 69.8, 80.0, 114.5, 127.2, 127.8, 128.4, 128.8, 131.7, 136.7, 157.5, 157.9; IR ($CHCl_3$) cm^{-1}: 3437, 2980, 1657, 1511, 1454, 1392, 1336, 1251, 1150, 1053, 873; HRMS calcd for $C_{22}H_{29}NO_4Na$ $(M+Na)^+$ 394.1994, found 394.1985.

[1-(4-Benzyloxyphenyl)-3-cyanopropyl]methylcarbamic acid *tert*-butyl ester (21). To a solution of **20** (1.90 g, 5.11 mmol) and Et_3N (1.07 mL, 7.66 mmol) in THF (10 mL) was added MsCl (475 μL, 6.13 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature and quenched with water (10 mL). The mixture was extracted with AcOEt (30 mL×2) and the combined extracts were washed with water (30 mL), brine (30 mL) and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to give the mesylate (2.24 g).

To a solution of the mesylate (2.24 g) and 15-crown-5 (1.52 mL, 7.66 mmol) in DMF (10 mL) was added NaCN (376 mg, 7.76 mmol) at room temperature. The reaction mixture was stirred for 12 h at room temperature. After addition of water (20 mL), the aqueous solution was extracted with AcOEt (30 mL×2). The combined extracts were washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered and evaporated in vacuo. Recrystallization from hexane–AcOEt gave **21** (1.54 g, 79% for two steps) as a colorless crystal. Mp 111–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.51 (s, 9H), 2.24–2.27 (m, 2H), 2.40 (br, 2H), 2.54 (s, 3H), 5.06 (s, 2H), 5.34 (br, 1H), 6.96 (d, 2H, J = 8.5 Hz), 7.17 (d, 2H, J = 8.5 Hz), 7.32–7.44 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 14.5, 26.4, 28.4, 56.1, 70.0, 114.9, 127.4, 128.0, 128.4, 128.6, 130.9, 136.8, 158.3; IR (KBr) cm^{-1}: 3439, 2976, 1684, 1608, 1510, 1389, 1333, 1236, 1167, 1131, 1009, 871, 755; HRMS calcd for $C_{23}H_{28}N_2O_3Na$ $(M+Na)^+$ 403.1998, found 403.1991. Anal. calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.44; H, 7.25; N, 7.35.

[1-(4-Benzyloxyphenyl)-4-hydroxybutyl]methylcarbamic acid *tert*-butyl ester (22). To a solution of **21** (1.54 g, 4.05 mmol) in CH_2Cl_2 (20 mL) was added DIBAL in hexane (8.52 mL, 1.0 M) dropwise at −78 °C. After leaving the solution to warm to room temperature for 2 h, the reaction was quenched with aq satd NH_4Cl (20 mL). The product was extracted with AcOEt (30 mL×2) and the organic solution was washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated to give crude aldehyde. To a solution of the aldehyde in MeOH (10 mL) was added $NaBH_4$ (150 mg, 4.05 mmol) at 0 °C. The reaction mixture was stirred for 20 min at room temperature. The reaction was quenched with water and extracted with AcOEt (20 mL×2), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 2:1 to 1:1) provided alcohol **22** (351 mg, 22% for 2 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.51 (s, 9H), 1.58–1.63 (m, 2H), 1.87–2.03 (m, 2H), 2.55 (br s, 3H), 3.01 (br, 1H), 3.70 (t, 2H, J = 5.5 Hz), 5.02 (s, 2H), 5.39 (br, 1H), 6.94 (d, 2H, J = 9.0 Hz), 7.23 (d, 2H, J = 9.0 Hz), 7.29–7.43 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 26.2, 27.6, 28.2, 29.1, 55.6, 56.9, 61.8, 69.7, 79.4, 114.4, 127.2, 127.6, 128.3, 132.5, 136.7, 156.1, 157.6; IR ($CHCl_3$) cm^{-1}: 3626, 2979, 2937, 1677, 1511, 1392, 1331, 1249, 1151, 1024, 909; HRMS calcd for $C_{23}H_{31}NO_4Na$ $(M+Na)^+$ 408.2151, found 408.2154.

