Synthesis and Pharmacological Evaluation of 3-Amino-1-(5-indanyloxy)-2-propanol Derivatives as Potent Sodium Channel Blockers for the Treatment of Stroke

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In investigating potent sodium (Na^+) channel blockers for the treatment of ischemic stroke, we synthesized a novel series of 3-amino-1-(5-indanyloxy)-2-propanol derivatives and evaluated their inhibitory effects on neuronal Na^+ channels. The 3-amino-1-(5-indanyloxy)-2-propanol derivatives exhibited potent blocking activity for Na^+ channels and a significantly low affinity for dopamine D_2 receptors, which demonstrates a minimal clinical risk for extrapyramidal side effects. In particular, compound 4b, a 3-amino-1-(5-indanyloxy)-2-propanol derivative bearing a benzimidazole moiety, showed desirable neuroprotective activity in a rat transient middle cerebral artery occlusion model. Furthermore, compound 4b displayed a high binding affinity for neurotoxin receptor site 2 of the Na^+ channels, which suggests that 4b would act as a use-dependent Na^+ channel blocker in sustained depolarization during ischemic stroke.

Key words sodium channel blocker; ischemic stroke; neuroprotection; neurotoxin receptor site 2

Despite their many efforts and the promising neuroprotective action of some drug candidates, such as *N*-methyl-D-aspartate (NMDA) receptor antagonists,^{1–3} α -amino-5-hydroxy-3-methyl-4-isoxazole propionic acid (AMPA) receptor antagonists,^{4,5} and Ca^{2+} channel blockers,⁶ no suitable neuroprotective drug has been approved for the treatment of ischemic stroke. Na^+ channel blockers inhibit neuronal depolarization, Na^+ influx, and glutamate release, which reduces Ca^{2+} influx through Ca^{2+} and NMDA receptor channels and prevents the reversal of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger.^{7,8}

Voltage-gated Na^+ channels have three distinct functional states: resting, open, and inactivated.⁹ These functional states determine the permeability of Na^+ ions. To date, at least eight distinct neurotoxin binding sites and a drug binding site have been identified on Na^+ channels. These binding sites either affect ion transport directly or modify the gating process. Neurotoxin receptor site 2 binding toxins, such as batrachotoxin (BTX), veratridine, and aconitine,^{10–12} cause Na^+ influx and a persistent tendency for depolarization by blocking Na^+ channel inactivation and shifting activation to a more negative membrane potential.^{13,14} Furthermore, compounds that bind to neurotoxin receptor site 2 are thought to block Na^+ channels in a use-dependent manner.^{15–17} The concept of use dependency can be further explained by the modulated receptor hypothesis,¹⁸ which proposes that drug binding is tighter to open or inactivated channels than to resting states. These observations suggest that site 2 Na^+ channel blockers may have a minimal effect on normal neuronal signaling but may act more effectively during ischemic conditions, where the membrane potential is persistently depolarized. In contrast, clinical trials of other neuroprotective agents, particularly NMDA receptor antagonists, have been discontinued because of their dose-limiting side effects.¹⁹ Thus, Na^+ channel blockers are promising agents for the treatment of stroke because of their mechanism of action, and they have been in clinical development (Fig. 1).^{20–23} In this paper, we report the synthesis,

modification, and pharmacological evaluation of 3-amino-1-(5-indanyloxy)-2-propanol derivatives as Na^+ channel blockers.

Chemistry

We previously discovered compound **1**, which had a potent binding affinity for the BTX binding site on Na^+ channels (Fig. 2), using high-throughput screening (HTS). However, this compound also showed a high affinity for dopamine D_2 receptors, which indicates a high clinical risk for extrapyramidal side effects.²⁴ Thus, we initiated a search for Na^+ channel blockers with high *in vivo* neuroprotective activity and a low affinity for dopamine D_2 receptors. SUN N8075 bearing a 1-phenoxy-3-piperazinyl-2-propanol moiety is a Na^+ channel blocker that lacks binding affinity to dopamine D_2 receptors.²³ Compound **1** has a 3-amino-1-(5-indanyloxy)-2-propanol moi-

Fig. 1. Chemical Structure of Na^+ Channel Blockers

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ety as a common structure with SUN N8075; therefore, we identified the 3-amino-1-(5-indanyloxy)-2-propanol moiety as a Na⁺ channel blocker pharmacophore and attempted to modify the amine moiety of compound **1**.

Syntheses of the biaryl piperidines (**8c**, **10a,c**) and biaryl piperazines (**6**, **14a–c**) are shown in Chart 1. Coupling compound **5** with 2,2'-dichloroethylamine hydrochloride yielded compound **6**. Compounds **8a**, **8b**, and **8d** were synthesized from piperidones **7a** or **7b** by the Grignard reaction.

Fig. 2. Synthetic Strategy from HTS Hit Compound **1**

respectively, and the cleavage of the ethyl carbamate group of compound **8b** afforded compound **8c**. Compound **9a** was hydrogenated to yield compound **10a**. Compound **9b** was converted to the biaryl piperidine **10b** in a four-step sequence, including (i) the protection of the piperidine moiety by a *tert*-

Reagents and conditions: (a) (i) 2-bromobenzyl alcohol, *n*-BuLi, THF, −78°C; (ii) TsCl, pyridine, CH₂Cl₂, rt; (b) 5 M aqueous NaOH, EtOH, reflux; (c) benzamidoxime, TsOH·H₂O, toluene, reflux; (d) Ba(OH)₂·8H₂O, EtOH/H₂O, reflux; (e) trifluoroacetic anhydride, Et₃N, CH₂Cl₂, 0°C; (f) 4 M HCl/EtOAc, EtOAc, rt.

Chart 2

Reagents and conditions: (a) 2,2'-dichloroethylamine hydrochloride, 200°C; (b) 4-biphenyl magnesium bromide (for **8a** and **8b**) or 4-(benzyloxy)bromobenzene, Mg (for **8d**), THF, 0°C; (c) 5 M aqueous NaOH, EtOH, reflux; (d) TFA, CH₂Cl₂, 0°C to rt; (e) H₂, Pd/C, MeOH/H₂O, 60°C; (f) (i) (Boc)₂O, THF, reflux; (ii) H₂, Pd/C, EtOH/THF, 50°C; (iii) trifluoromethanesulfonic anhydride, pyridine, CH₂Cl₂, 0°C to rt; (iv) pyridine-3-boronic acid, Pd(PPh₃)₄, 2 M aqueous Na₂CO₃, toluene/EtOH, 100°C; (g) 2 M HCl/MeOH, EtOAc, rt; (h) 2,5-dibromopyridine (for **12a**) or 3,6-dichloropyridazine (for **12b**), *N,N*-diisopropylethylamine, *N*-methylpyrrolidone, 120°C; (i) phenylboronic acid (for **13a** and **13b**) or pyridine-3-boronic acid (for **13c**), Pd(PPh₃)₄, 2 M aqueous Na₂CO₃, dioxane, 100°C; (j) TFA, CH₂Cl₂, 0°C to rt.

Chart 1

butyl carbamate (Boc) group, (ii) the reduction of the double bond and deprotection of the benzyl group, (iii) the conversion of the resulting phenol group to a triflate group, and (iv) coupling with pyridine-3-boronic acid. Deprotection of the Boc group of compound **10b** yielded compound **10c**. Compounds **12a** and **12b** were obtained from the corresponding hetero-aromatic halides by a nucleophilic substitution reaction with piperazine **11**. The Suzuki–Miyaura coupling of compounds **12a–c** with the corresponding boronic acids,^{26,27} followed by deprotection of the Boc group afforded biaryl piperazines **14a–c**.

The spiro-piperidines **15b** and **16b** were prepared from the piperidone **7b** as illustrated in Chart 2. Compound **15b** was synthesized according to the procedure of Kubota *et al.*²⁸ Condensation of **7b** with benzamidoxime in the presence of *p*-toluenesulfonic acid (TsOH) produced compound **16a**, which was then treated with barium hydroxide²⁹ to give compound **16b**. Protection of commercially available **17** by a trifluoroacetyl group, followed by the cleavage of the Boc group of **18a**

yielded compound **18b**.

Chart 3 shows the syntheses of the heteroaryl piperidines **20b** and **22b**. The oxadiazole **20a** was prepared by the cyclization of compound **19** with benzamidoxime under basic conditions,³⁰ and then, the deprotection of the Boc group of **20a** afforded compound **20b**. The benzimidazole **22a** was synthesized by the condensation reaction of phenylenediamine and imido ester hydrochloride, which was obtained from the nitrile **21**,³¹ and then, the deprotection of the benzyl carbamate (Cbz) group yielded compound **22b**.

