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A Conformational Restriction Approach to the Development of Dual Inhibitors of Acetylcholinesterase and Serotonin Transporter as Potential Agents for Alzheimer's Disease

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Abstract—Alzheimer's disease (AD) has been treated with acetylcholinesterase (AChE) inhibitors such as donepezil. However, the clinical usefulness of AChE inhibitors is limited mainly due to their adverse peripheral effects. Depression seen in AD patients has been treated with serotonin transporter (SERT) inhibitors. We considered that combining SERT and AChE inhibition could improve the clinical usefulness of AChE inhibitors. In a previous paper, we found a potential dual inhibitor, **1**, of AChE ($IC_{50}=101$ nM) and SERT ($IC_{50}=42$ nM), but its AChE inhibition activity was less than donepezil ($IC_{50}=10$ nM). Here, we report the conformationally restricted (*R*)-**18a** considerably enhanced inhibitory activity against AChE ($IC_{50}=14$ nM) and SERT ($IC_{50}=6$ nM).

Introduction

Alzheimer's disease (AD) affecting the aged is a neurodegenerative disorder characterized by a progressive deterioration in cognitive function.[1] The reduction in cholinergic neurotransmission is believed to be one of the major causes of memory impairments in AD patients. Increasing the level of acetylcholine has been regarded as one of the most promising methods for the palliative treatment of AD.[2] At present, several acetylcholinesterase (AChE) inhibitors have been introduced to the market such as tacrine,[3] donepezil[4] and rivastigmine.[5] However, the clinical efficacy of marketed AChE inhibitors is limited mainly due to their adverse peripheral effects.[6] AD patients often suffer from psychiatric disorder-related symptoms, such as irritability, anxiety and depression.[7] Depression in AD patients has been successfully treated with serotonin transporter (SERT) inhibitors[8] that lack anticholinergic action. Thus, AChE–SERT dual inhibitors would be a novel class of anti-AD drugs with greater clinical efficacy than known AChE inhibitors, since the antidepressive effect resulting from SERT inhibition could bring further alleviation of the symptoms of AD and a reduction of dose-related adverse effects caused by an excessive AChE inhibition.

In our previous paper,[9] we designed novel AChE–SERT dual inhibitors by the hybridization of rivastigmine (AChE inhibitor) and fluoxetine[10] (SERT inhibitor) based on a hypothetical model of the AChE active site. Among all the compounds, (*S*)-dimethyl carbamic acid 4-[1-methylamino-3-(4-nitrophenoxy)propyl] phenyl ester (**1**) showed the most potent inhibitory activity against both AChE ($IC_{50}=101$ nM) and SERT ($IC_{50}=42$ nM), but its AChE inhibition activity was less than donepezil ($IC_{50}=10$ nM) in our in vitro assay.

Here, we report that conformationally constrained derivatives with six- or seven-membered ring, especially (*R*)-**18a**, show considerably stronger inhibitory potencies against AChE and SERT than previously reported compound **1**.

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Chemistry

Our rigid analogues of compound **1** were designed by linking the methylamine moiety and *ortho*-carbon atom of phenyl ring with a carbon chain of appropriate length (Fig. 1).

Preparation of the 1,2,3,4-tetrahydroisoquinoline derivatives ($n=0$) using the Bischler–Napieralski reaction is shown in Scheme 1. Methoxyphenethylamine **2** was treated with ethyl malonyl chloride to give an *N*-acylated compound. The 1,2,3,4-tetrahydroisoquinoline skeleton was constructed by the Bischler–Napieralski reaction using $POCl_3$[11] or polyphosphate ester (PPE).[12] Following hydrogenation of the exo double bond with Adams' catalyst provided compound **3**. Demethylation of **3** with boron tribromide, followed by *N*-Boc protection and treatment with dimethylcarbamyl chloride, furnished intermediate **4**. The ethyl ester group was reduced with $LiAlH_4$ and the resulting primary alcohol was reacted with various phenols under the Mitsunobu reaction conditions. Deprotection of the Boc group afforded the derivatives **6a–g** and **7a**,**b**. A methyl group was introduced to the secondary amine moiety by the Eshweiler–Clarke reaction to give the derivatives **9a–g** and **10a**,**b**. Derivative **8** was prepared using the similar method via compound **5**.

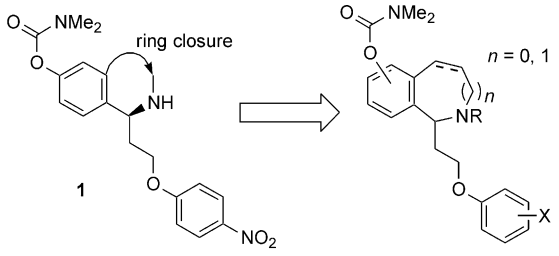
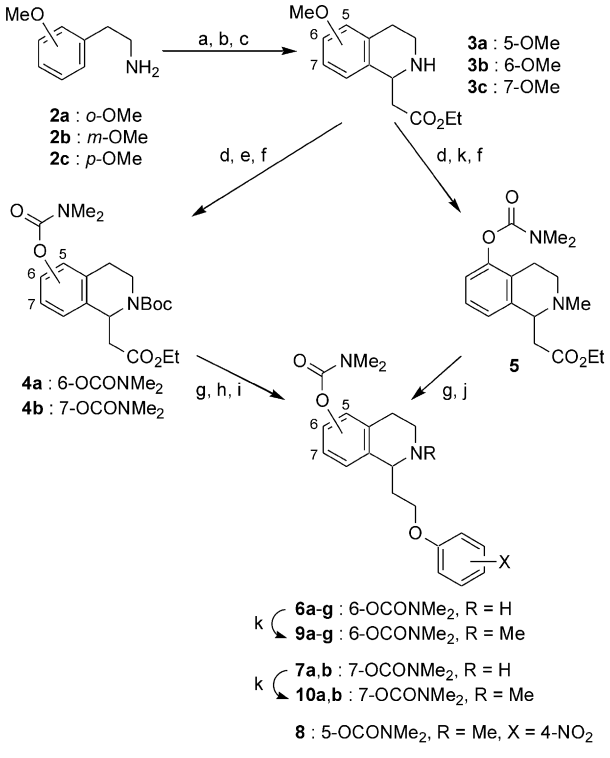


Figure 1. Our conformational restriction approach used in the development of novel AChE–SERT dual inhibitors.



Scheme 1. Reagents and conditions: (a) ethyl malonyl chloride, K_2CO_3, CH_2Cl_2, 0 °C; (b) $POCl_3$ or PPE, 80 °C; (c) H_2, PtO_2, AcOH, rt; (d) BBr_3, CH_2Cl_2, −78 °C to rt; (e) Boc_2O, THF, rt; (f) Me_2NCOCl, K_2CO_3, DMF, rt; (g) $LiAlH_4$, THF, −78 to 0 °C; (h) phenol, DEAD, PPh_3, THF, rt; (i) 2N HCl–AcOEt, rt; (j) 1-fluoro-4-nitrobenzene, NaH, DMF; (k) 37% HCHO aq, HCO_2H, 80 °C.

Scheme 2 shows the synthesis of the rigid derivatives having a saturated (**20a**,**b** and **21a**,**b**) or unsaturated (**17a**,**b** and **18a–h**) seven-membered ring ($n=1$). We formed the seven-membered ring by the ring-closing olefin metathesis reaction,[13] which is a very effective method for making rings of various sizes. Treatment of dihydroxybenzaldehyde **11** with dimethylcarbamyl chloride using sodium hydride or pyridine selectively provided a mono-carbamate product. The remaining phenol was converted to an aryl triflate by treatment with trifuluoromethanesulfonic anhydride. The resulting triflate was reacted with tributylvinylstannane by the Stille reaction[14] to give styrene compound **12**. The aldol reaction with ethyl acetate followed by reduction of the ethyl ester with $LiBH_4$ furnished the diol. Selective protection of the primary alcohol with *t*-$BuPh_2SiCl$ and imidazole provided benzyl alcohol **13**. Bromination of **13** using carbon tetrabromide and triphenylphosphine gave benzyl bromide. The benzyl bromide was treated with allylamine in acetonitrile, followed by *N*-Boc protection to afford **14**, the precursor for ring-closing olefin metathesis. Ring-closing olefin metathesis of **14** with Grubbs catalyst **15**[13] successfully gave a seven-membered ring product. Deprotection of the silyl group with TBAF furnished primary alcohol **16**. Treatment of **16** with various phenols under Mitsunobu reaction conditions and deprotection of the Boc group provided derivatives **17a**,**b**. *N*-Methylation by the Eshweiler–Clarke reaction gave the derivatives **18a–h**. Derivatives **20a**,**b** and **21a**,**b** were synthesized from **19**, prepared by the hydrogenation of intermediate **16**, in a similar manner as above.

Scheme 3 shows the synthesis of the *exo* olefin derivative **24** and substituted olefin derivatives **26a–d**. Hydroboration of **16b** with borane in THF, followed by an oxidation reaction,[15] furnished a regioisomeric mixture of alcohols, most notably a benzyl alcohol. From this mixture of regio isomers, benzyl alcohol was selectively oxidized with manganese oxide to give ketone **22**. Compound **22** was reacted with *p*-nitrophenol under Mitsunobu reaction conditions, following treatment with HCl and Boc protection of the amino group afforded **23**. This ketone was converted to an *exo* olefin by the Wittig reaction. The olefin was deproteced and *N*-methylated to give derivative **24**. The enolate of ketone **23** was reacted with 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine[16] to provide vinyl triflate **25**. Vinyl triflate **25** was coupled with organostannanes or organoborons in the presence of a palladium catalyst. Further deprotection and *N*-methylation of the resulting products led to derivatives **26a–d**.

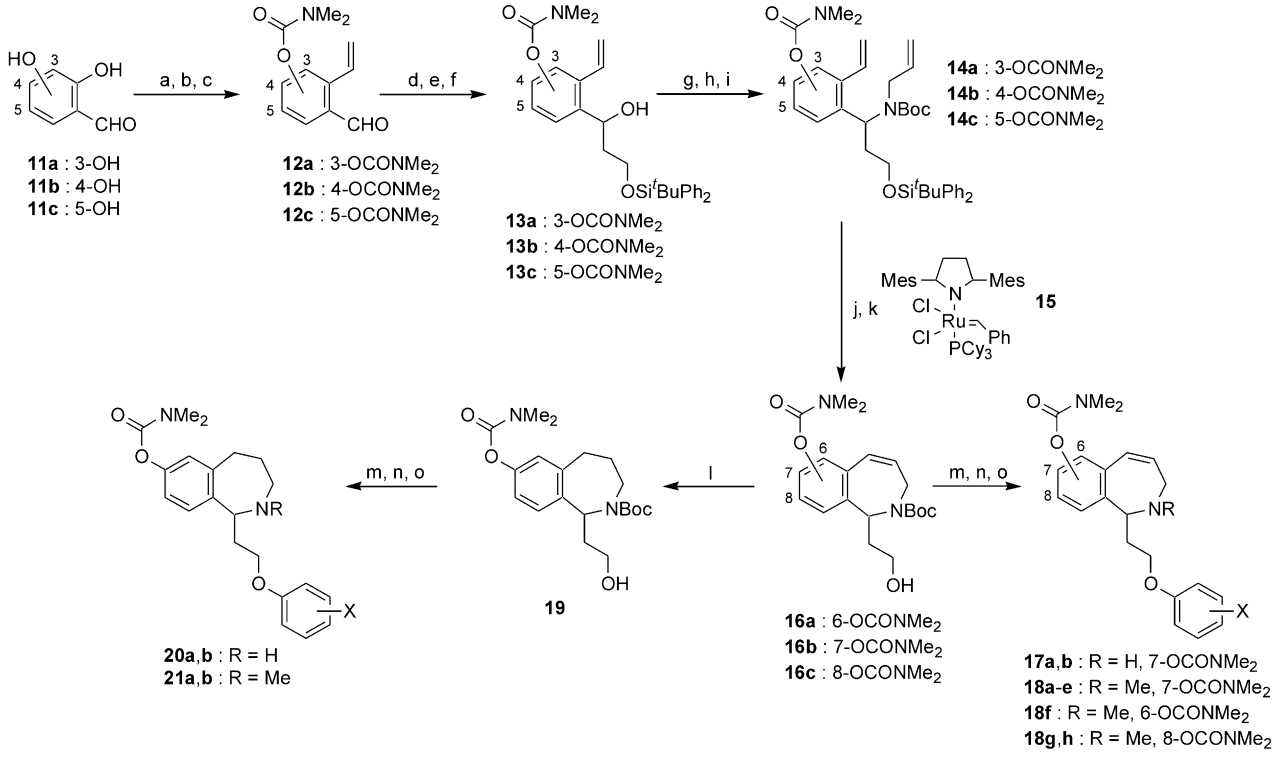
The asymmetric synthesis of (*R*)-**18a** is shown in Scheme 4. Phenol **27**[17] was protected with a methoxymethyl (MOM) group and the Horner–Wadsworth–Emmons reaction provided α,β-unsaturated ester **28**. Compound **28** was subjected to chiral amination by a method reported by Davies.[18] The resulting amine was protected with a Boc group to furnish (*R*)-**30** (99% ee).[19] Compound (*R*)-**30** was reacted with dimethylcarbamyl chloride and reduced with $LiAlH_4$ to afford primary alcohol (*R*)-**31**. Alcohol (*R*)-**31** was reacted with *p*-nitrophenol under Mitsunobu reaction conditions, and the following treatment with HCl and Boc protection gave (*R*)-**32**. This phenol was converted to a triflate and the Stille reaction with tributylvinylstannane provided a styrene compound. Following allylation of the *N*-Boc-protected amine afforded (*R*)-**33**. Ring-closing olefin metathesis of (*R*)-**33** with Grubbs catalyst **15**[13] provided a seven-membered ring product. Deprotection of the Boc group and the Eshweiler–Clarke methylation furnished (*R*)-**18a**. Enantiomer (*S*)-**18a** was prepared by the same method using chiral amine (*R*)-**29**.

Results and Discussion

All rigid derivatives were assayed for their in vitro inhibitions of AChE (mouse brain) and SERT (rat synaptosome). The protocols used here are described in the Experimental.

Table 1 summarizes the inhibitory activities against AChE and SERT of the conformationally restricted derivatives containing a 1,2,3,4-tetrahydroisoquinoline skeleton (**6a**,**b**, **7a**,**b**, **8**, **9a**–**g** and **10a**,**b**). In the previous paper,[9] we revealed that a nitro group for substituent X on the phenyl ether moiety and *para*-carbamate substitution were crucial for potent dual inhibitory activities. However, 1,2,3,4-tetrahydroisoquinoline derivatives were reinvestigated with respect to substituent X using, in particular, an electron-withdrawing group, and ideal carbamate position. A series of 1,2,3,4-tetrahydroisoquinoline derivatives that was observed had dramatically enhanced inhibitory activity toward AChE, but their inhibitory activity toward SERT had almost disappeared. We supposed that conformational restriction of the flexible amine moiety resulted in the appropriate binding to AChE. The reason for the disappearance of anti-SERT activity could not be determined because we had no information on the structure of SERT. Among the compounds with 1,2,3,4-tetrahydroisoquinoline structure, **6a** (R = H, X = 4-NO_2) showed the most potent inhibitory activity against AChE (IC_{50} = 8 nM). In comparison with compound **1** (IC_{50} = 101 nM against AChE), **6a** was about 13 times more active against AChE. Similarly to our previous results,[9] compound **6a** possessed a 4-NO_2 group as substituent X and 6-substituted carbamate moiety on the 1,2,3,4-tetrahydroisoquinoline skeleton.

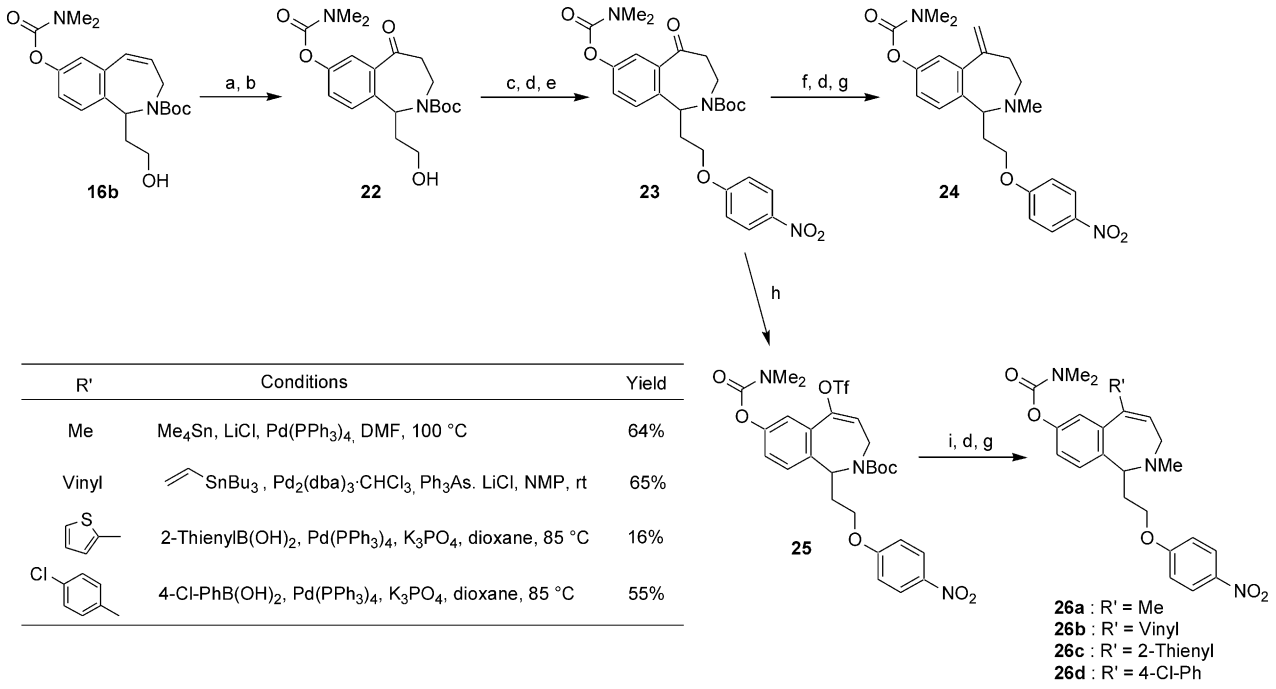
Next, we examined the rigid derivatives **20a**,**b**, **21a**,**b** containing a saturated seven-membered ring and **17a**,**b**, **18a**–**h** containing an unsaturated seven-membered ring (Table 2). Compounds **20a**,**b** (R = H) and **21a**,**b** (R = Me) showed higher inhibitory potencies against



Scheme 2. Reagents and conditions: (a) Me_2NCOCl, NaH, DMF, rt or Me_2NCOCl, py, CH_2Cl_2, rt; (b) Tf_2O, py, CH_2Cl_2, 0 °C; (c) (CH_2=CH)(n-Bu)$_3$Sn, Pd(PPh_3)$_4$, LiCl, dioxane, 100 °C; (d) AcOEt, LDA, THF, −78 °C; (e) $LiBH_4$, THF, rt; (f) t-BuPh_2SiCl, imidazole, DMF, rt; (g) CBr_4, PPh_3, CH_2Cl_2, rt; (h) allylamine, CH_3CN, rt; (i) Boc_2O, Et_3N, THF, 50 °C; (j) **15** (10 mol%), CH_2Cl_2, 45 °C; (k) TBAF, THF, rt; (l) H_2, Pd/C, MeOH, rt; (m) phenol, DEAD, PPh_3, THF, rt; (n) 2 N HCl–EtOAc, rt; (o) 37% HCHO aq, HCO_2H, 80 °C.

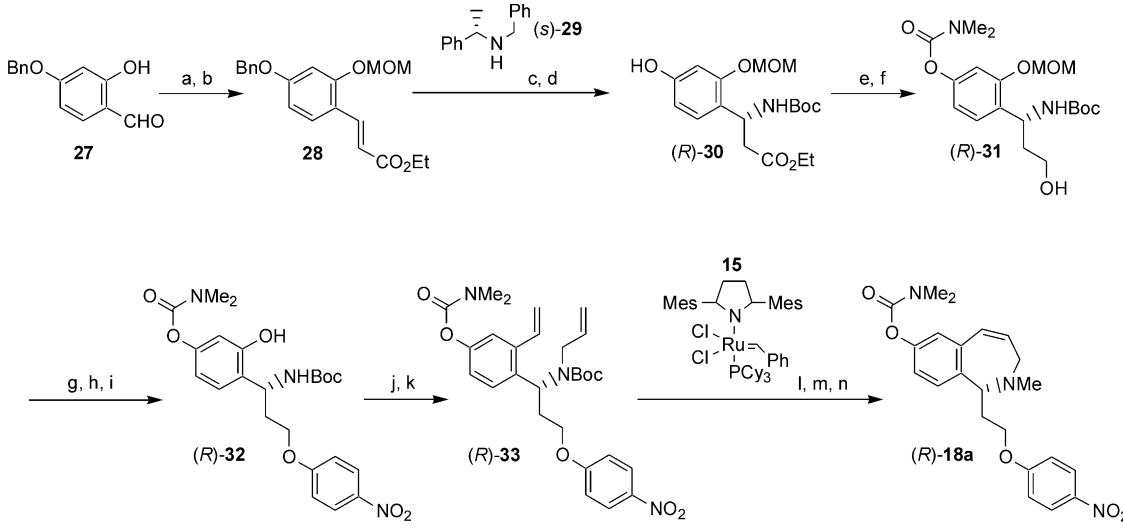
AChE but much lower potencies against SERT similarly to 1,2,3,4-tetrahydroquinoline derivatives. Compounds **17a**,**b** (R = H) which possessed a double bond on the seven-membered ring also exhibited good inhibitory activities but only against AChE, whereas compounds **18a–e** (R = Me) surprisingly showed potent inhibitory activities against not only AChE but also SERT. We have not determined the reason for this striking improvement in anti-SERT activities obtained by changing the secondary amine (R = H) to a tertiary amine (R = Me) on the seven-membered ring. However, it is clear that the olefin moiety on the seven-membered ring is essential for the inhibitory potency of SERT as can be seen by comparing derivatives **18a–e** with **21a**,**b**. Compound **18a** was the most potent dual inhibitor of AChE (IC_{50} = 66 nM) and SERT (IC_{50} = 63 nM). Changing the substitution position of the dimethylcarbamate from 7 to 6 (**18f**) and 8 (**18g**,**h**) resulted in the loss of inhibitory potency for SERT.

Table 3 shows the effects of changing the substituent on the olefin moiety of compound **18a**. Derivatives **26a**,**b**,



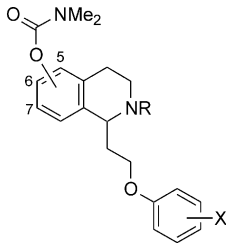
R'	Conditions	Yield
Me	Me_4Sn, LiCl, $Pd(PPh_3)_4$, DMF, 100 °C	64%
Vinyl	$SnBu_3$, $Pd_2(dba)_3{\cdot}CHCl_3$, Ph_3As. LiCl, NMP, rt	65%
2-Thienyl	2-ThienylB$(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, dioxane, 85 °C	16%
4-Cl-Ph	4-Cl-PhB$(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, dioxane, 85 °C	55%

Scheme 3. Reagents and conditions: (a) BH_3, THF, 0 °C to rt then $NaBO_3$, 0 °C to rt; (b) MnO_2, CH_2Cl_2, rt; (c) *p*-nitrophenol, DEAD, PPh_3, THF, rt; (d) 2N HCl–AcOEt, rt; (e) Boc_2O, Et_3N, THF, rt; (f) $Ph_3P^+CH_3Br^-$, *t*-BuOK, benzene, 80 °C; (g) 37% HCHO aq., HCO_2H, 80 °C; (h) 2-(5-Cl-Py)NTf_2, LHMDS, THF, −78 °C; (i) see scheme.



Scheme 4. Reagents and conditions: (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 79%; (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C, 99%; (c) (i) (*S*)-**29**, *n*-BuLi, THF, −78 °C; (ii) H_2, 20% $Pd(OH)_2$/C, MeOH–H_2O–AcOH (20:2:1), rt, 67% (two steps); (d) Boc_2O, Et_3N, MeOH, rt, 97%; (e) Me_2N-COCl, K_2CO_3, DMF, rt, 97%; (f) $LiAlH_4$, THF, −50 to 0 °C, 82%; (g) *p*-nitrophenol, DEAD, PPh_3, THF, rt; (h) concd HCl, MeOH, rt, 68% (two steps); (i) Boc_2O, Et_3N, MeOH, rt, 85%; (j) (i) Tf_2O, py, CH_2Cl_2, 0 °C; (ii) $(CH_2{=}CH)(n\text{-}Bu)_3Sn$, $Pd(PPh_3)_4$, LiCl, dioxane, 100 °C, 86% (two steps); (k) allyl bromide, NaH, DMF, 0 °C to rt, 86%; (l) **15** (10 mol%), CH_2Cl_2 (15 mM), 45 °C, 96%; (m) 2 N HCl–AcOEt, rt, 96%; (n) (i) 37% HCHO aq, HCO_2H, 80 °C, 78%.

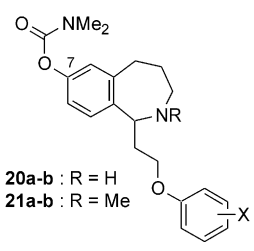
Table 1. In vitro AChE and SERT inhibition activity of 1,2,3,4-tetrahydroisoquinoline derivatives

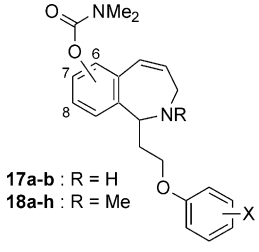


Compd[a]	Carbamate position	R	X	IC_{50} (nM)	
				AChE[b]	SERT[c]
6a	6–	H	4-NO_2	8	>1000
6b	6–	H	4-Cl	17	>1000
7a	7–	H	4-NO_2	101	>1000
7b	7–	H	4-Cl	219	>1000
9a	6–	Me	4-NO_2	11	940
9c	6–	Me	3-Me-4-NO_2	16	170
9d	6–	Me	3-NO_2	11	125
9b	6–	Me	4-Cl	33	660
9e	6–	Me	4-F	49	>1000
9f	6–	Me	4-Br	34	>1000
9g	6–	Me	4-OMe	20	>1000
8	5–	Me	4-NO_2	56	750
10a	7–	Me	4-NO_2	161	>1000
10b	7–	Me	4-Cl	265	520

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

Table 2. In vitro AChE and SERT inhibition activity of derivatives with a seven-membered ring





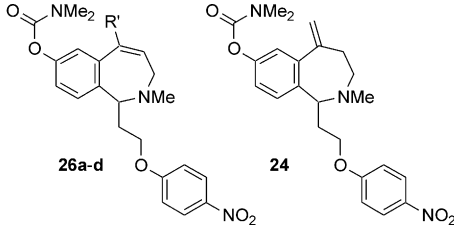
Compd[a]	Carbamate position	R	X	IC_{50} (nM)	
				AChE[b]	SERT[c]
20a	7–	H	4-NO_2	55	>1000
20b	7–	H	4-Cl	215	>1000
21a	7–	Me	4-NO_2	61	>1000
21b	7–	Me	4-Cl	116	>1000
17a	7–	H	4-NO_2	92	>1000
17b	7–	H	3-Me-4-Cl	153	>1000
18a	7–	Me	4-NO_2	66	63
18b	7–	Me	3-Me-4-Cl	103	61
18c	7–	Me	4-Cl	139	71
18d	7–	Me	4-F	135	850
18e	7–	Me	4-CF_3	285	62
18f	6–	Me	3-Me-4-Cl	146	900
18g	8–	Me	4-NO_2	>1000	>1000
18h	8–	Me	4-Cl	>1000	>1000

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

which have small substituents (R′ = Me, vinyl) maintained their inhibitory activities against AChE (IC_{50} = 60 and 43 nM, respectively), but lost their inhibitory activities against SERT (both IC_{50} = >1000 nM). Derivative **26d**, which has a large substituent (R′ = *p*-chlorophenyl), had little inhibitory activity against both AChE (IC_{50} = >1000 nM) and SERT (IC_{50} = >1000 nM). *exo* Olefin derivative **24** also had little inhibitory activity against SERT (IC_{50} = >1000 nM). These results revealed that a 1,2-di-substitued internal olefin was essential for SERT inhibition.

Compound **18a** was the most potent dual inhibitor and the activity of both enantiomers of **18a** was evaluated, as shown in Table 4. The enantiomer (*R*)-**18a** showed extremely potent inhibitory activities against both AChE (IC_{50} = 14 nM) and SERT (IC_{50} = 6 nM).

