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# Synthesis and Biological Evaluation of New 4-Arylpiperidines and 4-Aryl-4-piperidinols: Dual $Na^+$ and $Ca^{2+}$ Channel Blockers with Reduced Affinity for Dopamine $D_2$ Receptors

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**Abstract**—A series of novel 4-arylpiperidines and 4-aryl-4-piperidinols (**2a–f**, **3a–f** and **4a–f**) was synthesized and evaluated for blocking effects on both neuronal $Na^+$ and T-type $Ca^{2+}$ channels and binding affinity for dopamine $D_2$ receptors. Most of the compounds blockaded both ion channels with potency greater than or equal to flunarizine **1a** which was adopted as a reference standard. In addition, these compounds had significantly reduced affinity for dopamine $D_2$ receptors which is common in this class of structure. Compounds **2a–f**, **3a–f** and **4a–f** exhibited potent anticonvulsant effects following systemic (ip) administration on audiogenic seizures in DBA/2 mice, indicating their excellent brain permeability. The neuroprotective activity of **2a**, **3a** and **4a** was also assessed in a transient middle cerebral artery occlusion (MCAO) model. These compounds significantly reduced neuronal damage without affecting ischemic hyperthemia, while flunarizine **1a** produced only minor reductions. In particular, **4a** had 1.7-fold the potency in this MCAO model but only 1/20 the affinity for dopamine $D_2$ receptors of **1a**. The superposition of **2a**, **3a** and **4a** on the basis of analyses of systematic conformation and similar structure has revealed that the cinnamyl, phenacyl and phenoxypropanol groups are likely to be structurally and biologically equivalent. Moreover, the superposition of **2a** and **2f** shows that diphenyl ether and biphenyl groups occupy a similar space, suggesting that both groups act as a bioisostere for the blockade of ion channels; however, this is not the case for dopamine $D_2$ receptors since only biphenyl compounds such as **2f** had high affinity similar to flunarizine **1a**. Compound **4a** (SUN N5030) has a good pharmacological profile and may be useful in the alleviation and treatment of ischemic diseases. 

## Introduction

Calcium ion ($Ca^{2+}$) is indispensable to the survival of a cell and works as an almost universal signal messenger, controlling a diverse range of cellular processes under physiological conditions.[1] However, the rise in the intracellular concentration of $Ca^{2+}$ to a pathological level due to depletion of ATP following the failure of intracellular energy-dependent ion homeostasis caused by ischemia is directly connected to cell death or damage.[2] This phenomenon is known as $Ca^{2+}$ overload which induces functional disorders in the mitochondria and randomly activates various $Ca^{2+}$-dependent enzymatic reactions and invites further $Ca^{2+}$ overload. A better understanding of cell death and damage has revealed that $Ca^{2+}$ overload is a major causative factor in the progressive and delayed death of nerve cells that occurs in cerebral injury and cerebrovascular diseases such as stroke and trauma.[2,3] It has recently been demonstrated that the aberrant activation of $Na^+$ and $Ca^{2+}$ channels is closely involved in the pathway of $Ca^{2+}$ overload and the accumulation of intracellular $Na^+$ ions results in a rapid $Ca^{2+}$ overload by the reverse operation of the $Na^+/Ca^{2+}$ exchange mechanism.[2,3]

In 1985, van Zwieten advocated that a group of compounds, represented by flunarizine **1a** which blocks $Na^+$ and $Ca^{2+}$ channels to prevent the overloading of the cell with $Ca^{2+}$ ions under pathological and ischemic conditions, should be defined as $Ca^{2+}$ overload blockers and discriminated from conventional $Ca^{2+}$ entry blockers.[4] Although only a few types of $Na^+$ and/or $Ca^{2+}$ channel blockers, including **1a**,[3b,4,5] lomerizine (KB-2796) **1b**,[6] U-92032 **1c**,[7] and lifarizine (RS-87476) **1d**,[8] have been reported as $Ca^{2+}$ overload blockers and

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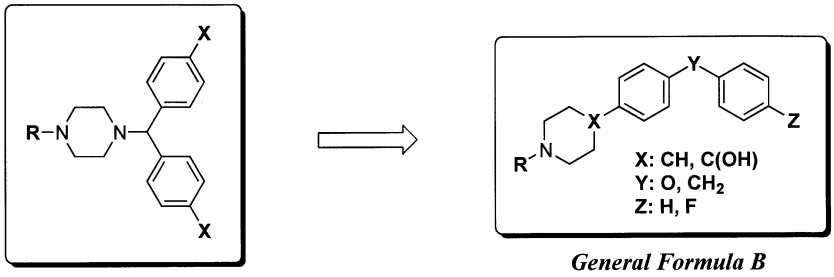
shown to prevent neuronal cell death in animal models of ischemia, they have in common a diphenylmethylpiperazine moiety shown as the general formula (A) which not only causes the blockade of ion channels but also has significant affinity for dopamine $D_2$ receptors, showing a clear link to the clinical risk of extrapyramidal side effects[9] (Chart 1). To overcome this problem, there is a need to develop a class of compounds that have significant effects on ischemia but whose structural features are distinctly different from those of **1a**–**d**. Consequently, the strategy we have adopted to achieve this objective is based upon the molecular modification of the general formula (A), in expectation of the discovery of a new scaffold. Recently, we have identified a structurally novel class of arylpiperidines having the general formula (B) as neuronal $Na^+$ and T-type $Ca^{2+}$ channel blockers with reduced affinity for dopamine $D_2$ receptors.[10] Here we provide a full account of this study including the structure–activity relationships (SAR) on the basis of a systematic conformation search and a similar structure analysis.

## Chemistry

Compounds **9a**–**f** were prepared using the pathway shown in Scheme 1. Treatment of *N*-*tert*-butoxycarbonyl-4-piperidone or *N*-benzyl-4-piperidone, **6a** or **6b**, with the Grignard or lithium reagent prepared from the corresponding aryl bromides **5a**–**d** in a conventional manner gave **7a**–**f** in 52–77% yields. Deprotection of the Boc group in **7a**–**c** by exposure to trifluoroacetic acid proceeded with dehydration of the *tert*-hydroxy group and gave the tetrahydropyridine derivatives, **8a** (92%), **8b** (67%) and **8c** (65%), respectively. Hydrogenation of **8a**–**c** in the presence of a catalytic amount of Pd–C in methanol yielded 4-arylpiperidines **9a** (88%), **9b** (87%) and **9c** (89%), respectively. 4-Aryl-4-piperidinols **9d**–**f** were also prepared by hydrogenation of **7d**–**f** in the presence of a catalytic amount of palladium hydroxide in methanol. Reactions between **9a**–**f** and cinnamyl bromide, and between **9a**–**f** and phenacyl bromide in the presence of triethylamine in acetonitrile gave **2a**–**f** in 35–76% yields and **3a**–**f** in 50–96% yields, respectively (Scheme 2). The coupling reaction of **9a**–**f** with phenyl glycidyl ether in 2-propanol proceeded smoothly to give **4a**–**f** in 74–96% yields. Compounds **4a**–**f** were essentially prepared in the racemic form. To clarify the effect of chirality with respect to the secondary alcohol moiety, (*S*)-**4a** and (*R*)-**4a**, both enantiomers of **4a**, were prepared in similar chemical yields by employing chiral phenyl glycidyl ethers[11] in the final step. Their optical purities were determined by normal phase HPLC using a Daicel Chiralpak OD column (*n*-hexane/2-PrOH/diethylamine = 500:500:1) and were found to be >98% ee. Compounds **2a**–**f**, **3a**–**f** and **4a**–**f** were converted into hydrochloride or fumarate salt in a conventional manner before the biological assays.

## Results and Discussion

Although flunarizine **1a** is regarded as a potent nonselective $Ca^{2+}$ channel blocker, extensive study has revealed that its mechanisms of action in preventing cell death is mainly the blockade of $Na^+$ and T-type $Ca^{2+}$ channels.[3] T-type $Ca^{2+}$ channels act as a trigger for depolarization, modulating cell excitability and sig-



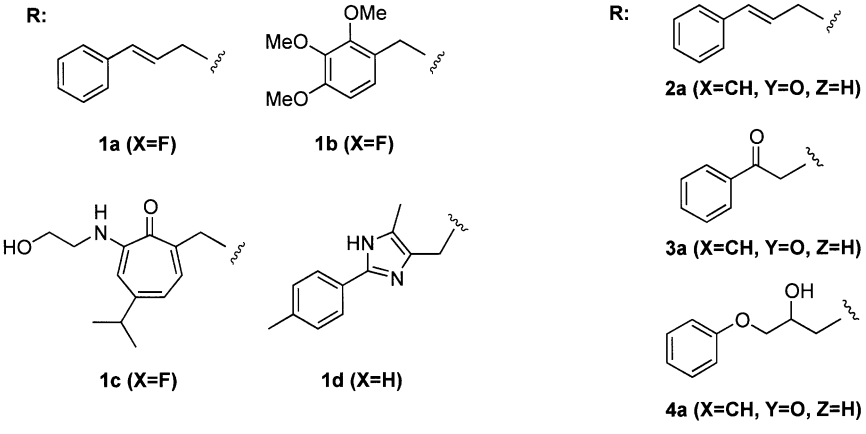
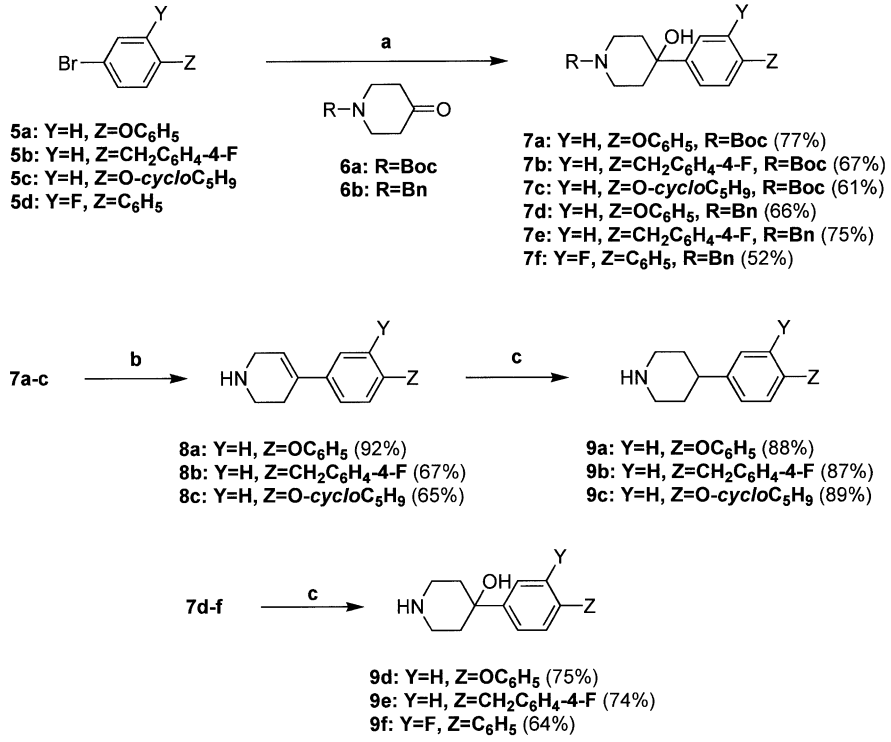




