Pergamon

Bioorganic & Medicinal Chemistry 10 (2002) 1347–1359

BIOORGANIC & MEDICINAL CHEMISTRY

Discovery of Diaminobutane Derivatives as Ca^{2+}-Permeable AMPA Receptor Antagonists

Yoshiyuki Yoneda,* Tetuya Mimura, Keiichi Kawagoe, Takanori Yasukouchi, Toshiaki Tatematu, Masayuki Ito, Masaki Saito, Masunobu Sugimura, Fusako Kito and Shinichi Kawajiri

Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co., Ltd., 16-13, Kitakasai 1-Chome, Edogawa-ku, Tokyo 134-8630, Japan

Received 21 September 2001; accepted 8 November 2001

Abstract—We designed and synthesized a series of the polyamine derivatives as potent Ca^{2+}-permeable AMPA receptor antagonists. In the course of this study, we found that the polyamine derivatives exhibited strong hypotensive activity which was undesirable activity for neuroprotective agents. Therefore, we tried to find non-hypotensive antagonists by structural modification of such compounds. Through this derivatization, we obtained the diamine compounds having desired profiles. Especially, compound **8f**, which was non-hypotensive and potent Ca^{2+}-permeable AMPA receptor antagonist, showed neuroprotective effects in transient global ischemia models in gerbils.

Introduction

L-Glutamate is a major excitatory neurotransmitter in the mammalian central nervous system.[1] Glutamate receptors are classified into two groups which are coupled to the opening of cation ion channels (ionotropic glutamate receptors) or linked to GTP binding proteins (metabotropic receptors). Ionotropic receptors are further classified into three groups, namely NMDA, AMPA and kainate (KA) receptors.[2] Overstimulation of these receptors causes excessive Ca^{2+} influx which triggers neuronal cell death in acute phase of cerebral ischemia.[3] Therefore, antagonists against the ionotropic receptors seem to be promising therapeutic agents for cerebral ischemia. Based on this hypothesis, several AMPA receptor antagonists such as NBQX, YM90K, YM872, GYKI52466, and LY300164 have been examined if they had neuroprotective effect. It is reported that YM872 and LY300164 are under Phase II clinical trials for stroke.[4] However, no Ca^{2+}-permeable AMPA antagonists reached clinical trial. On the other hand, although several NMDA receptor-antagonists have been proceeded to clinical studies for stroke, they could not succeed because of their undesirable side effects.[5] It is reported that global ischemia in rats and gerbils induced down-regulation of GluR2 mRNA and increased Ca^{2+}-permeable AMPA receptors, and formation of Ca^{2+}-permeable AMPA receptors would play a causal role in the selective cell death of CA1 pyramidal cells after global ischemia.[6] We therefore focused on Ca^{2+}-permeable AMPA receptors and designed antagonists based on the structures of prototype antagonist polyamines such as Joro spider toxin-3, JSTX-3 (**1**),[7] and 1-naphthylacetylsperimine, NAS (**2**) (Fig. 1).[8] First, we designed compounds bearing a ring structure in polyamine with a view to increasing lipophilicity. Compound **12a**, *N*-(1-(1-naphthylacetyl)piperidin-4-ylmethyl) - *N′* - (4 - piperidinylmethyl) - 1,4 - diaminobutane, showed moderate potency with IC_{50} value of 1.3 μM. However, these polyamine derivatives including **2** had potent hypotensive activity in rats. Such hypotensive activity is unfavorable for the therapeutic agents for acute cerebral ischemia because it may cause reduction of the pressure-dependent cerebral blood flow to the ischemic penumbra and increase cerebral damage.[9] In order to eliminate hypotensive activity, further modification of our compounds were carried out. As a result, we found the polyamine derivatives having both non-hypotensive and potent Ca^{2+}-permeable AMPA receptor antagonist activity. Through this study, we also found that the diamine compounds showed potent Ca^{2+}-permeable AMPA receptor

*Corresponding author. Tel.: +81-3-3680-0151; fax: +81-3-5696-8344; e-mail: yonedl0z@daiichipharm.co.jp