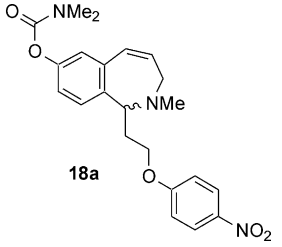
Table 3. Effect of various substituents on the inhibitory activity of **18a**



Compd[a]	R′	IC_{50} (nM)	
		AChE[b]	SERT[c]
18a	H	66	63
26a	Me	60	>1000
26b	Vinyl	43	>1000
26c	2-Thienyl	150	>1000
26d	4-Cl-Ph	>1000	>1000
24		27	>1000

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

Table 4. In vitro AChE and SERT inhibition activity of **18a** enantiomers



Compd[a]	IC_{50} (nM)	
	AChE[b]	SERT[c]
rac-**18a**	66	63
(*R*)-**18a**	14	6
(*S*)-**18a**	609	930

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

Although both **1** and its enantiomer showed similar levels of AChE inhibition,[9] (*R*)-**18a** showed a 44 times stronger inhibitory activity against AChE than (*S*)-**18a**. This difference of AChE inhibition would result from the conformational rigidity of **18a**. Similarly (*R*)-**18a** exhibited a 155 times stronger inhibitory activity against SERT than (*S*)-**18a**. Compound (*R*)-**18a** showed extremely weak inhibitory activities against butylcholinesterase, choline acetyltransferase, norepinephrine and dopamine transporters. In this way, we were able to further develop the AChE—SERT dual inhibitor **1** (IC_{50} = 101 and 42 nM, respectively) to (*R*)-**18a** (IC_{50} = 14 and 6 nM, respectively), which had an equal potency to donepezil (IC_{50} = 10 nM) and a 30 times more potent activity than fluoxetine (IC_{50} = 180 nM).

Conclusion

We have designed and synthesized conformationally restricted derivatives by linking a methylamine moiety to the *ortho*-carbon atom of the phenyl ring in **1** as potential dual inhibitors of AChE and SERT for AD. 1,2,3,4-Tetrahydroisoquinoline derivative **6a** showed a much greater inhibitory activity against AChE (IC_{50} = 8 nM) but loss of inhibitory activity against SERT (IC_{50} = > 1000 nM). Saturated seven-membered ring derivatives **20a** (R = H) and **21a** (R = Me) were found to have lost their anti-SERT activity as did six-membered ring derivative **6a**. Surprisingly, compound **18a** (R = Me) which possessed a double bond in its seven-membered ring showed potent inhibitory activities against not only AChE (IC_{50} = 66 nM) but also SERT (IC_{50} = 63 nM). Our conformational restriction approach finally led to find (*R*)-**18a** which was an extremely potent inhibitor of both AChE (IC_{50} = 14 nM) and SERT (IC_{50} = 6 nM). (*R*)-**18a** is an interesting compound that forms a novel class of treatment drugs for AD. Further pharmacological evaluation of (*R*)-**18a** is underway.

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 purchased. ^{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).

(6-Methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)acetic acid ethyl ester (3b).[11] To a solution of **2b** (1.00 g, 6.60 mmol) and K_2CO_3 (1.10 g, 8.00 mmol) in CH_2Cl_2 (10 mL) was added ethyl malonyl chloride (0.92 mL, 7.20 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. After dilution with water (50 mL), the mixutre was extracted with CH_2Cl_2 (30 mL×2), and the combined organic layers were washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel column chromatography (hexane–AcOEt 1:1 to 1:2) to give an amide (1.10 g, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.26 (t, 3H, *J* = 7.5 Hz), 2.81 (t, 2H, *J* = 7.0 Hz), 3.27 (s, 2H), 3.55 (q, 2H, *J* = 7.0 Hz), 3.80 (s, 3H), 4.17 (q, 2H, *J* = 7.5 Hz), 6.75–6.80 (m, 3H), 7.08 (br s, 1H), 7.22 (t, 1H, *J* = 8.0 Hz).

The solution of the above amide (20.8 g, 78.4 mmol) in $POCl_3$ (60 mL) was stirred for 4 h at 80 °C. The mixture was poured into iced water. This was neutralized with K_2CO_3, and extracted with AcOEt (300 mL×2). The combined organic extracts were washed with brine (300 mL×2), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 1:1) yielded 1-carbethoxymethylene-6-methoxy-1,2,3,4-tetrahydroisoquinoline (7.56 g) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.30 (t, 3H, *J* = 7.5 Hz), 2.88 (t, 2H, *J* = 7.0 Hz), 3.43 (dt, 2H, *J* = 3.0, 7.0 Hz), 3.84 (s, 3H), 4.16 (q, 2H, *J* = 7.5 Hz), 5.08 (s, 1H), 6.70 (d, 1H, *J* = 2.5 Hz), 6.80 (dd, 1H, *J* = 2.5, 9.0 Hz), 7.62 (d, 1H, *J* = 9.0 Hz), 9.04 (br s, 1H).

To a solution of 1-carbethoxymethylene-6-methoxy-1,2,3,4-tetrahydroisoquinoline (7.56 g) in AcOH (50 mL) was added PtO_2 (400 mg). The reaction mixture was stirred for 3 h under hydrogen atmosphere at room temperature. The mixture was filtered through a Celite pad, and the solvent was concentrated in vacuo. The residue was neutralized with 1 N NaOH and K_2CO_3, and then extracted with AcOEt (300 mL×2). The combined organic extracts were washed with brine (300 mL×2), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (AcOEt to AcOEt–MeOH 5:1) gave **3b** (4.88 g, 25% for 2 steps) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.26 (t, 3H, *J* = 7.2 Hz), 2.67–2.76 (m, 2H), 2.80–2.87 (m, 2H), 3.01 (ddd, 1H, *J* = 5.2, 7.6, 12.4 Hz), 3.19 (dt, 1H, *J* = 5.2, 12.4 Hz), 3.77 (s, 3H), 4.17 (q, 2H, *J* = 7.2 Hz), 4.41 (dd, 1H, *J* = 3.2, 9.6 Hz), 6.63 (d, 1H, *J* = 2.8 Hz), 6.72 (dd, 1H, *J* = 2.8, 8.8 Hz), 7.01 (d, 1H, *J* = 8.8 Hz).

(5-Methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)acetic acid ethyl ester (3a). This was prepared by a method similar to that used for **3b** using polyphosphate ester instead of $POCl_3$.

Amide. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.27 (t, 3H, *J* = 7.0 Hz), 2.86 (t, 2H, *J* = 7.0 Hz), 3.26 (s, 2H),

3.53 (q, 2H, $J=7.0$ Hz), 3.84 (s, 3H), 4.17 (q, 2H, $J=7.0$ Hz), 6.87 (d, 1H, $J=8.0$ Hz), 6.90 (t, 1H, $J=8.0$ Hz), 7.10 (br s, 1H), 7.14 (dd, 1H, $J=2.0$, 8.0 Hz), 7.22 (t, 1H, $J=8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.0, 30.0, 39.8, 41.4, 55.2, 61.4, 110.3, 120.5, 127.2, 127.8, 130.5, 157.5, 164.8, 169.3; IR (film) cm^{-1}: 3299, 2939, 1739, 1654, 1552, 1495, 1245, 1032, 756; HRMS calcd for $C_{14}H_{19}NO_4$ $(M)^+$ 265.1314, found 265.1316.

3a. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.26 (t, 3H, $J=7.6$ Hz), 2.67 (t, 2H, $J=5.6$ Hz), 2.74 (dd, 1H, $J=9.2$, 16.0 Hz), 2.85 (dd, 1H, $J=3.6$, 16.0 Hz), 3.01 (dt, 1H, $J=6.0$, 12.4 Hz), 3.19 (dt, 1H, $J=5.6$, 12.4 Hz), 3.81 (s, 3H), 4.18 (q, 2H, $J=7.6$ Hz), 4.44 (dd, 1H, $J=3.6$, 9.2 Hz), 6.71 (t, 2H, $J=8.4$ Hz), 7.12 (t, 1H, $J=8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.2, 23.6, 40.0, 41.1, 52.6, 55.3, 60.5, 107.5, 118.0, 124.4, 126.1, 138.7, 157.2, 172.3; IR ($CHCl_3$) cm^{-1}: 2940, 1724, 1587, 1470, 1262, 1165; HRMS calcd for $C_{14}H_{20}NO_3$ $(M+H)^+$ 250.1443, found 250.1430.

(7-Methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)acetic acid ethyl ester (3c). This was prepared by a method similar to that used for **3b** using polyphosphate ester instead of $POCl_3$.

Amide. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.27 (t, 3H, $J=7.2$ Hz), 2.78 (t, 2H, $J=6.4$ Hz), 3.27 (s, 2H), 3.50 (q, 2H, $J=6.8$ Hz), 3.79 (s, 3H), 4.17 (q, 2H, $J=6.8$ Hz), 6.85 (d, 2H, $J=8.0$ Hz), 7.08 (br s, 1H), 7.12 (d, 2H, $J=8.0$ Hz).

3c. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.26 (t, 3H, $J=7.6$ Hz), 2.65-2.79 (m, 3H), 2.84 (dd, 1H, $J=3.6$, 16.4 Hz), 2.96–3.02 (m, 1H), 3.18 (dt, 1H, $J=5.6$, 12.4 Hz), 3.77 (s, 3H), 4.18 (q, 2H, $J=7.2$ Hz), 4.42 (dd, 1H, $J=2.8$, 9.6 Hz), 6.62 (d, 1H, $J=2.0$ Hz), 6.72 (dd, 1H, $J=2.0$, 8.0 Hz), 7.01 (d, 1H, $J=8.0$ Hz); ^{13}C NMR (100 MHz, CDCl3) δ ppm: 14.2, 28.9, 40.8, 41.3, 52.8, 55.3, 60.6, 111.0, 112.5, 127.5, 130.3, 138.5, 157.7, 172.3; IR ($CHCl_3$) cm^{-1}: 2957, 1724, 1611, 1503, 1288, 1256, 1162, 1038; HRMS calcd for $C_{14}H_{20}NO_3$ $(M+H)^+$ 250.1443, found 250.1442.

6-Dimethylcarbamoyloxy-1-ethoxycarbonylmethyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (4a). To a solution of **3b** (4.88 g, 19.6 mmol) in CH_2Cl_2 (30 mL) was added BBr_3 in CH_2Cl_2 (30 mL, 1.0 M) dropwise at −78 °C. The mixture was stirred for 3 h at room temperature. The reaction was quenched with water (10 mL) and neutralized with saturated aq $NaHCO_3$. The product was extracted with CH_2Cl_2 (40 mL×2). The combined organic solution was washed with brine (40 mL), dried over Na_2SO_4, filtered and evaporated to give phenol (2.10 g). To a solution of this phenol (2.10 g) in THF (20 mL), Boc_2O (2.84 g, 13.0 mmol) was added at room temperature. The mixture was stirred for 1 h at room temperature. The solvent was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt 10:1 to 1:1) to give an *N*-Boc-protected phenol (1.72 g, 26% for two steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.25 (t, 3H, $J=8.0$ Hz), 1.48 (s, 9H), 2.59–2.90 (m, 4H), 3.23–3.30 (m, 0.5H), 3.32–3.42 (m, 0.5H), 3.84–3.92 (m, 0.5H), 4.02–4.10 (m, 0.5H), 4.08–4.18 (m, 2H), 5.26 (br s, 1H), 5.46 (t, 0.5H, $J=7.0$ Hz), 5.56 (t, 0.5H, $J=7.0$ Hz), 6.60 (s, 1H), 6.62–6.68 (m, 1H), 7.02 (d, 1H, $J=8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 28.4, 28.6, 37.5, 38.7, 42.0, 42.5, 51.2, 51.9, 60.5, 77.5, 80.0, 80.4, 113.7, 115.1, 115.2, 127.9, 128.2, 128.3, 135.8, 136.0, 154.5, 154.7, 154.8, 170.9; IR ($CHCl_3$) cm^{-1}: 3596, 3356, 2982, 1728, 1685, 1421, 1368, 1293, 1250, 1161, 1042; HRMS calcd for $C_{18}H_{26}NO_5$ $(M+H)^+$ 336.1811, found 336.1817.

To a solution of the above compound (1.70 g, 5.07 mmol) and K_2CO_3 (1.03 g, 7.50 mmol) in DMF (5 mL) was added Me_2NCOCl (0.690 mL, 7.50 mmol) at room temperature. The reaction mixture was stirred for 2.5 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 (30 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel column chromatography (hexane–AcOEt 2:1 to 1:1) to give **4a** (1.97 g, 95%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.25 (t, 3H, $J=7.0$ Hz), 1.47 (s, 9H), 2.62–2.98 (m, 4H), 3.00 (s, 3H), 3.08 (s, 3H), 3.18–3.26 (m, 0.5H), 3.32–3.40 m, (0.5H), 3.90–3.92 (m, 0.5H), 4.10–4.18 (m, 2.5H), 5.53 (t, 0.5H, $J=7.0$ Hz), 5.64 (t, 0.5H, $J=7.0$ Hz), 6.89 (s, 1H), 6.89–6.97 (m, 1H), 7.14–7.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 28.3, 28.6, 36.4, 36.7, 37.0, 38.5, 41.9, 42.3, 51.1, 51.9, 60.3, 76.5, 77.5, 79.8, 80.2, 119.8, 121.7, 122.0, 127.6, 128.0, 133.4, 135.5, 135.8, 150.1, 154.3, 154.4, 154.9, 170.7, 171.1; IR ($CHCl_3$) cm^{-1}: 2982, 1721, 1686, 1392, 1368, 1288, 1247, 1163, 1037; HRMS calcd for $C_{21}H_{31}N_2O_6$ $(M+H)^+$ 407.2182, found 407.2187.

7-Dimethylcarbamoyloxy-1-ethoxycarbonylmethyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (4b). This was prepared by the method used for **4a**.

***N*-Boc-protected phenol.** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.22–1.27 (m, 3H), 1.47 (s, 9H), 2.67 (br d, 2H, $J=15.5$ Hz), 2.74–2.90 (m, 2.5H), 3.20–3.26 (m, 0.5H), 3.34–3.40 (m, 0.5H), 3.93–4.00 (m, 0.5H), 4.06–4.18 (m, 2H), 5.47 (br t, 0.5H, $J=6.0$ Hz), 5.64 (br t, 0.5H, $J=6.0$ Hz), 6.66 (br s, 0.5H), 6.68 (d, 1H, $J=9.0$ Hz), 6.82 (br s, 0.5H), 6.97-7.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.1, 27.4, 27.6, 28.4, 37.8, 38.9, 41.6, 42.3, 51.8, 52.2, 60.8, 77.5, 80.4, 113.2, 113.5, 1145, 114.8, 125.3, 126.2, 129.9, 130.1, 137.1, 137.6, 154.2, 154.4, 154.8, 170.7, 171.0; IR (CHCl3) cm^{-1}: 3597, 3363, 1729, 1685, 1423, 1368, 1270, 1164; HRMS calcd for $C_{18}H_{26}NO_5$ $(M+H)^+$ 336.1811, found 336.1818.

4b. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.25 (t, 3H, $J=7.0$ Hz), 1.46 (s, 9H), 2.64–2.80 (m, 4H), 2.80–2.88 (m, 0.5H), 3.00 (s, 3H), 3.08 (s, 3H), 3.18-3.25 (m, 0.5H), 3.31–3.39 (m, 0.5H), 3.91–3.99 (m, 0.5H), 4.10–4.20 (m, 2H), 5.53 (br t, 0.5H, $J=10.5$ Hz), 5.63 (br t, 0.5H, $J=10.5$ Hz), 6.92–6.95 (m, 1H), 6.95 (s, 1H), 7.08–7.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.1, 14.2, 27.8, 28.3, 36.4, 36.7, 37.2, 42.2, 51.4, 52.1,

60.6, 80.2, 119.9, 120.6, 129.5, 129.8, 131.3, 137.4, 137.5, 149.7, 154.2, 154.8, 170.6; IR ($CHCl_3$) cm^{-1}: 2982, 1721, 1687, 1392, 1250, 1166; HRMS calcd for $C_{21}H_{31}N_2O_6$ $(M+H)^+$ 407.2182, found 407.2184.

Dimethylcarbamic acid 1-[2-(4-nitrophenoxy)ethyl]-1,2,3,4-tetrahydroisoquinolin-6-yl ester hydrochloride salt (6a·HCl). To a solution of **4a** (1.97 g, 4.84 mmol) in THF (30 mL) was added $LiAlH_4$ (270 mg, 7.2 mmol) at −78 °C. The reaction mixture was stirred for 20 min at −78 °C and for another 20 min at 0 °C. To the reaction mixture was successively added water (0.3 mL), 15% aq NaOH (0.3 mL), water (0.9 mL) and $MgSO_4$. 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 an alcohol (1.38 g, 78%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.49 (s, 9H), 1.74 (t, 1H, $J=12.4$ Hz), 2.00–2.10 (m, 1H), 2.71 (dt, 1H, $J=4.4$, 16.0 Hz), 2.86–2.94 (m, 1H), 3.00 (s, 3H), 3.09 (s, 3H), 3.54 (t, 1H, $J=11.0$ Hz), 3.65 (br, 1H), 4.02 (dt, 1H, $J=4.4$, 12.4 Hz), 4.12 (br, 0.8H), 4.23 (br, 0.2H), 5.30 (d, 1H, $J=12.0$ Hz), 6.89 (d, 1H, $J=2.0$ Hz), 6.93 (dd, 1H, $J=2.0$, 8.0 Hz), 7.15 (d, 1H, $J=8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 28.3, 28.8, 36.4, 36.7, 38.1, 38.9, 50.1, 58.5, 80.6, 119.9, 121.7, 127.8, 134.5, 135.1, 149.7, 154.9, 156.2; IR ($CHCl_3$) cm^{-1}: 3424, 2981, 2942, 1713, 1660, 1392, 1247, 1163, 1043; HRMS calcd for $C_{19}H_{29}N_2O_5$ $(M+H)^+$ 365.2077, found 365.2092.

To a solution of the alcohol (200 mg, 0.548 mmol), 4-nitrophenol (83.5 mg, 0.600 mmol), and Ph_3P (172 mg, 0.657 mmol) in THF (10 mL) was added 40% diethyl azodicaboxylic acid toluene solution (286 mg, 0.657 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 1:1 to 1:2) to give *N*-Boc-protected **6a**. This compound was treated with 2 N HCl in AcOEt (6 mL). After stirring for 12 h at room temperature, the reaction mixture was neutralized with saturated aq $NaHCO_3$ 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 silica gel column chromatography (AcOEt to AcOEt–MeOH 5:1) yielded **6a** (148 mg, 70% for two steps) as a colorless oil.

6a. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.16–2.23 (m, 1H), 2.30–2.34 (m, 1H), 2.71–2.83 (m, 2H), 3.00–3.05 (m, 1H), 3.01 (s, 3H), 3.09 (s, 3H), 3.14–3.20 (m, 1H), 4.16–4.23 (m, 2H), 4.31–4.36 (m, 1H), 6.87 (d, 1H, $J=2.0$ Hz), 6.92 (dd, 1H, $J=2.0$, 8.0 Hz), 6.98 (d, 2H, $J=9.5$ Hz), 7.13 (d, 1H, $J=8.0$ Hz), 8.20 (d, 2H, $J=9.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.8, 35.5, 36.4, 36.7, 40.2, 52.4, 66.2, 114.5, 119.5, 122.2, 125.9, 126.9, 135.4, 136.5, 141.4, 149.6, 155.0, 164.0; IR ($CHCl_3$) cm^{-1}: 2939, 1712, 1593, 1512, 1498, 1391, 1343, 1263, 1172, 1111, 1020, 846; HRMS calcd for $C_{20}H_{24}N_3O_5$ $(M+H)^+$ 386.1716, found 386.1716.

6a·HCl. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.50–2.70 (m, 2H), 3.00 (s, 3H), 3.09 (s, 3H), 3.09–3.16 (m, 2H), 3.32–3.35 (m, 1H), 3.48–3.58 (m, 1H), 4.23 (dt, 1H, $J=4.4$, 9.6 Hz), 4.53–4.59 (m, 1H), 4.82 (br s, 1H), 6.94 (d, 1H, $J=2.0$ Hz), 7.03 (dd, 1H, $J=2.0$, 9.0 Hz), 7.05 (d, 2H, $J=8.8$ Hz), 7.14 (d, 1H, $J=9.0$ Hz), 8.18 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 25.6, 33.7, 36.4, 36.7, 39.0, 52.0, 64.6, 114.8, 121.2, 122.4, 125.9, 127.5, 127.6, 132.9, 141.9, 151.1, 154.4, 163.1; IR (KBr) cm^{-1}: 2935, 2770, 1722, 1593, 1510, 1388, 1340, 1262, 1171, 1110, 1024, 849, 753; HRMS calcd for $C_{20}H_{24}N_3O_5$ $(M+H)^+$ 386.1716, found 386.1719.

Dimethylcarbamic acid 1-[2-(4-chlorophenoxy)ethyl]-1,2,3,4-tetrahydroisoquinolin-6-yl ester hydrochloride salt (6b·HCl). This was prepared by the method used for **6a**.

6b. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.09–2.18 (m, 1H), 2.26–2.34 (m, 1H), 2.70–2.84 (m, 2H), 2.97–3.04 (m, 1H), 3.00 (s, 3H), 3.09 (s, 3H), 3.14–3.20 (m, 1H), 4.04–4.23 (m, 3H), 6.83–6.87 (m, 3H), 6.90 (dd, 1H, $J=2.8$, 8.8 Hz), 7.12 (d, 1H, $J=8.0$ Hz), 7.22 (d, 2H, $J=8.8$ Hz; ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.9, 35.7, 36.4, 36.6, 40.3, 52.7, 65.7, 115.8, 119.4, 122.1, 125.4, 127.0, 129.2, 135.7, 136.5, 149.5, 155.0, 157.5; IR ($CHCl_3$) cm^{-1}: 2937, 1712, 1492, 1391, 1246, 1171; HRMS calcd for $C_{20}H_{24}N_2O_3Cl$ $(M+H)^+$ 375.1475, found 375.1488.

6b·HCl. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.43–2.62 (m, 2H), 3.00 (s, 3H), 3.09 (s, 3H), 3.09–3.13 (m, 2H), 3.28–3.38 (m, 1H), 3.48–3.58 (m, 1H), 4.05–4.12 (m, 1H), 4.32–4.40 (m, 1H), 4.82 (br s, 1H), 6.90 (d, 2H, $J=8.8$ Hz), 6.93 (s, 1H), 7.01 (d, 1H, $J=8.8$ Hz), 7.13 (d, 1H, $J=8.8$ Hz), 7.21 (d, 2H, $J=8.8$ Hz), 9.52 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 25.6, 33.8, 36.4, 36.7, 39.0, 52.2, 64.1, 116.1, 121.0, 122.2, 126.2, 127.6, 127.8, 129.4, 133.0, 150.9, 154.5, 156.7; IR (KBr) cm^{-1}: 2932, 2734, 1727, 1492, 1385, 1243, 1165, 823; HRMS calcd for $C_{20}H_{24}N_2O_3Cl$ $(M+H)^+$ 375.1475, found 375.1484.

Dimethylcarbamic acid 1-[2-(4-nitrophenoxy)ethyl]-1,2,3,4-tetrahydroisoquinolin-7-yl ester hydrochloride salt (7a·HCl). This was prepared by the method used for **6a**.

Alcohol. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.49 (s, 9H), 1.77 (t, 1H, $J=13.5$ Hz), 2.02–2.11 (m, 1H), 2.71 (dt, 1H, $J=4.0$, 15.5 Hz), 2.85-2.92 (m, 1H), 3.00 (s, 3H), 3.09 (s, 3H), 3.09–3.16 (m, 1H), 3.54 (t, 1H, $J=12.0$ Hz), 3.64 (br s, 1H), 4.03 (dt, 1H, $J=4.0$, 12.5 Hz), 4.07 (br s, 0.8H), 4.25 (br s, 0.2H), 5.29 (d, 1H, $J=10.0$ Hz), 6.92 (s, 1H), 6.93 (d, 1H, $J=8.0$ Hz), 7.09 (d, 1H, $J=8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 28.2, 28.3, 36.4, 36.7, 38.4, 38.7, 50.4, 58.4, 80.6, 120.0, 120.1, 129.4, 130.8, 138.6, 149.8, 154.9, 156.1; IR ($CHCl_3$) cm^{-1}: 3424, 2940, 1714, 1662, 1392, 1248, 1164; HRMS calcd for $C_{19}H_{29}N_2O_5$ $(M+H)^+$ 365.2077, found 365.2069.

7a. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.04–2.23 (m, 1H), 2.30–2.38 (m, 1H), 2.68–2.82 (m, 2H), 2.99–3.05 (m, 1H), 3.00 (s, 3H), 3.09 (s, 3H), 3.14–3.21 (m, 1H), 4.16–4.24 (m, 2H), 4.31–4.36 (m, 1H), 6.90 (dd, 1H, $J=2.0$, 8.8 Hz), 6.91 (s, 1H), 6.98 (d, 2H, $J=8.4$ Hz),

7.08 (d, 1H, $J=8.8$ Hz), 8.20 (d, 2H, $J=8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.2. 35.3, 36.4, 36.7, 40.4, 52.6, 66.1, 114.5, 119.2, 119.8, 125.9, 130.2, 132.1, 139.5, 141.4, 149.5, 155.0, 164.0; IR ($CHCl_3$) cm^{-1}: 2939, 1713, 1593, 1512, 1498, 1391, 1342, 1264, 1173, 1111, 1020; HRMS calcd for $C_{20}H_{24}N_3O_5$ $(M+H)^+$ 386.1716, found 386.1729.

7a·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.55–2.69 (m, 2H), 2.98 (s, 3H), 3.07 (s, 3H), 3.09–3.18 (m, 2H), 3.34 (quint, 1H, $J=7.0$ Hz), 3.58 (quint, 1H, $J=6.0$ Hz), 4.27 (dt, 1H, $J=5.0$, 10.0 Hz), 4.52–4.57 (m, 1H), 4.80–4.82 (m, 1H), 6.94 (d, 1H, $J=2.0$ Hz), 7.02 (dd, 1H, $J=2.0$, 8.0 Hz), 7.05 (d, 2H, $J=9.0$ Hz), 7.14 (d, 1H, $J=8.0$ Hz), 8.16 (d, 2H, $J=9.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 25.1, 33.5, 36.4, 36.7, 39.4, 52.2, 64.6, 114.9, 119.9, 121.9, 125.8, 128.3, 130.3, 131.6, 141.9, 150.5, 154.5, 163.1; IR ($CHCl_3$) cm^{-1}: 2970, 2767, 1720, 1593, 1514, 1499, 1391, 1344, 1260, 1172, 1111; HRMS calcd for $C_{20}H_{24}N_3O_5$ $(M+H)^+$ 386.1716, found 386.1719.

Dimethylcarbamic acid 1-[2-(4-chlorophenoxy)ethyl]-1,2,3,4-tetrahydroisoquinolin-7-yl ester hydrochloride salt (7b·HCl). This was prepared by the method used for **6a**.

7b. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.04–2.27 (m, 1H), 2.28–2.35 (m, 1H), 2.69–2.82 (m, 2H), 2.97–3.03 (m, 1H), 3.00 (s, 3H), 3.09 (s, 3H), 3.15–3.22 (m, 1H), 4.04–4.11 (m, 1H), 4.14–4.23 (m, 2H), 6.84 (d, 2H, $J=8.8$ Hz), 6.89 (dd, 1H, $J=2.0$, 9.6 Hz), 6.90 (s, 1H), 7.07 (d, 1H, $J=9.6$ Hz), 7.22 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.3, 35.5, 36.4, 36.7, 40.6, 52.9, 65.6, 115.8, 119.2, 119.7, 125.4, 129.2, 130.1, 132.1, 139.8, 149.4, 155.1, 157.5; IR ($CHCl_3$) cm^{-1}: 2937, 1713, 1492, 1391, 1249, 1171, 826; HRMS calcd for $C_{20}H_{24}N_2O_3Cl$ $(M+H)^+$ 375.1475, found 375.1472.

7b·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.52–2.62 (m, 2H), 2.99 (s, 3H), 3.02–3.14 (m, 2H), 3.07 (s, 3H), 3.29–3.34 (m 1H), 3.54–3.59 (m, 1H), 4.11 (dt, 1H, $J=6.0$, 9.5 Hz), 4.33–4.37 (m, 1H), 4.82 (t, 1H, $J=6.0$ Hz), 6.91 (d, 2H, $J=8.5$ Hz), 6.92 (s, 1H), 7.01 (dd, 1H, $J=3.0$, 8.5 Hz), 7.14 (d, 1H, $J=8.5$ Hz), 7.20 (d, 2H, $J=8.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 25.1, 33.6, 36.4, 36.7, 39.4, 52.3, 64.1, 116.2, 119.9, 121.8, 126.1, 128.5, 129.3, 130.2, 131.8, 150.4, 154.5, 156.7; IR ($CHCl_3$) cm^{-1}: 2968, 2768, 1720, 1586, 1492, 1391, 1247, 1171.

Dimethylcarbamic acid 2-methyl-1-[2-(4-nitrophenoxy)-ethyl]-1,2,3,4-tetrahydroisoquinolin-6-yl ester hydrochloride salt (9a·HCl). Compound **6a** (31 mg, 0.080 mmol) was dissolved in a mixture of HCO_2H (0.5 mL) and 37% aq HCHO (0.5 mL) and stirred for 3 h at 80 °C. After cooling to room temperature, saturated 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 column chromatography (AcOEt to AcOEt–MeOH 5:1) to give **9a** (27 mg, 84%) as a colorless oil.