[1-(4-Dimethylcarbamoyloxyphenyl)-4-hydroxybutyl]-methylcarbamic acid *tert*-butyl ester (23). To a solution of **22** (351 mg, 0.910 mmol) in MeOH (10 mL) was added 5% Pd/C (40 mg). The reaction mixture was stirred for 4 h under a hydrogen atmosphere at room temperature. Pd/C was removed by filtration and the filtrate was evaporated in vacuo to give a diol (274 mg) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.47 (s, 9H), 1.52–1.62 (m, 2H), 1.80–1.90 (m, 1H), 1.92–1.96 (m, 1H), 2.48 (s, 3H), 3.70 (br s, 2H), 5.12 (br, 0.5H), 5.27 (br, 0.5H), 6.76 (d, 2H, J = 9.0 Hz), 7.03 (d,

2H, $J=9.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 26.3, 28.0, 28.4, 28.9, 56.0, 57.1, 62.0, 79.9, 115.2, 128.4, 130.9, 155.7, 156.7; IR ($CHCl_3$) cm^{-1}: 3599, 3332, 2979, 1676, 1514, 1393, 1367, 1334, 1257, 1152, 909; HRMS calcd for $C_{16}H_{25}NO_4Na$ $(M+Na)^+$ 318.1681, found 318.1693.

To a solution of the diol (274 mg) and K_2CO_3 (251 mg, 1.81 mmol) in DMF (10 mL) was added Me_2NCOCl (100 μL, 1.09 mmol) at room temperature. The reaction mixture was stirred for 12 h at room temperature. After dilution with water (20 mL), the mixture was extracted with AcOEt (20 mL×2), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 1:1 to 1:2) gave alcohol **23** (256 mg, 77% for two steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.41 (s, 9H), 1.46–1.54 (m, 2H), 1.78–1.96 (m, 2H), 2.46 (br s, 3H), 2.92 (s, 3H), 3.01 (s, 3H), 3.54–3.61 (m, 2H), 5.12 (br, 0.5H), 5.31 (br, 0.5H), 7.00 (d, 2H, $J=9.0$ Hz), 7.19 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 26.2, 27.8, 28.2, 29.0, 36.1, 36.3, 55.6, 56.9, 61.7, 79.3, 121.2, 128.0, 137.0, 150.2, 154.5, 156.1, 162.3; IR ($CHCl_3$) cm^{-1}: 2936, 1713, 1674, 1480, 1454, 1391, 1331, 1254, 1174, 909; HRMS calcd for $C_{19}H_{30}N_2O_5Na$ $(M+Na)^+$ 389.2052, found 389.2043.

Dimethylcarbamic acid 4-[1-methylamino-4-(4-nitrophenoxy)butyl]phenyl ester hydrochloride salt (24·HCl). This was prepared from **23** by a method similar to that used for **5f**.

24. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.65–1.80 (m, 3H), 1.93–1.97 (m, 1H), 2.29 (s, 3H), 3.01 (s, 3H), 3.10 (s, 3H), 3.54 (t, 1H, $J=6.0$ Hz), 3.96 (t, 2H, $J=6.0$ Hz), 6.88 (d, 2H, $J=9.0$ Hz), 7.10 (d, 2H, $J=9.0$ Hz), 7.28 (d, 2H, $J=9.0$ Hz), 8.17 (d, 2H, $J=9.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 25.6, 33.5, 34.0, 36.3, 36.5, 64.3, 68.4, 114.3, 121.7, 125.7, 127.9, 139.2, 141.2, 150.6, 154.7, 163.9; IR ($CHCl_3$) cm^{-1}: 2942, 1714, 1593, 1512, 1498, 1392, 1343, 1264, 1173, 1111, 909; HRMS calcd for $C_{20}H_{26}N_3O_5$ $(M+H)^+$ 388.1872, found 388.1891.

24·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.60–1.67 (m, 1H), 1.73–1.82 (m, 1H), 2.30–2.42 (m, 1H), 2.46 (t, 3H, $J=5.0$ Hz), 2.53–2.62 (m, 1H), 3.02 (s, 3H), 3.10 (s, 3H), 3.96 (t, 2H, $J=6.5$ Hz), 4.04 (br t, 1H, $J=8.5$ Hz), 6.86 (d, 2H, $J=8.5$ Hz), 7.21 (d, 2H, $J=8.5$ Hz), 7.60 (d, 2H, $J=8.5$ Hz), 8.14 (d, 2H, $J=8.5$ Hz), 9.72 (br, 1H), 10.00 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 25.3, 30.1, 30.8, 36.6, 58.4, 63.8, 67.5, 114.3, 122.8, 125.7, 129.4, 130.1, 141.4, 152.4, 154.3, 163.4; IR ($CHCl_3$) cm^{-1}: 2963, 2710, 1723, 1593, 1513, 1392, 1344, 1262, 1175, 1111, 909; HRMS calcd for $C_{20}H_{26}N_3O_5$ $(M+H)^+$ 388.1872, found 388.1870.