**Chart 1.**



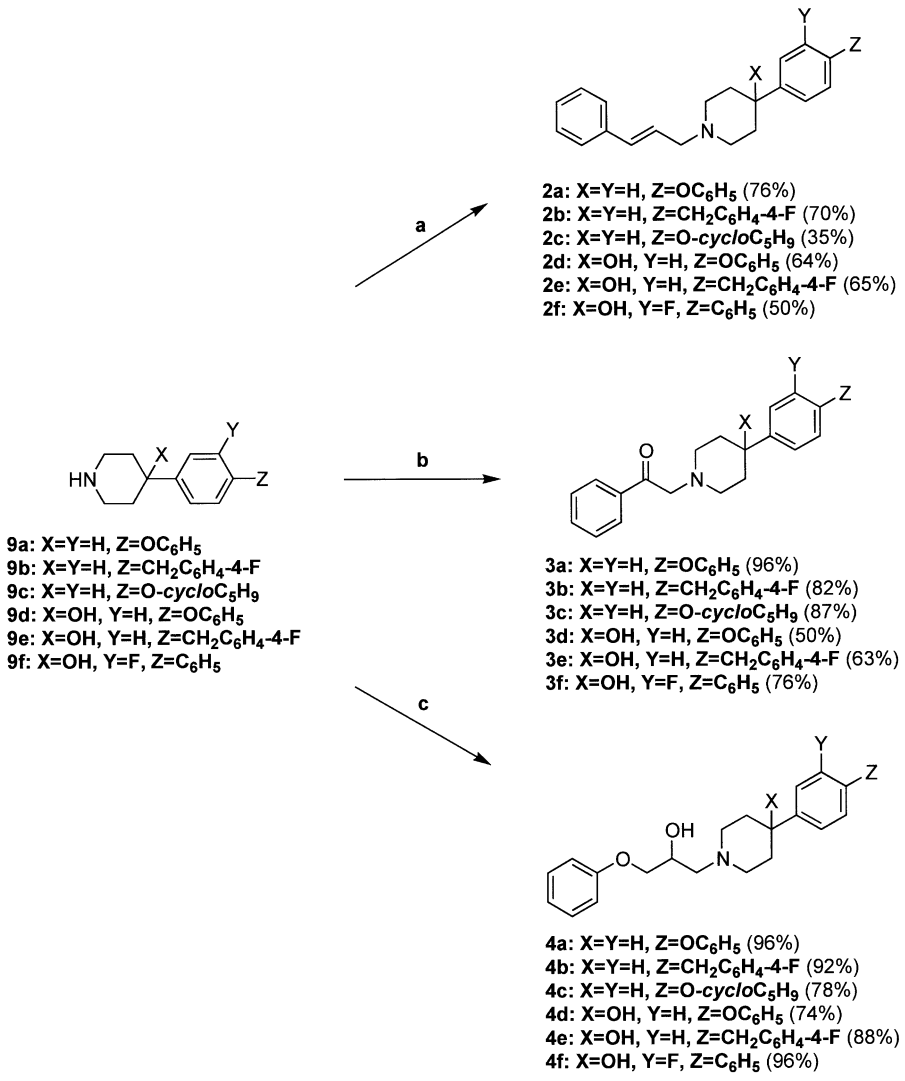

**Scheme 1.** Reagents and conditions: (a) Mg, THF or *n*-BuLi, THF; (b) TFA–$CH_2Cl_2$ (1:1), rt, 12 h; (c) $H_2$, cat Pd–C or $Pd(OH)_2$, MeOH, 12 h.

nificantly contribute to epileptic action.[12] Therefore, we first assessed the effects of a series of synthetic compounds **2a–f**, **3a–f** and **4a–f** on $Na^+$ channels and T-type $Ca^{2+}$ channels. The effects on $Na^+$ channels were evaluated based on the inhibitory action on veratridine-induced depolarization in rat cerebrocortical synaptosomes using the voltage-sensitive fluorescent dye Rhodamine 6G.[13] The effects on low-threshold (T-type) $Ca^{2+}$ currents in primary cultured rat cerebrocortical neurons were examined using a whole-cell voltage-clamp recording technique.[3d] As shown in Tables 1–3, most of the compounds were found to block both $Na^+$ and T-type $Ca^{2+}$ channels with potency greater than or equal to flunarizine **1a** which was adopted as a reference standard. As for the anti-veratridine effects, **2c**, **3c** and **4c**, possessing a cyclohexyloxy group as the Z substituent, showed the best results with $IC_{50}$ values of $<0.1\,\mu M$. The compounds in Table 1–3 showed a concentration-dependent block of T-type $Ca^{2+}$ currents induced by a depolarizing pulse to $-40\,mV$ from a holding potential ($V_H$) of $-100\,mV$. Interestingly, **2b** and **4f** are the most potent compounds, showing $IC_{50}$ values of $0.6\,\mu M$ for the blockade of T-type $Ca^{2+}$ channels, however, the phenacyl derivative **3d** had markedly decreased activity.

The binding affinity for dopamine $D_2$ receptors was assessed using [$^3$H]-racoplide as a ligand binding to rat striatum membranes.[14] In remarkable contrast to the potent activity against $Na^+$ and T-type $Ca^{2+}$ channels, our compounds exhibited extremely low affinity for dopamine $D_2$ receptors, with the exception of **2f**, **3f** and **4f** having the biphenyl group at the 4-position of the 4-piperidinol ring system. Surprisingly, **4b** practically lost all binding affinity for dopamine $D_2$ receptors ($IC_{50}$ $>10\,\mu M$). These differences clearly demonstrate that compounds **2a–e**, **3a–e** and **4a–e** possess structural features distinctly different from those of flunarizine **1a** and its analogues.

In addition, our compounds were found to cause reversible inhibition of $Na^+$ currents in a concentration- and voltage-dependent manner in primary cultured rat cerebrocortical neurons using a whole-cell voltage-clamp recording technique. For instance, the $IC_{50}$ values of **2a**, **3a** and **4a** obtained at a $V_H$ of $-100\,mV$ were more than 10, 10 and $5\,\mu M$, respectively, whereas these values dropped to 1.4, 1.5 and $0.7\,\mu M$, respectively, at a $V_H$ of $-70\,mV$. The racemate **4a** and both the enantiomers, (*S*)-**4a** and (*R*)-**4a**, could not be discriminated with respect to potency and selectivity in primary assays; however, (*S*)-**4a** showed a voltage-dependent block of $Na^+$ channels that was slightly greater than that of its enantiomer (*R*)-**4a**. This result may indicate that the blockade of ion channels strongly depends upon the membrane potential and state of the channel; resting, opening or inactivated.[15] It should be noted that the markedly enhanced voltage dependency promises event-specific inhibition of ion channels without primary haemodynamic adverse effects.

Computational chemistry has proved valuable tools in the study of molecular events and of SAR. To elucidate the common pharmacophores and/or the special arrangement of components essential for inhibition of ion channels, a systematic conformation search and a similar structure analysis by root-mean-square (rms) fitting were carried out for compounds **2a**, **2f**, **3a** and **4a**. Structures were minimized with MM2 parameters implemented by Macromodel.[16] Figures 1 and 2 show

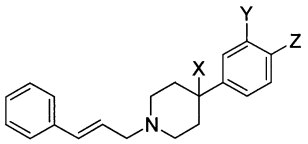



**Scheme 2.** Reagents and conditions: (a) cinnamyl bromide, $Et_3N$, MeCN, 80 °C, 2 h; (b) phenacyl bromide, $Et_3N$, MeCN, 80 °C, 2 h; (c) phenyl glycidyl ether, 2-PrOH, reflux, 2 h.

reasonable superposition of **2a**, **2f**, **3a** and **4a** the structures of which were 0.9, 1.5, 4.1 and 3.9 kcal/mol higher in energy than the lowest energy conformers, respectively. The RMS error for fitting **2f**, **3a** and **4a** to **2a** are 0.44, 0.51 and 0.10 Å, respectively. All compounds have the piperidine ring in the chair conformation and the 4-aryl group in an equatrial position relative to the piperidine ring. As depicted in Figure 1, the cinnnamyl group in **2a** (white), the phenacyl group in **3a** (red) and the phenoxypropanol group in **4a** (green) closely overlap. The distance from the center of each benzene ring in the above lipophilic parts of **3a** and **4a** to that of **2a** is 1.27 and 0.13 Å, respectively. From these results, it can be speculated that the three lipophilic parts are structurally and biologically equivalent and that these compounds occupy nearly the same area of the ion channels due to their possible conformational changes. Moreover, as shown in Figure 2, the diphenyl ether group in **2a** (white) and the biphenyl group in **2f** (magenta) occupy quite similar spatial positions, leading to suggestions that both the groups are a pair of bioisosteres for the blockade of ion channels. However, the biphenyl group does not possess the same profile as that of the diphenyl ether group since biphenyl compounds **2f**, **3f** and **4f** show high affinity for dopamine $D_2$ receptors similar to flunarizine **1a**, which has 6.7–32.5 times the affinity of other synthetic compounds. Interestingly, the simpler known compound (*E*)-4-phenyl-1-(3-phenyl-2-propenyl)piperidine[17] had decreased the inhibitory activity for $Na^+$ and T-type $Ca^{2+}$ channels (both $IC_{50} > 10\,\mu M$) but increased binding affinity for dopamine $D_2$ receptors ($IC_{50} = 0.19\,\mu M$). These results imply that the Z substitutent in **2a–f**, **3a–f** and **4a–f** plays a pivotal role in a hydrophobic interaction, where an optimum size is required. Therefore, the Z substituent may change certain interatomic distances and bond angles, which not only affect the potency for ion channels but also interfere with receptor binding.