9a. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.22–2.33 (m, 2H), 2.46 (s, 3H), 2.67–2.75 (m, 2H), 2.81–2.87 (m, 1H), 3.01 (s, 3H), 3.07–3.12 (m, 1H), 3.09 (s, 3H), 3.70 (t, 1H, $J=5.5$ Hz), 3.96–4.01 (m, 1H), 4.25 (dt, 1H, $J=8.0$, 8.5 Hz), 6.87 (d, 1H, $J=2.5$ Hz), 6.91 (d, 3H, $J=9.0$ Hz), 7.11 (d, 1H, $J=9.0$ Hz), 8.17 (d, 2H, $J=9.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 25.8, 34.0, 36.4, 36.7, 42.7, 47.7, 60.1, 65.8, 114.5, 119.6, 121.7, 125.8, 127.9, 133.9, 135.9, 141.3, 149.5, 155.0, 164.1; IR ($CHCl_3$) cm^{-1}: 2941, 1712, 1593, 1512, 1498, 1391, 1342, 1264, 1172, 1111, 1018, 846; HRMS calcd for $C_{21}H_{26}N_3O_5$ $(M+H)^+$ 400.1873, found 400.1865.

9a·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.19–2.27 (m, 1H), 2.89 (d, 3H, $J=5.2$ Hz), 3.02 (s, 3H), 3.04–3.20 (m, 3H), 3.10 (s, 3H), 3.32–3.40 (m, 1H), 3.71–3.80 (m, 1H), 4.14–4.20 (m, 1H), 4.50 (t, 1H, $J=6.4$ Hz), 4.60–4.65 (m, 1H), 7.02–7.10 (m, 5H), 8.23 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 22.0, 26.9, 34.8, 36.5, 36.8, 40.6, 44.8, 61.0, 64.5, 114.7, 121.6, 122.6, 126.0, 126.3, 129.0, 130.5, 142.0, 151.7, 154.3, 163.0; IR (KBr) cm^{-1}: 2932, 2529, 1722, 1591, 1511, 1388, 1341, 1260, 1172, 1110, 1029, 849; HRMS calcd for $C_{21}H_{26}N_3O_5$ $(M+H)^+$ 400.1873, found 400.1879.

Compounds **9b–g** and **10a, b** were prepared by the method used for **9a**.

Dimethylcarbamic acid 1-[2-(4-chlorophenoxy)ethyl]-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl ester hydrochloride salt (9b·HCl). **9b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.20 (dt, 2H, $J=5.5$, 7.0 Hz), 2.46 (s, 3H), 2.68–2.74 (m, 2H), 2.81–2.88 (m, 1H), 3.00 (s, 3H), 3.08 (s, 3H), 3.09–3.14 (m, 1H), 3.70 (t, 1H, $J=4.5$ Hz), 3.87 (dt, 1H, $J=7.0$, 9.5 Hz), 4.12 (dt, 1H, $J=7.0$, 9.5 Hz), 6.80 (d, 2H, $J=9.0$ Hz), 6.85 (d, 1H, $J=3.0$ Hz), 6.89 (dd, 1H, $J=3.0$, 9.0 Hz), 7.11 (d, 2H, $J=8.0$ Hz), 7.20 (d, 2H, $J=8.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 25.6, 34.3, 36.4, 36.6, 42.6, 47.3, 60.0, 65.2, 115.8, 119.5, 121.6, 125.2, 128.1, 129.2, 134.2, 135.7, 149.5, 155.0, 157.6; IR ($CHCl_3$) cm^{-1}: 2940, 1712, 1492, 1391, 1246, 1171, 909; HRMS calcd for $C_{21}H_{26}N_2O_3Cl$ $(M+H)^+$ 389.1632, found 389.1616.

9b·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.11–2.20 (m, 1H), 2.88 (s, 3H), 3.02 (s, 3H), 3.00–3.22 (m, 3H), 3.10 (s, 3H), 3.33–3.42 (m, 1H), 3.70–3.80 (m, 1H), 3.95–4.05 (m, 1H), 4.35–4.92 (m, 1H), 4.53 (br s, 1H), 6.88 (d, 2H, $J=9.2$ Hz), 7.02 (dd, 2H, $J=2.8$, 8.0 Hz), 7.04 (s, 1H), 7.10 (d, 2H, $J=8.0$ Hz), 7.25 (d, 2H, $J=9.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 22.2, 34.9, 36.4, 36.7, 40.6, 45.0, 61.1, 63.8, 115.8, 121.4, 122.4, 126.3, 129.2, 129.5, 130.6, 151.6, 154.3, 156.6; IR (film) cm^{-1}: 3423, 2936, 2622, 1720, 1493, 1390, 1240, 1171, 1044, 827, 754; HRMS calcd for $C_{21}H_{26}N_2O_3Cl$ $(M+H)^+$ 389.1632, found 389.1629.

Dimethylcarbamic acid 2-methyl-1-[2-(3-methyl-4-nitrophenoxy)ethyl]-1,2,3,4-tetrahydroisoquinolin-6-yl ester hydrochloride salt (9c·HCl). **9c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.25 (q, 2H, $J=6.5$ Hz), 2.46 (s, 3H), 2.61 (s, 3H), 2.69–2.76 (m, 2H), 2.81–2.88 (m, 1H), 3.01 (s, 3H), 3.09 (s, 3H), 3.09–3.14 (m, 1H), 3.70 (t, 1H, $J=6.0$ Hz), 3.96 (dt, 1H, $J=6.0$, 9.5 Hz), 4.22 (dt, 1H,

J = 6.5, 10.0 Hz), 6.74 (t, 1H, J = 3.0 Hz), 6.76 (dd, 1H, J = 3.0, 8.5 Hz), 6.87 (d, 1H, J = 2.0 Hz), 6.92 (dd, 1H, J = 2.0, 8.0 Hz), 7.11 (d, 1H, J = 8.0 Hz), 8.06 (d, 1H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 21.6, 34.1, 36.4, 36.7, 42.6, 47.5, 60.1, 65.4, 112.4, 117.8, 119.7, 121.7, 127.5, 128.0, 137.0, 142.0, 149.7, 154.9, 162.5; IR ($CHCl_3$) cm^{-1}: 2940, 1713, 1580, 1511, 1391, 1340, 1254, 1173, 1080, 1035; HRMS calcd for $C_{22}H_{28}N_3O_5$ $(M+H)^+$ 414.2029, found 414.2011.

9c·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.20 (br s, 1H), 2.64 (s, 3H), 2.89 (s, 3H), 3.02 (s, 3H), 3.00–3.25 (m, 2H), 3.10 (s, 3H), 3.36 (br s, 1H), 3.75 (br s, 1H), 4.13 (br s, 1H), 4.23 (br, 1H), 4.50 (br s, 1H), 4.56 (br s, 1H), 6.86 (s, 2H), 7.04–7.10 (m, 3H), 8.09 (d, 1H, J = 9.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 21.6, 22.0, 34.8, 36.5, 36.8, 40.7, 44.9, 50.7, 61.1, 64.3, 112.5, 118.0, 121.6, 122.6, 127.6, 129.1, 130.5, 137.2, 142.7, 151.7, 154.4, 161.4; IR ($CHCl_3$) cm^{-1}: 3631, 2967, 2337, 1722, 1590, 1513, 1392, 1342, 1253, 1171, 1016.

Dimethylcarbamic acid 2-methyl-1-[2-(3-nitrophenoxy)-ethyl]-1,2,3,4-tetrahydroisoquinolin-6-yl ester hydrochloride salt (9d·HCl). 9d. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.26 (q, 2H, J = 6.8 Hz), 2.46 (s, 3H), 2.68–2.76 (m, 2H), 2.81–2.88 (m, 1H), 3.00 (s, 3H), 3.09 (s, 3H), 3.10–3.14 (m, 1H), 3.71 (t, 1H, J = 6.0 Hz), 3.98 (dt, 1H, J = 6.8, 8.8 Hz), 4.25 (dt, 1H, J = 7.2, 9.6 Hz), 6.87 (d, 1H, J = 2.0 Hz), 6.92 (dd, 1H, J = 2.0, 8.8 Hz), 7.12 (d, 2H, J = 8.8 Hz), 7.19 (dd, 1H, J = 2.0, 8.0 Hz), 7.39 (t, 1H, J = 8.0 Hz), 7.72 (t, 1H, J = 2.0 Hz), 7.79 (dd, 1H, J = 2.0, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 25.6, 34.1, 36.4, 36.6, 42.6, 47.4, 60.0, 65.6, 108.9, 115.5, 119.6, 121.6, 121.7, 128.0, 129.8, 133.9, 135.8, 149.1, 155.0, 159.5; IR ($CHCl_3$) cm^{-1}: 2941, 1713, 1531, 1391, 1351, 1251, 1172, 1022; HRMS calcd for $C_{21}H_{26}N_3O_5$ $(M+H)^+$ 400.1873, found 400.1872.

9d·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.19–2.35 (m, 1H), 2.86–2.92 (m, 1H), 2.919 (d, 3H, J = 5.0 Hz), 3.02 (s, 3H), 3.05–3.24 (m, 2H), 3.10 (s, 3H), 3.35–3.41 (m, 1H), 3.73–3.81 (m, 1H), 4.12–4.18 (m, 1H), 4.51–4.60 (m, 2H), 7.05 (d, 1H, J = 9.0 Hz), 7.07 (s, 1H), 7.11 (d, 1H, J = 9.0 Hz), 7.34 (dd, 1H, J = 2.0, 8.0 Hz), 7.48 (t, 1H, J = 8.0 Hz), 7.75 (d, 1H, J = 2.0 Hz), 7.86 (dd, 1H, J = 2.0, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 22.0, 34.8, 36.4, 36.7, 40.6, 44.8, 61.0, 64.3, 109.5, 116.3, 121.1, 121.6, 122.5, 126.3, 129.1, 130.3, 130.5, 149.2, 151.7, 154.3, 158.5; IR ($CHCl_3$) cm^{-1}: 2969, 2337, 1723, 1532, 1392, 1353, 1248, 1171.

Dimethylcarbamic acid 1-[2-(4-fluorophenoxy)ethyl]-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl ester hydrochloride salt (9e·HCl). 9e. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.18–2.22 (m, 2H), 2.46 (s, 3H), 2.68–2.73 (m, 2H), 2.85 (dt, 1H, J = 7.0, 19.5 Hz), 3.00 (s, 3H), 3.09 (s, 3H), 3.09–3.13 (m, 1H), 3.70 (t, 1H, J = 5.5 Hz), 3.87 (dt, 1H, J = 7.0, 8.5 Hz), 4.11 (dt, 1H, J = 6.5, 9.0 Hz), 6.80–6.82 (m, 2H), 6.85 (d, 1H, J = 3.0 Hz), 6.90 (dd, 1H, J = 3.0, 8.0 Hz), 6.91–6.96 (m, 2H), 7.11 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 25.6, 34.4, 36.4, 36.6, 42.6, 47.3, 60.0, 65.4, 115.4, 115.5, 115.6, 115.7, 119.5, 121.6, 128.1, 135.7, 149.5, 155.0, 155.1, 156.1, 158.0; IR ($CHCl_3$) cm^{-1}: 2940, 1712, 1505, 1391, 1249, 1173, 909, 829; HRMS calcd for $C_{21}H_{26}N_2O_3F$ $(M+H)^+$ 373.1928, found 373.1922.

9e·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.10–2.20 (m, 1H), 2.89 (d, 3H, J = 4.0 Hz), 3.02 (s, 3H), 3.02–3.24 (m, 3H), 3.10 (s, 3H), 3.32–3.40 (m, 1H), 3.72–3.80 (m, 1H), 3.96–4.02 (m, 1H), 4.34–4.40 (m, 1H), 4.52–4.58 (m, 1H), 6.88–6.91 (m, 2H), 6.99 (d, 2H, J = 8.0 Hz), 7.03 (d, 1H, J = 7.5 Hz), 7.04 (s, 1H), 7.12 (d, 1H, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 22.1, 35.0, 36.4, 36.7, 40.6, 45.0, 61.1, 64.0, 115.6, 115.9, 116.0, 121.4, 122.4, 126.5, 129.3, 130.5, 151.5, 154.2, 154.3, 156.6, 158.5; IR (CHCl3) cm^{-1}: 2967, 2347, 1721, 1506, 1392, 1248, 1171, 1047, 829.

Dimethylcarbamic acid 1-[2-(4-bromophenoxy)ethyl]-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl ester hydrochloride salt (9f·HCl). 9f: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.18–2.23 (m, 2H), 2.46 (s, 3H), 2.69–2.74 (m, 2H), 2.82–2.88 (m, 1H), 3.01 (s, 3H), 3.09 (s, 3H), 3.09–3.14 (m, 1H), 3.70 (t, 1H, J = 5.5 Hz), 3.88 (dt, 1H, J = 7.0, 8.5 Hz), 4.13 (dt, 1H, J = 7.0, 9.5 Hz), 6.77 (d, 2H, J = 9.0 Hz), 6.87 (d, 1H, J = 3.0 Hz), 6.91 (dd, 1H, J = 3.0, 9.0 Hz), 7.11 (d, 1H, J = 9.0 Hz), 7.35 (d, 2H, J = 9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 25.6, 34.3, 36.4, 36.6, 42.6, 47.3, 60.0, 65.1, 112.5, 116.4, 119.5, 121.6, 128.1, 132.1, 134.1, 135.7, 149.5, 155.0, 158.1; IR ($CHCl_3$) cm^{-1}: 2940, 1712, 1488, 1391, 1285, 1248, 1171, 1022; HRMS calcd for $C_{21}H_{26}N_2O_3Br$ $(M+H)^+$ 433.1127, found 433.1111.

9f·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.08–2.20 (m, 2H), 2.89 (d, 3H, J = 5.0 Hz), 3.02 (s, 3H), 3.02–3.21 (m, 2H), 3.10 (s, 3H), 3.31–3.39 (m, 1H), 3.60–3.70 (m, 1H), 3.98–4.02 (m, 1H), 4.37–4.41 (m, 1H), 4.50–4.55 (m, 1H), 6.83 (d, 2H, J = 9.5 Hz), 7.03 (d, 1H, J = 8.5 Hz), 7.04 (s, 1H), 7.09 (d, 1H, J = 8.5 Hz), 7.40 (d, 1H, J = 9.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 22.1, 34.9, 36.4, 36.7, 40.6, 44.9, 61.1, 63.7, 113.6, 116.3, 116.4, 121.4, 122.4, 126.4, 129.2, 130.5, 132.4, 151.6, 154.3, 157.2; IR ($CHCl_3$) cm^{-1}: 2967, 2317, 1722, 1488, 1391, 1247, 1172, 1046, 908.

Dimethylcarbamic acid 1-[2-(4-methoxyphenoxy)ethyl]-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl ester hydrochloride salt (9g·HCl). 9g. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.14–2.23 (m, 2H), 2.46 (s, 3H), 2.67–2.74 (m, 2H), 2.83–2.89 (m, 1H), 3.00 (s, 3H), 3.08 (s, 3H), 3.10–3.14 (m, 1H), 3.72 (t, 1H, J = 6.0 Hz), 3.76 (s, 3H), 3.84–3.90 (m, 1H), 4.10 (dt, 1H, J = 6.5, 9.0 Hz), 6.79–6.84 (m, 4H), 6.85 (d, 1H, J = 2.0 Hz), 6.89 (dd, 1H, J = 2.0, 8.5 Hz), 7.11 (d, 1H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 25.5, 34.6, 36.4, 36.6, 42.5, 47.2, 55.7, 60.0, 65.4, 114.5, 115.5, 119.4, 121.6, 128.2, 134.4, 135.6, 149.5, 153.1, 153.6, 155.0; IR ($CHCl_3$) cm^{-1}: 2939, 1712, 1509, 1391, 1249, 1174, 1039, 909; HRMS calcd for $C_{22}H_{29}N_2O_4$ $(M+H)^+$ 385.2128, found 385.2117.

9g·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.08–2.16 (m, 2H), 2.89 (d, 3H, J = 4.5 Hz), 3.01 (s, 3H), 3.02–3.24 (m, 1H), 3.10 (s, 3H), 3.32–3.38 (m, 1H), 3.78 (s, 3H), 3.94–4.00 (m, 1H), 4.28–4.36 (m, 1H), 4.54–4.60

(m, 1H), 6.85 (d, 2H, $J=9.0$ Hz), 6.89 (d, 2H, $J=9.0$ Hz), 7.02 (d, 1H, $J=8.0$ Hz), 7.04 (s, 1H), 7.14 (d, 1H, $J=8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 22.2, 35.1, 36.4, 36.7, 40.6, 45.1, 55.7, 61.1, 63.9, 114.7, 115.5, 121.3, 122.3, 126.6, 129.4, 130.6, 151.5, 152.2, 154.2, 154.4; IR ($CHCl_3$) cm^{-1}: 2965, 2347, 1721, 1509, 1391, 1248, 1171, 1048.

Dimethylcarbamic acid 2-methyl-1-[2-(4-nitrophenoxy)-ethyl]-1,2,3,4-tetrahydroisoquinolin-7-yl ester hydrochloride salt (10a·HCl). 10a. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.22–2.32 (m, 2H), 2.46 (s, 3H), 2.67–2.73 (m, 2H), 2.81–2.86 (m, 1H), 3.00 (s, 3H), 3.08 (s, 3H), 3.08–3.13 (m, 1H), 3.70 (t, 1H, $J=5.5$ Hz), 3.99–4.04 (m, 1H), 4.26 (q, 1H, $J=8.5$ Hz), 6.89–6.93 (m, 4H), 7.08 (d, 1H, $J=7.5$ Hz), 8.17 (d, 2H, $J=9.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 25.2, 33.9, 36.4, 36.7, 42.7, 47.9, 60.3, 65.7, 114.5, 119.7, 120.2, 125.8, 129.6, 131.5, 138.1, 141.2, 149.6, 155.0, 164.1; IR ($CHCl_3$) cm^{-1}: 2941, 1713, 1593, 1512, 1498, 1391, 1342, 1264, 1172, 1111, 1018; HRMS calcd for $C_{21}H_{26}N_3O_5$ $(M+H)^+$ 400.1873, found 400.1852.

10a·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.22–2.29 (m, 1H), 2.90 (d, 3H, $J=5.0$ Hz), 2.96 (s, 3H), 3.05 (s, 3H), 3.07–3.23 (m, 3H), 3.36–3.38 (m, 1H), 3.73–3.78 (m, 1H), 4.22–4.26 (m, 1H), 4.44–4.48 (m, 1H), 4.58–4.62 (m, 1H), 6.87 (d, 1H, $J=2.0$ Hz), 7.05–7.10 (m, 3H), 7.25 (d, 1H, $J=7.5$ Hz), 8.23 (d, 2H, $J=8.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 21.5, 34.7, 36.4, 36.7, 40.6, 45.2, 61.1, 64.5, 114.9, 121.5, 122.6, 125.9, 130.4, 141.9, 150.6, 154.3, 163.0; IR (KBr) cm^{-1}: 2928, 2561, 1726, 1593, 1389, 1343, 1264, 1173, 845. Anal. calcd for $C_{21}H_{25}N_3O_5$·HCl·H_2O: C, 56.69; H, 6.12; N, 9.44. Found: C, 56.99; H, 5.91; N, 9.78.

Dimethylcarbamic acid 1-[2-(4-chlorophenoxy)ethyl]-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl ester hydrochloride salt (10b·HCl). 10b. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.20 (q, 2H, $J=6.2$ Hz), 2.45 (s, 3H), 2.64–2.74 (m, 2H), 2.80–2.88 (m, 1H), 3.00 (s, 3H), 3.07 (s, 3H), 3.09–3.14 (m, 1H), 3.70 (t, 1H, $J=5.6$ Hz), 3.88 (dt, 1H, $J=6.4$, 9.6 Hz), 4.13 (dt, 1H, $J=7.2$, 9.6 Hz), 6.81 (d, 2H, $J=8.8$ Hz), 6.87 (s, 1H), 6.89 (d, 1H, $J=8.8$ Hz), 7.06 (d, 1H, $J=8.8$ Hz), 7.20 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 25.0, 34.3, 36.4, 36.6, 42.6, 47.6, 60.3, 65.1, 115.9, 119.6, 120.2, 125.2, 129.1, 129.5, 131.4, 138.4, 149.5, 155.0, 157.6; IR ($CHCl_3$) cm^{-1}: 2940, 1713, 1492, 1391, 1247, 1171; HRMS calcd for $C_{21}H_{26}N_2O_3Cl$ $(M+H)^+$ 389.1632, found 389.1621.

10b·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.14–2.22 (m, 1H), 2.89 (d, 3H, $J=4.5$ Hz), 2.97 (s, 3H), 3.02 (s, 3H), 3.02–3.13 (m, 2H), 3.21 (br d, 1H, $J=15.5$ Hz), 3.31–3.38 (m, 1H), 3.71–3.78 (m, 1H), 4.03–4.09 (m, 1H), 4.37–4.42 (m, 1H), 4.50 (t, 1H, $J=6.5$ Hz), 6.86 (d, 1H, $J=2.0$ Hz), 6.91 (d, 2H, $J=8.5$ Hz), 7.09 (dd, 1H, $J=2.0$, 8.5 Hz), 7.24 (d, 1H, $J=8.5$ Hz), 7.25 (d, 2H, $J=8.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 21.7, 34.8, 36.3, 36.7, 40.7, 45.5, 61.2, 63.8, 116.1, 121.6, 122.5, 126.2, 129.4, 130.2, 150.6, 154.3, 156.6; IR (KBr) cm^{-1}: 2929, 2560, 1730, 1492, 1388, 1243, 1171, 823.

(5-Dimethylcarbamoyloxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetic acid ethyl ester (5). To a solution of **3a** (320 mg, 1.28 mmol) in CH_2Cl_2 (10 mL) was added BBr_3 in CH_2Cl_2 (3.0 mL, 1.0 M) dropwise at −30 °C. The mixture was stirred for 3 h at room temperature. The reaction was quenched with 1 N NaOH (10 mL). The product was extracted with CH_2Cl_2 (10 mL×2). The combined organic solution was dried over Na_2SO_4, filtered and evaporated to give a phenol (111 mg). This phenol (110 mg) was dissolved in a mixture of HCO_2H (1.0 mL) and 37% aq HCHO (1.0 mL) and stirred for 3 h at 80 °C. After cooling to room temperature, saturated aq $NaHCO_3$ (10 mL) was added and extracted with AcOEt (10 mL×3). The 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 10:1) gave a *N*-methyl product (85 mg, 27% for two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.26 (t, 3H, $J=6.4$ Hz), 2.46 (s, 3H), 2.54 (ddd, 1H, $J=2.8$, 5.2, 16.8 Hz), 2.59 (dd, 1H, $J=6.0$, 11.6 Hz), 2.71–2.80 (m, 1H), 2.81 (dd, 1H, $J=8.0$, 15.2 Hz), 2.88 (ddd, 1H, $J=2.8$, 6.0, 13.2 Hz), 3.08–3.15 (m, 1H), 4.09–4.21 (m, 3H), 6.62 (d, 1H, $J=8.0$ Hz), 6.68 (d, 1H, $J=8.0$ Hz), 7.01 (t, 1H, $J=8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.1, 18.6, 40.5, 41.8, 45.2, 59.5, 60.5, 112.5, 119.4, 120.7, 126.4, 138.4, 153.3, 172.2; IR (CHCl3) cm^{-1}: 3600, 2941, 1726, 1589, 1465, 1271, 1154, 1036; HRMS calcd for $C_{14}H_{20}NO_3$ $(M+H)^+$ 250.1443, found 250.1440.

To a solution of the above compound (85 mg, 0.34 mmol) and K_2CO_3 (276 mg, 2.0 mmol) in DMF (5 mL) was added Me_2NCOCl (92 μL, 1.0 mmol) at room temperature. The reaction mixture was stirred for 12 h at room temperature. After dilution with water (10 mL), the mixture was extracted with AcOEt (10 mL×2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel column chromatography (AcOEt to AcOEt–MeOH 5:1) to give **5** (65 mg, 59%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.25 (t, 3H, $J=6.8$ Hz), 2.45 (s, 3H), 2.45–2.51 (m, 1H), 2.61 (dd, 1H, $J=4.8$, 15.2 Hz), 2.73–2.84 (m, 3H), 3.01 (s, 3H), 3.06–3.10 (m, 1H), 3.12 (s, 3H), 4.13–4.21 (m, 3H), 6.96 (dd, 2H, $J=2.4$, 7.6 Hz), 7.15 (d, 1H, $J=7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.1, 18.7, 36.4, 36.7, 38.6, 41.9, 44.9, 59.4, 60.4, 120.0, 124.4, 126.3, 126.9, 138.5, 149.3, 154.4, 172.0; IR ($CHCl_3$) cm^{-1}: 2940, 1721, 1391, 1171, 909; HRMS calcd for $C_{17}H_{25}N_2O_4$ $(M+H)^+$ 321.1814, found 321.1822.

Dimethylcarbamic acid 2-methyl-1-[2-(4-nitrophenoxy)-ethyl]-1,2,3,4-tetrahydroisoquinolin-5-yl ester hydrochloride salt (8·HCl). To a solution of **5** (65 mg, 0.20 mmol) in THF (10 mL) was added $LiAlH_4$ (7.6 mg, 0.20 mmol) at −20 °C. The reaction mixture was stirred for 20 min at −20 °C. To the reaction mixture was successively added 1 N NaOH (0.3 mL) and $MgSO_4$. After filtration, the organic layer was concentrated in vacuo to give an alcohol (48 mg, 86%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.95–2.10 (m, 2H), 2.50 (s, 3H), 2.55–2.60 (m, 1H), 2.71–2.77 (m, 2H), 3.02 (s, 3H),

3.12 (s, 3H), 3.23–3.28 (m, 1H), 3.68–3.72 (m, 1H), 3.78–3.86 (m, 2H), 6.91 (d, 1H, $J=8.0$ Hz), 6.97 (d, 1H, $J=8.0$ Hz), 7.17 (t, 1H, $J=8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 18.5, 35.5, 36.4, 36.7, 42.1, 45.8, 62.7, 64.8, 119.9, 124.5, 126.5, 127.1, 137.7, 149.1, 154.4; IR ($CHCl_3$) cm^{-1}: 2947, 1718, 1462, 1391, 1172, 909; HRMS calcd for $C_{15}H_{23}N_2O_3$ $(M+H)^+$ 279.1708, found 279.1693.

To a solution of the above alcohol (48 mg, 0.17 mmol) and 1-fluoro-4-nitrobenzene (26 mg, 0.19 mmol) in DMF (5 mL) was added 55% NaH (13 mg, 0.30 mmol) at room temperature. The reaction mixture was stirred for 30 min at room temperature. The reaction was quenched with water (10 mL). The product was extracted with AcOEt (10 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated. Purification by preparative TLC (AcOEt–MeOH 10:1) gave **8** (27 mg, 39%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.26 (q, 2H, $J=6.4$ Hz), 2.45 (s, 3H), 2.46–2.56 (m, 1H), 2.71–2.80 (m, 2H), 3.02 (s, 3H), 3.09–3.16 (m, 1H), 3.13 (s, 3H), 3.73 (t, 1H, $J=6.0$ Hz), 4.10 (dt, 1H, $J=6.4$, 9.6 Hz), 4.27 (dt, 1H, $J=6.4$, 9.6 Hz), 6.93 (d, 2H, $J=8.4$ Hz), 6.97 (d, 1H, $J=7.6$ Hz), 7.00 (d, 1H, $J=7.6$ Hz), 7.18 (t, 1H, $J=7.6$ Hz), 8.18 (d, 2H, $J=8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 19.3, 34.2, 36.4, 36.7, 42.4, 46.5, 59.9, 65.8, 114.5, 120.0, 124.3, 125.8, 126.4, 141.3, 149.2, 154.4, 164.1; IR (film) cm^{-1}: 2938, 1723, 1591, 1511, 1387, 1338, 1263, 1170, 1028, 848, 753; HRMS calcd for $C_{21}H_{26}N_3O_5$ $(M+H)^+$ 400.1872, found 400.1867.

8·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.23–2.27 (m, 1H), 2.87 (dd, 1H, $J=5.2$, 14.0 Hz), 2.89 (d, 3H, $J=5.2$ Hz), 2.97–3.11 (m, 2H), 3.04 (s, 3H), 3.15 (s, 3H), 3.41–3.49 (mt, 1H), 3.68–3.72 (m, 1H), 4.16–4.21 (m, 1H), 4.54 (t, 1H, $J=6.4$ Hz), 4.61–4.65 (m, 1H), 6.99 (d, 1H, $J=7.2$ Hz), 7.05 (d, 2H, $J=8.8$ Hz), 7.16 (d, 1H, $J=7.2$ Hz), 7.33 (t, 1H, $J=7.2$ Hz), 8.23 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (100 MHz, CDCl3) δ ppm: 16.8, 34.8, 36.5, 36.9, 40.3, 44.0, 60.7, 64.5, 114.7, 122.7, 122.8, 125.1, 126.0, 128.5, 130.8, 142.0, 149.8, 153.7, 163.0; IR (CHCl3) cm^{-1}: 2970, 2322, 1722, 1594, 1516, 1392, 1344, 1258, 1169, 909; HRMS calcd for $C_{21}H_{26}N_3O_5$ $(M+H)^+$ 400.1872, found 400.1870.