Dimethylcarbamic acid 4-[3-(4-nitrophenyl)acryloyl]phenyl ester (26). To a solution of **25** (4.42 g, 32.4 mmol) and K_2CO_3 (8.95 g, 64.8 mmol) in DMF (30 mL) was added Me_2NCOCl (3.28 mL, 35.6 mmol) at room temperature. The reaction mixture was stirred for 5 h at room temperature. After dilution with water (50 mL), the mixture was extracted with AcOEt (30 mL×2), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated. Recrystallization from hexane–AcOEt gave a carbamate (5.16 g, 77%) as a colorless crystal. Mp 109–111 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.58 (s, 3H), 3.02 (s, 3H), 3.11 (s, 3H), 7.22 (d, 2H, $J=9.0$ Hz), 7.97 (d, 2H, $J=9.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 26.5, 36.4, 36.7, 121.6, 129.7, 134.0, 154.0, 155.3, 196.9; IR (KBr) cm^{-1}: 1729, 1675, 1389, 1268, 1212, 1169. Anal. calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.80; H, 6.13; N, 6.67.

To a solution of the carbamate (2.00 g, 9.65 mmol) and *p*-nitrobenzaldehyde (1.60 g, 10.6 mmol) in EtOH (20 mL) was added KOH (63 mg, 0.96 mmol) at room temperature. The reaction mixture was stirred for 18 h at room temperature. The reaction mixture was neutralized with 1 N HCl and extracted with AcOEt (30 mL×2). The combined organic layers were evaporated. Recrystallization from hexane–AcOEt gave **26** (3.17 g, 97%) as a colorless crystal. Mp 215–218 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 3.04 (s, 3H), 3.13 (s, 3H), 7.29 (d, 2H, $J=9.0$ Hz), 7.62 (d, 1H, $J=15.5$ Hz), 7.78 (d, 2H, $J=9.0$ Hz), 7.82 (d, 1H, $J=15.5$ Hz), 8.06 (d, 2H, $J=9.0$ Hz), 8.28 (d, 2H, $J=9.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 36.5, 36.7, 121.9, 124.2, 125.6, 128.9, 130.1, 134.3, 141.0, 141.4, 148.5, 153.9, 155.5, 188.4; IR (KBr) cm^{-1}: 3437, 1728, 1662, 1613, 1599, 1522, 1348, 1221, 1166, 1013, 847. Anal. calcd for $C_{18}H_{16}N_2O_5H_2O$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.61; H, 4.75; N, 7.93.

Dimethylcarbamic acid 4-[1-hydroxy-3-(4-nitrophenyl)-propyl]phenyl ester (27). To a suspension of **26** (807 mg, 2.37 mmol) in MeOH (10 mL) was added $NaBH_4$ (179 mg, 4.74 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched with water and extracted with AcOEt (20 mL×2), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated. Recrystallization from hexane–AcOEt gave benzyl alcohol (453 mg, 56%) as a colorless crystal. Mp 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.11 (d, 1H, $J=2.8$ Hz), 3.01 (s, 3H), 3.10 (s, 3H), 5.43 (t, 1H, $J=3.6$ Hz), 5.53 (dd, 1H, $J=5.6$, 16.2 Hz), 6.77 (d, 1H, $J=16.2$ Hz), 7.13 (d, 2H, $J=8.8$ Hz), 7.40 (d, 2H, $J=8.8$ Hz), 7.51 (d, 2H, $J=8.8$ Hz), 8.17 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 36.4, 36.7, 74.1, 122.1, 123.9, 127.1, 127.3, 127.8, 136.1, 138.8, 143.0, 147.0, 151.3, 154.7; IR (KBr) cm^{-1}: 3447, 1700, 1594, 1511, 1392, 1344, 1211, 1176, 857, 745; HRMS calcd for $C_{18}H_{18}N_2O_5Na$ $(M+Na)^+$ 365.1114, found 365.1105. Anal. calcd for $C_{18}H_{18}N_2O_5{\cdot}0.1H_2O$: C, 62.82; H, 5.33; N, 8.14. Found: C, 62.74; H, 5.08; N, 8.26.