Next, we investigated the effects of **2a–f**, **3a–f** and **4a–f** on audiogenic seizures in DBA/2 mice to confirm their in vivo activity and permeability into brain.[18] Anticonvulsant and neuroprotective activities are mutually related in several voltage-dependent $Na^+$ channel blockers.[18c] Compounds **2a–f**, **3a–f** and **4a–f** exhibited potent anticonvulsant effects following systemic (ip)

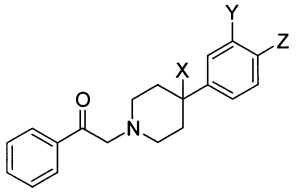
**Table 1.** Biological activity of **2a**–**g**[a]




| Compd[b] | X | Y | Z | $IC_{50}$ (μM) Anti-veratridine[c] | T-type $Ca^{2+}$ Currents[d] | $D_2$[e] | Anticonvulsant effect in DBA/2 mice[f] $ED_{50}$ (mg/kg; ip) |
|---|---|---|---|---|---|---|---|
| **2a** | H | H | $OC_6H_5$ | 0.32 | 0.8 | 2.68 | 4.2 |
| **2b** | H | H | $CH_2C_6H_4$-4-F | 0.19 | 0.6 | 3.38 | 2.2 |
| **2c** | H | H | O-*cyclo*$C_5H_9$ | <0.1 | 5.0 | 5.03 | 5.0 |
| **2d** | OH | H | $OC_6H_5$ | 0.36 | 1.7 | 4.80 | 2.5 |
| **2e** | OH | H | $CH_2C_6H_4$-4-F | 0.23 | 1.5 | 6.50 | 2.7 |
| **2f** | OH | F | $C_6H_5$ | 0.28 | 1.9 | 0.84 | 5.8 |
| **1a** | | | | 0.29 | 2.2 | 0.228 | 6.4 |

[a]Each value represents multiple determinations (≥2) with a deviation of less than 20%.
[b]Each assay was carried out after conversion to the hydrochloride or fumarate salt.
[c]Determined as inhibitory effects upon the veratridine-induced depolarization in rat cerebrocortical synaptosomes using a membrane potential sensitive fluorescent dye Rhodamine 6G.[13]
[d]Determined as inhibitory effects on low-threshold (T-type) $Ca^{2+}$ currents in primary cultured rat cerebrocortical neurons using a whole-cell voltage-clamp recording technique.[3d]
[e]Determined in competition experiments with [$^3$H]-raclopride.[14]
[f]Compounds were administered intraperitoneally to DBA/2 mice ($n=6$) 20 min prior to auditory stimulation of at least 90 dB for 1 min.[18]

**Table 2.** Biological activity of **3a**–**g**[a]



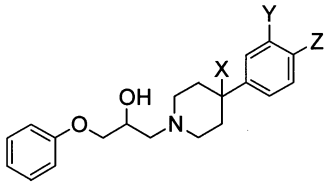

| Compd | X | Y | Z | $IC_{50}$ (μM) Anti-veratridine | T-type $Ca^{2+}$ Currents | $D_2$ | Anticonvulsant effect in DBA/2 mice $ED_{50}$ (mg/kg; ip) |
|---|---|---|---|---|---|---|---|
| **3a** | H | H | $OC_6H_5$ | 0.19 | 3.2 | 1.53 | 3.3 |
| **3b** | H | H | $CH_2C_6H_4$-4-F | 0.25 | 2.3 | 2.69 | 2.5 |
| **3c** | H | H | O-*cyclo*$C_5H_9$ | <0.1 | 4.1 | 2.91 | 1.6 |
| **3d** | OH | H | $OC_6H_5$ | 0.45 | >10 | 1.65 | 3.5 |
| **3e** | OH | H | $CH_2C_6H_4$-4-F | 0.78 | 1.5 | 4.12 | 2.5 |
| **3f** | OH | F | $C_6H_5$ | 0.32 | 3.0 | 0.71 | 1.9 |

[a]See footnotes in Table 1.

administration with $ED_{50}$ values as shown in Tables 1–3. We also assessed the neuroprotective activity of **2a**, **3a** and **4a** against transient MCAO[19] for 60 min in rats by measuring peripheral type benzodiazepine binding site (PTBBS) densities[5b] in ipsilateral cortical and striatal homogenates as a quantitative index for neuronal damage 10 days after reperfusion. Each compound was administered immediately after both MCAO and reperfusion (each 3 mg/kg, iv). Consequently, **2a**, **3a** and **4a** significantly reduced PTBBS levels by 47.5, 46.6 and 65.8%, respectively [$*p<0.05$ vs vehicle; each value represents multiple determinations (≥6) with a deviation of less than 20%]. In particular, **4a** had 1.7-fold the potency but only 1/20 the affinity for dopamine $D_2$ receptors of flunarizine **1a**, which reduces PTBBS levels by 37.9% ($*p<0.05$) in this MCAO model. Rectal temperature was found to increase during MCAO up to 38.5 °C. Our compounds did not significantly affect this ischemic hyperthermia at the doses tested, exhibiting neuroprotection. These results indicate that **2a**, **3a** and **4a** have a pronounced neuroprotective efficacy against neuronal damage induced by transient focal ischemia in rats. Interestingly, compounds **2a**, **3a** and **4a** at the effective doses had no effects on systemic blood pressure and heart rate in anesthetized rats.

In conclusion, we described a structurally novel class of 4-arylpiperidines and 4-aryl-4-piperidinols, represented by **2a**, **3a** and **4a**, that have not only highly potent blocking effects on both neuronal $Na^+$ and T-type

**Table 3.** Biological activity of **4a–g**[a]




| Compd | X | Y | Z | $IC_{50}$ (μM) Anti-veratridine | $IC_{50}$ (μM) T-type $Ca^{2+}$ Currents | $IC_{50}$ (μM) $D_2$ | Anticonvulsant effect in DBA/2 mice $ED_{50}$ (mg/kg; ip) |
|---|---|---|---|---|---|---|---|
| **4a** | H | H | $OC_6H_5$ | 0.22 | 3.5 | 4.64 | 5.0 |
| **(*S*)-4a** | H | H | $OC_6H_5$ | 0.13 | 2.0 | 4.34 | 2.5 |
| **(*R*)-4a** | H | H | $OC_6H_5$ | 0.12 | 2.7 | 4.08 | 2.5 |
| **4b** | H | H | $CH_2C_6H_4$-4-F | 0.36 | 0.8 | >10 | 7.5 |
| **4c** | H | H | O-*cyclo*$C_5H_9$ | <0.1 | 5.2 | 5.40 | <2.5 |
| **4d** | OH | H | $OC_6H_5$ | 0.39 | 2.1 | 3.20 | 3.9 |
| **4e** | OH | H | $CH_2C_6H_4$-4-F | 0.44 | 1.3 | 7.41 | 3.7 |
| **4f** | OH | F | $C_6H_5$ | 0.30 | 0.6 | 0.16 | 1.3 |

[a]See footnotes in Table 1.

$Ca^{2+}$ channels but also extremely low affinity for dopamine $D_2$ receptors. A systematic conformation search and a similar structure analysis have revealed that the cinnamyl, phenacyl and phenoxypropanol groups are likely to be bioisosteres for the blockade of ion channels. Furthermore, diphenyl ether and biphenyl groups are considered to act as a bioisostere for the blockade of ion channels; however, this is not the case for dopamine $D_2$ receptors since compounds with a biphenyl group had high affinity similar to flunarizine **1a**. The identification of compound **4a (SUN N5030)** may lead to new and more effective neuroprotectant strategies for ischemic diseases such as stroke and trauma, one of the leading causes of death and disability in industrialized societies.

## Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus or a Büchi 535 melting point apparatus and are uncorrected. $^1H$ NMR spectra were recorded on a Brucker ARX 400 FT NMR spectrometer. Chemical shifts are expressed in parts per million (δ, ppm) with tetramethylsilane as an internal standard. IR spectra were recorded on a Perkin–Elmer 1640 instrument. Optical rotations were determined on a JASCO DIP-181 polarimeter. The specific rotation has not been corrected. Elemental analyses of these elements fall within ±0.4% of the calculated values. Analytical TLC was carried out using Silica-gel 60 F254 plates (Merck Art 5715) or TLC plate NH (Fuji Silysia Chemical Ltd.). Column chromatography was performed on silica-gel 60 (Merck Art 9185, 230–400 mesh) or Chromatorex NH-DM1020 (Fuji Silysia Chemical Ltd., 100–200 mesh).

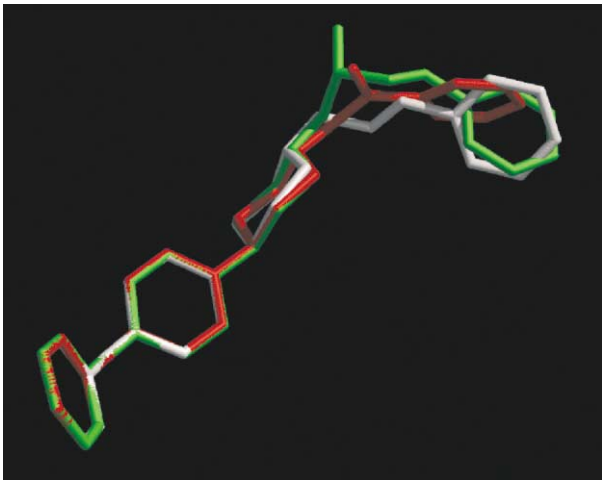


**Figure 1.** Superposition of biologically active compounds **2a** (white), **3a** (red) and **4a** (green).

***N*-*tert*-Butoxycarbonyl-4-(4-phenoxyphenyl)-4-piperidinol (7a).** A 35-mL volume of 4-phenoxyphenyl magnesium bromide [0.6 M in tetrahydrofuran (THF)] prepared from 4-bromodiphenyl ether **5a** was added to a stirred solution of N-*tert*-buthoxycarbonyl-4-piperidone **6a** (3.5 g, 17.6 mmol) in anhydrous THF (100 mL) at 0 °C under an argon atmosphere. After being stirred for 1 h

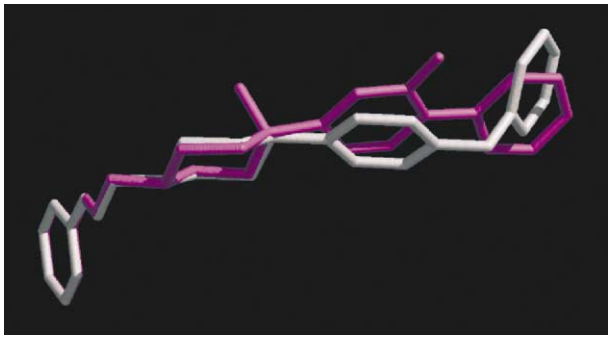


**Figure 2.** Superposition of diphenyl ether **2a** (white) and its biphenyl derivative **2f** (magenta).

at the same temperature, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ and the product was extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography over silica gel using *n*-hexane/AcOEt = 3:1 as an eluent to give **7a** (2.92 g, 45% yield) as a colorless oil. $^1$H NMR ($CDCl_3$) δ 1.48 (9H, s), 1.73–1.76 (2H, m), 1.99 (2H, m), 3.25 (2H, m), 4.02 (2H, m), 7.00 (3H, m), 7.11 (1H, m), 7.34 (2H, m), 7.43 (2H, d, $J$ = 8.8 Hz); IR ($CHCl_3$) 3094, 3436, 3010, 2980, 2875, 1682, 1589, 1507, 1489, 1430, 1367, 1242, 1168 $cm^{-1}$.