Dimethylcarbamic acid 4-formyl-3-vinylphenyl ester (12b). To a suspension of 55% NaH (5.74 g, 239 mmol) in DMF (100 mL) was added compound **11b** (15.0 g, 109 mmol) at 0 °C. After the reaction mixture was stirred for 30 min at 0 °C, Me_2NCOCl (10.1 mL, 110 mmol) was added at 0 °C and stirred for 2 h at room temperature. After dilution with water (300 mL), the mixture was neutralized with concentrated HCl and extracted with AcOEt (200 mL×2). The combined organic layers were washed with water (300 mL×2) and brine (200 mL×2), 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 a mono-carbamate (6.78 g, 30%) as a colorless solid. Mp 58–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.02 (s, 3H), 3.10 (s, 3H), 6.77 (d, 1H, $J=2.0$ Hz), 6.82 (dd, 1H, $J=2.0$, 8.0 Hz), 7.53 (d, 1H, $J=8.0$ Hz), 9.84 (s, 1H), 11.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 36.5, 36.7, 110.3, 113.8, 118.15, 134.7, 153.4, 158.3, 163.1, 195.3; IR (KBr) cm^{-1}: 1730, 1645, 1389, 1214, 1185, 810; HRMS calcd for $C_{10}H_{11}NO_4$ $(M)^+$ 209.0688, found 209.0671. Anal. calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.15; H, 5.29; N, 6.51.

To a solution of the above compound (2.60 g, 12.4 mmol) and pyridine (1.61 mL, 20.0 mmol) in CH_2Cl_2 (30 mL) was added trifluoromethanesulfonic anhydride (2.35 mL, 14.0 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, quenched with water (20 mL), and extracted with CH_2Cl_2 (20 mL×2). The extracts were washed with 1 N HCl (20 mL) and brine (20 mL) and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to give the triflate (4.14 g). To a solution of the triflate (4.13 g) in 1,4-dioxane (15 mL) were added $Pd(PPh_3)_4$ (693 mg, 0.600 mmol), LiCl (1.54 g, 36.4 mmol), 2,6-di-*t*-butylphenol (5 mg) and $(CH_2{=}CH)(n\text{-}Bu)_3Sn$ (4.23 mL, 14.5 mmol). The reaction mixture was stirred for 3 h at 100 °C. After adding saturated aq KF (10 mL), the mixture was filtered and evaporated in vacuo. The residue was diluted with water (40 mL) and extracted with AcOEt (50 mL×2). The combined organic layers were washed with 1 N HCl (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered and evaporated in vacuo. Purification by silica gel column chromatography (hexane–AcOEt 10:1 to 1:1) gave styrene **12b** (2.11 g, 79% for two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.04 (s, 3H), 3.12 (s, 3H), 5.53 (dd, 1H, $J=1.6$, 11.2 Hz), 5.72 (d, 1H, $J=18.0$ Hz), 7.21 (dd, 1H, $J=2.4$, 8.0 Hz), 7.33 (d, 1H, $J=2.4$ Hz), 7.53 (dd, 1H, $J=11.2$, 18.0 Hz), 7.84 (d, 1H, $J=8.0$ Hz), 10.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 36.5, 36.7, 119.9, 120.2, 121.2, 129.9, 132.7, 132.9, 142.2, 153.8, 155.7, 191.1; IR (film) cm^{-1}: 2935, 1728, 1692, 1601, 1387, 1226, 1169, 807; HRMS calcd for $C_{12}H_{13}NO_3$ $(M)^+$ 219.0896, found 219.0896.

Dimethylcarbamic acid 3-formyl-2-vinylphenyl ester (12a). Mono-carbamate. Mp 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.03 (s, 3H), 3.15 (s, 3H), 7.01 (t, 1H, $J=8.0$ Hz), 7.37 (dd, 1H, $J=1.6$, 8.0 Hz), 7.45 (dd, 1H, $J=1.6$, 8.0 Hz), 9.91 (s, 1H), 11.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 36.5, 36.8, 119.4, 121.8, 130.4, 130.4, 139.7, 153.8, 154.0, 196.3; IR (KBr) cm^{-1}: 1725, 1654, 1458, 1388, 1234, 1158, 852, 741. Anal. calcd for $C_{10}H_{11}NO_4{\cdot}0.1H_2O$: C, 56.92; H, 5.35; N, 6.64; O, 31.09. Found: C, 56.82; H, 5.16; N, 6.66; O, 30.95.

12a. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.02 (s, 3H), 3.13 (s, 3H), 5.42 (dd, 1H, $J=1.6$, 18.4 Hz), 5.76 (dd, 1H, $J=1.6$, 11.6 Hz), 6.92 (dd, 1H, $J=11.6$, 18.4 Hz), 7.36 (dd, 1H, $J=1.6$, 8.0 Hz), 7.42 (t, 1H, $J=8.0$ Hz), 7.79 (dd, 1H, $J=1.6$, 8.0 Hz), 10.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 36.4, 36.8, 124.4, 126.0, 128.1, 135.2, 135.3, 149.4, 154.1, 191.6; IR (film) cm^{-1}: 2934, 1726, 1458, 1387, 1235, 1162, 754; HRMS calcd for $C_{12}H_{13}NO_3$ $(M)^+$ 219.0896, found 219.0898.

Dimethylcarbamic acid 3-formyl-4-vinylphenyl ester (12c). Mono-carbamate: ^{1}H NMR (400 MHz, $CDCl_3$) δ

ppm: 2.96 (s, 3H), 3.05 (s, 3H), 6.91 (d, 1H, $J=8.8$ Hz), 7.22 (dd, 1H, $J=2.9$, 8.8 Hz), 7.29 (dd, 1H, $J=2.9$ Hz), 9.78 (s, 1H), 10.81 (s, 1H).

12c. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.98 (s, 3H), 3.08 (s, 3H), 5.46 (d, 1H, $J=11.0$ Hz), 5.63 (dd, 1H, $J=1.5$, 17.6 Hz), 7.30 (dd, 1H, $J=2.9$, 8.8 Hz), 7.43 (dd, 1H, $J=11.0$, 17.6 Hz), 7.52 (d, 1H, $J=8.8$ Hz), 7.54 (d, 1H, $J=2.9$ Hz), 10.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 36.4, 36.7, 119.4, 123.3, 127.4, 128.6, 132.5, 133.6, 137.5, 151.2, 191.2; IR ($CHCl_3$) cm^{-1}: 2937, 1724, 1485, 1389, 1170; HRMS calcd for $C_{12}H_{13}NO_3Na$ $(M+Na)^+$ 242.0794, found 242.0795.

Dimethylcarbamic acid 4-[3-(*tert*-butyldiphenylsilanyloxy)-1-hydroxypropyl]-3-vinylphenyl ester (13b). To a solution of *i*-Pr_2NH (1.26 g, 12.5 mmol) in THF (30 mL) was added *n*-BuLi in hexane (7.20 mL, 1.6 M) dropwise at −20 °C. After stirring for 20 min at −20 °C, AcOEt (1.07 mL, 11.0 mmol) was added to the reaction mixture at −78 °C. After stirring for 20 min at −78 °C, a solution of **12b** (2.11 g, 9.62 mmol) in THF was added to the reaction mixture at −78 °C. The mixture was stirred for 30 min at −78 °C and quenched with saturated aq NH_4Cl (40 mL). The product was extrcted with AcOEt (40 mL×2) and the organic solution was washed with water (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 1:1 to 1:2) afforded a benzyl alcohol (2.95 g, 99%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.28 (t, 3H, $J=7.5$ Hz), 2.65 (d, 2H, $J=6.0$ Hz), 3.01 (s, 3H), 3.10 (s, 3H), 3.23–3.25 (m, 1H), 4.19 (q, 2H, $J=7.5$ Hz), 5.35 (d, 1H, $J=11.0$ Hz), 5.38–5.43 (m, 1H), 5.63 (d, 1H, $J=17.0$ Hz), 6.99 (dd, 1H, $J=11.0$, 17.0 Hz), 7.05 (d, 1H, $J=8.5$ Hz), 7.20 (s, 1H), 7.52 (d, 1H, $J=8.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 36.1, 36.3, 42.4, 60.5, 66.4, 117.0, 118.8, 121.0, 126.4, 132.9, 136.2, 136.5, 150.6, 154.5, 171.9; IR (film) cm^{-1}: 3452, 2982, 1727, 1389, 1223, 1173; HRMS calcd for $C_{16}H_{21}NO_5Na$ $(M+Na)^+$ 330.1317, found 330.1304.

To a solution of the alcohol (5.28 g, 17.2 mmol) in THF (50 mL) was added $LiBH_4$ (544 mg, 25.0 mmol) at −20 °C. The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with water (20 mL) and 1 N HCl (20 mL). The product was extracted with AcOEt (40 mL×2) and the organic solution was dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (AcOEt to AcOEt–MeOH 5:1) provided a diol (4.44 g, 97%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.78–1.90 (m, 2H), 2.88 (s, 1H), 3.00 (s, 3H), 3.10 (s, 3H), 3.44 (s, 1H), 3.77 (br s, 2H), 5.14–5.19 (m, 1H), 5.32 (d, 1H, $J=11.0$ Hz), 5.60 (d, 1H, $J=17.5$ Hz), 6.96 (dd, 1H, $J=11.0$, 17.5 Hz), 7.03 (dd, 1H, $J=2.5$, 8.5 Hz), 7.17 (d, 1H, $J=2.5$ Hz), 7.51 (d, 1H, $J=8.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 36.4, 36.6, 39.3, 61.3, 70.3, 117.0, 119.0, 121.2, 126.6, 133.2, 136.3, 138.5, 150.5, 155.0; IR ($CHCl_3$) cm^{-1}: 2943, 1714, 1391, 1250, 1175, 1049; HRMS calcd for $C_{14}H_{19}NO_4$ $(M)^+$ 265.1314, found 265.1322.

To a solution of the diol (4.44 g, 16.7 mmol), Et_3N (4.18 mL, 30.0 mmol) and 4-dimethylaminopyridine (10 mg) in CH_2Cl_2 (40 mL) was added *t*-butyldiphenylsilyl chloride (4.67 g, 17.0 mmol) at 0 °C. The mixture was stirred for 5 h at room temperature. After the addition of water (30 mL), the aqueous solution was extracted with CH_2Cl_2 (40 mL×2). The combined organic extracts were washed with 1 N HCl (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 2:1–1:1) provided **13b** (5.87 g, 70%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.09 (s, 9H), 1.85–1.90 (m, 2H), 3.01 (s, 3H), 3.10 (s, 3H), 3.32 (s, 1H), 3.84–3.93 (m, 2H), 5.27 (d, 1H, $J=10.5$ Hz), 5.28–5.33 (br m, 1H), 5.60 (d, 1H, $J=17.0$ Hz), 6.97 (dd, 1H, $J=10.5$, 17.0 Hz), 7.05 (dd, 1H, $J=2.5$, 9.0 Hz), 7.19 (d, 1H, $J=2.5$ Hz), 7.38–7.45 (m, 6H), 7.51 (d, 1H, $J=9.0$ Hz), 7.69 (d, 4H, $J=7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 19.1, 26.8, 36.4, 36.7, 40.0, 62.8, 69.5, 116.8, 118.9, 121.1, 126.5, 127.8, 129.8, 133.0, 133.4, 135.5, 136.2, 138.5, 150.6, 154.9; IR (film) cm^{-1}: 3457, 2931, 1725, 1389, 1227, 1176, 1111, 704; HRMS calcd for $C_{30}H_{37}NO_4SiNa$ $(M+Na)^+$ 526.2390, found 526.2393.

Dimethylcarbamic acid 3-[3-(*tert*-butyldiphenylsilanyloxy)-1-hydroxypropyl]-2-vinylphenyl ester (13a). Benzyl alcohol: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.28 (t, 3H, $J=7.2$ Hz), 2.61–2.70 (m, 2H), 2.99 (s, 3H), 3.07 (s, 3H), 3.21 (d, 1H, $J=2.8$ Hz), 4.19 (q, 2H, $J=7.2$ Hz), 5.35–5.39 (m, 1H), 5.43 (dd, 1H, $J=2.0$, 17.6 Hz), 5.55 (dd, 1H, $J=2.0$, 11.6 Hz), 6.64 (dd, 1H, $J=11.6$, 17.6 Hz), 7.05 (dd, 1H, $J=1.2$, 8.0 Hz), 7.30 (t, 1H, $J=8.0$ Hz), 7.45 (d, 1H, $J=8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.1, 36.3, 36.7, 42.2, 60.3, 66.9, 121.3, 122.2, 122.6, 128.2, 129.6, 129.8, 141.7, 148.6, 154.6, 172.5; IR ($CHCl_3$) cm^{-1}: 2985, 1720, 1390, 1171, 1021; HRMS calcd for $C_{16}H_{21}NO_5Na$ $(M+Na)+$ 330.1317, found 330.1320.

Diol. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.88–2.00 (m, 2H), 2.38 (br s, 1H), 2.74 (br s, 1H), 2.99 (s, 3H), 3.08 (s, 3H), 3.86 (br s, 2H), 5.22 (d, 1H, $J=8.0$ Hz), 5.42 (dd, 1H, $J=2.4$, 18.4 Hz), 5.54 (dd, 1H, $J=2.4$, 11.6 Hz), 6.65 (dd, 1H, $J=11.6$, 18.4 Hz), 7.04 (dd, 1H, $J=1.6$, 8.0 Hz), 7.32 (t, 1H, $J=8.0$ Hz), 7.48 (d, 1H, $J=8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 36.3, 36.7, 39.2, 61.6, 70.7, 121.0, 121.8, 122.8, 128.1, 129.4, 129.9, 143.7, 148.5, 154.7; IR ($CHCl_3$) cm^{-1}: 2943, 1719, 1391, 1249, 1172, 1046; HRMS calcd for $C_{14}H_{19}NO_4Na$ $(M+Na)^+$ 288.1212, found 288.1212.

13a. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.09 (s, 9H), 1.83–1.95 (m, 2H), 2.99 (s, 3H), 3.07 (s, 3H), 3.32 (d, 1H, $J=3.2$ Hz), 3.82–3.92 (m, 2H), 5.26 (dt, 1H, $J=2.0$, 8.0 Hz), 5.39 (dd, 1H, $J=2.0$, 18.4 Hz), 5.47 (dd, 1H, $J=2.0$, 11.6 Hz), 6.62 (dd, 1H, $J=11.6$, 18.4 Hz), 7.02 (dd, 1H, $J=1.6$, 8.0 Hz), 7.29 (t, 1H, $J=8.0$ Hz), 7.37–7.46 (m, 6H), 7.49 (dd, 1H, $J=1.6$, 8.0 Hz), 7.67–7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 19.1, 26.8, 36.3, 36.7, 39.7, 62.6, 69.6, 120.7, 121.6, 122.7, 127.7, 127.9, 129.2, 129.8, 130.0, 133.0, 133.1, 135.5, 135.6, 143.9, 148.5, 154.7; IR ($CHCl_3$) cm^{-1}: 3485, 2932,

1719, 1390, 1250, 1172, 1111, 935; HRMS calcd for $C_{30}H_{37}NO_4SiNa$ $(M+Na)^+$ 526.2390, found 526.2379.

Dimethylcarbamic acid 3-[3-(*tert*-butyldiphenylsilanyloxy)-1-hydroxypropyl]-4-vinylphenyl ester (13c). Benzyl alcohol: ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.24 (t, 3H, $J=7.2$ Hz), 2.57 (d, 1H, $J=16.8$ Hz), 2.63 (dd, 1H, $J=3.7$, 16.8 Hz), 2.97 (s, 3H), 3.05 (s, 3H), 4.16 (q, 2H, $J=7.2$ Hz), 5.29 (d, 1H, $J=11.0$ Hz), 5.37 (dd, 1H, $J=3.7$, 8.8 Hz), 5.55 (d, 1H, $J=16.8$ Hz), 6.90 (dd, 1H, $J=11.0$, 16.8 Hz), 7.00 (dd, 1H, $J=2.9$, 8.0 Hz), 7.26 (d, 1H, $J=2.9$ Hz), 7.40 (d, 1H, $J=8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.1, 36.4, 36.6, 42.3, 60.9, 66.7, 116.8, 118.6, 121.1, 127.2, 132.2, 133.0, 140.7, 151.4, 154.7, 172.4; IR ($CHCl_3$) cm^{-1}: 2985, 1719, 1484, 1390, 1173, 1020; HRMS calcd for $C_{16}H_{21}NO_5Na$ $(M+Na)^+$ 330.1317, found 330.1315.

13c. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.05 (s, 9H), 1.79–1.95 (m, 2H), 2.97 (s, 3H), 3.05 (s, 3H), 3.80–3.89 (m, 2H), 5.20 (dd, 1H, $J=1.5$, 11.0 Hz), 5.27 (dd, 1H, $J=3.7$, 8.8 Hz), 5.52 (dd, 1H, $J=1.5$, 17.6 Hz), 6.89 (dd, 1H, $J=11.0$, 17.6 Hz), 6.99 (dd, 1H, $J=2.2$, 8.8 Hz), 7.35 (d, 1H, $J=2.2$ Hz), 7.33–7.43 (m, 7H), 7.64–7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 19.1, 26.8, 36.4, 36.6, 39.9, 62.8, 69.5, 116.0, 118.5, 120.6, 127.0, 127.8, 129.8, 132.0, 132.9, 133.0, 133.4, 135.5, 143.0, 151.4, 154.8; IR ($CHCl_3$) cm^{-1}: 3482, 2932, 1715, 1472, 1390, 1248, 1174, 1263, 918, 822; HRMS calcd for $C_{30}H_{37}NO_4SiNa$ $(M+Na)^+$ 526.2390, found 526.2366.

Allyl[3-(*tert*-butyldiphenylsilanyloxy)-1-(4-dimethylcarbamoyloxy-2-vinylphenyl)propyl]carbamic acid *tert*-butyl ester (14b). To a solution of compound **13b** (3.00 g, 5.95 mmol) and CBr_4 (3.98 g, 12.0 mmol) in CH_2CH_2 (20 mL) was added Ph_3P (3.14 g, 12.0 mmol) at room temperature. 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 furnish a benzyl bromide (2.62 g, 78%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.05 (s, 9H), 2.26–2.33 (m, 1H), 2.41–2.48 (m, 1H), 3.02 (s, 3H), 3.10 (s, 3H), 3.74 (dt, 1H, $J=5.0$, 9.0 Hz), 3.86–3.90 (m, 1H), 5.40 (d, 1H, $J=10.5$ Hz), 5.66 (d, 1H, $J=17.0$ Hz), 5.70 (dd, 1H, $J=5.0$, 9.0 Hz), 7.04 (dd, 1H, $J=2.0$, 9.0 Hz), 7.10 (dd, 1H, $J=10.5$, 17.0 Hz), 7.19 (d, 1H, $J=2.0$ Hz), 7.33–7.43 (m, 6H), 7.46 (d, 1H, $J=9.0$ Hz), 7.60 (d, 2H, $J=7.5$ Hz), 7.69 (d, 2H, $J=7.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 19.2, 26.8, 36.4, 36.7, 41.8, 47.8, 61.2, 118.1, 119.7, 121.5, 127.6, 127.7, 128.4, 129.6, 129.7, 133.3, 133.4, 133.5, 135.4, 135.5, 135.6, 135.7, 137.7, 151.2, 154.5; IR ($CHCl_3$) cm^{-1}: 2932, 1717, 1391, 1174, 1110; HRMS calcd for $C_{30}H_{36}NO_3BrSiK$ $(M+K)^+$ 604.1285, found 604.1278.

To a solution of the benzyl bromide (2.62 g, 4.62 mmol) in CH_3CN (20 mL) was added allylamine (1.87 mL, 25.0 mmol) at room temperature. The reaction mixture was stirred for 12 h at room temperature. The solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt 2:1 to AcOEt) to give an allylbenzylamine (1.82 g, 72%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.06 (s, 9H), 1.79–1.84 (m, 2H), 3.00 (dd, 1H, $J=7.0$, 16.0 Hz), 3.02 (s, 3H), 3.07–3.12 (m, 1H), 3.10 (s, 3H), 3.65 (dt, 1H, $J=5.0$, 11.0 Hz), 3.76 (dt, 1H, $J=5.0$, 11.0 Hz), 4.32 (t, 1H, $J=6.0$ Hz), 5.04 (d, 1H, $J=11.0$ Hz), 5.11 (d, 1H, $J=17.5$ Hz), 5.24 (d, 1H, $J=11.0$ Hz), 5.56 (d, 1H, $J=17.5$ Hz), 5.81–5.89 (m, 1H), 7.02 (dd, 1H, $J=3.0$, 9.0 Hz), 7.15 (dd, 1H, $J=11.0$, 17.5 Hz), 7.19 (d, 1H, $J=3.0$ Hz), 7.26–7.44 (m, 6H), 7.63–7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 19.1, 26.8, 36.4, 36.7, 40.3, 50.0, 54.8, 61.6, 77.4, 115.7, 116.5, 119.0, 121.2, 127.2, 127.6, 127.7, 129.6, 133.6, 133.7, 134.0, 135.5, 135.6, 137.0, 138.0, 138.2, 150.1, 154.9; IR (film) cm^{-1}: 2932, 1726, 1472, 1386, 1171, 1111, 917, 704; HRMS calcd for $C_{33}H_{43}N_2O_3Si$ $(M+H)^+$ 543.3043, found 543.3027.

To a solution of the allylbenzylamine (1.80 g, 3.31 mmol) and Et_3N (1.12 mL, 8.00 mmol) in THF (20 mL), Boc_2O (870 mg, 4.00 mmol) was added at room temperature. The mixture was stirred for 3 h at 50 °C. The solvent was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt 5:1–1:1) to give **14b** (1.90 g, 89%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.04 (s, 9H), 1.38 (s, 9H), 2.10–2.30 (m, 2H), 3.02 (s, 3H), 3.11 (s, 3H), 3.24–3.60 (br, 2H), 3.67 (q, 1H, $J=8.0$ Hz), 3.72–3.82 (m, 1H), 4.72–4.79 (m, 0.4H), 4.79 (d, 0.6H, $J=9.6$ Hz), 5.24 (d, 1H, $J=11.2$ Hz), 5.37 (br, 1H), 5.51 (br, 1H), 5.55 (d, 1H, $J=17.6$ Hz), 6.98 (d, 1H, $J=8.0$ Hz), 7.01 (dd, 1H, $J=11.2$, 17.6 Hz), 7.19 (d, 1H, $J=8.0$ Hz), 7.22 (d, 1H, $J=2.4$ Hz), 7.32–7.43 (m, 5H), 7.60 (br s, 1.6H), 7.66 (d, 2.4H, $J=7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 19.2, 24.8, 26.9, 28.4, 35.1, 36.4, 36.7, 45.5, 51.0, 51.7, 61.6, 79.3, 115.4, 116.4, 119.2, 120.3, 127.4, 127.6, 129.3, 133.5, 133.8, 135.0, 135.2, 135.3, 139.6, 150.7, 154.4; IR ($CHCl_3$) cm^{-1}: 2932, 1715, 1678, 1391, 1172, 1111; HRMS calcd for $C_{38}H_{51}N_2O_5Si$ $(M+H)^+$ 643.3567, found 643.3569.

Allyl[3-(*tert*-butyldiphenylsilanyloxy)-1-(3-dimethylcarbamoyloxy-2-vinylphenyl)propyl]carbamic acid *tert*-butyl ester (14a). Benzyl bromide. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.05 (s, 9H), 2.26–2.33 (m, 1H), 2.38–2.45 (m, 1H), 3.00 (s, 3H), 3.08 (s, 3H), 3.75 (dt, 1H, $J=5.0$, 9.5 Hz), 3.89 (dt, 1H, $J=4.0$, 9.5 Hz), 5.54 (dd, 1H, $J=2.0$, 18.5 Hz), 5.59 (dd, 1H, $J=2.0$, 12.0 Hz), 5.75 (dd, 1H, $J=4.0$, 10.0 Hz), 6.71 (dd, 1H, $J=12.0$, 18.5 Hz), 7.07 (d, 1H, $J=8.0$ Hz), 7.28 (t, 1H, $J=8.0$ Hz), 7.34–7.45 (m, 6H), 7.61 (d, 1H, $J=6.0$ Hz), 7.68–7.71 (m, 3H).

Allylbenzylamine. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.05 (s, 9H), 1.79–1.88 (m, 2H), 2.95–3.10 (m, 2H), 2.99 (s, 3H), 3.06 (s, 3H), 3.67 (dt, 1H, $J=5.2$, 11.2 Hz), 3.74–3.80 (m, 1H), 4.28 (dd, 1H, $J=5.2$, 8.4 Hz), 5.02 (dd, 1H, $J=1.6$, 11.4 Hz), 5.09 (dd, 1H, $J=1.6$, 16.8 Hz), 5.34 (dd, 1H, $J=2.0$, 17.6 Hz), 5.44 (dd, 1H, $J=2.0$, 11.6 Hz), 5.79–5.89 (m, 1H), 6.68 (dd, 1H, $J=11.6$, 17.6 Hz), 6.99 (d, 1H, $J=8.0$ Hz), 7.25 (t, 1H, $J=8.0$ Hz), 7.34–7.44 (m, 7H), 7.63–7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 19.1, 26.8, 36.3, 36.7, 50.0, 55.5, 61.7, 115.5, 120.4, 121.0, 123.1, 127.6, 127.8,

129.5, 129.6, 130.5, 131.1, 133.6, 133.7, 135.5, 135.6, 137.1, 143.9, 148.6, 154.7; IR (CHCl3) cm^{-1}: 2932, 1718, 1390, 1249, 1173, 1110; HRMS calcd for $C_{33}H_{43}N_2O_3Si$ $(M+H)^+$ 543.3043, found 543.3060.

14a. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.03 (s, 9H), 1.36 (s, 9H), 2.13–2.18 (m, 1H), 2.23–2.32 (m, 1H), 2.98 (s, 3H), 3.05 (s, 3H), 3.38–3.53 (br, 2H), 3.63–3.68 (m, 1H), 3.70–3.80 (m, 1H), 4.74–4.80 (m, 1H), 4.79 (d, 1H, $J=10.0$ Hz), 5.34–5.44 (m, 4H), 6.58 (dd, 1H, $J=12.0$, 17.6 Hz), 7.05 (d, 1H, $J=8.0$ Hz), 7.12 (d, 1H, $J=8.0$ Hz), 7.21 (d, 1H, $J=8.0$ Hz), 7.32–7.43 (m, 6H), 7.59 (br s, 2H), 7.65 (d, 2H, $J=8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 19.1, 26.8, 28.3, 25.3, 36.3, 36.7, 61.7, 77.4, 115.7, 120.2, 122.5, 127.2, 127.6, 129.5, 130.1, 132.5, 135.5, 135.6, 149.0; IR ($CHCl_3$) cm^{-1}: 2932, 1718, 1680, 1452, 1392, 1171, 1111, 909; HRMS calcd for $C_{38}H_{50}N_2O_5SiNa$ $(M+Na)^+$ 665.3387, found 665.3412.

Allyl[3-(*tert*-butyldiphenylsilanyloxy)-1-(5-dimethylcarbamoyloxy-2-vinylphenyl)propyl]carbamic acid *tert*-butyl ester (14c). Benzyl bromide: ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.01 (s, 9H), 2.22–2.31 (m, 1H), 2.33–2.41 (m, 1H), 2.97 (s, 3H), 3.05 (s, 3H), 3.71 (dt, 1H, $J=4.8$, 11.0 Hz), 3.83–3.89 (m, 1H), 5.33 (dd, 1H, $J=1.5$, 11.0 Hz), 5.59 (dd, 1H, $J=1.5$, 17.6 Hz), 5.67 (dd, 1H, $J=4.4$, 9.5 Hz), 7.02 (d, 1H, $J=8.8$ Hz), 7.04 (dd, 1H, $J=11.0$, 17.6 Hz), 7.20 (d, 1H, $J=2.2$ Hz), 7.29–7.40 (m, 7H), 7.55–7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 19.2, 26.5, 26.8, 36.4, 36.7, 41.7, 47.7, 61.2, 117.5, 120.3, 121.9, 127.6, 127.7, 127.8, 129.6, 129.7, 133.2, 133.3, 133.4, 134.7, 135.4, 139.9, 151.3, 154.5; IR ($CHCl_3$) cm^{-1}: 2932, 1721, 1742, 1390, 1248, 1173, 1111, 823; HRMS calcd for $C_{30}H_{36}NO_3BrSiNa$ $(M+Na)^+$ 588.1546, found 588.1523.