Compounds **2a–g**, **3a–c**, and **4a–b** were synthesized as illustrated in Chart 4. Compound **24** was obtained from 5-indanol (**23**) and epichlorohydrin by a nucleophilic substitution reaction. Next, the epoxide **24** was coupled with a corresponding piperidine (**8c**, **10a, c**, **15b**, **16b**, **18b**, **20b**, or **22b**) or piperazine (**6** or **14a–c**), followed by treatment with hydrochloric acid to give the piperidine derivatives (**2b–d**, **3a–c**, **4a, b**) or piperazine derivatives (**2a, e–g**), respectively.

Results and Discussion

The effect of the synthesized compounds on Na⁺ channels was evaluated in rat cerebrocortical synaptosomes. The inhibitory activity on veratridine-induced depolarization was measured using voltage-sensitive dye rhodamine 6G.³² The binding affinity for dopamine D₂ receptors was assessed in rat striatum membranes using [³H]-spiperone as a radioligand.

As shown in Table 1, most of the biaryl piperidines and biaryl piperazines (**2a–g**) showed inhibitory activity for Na⁺ channels comparable to compound **1**. Aryl- or heteroaryl-substituted piperidines or piperazines, such as haloperidol and risperidone, have been reported to represent one of the largest categories of chemical structures with dopaminergic properties.³³ Surprisingly, compounds **2a–g** showed no binding affinity for the dopamine D₂ receptors ($K_i > 10 \mu\text{M}$), although they would be classified as a similar chemical class. These results suggest that the terminal aromatic ring of the biaryl piperidines and biaryl piperazines may interfere with binding to the dopa-

Reagents and conditions: (a) benzamidoxime, NaOEt, THF/EtOH, 70°C; (b) 4 M HCl/EtOAc, EtOAc, rt; (c) EtOH, acetyl chloride, CH₂Cl₂, 0°C to rt; (ii) *o*-phenylenediamine, EtOH, reflux; (d) H₂, Pd/C, MeOH, rt.

Chart 3

Reagents and conditions: (a) (i) NaH, DMF, 0°C to rt; (ii) epichlorohydrin, 0°C to rt; (b) (i) **6** (for **2a**), **8c** (for **2b**), **10a** (for **2c**), **10c** (for **2d**), **14a** (for **2e**), **14b** (for **2f**), or **14c** (for **2g**), 2-propanol, reflux; (ii) 4 M HCl/EtOAc, EtOAc, rt; (c) (i) **15b** (for **3a**), **16b** (for **3b**), or **18b** (for **3c**), 2-propanol, reflux; (ii) 4 M HCl/EtOAc, EtOAc, rt; (d) (i) **20b** (for **4a**) or **22b** (for **4b**), 2-propanol, reflux; (ii) 4 M HCl/EtOAc, EtOAc, rt.

Chart 4

Table 1. Biological Activity of Biarylpipecridine and Biarylpipecazine Derivatives (**2a–g**)

Compound ^{a)}	R
		Anti-veratridine ^{b)} IC ₅₀ (μM)	D ₂ binding affinity ^{c)} K _i (μM)	ClogD ^{d)}
1		0.43	0.61	3.21
2a		0.74	>10	6.08
2b		0.22	>10	4.34
2c		0.24	>10	5.48
2d		0.29	>10	3.99
2e		0.85	>10	5.04
2f		0.64	>10	4.35
2g		0.75	>10	4.46

^{a)} Each assay was carried out using a hydrochloride or dihydrochloride salt of the synthesized compounds. ^{b)} Inhibitory effect on veratridine-induced depolarization in rat cerebrocortical synaptosomes. See Experimental. ^{c)} Determined by a competition assay using [³H]-spiperone. ^{d)} ClogD values at pH 7.4 were calculated from ClogP using Daylight version 4.9 and pK_a using ChemAxon's Calculator Plugins version 5.0.0.

mine D₂ receptors.

Optimal logD values, namely 1-octanol/water distribution coefficients measured at pH 7.4, have been reported to be in the range of 1–4 for brain penetration.³⁴⁾ Compounds **2a–g** were further optimized using ClogD values as a reference because they had higher ClogD values. This optimization allowed us to obtain active compounds bearing a spiro-piperidine or heteroarylpipecridine moiety. As shown in Table 2, the spiro-piperidine **3b** and heteroarylpipecridines **4a,b** showed potent inhibitory activity for Na⁺ channels and no binding affinity for the dopamine D₂ receptors. In contrast,

the spiro-piperidine **3a** bearing a 1,3-dihydroisobenzofuran moiety potently inhibited the Na⁺ channels and had a moderate affinity for the dopamine D₂ receptors, and **3c** bearing an indoline moiety showed reduced activity for the Na⁺ channels. Compounds **3b**, **4a**, and **4b** exhibited a similar level of activity, but **4b** showed high metabolic stability in rats compared with **3b** and **4a** (Table 2). Compound **4b** was further evaluated for its neuroprotective activity in a rat transient middle cerebral artery (MCA) occlusion model.³⁵⁾ Briefly, compound **4b** was administered intraperitoneally immediately after both occlusion and reperfusion at a dose of 30 mg/kg each

Table 2. Biological Activity of Spiro-Piperidine and Heteroaryl-piperidine Derivatives (**3a–c**, **4a, b**)

Structure	Compound ^{a)}	R	Anti-veratridine ^{b)} IC ₅₀ (μM)	D ₂ binding affinity ^{c)} K _i (μM)	ClogD ^{d)}	CL (male rats) ^{e)} (mL/min/mg protein)
	3a		0.44	2.68	2.62	
	3b		0.46	>10	2.26	0.32
3c		1.20	>10	2.63	
	4a		0.37	>10	3.39	0.15
	4b		0.56	>10	2.83	0.10
SUN N8075 ²³⁾		0.42	>10	5.37	

a–d) See footnotes in Table 1. e) Microsomal intrinsic clearance.

time. Using a computerized image analysis system, the cortical infarct areas were determined 24 h after the occlusion of the MCA by staining brains with 2,3,5-triphenyltetrazolium chloride (TTC).³⁶⁾ Compound **4b** reduced its infarct volume by 33% compared with the vehicle [$201.1 \pm 50.2 \text{ mm}^3$ ($n=4$) vs. $302.3 \pm 26.5 \text{ mm}^3$ ($n=6$) (mean $\pm$ S.E.M.)]. SUN N8075 was also evaluated in our rat MCA occlusion model and exhibited 35% reduction in mean infarct volume compared with the vehicle [$166.2 \pm 38.1 \text{ mm}^3$ ($n=8$) vs. $255.8 \pm 31.0 \text{ mm}^3$ ($n=8$) (mean $\pm$ S.E.M.)]. Therefore, our results revealed that compound **4b** was as effective as SUN N8075. Then, we investigated the effect of **4b** on neurotoxin receptor site 2 of the Na⁺ channels. Compound **4b** displaced [³H]BTX with higher affinity (IC₅₀: $0.30 \mu\text{M}$) than SUN N8075 (IC₅₀: $0.75 \mu\text{M}$),²³⁾ further suggesting that **4b** may block Na⁺ channels with high use dependency.

In conclusion, we discovered 3-amino-1-(5-indanyloxy)-2-propanol derivatives that are potent Na⁺ channel blockers with low affinity for dopamine D₂ receptors. In this study, we also showed that the lowering of ClogD values in these compounds yielded compound **4b**, which showed potent neuroprotective activity in the rat transient MCA occlusion model. Moreover, **4b** had a high binding affinity for neurotoxin receptor site 2 of Na⁺ channels and may preferentially block Na⁺ channels during conditions of sustained cellular depolarization such as ischemia. Compound **4b** could serve as a lead compound for further studies.

Experimental

All melting points (mp) were determined on a Büchi B-535

melting point apparatus and are uncorrected. ¹H-NMR spectra were recorded on a Bruker ARX300 spectrometer (300 MHz) or a Bruker AVANCE 400 spectrometer (400 MHz), and chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations for signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. IR spectra were obtained with a PerkinElmer Spectrum One FT-IR spectrometer. Elemental analyses were performed with a PerkinElmer 2400 II (C, H, N) and were within $\pm 0.4\%$ of the theoretical values. LC/MS spectra were recorded on a Waters LC/MS system using a Acquity UPLC BEH C₁₈ column (2 $\times$ 50 mm) coupled with micromass ZQ as a MS detector, and a gradient of 5–98% B over 1 min was used. TFA 0.05% (v/v) was added to solvents A and B (water (A) and acetonitrile (B)). Mass spectra were obtained on a ThermoFisher FINNIGAN LXQ mass spectrometer. Column chromatography was carried out on silica gel (Fuji Silysia Chemical Ltd., BW-300) or Chromatorex NH DM1020 (Fuji Silysia Chemical Ltd., 100–200 mesh).