***N*-*tert*-Butoxycarbonyl-4-[4-(4-fluorobenzyl)phenyl]-4-piperidinol (7b).** The starting material, 4-bromo-4α-fluorodiphenylmethane **5b**, was prepared as follows: 13 mL of 4-fluorophenyl magnesium bromide (1.54 M in THF) prepared from 4-bromofluorobenzene was added to a stirred solution of 4-bromobenzaldehyde (3.3 g, 18.0 mmol) in anhydrous THF (10 mL) at 0 °C under an argon atmosphere. After being stirred for 30 min at the same temperature, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ and the product was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography over silica gel using *n*-hexane/AcOEt = 6:1 as an eluent to give 4-bromo-4′-fluorodiphenylmethanol as a colorless oil. To a stirred solution of the obtained 4-bromo-4′-fluorodiphenylmethanol in trifluoroacetic acid (25 mL) was added triethylsilane (5.6 mL, 35 mmol) at 0 °C under an argon atmosphere. After being stirred for 1 h at room temperature, the reaction mixture was made basic with 10% aqueous NaOH until the pH was 10 at 0 °C and the product was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography over silica gel using *n*-hexane as an eluent to give **5b** (3.9 g, 82% yield) as a colorless oil. $^1$H NMR ($CDCl_3$) δ 3.89 (2H, s), 6.97 (2H, t, $J$ = 8.6 Hz), 7.03 (2H, d, $J$ = 8.3 Hz), 7.10 (2H, dd, $J$ = 8.6, 5.4 Hz), 7.40 (2H, d, $J$ = 8.3 Hz); IR (neat) 3039, 1603, 1508, 1488, 1222, 1156, 1069 1011, 797 $cm^{-1}$.

Next, 6.5 mL of *n*-BuLi (0.6 M in *n*-hexane) was added dropwise to a stirred solution of **5b** (2.5 g, 9.4 mmol) in anhydrous ether (25 mL) at −78 °C under an argon atmosphere. The reaction mixture was warmed to −20 °C and stirred for 1 h. Then, a solution of **6a** (3.5 g, 17.6 mmol) in anhydrous THF (100 mL) was added at the same temperature and stirring was continued for 1 h at 0 °C. After being quenched with saturated aqueous $NH_4Cl$, the product was extracted with ether, washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave a residue, which was chromatographed over silica gel using *n*-hexane/AcOEt = 4:1 as an eluent to afford **7b** (2.69 g, 77% yield) as a colorless oil. $^1$H NMR ($CDCl_3$) δ 1.48 (9H, s), 1.70–1.73 (2H, m), 1.97 (2H, m), 3.24 (2H, m), 3.94 (2H, s), 3.99 (2H, m), 6.96 (2H, t, $J$ = 8.7 Hz), 7.11–7.17 (4H, m), 7.38 (2H, d, $J$ = 8.3 Hz); IR ($CHCl_3$) 3018, 1682, 1508, 1431, 1367, 1168 $cm^{-1}$.

***N*-*tert*-Butoxycarbonyl-(4-(4-cyclopentyloxy)phenyl)-4-piperidinol (7c).** The starting material, 4-bromophenyl cyclopentyl ether **5c**, was prepared as follows: a mixture of *p*-bromophenol (1.00 g, 5.78 mmol), cyclopentyl bromide (682 μM, 6.36 mmol) and sodium hydroxide (254 mg, 6.36 mmol) in EtOH (10 mL) was refluxed overnight. The reaction mixture was concentrated in vacuo and then diluted with water. The product was extracted with AcOEt and the extract was washed with 1 N NaOH and water. After being dried over $MgSO_4$ and removal of the solvent in vacuo, the obtained residue was purified by column chromatography over silica gel using *n*-hexane as an eluent to give **5c** (878 mg, 63% yield) as a colorless oil. $^1$H NMR ($CDCl_3$) δ 1.59–1.63 (2H, m), 1.76–1.90 (6H, m), 4.69–4.71 (1H, m), 6.74 (2H, d, $J$ = 8.9 Hz), 7.34 (2H, d, $J$ = 8.9 Hz); IR ($CHCl_3$) 2965, 1487, 1242, 1170, 986, 824 $cm^{-1}$.

Compound **7c** was prepared by the same procedure described for the synthesis of **7b** using **5c** (1.27 g, 5.27 mmol) and **6a** (997 mg, 5.00 mmol) in 65% yield (1.168 g) as a pale yellow oil. $^1$H NMR ($CDCl_3$) δ 1.48 (9H, s), 1.61–1.63 (2H, m), 1.72–1.99 (10H, m), 3.25 (2H, m), 3.97 (2H, m), 4.75 (1H, m), 6.85 (2H, d, $J$ = 8.8 Hz), 7.35 (2H, d, $J$ = 8.8 Hz); IR ($CHCl_3$) 3011, 2971, 1682, 1609, 1509, 1478, 1430, 1367, 1279, 1269, 1086, 1030, 986 $cm^{-1}$.

***N*-Benzyl-4-(4-phenoxyphenyl)-4-piperidinol (7d).** This compound was prepared in 66% yield as a pale orange oil from commercially available 4-bromodiphenyl ether **5a** and *N*-benzyl-4-piperidone **6b**, using the procedure described for **7a**. $^1$H NMR ($CDCl_3$) δ 1.73–1.78 (2H, m), 2.15 (2H, m), 2.58 (2H, m), 2.77–2.81 (2H, m), 3.58 (2H, s), 6.96–7.02 (4H, m), 7.09 (1H, m), 7.28–7.35 (7H, m), 7.47 (2H, d, $J$ = 8.8Hz); IR ($CHCl_3$) 2946, 2818, 2399, 1704, 1590, 1506, 1490, 1106 $cm^{-1}$.

***N*-Benzyl-4-[4-(4-fluorobenzyl)phenyl]-4-piperidinol (7e).** This compound was prepared in 75% yield as a yellow oil from 4-bromo-4′-fluorodiphenylmethane **5b** and *N*-benzyl-4-piperidone **6b**, using the procedure described for **7b**. $^1$H NMR ($CDCl_3$) δ 1.71–1.74 (2H, m), 2.14 (2H, m), 2.44–2.49 (2H, m), 2.74–2.79 (2H, m), 3.58 (2H, s), 3.93 (2H, s), 6.96 (2H, t, $J$ = 8.7 Hz), 7.12–7.15 (4H, m), 7.29–7.36 (5H, m), 7.43 (2H, d, $J$ = 8.3 Hz); IR ($CHCl_3$) 2950, 2816, 1711, 1603, 1508, 1367, 1344, 1157, 1110, 1043 $cm^{-1}$.

***N*-Benzyl-4-(3-fluoro-4-phenyl)phenyl-4-piperidinol (7f).** This compound was prepared in 62% yield as a reddish orange oil from 4-bromo-3-fluorobiphenyl **5f** and *N*-benzyl-4-piperidone **6b**, using the procedure described for **7a**. $^1$H NMR ($CDCl_3$) δ 1.74–1.78 (2H, m), 2.18 (2H, m), 2.48 (2H, m), 2.79–2.83 (2H, m), 3.60 (2H, s), 7.29–7.38 (8H, m), 7.40–7.45 (3H, m), 7.54 (2H, d, $J$ = 8.2 Hz); IR ($CHCl_3$) 2946, 2817, 1706, 1483, 1406, 1367, 1345, 1119 $cm^{-1}$.

**4-(4-Phenoxyphenyl)-1,2,3,6-tetrahydropyridine (8a).** To a stirred solution of **7a** (10.5 mmol) in $CH_2Cl_2$ (40 mL) was added dropwise trifluoroacetic acid (10 mL) at 0 °C. After being stirred for 30 min at room temperature, the

reaction mixture was made basic with 10% aqueous NaOH until the pH was 9 at 0 °C and the product was extracted with $CH_2Cl_2$. The extract was washed with brine and dried over $MgSO_4$. The solvent was concentrated in vacuo to give **8a** (2.43 g, 92% yield) as an orange powder. Its hydrochloride was obtained by treating with 2-PrOH saturated with HCl in a conventional manner followed by recrystallization from MeOH–ether in 80% yield (2.25 g), and which was used in the next step. $^1$H NMR ($CDCl_3$) δ 2.45 (2H, m), 3.11 (2H, t, $J$ = 5.7 Hz), 3.53 (2H, m), 6.09 (1H, m), 6.96 (2H, d, $J$ = 8.7 Hz), 7.05 (2H, d, $J$ = 7.7 Hz), 7.09 (2H, t, $J$ = 7.4 Hz), 7.30–7.37 (4H, m); IR ($CHCl_3$) 3024, 3018, 1674, 1606, 1508, 1489, 1243 cm$^{-1}$.

**4-[4-(4-Fluorobenzyl)phenyl]-1,2,3,6-tetrahydropyridine (8b).** To a stirred solution of **7b** (6.34 mmol) in $CH_2Cl_2$ (15 mL) was added dropwise trifluoroacetic acid (5 mL) at 0 °C. After being stirred overnight at room temperature, the reaction mixture was concentrated in vacuo. The residue was chromatographed over NH–silica gel using $CH_2Cl_2$/MeOH = 30:1 as an eluent to give **8b** (1.14 g, 67% yield) as a yellow oil. $^1$H NMR ($CDCl_3$) δ 2.41–2.46 (2H, m), 3.09 (2H, t, $J$ = 5.8 Hz), 3.50–3.53 (2H, m), 3.93 (2H, s), 6.10 (1H, m), 6.96 (2H, t, $J$ = 8.7), 7.10–7.15 (4H, m), 7.31 (2H, d, $J$ = 8.2 Hz); IR ($CHCl_3$) 3020, 2926, 2993, 1604, 1508, 1434, 1157, 1016, 930 cm$^{-1}$.

**4-(4-Cyclopentyloxyphenyl)-1,2,3,6-tetrahydropyridine (8c).** This compound was obtained as a yellow powder from **7c** using the procedure described for **8b** in 65% yield. $^1$H NMR ($CDCl_3$) δ 1.59–1.62 (2H, m), 1.77–1.91 (6H, m), 2.40–2.44 (2H, m), 3.09 (2H, t, $J$ = 5.7 Hz), 3.51 (2H, dd, $J$ = 5.8, 2.8 Hz), 4.75 (1H, m), 6.03 (1H, m), 6.82 (1H, d, $J$ = 8.8 Hz), 7.29 (2H, d, $J$ = 8.8 Hz); IR ($CHCl_3$) 2963, 1606, 1509, 1438, 1358, 1317, 1274, 1177, 1114, 1090, 988 cm$^{-1}$.