Allylbenzylamine. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.06 (s, 9H), 1.82 (q, 2H, $J=5.8$ Hz), 2.99–3.12 (m, 2H), 3.01 (s, 3H), 3.09 (s, 3H), 3.67 (dt, 1H, $J=5.8$, 11.0 Hz), 3.76 (dd, 1H, $J=5.1$, 11.0 Hz), 3.82 (t, 1H, $J=5.8$ Hz), 4.34 (t, 1H, $J=5.8$ Hz), 5.04 (d, 1H, $J=11.0$ Hz), 5.12 (d, 1H, $J=16.8$ Hz), 5.22 (d, 1H, $J=11.0$ Hz), 5.53 (dd, 1H, $J=1.5$, 16.8 Hz), 5.82–5.91 (m, 1H), 7.00 (dd, 1H, $J=2.2$, 8.8 Hz), 7.11 (dd, 1H, $J=11.0$, 16.8 Hz), 7.22 (d, 1H, $J=2.2$ Hz), 7.33–7.45 (m, 7H), 7.64–7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 19.1, 26.8, 36.4, 36.6, 49.9, 55.0, 61.7, 115.9, 119.1, 127.1, 127.6, 127.7, 129.5, 129.6, 133.5, 133.6, 133.9, 135.5, 135.6, 151.6, 154.8; IR ($CHCl_3$) cm^{-1}: 2932, 1719, 1472, 1390, 1259, 1174, 1110, 918; HRMS calcd for $C_{33}H_{43}N_2O_3Si$ $(M+H)^+$ 543.3043, found 543.3042.

14c. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 0.93 (s, 9H), 1.27 (s, 9H), 2.00–2.21 (m, 2H), 2.92 (s, 3H), 3.01 (s, 3H), 3.33 (br, 2H), 3.54–3.64 (m, 1H), 3.71 (br, 1H), 4.68 (br, 2H), 5.12 (d, 1H, $J=11.0$ Hz), 5.19–5.50 (m, 2H), 6.86–6.93 (m, 1H), 6.94 (br s, 1H), 7.21–7.30 (m, 7H), 7.35 (d, 1H, $J=8.8$ Hz), 7.49 (br s, 2H), 7.55 (d, 2H, $J=7.3$ Hz); ^{13}C NMR (100 MHz, CD_3OD) δ ppm: 19.9, 27.3, 28.7, 35.7, 36.7, 36.9, 46.5, 61.5, 62.5, 97.2, 116.4, 121.9, 122.2, 128.7, 128.8, 130.7, 130.8, 134.7, 135.2, 136.6, 136.7, 139.1, 152.3, 156.5; IR ($CHCl_3$) cm^{-1}: 2932, 1720, 1678, 1451, 1392, 1251, 1171, 1111, 918, 823; HRMS calcd for $C_{38}H_{50}N_2O_5SiNa$ $(M+Na)^+$ 665.3387, found 665.3404.

7-Dimethylcarbamoyloxy-1-(2-hydroxyethyl)-1,3-dihydrobenzo[*c*]azepine-2-carboxylic acid *tert*-butyl ester (16b). To a solution of **14b** (360 mg, 0.56 mmol) in CH_2Cl_2 (40 mL) was added Grubbs catalyst **15** (48 mg, 0.056 mmol). The reaction mixture was stirred for 3 h at 45 °C. The organic solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane–AcOEt 5:1 to 2:1) to give closed-ring compound (330 mg, 96%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.09 (s, 9H), 1.32 (s, 9H), 1.92 (br, 1H), 2.11 (br, 1H), 3.02 (s, 3H), 3.10 (s, 3H), 3.57 (br, 1H), 3.70 (br, 2H), 4.92 (br, 0.4H), 5.39 (br, 0.6H), 5.76 (d, 1H, $J=12.0$ Hz), 6.30 (d, 1H, $J=12.0$ Hz), 6.90 (dd, 1H, $J=2.0$, 8.0 Hz), 6.93 (d, 1H, $J=2.0$ Hz), 7.13 (d, 1H, $J=8.0$ Hz), 7.36–7.45 (m, 6H), 7.66 (d, 4H, $J=7.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 19.1, 26.8, 28.1, 28.2, 33.6, 36.3, 36.5, 43.8, 56.2, 56.3, 59.8, 60.6, 79.6, 79.8, 119.2, 119.7, 124.5, 124.8, 127.6, 128.3, 128.5, 129.5, 129.6, 130.4, 131.2, 133.5, 135.4, 135.5, 138.8, 150.2, 154.7, 155.5; IR ($CHCl_3$) cm^{-1}: 2932, 1713, 1684, 1392, 1250, 1168, 1111; HRMS calcd for $C_{36}H_{47}N_2O_5Si$ $(M+H)^+$ 615.3219, found 615.3237.

To a solution of this closed-ring compound (1.82 g, 2.96 mmol) in THF (10 mL) was added tetrabutylammonium fluoride in THF (6.0 mL, 1.0 M) at room temperature. The mixture was stirred for 1 h at room temperature and quenched with water (40 mL). The product was extracted with AcOEt (40 mL×2) and the organic solution was washed with water (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 1:1 to AcOEt) provided **16b** (1.07 g, 96%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.30 (s, 5H), 1.40 (s, 4H), 1.90–2.08 (m, 1H), 2.07–2.24 (br, 1H), 3.00 (s, 3H), 3.09 (s, 3H), 3.59 (br s, 1H), 3.65 (br s, 1H), 3.76–3.88 (br, 0.4H), 3.98 (d, 0.6H, $J=19.0$ Hz), 4.58 (d, 0.6H, $J=19.0$ Hz), 4.78–5.10 (br, 0.4H), 4.92–5.20 (br, 0.4H), 5.31 (br t, 0.6H, $J=7.5$ Hz), 5.77–5.83 (m, 1H), 6.32 (d, 0.6H, $J=11.5$ Hz), 6.39 (d, 0.4H, $J=13.0$ Hz), 6.92 (dd, 1H, $J=2.0$, 8.0 Hz), 6.95 (s, 1H), 7.13 (d, 0.6H, $J=8.0$ Hz), 7.25, (d, 0.4H, $J=8.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 28.0, 28.2, 33.2, 33.8, 36.2, 36.5, 44.0, 44.8, 56.0, 56.8, 58.8, 58.9, 79.9, 119.2, 119.8, 124.4, 124.7, 128.3, 128.9, 129.8, 129.9, 131.3, 134.8, 138.0, 138.7, 150.1, 154.7, 154.9, 155.4; IR ($CHCl_3$) cm^{-1}: 2980, 1713, 1686, 1392, 1368, 1250, 1167, 1040; HRMS calcd for $C_{20}H_{29}N_2O_5$ $(M+H)^+$ 377.2076, found 377.2073.

6-Dimethylcarbamoyloxy-1-(2-hydroxyethyl)-1,3-dihydrobenzo[*c*]azepine-2-carboxylic acid *tert*-butyl ester (16a). closed-ring compound: ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.08 (s, 9H), 1.31 (s, 9H), 1.97 (br, 1H), 2.20 (br, 1H), 3.01 (s, 3H), 3.13 (s, 3H), 3.56 (br, 1H), 3.68 (br, 2H), 4.63–4.90 (m, 1H), 5.37 (br, 1H), 5.82 (d, 1H, $J=12.4$ Hz), 6.53 (d, 1H, $J=12.4$ Hz), 6.98 (d, 1H, $J=8.0$ Hz), 7.03 (d, 1H, $J=8.0$ Hz), 7.15 (t, 1H, $J=8.0$ Hz), 7.35–7.45 (m, 6H), 7.65 (d, 4H, $J=7.2$ Hz); ^{13}C

NMR (100 MHz, $CDCl_3$) δ ppm: 19.2, 21.0, 26.9, 28.0, 28.2, 28.3, 33.1, 36.4, 36.7, 60.3, 80.0, 121.5, 126.9, 127.7, 129.6, 133.5, 135.5, 150.0, 154.5, 155.5; IR ($CHCl_3$) cm^{-1}: 2932, 1723, 1685, 1390, 1251, 1165, 1110; HRMS calcd for $C_{36}H_{46}N_2O_5SiNa$ $(M+Na)^+$ 637.3074, found 637.3059.

16a. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.31 (s, 5.4H), 1.42 (s, 3.2H), 1.88–2.28 (m, 2H), 3.02 (s, 3H), 3.13 (s, 3H), 3.59 (br s, 1H), 3.66 (br s, 1H), 3.85–4.05 (br, 0.4H), 3.98 (d, 0.6H, $J=15.6$ Hz), 4.41 (d, 0.6H, $J=15.6$ Hz), 4.60–5.00 (br, 0.4H), 5.00–5.20 (br, 0.4H), 5.35 (br t, 0.6H, $J=7.2$ Hz), 5.86–5.91 (m, 1H), 6.56 (d, 0.6H, $J=12.4$ Hz), 6.64 (d, 0.4H, $J=12.4$ Hz), 6.99–7.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 27.8, 28.2, 28.3, 33.0, 33.3, 36.4, 36.8, 55.6, 59.5, 80.2, 121.8, 125.9, 126.5, 127.0, 131.9, 154.5; IR ($CHCl_3$) cm^{-1}: 2980, 1722, 1685, 1390, 1252, 1164, 1044; HRMS calcd for $C_{20}H_{29}N_2O_5$ $(M+H)^+$ 377.2076, found 377.2078.

8-Dimethylcarbamoyloxy-1-(2-hydroxyethyl)-1,3-dihydrobenzo[*c*]azepine-2-carboxylic acid *tert*-butyl ester (16c). Closed-ring compound. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.04 (s, 9H), 1.28 (s, 9H), 1.88 (br, 1H), 2.05 (br, 1H), 2.97 (s, 3H), 3.05 (s, 3H), 3.54 (br, 1H), 3.63 (br, 2H), 4.59–4.84 (m, 1H), 5.30 (br, 1H), 5.57–5.67 (m, 1H), 6.29 (d, 1H, $J=14.7$ Hz), 6.93–7.01 (m, 2H), 7.09–7.12 (m, 1H), 7.31–7.40 (m, 6H), 7.61–7.63 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ ppm: 20.1, 27.4, 28.5, 28.6, 34.6, 36.7, 36.8, 45.1, 57.8, 58.2, 61.4, 61.5, 81.4, 81.6, 97.2, 121.3, 128.8, 128.9, 129.3, 130.9, 131.0, 132.3, 134.4, 134.5, 134.6, 136.6, 151.2, 156.4, 157.3; IR ($CHCl_3$) cm^{-1}: 2932, 1721, 1685, 1391, 1367, 1250, 1168, 1110; HRMS calcd for $C_{36}H_{46}N_2O_5SiNa$ $(M+Na)^+$ 637.3074, found 637.3074.

16c. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.26 (s, 5.4H), 1.36 (s, 3.2H), 1.85–2.15 (m, 2H), 2.96 (s, 3H), 3.06 (s, 3H), 3.55 (br, 2H), 3.82 (br, 0.4H), 3.94 (d, 0.6H, $J=18.3$ Hz), 4.55 (d, 0.6H, $J=20.5$ Hz), 4.57 (br, 0.4H), 5.01 (br, 0.4H), 5.22 (br t, 0.6H, $J=7.3$ Hz), 5.68–5.75 (m, 1H), 6.33 (d, 0.6H, $J=12.4$ Hz), 6.39 (d, 0.4H, $J=12.4$ Hz), 6.99–7.01 (m, 2H), 7.13 (d, 1H, $J=8.8$ Hz);^{13}C NMR (100 MHz, CD_3OD) δ ppm: 28.4, 28.6, 34.4, 34.6, 36.7, 36.8, 57.7, 59.1, 59.2, 61.5, 81.4, 81.6, 97.2, 121.3, 123.2, 129.3, 130.5, 131.1, 134.2, 151.2, 156.5, 157.4; IR ($CHCl_3$) cm^{-1}: 2979, 1720, 1686, 1479, 1454, 1392, 1250, 1167, 1040; HRMS calcd for $C_{20}H_{29}N_2O_5$ $(M+H)^+$ 377.2076, found 377.2075.

Dimethylcarbamic acid 1-[2-(4-nitrophenoxy)ethyl]-2,3-dihydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (17a·HCl). This was prepared by the method used for **6a**.

17a. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.23–2.35 (m, 2H), 3.01 (s, 3H), 3.09 (s, 3H), 3.67 (ddd, 1H, $J=2.0$, 3.6, 20.4 Hz), 3.77 (dt, 1H, $J=2.4$, 20.4 Hz), 4.14 (dt, 1H, $J=6.0$, 8.8 Hz), 4.19–4.27 (m, 2H), 5.95 (dt, 1H, $J=3.6$, 12.4 Hz), 6.40 (d, 1H, $J=12.4$ Hz), 6.88 (dd, 1H, $J=2.0$, 8.0 Hz), 6.95 (d, 2H, $J=9.2$ Hz), 7.00, (d, 1H, $J=2.0$ Hz), 7.08 (d, 1H, $J=8.0$ Hz), 8.19 (d, 2H, $J=9.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 32.3, 37.5, 37.8, 49.8, 58.1, 67.1, 115.4, 120.5, 125.8, 126.7, 128.0, 129.5, 136.8, 137.1, 142.1, 142.2, 151.2, 155.6, 164.8; IR ($CHCl_3$) cm^{-1}: 2939, 1714, 1593, 1512, 1498, 1391, 1343, 1264, 1172, 1112, 1020, 846; HRMS calcd for $C_{21}H_{24}N_3O_5$ $(M+H)^+$ 398.1716, found 398.1743.

17a·HCl. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.38–2.44 (m, 1H), 2.71–2.76 (m, 1H), 2.97 (s, 3H), 3.07 (s, 3H), 3.75 (br d, 1H, $J=18.4$ Hz), 3.97–4.00 (m, 2H), 4.09–4.15 (m, 1H), 4.85 (1H, dd, $J=6.0$, 9.6 Hz), 5.95 (dt, 1H, $J=4.4$, 11.6 Hz), 6.68 (d, 1H, $J=11.6$ Hz), 6.88 (d, 2H, $J=8.8$ Hz), 6.98 (dd, 1H, $J=2.0$, 8.0 Hz), 7.07 (d, 1H, $J=2.0$ Hz), 7.32 (d, 1H, $J=8.0$ Hz), 8.14 (d, 2H, $J=8.8$ Hz), 9.90 (br s, 1H), 10.71 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 28.6, 36.4, 36.7, 42.5, 56.3, 64.7, 114.6, 121.4, 124.2, 124.8, 125.8, 130.4, 132.1, 136.0, 141.7, 152.0, 154.3, 163.1; IR (CHCl3) cm−1: 2972, 2658, 1722, 1593, 1514, 1498, 1392, 1343, 1260, 1171, 1112; HRMS calcd for $C_{21}H_{24}N_3O_5$ $(M+H)^+$ 398.1716, found 398.1743.

Dimethylcarbamic acid 1-[2-(4-chloro-3-methylphenoxy)-ethyl]-2,3-dihydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (17b·HCl). This was prepared by the method used for **6a**.

17b. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.22 (dd, 1H, $J=2.0$, 6.0 Hz), 2.25 (d, 1H, $J=7.2$ Hz), 2.32 (s, 3H), 3.01 (s, 3H), 3.09 (s, 3H), 3.66 (ddd, 1H, $J=2.4$, 3.6, 19.6 Hz), 3.76 (dt, 1H, $J=2.4$, 19.6 Hz), 3.98 (dt, 1H, $J=6.0$, 9.6 Hz), 4.08 (dt, 1H, $J=6.0$, 9.6 Hz), 4.21 (t, 1H, $J=8.0$ Hz), 5.93 (dt, 1H, $J=3.6$, 12.4 Hz), 6.38 (d, 1H, $J=12.4$ Hz), 6.67 (dd, 1H, $J=3.2$, 8.8 Hz), 6.77 (d, 1H, $J=3.2$ Hz), 6.86 (dd, 1H, $J=3.2$, 8.0 Hz), 6.99 (d, 1H, $J=3.2$ Hz), 7.08 (d, 1H, $J=8.0$ Hz), 7.20 (d, 1H, $J=8.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 20.3, 31.3, 36.4, 36.7, 48.5, 57.2, 65.2, 113.1, 117.0, 119.5, 124.8, 125.6, 127.4, 128.7, 129.5, 135.7, 136.3, 136.9, 141.4, 150.2, 154.9, 157.4; IR ($CHCl_3$) cm^{-1}: 2935, 1714, 1484, 1391, 1247, 1171, 909; HRMS calcd for $C_{22}H_{26}N_2O_3Cl$ $(M+H)^+$ 401.1632, found 401.1628.

17b·HCl. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.29 (s, 3H), 2.31–2.40 (m, 1H), 2.63–2.72 (m, 1H), 2.97 (s, 3H), 3.07 (s, 3H), 3.75 (br d, 1H, $J=18.0$ Hz), 3.80 (dt, 1H, $J=5.2$, 8.8 Hz), 3.95 (br s, 1H), 3.98 (q, 1H, $J=5.2$ Hz), 4.83 (1H, dd, $J=5.2$, 9.6 Hz), 5.94 (dt, 1H, $J=4.4$, 11.6 Hz), 6.59 (dd, 1H, $J=2.0$, 8.8 Hz), 6.67 (d, 1H, $J=11.6$ Hz), 6.69 (d, 1H, $J=2.0$ Hz), 6.98 (dd, 1H, $J=2.0$, 8.0 Hz), 7.06 (d, 1H, $J=2.0$ Hz), 7.15 (d, 1H, $J=8.0$ Hz), 7.30 (d, 1H, $J=8.8$ Hz), 9.87 (br s, 1H), 10.65 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 20.2, 29.0, 36.4, 36.7, 42.5, 56.3, 64.0, 113.2, 117.1, 121.3, 124.1, 124.6, 126.2, 129.5, 130.4, 130.5, 132.3, 136.0, 137.0, 151.9, 154.3, 156.7; IR ($CHCl_3$) cm^{-1}: 2970, 2694, 1722, 1576, 1483, 1391, 1250, 1170, 1040.

Compounds **18a–h** were prepared by the method used for **9a**.

Dimethylcarbamic acid 2-methyl-1-[2-(4-nitrophenoxy)ethyl]-2,3-dihydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (18a·HCl). 18a. ^1H NMR (400 MHz, $CDCl_3$)

δ ppm: 2.05–2.13 (m, 1H), 2.23–2.33 (m, 1H), 2.28 (s, 3H), 3.01 (s, 3H), 3.09 (s, 3H), 3.46 (dd, 1H, J = 3.6, 19.6 Hz), 3.87 (dt, 1H, J = 2.0, 19.6 Hz), 3.97–4.02 (m, 1H), 4.06–4.12 (m, 2H), 5.81 (ddd, 1H, J = 2.8, 4.4, 12.4 Hz), 6.37 (d, 1H, J = 12.4 Hz), 6.89 (dd, 1H, J = 3.0, 8.0 Hz), 6.92 (d, 2H, J = 8.8 Hz), 7.00 (d, 1H, J = 3.0 Hz), 7.04 (d, 1H, J = 8.0 Hz), 8.19 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 31.3, 36.3, 36.6, 41.4, 53.2, 64.0, 65.6, 114.2, 119.6, 124.2, 125.5, 128.6, 129.5, 132.3, 135.9, 137.8, 141.0, 150.1, 154.4, 163.6; IR ($CHCl_3$) cm^{-1}: 2938, 1714, 1593, 1513, 1498, 1391, 1343, 1263, 1172, 1112, 1024, 846; HRMS calcd for $C_{22}H_{26}N_3O_5$ $(M+H)^+$ 412.1872, found 412.1902.

18a·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.12–2.21 (m, 1H), 2.60 (s, 3H), 2.85–2.93 (m, 1H), 3.02 (s, 3H), 3.10 (s, 3H), 3.81 (dd, 1H, J = 4.4, 19.6 Hz), 3.85–3.90 (m, 1H), 4.06 (dt, 1H, J = 5.2, 9.6 Hz), 4.39 (d, 1H, J = 19.6 Hz), 4.77 (d, 1H, J = 11.6 Hz), 5.85 (ddd, 1H, J = 3.2, 4.4, 12.4 Hz), 6.36 (d, 1H, J = 12.4 Hz), 6.86 (d, 2H, J = 8.8 Hz), 7.04 (dd, 1H, J = 2.4, 8.8 Hz), 7.14 (d, 1H, J = 8.8 Hz), 7.21 (d, 1H, J = 2.4 Hz), 8.16 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.7, 36.2, 36.5, 40.3, 51.0, 64.0, 65.4, 114.1, 121.5, 121.8, 125.3, 125.6, 127.4, 129.7, 131.5, 134.2, 141.1, 151.9, 153.5, 162.4; IR ($CHCl_3$) cm^{-1}: 2971, 2222, 1725, 1594, 1514, 1498, 1469, 1392, 1344, 1258, 1171, 1112, 1021, 909, 846; HRMS calcd for $C_{22}H_{26}N_3O_5$ $(M+H)^+$ 412.1872, found 412.1870.

Dimethylcarbamic acid 1-[2-(4-chloro-3-methylphenoxy)ethyl]-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (18b·HCl). 18b. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.97–2.05 (m, 1H), 2.19–2.26 (m, 1H), 2.28 (s, 3H), 2.32 (s, 3H), 3.01 (s, 3H), 3.09 (s, 3H), 3.45 (dd, 1H, J = 4.4, 20.4 Hz), 3.81–3.96 (m, 3H), 4.08 (dd, 1H, J = 6.4, 8.8 Hz), 5.80 (ddd, 1H, J = 2.4, 4.4, 12.4 Hz), 6.36 (d, 1H, J = 12.4 Hz), 6.64 (dd, 1H, J = 2.0, 8.0 Hz), 6.74 (d, 1H, J = 2.0 Hz), 6.88 (dd, 1H, J = 2.0, 8.0 Hz), 6.99 (d, 1H, J = 2.0 Hz), 7.06 (d, 1H, J = 8.0 Hz), 7.19 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 20.2, 31.6, 36.4, 36.7, 41.6, 53.2, 64.4, 64.9, 113.2, 117.0, 119.8, 124.5, 125.6, 129.0, 129.5, 130.1, 132.4, 136.1, 136.8, 138.3, 150.4, 154.8, 157.4; IR ($CHCl_3$) cm^{-1}: 2934, 1714, 1483, 1391, 1246, 1171, 1034, 909; HRMS calcd for $C_{23}H_{28}N_2O_3Cl$ $(M+H)^+$ 415.1788, found 415.1793.

18b·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.03–2.12 (m, 1H), 2.30 (s, 3H), 2.60 (d, 3H, J = 5.2 Hz), 2.77–2.86 (m, 1H), 3.02 (s, 3H), 3.10 (s, 3H), 3.65 (dt, 1H, J = 4.4, 9.6 Hz), 3.78 (dd, 1H, J = 2.0, 4.4 Hz), 3.88 (dt, 1H, J = 5.2, 8.8 Hz), 4.37 (d, 1H, J = 17.2 Hz), 4.79 (dt, 1H, J = 3.6, 12.4 Hz), 5.82 (ddd, 1H, J = 2.8, 4.4, 12.4 Hz), 6.55 (dd, 1H, J = 2.8, 8.8 Hz), 6.64 (d, 2H, J = 12.4 Hz), 6.68 (d, 1H, J = 2.8 Hz), 7.04 (dd, 1H, J = 2.8, 8.8 Hz), 7.15 (d, 1H, J = 8.8 Hz), 7.17 (d, 1H, J = 8.8 Hz), 7.19 (d, 1H, J = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 20.2, 30.2, 36.5, 36.7, 40.6, 51.3, 63.4, 66.0, 113.0, 117.1, 121.9, 122.0, 126.0, 126.3, 128.2, 129.5, 130.4, 132.1, 134.5, 137.0, 152.4, 154.1, 156.6; IR ($CHCl_3$) cm^{-1}: 2969, 2230, 1724, 1483, 1392, 1250, 1170, 1041, 1022; HRMS calcd for $C_{23}H_{28}N_2O_3Cl$ $(M+H)^+$ 415.1788, found 415.1793.

Dimethylcarbamic acid 1-[2-(4-chlorophenoxy)ethyl]-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (18c·HCl). 18c: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.94–2.03 (m, 1H), 2.16–2.24 (m, 1H), 2.24 (s, 3H), 2.97 (s, 3H), 3.05 (s, 3H), 3.40 (dd, 1H, J = 3.7, 19.8 Hz), 3.78–3.93 (m, 3H), 4.05 (t, 1H, J = 8.0 Hz), 5.75 (ddd, 1H, J = 2.9, 4.4, 12.5 Hz), 6.32 (d, 1H, J = 12.5 Hz), 6.75 (d, 2H, J = 8.8 Hz), 6.84 (dd, 1H, J = 2.2, 8.0 Hz), 6.95 (d, 1H, J = 2.2 Hz), 7.01 (d, 1H, J = 8.0 Hz), 7.16 (d, 2H, J = 8.8 Hz); IR (film) cm^{-1}: 2931, 1722, 1491, 1386, 1242, 1167, 1028, 824.

18c·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.98–2.09 (m, 1H), 2.65 (d, 3H, J = 4.4 Hz), 2.74–2.82 (m, 1H), 2.98 (s, 3H), 3.06 (s, 3H), 3.61–3.66 (m, 1H), 3.73 (d, 1H, J = 19.8 Hz), 3.83–3.88 (m, 1H), 4.83 (d, 1H, J = 18.3 Hz), 4.72 (d, 1H, J = 11.7 Hz), 5.78 (d, 1H, J = 13.2 Hz), 6.60 (d, 1H, J = 13.2 Hz), 6.68 (d, 2H, J = 8.8 Hz), 6.99 (dd, 1H, J = 2.2, 8.0 Hz), 7.10 (d, 1H, J = 8.0 Hz), 7.15 (d, 1H, J = 2.2 Hz), 7.16 (d, 2H, J = 8.8 Hz); IR (KBr) cm^{-1}: 2933, 2436, 1723, 1492, 1388, 1243, 1170, 1020, 825; HRMS calcd for $C_{22}H_{26}N_2O_3Cl$ $(M+H)^+$ 401.1632, found 401.1624.

Dimethylcarbamic acid 1-[2-(4-fluorophenoxy)ethyl]-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (18d·HCl). 18d. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.93–2.04 (m, 1H), 2.13–2.23 (m, 1H), 2.25 (s, 3H), 2.97 (s, 3H), 3.05 (s, 3H), 3.42 (dd, 1H, J = 4.4, 20.5 Hz), 3.77-3.91 (m, 3H), 4.02–4.10 (m, 1H), 5.75 (ddd, 1H, J = 2.9, 4.4, 12.5 Hz), 6.33 (d, 1H, J = 12.5 Hz), 6.76 (dd, 2H, J = 4.4, 8.8 Hz), 6.85 (dd, 1H, J = 2.2, 8.0 Hz), 6.90 (d, 2H, J = 8.8 Hz), 6.95 (d, 1H, J = 2.2 Hz), 7.02 (d, 1H, J = 8.0 Hz); IR (film) cm^{-1}: 2932, 1723, 1506, 1387, 1245, 1207, 1168, 1032, 829.

18d·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.07–2.13 (m, 1H), 2.61 (d, 3H, J = 4.9 Hz), 2.80–2.86 (m, 1H), 3.04 (s, 3H), 3.12 (s, 3H), 3.66–3.71 (m, 1H), 3.79 (dd, 1H, J = 4.9, 20.5 Hz), 3.90 (dt, 1H, J = 4.9, 8.8 Hz), 4.40 (d, 1H, J = 19.5 Hz), 4.78–4.82 (m, 1H), 5.83 (d, 1H, J = 12.7 Hz), 6.66 (d, 1H, J = 12.7 Hz), 6.74–6.76 (m, 2H), 6.94 (d, 2H, J = 8.8 Hz), 7.05 (dd, 1H, J = 2.9, 8.8 Hz), 7.18 (d, 1H, J = 8.8 Hz), 7.20 (d, 1H, J = 2.9 Hz); IR (KBr) cm^{-1}: 3428, 2933, 2461, 1724, 1507, 1389, 1209, 1169, 1019, 831; HRMS calcd for $C_{22}H_{26}N_2O_3F$ $(M+H)^+$ 385.1928, found 385.1930.

Dimethylcarbamic acid 2-methyl-1-[2-(4-trifluoromethylphenoxy)ethyl]-2,3-dihydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (18e·HCl). 18e. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.02–2.10 (m, 1H), 2.23–2.29 (m, 1H), 2.29 (s, 3H), 3.01 (s, 3H), 3.09 (s, 3H), 3.42–3.49 (m, 1H), 3.85–3.96 (m, 2H), 4.00–4.05 (m, 1H), 4.08–4.13 (m, 1H), 5.80 (ddd, 1H, J = 2.9, 4.4, 12.5 Hz), 6.37 (d, 1H, J = 12.5 Hz), 6.89 (dd, 1H, J = 2.9, 8.0 Hz), 6.93 (d, 2H, J = 8.0 Hz), 7.00 (d, 1H, J = 2.9 Hz), 7.06 (d, 1H, J = 8.0 Hz), 7.52 (d, 2H, J = 8.0 Hz); IR (film) cm^{-1}: 2932, 1724, 1615, 1386, 1328, 1256, 1164, 1111, 837,

756; HRMS calcd for $C_{23}H_{26}N_2O_3F_3$ $(M+H)^+$ 435.1896, found 435.1902.