0968-0896/02/$ - see front matter
PII: S0968-0896(01)00398-4

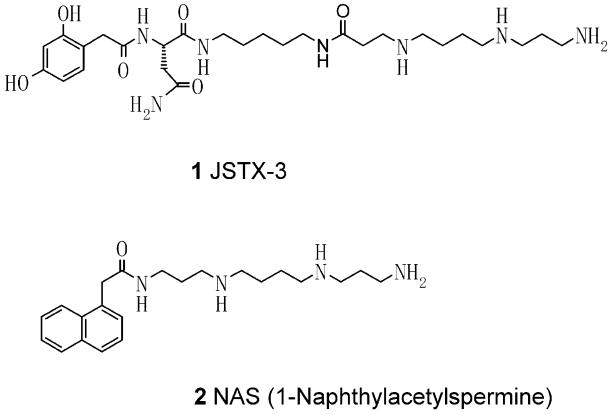
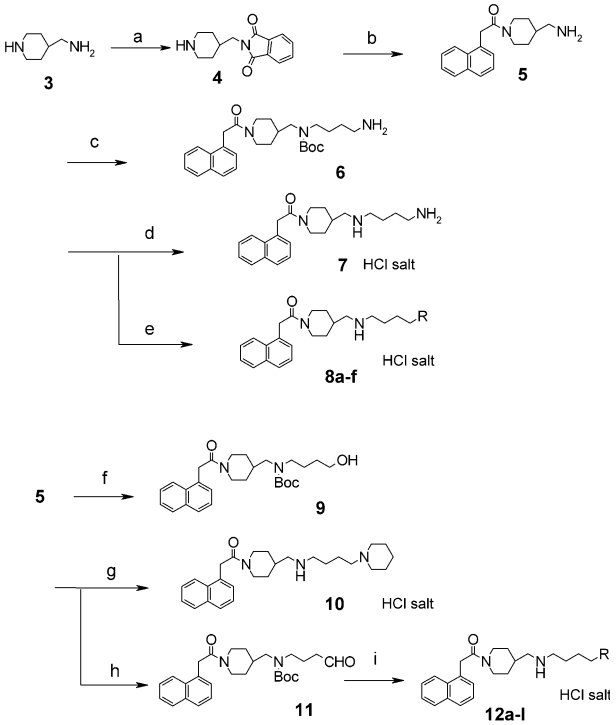


Figure 1.

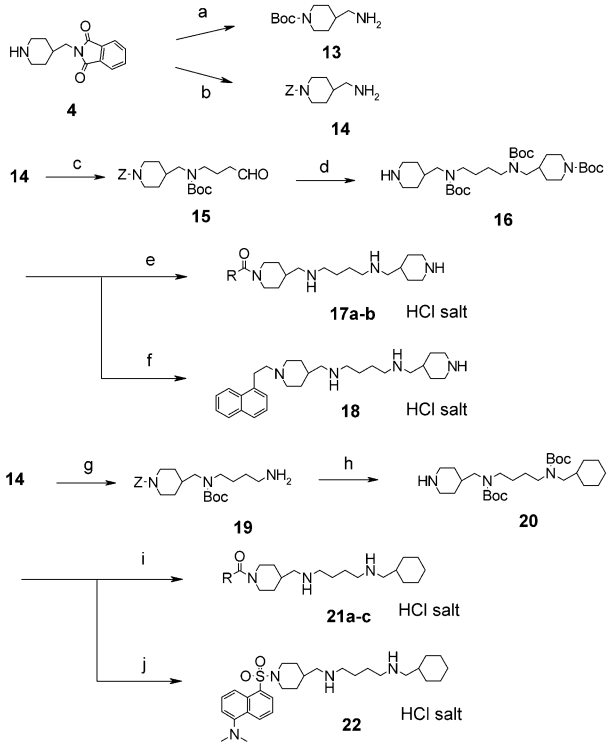
antagonist activity with non-hypotensive activity, and that one of the diamine compounds exhibited neuroprotective effects in transient global ischemia model in gerbils. Following the preliminary account of this work presented previously,[10] we describe the details of the synthesis and biological activity of a novel series of diaminobutane derivatives.



Scheme 1. Synthesis of compounds **7**, **8a**–**f**, **10** and **12a**–**l**. Reagents and conditions: (a) phthalic anhydride, △ (61%); (b) (i) (1-naphthyl)-acetic acid, EDC·HCl, TEA, CH_2Cl_2 (69%); (ii) $NH_2NH_2{\cdot}H_2O$, EtOH (quant); (c) (i) 4-bromobutyl phthalimide, KF-Celite, MeCN; (ii) Boc_2O, CH_2Cl_2; (iii) $NH_2NH_2{\cdot}H_2O$, EtOH (three steps 55%); (d) c HCl, EtOH (62%); (e) (i) aldehyde, $NaBH_4$, MeOH; (ii) Boc_2O, CH_2Cl_2; (iii) c HCl, EtOH (three steps 21–57%); (f) (i) 4-bromobutyl acetate, KF-Celite, MeCN; (ii) Boc_2O, CH_2Cl_2; (iii) K_2CO_3, MeOH (three steps 48%); (g) (i) MsCl, Py; (ii) piperidine, KF-Celite, MeCN; (iii) c HCl, EtOH (three steps 40%); (h) Swern oxidation (71%); (i) amine, $NaBH_4$, MeOH; (ii) Boc_2O, CH_2Cl_2; (iii) c HCl, EtOH (three steps 21–72%).