**4-(4-Phenoxyphenyl)piperidine (9a).** The hydrochloride of **8a** (2.25 g, 7.82 mmol) was dissolved in MeOH (50 mL) and hydrogenated in the presence of 10% Pd–C (338 mg) under atmospheric pressure for 20 h. The catalyst was filtered off and the filtrate was concentrated in vacuo. To the residue was added 10% aqueous NaOH and the product was extracted with AcOEt. The extract was washed with brine and dried over $MgSO_4$ to give **9a** (1.74 g, 88% yield) as a pale yellow oil. $^1$H NMR ($CDCl_3$) δ 1.63 (2H, ddd, $J$ = 12.7, 12.2, 3.7 Hz), 1.82–1.85 (2H, m), 2.60 (1H, tt, $J$ = 12.2, 3.7 Hz), 2.74 (2H, td, $J$ = 12.2, 3.7 Hz), 3.17–3.20 (2H, m), 6.95 (2H, d, $J$ = 8.5 Hz), 7.00 (2H, d, $J$ = 8.0 Hz), 7.08 (1H, t, $J$ = 7.5 Hz), 7.18 (2H, d, $J$ = 8.5 Hz), 7.32 (2H, dd, $J$ = 8.0, 7.5 Hz); IR ($CHCl_3$) 3024, 2960, 2712, 1590, 1508, 1489, 1241, 1208 cm$^{-1}$.

**4-[4-(4-Fluorobenzyl)phenyl]piperidine (9b).** To a solution of **8b** (717 mg, 2.68 mmol) in MeOH was added acetic acid (228 μL, 4.02 mmol) and the mixture was hydrogenated in the presence of 10% Pd–C (338 mg) under atmospheric pressure overnight. The catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was chromatographed over NH–silica gel using $CH_2Cl_2$/MeOH = 30:1 as an eluent to give **9b** (627 mg, 87% yield) as a white powder. $^1$H NMR ($CDCl_3$) δ 1.62 (2H, ddd, $J$ = 12.9, 12.2, 3.9 Hz), 1.79–1.82 (2H, m), 2.58 (1H, tt, $J$ = 12.2, 3.6 Hz), 2.73 (2H, td, $J$ = 12.2, 2.4 Hz), 3.16–3.19 (2H, m), 3.91 (2H, s), 6.96 (2H, dd, $J$ = 8.7, 8.7 Hz), 7.08–7.15 (6H, m); IR ($CHCl_3$) 2930, 2337, 1603, 1508, 1446, 1318, 1016, 862, 820 cm$^{-1}$.

**4-(4-Cyclopentyloxyphenyl)piperidine (9c).** This compound was obtained as a pale yellow powder from **8c** using the procedure described for **9b** in 89% yield. $^1$H NMR ($CDCl_3$) δ 1.56–1.64 (2H, m), 1.77–1.89 (8H, m), 2.54 (1H, tt, $J$ = 7.3, 3.6 Hz), 2.72 (2H, td, $J$ = 12.2, 2.4 Hz), 3.15–3.18 (2H, m), 4.70–4.74 (1H, m), 6.81 (2H, d, $J$ = 8.6 Hz), 7.10 (2H, d, $J$ = 8.6 Hz); IR ($CHCl_3$) 2940, 1610, 1509, 1445, 1364, 1318, 1177, 1138, 1101, 1052, 989 cm$^{-1}$.

### General procedure for the synthesis of 4-Aryl-4-piperidinol (9d–f)

Compounds **7d–f** were dissolved in MeOH and hydrogenated in the presence of $Pd(OH)_2$ (20% w/w of **7d–f**) under 5 atom at room temperature for 2–5 days. After completion of the reaction, the catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was chromatographed over NH–silica gel using $CH_2Cl_2$/MeOH = 20:1 as an eluent to give **9d–f**.

**4-(4-phenoxyphenyl)-4-piperidinol (9d).** This compound was obtained as a yellow oil in 75% yield. $^1$H NMR ($CDCl_3$) δ 1.73–1.77 (2H, m), 2.02 (2H, td, $J$ = 12.5, 4.6 Hz), 2.96–2.99 (2H, m), 3.12 (2H, td, $J$ = 12.5, 2.6 Hz), 6.99 (2H, d, $J$ = 8.8 Hz), 7.01 (2H, d, $J$ = 7.7 Hz), 7.10 (1H, t, $J$ = 7.5 Hz), 7.33 (2H, dd, $J$ = 7.7, 7.5 Hz), 7.46 (2H, d, $J$ = 8.8 Hz); IR ($CHCl_3$) 2949, 1702, 1589, 1507, 1490, 1320, 1170, 1132, 1014 cm$^{-1}$.

**4-[4-(4-fluorobenzyl)phenyl]-4-piperidinol (9e).** This compound was obtained as a colorless crystal in 74% yield. $^1$H NMR ($CDCl_3$) δ 1.74–1.78 (2H, m), 2.04 (2H, td, $J$ = 12.5, 4.5 Hz), 2.99–3.01 (2H, m), 3.13 (2H, td, $J$ = 12.5, 2.6 Hz), 7.31–7.32 (1H, m), 7.34 (1H, s), 7.34–7.38 (1H, m), 7.41–7.46 (3H, m), 7.55 (2H, d, $J$ = 8.3 Hz); IR ($CHCl_3$) 2949, 2842, 1709, 1603, 1508, 1438, 1320, 1157, 1131, 1018 cm$^{-1}$.

**4-(3-fluoro-4-phenyl)phenyl-4-piperidinol (9f).** This compound was obtained as a yellow oil in 64% yield. $^1$H NMR ($CDCl_3$) δ 1.75–1.78 (2H, m), 2.01–2.08 (2H, m), 2.99–3.02 (2H, m), 3.10–3.16 (2H, m), 7.31–7.38 (3H, m), 7.42–7.46 (3H, m), 7.54–7.56 (2H, m); IR ($CHCl_3$) 3589, 2950, 1484, 1406, 1320, 1270, 1134, 1010 cm$^{-1}$.

### General procedure for the synthesis of compounds 2a–f and 3a–f

A mixture of **9a–f** (2 mmol) and cinnamyl bromide (394 mg) or **9a–f** (2 mmol) and phenacyl bromide (398 mg) in the presence of $Et_3N$ (0.56 mL) in MeCN (8 mL) was stirred at reflux under a nitrogen atmosphere. After consumption of the starting material, the reaction mixture was concentrated in vacuo and the

residue was purified by column chromatography over silica gel using $CH_2Cl_2$/MeOH = 30:1 as an eluent to give **2a–f** or **3a–f**. These compounds were converted to hydrochloride or fumarate salt using excess 4 N HCl/dioxane or a suitable molar excess of fumaric acid in MeOH, and which were subjected to biological assays.

**1-Cinnamyl-4-(4-phenoxyphenyl)piperidine (2a).** This compound was obtained in 76% yield as an oil, which was subsequently converted to its hydrochloride in 64% overall yield from the starting material after recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.75–1.87 (4H, m), 2.10 (2H, td, $J$ = 11.5, 3.0 Hz), 2.46–2.54 (1H, m), 3.11–3.14 (2H, m), 3.20 (2H, dd, $J$ = 6.7, 0.8 Hz), 6.33 (1H, dt, $J$ = 15.8, 6.7 Hz), 6.55 (1H, d, $J$ = 15.8 Hz), 6.94 (2H, d, $J$ = 8.6 Hz), 6.99 (2H, d, $J$ = 7.7 Hz), 7.07 (1H, t, $J$ = 7.4 Hz), 7.19 (2H, d, $J$ = 8.6 Hz), 7.22 (1H, t, $J$ = 7.4 Hz), 7.29–7.34 (4H, m), 7.39 (2H, d, $J$ = 7.3 Hz); IR (KBr, hydrochloride salt) 2930, 2526, 1654, 1589, 1504, 1490, 1239, 1170, 978, 869, 749, 693 cm$^{-1}$; mp (hydrochloride salt) 200–204 °C. Anal. calcd for $C_{26}H_{27}NO$·HCl: C, 76.92; H, 6.95; N, 3.45. Found: C, 76.77; H, 6.95; N, 3.45.

**1-Cinnamyl-4-[4-(4-fluorobenzyl)phenyl]piperidine (2b).** This compound was obtained in 70% yield as an oil, which was subsequently converted to its hydrochloride in 55% overall yield from the starting material after recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.77–1.84 (4H, m), 2.09 (2H, td, $J$ = 11.2, 3.6 Hz), 2.48 (1H, m), 3.19–3.12 (2H, m), 3.19 (2H, dd, $J$ = 6.9, 0.8 Hz), 3.91 (2H, s), 6.33 (1H, dt, $J$ = 15.9, 6.9 Hz), 6.53 (1H, d, $J$ = 15.9 Hz), 6.96 (2H, dd, $J$ = 8.8, 8.7 Hz), 7.07–7.16 (6H, m), 7.22 (1H, t, $J$ = 7.3 Hz), 7.30 (1H, dd, $J$ = 7.5, 7.3 Hz), 7.38 (2H, d, $J$ = 7.5 Hz); IR (KBr, hydrochloride salt) 2940, 2488, 1600, 1504, 1458, 1221, 1158, 978, 816, 752, 695 cm$^{-1}$; mp (hydrochloride salt) 203–205 °C. Anal. calcd for $C_{27}H_{28}FN$·HCl: C, 76.85; H, 6.93; N, 3.32. Found: C, 76.76; H, 6.86; N, 3.33.

**1-Cinnamyl-4-(4-cyclopentyloxyphenyl)piperidine (2c).** This compound was obtained in 35% yield as an oil, which was subsequently converted to its hydrochloride in 32% overall yield from the starting material after recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.58–1.62 (2H, m), 1.76–1.93 (10H, m), 2.24 (2H, m), 2.50 (1H, m), 3.21–3.23 (2H, m), 3.32 (2H, m), 4.69–4.72 (1H, m), 6.38 (1H, dt, $J$ = 15.8, 6.9 Hz), 6.58 (1H, d, $J$ = 15.8 Hz), 6.80 (2H, d, $J$ = 8.6 Hz), 7.12 (2H, d, $J$ = 8.6 Hz), 7.21–7.25 (1H, m), 7.31 (2H, dd, $J$ = 7.5, 7.2 Hz), 7.40 (2H, d, $J$ = 7.5 Hz); IR (KBr, hydrochloride salt) 2947, 1612, 1512, 1450, 1244, 1184, 834, 749, 692 cm$^{-1}$; mp (hydrochloride salt): 243–244 °C. Anal. calcd for $C_{25}H_{31}NO$·HCl·1/2$H_2O$: C, 73.78; H, 8.17; N, 3.44. Found: C, 73.62; H, 7.97; N, 3.44.