1-(4-Phenoxyphenyl)piperazine (6) A mixture of 4-phenoxyaniline (**5**) (5.0 g, 27.0 mmol) and 2,2'-dichloroethylamine hydrochloride (4.8 g, 27.0 mmol) was heated to 200°C with stirring for 4 h. After cooling, 1 M aqueous NaOH was added, and the whole was extracted with ethyl acetate (EtOAc). The extract was dried over anhydrous MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CHCl₃/methanol (MeOH)=20/1) to give **6** as a pale yellow solid (4.4 g, 64% yield). mp 114°C. ¹H-NMR (CDCl₃) δ : 3.03–3.06 (4H, m), 3.09–3.12 (4H, m), 6.90–7.05 (7H, m), 7.27–7.32 (2H, m). LC/MS [electrospray ionization

(ESI) m/z : 255 $[M+H]^+$.

tert-Butyl 4-Biphenyl-4-yl-4-hydroxypiperidine-1-carboxylate (8a) A 0.5M solution of 4-biphenyl magnesium bromide (11 mL, 5.5 mmol) in tetrahydrofuran (THF) was added dropwise to a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (**7a**) (1.0 g, 5.0 mmol) in THF (25 mL) at 0°C under a nitrogen atmosphere. The mixture was stirred for 2 h at the same temperature. One molar aqueous HCl was then added, and the whole was extracted with EtOAc. The extract was washed with saturated NaHCO₃ solution, dried over anhydrous MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc=4/1) to give **8a** as a colorless solid (0.58 g, 33% yield). mp 159–163°C. ¹H-NMR (CDCl₃) δ : 1.49 (9H, s), 1.78 (2H, d, J =12.3 Hz), 2.04 (2H, m), 3.27 (2H, t, J =12.3 Hz), 4.04 (2H, m), 7.35 (1H, t, J =7.5 Hz), 7.44 (2H, t, J =7.5 Hz), 7.53–7.62 (6H, m). MS [atmospheric pressure chemical ionization (APCI)] m/z : 352 $[M-H]^-$.

Ethyl 4-Biphenyl-4-yl-4-hydroxypiperidine-1-carboxylate (8b) This compound was prepared as a colorless solid (36% yield) by the same procedure as described for **8a** using ethyl 4-oxopiperidine-1-carboxylate (**7b**) instead of **7a**. mp 95–100°C. ¹H-NMR (CDCl₃) δ : 1.29 (3H, t, J =7.2 Hz), 1.80 (2H, d, J =12.6 Hz), 2.05 (2H, m), 3.32 (2H, t, J =13.1 Hz), 4.14 (2H, m), 4.17 (2H, q, J =7.2 Hz), 7.35 (1H, t, J =7.2 Hz), 7.45 (2H, t, J =7.4 Hz), 7.53–7.62 (6H, m). MS (APCI) m/z : 324 $[M-H]^-$.

4-Biphenyl-4-ylpiperidin-4-ol (8c) A mixture of **8b** (1.4 g, 4.2 mmol) and 5M aqueous NaOH (10 mL) in EtOH (20 mL) was refluxed overnight and then concentrated *in vacuo*. The residue was diluted with H₂O, and the whole was extracted with CH₂Cl₂. The extract was dried over anhydrous MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on NH-silica gel (CH₂Cl₂/MeOH=2/1) to give **8c** as a colorless solid (0.74 g, 70% yield). mp 183–186°C. ¹H-NMR (CDCl₃) δ : 1.77–1.81 (2H, m), 2.08 (2H, dt, J =4.5, 12.8 Hz), 2.98–3.02 (2H, m), 3.15 (2H, dt, J =2.4, 12.0 Hz), 7.34 (1H, t, J =6.9 Hz), 7.44 (2H, t, J =6.9 Hz), 7.58–7.61 (6H, m). LC/MS (ESI) m/z : 254 $[M+H]^+$.

tert-Butyl 4-[4-(Benzyloxy)phenyl]-4-hydroxypiperidine-1-carboxylate (8d) This compound was prepared as a colorless solid (55% yield) by the same procedure as described for **8a** using 4-benzyloxyphenyl magnesium bromide prepared from (4-benzyloxy)bromobenzene instead of 4-biphenyl magnesium bromide. mp 123°C. ¹H-NMR (CDCl₃) δ : 1.48 (9H, s), 1.72–1.75 (2H, m), 1.97 (2H, m), 3.24 (2H, t, J =12.3 Hz), 4.00 (2H, brs), 5.07 (2H, s), 6.95–6.98 (2H, m), 7.32–7.35 (1H, m), 7.36–7.44 (6H, m). MS (APCI) m/z : 383 $[M-H]^-$.

4-Biphenyl-4-yl-1,2,3,6-tetrahydropyridine (9a) To a solution of **8a** (0.58 g, 1.6 mmol) in CH₂Cl₂ (5 mL) was added TFA (1.4 mL) at 0°C. After stirring for 6 h at room temperature, the reaction mixture was poured into 1M aqueous NaOH, and the whole was extracted with EtOAc. The extract was dried over anhydrous MgSO₄ and concentrated *in vacuo*. Compound **9a** was obtained as a colorless solid (0.33 g, 69% yield). mp 261°C. ¹H-NMR (CDCl₃) δ : 2.48–2.57 (2H, m), 3.15 (2H, t, J =5.7 Hz), 3.58 (2H, q, J =2.9 Hz), 6.19–6.21 (1H, m), 7.32–7.36 (1H, m), 7.42–7.48 (4H, m), 7.56–7.61 (4H, m). LC/MS (ESI) m/z : 236 $[M+H]^+$.

4-[4-(Benzyloxy)phenyl]-1,2,3,6-tetrahydropyridine (9b) To a solution of **8d** (1.53 g, 4.0 mmol) in CH₂Cl₂ (20 mL) was added TFA (3.1 mL) at 0°C. After stirring for 1 h at room

temperature, the reaction mixture was poured into 1M aqueous NaOH, and the precipitate was collected by filtration. Compound **9b** was obtained as a colorless solid (1.03 g, 97% yield). ¹H-NMR (CDCl₃) δ : 2.40–2.50 (2H, m), 3.12 (2H, t, J =5.7 Hz), 3.53 (2H, dd, J =2.6, 5.7 Hz), 5.07 (2H, s), 6.00–6.09 (1H, m), 6.94 (2H, d, J =8.7 Hz), 7.29–7.35 (3H, m), 7.36–7.46 (4H, m). LC/MS (ESI) m/z : 266 $[M+H]^+$.

4-Biphenyl-4-ylpiperidine (10a) To a solution of **9a** (0.32 g, 1.2 mmol) in MeOH (20 mL) and H₂O (5 mL) was added 10% palladium on carbon (15 w/w%; 0.10 g), and the mixture was stirred at 60°C under a hydrogen atmosphere for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. To the residue was added 1M aqueous NaOH, and the whole was extracted with EtOAc. The extract was dried over anhydrous MgSO₄ and concentrated *in vacuo*. Compound **10a** was obtained as a colorless solid (0.22 g, 80% yield). mp 109–114°C. ¹H-NMR (CDCl₃) δ : 1.68 (2H, dq, J =3.9, 12.5 Hz), 1.88 (2H, d, J =13.2 Hz), 2.63–2.68 (1H, m), 2.77 (2H, dt, J =2.4, 12.2 Hz), 3.21 (2H, d, J =12.0 Hz), 7.29–7.35 (3H, m), 7.43 (2H, t, J =7.5 Hz), 7.56 (4H, dd, J =7.7, 11.6 Hz). LC/MS (ESI) m/z : 238 $[M+H]^+$.