Chemistry

The synthetic pathways of compounds **7, 8a**–**f**, **10** and **12a**–**l** are shown in Scheme 1. Commercially available 4-aminomethylpiperidine **3** was converted to phthalimide **4**, which was coupled with 1-naphthylacetic acid and then treated with hydrazine to give amine **5**. Amine **5** was alkylated with 4-bromobutylphthalimide followed by protection with a *tert*-butoxycarbonyl (Boc) group, and then the phthaloyl group was removed to yield amine **6**. Amine **6** was converted to compound **7** by treatment with concentrated HCl. Compounds **8a**–**f** were prepared by reductive alkylation using the corresponding aldehydes and successive deprotection of the Boc group with concentrated HCl. Alcohol **9** was synthesized from amine **5** by alkylation with 4-bromobutyl acetate followed by protection with a Boc group and alkaline hydrolysis. Alcohol **9** was mesylated with mesyl chloride, coupled with piperidine and then treated with concentrated HCl to afford compound **10**. Swern oxidation of alcohol **9** gave aldehyde **11**, which was converted to compounds **12a**–**l** by reductive alkylation



Scheme 2. Synthesis of compounds **17a**–**b**, **18**, **21a**–**c** and **22**. Reagents and conditions: (a) (i) Boc_2O, TEA, CH_2Cl_2 (59%); (ii) $NH_2NH_2{\cdot}H_2O$, EtOH (quant); (b) (i) Z-Cl, aq $NaHCO_3$, CH_2Cl_2 (74%); (ii) $NH_2NH_2{\cdot}H_2O$, EtOH (quant); (c) (i) 4-bromobutyl acetate, KF-Celite, MeCN; (ii) Boc_2O, CH_2Cl_2 (two steps 71%); (iii) K_2CO_3, MeOH (quant); (iv) Swern oxidation. (quant); (d) (i) **13**, $NaBH_4$, MeOH; (ii) Boc_2O, CH_2Cl_2 (two steps 64%); (iii) H_2, Pd-C, EtOH (quant.); (e) (i) carboxylic acid, EDC·HCl, HOBt, NMM, CH_2Cl_2; (ii) c HCl, EtOH (two steps 37–40%); (f) (i) 2-(1-naphthyl)ethyl methanesulfonate, K_2CO_3, DMF; (ii) c HCl, EtOH (two steps 34%); (g) (i) 4-bromobutylphthalimide, KF-Celite, MeCN; (ii) Boc_2O, CH_2Cl_2 (55%); (iii) $NH_2NH_2{\cdot}H_2O$, EtOH, (quant.); (h) (i) cyclohexanecarboxaldehyde, $NaBH_4$, MeOH; (ii) Boc_2O, TEA, CH_2Cl_2 (two steps 44%); (iii) H_2, Pd/C, EtOH (quant); (i) (i) carboxylic acid, EDC·HCl, HOBt, NMM, CH_2Cl_2; (ii) c HCl, EtOH (two steps, 35–87%); (j) (i) dansyl chloride, TEA, CH_2Cl_2; (ii) c HCl, EtOH (two steps 76%).

using the corresponding amines and treatment with concentrated HCl.

The synthetic pathways of compounds **17a**,**b**, **18**, **21a**–**c** and **22** are shown in Scheme 2. Phthalimide **4** was converted to two compounds **13** and **14** by protection with a Boc group and benzyloxycarbonyl (Z) groups, respectively, and subsequent cleavage of the phthalimide moiety. Compound **14** was treated with 4-bromobutyl acetate in the presence of KF-Celite, followed by protection with a Boc group, alkaline hydrolysis and Swern oxidation, to give aldehyde **15**. Aldehyde **15** was used for reductive alkylation of **13**, and the resulting product was protected by a Boc group and reduced catalytically to give tri-Boc-protected amine **16**. Condensation of **16** with arylacetic acids followed by treatment with concentrated HCl gave compouds **17a**–**b**. Reaction of **16** with 2-(1-naphthyl)ethyl methanesulfonate followed by treatment with concd HCl afforded compound **18**. Amine **20** was prepared by alkylation of **14** with 4-bromobutylphthalimide, followed by protection with a Boc group, removal of a phthaloyl group, reductive alkylation with cyclohexanecarboxaldehyde, protection with a Boc group, and catalytic reduction. Compound **21a**–**c** were synthesized by condensation of **20** with arylacetic acids follwed by treatment with concentrated HCl. Reaction of **20** with dansyl chloride followed by treatment with concentrated HCl gave compound **22**.

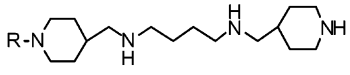
Results and Discussion

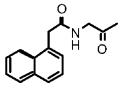
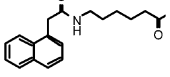
Antagonist activity of test compounds against Ca^{2+}-permeable AMPA receptor (IC_{50}) was measured using a two-electrode voltage clamp method:[11] kainate (KA) was used as an agonist for the receptors expressed in *Xenopus* oocytes by injection of rat brain mRNA. However, since KA non-selectively induces inward currents via stimulation of KA receptors, Ca^{2+}-permeable and Ca^{2+}-impermeable receptors, antagonist activity of test compounds for Ca^{2+}-permeable AMPA receptors was calculated by offsetting the inward currents due to blockade of the other two receptors.[12] Hypotensive activity was evaluated after intravenous (iv) administration to Wistar rats. These activities are shown in Tables 1–5.