**1-Cinnamyl-4-(4-phenoxyphenyl)-4-piperidinol (2d).** This compound was obtained in 64% yield as an oil, which was subsequently converted to its hydrochloride in 42% overall yield from the starting material after recrystallization from ether–2-PrOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.80 (2H, m), 2.19 (2H, m), 2.51 (2H, m), 2.90 (2H, m), 3.25 (2H, d, $J$ = 6.7 Hz), 6.33 (1H, dt, $J$ = 15.8, 6.7 Hz), 6.56 (1H, d, $J$ = 15.8 Hz), 6.98 (2H, d, $J$ = 8.8 Hz), 7.01 (2H, d, $J$ = 7.7 Hz), 7.10 (1H, t, $J$ = 7.4 Hz), 7.23 (1H, t, $J$ = 7.6 Hz), 7.29–7.35 (4H, m), 7.39 (2H, d, $J$ = 7.2 Hz), 7.47 (2H, d, $J$ = 8.8 Hz); IR (KBr, fumarate salt) 1702, 1589, 1508, 1490, 1372, 1287, 1240, 1171, 984 cm$^{-1}$; mp (fumarate salt) 93–97 °C. Anal. calcd for $C_{26}H_{27}NO_2$·$C_4H_4O_4$·1/2$H_2O$: C, 70.57; H, 6.32; N, 2.74. Found: C, 70.37; H, 6.26; N, 3.06.

**1-Cinnamyl-4-[4-(4-fluorobenzyl)phenyl]-4-piperidinol (2e).** This compound was obtained in 65% yield as an oil, which was subsequently converted to its fumarate in 39% overall yield from the starting material after recrystallization from ether–2-PrOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.76 (2H, m), 2.18 (2H, m), 2.51 (2H, m), 2.89 (2H, m), 3.24 (2H, d, $J$ = 6.7 Hz), 3.93 (2H, s), 6.32 (1H, dt, $J$ = 15.9, 6.7 Hz), 6.55 (1H, d, $J$ = 15.9 Hz), 6.96 (2H, dd, $J$ = 8.7, 8.4 Hz), 7.13 (2H, d, $J$ = 8.3 Hz), 7.15 (2H, d, $J$ = 8.4 Hz), 7.22 (2H, t, $J$ = 7.3 Hz), 7.31 (2H, dd, $J$ = 7.6, 7.3 Hz), 7.39 (2H, d, $J$ = 7.6 Hz), 7.43 (2H, d, $J$ = 8.3 Hz); IR (KBr, fumarate salt) 1700, 1600, 1578, 1508 1364, 1221, 1158, 984 cm$^{-1}$; mp (fumarate salt) 100–103 °C. Anal. calcd for $C_{27}H_{28}FNO$·$C_4H_4O_4$: C, 71.94; H, 6.23; N, 2.71. Found: C, 71.75; H, 6.28; N, 2.90.

**1-Cinnamyl-4-(3-fluoro-4-phenyl)phenyl-4-piperidinol (2f).** This compound was obtained in 50% yield as an oil, which was subsequently converted to its fumarate in 37% overall yield from the starting material after recrystallization from ether–EtOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.80 (2H, m), 2.20 (2H, dt, $J$ = 13.2, 5.3 Hz), 2.51 (2H, m), 2.2 (2H, m), 3.25 (2H, d, $J$ = 6.7 Hz), 6.33 (1H, dt, $J$ = 15.9, 6.7 Hz), 6.57 (1H, d, $J$ = 15.9 Hz), 7.23 (1H, m), 7.29–7.45 (10H, m), 7.54 (2H, d, $J$ = 8.2 Hz); IR (KBr, fumarate salt) 3384, 3030, 2934, 2576, 1701, 1582, 1485, 1449, 1407, 1272 cm$^{-1}$; mp (fumarate salt) 107–109 °C. Anal. calcd for $C_{26}H_{26}FNO$·$C_4H_4O_4$·1/4$H_2O$: C, 70.92; H, 6.05; N, 2.76. Found: C, 70.99; H, 5.97; N, 2.83.

**1-Phenacyl-4-(4-phenoxyphenyl)piperidine (3a).** This compound was obtained in 96% yield as an oil, which was subsequently converted to its hydrochloride in 91% overall yield from the starting material after recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.82–1.94 (4H, m), 2.29 (2H, td, $J$ = 11.2, 3.2 Hz), 2.52 (1H, m), 3.13 (2H, m), 3.85 (2H, s), 6.94 (2H, dd, $J$ = 8.6, 1.9 Hz), 7.00 (2H, d, $J$ = 8.1 Hz), 7.08 (1H, t, $J$ = 7.4 Hz), 7.19 (2H, d, $J$ = 8.6 Hz), 7.32 (2H, dd, $J$ = 8.1, 7.4 Hz), 7.47 (2H, dd, $J$ = 7.6, 7.4 Hz), 7.57 (1H, t, $J$ = 7.4 Hz), 8.03 (2H, d, $J$ = 7.6 Hz); IR (KBr, hydrochloride salt) 3391, 2948, 2537, 1703, 1590, 1508, 1490, 1450, 1248, 755, 691 cm$^{-1}$; mp (hydrochloride salt) 183–185 °C. Anal. calcd for $C_{25}H_{25}NO_2$·HCl·1/4$H_2O$: C, 72.80; H, 6.48; N, 3.40. Found: C, 72.75; H, 6.36; N, 3.43.

**1-Phenacyl-4-[4-(4-fluorobenzyl)phenyl]piperidine (3b).** This compound was obtained in 82% yield as an oil, which was subsequently converted to its hydrochloride in 54% overall yield from the starting material after

recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.81–1.96 (4H, m), 2.30 (2H, td, $J$ = 11.5, 2.3 Hz), 2.51 (1H, m), 3.14 (2H, m), 3.88 (2H, s), 3.92 (2H, m), 6.96 (2H, dd, $J$ = 8.8, 8.7 Hz), 7.07–7.17 (6H, m), 7.47 (2H, dd, $J$ = 7.5, 7.4 Hz), 7.58 (1H, t, $J$ = 7.4 Hz), 2.30 (2H, td, $J$ = 11.5, 2.3 Hz), 8.02 (2H, d, $J$ = 7.5 Hz); IR (KBr, hydrochloride salt) 3402, 2928, 2620, 2544, 1694, 1599, 1508, 1450, 1225, 962, 755, 690 cm$^{-1}$; mp (hydrochloride salt) 179–181 °C. Anal. calcd for $C_{26}H_{26}FNO{\cdot}HCl{\cdot}1/3H_2O$: C, 72.63; H, 6.49; N, 3.26. Found: C, 72.52; H, 6.35; N, 3.30.

**1-Phenacyl-4-(4-Cyclopentyloxyphenyl)piperidine (3c).** This compound was obtained in 87% yield as an oil, which was subsequently converted to its hydrochloride in 68% overall yield from the starting material after recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.59 (2H, m), 1.79–1.90 (10H, m), 2.28 (2H, td, $J$ = 11.2, 3.2 Hz), 2.46 (1H, m), 3.11 (2H, m), 3.83 (2H, s), 4.69–4.72 (1H, m), 6.80 (2H, d, $J$ = 8.6 Hz), 7.11 (2H, d, $J$ = 8.6 Hz), 7.46 (2H, dd, $J$ = 7.6, 7.4 Hz), 7.56 (1H, t, $J$ = 7.4 Hz), 8.03 (2H, d, $J$ = 7.6 Hz); IR (KBr, hydrochloride salt) 2957, 1706, 1512, 1450, 1400, 1358, 1244, 1179, 962, 832, 753, 685 cm$^{-1}$; mp (hydrochloride salt) 233–235 °C. Anal. calcd for $C_{24}H_{29}NO_2{\cdot}HCl$: C, 72.07; H, 7.56; N, 3.50. Found: C, 72.12; H, 7.60; N, 3.56.

**1-Phenacyl-4-(4-phenoxyphenyl)-4-piperidinol (3d).** This compound was obtained in 50% yield as an oil, which was subsequently converted to its 1/2 fumarate in 35% overall yield from the starting material after recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.79 (2H, m), 2.27 (2H, td, $J$ = 13.0, 4.3 Hz), 2.67 (2H, m), 2.92 (2H, m), 3.89 (2H, s), 6.98 (2H, dd, $J$ = 8.6, 2.0 Hz), 7.10 (1H, d, $J$ = 7.6 Hz), 7.10 (1H, t, $J$ = 7.4 Hz), 7.33 (2H, dd, $J$ = 7.6, 7.4 Hz), 7.45–7.48 (2H, m), 7.48 (2H, d, $J$ = 8.6 Hz), 7.57 (1H, t, $J$ = 7.4 Hz), 8.02 (2H, d, $J$ = 7.1 Hz); IR (KBr, 1/2 fumarate salt) 1697, 1589, 1508, 1490, 1450, 1368, 1234, 1171 cm$^{-1}$; mp (1/2 fumarate salt) 173–175 °C. Anal. calcd for $C_{25}H_{25}NO_3{\cdot}1/2C_4H_4O_4{\cdot}H_2O$: C, 69.96; H, 6.31; N, 3.02. Found: C, 70.09; H, 5.98; N, 3.07.

**1-Phenacyl-4-[4-(4-fluorobenzyl)phenyl]-4-piperidinol (3e).** This compound was obtained in 63% yield as an oil, which was subsequently converted to its 1/2 fumarate in 40% overall yield from the starting material after recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.76 (2H, m), 2.26 (2H, td, $J$ = 12.4, 4.4 Hz), 2.65 (2H, td, $J$ = 12.4, 2.2 Hz), 2.91 (2H, m), 3.89 (2H, s), 3.94 (2H, s), 6.96 (2H, t, $J$ = 8.7 Hz), 7.12–7.16 (4H, m), 7.44 (2H, d, $J$ = 8.3 Hz), 7.57 (1H, t, $J$ = 7.3 Hz), 8.02 (2H, d, $J$ = 7.5 Hz); IR (KBr, 1/2 fumarate salt) 1699, 1599, 1582, 1508, 1450, 1372, 1261, 1224, 1158 cm$^{-1}$; mp (1/2 fumarate salt) 75–78 °C. Anal. calcd for $C_{26}H_{26}FNO_2{\cdot}1/2C_4H_4O_4{\cdot}H_2O$: C, 70.13; H, 6.31; N, 2.92. Found: C, 70.21; H, 6.19; N, 3.12.