tert-Butyl 4-(4-Pyridin-3-ylphenyl)piperidine-1-carboxylate (10b) To a solution of **9b** (0.98 g, 3.7 mmol) in THF (20 mL) was added di-*tert*-butyl dicarbonate (0.89 g, 4.1 mmol). The mixture was heated to reflux for 3 h and then concentrated *in vacuo*. The residue was extracted with EtOAc, and the extract was dried over anhydrous MgSO₄ and concentrated *in vacuo*. The resulting crystals were dissolved in EtOH (14 mL) and THF (7 mL), and 10% palladium on carbon (15 w/w%; 0.34 g) was added. The mixture was then stirred at 50°C under a hydrogen atmosphere for 5 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. To the resulting crystals and pyridine (0.35 mL) in CH₂Cl₂ (10 mL) was added dropwise a solution of trifluoromethanesulfonic anhydride (0.52 mL) in CH₂Cl₂ (3 mL) at 0°C. After stirring for 1 h at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was extracted with EtOAc, and the extract was dried over anhydrous MgSO₄ and concentrated *in vacuo*. The residual oil was dissolved in toluene (10 mL) and EtOH (1.0 mL). To the solution was added pyridine-3-boronic acid (0.35 g, 2.8 mmol), tetrakis(triphenylphosphine) palladium(0) (0.13 g, 0.12 mmol), and 2M aqueous Na₂CO₃ (2.3 mL). The mixture was then heated to 100°C with stirring for 15 h. After cooling, H₂O was added, and the whole was extracted with EtOAc. The extract was washed with brine, dried over anhydrous MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc=2/1) to give **10b** (0.67 g, 4 steps 54% yield) as a colorless solid. mp 104°C. ¹H-NMR (CDCl₃) δ : 1.49 (9H, s), 1.61–1.71 (2H, m), 1.85–1.88 (2H, m), 2.68–2.74 (1H, m), 2.77–2.93 (2H, m), 4.27 (2H, m), 7.31–7.38 (3H, m), 7.54 (2H, d, J =8.2 Hz), 7.85–7.88 (1H, m), 8.58 (1H, dd, J =1.5, 5.1 Hz), 8.84 (1H, m). LC/MS (ESI) m/z : 339 $[M+H]^+$.

3-(4-Piperidin-4-ylphenyl)pyridine Dihydrochloride (10c) To a solution of **10b** (0.59 g, 1.7 mmol) in EtOAc (8 mL) was added 2M HCl–MeOH solution (8.7 mL). After stirring for 1 h at room temperature, the precipitate was collected by filtration. Compound **10c** was obtained as a colorless solid (0.48 g, 89% yield). mp 276–280°C. ¹H-NMR (CD₃OD) δ : 1.92–2.03 (2H, m), 2.11–2.15 (2H, m), 3.04 (1H, tt, J =3.6, 12.3 Hz), 3.15–3.21 (2H, m), 3.52–3.55 (2H, m), 7.53 (2H, d, J =8.2 Hz),

7.83 (2H, d, $J=8.2$ Hz), 8.15 (1H, dd, $J=5.7, 8.2$ Hz), 8.82 (1H, d, $J=5.7$ Hz), 8.89–8.92 (1H, m), 9.17 (1H, d, $J=2.1$ Hz). LC/MS (ESI) m/z : 239 $[M+H]^+$.

tert-Butyl 4-(5-Bromopyridin-2-yl)piperazine-1-carboxylate (12a) A mixture of *tert*-butyl piperazine-1-carboxylate (**11**) (5.0 g, 26.9 mmol), 2,5-dibromopyridine (6.4 g, 26.9 mmol), and *N,N*-diisopropylethylamine (6.9 g, 51.7 mmol) in *N*-methylpyrrolidone (70 mL) was heated to 120°C with stirring for 5 h. After cooling, H₂O was added, and the whole was extracted with EtOAc. The extract was washed with brine, dried over anhydrous MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc=10/1) to give **12a** as a pale yellow solid (4.5 g, 49% yield). mp 89°C. ¹H-NMR (CDCl₃) δ : 1.48 (9H, s), 3.47–3.57 (8H, m), 6.55 (1H, d, $J=9.0$ Hz), 7.55 (1H, dd, $J=2.4, 9.0$ Hz), 8.20 (1H, d, $J=2.4$ Hz). LC/MS (ESI) m/z : 342 $[M+H]^+$, 344 $[M+2H]^+$.

tert-Butyl 4-(6-Chloropyridazin-3-yl)piperazine-1-carboxylate (12b) This compound was prepared as a pale yellow solid (62% yield) by the same procedure as described for **12a** using 3,6-dichloropyridazine instead of 2,5-dibromopyridine. mp 172°C. ¹H-NMR (CDCl₃) δ : 1.49 (9H, s), 3.56–3.62 (8H, m), 6.90 (1H, d, $J=9.9$ Hz), 7.24 (1H, d, $J=9.9$ Hz). LC/MS (ESI) m/z : 299 $[M+H]^+$.

tert-Butyl 4-(5-Phenylpyridin-2-yl)piperazine-1-carboxylate (13a) To a solution of **12a** (0.68 g, 2.0 mmol) and 2 M aqueous Na₂CO₃ (5 mL) in dioxane (10 mL) was added phenylboronic acid (0.36 g, 3.0 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.11 g, 0.10 mmol). The mixture was heated to 100°C with stirring for 6 h. After cooling, H₂O was added, and the whole was extracted with EtOAc. The extract was washed with brine, dried over anhydrous MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc=4/1) to give **13a** as a pale yellow solid (0.52 g, 77% yield). mp 133–137°C. ¹H-NMR (CDCl₃) δ : 1.46 (9H, s), 3.58 (8H, m), 6.73 (1H, d, $J=9.3$ Hz), 7.31–7.34 (1H, m), 7.43 (2H, t, $J=7.2$ Hz), 7.51–7.54 (2H, m), 7.74 (1H, d, $J=8.7$ Hz), 8.46 (1H, s). LC/MS (ESI) m/z : 340 $[M+H]^+$.

tert-Butyl 4-(6-Phenylpyridazin-3-yl)piperazine-1-carboxylate (13b) This compound was prepared as a pale yellow solid (64% yield) by the same procedure as described for **13a** using **12b** instead of **12a**. mp 177–180°C. ¹H-NMR (CDCl₃) δ : 1.50 (9H, s), 3.59–3.62 (4H, m), 3.71 (4H, m), 7.00 (1H, d, $J=9.6$ Hz), 7.41–7.51 (3H, m), 7.69 (1H, d, $J=9.9$ Hz), 8.02 (2H, dd, $J=1.4, 8.0$ Hz). LC/MS (ESI) m/z : 341 $[M+H]^+$.

tert-Butyl 4-(4-Pyridin-3-ylphenyl)piperazine-1-carboxylate (13c) This compound was prepared as a pale yellow solid (47% yield) by the same procedure as described for **13a** using commercially available **12c** instead of **12a** and pyridine-3-boronic acid instead of phenylboronic acid. mp 150°C. ¹H-NMR (CDCl₃) δ : 1.49 (9H, s), 3.20–3.23 (4H, m), 3.59–3.63 (4H, m), 7.02 (2H, d, $J=8.7$ Hz), 7.32 (1H, dd, $J=5.1, 7.8$ Hz), 7.52 (2H, d, $J=8.7$ Hz), 7.82–7.85 (1H, m), 8.53 (1H, dd, $J=1.5, 5.1$ Hz), 8.82 (1H, d, $J=2.4$ Hz). LC/MS (ESI) m/z : 340 $[M+H]^+$.

1-(5-Phenylpyridin-2-yl)piperazine (14a) To a solution of **13a** (0.52 g, 1.5 mmol) in CH₂Cl₂ (2 mL) was added trifluoroacetic acid (2 mL) at 0°C. After stirring for 1 h at room temperature, the reaction mixture was poured into 1 M aqueous NaOH, and the whole was extracted with CH₂Cl₂. The extract

was dried over anhydrous MgSO₄ and concentrated *in vacuo*. Compound **14a** was obtained as a colorless solid (0.33 g, 90% yield). mp 150–153°C. ¹H-NMR (CDCl₃) δ : 3.00–3.03 (4H, m), 3.54–3.58 (4H, m), 6.72 (1H, d, $J=9.0$ Hz), 7.31–7.45 (1H, m), 7.40–7.45 (2H, m), 7.51–7.54 (2H, m), 7.72 (1H, dd, $J=2.4, 9.0$ Hz), 8.45 (1H, d, $J=2.4$ Hz). LC/MS (ESI) m/z : 240 $[M+H]^+$.

3-Phenyl-6-piperazin-1-ylpyridazine (14b) This compound was prepared as a pale yellow solid (83% yield) by the same procedure as described for **14a** using **13b** instead of **13a**. mp 156–158°C. ¹H-NMR (CDCl₃) δ : 3.02–3.05 (4H, m), 3.68–3.70 (4H, m), 6.98 (1H, d, $J=9.8$ Hz), 7.38–7.42 (1H, m), 7.45–7.49 (2H, m), 7.66 (1H, d, $J=9.8$ Hz), 8.00–8.02 (2H, m). LC/MS (ESI) m/z : 241 $[M+H]^+$.