To a solution of the benzyl alcohol (432 mg, 1.26 mmol) in THF (10 mL) was added $Rh(PPh)_3Cl$ (100 mg). The reaction mixture was stirred for 3 h under a hydrogen atmosphere at room temperature. The solvent was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt 1:1 to AcOEt) to give **27** (348 mg, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.89 (s, 1H), 1.98–2.05 (m, 1H), 2.10–2.17 (m, 1H), 2.75–2.81 (m, 1H), 2.83–2.89

(m, 1H), 3.01 (s, 3H), 3.10 (s, 3H), 4.68 (t, 1H, $J=6.0$ Hz), 7.11 (d, 2H, $J=8.5$ Hz), 7.33 (d, 2H, $J=8.5$ Hz), 7.34 (d, 2H, $J=8.5$ Hz), 8.14 (d, 2H, $J=8.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 31.8, 36.3, 36.6, 39.7, 72.8, 121.7, 123.5, 126.6, 129.1, 141.0, 146.2, 149.8, 150.9, 154.8; IR ($CHCl_3$) cm^{-1}: 3605, 2942, 1714, 1604, 1518, 1392, 1348, 1173, 1059, 1016, 856; HRMS calcd for $C_{18}H_{20}N_2O_5Na$ $(M+Na)^+$ 367.1270, found 367.1283.

Dimethylcarbamic acid 4-[1-methylamino-3-(4-nitrophenyl)propyl]phenyl ester hydrochloride salt (28·HCl). This was prepared from **27** by a method similar to that used for **14g**.

28. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.02–2.11 (m, 1H), 2.16–2.26 (m, 1H), 2.29 (s, 3H), 2.63 (t, 2H, $J=7.6$ Hz), 3.02 (s, 3H), 3.11 (s, 3H), 3.55 (dd, 1H, $J=5.2$, 8.4 Hz), 7.13 (d, 2H, $J=8.8$ Hz), 7.26 (d, 2H, $J=8.8$ Hz), 7.31 (d, 2H, $J=8.8$ Hz), 8.11 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 32.0, 33.5, 36.3, 36.5, 37.5, 63.8, 121.9, 123.4, 128.1, 129.0, 137.6, 146.2, 149.3, 150.9, 154.6; IR ($CHCl_3$) cm^{-1}: 2945, 1714, 1604, 1518, 1392, 1348, 1174, 909; HRMS calcd for $C_{19}H_{24}N_3O_4$ $(M+H)^+$ 358.1767, found 358.1767.

28·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.38 (t, 3H, $J=5.2$ Hz), 2.48–2.66 (m, 3H), 2.79–2.84 (m, 1H), 3.02 (s, 3H), 3.11 (s, 3H), 3.84–3.92 (m, 1H), 7.23 (d, 2H, $J=8.8$ Hz), 7.27 (d, 2H, $J=8.8$ Hz), 7.53 (d, 2H, $J=8.8$ Hz), 8.08 (d, 2H, $J=8.8$ Hz), 9.91 (br, 1H), 10.27 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 30.8, 31.5, 34.2, 36.4, 36.7, 63.3, 122.7, 123.5, 128.9, 129.2, 129.5, 146.2, 147.1, 152.2, 153.9; IR ($CHCl_3$) cm^{-1}: 2975, 2708, 1723, 1606, 1586, 1523, 1392, 1348, 1176, 1016, 909, 856; HRMS calcd for $C_{19}H_{24}N_3O_4$ $(M+H)^+$ 358.1767, found 358.1755.

Compounds **29**–**31** were prepared by a method similar to that used for **5a** from alcohol **4b**.

Dimethylcarbamic acid 4-[1-methylamino-3-(4-nitrophenylamino)propyl]phenyl ester dihydrochloride salt (29·2HCl). **29**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.92–2.03 (m, 2H), 2.26 (s, 3H), 2.98 (s, 3H), 3.07 (s, 3H), 3.17 (t, 2H, $J=6.6$ Hz), 3.61 (t, 1H, $J=6.6$ Hz), 6.40 (d, 2H, $J=8.8$ Hz), 7.07 (d, 2H, $J=8.8$ Hz), 7.21 (d, 2H, $J=8.5$ Hz), 8.02 (d, 2H, $J=8.8$ Hz); IR ($CHCl_3$) cm^{-1}: 2941, 1715, 1601, 1323, 1174, 1112.