**1-Phenacyl-4-(3-fluoro-4-phenyl)phenyl-4-piperidinol (3f).** This compound was obtained in 76% yield as an oil, which was subsequently converted to its 1/2 fumarate in 40% overall yield from the starting material after recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.80 (2H, m), 2.29 (2H, m), 2.68 (2H, m), 2.95 (2H, m), 3.90 (2H, s), 7.31–7.37 (3H, m), 7.41–7.49 (5H, m), 7.54–7.60 (3H, m), 8.03 (2H, d, $J$ = 7.6 Hz); IR (KBr, 1/2 fumarate) 3292, 1706, 1582, 1484, 1450, 1407, 1266, 1226, 975, 944 cm$^{-1}$; mp (1/2 fumarate salt) 172–174 °C. Anal. calcd for $C_{25}H_{24}FNO_2{\cdot}1/2C_4H_4O_4{\cdot}3/5H_2O$: C, 70.76; H, 5.98; N, 3.06. Found: C, 70.85; H, 5.88; N, 3.06.

### General procedure for the synthesis of compounds 4a–f

A mixture of **9a–f** (2 mmol) and 1,2-epoxy-3-phenoxypropane (phenyl glycidyl ether) (507 mg) in 2-PrOH (10 mL) was refluxed under a nitrogen atmosphere. After consumption of the starting material, the reaction mixture was concentrated in vacuo and the residue was purified by column chromatography over silica gel using $CH_2Cl_2$/MeOH = 30:1 as an eluent to give **4a–f**. These compounds were converted into hydrochloride or fumarate salt in a conventional manner and subjected to biological assays.

**1-(2-Hydroxy-3-phenoxypropyl)-4-(4-phenoxyphenyl)piperidine (4a).** This compound was obtained in 96% yield as an oil, which was subsequently converted to its hydrochloride in 88% overall yield from the starting material after recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.68–1.88 (4H, m), 2.14 (1H, m), 2.43 (1H, td, $J$ = 11.4, 2.8 Hz), 2.50–2.59 (3H, m), 2.98 (1H, m), 3.14 (1H, m), 4.00–4.02 (2H, m), 4.09–4.15 (1H, m), 6.93–6.97 (5H, m), 7.01 (2H, d, $J$ = 7.8 Hz), 7.08 (1H, t, $J$ = 7.4 Hz), 7.18 (2H, d, $J$ = 8.5 Hz), 7.26–7.34 (4H, m); IR (KBr, hydrochloride salt) 3268, 2657, 1590, 1509, 1490, 1246, 1171, 1050, 755, 693 cm$^{-1}$; mp (hydrochloride salt) 151–152 °C. Anal. calcd for $C_{26}H_{29}NO_3{\cdot}HCl$: C, 70.98; H, 6.87; N, 3.18. Found: C, 70.90; H, 6.82; N, 3.20.

**(*S*)-1-(2-Hydroxy-3-phenoxypropyl)-4-(4-phenoxyphenyl)-piperidine [(*S*)-4a].** This compound was obtained by employing (2*S*)-1,2-epoxy-3-phenoxypropane[11a] in 77% yield as an oil, which was subsequently converted to its hydrochloride in 67% overall yield from the starting material after recrystallization from ether–MeOH. The spectroscopic data of (*S*)-**4a** were identical to those of racemic **4a**. The optical purity was estimated to be >98% ee by HPLC (Daicel Chiralpak OD, flow rate 1.8 mL/min, *n*-hexane/2-PrOH/diethylamine = 500:500:1). Typical retention times were 12.3 min for (*S*)-**4a** and 9.3 min for (*R*)-**4a**. $[\alpha]_D$ −12.8° (*c* 1.02, MeOH; hydrochloride salt); mp (hydrochloride salt) 177–178 °C. Anal. calcd for $C_{26}H_{29}NO_3{\cdot}HCl$: C, 70.98; H, 6.87; N, 3.18. Found: C, 70.77; H, 6.91; N, 3.05.

**(*R*)-1-(2-Hydroxy-3-phenoxypropyl)-4-(4-phenoxyphenyl)-piperidine [(*R*)-4a].** This compound was obtained by employing (2*R*)-1,2-epoxy-3-phenoxypropane[11b] in 86% yield as an oil, which was subsequently converted to its hydrochloride in 72% overall yield from the starting material after recrystallization from ether–MeOH. The spectroscopic data of (*R*)-**4a** were identical to those of

racemic **4a**. The optical purity was estimated to be >98% ee by HPLC (Daicel Chiralpak OD, flow rate 1.8 ml/min, *n*-hexane:2-PrOH:diethylamine = 500:500:1). $[\alpha]_D$ +12.8° ($c$ = 1.39, MeOH; hydrochloride salt); mp (hydrochloride salt) 177–178 °C. Anal. calcd for $C_{26}H_{29}NO_3$·HCl: C, 70.98; H, 6.87; N, 3.18. Found: C, 70.74; H, 6.86; N, 3.09.

**1-(2-Hydroxy-3-phenoxypropyl)-4-[4-(4-fluorobenzyl)phenyl]piperidine (4b).** This compound was obtained in 92% yield as an oil, which was subsequently converted to its hydrochloride in 82% overall yield from the starting material after recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.70–1.86 (4H, m), 2.16 (1H, m), 2.44 (1H, td, $J$ = 11.3, 3.3 Hz), 2.50–2.64 (3H, m), 3.10 (1H, m), 3.16 (1H, m), 3.95 (2H, s), 3.99–4.06 (2H, m), 4.12–4.16 (1H, m), 6.95–7.01 (4H, m), 7.11–7.18 (5H, m), 7.28–7.33 (4H, m); IR (KBr, hydrochloride salt) 3306, 2930, 2646, 1599, 1508, 1250, 1222, 812, 762, 694 cm$^{-1}$; mp (hydrochloride salt) 160–161 °C. Anal. calcd for $C_{27}H_{30}FNO_2$·HCl: C, 71.12; H, 6.85; N, 3.07. Found: C, 71.02; H, 6.78; N, 3.16.

**1-(2-Hydroxy-3-phenoxypropyl)-4-(4-cyclopentyloxyphenyl)piperidine (4c).** This compound was obtained in 78% yield as an oil, which was subsequently converted to its hydrochloride in 73% overall yield from the starting material after recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.58–1.61 (2H, m), 1.69–1.90 (10H, m), 2.12 (1H, td, $J$ = 11.9, 2.3 Hz), 2.38–2.48 (2H, m), 2.53–2.58 (2H, m), 2.96 (1H, m), 3.12 (1H, m), 3.99–4.01 (2H, m), 4.08–4.14 (1H, m), 4.70–4.73 (1H, m), 6.81 (2H, d, $J$ = 8.6 Hz), 6.93–6.97 (3H, m), 7.11 (2H, d, $J$ = 8.6 Hz), 7.23–7.30 (3H, m); IR (KBr, hydrochloride salt) 2961, 1600, 1512, 1497, 1290, 1244, 1175, 831, 754, 691 cm$^{-1}$; mp (hydrochloride salt) 184–187 °C. Anal. calcd for $C_{25}H_{33}NO_3$·HCl: C, 69.51; H, 7.93; N, 3.24. Found: C, 69.78; H, 7.91; N, 3.29.

**1-(2-Hydroxy-3-phenoxypropyl)-4-(4-phenoxyphenyl)-4-piperidinol (4d).** This compound was obtained in 74% yield as an oil, which was subsequently converted to its 1/2 fumarate in 53% overall yield from the starting material after recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.81 (2H, m), 2.08–2.22 (2H, m), 2.55 (1H, m), 2.63 (2H, d, $J$ = 6.8 Hz), 2.79–2.83 (2H, m), 2.93 (1H, m), 4.01 (2H, dd, $J$ = 5.0, 0.7 Hz), 4.14 (1H, m), 6.93 (2H, d, $J$ = 8.9 Hz), 6.97–7.05 (4H, m), 7.10 (1H, t, $J$ = 7.4 Hz), 7.26–7.35 (5H, m), 7.46 (2H, d, $J$ = 8.9 Hz); IR (KBr, 1/2 fumarate salt) 1588, 1508, 1490, 1368, 1292, 1240, 1172, 1044, 984 cm$^{-1}$; mp (1/2 fumarate salt) 180–182 °C. Anal. calcd for $C_{26}H_{29}NO_4$·1/2$C_4H_4O_4$·1/3$H_2O$: C, 69.55; H, 6.60; N, 2.90. Found: C, 69.54; H, 6.64; N, 2.96.

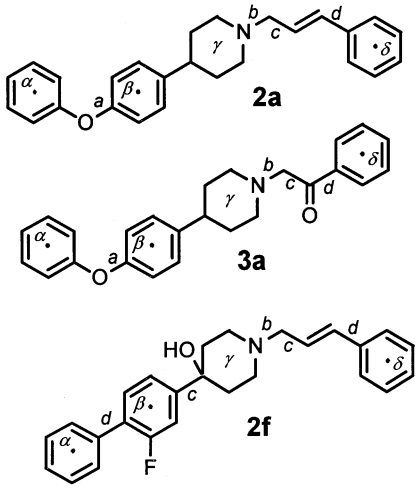
**1-(2-Hydroxy-3-phenoxypropyl)-4-[4-(4-fluorobenzyl)phenyl]-4-piperidinol (4e).** This compound was obtained in 88% yield as an oil, which was subsequently converted to its 1/2 fumarate in 66% overall yield from the starting material after recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.78 (2H, m), 2.14 (2H, m), 2.55 (1H, m), 2.62 (2H, d, $J$ = 6.7 Hz), 2.78–2.85 (2H, m), 2.92 (1H, m), 3.94 (2H, s), 4.01 (2H, d, $J$ = 5.0 Hz), 4.14 (1H, m), 6.92–6.99 (5H, m), 7.12–7.17 (4H, m), 7.26–7.30 (2H, m), 7.42 (2H, d, $J$ = 8.3 Hz); IR (KBr, 1/2 fumarate salt) 1600, 1574, 1508, 1450, 1368, 1245, 1043, 984 cm$^{-1}$; mp (1/2 fumarate salt) 160–161 °C. Anal. calcd for $C_{27}H_{30}FNO_3$·1/2$C_4H_4O_4$: C, 70.57; H, 6.53; N, 2.84. Found: C, 70.34; H, 6.36; N, 2.87.