1-(4-Pyridin-3-ylphenyl)piperazine (14c) This compound was prepared as a pale yellow solid (81% yield) by the same procedure as described for **14a** using **13c** instead of **13a**. mp 156–158°C. ¹H-NMR (CDCl₃) δ : 3.04–3.08 (4H, m), 3.21–3.24 (4H, m), 7.02 (2H, d, $J=8.7$ Hz), 7.32 (1H, dd, $J=4.5, 8.0$ Hz), 7.51 (2H, d, $J=8.4$ Hz), 7.81–7.85 (1H, m), 8.52 (1H, dd, $J=1.5, 4.5$ Hz), 8.82 (1H, d, $J=2.4$ Hz). LC/MS (ESI) m/z : 240 $[M+H]^+$.

Ethyl Spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxylate (15a) This compound was synthesized as a colorless oil (85% yield) by the procedure of Kubota *et al.*²⁸⁾ ¹H-NMR (CDCl₃) δ : 1.29 (3H, t, $J=7.1$ Hz), 1.71–1.75 (2H, m), 1.84 (2H, dt, $J=4.8, 13.0$ Hz), 3.23 (2H, t, $J=12.2$ Hz), 4.09–4.14 (2H, m), 4.17 (2H, q, $J=7.1$ Hz), 5.08 (2H, s), 7.07–7.10 (1H, m), 7.20–7.29 (3H, m). LC/MS (ESI) m/z : 262 $[M+H]^+$.

Spiro[isobenzofuran-1(3H),4'-piperidine] (15b) This compound was synthesized as a colorless solid (83% yield) by the procedure of Kubota *et al.*²⁸⁾ mp 88–89°C. ¹H-NMR (CDCl₃) δ : 1.73–1.91 (4H, m), 3.01–3.11 (4H, m), 5.08 (2H, s), 7.13–7.16 (1H, m), 7.21–7.29 (3H, m). LC/MS (ESI) m/z : 190 $[M+H]^+$.

tert-Butyl 3-Phenyl-1-oxa-2,4,8-triazaspiro[4,5]dec-2-ene-8-carboxylate (16a) A mixture of **7b** (5.0 g, 29.2 mmol), benzamidoxime (4.0 g, 29.2 mmol), and *p*-toluenesulfonic acid monohydrate (1.0 g, 5.8 mmol) in toluene (30 mL) was heated to reflux with a Dean–Stark apparatus for 7 h. After cooling, the resulting precipitate was collected by filtration and recrystallized from 2-propanol/EtOAc to give **16a** as a colorless solid (4.2 g, 50% yield). mp 189°C. ¹H-NMR (CDCl₃) δ : 1.28 (3H, t, $J=7.2$ Hz), 1.73–1.83 (2H, m), 2.04–2.08 (2H, m), 3.40 (2H, ddd, $J=3.0, 10.8, 13.8$ Hz), 3.91–3.95 (2H, m), 4.16 (2H, q, $J=7.2$ Hz), 4.43 (1H, brs), 7.39–7.47 (3H, m), 7.68 (2H, td, $J=1.8, 6.3$ Hz). LC/MS (ESI) m/z : 290 $[M+H]^+$.

3-Phenyl-1-oxa-2,4,8-triazaspiro[4,5]dec-2-ene (16b) A mixture of **16a** (4.2 g, 14.6 mmol) and Ba(OH)₂·8H₂O (6.4 g, 20.4 mmol) in EtOH (30 mL) and H₂O (20 mL) was heated to reflux with stirring overnight. The mixture was then concentrated *in vacuo*, and the residue was diluted with H₂O. The resulting precipitate was removed by filtration, and the filtrate was extracted with CH₂Cl₂. The extract was dried over anhydrous MgSO₄ and concentrated *in vacuo*. The residue was washed with hexane/EtOAc (1/1) to give **16b** as a colorless solid (2.2 g, 68% yield). mp 169°C. ¹H-NMR (CDCl₃) δ : 1.79–1.85 (2H, m), 2.0–2.06 (2H, m), 2.93–2.97 (2H, m), 2.99–3.08 (2H, m), 4.45 (1H, brs), 7.27–7.46 (3H, m), 7.68–7.71 (2H, m). LC/MS (ESI) m/z : 218 $[M+H]^+$.

tert-Butyl 1-(Trifluoroacetyl)-1,2-dihydro-1'H-spiro[in-

dole-3,4'-piperidine]-1'-carboxylate (18a) To a solution of commercially available *tert*-butyl 1,2-dihydro-1'*H*-spiro[indole-3,4'-piperidine]-1'-carboxylate (**17**) (0.8 g, 2.8 mmol) and triethylamine (0.46 mL, 3.3 mmol) in CH₂Cl₂ (10 mL) was added trifluoroacetic anhydride (0.41 mL, 2.9 mmol) at 0°C. After stirring for 4 h at the same temperature, H₂O was added, and the whole was extracted with CH₂Cl₂. The extract was dried over anhydrous MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc=5/1) to give **18a** as a colorless solid (0.99 g, 92% yield). mp 124–125°C. ¹H-NMR (CDCl₃) δ: 1.49 (9H, s), 1.66–1.70 (2H, m), 1.88 (2H, dt, *J*=4.2, 13.2 Hz), 2.89 (2H, t, *J*=12.6 Hz), 4.13 (2H, s), 4.19 (2H, m), 7.21 (2H, d, *J*=4.2 Hz), 7.29–7.35 (1H, m), 8.20 (1H, d, *J*=8.2 Hz). MS (APCI) *m/z*: 402 [M+NH₄]⁺.

2,2,2-Trifluoro-1-(spiro[indole-3,4'-piperidin]-1-(2H)-yl)ethanone (18b) To a solution of **18a** (0.97 g, 2.5 mmol) in EtOAc (10 mL) was added 4M HCl–EtOAc solution (6 mL). After stirring for 6 h at room temperature, saturated NaHCO₃ solution was added, and the whole was extracted with CH₂Cl₂. The extract was dried over anhydrous MgSO₄ and concentrated *in vacuo* to give **18b** as a pale yellow oil (0.41 g, 58% yield). ¹H-NMR (CDCl₃) δ: 1.67–1.71 (2H, m), 1.95 (2H, dt, *J*=4.5, 13.2 Hz), 2.78 (2H, dt, *J*=2.4, 12.6 Hz), 3.16–3.20 (2H, m), 4.13 (2H, s), 7.19–7.34 (m, 3H), 8.19 (1H, d, *J*=7.8 Hz). LC/MS (ESI) *m/z*: 285 [M+H]⁺.

***tert*-Butyl 4-(3-Phenyl-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (20a)** To a solution of *tert*-butyl 4-(ethoxycarbonyl)piperidine-1-carboxylate (**19**) (6.4 g, 25.0 mmol) in THF (20 mL) and EtOH (20 mL) was added benzamidoxime (3.4 g, 25.0 mmol), then NaOEt (1.7 g, 25 mmol). After stirring for 3 h at 70°C, 1M aqueous HCl was added, and the whole was extracted with EtOAc. The extract was dried over anhydrous MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc=4/1) to give **20a** as a colorless solid (2.8 g, 34% yield). mp 101–102°C. ¹H-NMR (CDCl₃) δ: 1.48 (9H, s), 1.85–1.95 (2H, m), 2.12 (2H, dd, *J*=3.3, 13.1 Hz), 3.00 (2H, t, *J*=11.6 Hz), 3.15–3.20 (1H, m), 4.11–4.14 (2H, m), 7.44–7.54 (3H, m), 8.03–8.11 (2H, m). MS (APCI) *m/z*: 330 [M+H]⁺.

4-(3-Phenyl-1,2,4-oxadiazol-5-yl)piperidine Hydrochloride (20b) To a solution of **20a** (0.99 g, 3.0 mmol) in EtOAc (3 mL) was added 4M HCl–EtOAc solution (3 mL). After stirring for 4 h at room temperature, the resulting precipitate was collected by filtration and washed with EtOAc to give **20b** as a colorless solid (0.79 g, 99% yield). mp 250–251°C. ¹H-NMR (CD₃OD) δ: 2.15 (2H, dtd, *J*=3.9, 12.0, 14.8 Hz), 2.41–2.46 (2H, m), 3.21–3.27 (2H, m), 3.49–3.56 (3H, m), 7.49–7.57 (3H, m), 8.04–8.07 (2H, m). LC/MS (ESI) *m/z*: 230 [M+H]⁺.