NAS, a prototype Ca^{2+}-permeable AMPA receptor antagonist, did not show neuroprotective effect in transient ischemia models in gerbils after intraperitoneal (ip) administration. We supposed that NAS lacked the permeability into the brain tissues due to its low lipophilicity. Therefore, we designed compounds having a ring structure by modification of the linear polyamine structure of NAS in order to elevate lipophilicity. Compound **12a**, *N*-[1-(1-naphthylacetyl)piperidin-4-ylmethyl]-*N*′-(4-piperidinylmethyl)-1,4-diaminobutane, exhibited moderate potency with an IC_{50} value of 1.3 μM (Table 1). Reduction of the amide function of **12a** significantly decreased in potency (**18**), suggesting that the carbonyl group plays an important role in exhibiting potent activity. Insertion of an amino acid moiety between the naphthylacetyl and piperidine groups of **12a** gave **17a**,**b** showing 3-fold higher potency. Compound **12a** showed potent hypotensive activity at a dose of 3 mg/kg. Insertion of an amino acid moiety between the naphthaleneacetyl and piperidine groups of **12a** resulted in a moderate decrease in potency (**17a**,**b**).

Next, we modified the polyamine structure of **12a** in order to improve antagonist activity and eliminate hypotensive activity. In the course of this study, we found several compounds derived from **12a** showed both potent antagonist activity and non-hypotensive activity. Compounds **17a** and **17b** seemed to have lower permeability into the brain tissues compared to **12a** because of insertion of an amino acid moiety. Therefore, we did not investigate further modification the polyamine structure of **17a** or **17b**. These results are described in Table 2. The amino-ethyl and-propyl derivatives **8a**, **12b** had 4-fold higher antagonist activity than that of **12a**. Compounds **8b**,**c**, isomeric 2- and 3-piperidinylmethyl congeners of **12a**, showed potency almost similar to that of **12a**. Compound **8d** with a piperidin-1-yl group showed 7-fold higher potency than **12a**. The *N*-methylpiperidine derivative **12c** showed 2-fold higher potency than **12a**. Compounds with an aromatic heterocyclic moiety showed the most potent activity (**12f**). With respect to hypotensive activity, compounds **8c**,**d** showed no hypotensive effect at a dose of 3 mg/kg. Among the piperidinyl derivatives, the order of the hypotensive activity is **12a** > **8b** > > **8c** = **8d**. Thus, the basic nitrogen atom in the piperidinine ring apparently contributes to the activity. We suppose that

Table 1. Inhibitory effect of polyamine derivatives on Ca^{2+}-permeable AMPA receptor and effect on blood pressure (**1**)



Compound	R	IC_{50} (μM)[a]	SBP (mmHg)[c]
12a		1.3	−120
17a		0.49	−50
17b		0.42	−40
18		28%[b]	NT[d]
NAS (2)	—	0.69	−55[e]

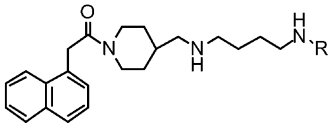
[a]IC_{50} (M) was defined as the concentration of a compound that reduces the inward current induced by kainate by 50%. The compound was co-administered with kainate to *Xenopus* oocytes and the inward current was measured by the two-electrode voltage clamp method. The values represent the means of results from six *Xenopus* oocytes.
[b]Because some compounds could not exert 50% inhibition, the amount of inhibition (%) exerted at a concentration of 1 M is shown.
[c]The systolic blood pressure (mmHg) of rats after intravenous (iv) administration of a 3 mg/kg dose was compared with the systolic blood pressure before administration (n = 1–2).
[d]Not tested.
[e]A 1.0 mg/kg dose was used.

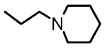
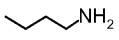
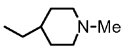
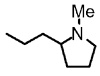
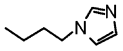
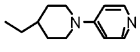
compounds having a basic nitrogen atom in the piperidin-2-yl and piperidin-1-yl groups do not show hypotensive activity because of its steric hindrance. However, the *N*-methylpiperidine derivative **12c** and the (1-methylpyrrolidin-2-yl)ethyl derivative **12d** had potent hypotensive activity. These results would indicate that non-hypotensive compounds have the two common characteristics: (1) the two-carbon length between the terminal nitrogen atom and the closest nitrogen atom and (2) the steric hindrance around the terminal nitrogen atom.

As a decrease in the number of basic nitrogen atoms of **12a** leads to improvement of lipophilicity, we designed compound **7** which does not have a piperidine-4-ylmethyl group. Compound **7** showed an antagonist activity, and therefore we selected compounds having diaminobutane skeleton for further modification, expecting that these compounds would exhibit neuroprotective effect in vivo models. These results are shown in Table 3. Alkylation of the terminal amino group in compound **7** caused improvement of antagonist activity (**10**, **12g**, **12i** and **12j**). On the other hand, introduction of an oxygen or a sulfur atom into the terminal alkyl group resulted in a slight decrease in potency (**8e** and **12h**). Alkylation of the terminal amino group in **7** eliminated hypotensive activity, except for compound **8e**.