18e·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.05–2.13 (m, 1H), 2.55 (d, 3H, J = 4.4 Hz), 2.77–2.87 (m, 1H), 2.98 (s, 3H), 3.06 (s, 3H), 3.69–3.77 (m, 2H), 3.91–3.96 (m, 1H), 4.34 (d, 1H, J = 19.0 Hz), 4.73 (d, 1H, J = 11.0 Hz), 5.79 (d, 1H, J = 12.5 Hz), 6.62 (d, 1H, J = 12.5 Hz), 6.81 (d, 2H, J = 8.8 Hz), 6.99 (dd, 1H, J = 2.2, 8.0 Hz), 7.09 (d, 1H, J = 8.0 Hz), 7.16 (d, 1H, J = 2.2 Hz), 7.46 (d, 2H, J = 8.8 Hz); IR (KBr) cm^{-1}: 2934, 2466, 1725, 1615, 1389, 1329, 1255, 1168, 1112, 1067, 839; HRMS calcd for $C_{23}H_{26}N_2O_3F_3$ $(M+H)^+$ 435.1896, found 435.1895.

Dimethylcarbamic acid 1-[2-(4-chloro-3-methylphenoxy)-ethyl]-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-6-yl ester hydrochloride salt (18f·HCl). 18f. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.04–2.12 (m, 1H), 2.21–2.28 (m, 1H), 2.30 (s, 3H), 2.32 (s, 3H), 3.02 (s, 3H), 3.15 (s, 3H), 3.47 (dd, 1H, J = 3.6, 19.6 Hz), 3.81–3.87 (m, 2H), 3.94 (dt, 1H, J = 5.6, 8.8 Hz), 4.11 (t, 1H, J = 7.2 Hz), 5.88 (ddd, 1H, J = 2.4, 3.6, 12.4 Hz), 6.59 (d, 1H, J = 12.4 Hz), 6.63 (dd, 1H, J = 3.2, 8.0 Hz), 6.73 (d, 1H, J = 3.2 Hz), 6.95 (d, 1H, J = 8.0 Hz), 6.99 (dd, 1H, J = 1.2, 8.0 Hz), 7.13 (t, 1H, J = 8.0 Hz), 7.19 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 20.3, 30.7, 36.4, 36.8, 53.7, 65.0, 113.1, 117.0, 121.0, 121.6, 125.6, 126.4, 127.5, 127.7, 129.5, 136.8, 149.7, 154.6, 157.4; IR ($CHCl_3$) cm^{-1}: 2935, 1720, 1483, 1389, 1168, 1037, 909; HRMS calcd for $C_{23}H_{28}N_2O_3Cl$ $(M+H)^+$ 415.1788, found 415.1789.

18f·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.14–2.21 (m, 1H), 2.30 (s, 3H), 2.64 (d, 3H, J = 4.8 Hz), 2.78–2.89 (m, 1H), 3.04 (s, 3H), 3.18 (s, 3H), 3.65 (dt, 1H, J = 4.4, 10.0 Hz), 3.78 (d, 1H, J = 19.2 Hz), 3.89 (dt, 1H, J = 5.2, 10.0 Hz), 4.34 (dd, 1H, J = 3.6, 19.2 Hz), 4.79 (dt, 1H, J = 3.6, 12.4 Hz), 5.91 (dt, 1H, J = 3.6, 12.4 Hz), 6.52 (dd, 1H, J = 2.8, 8.8 Hz), 6.67 (d, 1H, J = 2.8 Hz), 6.88 (d, 1H, J = 12.4 Hz), 7.04 (d, 1H, J = 7.2 Hz), 7.15–7.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 20.2, 20.5, 29.6, 36.5, 36.9, 41.0, 51.4, 63.6, 66.5, 113.0, 113.2, 117.0, 122.7, 123.6, 124.4, 126.3, 126.7, 128.2, 129.5, 129.7, 133.0, 137.0, 150.7, 154.0, 156.6; IR ($CHCl_3$) cm^{-1}: 2970, 2250, 1726, 1471, 1387, 1245, 1166, 1042, 1020.

Dimethylcarbamic acid 2-methyl-1-[2-(4-nitrophenoxy)-ethyl]-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl ester hydrochloride salt (18g·HCl). 18g: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.06–2.15 (m, 1H), 2.25–2.35 (m, 1H), 2.30 (s, 3H), 2.97 (s, 3H), 3.04 (s, 3H), 3.47 (dd, 1H, J = 4.4, 20.0 Hz), 3.86 (d, 1H, J = 20.0 Hz), 4.02–4.15 (m, 3H), 5.75 (ddd, 1H, J = 2.9, 4.4, 12.5 Hz), 6.42 (d, 1H, J = 12.5 Hz), 6.63 (dd, 1H, J = 3.2, 8.0 Hz), 6.73 (d, 1H, J = 3.2 Hz), 6.95 (d, 1H, J = 8.0 Hz), 6.84 (d, 1H, J = 2.2 Hz), 6.95 (d, 2H, J = 8.8 Hz), 6.97 (dd, 1H, J = 2.2, 8.0 Hz), 7.22 (d, 1H, J = 8.0 Hz), 8.18 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 31.4, 36.3, 36.6, 41.3, 53.2, 64.5, 65.7, 76.7, 114.6, 120.3, 122.3, 125.8, 128.9, 132.0, 132.8, 141.3, 150.1, 154.5, 163.9; IR ($CHCl_3$) cm^{-1}: 2938, 1719, 1593, 1498, 1390, 1343, 1263, 1171, 1111, 1022, 846; HRMS calcd for $C_{22}H_{26}N_3O_5$ $(M+H)^+$ 412.1872, found 412.1868.

18g·HCl. ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 2.29–2.37 (m, 1H), 2.55–2.63 (m, 1H), 2.90 (s, 6H), 2.99 (s, 3H), 3.84–3.90 (m, 1H), 4.08–4.31 (m, 3H), 5.86 (ddd, 1H, J = 3.7, 7.8, 12.8 Hz), 6.80 (d, 1H, J = 12.8 Hz), 7.02-7.05 (m, 3H), 7.21 (d, 1H, J = 8.4 Hz), 7.48 (d, 1H, J = 8.4 Hz), 8.19 (d, 2H, J = 9.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ ppm: 36.5, 36.8, 42.3, 53.7, 65.5, 67.7, 97.2, 116.0, 123.0, 124.3, 125.5, 126.7, 130.9, 132.4, 135.1, 137.5, 143.1, 152.4, 155.9, 164.7; IR ($CHCl_3$) cm^{-1}: 2971, 2219, 1726, 1594, 1498, 1391, 1343, 1259, 1168, 1112, 846.

Dimethylcarbamic acid 1-[2-(4-chlorophenoxy)ethyl]-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl ester hydrochloride salt (18h·HCl). 18h. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.00–2.08 (m, 1H), 2.20–2.27 (m, 1H), 2.29 (s, 3H), 2.99 (s, 3H), 3.04 (s, 3H), 3.46 (dd, 1H, J = 3.7, 20.0 Hz), 3.84–4.00 (m, 3H), 4.05 (t, 1H, J = 8.0 Hz), 5.74 (ddd, 1H, J = 2.2, 4.4, 12.5 Hz), 6.40 (d, 1H, J = 12.5 Hz), 6.81–6.83 (m, 3H), 6.97 (dd, 1H, J = 2.9, 8.8 Hz), 7.19–7.21 (m, 3H).

18 h·HCl. ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 2.21–2.29 (m, 1H), 2.50–2.57 (m, 1H), 2.95 (s, 6H), 3.02 (s, 3H), 3.66–3.72 (m, 1H), 4.01–4.13 (m, 2H), 4.28 (br d, 1H, J = 18.4 Hz), 5.85 (dt, 1H, J = 4.0, 12.8 Hz), 6.79 (d, 1H, J = 12.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 7.03 (d, 1H, J = 2.4 Hz), 7.20–7.25 (m, 3H), 7.48 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ ppm: 36.6, 36.8, 64.8, 67.8, 81.1, 97.2, 117.2, 124.2, 125.5, 127.1, 130.3, 131.0, 132.3, 135.1, 152.4, 155.9, 158.4; IR ($CHCl_3$) cm^{-1}: 2970, 2222, 1726, 1492, 1391, 1248, 1168; HRMS calcd for $C_{22}H_{26}N_2O_3Cl$ $(M+H)^+$ 401.1632, found 401.1635.

7-Dimethylcarbamoyloxy-1-(2-hydroxyethyl)-1,3,4,5-tetrahydrobenzo[*c*]azepine-2-carboxylic acid *tert*-butyl ester (19). To a solution of **16b** (207 mg, 0.550 mmol) in MeOH (10 mL) was added 10% Pd/C (27 mg). The reaction mixture was stirred for 1 h under a hydrogen atmosphere at room temperature. Pd/C was removed by filtration and filtrate was evaporated in vacuo. Purification by silica gel column chromatography (hexane–AcOEt 1:1 to AcOEt) provided **19** (189 mg, 91%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.36 (s, 5.4H), 1.45 (s, 3.6H), 1.68–1.84 (br, 1H), 1.86–2.00 (br, 1H), 1.88–2.06 (br, 0.4H), 2.06–2.18 br, (0.6H), 2.22–2.44 (br, 1H), 2.83 (br s, 2H), 3.00 (s, 3H), 3.08 (s, 3H), 3.55–3.68 (br, 1H), 3.67 (br s, 2H), 3.75–3.90 (br, 1H), 5.03–5.18 (br, 0.4H), 5.38–5.52 (br, 0.6H), 6.88 (s, 2H), 7.15 (br s, 0.4H), 7.24 (br s, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.2, 27.5, 28.4, 33.6, 35.2, 36.4, 36.6, 55.9, 59.1, 77.6, 80.1, 118.7, 119.2, 123.6, 129.3, 141.0, 150.2, 154.9; IR ($CHCl_3$) cm^{-1}: 2938, 1713, 1680, 1478, 1392, 1252, 1168, 909; HRMS calcd for $C_{20}H_{31}N_2O_5$ $(M+H)^+$ 379.2233, found 379.2244.

Dimethylcarbamic acid 1-[2-(4-nitrophenoxy)ethyl]-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (20a·HCl). This was prepared by the method used for 6a. 20a. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.53–1.64 (m, 2H), 1.75–1.80 (m, 1H), 2.18–2.26

(m, 1H), 2.36–2.44 (m, 1H), 2.90 (dd, 1H, $J=7.2$, 12.4 Hz), 3.01 (s, 3H), 3.02–3.06 (m, 1H), 3.09 (s, 3H), 3.33 (dt, 1H, $J=4.4$, 14.0 Hz), 4.11 (dd, 1H, $J=5.2$, 10.4 Hz), 4.25 (dt, 1H, $J=6.0$, 9.6 Hz), 4.34 (q, 1H, $J=7.6$ Hz), 6.89 (dd, 1H, $J=2.8$, 8.0 Hz), 6.94 (d, 1H, $J=2.8$ Hz), 6.98 (d, 2H, $J=9.6$ Hz), 7.15 (d, 1H, $J=8.0$ Hz), 8.20 (d, 2H, $J=9.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 30.1, 33.1, 35.3, 36.4, 50.3, 56.7, 66.7, 77.2, 114.5, 118.9, 123.2, 125.9, 126.1, 141.4, 143.6, 150.2, 154.9, 164.1; IR ($CHCl_3$) cm^{-1}: 2934, 1713, 1593, 1512, 1498, 1390, 1342, 1264, 1172, 1111, 1019; HRMS calcd for $C_{21}H_{26}N_3O_5$ $(M+H)^+$ 400.1873, found 400.1870.

20a·HCl. ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 1.90–2.00 (m, 1H), 2.00–2.12 (m, 1H), 2.49–2.58 (m, 1H), 2.68–2.76 (m, 1H), 2.94 (s, 3H), 2.98–3.08 (m, 1H), 3.08 (s, 3H), 3.18 (dd, 1H, $J=11.2$, 13.2 Hz), 3.40–3.46 (m, 1H), 3.52–3.57 (m, 1H), 3.98–4.06 (m, 1H), 4.24 (dt, 1H, $J=4.8$, 10.4 Hz), 6.95 (dd, 1H, $J=2.0$, 8.8 Hz), 7.02–7.05 (m, 3H), 7.31 (d, 1H, $J=8.8$ Hz), 8.17, (d, 2H, $J=8.8$ Hz); ^{13}C NMR (100 MHz, CD_3OD) δ ppm: 14.5, 20.8, 26.1, 30.4, 34.0, 36.7, 36.9, 61.5, 66.2, 115.9, 121.3, 125.5, 126.8, 131.7, 143.2, 144.6, 153.6, 156.4, 164.7; IR (KBr) cm^{-1}: 2939, 1718, 1592, 1512, 1385, 1342, 1264, 1171, 1113, 1021; HRMS calcd for $C_{21}H_{26}N_3O_5$ $(M+H)^+$ 400.1873, found 400.1870.

Dimethylcarbamic acid 1-[2-(4-chlorophenoxy)ethyl]-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (20b·HCl). This was prepared by the method used for **6a**.

20b. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.59–1.64 (m, 2H), 1.73–1.80 (m, 1H), 2.14–2.23 (m, 1H), 2.31–2.39 (m, 1H), 2.90 (dd, 1H, $J=8.0$, 14.0 Hz), 3.01 (s, 3H), 3.04 (dt, 1H, $J=3.6$, 14.0 Hz), 3.09 (s, 3H), 3.32 (dt, 1H, $J=4.4$, 14.0 Hz), 4.07–4.13 (m, 2H), 4.18 (q, 1H, $J=8.0$ Hz), 6.84 (d, 2H, $J=8.4$ Hz), 6.86 (dd, 1H, $J=2.8$, 8.0 Hz), 6.92 (d, 1H, $J=2.8$ Hz), 7.15 (d, 1H, $J=8.0$ Hz), 7.22 (d, 2H, $J=8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 30.2, 33.3, 35.3, 36.4, 36.7, 50.3, 57.0, 66.1, 115.9, 118.8, 123.1, 125.4, 126.2, 129.2, 141.4, 143.6, 150.0, 155.0, 157.6; IR ($CHCl_3$) cm^{-1}: 2933, 1713, 1492, 1390, 1248, 1172; HRMS calcd for $C_{21}H_{26}N_2O_3Cl$ $(M+H)^+$ 389.1632, found 389.1637.

20b·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.01–2.20 (m, 2H), 2.52–2.61 (m, 1H), 2.78–2.88 (m, 1H), 2.90–3.00 (m, 1H), 2.99 (s, 3H), 3.02–3.11 (m, 1H), 3.08 (s, 3H), 3.25–3.40 (m, 2H), 3.93 (q, 1H, $J=8.8$ Hz), 4.11 (dt, 1H, $J=4.4$, 9.2 Hz), 4.77 (br s, 1H), 6.79 (d, 2H, $J=9.6$ Hz), 6.96 (dd, 1H, $J=2.4$, 8.8 Hz), 6.99 (d, 1H, $J=2.4$ Hz), 7.19, (d, 2H, $J=9.6$ Hz), 7.22 (d, 1H, $J=8.8$ Hz), 9.84 (br s, 1H), 9.91 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 24.0, 30.6, 32.2, 36.4, 36.7, 44.3, 57.7, 64.2, 115.9, 120.1, 123.8, 126.0, 129.3, 129.4, 130.3, 141.2, 152.0, 154.4, 156.8; IR ($CHCl_3$) cm^{-1}:2965, 2724, 1720, 1492, 1390, 1248, 1171; HRMS calcd for $C_{21}H_{26}N_2O_3Cl$ $(M+H)^+$ 389.1632, found 389.1645.

Dimethylcarbamic acid 2-methyl-1-[2-(4-nitrophenoxy)-ethyl]-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (21a·HCl). This was prepared by the method used for **9a**.

21a. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.60–1.80 (m, 2H), 2.10 (br s, 3H), 2.25–2.32 (m, 1H), 2.35–2.48 (m, 1H), 2.91 (br s, 2H), 3.01 (s, 3H), 3.09 (s, 3H), 3.22–3.33 (m, 1H), 4.10–4.30 (m, 4H), 6.88 (dd, 1H, $J=2.4$, 8.0 Hz), 6.93 (d, 1H, $J=2.4$ Hz), 6.96 (d, 2H, $J=8.8$ Hz), 7.08 (d, 1H, $J=8.0$ Hz), 8.18 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 30.4, 35.9, 36.4, 36.6, 66.7, 114.5, 118.7, 125.8, 141.3, 154.9, 164.1; IR ($CHCl_3$) cm^{-1}: 2934, 1713, 1593, 1512, 1498, 1390, 1343, 1265, 1173, 909; HRMS calcd for $C_{22}H_{28}N_3O_5$ $(M+H)^+$ 414.2029, found 414.2042.

21a·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.00–2.19 (m, 2H), 2.40 (br s, 1H), 2.55–2.68 (m, 1H), 2.68 (d, 3H, $J=4.8$ Hz), 2.86 (dd, 1H, $J=4.8$, 18.0 Hz), 3.02 (s, 3H), 3.09 (s, 3H), 3.12–3.28 (m, 1H), 3.35 (d, 1H, $J=16.4$ Hz), 3.76–3.85 (m, 1H), 3.92–4.00 (m, 1H), 4.11 (dt, 1H, $J=6.4$, 10.4 Hz), 4.52 (d, 1H, $J=9.2$ Hz), 6.83 (d, 2H, $J=9.6$ Hz), 6.92–6.95 (m, 1H), 7.06–7.10 (m, 2H), 8.15 (d, 2H, $J=9.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 21.0, 29.6, 33.9, 36.4, 36.7, 39.4, 51.1, 64.9, 68.2, 114.5, 120.5, 125.8, 127.6, 133.2, 141.3, 141.8, 152.5, 154.1, 162.9, 174.4; IR ($CHCl_3$) cm^{-1}: 2966, 2310, 1722, 1594, 1391, 1343, 1259, 1172, 1111; HRMS calcd for $C_{22}H_{28}N_3O_5$ $(M+H)^+$ 414.2029, found 414.2048.

Dimethylcarbamic acid 1-[2-(4-chlorophenoxy)ethyl]-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (21b·HCl). This was prepared by the method used for **9a**.

21b. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.60–1.78 (m, 2H), 2.10 (br s, 3H), 2.20–2.30 (m, 1H), 2.32–2.42 (m, 1H), 2.91 (br s, 2H), 3.01 (s, 3H), 3.09 (s, 3H), 3.22–3.32 (m, 1H), 3.96–4.20 (m, 4H), 6.82 (d, 2H, $J=8.8$ Hz), 6.87 (dd, 1H, $J=2.0$, 8.0 Hz), 6.91 (d, 1H, $J=2.0$ Hz), 7.08 (d, 1H, $J=8.0$ Hz), 7.21 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 22.1, 30.6, 35.9, 36.4, 36.6, 66.1, 115.8, 118.5, 123.5, 125.2, 129.2, 149.5, 154.9, 157.6; IR ($CHCl_3$) cm^{-1}: 2933, 1712, 1492, 1390, 1247, 1172, 909; HRMS calcd for $C_{22}H_{28}N_2O_3Cl$ $(M+H)^+$ 403.1788, found 403.1806.

21b·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.98–2.17 (m, 2H), 2.41 (br s, 1H), 2.50–2.62 (m, 1H), 2.67 (d, 3H, $J=4.4$ Hz), 2.87 (d, 1H, $J=14.0$ Hz), 3.02 (s, 3H), 3.09 (s, 3H), 3.21 (t, 1H, $J=14.0$ Hz), 3.34 (d, 1H, $J=14.0$ Hz), 3.65–3.74 (m, 2H), 3.94 (dt, 1H, $J=4.0$, 9.2 Hz), 4.53 (d, 1H, $J=10.8$ Hz), 6.68 (d, 2H, $J=8.8$ Hz), 6.77 (d, 1H, $J=8.4$ Hz), 6.94 (dd, 1H, $J=2.4$, 8.4 Hz), 7.05 (d, 1H, $J=2.4$ Hz), 7.17 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 20.5, 21.0, 29.8, 33.8, 36.4, 36.7, 39.5, 51.1, 64.2, 68.3, 115.8, 120.3, 124.8, 126.0, 127.8, 129.3, 133.3, 141.2, 152.4, 154.2, 156.6, 174.6; IR ($CHCl_3$) cm^{-1}: 2966, 2315, 1721, 1492, 1391, 1247, 1171; HRMS calcd for $C_{22}H_{28}N_2O_3Cl$ $(M+H)^+$ 403.1788, found 403.1808.

7-Dimethylcarbamoyloxy-1-(2-hydroxyethyl)-5-oxo-1,3,4,5-tetrahydrobenzo[*c*]azepine-2-carboxylic acid *tert*-butyl ester (22). To a solution of **16b** (3.07 g, 8.16 mmol) in

THF (20 mL) was added a solution of BH_3 in THF (10.8 mL, 16.3 mmol) at 0 °C. After stirring for 12 h at room temperature, another solution of BH_3 in THF (10.8 mL, 16.3 mmol) was added at 0 °C and stirred for 3 h at room temperature. After quenching with water (20 mL) at 0 °C, $NaBO_3{\cdot}4H_2O$ (12.3 g, 80.0 mmol) was added to the reaction mixture at 0 °C and stirred for 2 h at room temperature. The organic solvent was evaporated and water (20 mL) was added. The product was extracted with AcOEt (40 mL×2) and washed with brine (30 mL). Then it was dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (AcOEt to AcOEt–MeOH 5:1) provided a regioisomeric mixture of an alcohol (2.65 g) as a colorless oil. To a solution of this mixture of alcohol (2.65 g) in CH_2Cl_2 (30 mL) was added manganese oxide (7.95 g) at room temperature. The reaction mixture was stirred for 2 h at room temperature. After filtration through a Celite pad, the solvent was removed in vacuo. Purification by silica gel column chromatography (hexane–AcOEt 1:1 to AcOEt) gave **22** (1.87 g, 58% for two steps) as a colorless oil. ^{1}H NMR (500 MHz, CD_3OD) δ ppm: 1.34–1.48 (br, 9H), 2.94 (br s, 2H), 2.98 (s, 3H), 3.11 (s, 3H), 3.44–3.54 (m, 2H), 3.73 (br, 1H), 3.96 (br, 1H), 5.38 (br, 0.5H), 5.49 (br, 0.5H), 7.23–7.25 (m, 2H), 7.38 (br s, 1H); ^{13}C NMR (125 MHz, CD3OD) δ ppm: 28.5, 36.7, 36.9, 39.3, 39.8, 44.8, 57.4, 58.0, 59.3, 81.9, 123.2, 126.0, 131.3, 131.7, 139.0, 141.0, 152.0, 156.1, 156.6, 204.6; IR ($CHCl_3$) cm^{-1}: 3439, 2980, 1722, 1681, 1478, 1410, 1392, 1257, 1161, 1055, 888; HRMS calcd for $C_{20}H_{28}N_2O_6Na$ $(M+Na)^+$ 415.1845, found 415.1849.

7-Dimethylcarbamoyloxy-1-[2-(4-nitrophenoxy)ethyl]-5-oxo-1,3,4,5-tetrahydrobenzo[*c*]azepine-2-carboxylic acid *tert*-butyl ester (23). *N*-Boc-deprotected **23** was prepared by the method used for **6a**.

***N*-Boc-deprotected 23**. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.22–2.29 (m, 1H), 2.31–2.38 (m, 1H), 2.82–2.92 (m, 2H), 3.01 (s, 3H), 3.09 (s, 3H), 3.18 (t, 2H, J = 5.5 Hz), 4.09 (dt, 1H, J = 6.0, 9.5 Hz), 2.25 (dt, 1H, J = 6.0, 8.5 Hz), 4.40 (dd, 1H, J = 5.0, 8.0 Hz), 6.92 (d, 2H, J = 9.0 Hz), 7.26 (s, 2H), 7.32 (s, 1H), 8.18 (d, 2H, J = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 35.0, 36.4, 36.7, 40.7, 44.7, 56.2, 65.7, 114.4, 121.6, 125.1, 125.8, 127.6, 138.0, 140.4, 141.5, 150.7, 154.4, 163.7, 204.7; IR ($CHCl_3$) cm^{-1}: 2941, 1720, 1594, 1514, 1499, 1390, 1342, 1263, 1171, 1111, 909; HRMS calcd for $C_{21}H_{24}N_3O_6$ $(M+H)^+$ 414.1665, found 414.1659.

To a solution of the above *N*-Boc-deprotected **23** (1.22 g, 2.95 mmol) and Et_3N (0.840 mL, 6.00 mmol) in THF (20 mL) was added Boc_2O (964 mg, 4.42 mmol) at room temperature. The mixture was stirred for 1 h at room temperature. The solvent was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt 2:1–1:2) to give **23** (1.20 g, 79%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.42 (s, 9H), 2.13 (br, 1H), 2.43–2.50 (m, 1H), 2.95 (br, 2H), 3.01 (s, 3H), 3.09 (s, 3H), 3.86–4.01 (br, 4H), 5.43 (br, 0.5H), 5.61 (br, 0.5H), 6.88 (d, 2H, J = 8.5 Hz), 7.21 (br, 2H), 7.36 (s, 1H), 8.17 (d, 2H, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 29.0, 36.6, 37.1, 37.4, 39.1, 39.8, 44.5, 57.5, 57.9, 65.7, 66.2, 81.6, 115.0, 123.3, 126.0, 126.6, 131.1, 131.5, 136.1, 140.4, 142.3, 152.0, 154.9, 155.3, 164.2, 203.9; IR ($CHCl_3$) cm^{-1}: 2979, 1724, 1686, 1594, 1514, 1392, 1342, 1263, 1161, 1112, 1031, 846; HRMS calcd for $C_{26}H_{31}N_3O_8Na$ $(M+Na)^+$ 536.2009, found 536.2009.

Dimethylcarbamic acid 2-methyl-5-methylene-1-[2-(4-nitrophenoxy)ethyl]-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (24·HCl). To a solution of **23** (435 mg, 0.848 mmol) and $Ph_3P^+CH_3Br^-$ (607 mg, 1.70 mmol) in benzene (5 mL) was added a solution of *t*-BuOK in THF (1.70 mL, 1.0 M) at 80 °C. The mixture was stirred for 1 h at 80 °C. After quenching with water (10 mL), the product was extracted with AcOEt (10 mL×2) and washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 2:1–1:1) gave an exo methylene compound (106 mg, 24%) as a colorless oil. ^{1}H NMR (500 MHz, CD_3OD) δ ppm: 1.35 (s, 9H), 2.29–2.61 (m, 4H), 2.98 (s, 3H), 3.10 (s, 3H), 3.40–3.51 (m, 1H), 3.97–4.04 (m, 2H), 4.16 (br d, 1H, J = 13.5 Hz), 5.15 (s, 1H), 5.25 (s, 1H), 5.34 (br t, 0.5H, J = 7.5 Hz), 5.43 (br t, 0.5H, J = 7.5 Hz), 6.92–6.98 (m, 2H), 7.05 (d, 2H, J = 9.0 Hz), 7.17 (d, 0.5H, J = 8.0 Hz), 7.22 (d, 0.5H, J = 8.0 Hz), 8.17–8.21 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ ppm: 26.6, 32.6, 36.7, 36.8, 38.3, 38.9, 44.5, 57.8, 58.6, 66.5, 66.7, 81.4, 81.7, 115.7, 116.7, 117.8, 121.3, 124.0, 126.7, 126.8, 127.1, 130.9, 131.5, 136.5, 136.6, 142.8, 144.3, 144.5, 150.4, 152.0, 156.6, 157.0, 165.3; IR (film) cm^{-1}: 2975, 1723, 1690, 1593, 1514, 1390, 1340, 1263, 1163, 1020, 846, 753; HRMS calcd for $C_{27}H_{33}N_3O_7Na$ $(M+Na)^+$ 534.2216, found 534.2224.

Compound **24** was prepared by the method used for **9a** from the above compound.

24. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.29–2.43 (m, 2H), 2.36 (s, 3H), 2.64 (br, 1H), 2.96–3.05 (m, 2H), 3.01 (s, 3H), 3.09 (s, 3H), 3.36–3.42 (m, 1H), 3.93–3.96 (m, 2H), 4.02–4.07 (m, 1H), 5.07 (d, 1H, J = 1.6 Hz), 5.12 (s, 1H), 6.89 (d, 2H, J = 8.8 Hz), 6.92 (dd, 1H, J = 2.4, 8.0 Hz), 7.00 (d, 1H, J = 2.4 Hz), 7.04 (d, 1H, J = 8.0 Hz), 8.17 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 31.6, 32.1, 36.4, 36.7, 40.0, 52.1, 64.9, 66.2, 114.3, 115.4, 119.8, 122.2, 125.6, 129.8, 134.4, 141.1, 143.6, 149.8, 150.4, 154.5, 163.7; IR ($CHCl_3$) cm^{-1}: 2934, 1714, 1593, 1512, 1390, 1343, 1264, 1171, 1112, 1020, 909; HRMS calcd for $C_{23}H_{28}N_3O_5$ $(M+H)^+$ 426.2029, found 426.2008.