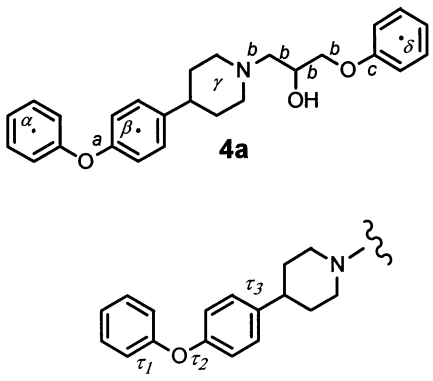
**1-(2-Hydroxy-3-phenoxypropyl)-4-(3-fluoro-4-phenyl)-phenyl-4-piperidinol (4f).** This compound was obtained in 96% yield as an oil, which was subsequently converted to its 1/2 fumarate in 78% overall yield from the starting material after recrystallization from ether–MeOH. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.82 (2H, m), 2.11–2.25 (2H, m), 2.56 (1H, m), 2.64 (2H, d, $J$ = 6.8 Hz), 2.81–2.86 (2H, m), 2.95 (1H, m), 4.02 (2H, d, $J$ = 5.0 Hz), 4.15 (1H, m), 6.93–6.99 (3H, m), 7.26–7.38 (5H, m), 7.42–7.46 (3H, m), 7.55 (2H, d, $J$ = 8.1 Hz); IR (KBr, 1/2 fumarate salt) 3188, 2935, 1577, 1372, 1450, 1242, 1048, 989 cm$^{-1}$; mp (1/2 fumarate salt) 193–194 °C. Anal. ($C_{26}H_{28}FNO_3$·1/2$C_4H_4O_4$·1/5$H_2O$: C, 69.61; H, 6.34; N, 2.90. Found: 69.95; H, 6.35; N, 2.89.

**Systematic conformation search and similar structure analysis of compounds 2a, 2f, 3a and 4a.** A conformation search of three structures, compounds **2a**, **3a** and **4a**, was carried out in two steps. First, a conformation analysis was performed on the common structural unit, 4-(4′-phenoxy)phenylpiperadine (**i**). Two stable conformations were obtained by the energy minimization of their conformers generated by the rotation of three bonds at angle values of ±30, ±90, ±150° using the MM2 parameters in Macromodel. Next, energetically favored conformations of whole structure were identified by the energy minimization of initial conformers generated by the rotation of the bonds of the angle values. In this step, initial torsion angles of 4-(4′-phenoxy)-phenylpiperidine moiety were set to afford stable conformations. Calculated stable conformations of substructure **i** are ($\tau_1$ = 90, $\tau_2$ = 90, $\tau_3$ = 60°) and ($\tau_1$ = 90, $\tau_2$ = −90, $\tau_3$ = 60°). Energetically favored conformations were also obtained by the energy minimization of initial conformers of **2f** generated in the same manner. Through this search, 12, 56, 22 and 72 distingished conformers of **2a**, **3a**, **4a** and **2f**, respectively, were obtained within 5 kcal/mol from the most stable conformers. Similar structures of **3a**, **4a** and **2f** to **2a** were identified in the energetically favored conformations of these molecules by RMS fitting of three centers of the phenyl group (α, β and δ) and six atoms of the piperidine ring (γ).

## Inhibitory effect of veratridine-induced sodium channel activity

The membrane potential of the synaptosomes prepared from the brain membrane of Wister rats (male, 10–12 weeks old) was measured as reported[13] using a membrane potential sensitive fluorescent dye Rhodamine 6G to evaluate the effects of suppression of the compound on the veratridine-inducing depolarization response.







### T-Type calcium channel inhibitory effect

The hippocampal CA1 pyramidal cells were isolated from Wister rats (female, 1 week old) according to a reported method[3e] and the T-type calcium current was measured under conditions of a fixed membrane potential using the whole-cell configuration of the patch clamp technique. The effects of the compounds were evaluated from the rate of suppression of the peak current after 1 min of application using the concentration clamp method.

### Dopamine $D_2$ receptor blocking action

A 57 μL volume of the membrane fraction prepared from the striatum of rats (male, 6 weeks old) was incubated together with the compound and 1.0 nM [$^3$H]raclopride in a buffer at 25 °C for 1 h. A GF/C glass filter (0.1% polyethylene imine treatment) was used for B/F separation. A betaplate was used for measurement of the radioactivity to evaluate the effect of the compound.[14]

### Audiogenic seizure suppressing effect

The audiogenic seizure suppressing effect of the compounds was evaluated by the method of Sarro et al.[16] That is, the compound dissolved in 10% of 2-hydroxypropyl-*b*-cyclodextrin was administered intraperitoneally to DBA/2N type mice (male, 3 weeks old). After 20 min, a supersonic washer was used to apply an audio stimulus of at least 90 dB for 1 min. Wild running (WR), clonic seizures (clonus), tonic seizures (tonus) and respiratory arrest (RA) were observed. The seizure suppressing effect was evaluated from the rate of suppression of the average value of the seizure score as 0 = no response, 1 = WR, 2 = clonus, 3 = tonus and 4 = RA.

### Effects on neuronal damages induced by transient middle cerebral artery occlusion (*t*-MCAO) in rats

Rats were subjected to transient MCAO for 60 min by intraluminal insertion of a nylon suture from the bifurcation of the common carotid artery into the internal carotid artery after ligation of the ipsilateral common and external carotid arteries. The measurement of peripheral type benzodiazepine binding site (PTBBS) densities[5b] in ipsilateral cortical and striatal homogenates was carried out as an index for quantification of neuronal damage 10 days after reperfusion. Compounds and flunarizine were administered intravenously immediately after MCAO and immediately after reperfusion (each 3 mg/kg).

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### References and Notes

1. For a review: Brini, M.; Carafoli, E. *Cell Mol. Life Sci.* **2000**, *57*, 354.
2. (a) For reviews: Farber, J. L. *Life Sci.* **1981**, *29*, 1289. (b) Meyer, F. B. *Brain Res. Brain Res. Rev.* **1989**, *14*, 227. (c) Boddeke, E.; Hugtenburg, J.; Jap, W.; Heynis, J.; van Zwieten, P. *Trends Pharmacol. Sci.* **1989**, *10*, 397. (d) Choi, D. W. *Trends Neurosci.* **1995**, *18*, 58. (e) Kristián, T.; Siesjö, B. K. *Life Sci.* **1996**, *59*, 357. (f) Kristián, T.; Siesjö, B. K. *Stroke* **1998**, *29*, 705.
3. (a) Pauwels, P. J.; Van Assouw, H. P.; Leysen, J. E.; Janssen, P. A. J. *Mol. Pharmacol.* **1989**, *36*, 525. (b) Pauwels, P. J.; Leysen, J. E.; Janssen, P. A. J. *Life Sci.* **1991**, *48*, 1881. (c) Peters, T.; Wilffert, B.; Vanhoutte, P. M.; van Zwieten, P. A. *J. Cardiovasc. Pharmcol.* **1991**, *18* (Suppl. 8), S1. (d) Takahashi, K.; Akaike, N. *J. Pharmacol. Exp. Ther.* **1991**, *256*, 169. (e) Urenjak, J.; Obrenovitch, T. P. *Pharmacol. Rev.* **1996**, *48*, 21.
4. (a) van Zwieten, P. A. *Arzneim.-Forsch.* **1985**, *35*, 298. (b) van Zwieten, P. A. *Eur. Neurol.* **1986**, *25* (Suppl. 1), 57.
5. (a) Alps, B. J.; Calder, C.; Hass, W. K.; Wilson, A. D. *Br. J. Pharmacol.* **1988**, *93*, 877. (b) Gotti, B.; Benavides, J.; MacKenzie, E. T.; Scatton, B. *Brain Res.* **1990**, *522*, 290. (c) De Ryck, M. *Eur. Neurol.* **1990**, *30* (Suppl. 2), 21.
6. (a) Ohtaka, H.; Hori, M.; Iemura, R.; Yumioka, H. *Chem. Pharm. Bull.* **1989**, *37*, 3122. (b) Hara, H.; Ozaki, A.; Yoshi-

domi, M.; Sukamoto, T. *Arch. Int. Pharmacodyn. Ther.* **1990**, *304*, 206.
7. Ito, C.; Im, W. B.; Takagi, H.; Takahashi, M.; Tsuzuki, K.; Liou, S.-Y.; Kunihara, M. *Eur. J. Pharmacol.* **1994**, *257*, 203.
8. Brown, C. M.; Calder, C.; Alps, B. J.; Spedding, M. *Br. J. Pharmacol.* **1993**, *109*, 175.
9. (a) For reviews: Montastruc, J. L.; Llau, M. E.; Rascol, O.; Senard, J. M. *Fundam. Clin. Pharmacol.* **1994**, *8*, 293. (b) Daniel, J. R.; Mauro, V. F. *Ann. Pharmacother.* **1995**, *29*, 73.
10. Annoura, H.; Nakanishi, K.; Uesugi, M.; Fukunaga, A.; Miyajima, A.; Tamura-Horikawa, Y.; Tamura, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2999.
11. (a) Kitaori, K.; Furukawa, Y.; Yoshimoto, H.; Otera, J. *Tetrahedron* **1999**, *55*, 14381. (b) Collington, E. W.; Finch, H.; Montana, J. G.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans.* **1990**, *1*, 1839.
12. (a) van Luijtelaar, G.; Wiaderna, D.; Elants, C.; Scheenen, W. *Eur. J. Pharmacol.* **2000**, *406*, 381. (b) Perez-Reyes, E.; Cribbs, L. L.; Daud, A.; Lacerda, A. E.; Barclay, J.; Williamson, M. P.; Fox, M.; Rees, M.; Lee, J.-H. *Nature* **1998**, *391*, 896.
13. Aiuchi, T.; Matsunaga, M.; Daimatsu, T.; Nakaya, K.; Nakamura, Y. *Biochim. Biophys. Acta* **1984**, *771*, 228.
14. Kohler, C.; Hall, H.; Ogren, S. O.; Gawell, L. *Biochem. Pharmacol.* **1985**, *34*, 2251.
15. For a review: Kwon, Y.-W.; Triggle, D. J. *Chirality* **1991**, *3*, 393.
16. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.
17. Carter, P. A.; Tapp, S. J.; Daniels, N. J. Eur. Pat. Appl. 0494717, 1992; *Chem. Abstr.* 1992, *116*, 194341u. (E)-4-phenyl-1-(3-phenyl-2-propenyl)piperidine was claimed as a fungicide in this patent.
18. (a) De Sarro, G. B.; Meldrum, B. S.; Nisticó, G. *Br. J. Pharmacol.* **1988**, *93*, 247. (b) Eigyo, M.; Shiomi, T.; Inoue, Y.; Sakaguchi, I.; Ishibashi, C.; Murata, S.; Koyabu, K.; Matsushita, A.; Adachi, I.; Ueda, M. *Jpn. J. Pharmacol.* **1994**, *65*, 175. (c) Rataud, J.; Debarnot, F.; Mary, V.; Pratt, J.; Stutzmann, J.-M. *Neurosci. Lett.* **1994**, *172*, 19.
19. Koizumi, J.; Yoshida, Y.; Nakazawa, T.; Ooneda, G. *Jpn. J. Stroke* **1986**, *8*, 1.