Based on these results, we focused on the synthesis of diamine derivatives having a mono-alkylated terminal amino group for further modification because of its easiness and higher possibility in modification. We also evaluated NMDA antagonist activity of these compounds, as well as Ca^{2+}-permeable AMPA receptor antagonist activity and hypotensive activity. These results are shown in Table 4. Among these compounds, all the compounds showed non-hypotensive activity. Especially, the cyclohexylmethyl derivative **8f** exhibited the highest Ca^{2+}-permeable AMPA receptor antagonist activity. The other compounds exhibited moderate

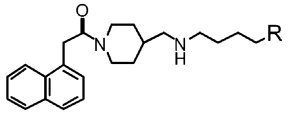
Table 2. Inhibitory effect of polyamine derivatives on Ca^{2+}-permeable AMPA receptor and effect on blood pressure (**2**)

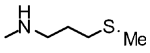
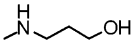
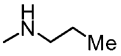
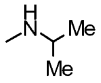


Compound	R	IC_{50} (μM)[a]	SBP (mmHg)[b]
8a		0.33	−50
8b		0.82	−58
8c		1.1	0
8d		0.19	5
12b		0.32	−35
12c		0.57	−50
12d		0.78	−55
12e		0.26	−25
12f		0.17	−43

[a]IC_{50} (M) was defined as the concentration of a compound that reduces the inward current induced by kainate by 50%. The compound was co-administered with kainate to *Xenopus* oocytes and the inward current was measured by the two-electrode voltage clamp method. The values represent the means of results from 6 *Xenopus* oocytes.
[b]The systolic blood pressure (mmHg) of rats after intravenous (iv) administration of a 3 mg/kg dose was compared with the systolic blood pressure before administration ($n = 1$–2).

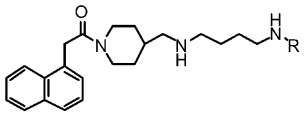
Table 3. Inhibitory effect of diamine derivatives on the Ca^{2+}-permeable AMPA receptor and effect on blood pressure

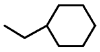
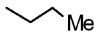
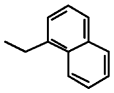


Compound	R	IC_{50} (μM)[a]	SBP (mmHg)[c]
7		54%[b]	−53
8e		20%[b]	−36
10		0.39	4
12g		0.53	12
12h		44%[b]	−6
12i		0.74	9
12j		0.73	10

[a]IC_{50} (μM) was defined as the concentration of a compound that reduces the inward current induced by kainate by 50%. The compound was co-administered with kainate to *Xenopus* oocytes and the inward current was measured by the two-electrode voltage clamp method. The values represent the means of results from six *Xenopus* oocytes.
[b]Because some compounds could not exert 50% inhibition, the amount of inhibition (%) exerted at a concentration of 1 μM is shown.
[c]The systolic blood pressure (mmHg) of rats after intravenous (iv) administration of a 3 mg/kg dose was compared with the systolic blood pressure before administration ($n = 1$–2).

Table 4. Inhibitory effect of diamine derivatives on the Ca^{2+}-permeable AMPA receptor and NMDA receptor, and effect on blood pressure (**1**)



Compound	R	AMPA IC_{50} (μM)[a]	NMDA IC_{50} (μM)[b]	NMDA /AMPA	SBP (mmHg)[c]
8f		0.25	13.6	54.4	11 (17)[d]
12i		0.74	41	55.4	9
12k		1.5	9.5	6.3	15
12l		0.77	3.9	5.1	8
NAS (**2**)	—	0.69	0.44	0.64	−55[e]

[a]IC_{50} (μM) was defined as the concentration of a compound that reduces the inward current induced by kainate by 50%. The compound was co-administered with kainate to *Xenopus* oocytes and the inward current was measured by the two-electrode voltage clamp method. The values represent the means of results from six *Xenopus* oocytes.
[b]IC_{50} (μM) was defined as the concentration of a compound that reduced the inward current induced by NMDA and glycine by 50%. The compound was co-administered with NMDA and glycine to *Xenopus* ooccytes and the inward current was measured by the two-electrode voltage clamp method. The values represent the means of results from six *Xenopus* oocytes.
[c]The systolic blood pressure (mmHg) of rats after intravenous (iv) administration of a 3 mg/kg dose was compared with the systolic blood pressure before administration ($n = 1$–2).
[d]A 10 mg/kg dose was used.
[e]A 1.0 mg/kg dose was used.

potency with an IC_{50} value of 0.74–1.5 μM. With respect to selectivity of Ca^{2+}-permeable AMPA receptor over NMDA receptor antagonist activity, compounds **8f** and **12i**, which had comparatively small alkyl groups in the terminal amino group, had higher selectivity than **12k** and **12l**.