29·2HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.42 (br s, 3H), 2.70 (br, 1H), 2.83 (br, 1H), 2.98 (s, 3H), 3.05 (br, 1H), 3.07 (s, 3H), 3.15 (br, 1H), 4.09 (br, 1H), 6.78 (br, 2H), 7.17 (br s, 2H), 7.53 (br, 2H), 8.05 (d, 2H, $J=7.3$ Hz).

Dimethylcarbamic acid 4-[3-[acetyl-(4-nitrophenyl)amino]-1-methylaminopropyl]phenyl ester hydrochloride salt (30·HCl). **30**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.80–1.95 (m, 2H), 1.90 (s, 3H), 2.23 (s, 3H), 3.01 (s, 3H), 3.10 (s, 3H), 3.51 (t, 1H, $J=6.5$ Hz), 3.72–3.83 (m, 2H), 7.05 (d, 2H, $J=8.8$ Hz), 7.19 (d, 2H, $J=8.8$ Hz), 7.22 (d, 2H, $J=8.5$ Hz), 8.25 (d, 2H, $J=8.8$ Hz); IR (film) cm^{-1}: 2937, 1722, 1664, 1592, 1522, 1389, 1343, 1212, 1172, 856.

30·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.93 (s, 3H), 2.23 (br, 1H), 2.44 (s, 3H), 2.73 (br, 1H), 3.02 (s, 3H), 3.11 (s, 3H), 3.77–3.82 (m, 1H), 4.01 (br, 2H), 7.19 (d, 2H, $J=8.8$ Hz), 7.50 (d, 2H, $J=8.8$ Hz), 7.63 (d, 2H, $J=8.5$ Hz), 8.31 (d, 2H, $J=8.8$ Hz).

Dimethylcarbamic acid 4-[1-methylamino-3-(4-nitrophenylsulfanyl)propyl]phenyl ester hydrochloride salt (31·HCl). **31**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.98–2.12 (m, 2H), 2.28 (s, 3H), 2.84–2.98 (m, 2H), 3.02 (s, 3H), 3.11 (s, 3H), 3.65 (dd, 1H, $J=5.6$, 8.0 Hz), 7.12 (d, 2H, $J=8.8$ Hz), 7.19 (d, 2H, $J=8.8$ Hz), 7.28 (d, 2H, $J=8.8$ Hz), 8.08 (d, 2H, $J=8.8$ Hz); IR (film) cm^{-1}: 2935, 1720, 1510, 1388, 1337, 1212, 1172, 1090, 853.

31·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.43 (s, 3H), 2.55 (br, 1H), 2.82 (br, 2H), 2.86 (br, 1H), 3.02 (s, 3H), 3.11 (s, 3H), 4.11–4.15 (m, 2H), 7.23 (d, 4H, $J=8.8$ Hz), 7.57 (d, 2H, $J=8.8$ Hz), 8.09 (d, 2H, $J=8.8$ Hz).

Biological methods

In vitro AChE inhibition assay. AChE activity was measured in duplicate by the spectrophotometric method of Ellman et al.[20] with some modifications. Brain homogenate was used as the enzyme source. The whole brain except for the cerebellum was homogenized in 9 volumes of 100 mM sodium phosphate buffer (pH 7.0). The test compounds were dissolved in dimethyl sulphoxide (DMSO). The AChE activity was expressed as a change in OD at 412 nm.

In vitro SERT inhibition assay. The whole brain except for the cerebellum was homogenized in 100 mM sodium phosphate buffer (pH 7.0) and synaptosome was prepared. The uptake of [^{3}H]5-HT into the synaptosome was determined at 37 °C in the presence and absence of the test compounds. The blank was determined by measuring the uptake of [^{3}H]5-HT at 4 °C.

Ex vivo AChE and SERT inhibition assays in mouse brain. Mice were sacrificed at 1 h after oral administration, and the brains were removed. The brain was homogenized in 1.6 volumes of 100 mM sodium phosphate buffer (pH 7.0) for the determination of AChE activity by the spectrophotometric method. The brain was homogenized in 3 volumes of 50 mM Tris–HCl buffer (pH 7.7) for the SERT inhibition measurement as determined by the displacement of [^{3}H]citalopram binding.

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