24·HCl. ^{1}H NMR (500 MHz, CD_3OD) δ ppm: 2.49–2.94 (m, 4H), 2.91 (s, 3H), 2.99 (s, 3H), 3.11 (s, 3H), 3.45–3.59 (m, 1.5H), 3.76–3.95 (m, 1.5H), 4.08–4.14 (m, 1H), 4.77–4.80 (m, 1H), 5.30 (s, 0.5H), 5.33 (s, 0.5H), 5.46 (s, 0.5H), 5.47 (s, 0.5H), 6.97 (d, 2H, J = 9.0 Hz), 7.04 (dd, 0.5H, J = 3.0, 8.0 Hz), 7.09 (d, 0.5H, J = 8.0 Hz), 7.14 (d, 1H, J = 3.0 Hz), 7.31 (d, 0.5H, J = 8.0 Hz), 7.39 (br s, 0.5H), 8.17 (d, 2H, J = 9.0 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ ppm: 27.4, 30.3, 32.0, 36.7, 36.9, 40.1, 51.9, 54.5, 65.6, 68.8, 115.8, 119.4, 120.1, 122.4, 122.5, 124.0, 124.6, 126.6, 126.7, 134.4, 142.9, 144.7,

145.4, 146.0, 146.6, 154.1, 156.0, 164.6; IR (KBr) cm^{-1}: 3426, 2932, 2454, 1724, 1591, 1511, 1387, 1341, 1261, 1200, 1169, 1110, 850, 753; HRMS calcd for $C_{23}H_{28}N_3O_5$ $(M+H)^+$ 426.2029, found 426.2029.

7-Dimethylcarbamoyloxy-1-[2-(4-nitrophenoxy)ethyl]-5-trifluoromethanesulfonyloxy-1,3-dihydrobenzo[*c*]azepine-2-carboxylic acid *tert*-butyl ester (25). To a solution of compound **23** (1.04 g, 2.02 mmol) in THF (10 mL) was added a solution of LHMDS in THF (2.43 mL, 1.0 M) at −78 °C and the mixture was stirred for 30 min at −78 °C. To the reaction mixture was added 2-[*N,N*-bis (trifluoromethylsulfonyl)amino]-5-chloropyridine (1.19 g, 3.03 mmol) at −78 °C. The resulting mixture was stirred for 1 h at −78 °C. After quenching with water (10 mL) at −78 °C, the product was extracted with AcOEt (20 mL×2) and washed with water (10 mL). Then it was dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 5:1 to 1:1) gave **25** (1.28 g, 98%) as a colorless oil. ^1H NMR (400 MHz, CD_3OD) δ ppm: 1.25 (s, 9H), 2.35 (br, 1H), 2.53 (br, 1H), 2.93 (s, 3H), 3.06 (s, 3H), 3.93–4.24 (br, 3H), 5.24–5.23 (br, 1H), 6.27 (br s, 1H), 6.99 (d, 2H, $J=8.8$ Hz), 7.05–7.12 (m, 1H), 7.27–7.30 (m, 2H), 8.13 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (125 MHz, CD_3OD) δ ppm: 28.4, 30.3, 36.7, 36.9, 42.8, 57.6, 58.3, 66.6, 82.3, 115.8, 121.5, 121.7, 123.8, 126.0, 126.8, 131.9, 132.4, 137.7, 138.2, 142.9, 144.9, 145.1, 152.5, 156.0, 156.3, 165.1; IR ($CHCl_3$) cm^{-1}: 2979, 1724, 1691, 1594, 1514, 1498, 1414, 1392, 1342, 1262, 1170, 1140, 1113, 991, 859; HRMS calcd for $C_{27}H_{30}N_3O_{10}F_3SNa$ $(M+Na)^+$ 668.1502, found 668.1498.

Dimethylcarbamic acid 2,5-dimethyl-1-[2-(4-nitrophenoxy)-ethyl]-2,3-dihydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (26a·HCl). To a solution of 25 (300 mg, 0.465 mmol) in DMF (5 mL) were added $Pd(PPh_3)_4$ (27 mg, 0.023 mmol), LiCl (59.3 mg, 1.40 mmol) and Me_4Sn (77 μL, 0.56 mmol). The reaction mixture was stirred for 4 h at 100 °C. After adding water (10 mL), the mixture was extracted with AcOEt (10 mL×2). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and evaporated in vacuo. Purification by silica gel column chromatography (hexane–AcOEt 5:1 to 1:1) gave a related compound (153 mg, 64%) as a colorless oil. ^1H NMR (500 MHz, CD_3OD) δ ppm: 1.44 (s, 9H), 2.13 (s, 3H), 2.17 (br, 1H), 2.42 (br, 1H), 2.97 (s, 3H), 3.08 (s, 3H), 3.36–3.52 (br, 1H), 3.78 (br, 1H), 3.92 (br, 1H), 4.27 (dd, 1H, $J=6.0$, 15.0 Hz), 5.17–5.25 (br, 1H), 5.93 (t, 1H, $J=6.0$ Hz), 6.88 (br s, 2H), 6.96 (d, 1H, $J=8.0$ Hz), 7.18 (s, 1H), 7.22 (d, 1H, $J=8.0$ Hz), 8.08 (br s, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ ppm: 22.7, 23.2, 34.1, 36.7, 36.9, 43.1, 59.8, 67.1, 67.4, 81.5, 115.6, 121.8, 122.0, 122.3, 125.1, 126.0, 126.6, 132.4, 132.7, 136.5, 139.5, 141.3, 142.5, 152.5, 155.5, 156.3, 165.1; IR ($CHCl_3$) cm^{-1}: 2979, 1716, 1676, 1593, 1512, 1391, 1342, 1263, 1168, 1298, 1020, 846; HRMS calcd for $C_{27}H_{33}N_3O_7Na$ $(M+Na)^+$ 534.2217, found 534.2213.

The above compound was deprotected by the method used for **6a**.

^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.15 (s, 3H), 2.18 (br, 1H), 2.27–2.33 (m, 1H), 2.38–2.45 (m, 1H), 3.01 (s, 3H), 3.04 (dd, 1H, $J=6.0$, 15.0 Hz), 3.11 (s, 3H), 3.27 (dd, 1H, $J=6.0$, 15.0 Hz), 3.96 (dd, 1H, $J=5.5$, 9.0 Hz), 4.15 (dt, 1H, $J=5.5$, 10.0 Hz), 4.22 (dt, 1H, $J=6.5$, 10.0 Hz), 5.98 (t, 1H, $J=6.0$ Hz), 6.93 (d, 2H, $J=9.0$ Hz), 7.03 (dd, 1H, $J=2.0$, 8.0 Hz), 7.13 (d, 1H, $J=2.0$ Hz), 7.27 (d, 1H, $J=8.0$ Hz), 8.16 (d, 2H, $J=9.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 22.8, 32.7, 36.3, 36.5, 44.5, 53.8, 66.6, 114.3, 119.9, 120.2, 125.7, 126.2, 127.2, 137.2, 137.6, 141.2, 142.1, 150.4, 154.7, 163.8; IR ($CHCl_3$) cm^{-1}: 2947, 1714, 1593, 1513, 1391, 1342, 1263, 1173, 1111, 1018, 909, 846.

Compound **26a** was prepared by the method used for **9a** from the above compound.

26a. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.11–2.18 (m, 1H), 2.14 (s, 3H), 2.29 (s, 1H), 2.31–2.37 (m, 1H), 2.88 (d, 2H, $J=6.0$ Hz), 3.02 (s, 3H), 3.11 (s, 3H), 3.83 (t, 1H, $J=7.5$ Hz), 3.98 (dt, 1H, $J=5.5$, 9.0 Hz), 4.08–4.13 (m, 1H), 5.95 (t, 1H, $J=6.0$ Hz), 6.90 (d, 2H, $J=9.0$ Hz), 7.01 (dd, 1H, $J=2.0$, 8.0 Hz), 7.15 (d, 1H, $J=2.0$ Hz), 7.17 (d, 1H, $J=8.0$ Hz), 8.16 (d, 2H, $J=9.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 22.4, 32.2, 36.3, 36.6, 42.1, 52.8, 63.1, 66.5, 114.4, 120.2, 125.7, 129.8, 134.7, 138.3, 141.1, 141.2, 150.6, 154.7, 163.9; IR ($CHCl_3$) cm^{-1}: 2942, 1714, 1593, 1512, 1498, 1390, 1342, 1264, 1172, 1112, 1024, 909, 846; HRMS calcd for $C_{23}H_{27}N_3O_5Na$ $(M+Na)^+$ 448.1848, found 448.1861.

26a·HCl. ^1H NMR (500 MHz, CD_3OD) δ ppm: 2.22 (s, 3H), 2.60–2.85 (br, 2H), 2.75 (s, 3H), 2.99 (s, 3H), 3.02 (br s, 1H), 3.11 (s, 3H), 3.62 (br, 0.5H), 3.81 (br, 0.5H), 3.83 (br, 0.5H), 4.04 (br, 0.5H), 4.11 (br, 0.5H), 4.27 (br, 0.5H), 4.57 (br, 0.5H), 4.69 (br, 0.5H), 6.11 (br s, 1H), 6.90 (br, 1H), 6.96 (br, 1H), 7.15 (br, 0.5H), 7.30 (br, 0.5H), 7.35 (s, 1H), 7.55 (br, 0.5H), 7.78 (br, 0.5H), 8.08 (br s, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ ppm: 21.7, 28.0, 35.5, 36.7, 36.9, 43.5, 52.5, 53.4, 59.1, 66.5, 115.8, 120.1, 121.8, 122.6, 123.3, 126.7, 129.9, 130.8, 134.0, 142.8, 145.0, 148.0, 154.2, 156.0, 164.7; IR ($CHCl_3$) cm^{-1}: 2967, 2336, 1725, 1594, 1514, 1498, 1391, 1260, 1171, 1112, 846; HRMS calcd for $C_{23}H_{28}N_3O_5$ $(M+H)^+$ 426.2029, found 426.2009.

Dimethylcarbamic acid 2-methyl-1-[2-(4-nitrophenoxy)-ethyl]-5-vinyl-2,3-dihydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (26b·HCl). To a solution of 25 (100 mg, 0.155 mmol) in NMP (5 mL) were added $Pd_2(dba)_3{\cdot}CHCl_3$ (3.9 mg, 0.0038 mmol), Ph_3As (4.7 mg, 0.015 mmol), LiCl (20.0 mg, 0.464 mmol) and $(CH_2{=}CH)(n\text{-}Bu)_3Sn$ (54 μL, 0.19 mmol). The reaction mixture was stirred for 2 h at room temperature. After adding saturated aq KF (10 mL), the mixture was extracted with AcOEt (10 mL×2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated. Purification by preparative TLC (hexane–AcOEt 2:1) gave a related compound (53 mg, 65%) as a colorless oil. ^1H NMR (500 MHz, CD_3OD) δ ppm: 1.47 (s, 9H), 2.15 (br, 1H), 2.35 (br, 1H), 2.98 (s, 3H), 3.10 (s, 3H), 3.20 (dd, 1H, $J=7.5$, 13.5 Hz), 3.72–3.80 (br, 1H), 3.92 (br, 1H), 4.45

(br, 1H), 5.22 (br, 1H), 5.26 (d, 1H, $J=10.5$ Hz), 5.35 (d, 1H, $J=17.5$ Hz), 6.16 (t, 1H, $J=8.0$ Hz), 6.63 (dd, 1H, $J=10.5$, 17.5 Hz), 6.89 (d, 2H, $J=8.5$ Hz), 7.03 (dd, 1H, $J=2.0$, 8.0 Hz), 7.16 (d, 1H, $J=2.0$ Hz), 7.30 (d, 1H, $J=8.0$ Hz), 8.11 (d, 2H, $J=8.5$ Hz); ^{13}C NMR (125 MHz, CD_3OD) δ ppm: 28.7, 34.7, 36.7, 36.9, 41.6, 42.3, 60.2, 67.3, 81.7, 115.6, 118.3, 122.7, 124.5, 126.7, 127.3, 133.3, 136.7, 138.1, 142.6, 145.3, 152.2, 155.4, 156.4, 165.2; IR ($CHCl_3$) cm^{-1}: 2979, 1718, 1678, 1593, 1513, 1391, 1342, 1262, 1168, 1112, 1025, 846; HRMS calcd for $C_{28}H_{33}N_3O_7Na$ $(M+Na)^+$ 546.2216, found 546.2203.

The above compound was deprotected by the method used for **6a**.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.29–2.36 (m, 1H), 2.41–2.48 (m, 1H), 2.93 (dd, 1H, $J=7.0$, 13.5 Hz), 3.01 (s, 3H), 3.10 (s, 3H), 3.26 (dd, 1H, $J=7.0$, 13.5 Hz), 3.92 (t, 1H, $J=7.0$ Hz), 4.14 (dt, 1H, $J=6.0$, 10.0 Hz), 4.21 (dt, 1H, $J=7.0$, 8.5 Hz), 5.23 (d, 1H, $J=11.0$ Hz), 5.36 (d, 1H, $J=17.5$ Hz), 6.18 (t, 1H, $J=7.0$ Hz), 6.57 (dd, 1H, $J=11.0$, 17.5 Hz), 6.93 (d, 2H, $J=9.0$ Hz), 7.11 (dd, 1H, $J=2.0$, 9.0 Hz), 7.16 (d, 1H, $J=2.0$ Hz), 7.36 (d, 1H, $J=9.0$ Hz), 8.16 (d, 2H, $J=9.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 32.9, 36.4, 36.6, 42.9, 52.9, 66.7, 114.4, 116.8, 121.0, 122.0, 125.8, 126.3, 128.2, 136.8, 137.1, 138.8, 141.3, 142.4, 150.2, 154.7, 163.8; IR ($CHCl_3$) cm^{-1}: 2939, 1717, 1593, 1513, 1390, 1342, 1263, 1390, 1112, 1019, 846.

Compound **26b** was prepared by the method used for **9a** from the above compound.

26b. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.11–2.20 (m, 1H), 2.30 (s, 3H), 2.32–2.39 (m, 1H), 2.73 (dd, 1H, $J=7.2$, 11.6 Hz), 2.82 (dd, 1H, $J=7.2$, 11.6 Hz), 3.02 (s, 3H), 3.10 (s, 3H), 3.79 (t, 1H, $J=7.2$ Hz), 3.95 (dt, 1H, $J=6.4$, 8.8 Hz), 4.12 (dt, 1H, $J=6.4$, 9.6 Hz), 5.24 (d, 1H, $J=10.8$ Hz), 5.36 (d, 1H, $J=17.6$ Hz), 6.16 (t, 1H, $J=7.6$ Hz), 6.57 (dd, 1H, $J=10.8$, 17.6 Hz), 6.90 (d, 2H, $J=8.8$ Hz), 7.08 (dd, 1H, $J=2.4$, 8.0 Hz), 7.20 (d, 1H, $J=2.4$ Hz), 7.23 (d, 1H, $J=8.0$ Hz), 8.16 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 32.6, 36.4, 36.6, 42.3, 52.3, 62.4, 66.6, 114.4, 117.1, 120.8, 122.4, 125.8, 127.2, 129.8, 134.5, 136.7, 137.7, 141.3, 143.5, 150.3, 154.6, 164.0; IR ($CHCl_3$) cm^{-1}: 2943, 1717, 1593, 1512, 1390, 1342, 1264, 1172, 1112, 1022, 909; HRMS calcd for $C_{24}H_{28}N_3O_5$ $(M+H)^+$ 438.2029, found 438.2027.

26b·HCl. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.55–2.70 (br, 4H), 2.91 (br s, 2H), 3.03 (s, 3H), 3.08–3.22 (m, 1H), 3.12 (s, 1H), 3.72–3.91 (m, 1H), 4.23 (br, 1H), 4.32 (br, 0.5H), 4.67 (br, 0.5H), 5.34–5.47 (m, 2H), 6.28–6.31 (m, 1H), 6.58–6.65 (m, 1H), 6.81 (d, 1H, $J=9.0$ Hz), 6.88 (d, 1H, $J=9.0$ Hz), 7.17–7.31 (m, 2H), 7.33 (d, 0.5H, $J=9.0$ Hz), 7.58 (d, 0.5H, $J=9.0$ Hz), 8.13 (d, 2H, $J=9.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 27.0, 34.3, 36.4, 36.7, 51.2, 52.0, 56.6, 65.1, 65.3, 114.3, 114.5, 120.0, 121.1, 122.5, 122.6, 123.2, 125.8, 128.2, 134.9, 139.4, 141.7, 147.0, 152.4, 152.6, 153.9, 162.9, 163.0; IR ($CHCl_3$) cm^{-1}: 2968, 2337, 1725, 1594, 1515, 1498, 1391, 1343, 1259, 1171, 1112, 908; HRMS calcd for $C_{24}H_{28}N_3O_5$ $(M+H)^+$ 438.2029, found 438.2027.

Dimethylcarbamic acid 2-methyl-1-[2-(4-nitrophenoxy)-ethyl]-5-thiophen-2-yl-2,3-dihydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (26c·HCl). To a solution of **25** (300 mg, 0.465 mmol) in 1,4-dioxane (5 mL) were added $Pd(PPh_3)_4$ (40 mg, 0.034 mmol), K_3PO_4 (218 mg, 1.03 mmol) and 2-thienylboronic acid (96 mg, 0.75 mmol). The reaction mixture was stirred for 6 h at 85 °C. After adding water (10 mL), the mixture was extracted with AcOEt (10 mL×2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated in vacuo. Purification by silica gel column chromatography (hexane–AcOEt 5:1–2:1) gave the corresponding compound (62 mg, 16%) as a colorless oil. ^{1}H NMR (500 MHz, CD3OD) δ ppm: 1.49 (s, 9H), 2.26 (br, 1H), 2.39 (br, 1H), 2.97 (s, 3H), 3.08 (s, 3H), 3.25 (br, 1H), 3.81 (br, 1H), 3.98 (br, 1H), 4.53 (br, 1H), 5.32 (br, 1H), 6.44 (t, 1H, $J=7.5$ Hz), 6.92 (d, 2H, $J=8.0$ Hz), 7.02 (s, 1H), 7.02–7.04 (m, 1H), 7.09 (dd, 1H, $J=2.0$, 8.0 Hz), 7.12 (d, 1H, $J=2.0$ Hz), 7.36 (d, 1H, $J=8.0$ Hz), 7.40 (d, 1H, $J=5.0$ Hz), 8.13 (d, 2H, $J=8.0$ Hz); ^{13}C NMR (125 MHz, CD_3OD) δ ppm: 28.7, 35.0, 36.7, 36.9, 41.6, 42.3, 60.4, 67.4, 81.7, 115.7, 123.3, 123.8, 124.8, 126.7, 126.9, 127.8, 128.7, 133.2, 136.9, 139.9, 141.0, 142.6, 144.4, 152.4, 155.3, 156.2, 165.1; IR ($CHCl_3$) cm^{-1}: 2979, 1719, 1676, 1593, 1512, 1392, 1342, 1263, 1166, 1112, 1024; HRMS calcd for $C_{30}H_{33}N_3O_7SNa$ $(M+Na)^+$ 602.1937, found 602.1924.

The above compound was deprotected by the method used for **6a**.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.35–2.41 (m, 1H), 2.46–2.52 (m, 1H), 2.57 (br, 1H), 2.96 (dd, 1H, $J=7.0$, 13.5 Hz), 2.99 (s, 3H), 3.07 (s, 3H), 3.31 (dd, 1H, $J=7.0$, 13.5 Hz), 4.06 (dd, 1H, $J=6.0$, 8.0 Hz), 4.15 (dt, 1H, $J=5.5$, 10.0 Hz), 4.23 (dt, 1H, $J=6.5$, 10.0 Hz), 6.50 (t, 1H, $J=7.0$ Hz), 6.91 (d, 2H, $J=9.0$ Hz), 6.95 (d, 1H, $J=5.0$ Hz), 7.16 (dd, 1H, $J=2.0$, 8.0 Hz), 7.18 (s, 1H), 7.24 (d, 1H, $J=5.0$ Hz), 7.41 (d, 1H, $J=8.0$ Hz), 8.15 (d, 2H, $J=9.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 33.0, 36.3, 36.6, 42.9, 53.1, 66.7, 114.4, 121.7, 122.4, 124.9, 125.7, 126.3, 126.4, 127.4, 137.1, 138.1, 140.4, 141.4, 143.8, 150.4, 154.6, 163.8; IR ($CHCl_3$) cm^{-1}: 2939, 1719, 1593, 1513, 1391, 1342, 1263, 1171, 1112, 909; HRMS calcd for $C_{25}H_{26}N_3O_5S$ $(M+H)^+$ 480.1594, found 480.1587.

Compound **26c** was prepared by the method used for **9a** from the above compound.

26c. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 2.17–2.24 (m, 1H), 2.34 (s, 3H), 2.35–2.42 (m, 1H), 2.75–2.84 (m, 2H), 2.99 (s, 3H), 3.07 (s, 3H), 3.87 (t, 1H, $J=8.0$ Hz), 3.97 (dt, 1H, $J=6.5$, 9.0 Hz), 4.14 (dt, 1H, $J=5.5$, 9.0 Hz), 6.46 (t, 1H, $J=7.0$ Hz), 6.88 (d, 2H, $J=8.5$ Hz), 6.96 (d, 1H, $J=5.0$ Hz), 7.01 (t, 1H, $J=5.0$ Hz), 7.13 (dd, 1H, $J=2.0$, 7.5 Hz), 7.20 (d, 1H, $J=2.0$ Hz), 7.24–7.28 (m, 2H), 8.15 (d, 2H, $J=8.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 32.8, 36.3, 36.6, 42.4, 52.3, 62.8, 66.6, 114.4, 121.4, 122.8, 124.1, 125.1, 125.7, 126.3,

127.5, 129.8, 134.9, 139.1, 139.3, 141.2, 143.7, 150.5, 154.5, 163.9; IR ($CHCl_3$) cm^{-1}: 2943, 1719, 1593, 1512, 1390, 1342, 1263, 1171, 1112, 1023, 909; HRMS calcd for $C_{26}H_{28}N_3O_5S$ $(M+H)^+$ 494.1750, found 494.1748.

26c·HCl. ^1H NMR (400 MHz, CD_3OD) δ ppm: 2.62–2.89 (m, 2H), 2.73 (s, 3H), 2.92 (s, 3H), 3.05 (s, 3H), 3.32 (br, 0.5H), 3.88 (br, 0.5H), 3.91–4.09 (m, 2H), 4.29–4.32 (m, 1H), 4.66–4.78 (m, 1H), 6.46–6.52 (m, 1H), 6.85–6.88 (m, 2H), 6.94 (d, 0.5H, $J=2.8$ Hz), 6.98 (dd, 0.5H, $J=3.6$, 5.2 Hz), 7.03 (dd, 0.5H, $J=3.6$, 5.2 Hz), 7.08 (d, 0.5H, $J=2.8$ Hz), 7.21–7.24 (m, 1H), 7.38 (dd, 1H, $J=2.0$, 8.8 Hz), 7.45 (d, 0.5H, $J=5.2$ Hz), 7.47 (d, 0.5H, $J=5.2$ Hz), 7.61 (br, 0.5H), 7.85 (d, 0.5H, $J=8.8$ Hz), 8.02–8.06 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ ppm: 28.0, 35.4, 36.7, 36.9, 52.6, 53.5, 58.9, 60.0, 66.4, 66.8, 115.6, 117.7, 124.1, 124.4, 126.5, 128.6, 128.8, 128.9, 129.5, 130.5, 142.0, 142.8, 144.3, 145.0, 153.8, 155.7, 164.3, 164.4; IR ($CHCl_3$) cm^{-1}: 2968, 2317, 1726, 1594, 1514, 1391, 1343, 1259, 1169; HRMS calcd for $C_{26}H_{28}N_3O_5S$ $(M+H)^+$ 494.1750, found 494.1737.

Dimethylcarbamic acid 5-(4-chlorophenyl)-2-methyl-1-[2-(4-nitrophenoxy)ethyl]-2,3-dihydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt (26d·HCl). The Suzuki coupling was performed by the method used for **26c**.

Coupling product. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.49 (s, 9H), 2.22 (br, 1H), 2.38–2.46 (m, 1H), 2.96 (s, 3H), 3.03 (s, 3H), 3.32 (dd, 1H, $J=6.0$, 13.2 Hz), 3.78 (br, 1H), 3.93 (br, 1H), 4.47–4.60 (br, 1H), 5.21–5.31 (br, 1H), 6.32 (t, 1H, $J=7.2$ Hz), 6.79 (br s, 2H), 6.82 (d, 1H, $J=2.0$ Hz), 7.05 (dd, 1H, $J=2.0$, 8.4 Hz), 7.23 (d, 2H, $J=8.4$ Hz), 7.24 (br, 1H), 7.33 (d, 2H, $J=8.4$ Hz), 8.15 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 28.5, 34.1, 36.4, 36.6, 41.0, 58.8, 66.1, 80.1, 114.2, 121.8, 123.7, 124.4, 125.6, 128.5, 129.1, 131,6, 133.8, 135.8, 138.6, 138.9, 141.1, 144.4, 145.1, 150.7, 153.5, 154.1, 163.4; IR ($CHCl_3$) cm^{-1}: 2979, 1721, 1677, 1593, 1513, 1392, 1342, 1262, 1168, 1111, 1015, 845.

The above compound was deprotected by the method used for **6a**.

^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.33–2.40 (m, 1H), 2.45–2.51 (m, 1H), 2.96 (s, 3H), 3.04 (s, 3H), 3.07 (dd, 1H, $J=6.5$, 13.0 Hz), 3.38 (dd, 1H, $J=6.5$, 13.0 Hz), 4.05 (dt, 1H, $J=6.0$, 8.0 Hz), 4.18 (dt, 1H, $J=6.0$, 10.0 Hz), 4.26 (dt, 1H, $J=6.0$, 10.0 Hz), 6.38 (t, 1H, $J=7.0$ Hz), 6.79 (d, 1H, $J=2.0$ Hz), 6.93 (d, 2H, $J=9.0$ Hz), 7.13 (dd, 1H, $J=2.0$, 8.0 Hz), 7.24 (d, 2H, $J=9.0$ Hz), 7.32 (d, 2H, $J=9.0$ Hz), 7.39 (d, 1H, $J=8.0$ Hz), 8.17 (d, 2H, $J=9.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 32.9, 36.2, 36.5, 43.7, 53.4, 66.6, 114.3, 121.4, 122.4, 125.6, 126.3, 127.5, 128.4, 129.3, 133.4, 138.1, 139.4, 140.6, 141.2, 143.2, 150.2, 154.4, 163.7; IR ($CHCl_3$) cm^{-1}: 2939, 1719, 1593, 1513, 1391, 1343, 1263, 1171, 1112, 1015, 909, 846; HRMS calcd for $C_{27}H_{27}N_3O_5Cl$ $(M+H)^+$ 508.1639, found 508.1631.

Compound **26d** was prepared by the method used for **9a** from the above compound.

26d. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 2.14–2.19 (m, 1H), 2.34 (m, 1H), 2.35 (s, 3H), 2.87 (d, 2H, $J=7.0$ Hz), 2.97 (s, 3H), 3.03 (s, 3H), 3.87 (t, 1H, $J=8.0$ Hz), 4.01 (dt, 1H, $J=6.0$, 10.0 Hz), 4.18 (dt, 1H, $J=7.0$, 10.0 Hz), 6.35 (t, 1H, $J=6.5$ Hz), 6.81 (d, 1H, $J=3.0$ Hz), 6.91 (d, 2H, $J=8.5$ Hz), 7.10 (dd, 1H, $J=3.0$, 8.0 Hz), 7.22 (d, 2H, $J=8.5$ Hz), 7.27 (d, 1H, $J=8.0$ Hz), 7.32 (d, 2H, $J=8.5$ Hz), 8.17 (d, 2H, $J=8.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 32.9, 36.3, 36.6, 42.7, 52.7, 63.2, 66.5, 114.4, 121.3, 122.9, 125.7, 126.3, 128.6, 129.4, 130.0, 133.7, 135.8, 139.2, 139.6, 141.3, 144.5, 150.5, 154.5, 163.9; IR ($CHCl_3$) cm^{-1}: 2943, 1720, 1593, 1512, 1391, 1342, 1263, 1171, 1112, 1015, 909; HRMS calcd for $C_{28}H_{29}N_3O_5Cl$ $(M+H)^+$ 522.1796, found 522.1784.

26d·HCl. ^1H NMR (500 MHz, CD_3OD) δ ppm: 2.68–2.88 (m, 2H), 2.83 (s, 3H), 2.94 (s, 3H), 3.06 (s, 3H), 3.40 (br, 0.5H), 3.86 (br, 0.5H), 4.02–4.06 (m, 1H), 4.16–4.21 (m, 1H), 4.36–4.39 (m, 1H), 4.69–4.83 (br, 1H), 6.53–6.60 (m, 1H), 6.94–6.97 (m, 4H), 7.25 (d, 1H, $J=8.5$ Hz), 7.33 (d, 1H, $J=8.5$ Hz), 7.39–7.42 (m, 2H), 7.68 (br, 0.5H), 7.93 (d, 0.5H, $J=7.5$ Hz), 8.09–8.11 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ ppm: 27.9, 35.5, 36.7, 36.9, 52.6, 53.5, 59.2, 66.5, 66.9, 115.8, 120.7, 124.2, 124.5, 126.7, 126.8, 129.9, 130.1, 130.9, 136.3, 136.4, 138.3, 143.0, 143.3, 150.3, 150.8, 154.0, 154.1, 164.6, 164.7; IR ($CHCl_3$) cm^{-1}: 2968, 2307, 1726, 1594, 1515, 1497, 1391, 1343, 1259, 1168, 1112; HRMS calcd for $C_{28}H_{29}N_3O_5Cl$ $(M+H)^+$ 522.1796, found 522.1801.