Next, we modified acyl moiety group in **8f** in order to investigate the possibility for improvement of the selectivity. These results are shown in Table 5. Among these compounds, the adamantane derivative **21c** exhibited the highest selectivity for Ca^{2+}-permeable AMPA receptor over NMDA receptor, as well as the highest Ca^{2+}-permeable AMPA receptor antagonist activity. However, **21c** showed hypotensive activity.

We evaluated neuroprotective effects using a transient global ischemia models in gerbils.[13] Compounds **8d**, **10**, **8f** and **21c** were selected for evaluation of neuroprotective effects because they had potent antagonist activity, and non-hypotensive activity except for **21c**. Among these compounds, only **8f** exhibited neuroprotective effects in this model after ip administration. A 4-time repeated dose of 2.5, 5.0 or 10 mg/kg of **8f** was intraperitoneally administered at 0, 2, 4 and 6 h after 5-min ischemia: compound **8f** significantly protected neurons from cell death at a repeated dose of 10 mg/kg (Fig. 2). In addition, compound **8f** would not show hypotensive effects in the gerbil transient global ischemia models, since the compound did not reduce blood pressure in rat up to at least 10 mg/kg iv administration. On the other hand, compounds **8d** and **10** did not show neuroprotective effects suggesting that high lipophilicity would contribute to exhibiting neuroprotective effects after ip administration: predicted Log P[14] for **8d**, **10**, **8f** and **21c** were 3.72, 4.22, 5.32 and 5.41, respectively. Compound **21c** also showed no neuroprotective effects, and the reason might be hypotensive activity but uncertain.

Selectivity of **8f** between Ca^{2+}-permeable and Ca^{2+}-impermeable AMPA receptors was determined by using recombinant AMPA receptors according to the described method (Table 6).[15] Ca^{2+}-permeable AMPA receptors are assembled from only GluR3 subunits, while Ca^{2+}-impermeable AMPA receptors are assembled from GluR3 and GluR2 subunits.[16] Compound **8f** as well as JSTX-3[17] showed selective inhibition for

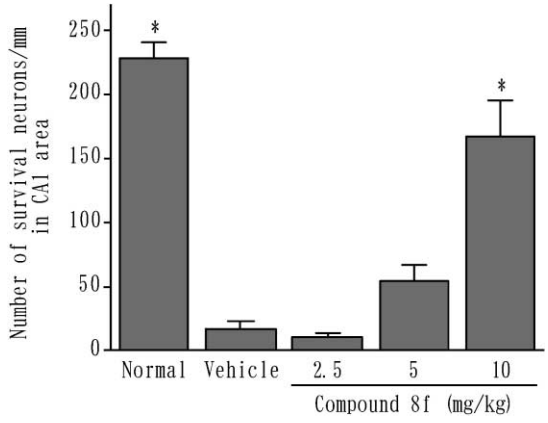
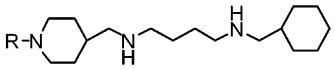
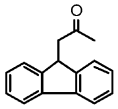
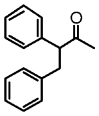
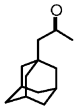
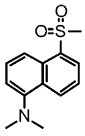


Figure 2. Effect of compound **8f** on number of survived neurons in the hippocampal CA1 area in gerbils 5 days after global ischemia. Values are means±SEM of individual hippocampi in each group ($n = 6$–20). Compound **8f** was intraperitoneally administrated four times after ischemia. *$p < 0.01$ versus vehicle.

Table 5. Inhibitory effect of diamine derivatives on the Ca^{2+}-permeable AMPA receptor and NMDA receptor, and effect on blood pressure (**2**)



Compound	R	AMPA IC_{50} (μM)[a]	NMDA IC_{50} (μM)[b]	NMDA/AMPA	SBP (mmHg)[c]
21a		0.96	8.3	8.6	0
21b		0.71	12.4	17.5	8
21c		0.25	90	360	−19
22		0.56	13	23.2	0

[a]IC_{50} (μM) was defined as the concentration of a compound that reduces the inward current induced by kainate by 50%. The compound was co-administered with kainate to *Xenopus* oocytes and the inward current was measured by the two-electrode voltage clamp method. The values represent the means of results from six *Xenopus* oocytes.
[b]IC_{50} (μM) was defined as the concentration of a compound that reduced the inward current induced by NMDA and glycine by 50%. The compound was co-administered with NMDA and glycine to *Xenopus* ooccytes and the inward current was measured by the two-electrode voltage clamp method. The values represent the means of results from six *Xenopus* oocytes.
[c]The systolic blood pressure (mmHg) of rats after intravenous (iv) administration of a 3 mg/kg dose was compared with the systolic blood pressure before administration ($n = 1$–2).

Ca^{2+}-permeable AMPA receptors. On the other hand, in this study, it is uncertain whether compound **8f** has antagonist activity against kainate receptors. Hence, experiments using recombinant kainate receptors are in progress.