Benzyl 4-(1*H*-Benzimidazol-2-yl)piperidine-1-carboxylate (22a) To a solution of anhydrous EtOH (16 mL) in CH₂Cl₂ (18 mL) was added dropwise acetyl chloride (18 mL) at 0°C. To the reaction mixture was added dropwise benzyl 4-cyanopiperidine-1-carboxylate (**21**) (2.1 g, 8.4 mmol) in CH₂Cl₂ (10 mL) at the same temperature. After stirring for 2 h at room temperature, the resulting precipitate was collected by filtration and then dissolved in anhydrous EtOH (50 mL). To the solution was added *o*-phenylenediamine (1.2 g, 11.0 mmol), and the mixture was heated to reflux for 4 h. After cooling, 1M aqueous NaOH was added, and the whole was extracted

with CHCl₃. The extract was washed with 1M aqueous HCl, then brine, dried over anhydrous MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CHCl₃/MeOH=10/1) to give **22a** as a colorless solid (2.6 g, 92% yield). mp 185–186°C. ¹H-NMR (CDCl₃) δ: 1.64–1.77 (2H, dq, *J*=4.1, 12.2 Hz), 1.92–1.95 (2H, m), 2.58–2.69 (2H, m), 2.92 (1H, tt, *J*=3.9, 11.6 Hz), 3.00–3.09 (2H, m), 7.06–7.15 (2H, m), 7.47 (2H, m), 12.11 (1H, br s). LC/MS (ESI) *m/z*: 336 [M+H]⁺.

2-Piperidin-4-yl-1*H*-benzimidazole (22b) To a solution of **22a** (2.5 g, 7.5 mmol) in MeOH (50 mL) was added 10% palladium on carbon (10 w/w%; 0.50 g), and the mixture was stirred at room temperature under a hydrogen atmosphere for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to give **22b** as a pale yellow solid (1.5 g, 99% yield). mp 259–265°C. ¹H-NMR (DMSO-*d*₆) δ: 1.70 (2H, dq, *J*=4.1, 12.2 Hz), 1.92–1.95 (2H, m), 2.60–2.66 (2H, m), 2.92 (1H, tt, *J*=3.9, 11.6 Hz), 3.03–3.06 (2H, m), 7.09–7.12 (2H, m), 7.47 (2H, brs), 12.11 (1H, brs). LC/MS (ESI) *m/z*: 202 [M+H]⁺.

2-[(2,3-Dihydro-1*H*-inden-5-yloxy)methyl]oxirane (24) To a solution of 5-indanol (**23**) (10.0 g, 74.5 mmol) in *N,N*-dimethylformamide (DMF) (100 mL) was added 60% sodium hydride in oil (3.3 g, 82.0 mmol) at 0°C. The mixture was stirred at 0°C for 30 min, then at room temperature for 1 h. To the resulting mixture was added epichlorohydrin (6.5 mL, 82.0 mmol) at 0°C. After stirring overnight at room temperature, 1M aqueous HCl was added, and the whole was extracted with diethyl ether. The extract was washed with brine, dried over anhydrous MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc=20/1) to give **24** as a colorless oil (10.3 g, 73% yield). ¹H-NMR (CDCl₃) δ: 2.08 (2H, q, *J*=7.5 Hz), 2.74 (1H, dd, *J*=2.7, 5.0 Hz), 2.81–2.91 (5H, m), 3.33–3.35 (1H, m), 3.95 (1H, dd, *J*=5.4, 11.1 Hz), 4.17 (1H, dd, *J*=3.3, 11.1 Hz), 6.70 (1H, dd, *J*=2.7, 8.1 Hz), 6.80 (1H, s), 7.11 (1H, d, *J*=8.1 Hz). LC/MS (ESI) *m/z*: 191 [M+H]⁺.

General Procedure for the Synthesis of 3-Amino-1-(5-indanyloxy)-2-propanol Derivatives (2a–g, 3a–c, 4a, b) A mixture of **24** and a corresponding piperidine (**8c**, **10a, c**, **15b**, **16b**, **18b**, **20b**, **22b**) or piperazine (**6**, **14a–c**) in 2-propanol was heated to reflux with stirring for 3 h. After cooling, H₂O was added, and the whole was extracted with CH₂Cl₂. The extract was dried over anhydrous MgSO₄ and concentrated *in vacuo*. The residual oil product was purified by column chromatography on silica gel (CH₂Cl₂/MeOH=30/1), or the crystalline product was washed with EtOAc. The obtained compounds were dissolved in EtOAc, and excess 4M HCl–EtOAc solution was added. After stirring for 1 h at room temperature, the resulting precipitate was collected by filtration and washed with EtOAc to give the piperidine derivatives (**2b–d**, **3a–c**, or **4a, b**) or piperazine derivatives (**2a** or **2e–g**), respectively.

1-(2,3-Dihydro-1*H*-inden-5-yloxy)-3-[4-(4-phenoxyphenyl)piperazin-1-yl]propan-2-ol Hydrochloride (2a) This compound was obtained in 83% yield from **6** as a colorless solid. mp 163°C. ¹H-NMR (DMSO-*d*₆) δ: 1.96–2.06 (2H, m), 2.78 (2H, t, *J*=7.5 Hz), 2.83 (2H, t, *J*=7.2 Hz), 3.02–3.20 (2H, m), 3.22–3.32 (4H, m), 3.58–3.82 (4H, m), 3.88–3.99 (2H, m), 4.39 (1H, brs), 6.00 (1H, brs), 6.72 (1H, dd, *J*=2.6, 8.2 Hz), 6.85 (1H, s), 6.92 (2H, dd, *J*=1.0, 8.7 Hz), 6.97–7.01 (2H, m), 7.02–7.16 (4H, m), 7.31–7.39 (2H, m), 10.03 (1H, brs). LC/

MS (ESI) m/z : 445 $[M+H]^+$. IR [attenuated total reflectance (ATR)] cm^{-1} : 3235, 2944, 1585, 1509, 1485, 1451, 1240, 869, 765, 519. *Anal.* Calcd for $C_{28}H_{32}N_2O_3 \cdot HCl \cdot 0.5H_2O$: C, 68.63; H, 6.99; N, 5.72. Found: C, 68.48; H, 6.86; N, 5.66.

4-Biphenyl-4-yl-1-[3-(2,3-dihydro-1H-inden-5-yloxy)-2-hydroxypropyl]piperidin-4-ol Hydrochloride (2b) This compound was obtained in 76% yield from **8c** as a colorless solid. mp 228°C. 1H -NMR (DMSO- d_6) δ : 1.85 (2H, t, $J=15.4$ Hz), 1.96–2.07 (2H, m), 2.30–2.42 (2H, m), 2.74–2.88 (4H, m), 3.27–3.45 (4H, m), 3.48–3.61 (2H, m), 3.89–4.02 (2H, m), 4.31–4.45 (1H, m), 5.54 (1H, s), 5.96 (1H, d, $J=5.1$ Hz), 6.69–6.77 (1H, m), 6.86 (1H, s), 7.13 (1H, d, $J=8.2$ Hz), 7.37 (1H, t, $J=8.2$ Hz), 7.47 (2H, t, $J=7.7$ Hz), 7.56 (2H, d, $J=8.2$ Hz), 7.68 (4H, m), 9.63 (1H, brs). LC/MS (ESI) m/z : 444 $[M+H]^+$. IR (ATR) cm^{-1} : 3312, 3179, 2924, 1604, 1488, 1473, 1049, 763, 635. *Anal.* Calcd for $C_{29}H_{33}NO_3 \cdot HCl$: C, 72.56; H, 7.14; N, 2.92. Found: C, 72.36; H, 7.12; N, 2.89.

1-(4-Biphenyl-4-ylpiperidin-1-yl)-3-(2,3-dihydro-1H-inden-5-yloxy)propan-2-ol Hydrochloride (2c) This compound was obtained in 79% yield from **10a** as a colorless solid. mp 243°C. 1H -NMR (DMSO- d_6) δ : 1.94–2.20 (6H, m), 2.74–2.94 (5H, m), 3.05–3.24 (4H, m), 3.62–3.73 (2H, m), 3.89–3.99 (2H, m), 4.31–4.42 (1H, m), 5.95 (1H, d, $J=5.1$ Hz), 6.73 (1H, dd, $J=2.3$, 8.0 Hz), 6.86 (1H, d, $J=2.1$ Hz), 7.13 (1H, d, $J=8.2$ Hz), 7.31–7.39 (3H, m), 7.46 (2H, t, $J=8.2$ Hz), 7.61–7.69 (4H, m), 9.60 (1H, brs). LC/MS (ESI) m/z : 428 $[M+H]^+$. IR (ATR) cm^{-1} : 3278, 2939, 1604, 1483, 1251, 1045, 832, 760, 693. *Anal.* Calcd for $C_{29}H_{33}NO_2 \cdot HCl \cdot 0.1H_2O$: C, 74.77; H, 7.40; N, 3.01. Found: C, 74.62; H, 7.24; N, 2.98.