3-(4-Benzyloxy-2-methoxymethoxyphenyl)acrylic acid ethyl ester (28). To a solution of **27** (44.9 g, 197 mmol) in CH_2Cl_2 (200 mL) were added $(i\text{-}Pr)_2NH$ (52.0 mL, 300 mmol) and methoxymethyl chloride (20.5 mL, 270 mmol) at 0 °C. The reaction mixture was stirred for 18 h at room temperature. After adding water (200 mL), the aqueous layer was extracted with CH_2Cl_2 (300 mL). The combined organic extracts were washed with brine (300 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel column chromatography (hexane–AcOEt 5:1–1:1) to give an aldehyde (42.2 g, 79%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 3.51 (s, 3H), 5.11 (s, 2H), 5.26 (s, 2H), 6.68 (dd, 1H, $J=2.0$, 9.0 Hz), 6.80 (d, 1H, $J=9.0$ Hz), 7.34–7.43 (m, 5H), 7.81 (d, 1H, $J=9.0$ Hz), 9.72 (s, 1H), 11.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 56.4, 70.3, 94.6, 101.5, 108.4, 119.6, 127.6, 128.3, 128.7, 130.3, 135.8, 161.4, 165.0, 188.2; IR (film) cm^{-1}: 1679, 1600, 1499, 1393, 1258, 1155, 1112, 1078, 992, 924, 816, 736, 697; HRMS calcd for $C_{16}H_{16}O_4Na$ $(M+Na)^+$ 295.0946, found 295.0931.

To a suspension of 55% NaH (1.57 g, 36.0 mmol) in THF (100 mL) was added $(EtO)_2POCH_2CO_2Et$ (7.17 g, 32.0 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. To the reaction mixture was added the above aldehyde (7.46 g, 27.4 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and quenched with water (200 mL). The mixture was extracted with AcOEt (200 mL×2). The combined extracts were washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered and evaporated. Purification by silica gel column chromatography (hexane–AcOEt 5:1–1:1)

gave **28** (9.32g, 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.32 (t, 3H, J = 7.2 Hz), 3.47 (s, 3H), 4.24 (q, 2H, J = 7.2 Hz), 5.05 (s, 2H), 5.21 (s, 2H), 6.39 (d, 1H, J = 16.0 Hz), 6.62 (dd, 1H, J = 2.0, 8.8 Hz), 6.81 (d, 1H, J = 2.0 Hz), 7.30–7.43 (m, 5H), 7.45 (d, 1H, J = 8.8 Hz), 7.95 (d, 1H, J = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.4, 56.2, 60.2, 70.1, 94.6, 102.1, 108.1, 116.3, 117.3, 127.5, 128.1, 128.6, 129.6, 136.3, 139.6, 157.4, 161.6, 167.8; IR (film) cm^{-1}: 1706, 1605, 1503, 1261, 1162, 1077, 994, 736, 697; HRMS calcd for $C_{20}H_{22}O_5Na$ $(M+Na)^+$ 365.1365, found 365.1354.

3-*tert*-Butoxycarbonylamino-3-(4-hydroxy-2-methoxymethoxyphenyl)propionic acid ethyl ester [(*R*)-30]. To a solution of (*S*)-*N*-benzyl-1-phenylethyl amine [(*S*)-**29**] (4.24 g, 20.1 mmol) in THF (40 mL) was added *n*-butyl lithium in hexane (12.4 mL, 1.6 M) at −78 °C. The solution was stirred for 30 min at −78 °C. To the solution was added a solution of **28** (4.32 g, 12.6 mmol) in THF (20 mL) at −78 °C. After stirring for 30 min at this temperature, the reaction mixture was quenched with saturated aq NH_4Cl (40 mL) at −78 °C, and then extracted with AcOEt (50 mL×2). The organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel flash column chromatography (hexane–AcOEt 10:1–5:1) to give a benzyl amine (7.21 g) as a yellow oil. This compound was used in the following reaction without further purification. Purified compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 0.98 (t, 3H, J = 7.0 Hz), 1.23 (d, 3H, J = 7.0 Hz), 2.60 (dd, 1H, J = 9.0, 13.5 Hz), 2.73 (dd, 1H, J = 7.0, 15.0 Hz), 3.47 (s, 3H), 3.73 (dd, 2H, J = 14.5, 22.5 Hz), 3.79–3.92 (m, 2H), 4.08 (q, 1H, J = 7.0 Hz), 4.80 (dd, 1H, J = 6.0, 8.0 Hz), 5.03 (s, 2H), 5.15 (dd, 2H, J = 7.0, 17.0 Hz), 6.61 (dd, 1H, J = 2.5, 8.5 Hz), 6.83 (d, 1H, J = 2.5 Hz), 7.13–7.44 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 13.9, 14.5, 24.4, 39.0, 50.6, 51.6, 53.5, 56.1, 56.3, 57.5, 59.9, 70.0, 94.7, 102.3, 107.0, 123.0, 126.3, 126.5, 126.7, 127.6, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 129.4, 136.9, 142.0, 144.5, 156.6, 158.9, 171.7; IR ($CHCl_3$) cm^{-1}: 2981, 1728, 1608, 1503, 1494, 1454, 1375, 1254, 1155, 1114, 1074, 1010; HRMS calcd for $C_{36}H_{40}O_5Na$ $(M+Na)^+$ 576.2726, found 576.2710; $[\alpha]_D^{23} = -16.3°$ (*c* 1.04, $CHCl_3$).

To a solution of the above benzyl amine (7.21 g) in MeOH–H_2O–AcOH (20:2:1, 92 mL) was added 20% $Pd(OH)_2$/C (1.8 g). The reaction mixture was stirred for 4 h under a hydrogen atmosphere at room temperature. $Pd(OH)_2$/C was removed by filtration and the filtrate was evaporated in vacuo to give an amine AcOH salt (2.77 g, 67% for two steps) as a colorless solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 1.20 (t, 3H, J = 7.6 Hz), 1.90 (s, 3H), 2.93 (dd, 1H, J = 6.0, 16.4 Hz), 2.98 (dd, 1H, J = 8.8, 16.4 Hz), 3.49 (s, 3H), 4.13 (q, 2H, J = 7.6 Hz), 4.71 (t, 1H, J = 7.4 Hz), 5.24 (s, 2H), 6.45 (dd, 1H, J = 2.4, 8.8 Hz), 6.69 (d, 1H, J = 2.8 Hz), 7.12 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ ppm: 14.4, 23.5, 39.0, 49.2, 56.6, 62.1, 95.6, 103.3, 109.7, 117.3, 127.5, 130.1, 157.4, 160.7, 171.9; IR (film) cm^{-1}: 2982, 1731, 1615, 1596, 1554, 1512, 1472, 1404, 1300, 1216, 1156, 1076, 1002, 950, 756, 655; HRMS calcd for $C_{13}H_{20}NO_5$ $(M-OAc)^+$ 270.1342, found 270.1339; $[\alpha]_D^{23} = -8.0°$ (*c* 0.82, MeOH).

To a solution of the amine AcOH salt (4.26 g, 12.9 mmol) and Et_3N (3.26 mL, 26.0 mmol) in MeOH (20 mL) was added Boc_2O (3.27 g, 15.0 mol) dropwise at room temperature. The reaction mixture was stirred for 30 min at room temperature and concentrated in vacuo. Purification by silica gel column chromatography (hexane–AcOEt 2:1–1:2) provided (*R*)-**30** (4.64 g, 97%) as a colorless solid. Mp 82–86 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.16 (t, 3H, J = 7.0 Hz), 1.43 (s, 9H), 2.79 (dd, 1H, J = 7.0, 14.5 Hz), 2.86 (dd, 1H, J = 6.0, 14.5 Hz), 3.45 (s, 3H), 4.05 (q, 2H, J = 7.0 Hz), 4.85–5.20 (m, 3H), 5.43 (br s, 0.2H), 5.81 (d, 0.8H, J = 8.0 Hz), 6.28 (d, 1H, J = 8.0 Hz), 6.50 (br s, 1H), 6.57 (br s, 1H), 6.98 (d, 1H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 14.7, 29.0, 40.7, 49.1, 56.8, 61.3, 80.4, 94.7, 102.8, 108.8, 121.3, 129.4, 155.8, 157.5, 172.2; IR (KBr) cm^{-1}: 3355, 2982, 1699, 1687, 1616, 1510, 1368, 1272, 1172, 1019, 953, 839; HRMS calcd for $C_{18}H_{27}NO_7Na$ $(M+Na)^+$ 392.1686, found 392.1692. Anal. calcd for $C_{18}H_{27}NO_7$: C, 58.52; H, 7.37; N, 3.79. Found: C, 58.71; H, 7.38; N, 3.83; $[\alpha]_D^{23} = +42.6°$ (*c* 0.86, $CHCl_3$).

[1-(4-Dimethylcarbamoyloxy-2-methoxymethoxyphenyl)-3-hydroxy-propyl]carbamic acid *tert*-butyl ester [(*R*)-31]. To a solution of phenol (*R*)-**30** (2.35 g, 6.36 mmol) and K_2CO_3 (1.80 g, 13.0 mmol) in DMF (10 mL) was added Me_2NCOCl (0.65 mL, 7.0 mmol). The reaction mixture was stirred for 3 h at room temperature. After dilution with water (30 mL), the mixture was extracted with AcOEt (40 mL×2), and the combined organic layers were washed with brine (40 mL) and dried over Na_2SO_4. The residue was purified by silica gel column chromatography (hexane–AcOEt 2:1–1:2) to give a carbamate (2.73 g, 97%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.17 (t, 3H, J = 7.0 Hz), 1.41 (s, 9H), 2.77–2.89 (m, 2H), 2.99 (s, 3H), 3.07 (s, 3H), 3.49 (s, 3H), 4.01–4.10 (m, 2H), 5.24 (dd, 2H, J = 7.0, 10.0 Hz), 5.30 (br s, 1H), 5.74 (br d, 1H, J = 9.0 Hz), 6.73 (dd, 1H, J = 2.0, 9.0 Hz), 6.89 (d, 1H, J = 2.0 Hz), 7.23 (d, 1H, J = 9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.1, 28.4, 36.4, 36.7, 39.8, 48.2, 56.3, 60.5, 79.4, 94.3, 108.2, 114.7, 126.2, 128.4, 151.6, 154.6, 154.7, 154.8, 171.1; IR ($CHCl_3$) cm^{-1}: 1714, 1496, 1391, 1254, 1167, 1001; HRMS calcd for $C_{21}H_{32}N_2O_8Na$ $(M+Na)^+$ 463.2056, found 463.2051; $[\alpha]_D^{23} = +25.3°$ (*c* 1.09, $CHCl_3$).

To a solution of the carbamate (4.68 g, 10.6 mmol) in THF (30 mL) was added $LiAlH_4$ (524 mg, 13.8 mmol) at −50 °C. The reaction mixture was stirred for 10 min at −50 °C and for 15 min at 0 °C. To the reaction mixture were successively added water (0.5 mL), 15% aq NaOH (0.5 mL), water (1.5 mL) and $MgSO_4$. After filtration, the organic solvent was concentrated in vacuo. Purification by silica gel column chromatography (hexane–AcOEt 2:1 to AcOEt) gave compound (*R*)-**31** (3.48 g, 82%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.43 (s, 9H), 1.94 (dt, 2H, J = 4.8, 6.0 Hz), 3.00 (s, 3H), 3.08 (s, 3H), 3.30 (br s, 1H), 3.49 (s, 3H), 3.61–

3.74 (m, 2H), 5.06 (q, 1H, $J=5.6$ Hz), 5.23 (dd, 2H, $J=6.4$, 10.8 Hz), 5.47 (d, 1H, $J=9.6$ Hz), 6.74 (dd, 1H, $J=2.4$, 8.8 Hz), 6.90 (d, 1H, $J=2.4$ Hz), 7.19 (d, 1H, $J=8.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 29.0, 37.1, 37.4, 39.0, 49.4, 57.1, 59.7, 80.5, 95.1, 105.4, 109.3, 115.8, 127.8, 128.8, 129.1, 152.2, 155.3, 155.7, 157.3; IR ($CHCl_3$) cm^{-1}: 3451, 1715, 1497, 1392, 1253, 1166, 1050, 1000, 941, 875; HRMS calcd for $C_{19}H_{30}N_2O_7Na$ $(M+Na)^+$ 421.1950, found 421.1950; $[\alpha]_D^{23}=+48.0°$ (c 1.09, $CHCl_3$).

[1-(4-Dimethylcarbamoyloxy-2-hydroxyphenyl)-3-(4-nitrophenoxy)propyl]carbamic acid *tert*-butyl ester [(*R*)-32]. To a solution of alcohol (*R*)-**31** (3.00 g, 7.53 mmol), 4-nitrophenol (1.15 g, 8.28 mmol) and Ph_3P (2.96 g, 11.3 mmol) in THF (20 mL) was added a 40% diethyl azodicarboxylic acid toluene solution (4.92 g, 11.3 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 2:1–1:2) to give a 4-nitrophenoxy ether derivative (6.49 g). This compound was used in the following reaction without further purification.

To a solution of the 4-nitrophenoxy ether derivative (6.49 g) in MeOH (21 mL) was added concentrated HCl (8 mL) at room temperature. The reaction mixture was stirred for 18 h at room temperature. Then, the reaction mixture was quenched with 15% aq NaOH and adjusted to pH 10 by the addition of saturated aq $NaHCO_3$. The resulting mixture was extracted with AcOEt (50 mL×2). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel column chromatography (AcOEt to AcOEt–MeOH 5:1) to give an amine (1.91 g, 68%) as a colorless solid. Mp 146–147 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.26 (q, 2H, $J=6.8$ Hz), 2.99 (s, 3H), 3.07 (s, 3H), 3.96 (dt, 1H, $J=6.8$, 9.6 Hz), 4.09 (dt, 1H, $J=5.2$, 9.6 Hz), 4.44 (t, 1H, $J=6.8$ Hz), 6.51 (dd, 1H, $J=2.0$, 8.0 Hz), 6.61 (d, 1H, $J=2.0$ Hz), 6.83 (d, 1H, $J=8.0$ Hz), 6.91 (d, 2H, $J=9.4$ Hz), 8.20 (d, 2H, $J=9.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 36.7, 37.6, 37.8, 67.1, 112.2, 113.4, 115.4, 123.4, 126.9, 129.3, 142.6, 153.0, 155.6, 159.4, 164.3; IR (KBr) cm^{-1}: 2938, 1711, 1592, 1510, 1387, 1340, 1263, 1177, 1110, 1011, 848, 753, 659; HRMS calcd for $C_{18}H_{22}N_3O_6$ $(M+H)^+$ 376.1509, found 376.1512. Anal. calcd for $C_{18}H_{21}N_3O_6$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.63; H, 5.65; N, 11.13; $[\alpha]_D^{23}=-110.0°$ (c 0.61, $CHCl_3$).

To a solution of the amine (1.19 g, 5.10 mmol) and Et_3N (1.53 mL, 11.0 mmol) in MeOH (10 mL) was added Boc_2O (1.22 g, 5.60 mmol) dropwise at room temperature. The reaction mixture was stirred for 1 h at room temperature and concentrated in vacuo. Purification by silica gel column chromatography (hexane–AcOEt 2:1–AcOEt) provided (*R*)-**32** (2.07 g, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.41 (s, 9H), 2.26–2.38 (m, 2H), 3.02 (s, 3H), 3.08 (s, 3H), 3.96–4.02 (m, 1H), 4.05–4.11 (m, 1H), 4.97 (br s, 1H), 5.29 (br s, 1H), 6.59 (d, 1H, $J=8.0$ Hz), 6.64 (d, 1H, $J=2.0$ Hz), 6.90 (d, 2H, $J=9.6$ Hz), 7.08 (d, 1H, $J=8.0$ Hz), 8.17 (d, 2H, $J=9.6$ Hz), 8.33 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 29.0, 34.3, 37.1, 37.4, 49.0, 66.8, 81.0, 111.5, 113.6, 115.1, 125.1, 126.5, 128.6, 142.1, 152.1, 155.8, 156.1, 157.0, 164.5; IR ($CHCl_3$) cm^{-1}: 3209, 1712, 1593, 1498, 1392, 1342, 1263, 1171, 1112, 1050, 1023, 966, 846; HRMS calcd for $C_{23}H_{29}N_3O_8Na$ $(M+Na)^+$ 498.1852, found 498.1854; $[\alpha]_D^{23}=-2.7°$ (c 1.91, $CHCl_3$).

Allyl[1-(4-dimethylcarbamoyloxy-2-vinylphenyl)-3-(4-nitrophenoxy)propyl]carbamic acid *tert*-butyl ester [(*R*)-33]. To a solution of phenol (*R*)-**32** (1.69 g, 3.55 mmol) and pyridine (1.15 mL, 14.2 mmol) in CH_2Cl_2 (10 mL) was added Tf_2O (0.72 mL, 4.2 mmol) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C, quenched with water (20 mL) and extracted with CH_2Cl_2 (20 mL×2). The extracts were washed with 0.5 N HCl (20 mL) and brine (20 mL), and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to give a triflate (1.89 g). To a solution of the triflate (1.89 g) in dioxane (20 mL) were added $Pd(PPh_3)_4$ (410 mg, 0.355 mmol), LiCl (451 mg, 10.6 mmol), 2,6-di-*t*-butylphenol (5 mg) and $(CH_2{=}CH)(n\text{-}Bu)_3Sn$ (1.14 mL, 3.90 mmol). The reaction mixture was stirred for 2 h at 100 °C. After cooling to room temperature, saturated aq KF (10 mL) was added to the reaction mixture. The resulting solution was concentrated in vacuo and diluted with water (40 mL). The aqueous layer was extracted with AcOEt (50 mL×2). The combined organic layers were washed with 1N HCl (40 mL) and brine (40 mL), and dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel column chromatography (hexane–AcOEt 5:1–1:1) to give a styrene derivative (1.47 g, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.40 (s, 9H), 2.24 (br m, 2H), 3.02 (s, 3H), 3.10 (s, 3H), 3.97 (dt, 1H, $J=5.8$, 9.6 Hz), 4.06 (dt, 1H, $J=6.2$, 9.6 Hz), 5.02 (br s, 1H), 5.23 (br s, 1H), 5.29 (d, 1H, $J=11.2$ Hz), 5.56 (dd, 1H, $J=1.2$, 17.2 Hz), 6.90 (d, 2H, $J=9.6$ Hz), 7.05 (dd, 1H, $J=2.0$, 8.0 Hz), 7.07 (br s, 1H), 7.20 (d, 1H, $J=2.0$ Hz), 7.26 (d, 1H, $J=8.0$ Hz), 8.18 (d, 2H, $J=9.6$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 28.3, 35.5, 36.4, 36.6, 47.6, 65.6, 79.4, 114.2, 117.3, 119.4, 121.3, 125.5, 126.0, 133.0, 135.8, 137.4, 141.1, 150.4, 154.5, 154.8, 163.3; IR ($CHCl_3$) cm^{-1}: 1593, 1497, 1391, 1342, 1263, 1172, 1112, 846; HRMS calcd for $C_{25}H_{31}N_3O_7Na$ $(M+Na)^+$ 508.2060, found 508.2066; $[\alpha]_D^{23}=-20.4°$ (c 0.78, $CHCl_3$).

To a suspension of 55% NaH (216 mg, 9.00 mmol) in DMF (10 mL) was added a solution of the styrene derivative (1.47 g, 3.03 mmol) in DMF (5 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. To the reaction mixture was added allyl bromide (0.78 mL, 9.00 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and an additional 2 h at room temperature. After addition of water (30 mL), the aqueous layer was extracted with AcOEt (30 mL×2). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated in vacuo. Purification by silica gel column chromatography (hexane–AcOEt 2:1–1:1) gave (*R*)-**33** (1.37 g, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.34 (s, 9H),

2.28–2.38 (br m, 1H), 2.40–2.50 (br m, 1H), 2.95 (s, 3H), 3.04 (s, 3H), 3.42 (br s, 2H), 3.97 (dt, 1H, $J=6.2$, 8.8 Hz), 4.06 (m, 1H), 4.82 (m, 2H), 5.23 (d, 1H, $J=11.2$ Hz), 5.41 (br s, 1H), 5.53 (d, 1H, $J=17.6$ Hz), 5.65 (br s, 1H), 6.86 (d, 2H, $J=9.6$ Hz), 6.94 (dd, 1H, $J=10.0$, 17.6 Hz), 7.01 (d, 1H, $J=8.4$ Hz), 7.19 (s, 1H), 7.27 (d, 1H, $J=8.4$ Hz), 8.11 (d, 2H, $J=9.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.5, 32.6, 37.6, 37.8, 46.6, 52.3, 67.2, 81.0, 115.4, 117.0, 118.0, 120.7, 121.7, 126.8, 128.5, 134.0, 134.7, 135.8, 140.9, 142.3, 152.2, 155.5, 156.2, 164.7; IR ($CHCl_3$) cm^{-1}: 1716, 1678, 1593, 1513, 1392, 1342, 1264, 1172, 1111, 1025, 922, 846; HRMS calcd for $C_{28}H_{35}N_3O_7Na$ $(M+Na)^+$ 548.2373, found 548.2352; $[\alpha]_D^{23}=+92.0°$ (*c* 1.12, $CHCl_3$).

Dimethyl-carbamic acid 2-methyl-1-[2-(4-nitrophenoxy)-ethyl]-2,3-dihydro-1*H*-benzo[*c*]azepin-7-yl ester hydrochloride salt [(*R*)-18a·HCl]. To a solution of allyl amine (*R*)-**33** (1.27 g, 2.33 mmol) in CH_2Cl_2 (150 mL) was added Grubbs catalyst **15** (198 mg, 0.233 mmol). The reaction mixture was stirred for 3 h at 45 °C. The organic solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane–AcOEt 2:1–1:1) to give a closed-ring compound (1.11 g, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.30 (s, 6H), 1.38 (s, 3H), 2.25–2.55 (br m, 2H), 3.00 (s, 3H), 3.09 (s, 3H), 3.80–4.10 (br m, 3H), 4.74 (br d, 0.34H, $J=19.2$ Hz), 4.99 (br s, 0.66H), 5.19 (br s, 0.66H), 5.35 (br m, 0.34H), 5.80 (d, 0.34H, $J=12.4$ Hz), 5.86 (d, 0.66H, $J=12.4$ Hz), 6.37 (d, 1H, $J=12.4$ Hz), 6.87–6.94 (m, 3H), 6.98 (s, 1H), 7.06 (br s, 0.66H), 7.19 (d, 0.34H, $J=8.8$ Hz), 8.16–8.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 28.9, 29.0, 30.7, 37.1, 37.3, 44.8, 46.2, 56.8, 57.6, 66.0, 66.2, 80.9, 81.0, 115.1, 120.3, 120.7, 125.7, 125.8, 126.6, 129.2, 129.4, 130.1, 130.5, 131.1, 132.0, 135.5, 135.8, 138.0, 138.3, 142.3, 151.3, 155.3, 155.4, 156.0, 164.3; IR ($CHCl_3$) cm^{-1}: 1714, 1514, 1498, 1392, 1342, 1262, 1171, 1112, 1026, 846; HRMS calcd for $C_{26}H_{31}N_3O_7Na$ $(M+Na)^+$ 520.2060, found 528.2058; $[\alpha]_D^{23}=-40.9°$ (*c* 0.98, $CHCl_3$).

The closed-ring compound (955 mg, 1.92 mmol) was treated with 2 N HCl in AcOEt (10 mL). After stirring for 18 h at room temperature, the reaction mixture was concentrated under reduced pressure. To the residue was added saturated aq $NaHCO_3$. The aqueous solution 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 to give an amine (730 mg, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.23–2.35 (m, 2H), 3.01 (s, 3H), 3.09 (s, 3H), 3.67 (ddd, 1H, $J=2.0$, 3.6, 20.4 Hz), 3.77 (dt, 1H, $J=2.4$, 20.4 Hz), 4.14 (dt, 1H, $J=6.0$, 8.8 Hz), 4.19-4.27 (m, 2H), 5.95 (dt, 1H, $J=3.6$, 12.4 Hz), 6.40 (d, 1H, $J=12.4$ Hz), 6.88 (dd, 1H, $J=2.0$, 8.0 Hz), 6.95 (d, 2H, $J=9.2$ Hz), 7.00, (d, 1H, $J=2.0$ Hz), 7.08 (d, 1H, $J=8.0$ Hz), 8.19 (d, 2H, $J=9.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 32.3, 37.5, 37.8, 49.8, 58.1, 67.1, 115.4, 120.5, 125.8, 126.7, 128.0, 129.5, 136.8, 137.1, 142.1, 142.2, 151.2, 155.6, 164.8; IR ($CHCl_3$) cm^{-1}: 2939, 1714, 1593, 1512, 1498, 1391, 1343, 1264, 1172, 1112, 1020, 846; HRMS calcd for $C_{21}H_{24}N_3O_5$ $(M+H)^+$ 398.1716, found 398.1743; $[\alpha]_D^{23}=-92.2°$ (*c* 0.80, $CHCl_3$).

The above amine (672 mg, 1.69 mmol) was dissolved in a mixture of HCO_2H (5 mL) and 37% aq HCHO (5 mL) and stirred for 3 h at 80 °C. After cooling to room temperature, saturated aq $NaHCO_3$ (20 mL) was added and extracted with AcOEt (20 mL×2). The extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated in vacuo. Purification by silica gel column chromatography (AcOEt to AcOEt–MeOH 5:1) gave (*R*)-**18a** (543 mg, 78%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.05–2.13 (m, 1H), 2.23–2.33 (m, 1H), 2.28 (s, 3H), 3.01 (s, 3H), 3.09 (s, 3H), 3.46 (dd, 1H, $J=3.6$, 19.6 Hz), 3.87 (dt, 1H, $J=2.0$, 19.6 Hz), 3.97–4.02 (m, 1H), 4.06–4.12 (m, 2H), 5.81 (ddd, 1H, $J=2.8$, 4.4, 12.4 Hz), 6.37 (d, 1H, $J=12.4$ Hz), 6.89 (dd, 1H, $J=3.0$, 8.0 Hz), 6.92 (d, 2H, $J=8.8$ Hz), 7.00, (d, 1H, $J=3.0$ Hz), 7.04 (d, 1H, $J=8.0$ Hz), 8.19 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 31.3, 36.3, 36.6, 41.4, 53.2, 64.0, 65.6, 114.2, 119.6, 124.2, 125.5, 128.6, 129.5, 132.3, 135.9, 137.8, 141.0, 150.1, 154.4, 163.6; IR ($CHCl_3$) cm^{-1}: 2938, 1714, 1593, 1513, 1498, 1391, 1343, 1263, 1172, 1112, 1024, 846; HRMS calcd for $C_{22}H_{26}N_3O_5$ $(M+H)^+$ 412.1872, found 412.1902; $[\alpha]_D^{23}=-72.3°$ (*c* 1.25, $CHCl_3$).

(*R*)-18a·HCl. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.12–2.21 (m, 1H), 2.60 (s, 3H), 2.85–2.93 (m, 1H), 3.02 (s, 3H), 3.10 (s, 3H), 3.81 (dd, 1H, $J=4.4$, 19.6 Hz), 3.85–3.90 (m, 1H), 4.06 (dt, 1H, $J=5.2$, 9.6 Hz), 4.39 (d, 1H, $J=19.6$ Hz), 4.77 (d, 1H, $J=11.6$ Hz), 5.85 (ddd, 1H, $J=3.2$, 4.4, 12.4 Hz), 6.36 (d, 1H, $J=12.4$ Hz), 6.86 (d, 2H, $J=8.8$ Hz), 7.04 (dd, 1H, $J=2.4$, 8.8 Hz), 7.14 (d, 1H, $J=8.8$ Hz), 7.21 (d, 1H, $J=2.4$ Hz), 8.16 (d, 2H, $J=8.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 29.7, 36.2, 36.5, 40.3, 51.0, 64.0, 65.4, 114.1, 121.5, 121.8, 125.3, 125.6, 127.4, 129.7, 131.5, 134.2, 141.1, 151.9, 153.5, 162.4; IR ($CHCl_3$) cm^{-1}: 2971, 2222, 1725, 1594, 1514, 1498, 1469, 1392, 1344, 1258, 1171, 1112, 1021, 909, 846; HRMS calcd for $C_{22}H_{26}N_3O_5$ $(M+H)^+$ 412.1873, found 412.1870; $[\alpha]_D^{23}=-25.0°$ (*c* 0.70, $CHCl_3$).

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.

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