Conclusion

We designed and synthesized novel polyamine derivatives as Ca^{2+}-permeable AMPA receptor antagonists based on JSTX-3 or NAS. In this study, we tried to address three issues which NAS had as follows. (1) NAS did not exhibit neuroprotective effect after ip or iv administration due to low lipophilicity. (2) NAS had strong hypotensive activity, which was unfavorable for the therapeutic agents for stroke. (3) NAS showed considerable antagonist activity against NMDA receptors, which may cause undesirable side effects. First we tried to elevate lipophilicity of NAS by introducing a ring structure into polyamine. In the course of this study, we found compounds bearing a ring amine structure, *N,N′*-bis(piperidin-4-ylmethyl)diaminobutane, showed potent antagonist activity. However, most of the compounds having this polyamine structure showed strong hypotensive activity. Hence, we tried to eliminate hypotensive activity by modification of this polyamine structure. As a result, we found the terminal polyamine structure played an important role in hypotensive activity, and discovered compounds with both potent antagonist activity and non-hypotensive activity. However, among these polyamine derivatives, no compounds exhibited neuroprotective effect after ip administration. Therefore, we designed diamine derivatives in order to improve lipophilicity further. We found diamine compounds, the terminal amino group of which was alkylated, showed both potent antagonist activity and non-hypotensive activity. Among this diamine derivatives, compound **8f** showed neuroprotective effect in transient global ischemia models after ip administration. Moreover, compound **8f** showed higher selective antagonist activity for AMPA over NMDA receptor compared to NAS, expecting that **8f** might be neuroprotective agent with fewer side effects. Now further investigation of **8f** is in progress.

Table 6. Blocking effects of JSTX-3 and **8f** on Ca^{2+}-permeable (GluR3 only) or Ca^{2+}-impermeable AMPA receptors (GluR3+-GluR2)

Sample	%inhibition[a] (GluR3 only)	% inhibition[a] (GluR3 + GluR2)
JSTX-3 (**1**)	79.7	4.3
8f	65.8	4.4

[a]*Xenopus* oocytes that had been injected with GluR3cRNA (50 ng) had Ca^{2+}-permeable AMPA receptors. On the other hand, *Xenopus* oocytes that had been injected with both GluR3cRNA and GluR2cRNA (1:9, total 100 ng) had Ca^{2+}-impermeable AMPA receptors. Both of these compounds strongly decreased the inward current via Ca^{2+}-permeable AMPA receptors but had a little effect on the current via Ca^{2+}-impermeable AMPA receptors. JSTX-3 or **8f** was administered at the dose of 3 μM with 300 μM KA. Each value is the mean of results from 2–3 *Xenopus* oocytes.

Experimental

Melting points were obtained on a Büchi 535 digital melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Hitachi 270-30 spectrometer. ^{1}H NMR spectra were obtained on a JEOL EX-400 spectrometer, with tetramethylsilane as an internal standard. Mass (MS) spectra were obtained on a JEOL JMS-AX505W mass spectrometer. Elemental analyzers were performed using a Perkin-Elmer Model 240C elemental analyzer. Thin layer chromatography (TLC) was performed with Merck Kieselgel F_{254} precoated plates. Merck Kieselgel 60 (70–230 mesh) was used for column chromatography. Unless otherwise specified, materials were obtained from commercial suppliers and were used without further purification. The following solvent and reagent names are abbreviated as follows: acetonitrile (MeCN), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), ethyl acetate (EtOAc), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC·HCl), 1-hydroxybenzotriazole (HOBt), *N*-methylmorpholine (NMM), potassium fluoride, 50 wt.% on Celite. Aldrich (KF-Celite), and triethylamine (TEA).

***N*-(4-Piperidinylmethyl)phthalimide hydrochloride (4).** A mixture of phthalic anhydride (10.4 g, 70.2 mmol) and 4-aminomethylpiperidine (8.0 g, 70.2 mmol) was heated at 170 °C for 1 h. After cooling, the reaction mixture was dissolved in 1 N HCl EtOH solution (80 mL) and concentrated in vacuo. The residue was recrystallized from EtOH to give **4** as a colorless crystalline powder (12 g, 61%): mp 239–240 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.37–1.46 (m, 2 H), 1.77 (m, 2H), 1.97 (m, 2H), 2.79 (m, 3H), 3.21 (m, 2H), 3.47 (d, J = 6.8 Hz, 2H), 7.83–7.90 (m, 4H).

4-Aminomethyl-1-(1-naphthyl)acetylpiperidine (5). To a stirred solution of **4** (9.2 g, 32.8 mmol), 1-naphthaleneacetic acid (6.1 g, 32.8 mmol), and triethylamine (24 mL) in CH_2Cl_2 (80 mL) was added EDC·HCl (8.18 g, 42.6 mmol) at room temperature. The mixture was stirred overnight at the same temperature. After removal of the solvent, the residue was diluted with H_2O and extracted with EtOAc. The extracts were washed with H_2O, 1 N HCl, and aq $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was recrystallized from EtOH-hexane to afford ***N*-[1-(1-naphthyl)acetylpiperidin-4-yl]methylphthalimide** as a colorless crystalline powder (9.5 g, 69%): mp 137–140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11–1.25 (m, 2H), 1.60–1.72 (m, 2H), 2.00 (m, 2H), 2.63 (m, 1H), 2.93 (m, 1H), 3.57 (d, J = 6.8 Hz, 2H), 3.85 (m, 1H), 4.14 (s, 2H), 7.29–7.54 (m, 4H), 7.72–7.97 (m, 7H).