1-(2,3-Dihydro-1H-inden-5-yloxy)-3-[4-(4-pyridin-3-ylphenyl)piperidin-1-yl]propan-2-ol Dihydrochloride (2d) This compound was obtained in 21% yield from **10c** as a colorless solid. mp 216°C. 1H -NMR (DMSO- d_6) δ : 1.95–2.22 (6H, m), 2.78 (2H, t, $J=7.2$ Hz), 2.83 (2H, t, $J=7.5$ Hz), 2.88–2.98 (1H, m), 3.25 (4H, m), 3.63–3.74 (2H, m), 3.90–4.01 (2H, m), 4.34–4.44 (1H, m), 6.69–6.77 (1H, m), 6.86 (1H, s), 7.13 (1H, d, $J=8.2$ Hz), 7.42 (2H, d, $J=8.2$ Hz), 7.70–7.83 (3H, m), 8.33–8.43 (1H, m), 8.69 (1H, d, $J=4.6$ Hz), 9.03 (1H, s), 9.66 (1H, br s). LC/MS (ESI) m/z : 429 $[M+H]^+$. IR (ATR) cm^{-1} : 3281, 2918, 2662, 1473, 1044, 808. *Anal.* Calcd for $C_{28}H_{32}N_2O_2 \cdot 2HCl \cdot 1.5H_2O$: C, 63.63; H, 7.06; N, 5.30. Found: C, 63.28; H, 7.01; N, 5.24.

1-(2,3-Dihydro-1H-inden-5-yloxy)-3-[4-(5-phenylpyridin-2-yl)piperazin-1-yl]propan-2-ol Dihydrochloride (2e) This compound was obtained in 46% yield from **14a** as a colorless solid. mp 237°C. 1H -NMR (DMSO- d_6) δ : 1.95–2.06 (2H, m), 2.78 (2H, t, $J=7.2$ Hz), 2.83 (2H, t, $J=7.5$ Hz), 3.10–3.43 (6H, m), 3.60–3.71 (2H, m), 3.89–3.99 (2H, m), 4.32–4.52 (3H, m), 6.72 (1H, dd, $J=2.6$, 8.2 Hz), 6.84 (1H, s), 7.08 (1H, d, $J=8.7$ Hz), 7.12 (1H, d, $J=8.2$ Hz), 7.31–7.38 (1H, m), 7.45 (2H, t, $J=7.7$ Hz), 7.65 (2H, d, $J=7.2$ Hz), 7.95–8.02 (1H, m), 8.50 (1H, d, $J=2.1$ Hz), 10.03 (1H, brs). LC/MS (ESI) m/z : 430 $[M+H]^+$. IR (ATR) cm^{-1} : 3682, 3325, 2952, 2844, 2722, 1649, 1616, 1492, 1440, 1277, 1244, 1055, 1033, 990, 797, 757, 693. *Anal.* Calcd for $C_{27}H_{31}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$: C, 63.40; H, 6.70; N, 8.22. Found: C, 63.66; H, 6.47; N, 8.20.

1-(2,3-Dihydro-1H-inden-5-yloxy)-3-[4-(6-phenylpyridazin-3-yl)piperazin-1-yl]propan-2-ol Hydrochloride (2f) This compound was obtained in 37% yield from **14b** as a colorless solid. mp 229°C. 1H -NMR (DMSO- d_6) δ : 1.95–2.05 (2H, m), 2.80 (4H, dt, $J=7.3$, 19.4 Hz),

3.19–3.30 (4H, m), 3.42–3.57 (2H, m), 3.63–3.74 (2H, m), 3.89–4.00 (2H, m), 4.33–4.43 (1H, m), 4.47–4.63 (2H, m), 6.72 (1H, dd, $J=2.3$, 8.5 Hz), 6.84 (1H, s), 7.12 (1H, d, $J=8.2$ Hz), 7.41–7.56 (4H, m), 8.01–8.12 (3H, m), 10.06 (1H, brs). LC/MS (ESI) m/z : 431 $[M+H]^+$. IR (ATR) cm^{-1} : 3306, 2937, 2578, 1642, 1592, 1579, 1548, 1481, 1462, 1442, 1419, 1239, 1055, 1033, 779, 690. *Anal.* Calcd for $C_{26}H_{30}N_4O_2 \cdot HCl \cdot 0.5H_2O$: C, 65.60; H, 6.78; N, 11.77. Found: C, 65.36; H, 6.47; N, 11.67.

1-(2,3-Dihydro-1H-inden-5-yloxy)-3-[4-(4-pyridin-3-ylphenyl)piperazin-1-yl]propan-2-ol Dihydrochloride (2g) This compound was obtained in 75% yield from **14c** as a yellow solid. mp 199°C. 1H -NMR (DMSO- d_6) δ : 1.95–2.06 (2H, m), 2.80 (4H, dt, $J=7.3$, 19.8 Hz), 3.22 (4H, m), 3.61–3.74 (4H, m), 3.88–4.05 (4H, m), 4.34–4.44 (1H, m), 6.72 (1H, dd, $J=2.6$, 8.2 Hz), 6.85 (1H, s), 7.13 (1H, d, $J=8.2$ Hz), 7.17 (2H, d, $J=8.7$ Hz), 7.71–7.83 (3H, m), 8.42–8.51 (1H, m), 8.65 (1H, d, $J=5.1$ Hz), 9.05 (1H, s), 10.10 (1H, brs). LC/MS (ESI) m/z : 430 $[M+H]^+$. IR (ATR) cm^{-1} : 3269, 2968, 2596, 1607, 1522, 1471, 1258, 1241, 1044, 1034, 799, 678, 618. *Anal.* Calcd for $C_{27}H_{31}N_3O_2 \cdot 2HCl \cdot 2H_2O$: C, 60.22; H, 6.93; N, 7.80. Found: C, 60.34; H, 6.70; N, 7.73.

1-(2,3-Dihydro-1H-inden-5-yloxy)-3-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propan-2-ol Hydrochloride (3a) This compound was obtained in 85% yield from **15b** as a colorless solid. mp 207°C. 1H -NMR (DMSO- d_6) δ : 1.85 (2H, t, $J=15.7$ Hz), 2.01 (2H, m), 2.22–2.46 (2H, m), 2.81 (4H, dt, $J=7.6$, 19.8 Hz), 3.19–3.38 (4H, m), 3.55–3.65 (2H, m), 3.88–4.02 (2H, m), 4.32–4.42 (1H, m), 5.06 (2H, s), 5.96 (1H, d, $J=8.2$ Hz), 6.73 (1H, d, $J=8.2$ Hz), 6.85 (1H, s), 7.09–7.20 (2H, m), 7.30–7.39 (3H, m), 9.73 (1H, br s). LC/MS (ESI) m/z : 380 $[M+H]^+$. IR (ATR) cm^{-1} : 3681, 3215, 2937, 2844, 1606, 1494, 1475, 1252, 1046, 1038, 1017, 833, 749. *Anal.* Calcd for $C_{24}H_{29}NO_3 \cdot HCl$: C, 69.30; H, 7.27; N, 3.37. Found: C, 68.97; H, 7.16; N, 3.32.

1-(2,3-Dihydro-1H-inden-5-yloxy)-3-(3-phenyl-1-oxa-2,4,8-triazaspiro[4,5]dec-2-en-8-yl)propan-2-ol Hydrochloride (3b) This compound was obtained in 87% yield from **16b** as a colorless solid. mp 241°C. 1H -NMR (DMSO- d_6) δ : 1.99–2.15 (6H, m), 2.80 (4H, dt, $J=7.5$, 19.5 Hz), 3.17–3.40 (4H, m), 3.62 (2H, m), 3.87–3.99 (2H, m), 4.31 (1H, m), 6.00 (1H, m), 6.72 (1H, d, $J=8.7$ Hz), 6.85 (1H, s), 7.13 (1H, d, $J=8.2$ Hz), 7.48–7.52 (3H, m), 7.68 (2H, d, $J=7.7$ Hz), 7.84 (1H, m), 9.53 (1H, brs). LC/MS (ESI) m/z : 408 $[M+H]^+$. IR (ATR) cm^{-1} : 3682, 3234, 2938, 2667, 1607, 1513, 1461, 1433, 1051, 1033, 839, 770, 692. *Anal.* Calcd for $C_{24}H_{29}N_3O_3 \cdot HCl$: C, 64.93; H, 6.81; N, 9.46. Found: C, 64.71; H, 6.44; N, 9.36.

1-(2,3-Dihydro-1H-inden-5-yloxy)-3-(1,2-dihydro-1'H-spiro[indole-3,4'-piperidin]-1'-yl)propan-2-ol Hydrochloride (3c) This compound was obtained in 53% yield from **18b** as a colorless solid. mp 250°C. 1H -NMR (DMSO- d_6) δ : 1.74–1.83 (2H, m), 1.97–2.12 (3H, m), 2.18–2.24 (1H, m), 2.80 (4H, dt, $J=7.3$, 19.8 Hz), 3.06–3.38 (6H, m), 3.55 (2H, m), 3.88–4.00 (2H, m), 4.33 (1H, m), 5.66 (1H, brs), 5.97 (1H, d, $J=4.6$ Hz), 6.51 (1H, d, $J=7.7$ Hz), 6.60 (1H, t, $J=7.2$ Hz), 6.71–6.73 (1H, m), 6.85 (1H, s), 6.91–6.98 (2H, m), 7.13 (1H, d, $J=8.2$ Hz), 9.42 (1H, brs). LC/MS (ESI) m/z : 379 $[M+H]^+$. IR (ATR) cm^{-1} : 3244, 2961, 2837, 2693, 1606, 1486, 1463, 1251, 1048, 1033, 830, 734. *Anal.* Calcd for $C_{24}H_{30}N_2O_2 \cdot HCl \cdot 0.2H_2O$: C, 68.87; H, 7.56; N, 6.69. Found: C, 68.55; H, 7.17; N, 6.65.

1-(2,3-Dihydro-1H-inden-5-yloxy)-3-[4-(3-phenyl-1,2,4-

oxadiazol-5-yl)piperidin-1-yl]propan-2-ol Hydrochloride (4a) This compound was obtained in 35% yield from **20b** as a colorless solid. mp 202°C. ¹H-NMR (DMSO-*d*₆) δ : 1.97–2.29 (4H, m), 2.35–2.43 (2H, m), 2.80 (4H, dt, *J*=7.1, 20.0 Hz), 3.15–3.30 (4H, m), 3.63–3.77 (2H, m), 3.91–3.99 (2H, m), 4.33 (1H, m), 5.98 (1H, d, *J*=4.6 Hz), 6.71–6.73 (1H, m), 6.82–6.85 (1H, m), 7.10–7.14 (1H, m), 7.57–7.63 (3H, m), 8.00–8.08 (2H, m), 9.58 (1H, brs). LC/MS (ESI) *m/z*: 420 [M+H]⁺. IR (ATR) cm⁻¹: 3682, 3257, 2967, 2845, 2519, 1570, 1493, 1474, 1447, 1047, 1033, 1015, 695. *Anal.* Calcd for C₂₅H₂₉N₃O₃·HCl: C, 65.85; H, 6.63; N, 9.22. Found: C, 65.95; H, 6.48; N, 9.18.

1-[4-(1*H*-Benzimidazol-2-yl)piperidin-1-yl]-3-(2,3-dihydro-1*H*-inden-5-yloxy)propan-2-ol Dihydrochloride (4b) This compound was obtained in 54% yield from **22b** as a colorless solid. mp 264°C. ¹H-NMR (DMSO-*d*₆) δ : 1.97–2.03 (2H, m), 2.41 (4H, m), 2.81 (4H, dt, *J*=7.2, 19.8 Hz), 3.15–3.30 (4H, m), 3.68–3.80 (2H, m), 3.87–4.01 (2H, m), 4.39 (1H, m), 5.99 (1H, brs), 6.73 (1H, d, *J*=8.7 Hz), 6.83–6.86 (1H, m), 7.08–7.14 (1H, m), 7.43 (2H, m), 7.72 (2H, m), 9.58 (1H, brs). LC/MS (ESI) *m/z*: 392 [M+H]⁺. IR (ATR) cm⁻¹: 3681, 2939, 2844, 2725, 1608, 1491, 1461, 1054, 1033, 1017, 819, 742. *Anal.* Calcd for C₂₄H₂₉N₃O₂·2HCl·0.5H₂O: C, 60.89; H, 6.81; N, 8.88. Found: C, 60.74; H, 6.67; N, 8.79.

Inhibitory Effect on Veratridine-Induced Na⁺ Channel Depolarization The membrane potential of synaptosomes was measured according to the procedure of Aiuchi *et al.*³² The standard medium consisted of 132 mM NaCl, 5 mM KCl, 20 mM Tris-HCl (pH 7.4), and 10 mM glucose. Synaptosomes were prepared from rat brain membranes (male Wistar rats, 7–15 weeks old). Fluorescence was measured with a spectrofluorometer (an excitation wavelength of 520 nm and an emission wavelength of 550 nm). Rhodamine 6G, each test compound, and veratridine were added to 1 mL of the standard medium in a fluorometer cuvette, and the initial fluorescence, *f*_i, was measured. Then, 50 μ L of synaptosomes suspension was added to the cuvette, and the fluorescence in the steady state, *f*_s, was measured. The fluorescence, *f*, was defined as *f*=(*f*_s/*f*_i).

Binding Affinity for Dopamine D₂ Receptors A membrane fraction prepared from the striatum of female Lewis rats (450 μ L) was incubated with each test compound and 0.2 nM [³H]-spiperone in a buffer solution (50 mM Tris-HCl, 120 mM NaCl, 5 mM KCl, 2 mM CaCl₂, and 1 mM MgCl₂, pH 7.4) at 37°C for 20 min. Bound radioactivity was counted after rapid vacuum filtration through a GF/B glass filter. Nonspecific binding was determined using 100 μ M (–)-sulpiride.

Effect of Compound 4b on Ischemic Brain Damage in a Rat Transient Middle Cerebral Artery (MCA) Occlusion Model Wistar rats (male, 8 weeks old) were anesthetized with halothane. They were then subjected to transient MCA occlusion for 90 min according to the modified method of Koizumi *et al.*,³⁵ followed by reperfusion. Compound **4b** was administered intraperitoneally immediately after both occlusion and reperfusion at a dose of 30 mg/kg (salt form) each time. Control rats that also underwent transient MCA occlusion received an equal volume of saline at the corresponding time points. The brains were dissected into 7 slices 24 h after the occlusion and stained with TTC.³⁶ The area of infarct tissue for each slice was determined with a computerized image analysis system, and the infarct volume was calculated.

Binding Affinity for [³H]-BTX [³H]-Batrachotoxin-A-

20- α -benzoate (BTX-b) was purchased from PerkinElmer. [³H]-BTX-b binding was measured in synaptosomal preparations of rat cerebral cortex using a modified procedure previously described.¹¹ The standard binding medium consisted of 130 mM chlorine chloride, 50 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (adjusted to pH 7.4 at 36°C with Tris base), 5.5 mM glucose, 0.8 mM MgSO₄, 5.4 mM KCl, 1 mg/mL of bovine serum albumin. Binding reactions were initiated by addition of synaptosomes suspended in 100 μ M of the standard binding medium to a reaction mixture containing 10 nM [³H]-BTX, 300 μ M veratridine, and 30 μ g/mL of scorpion toxin in 150 μ M of the standard binding medium. Compound **4b** was mixed and incubated for 1 h at 37°C. The reactions were stopped by addition of 3 mL of ice-cold wash medium consisting of 163 mM chlorine chloride, 5 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (adjusted to pH 7.4 at 36°C with Tris base), 1.8 mM CaCl₂, 0.8 mM MgSO₄, 1 mg/mL of bovine serum albumin. The synaptosomes were immediately collected on GF/C glass filters under vacuum and washed 3 times with 3 mL of the wash medium. The filters were suspended in liquid scintillation fluid, and bound radioactivity was counted in a liquid scintillation spectrometer.

In Vitro Metabolic Stability in Rat Liver Microsomes

To a 0.1 M potassium phosphate buffer (pH 7.4) containing a test compound (1 μ M), 0.25 mg/mL of male rat liver microsomes, and 5 mM MgCl₂, 1 mM reduced nicotinamide adenine dinucleotide phosphate (NADPH) was added to start a reaction. After incubation for 0, 5, or 10 min at 37°C, CH₃CN was added to stop the reaction. The concentration of the test compound at each time point was measured by LC/MS. Hepatic intrinsic clearance (CL) was determined by the temporal changes in the concentration of the test compound.

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