A mixture of ***N*-[1-(1-naphthyl)acetylpiperidin-4-yl]methylphthalimide** (4.12 g, 10 mmol) and hydrazine monohydrate (5.0 mL) in EtOH (100 mL) was stirred at 80 °C for 2 h. The mixture was concentrated in vacuo, and resulting solid was filtered off and washed with $CHCl_3$. The filtrate was concentrated in vacuo, and resulting solid was filtered off and washed with $CHCl_3$ again. The filtrate was concentrated in vacuo to give **5** as a colorless crystalline powder: mp 108–110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92–0.96 (m, 1H), 1.09–1.13 (m, 1H), 1.55–1.64 (m, 3H), 1.76 (m, 1H), 2.55–2.63 (m, 3H), 2.95 (m, 1H), 3.84 (m, 1H), 4.15 (s, 2H), 4.72 (m, 1H), 7.31 (d, J = 6.8 Hz, 1H), 7.40 (m, 1H), 7.51 (m, 2H), 7.76 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H).

***N*-(*tert*-Butoxycarbonyl)-*N*-[1-(1-naphthylacetyl)piperidin-4-ylmethyl]-1,4-diaminobutane (6).** To a stirred solution of **5** (5.6 g, 20 mmol) and *N*-(4-bromobutyl)phthalimide (5.6 g, 20 mmol) in MeCN (100 mL) was added KF-Celite (5.0 g). The mixture was stirred overnight at 50 °C. Insoluble material was filtered off and washed with MeCN. The filtrate was concentrated in vacuo. To a solution of the residue in CH_2Cl_2 (50 mL) was added di-*tert*-butyl dicarbonate (4.36 g, 20 mmol) at room temperature. The mixture was stirred overnight at the same temperature. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc, 1:2, v/v) to afford a brown oil. A solution of the obtained oil and hydrazine monohydrate (4.0 mL) in EtOH (50 mL) was stirred at 80 °C for 2 h. The mixture was concentrated in vacuo, and resulting solid was filtered off and washed with $CHCl_3$. The filtrate was concentrated in vacuo, and resulting solid was filtered off and washed with $CHCl_3$ again. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 99:1 to 4:1, v/v) to afford **6** as a tan oil (5.0 g, 55%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9H), 1.16–1.68 (m, 9H), 2.55–2.69 (m, 3H), 2.92–3.10 (m, 5H), 3.80 (m, 1H), 4.13 (s, 2H), 4.66 (m, 1H), 7.28–7.52 (m, 4H), 7.74 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 7.3 Hz, 1H), 7.95 (m, 1H).

***N*-[1-(1-naphthylacetyl)piperidin-4-ylmethyl]-1,4-diaminobutane (7).** To solution of **6** (300 mg, 0.6 mmol) in EtOH (6.0 mL) was added concd HCl (3.0 mL) at 0 °C. The mixture was stirred at room temperature for 5 h and concentrated in vacuo. The resulting solid was collected and washed with Et_2O to give **7** as an amorphous powder (170 mg, 60%): IR (KBr, cm^{-1}) 3408, 2936, 1622, 1452, 790, 586, 536; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.15–1.22 (m, 2H), 1.75–2.05 (m, 7H), 2.74 (m, 3H), 2.89–3.11 (m, 5H), 4.05 (m, 1H), 4.23 (m, 2H), 4.63 (m, 1H), 7.32–7.53 (m, 4H), 7.79 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 7.3 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H); MS (FAB) m/z 354 $(M+H)^+$. Anal. calcd for $C_{22}H_{31}N_3O{\cdot}2HCl{\cdot}1.2H_2O$: C, 58.98; H, 7.96; N, 9.38. Found: C, 58.89; H, 7.78; N, 9.60.

***N*-(2-Aminoethyl)-*N'*-[1-(1-naphthylacetyl)piperidin-4-ylmethyl]-1,4-diaminobutane (8a).** A solution of **6** (400 mg, 0.88 mmol) and *tert*-butyl *N*-(2-oxoethyl)carbamate (140 mg, 0.88 mmol) in CH_2Cl_2 was stirred at room temperature for 1 h, and then concentrated in vacuo. The residue was dissolved in MeOH, and $NaBH_4$ (274 mg, 7.2 mmol) was added. The mixture was stirred for 1 h. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was

purified by silica gel column chromatography ($CHCl_3$/MeOH, 99:1 to 9:1, v/v) to afford a yellowish oil. This oil was dissolved in EtOH (6.0 mL), and concd HCl (3.0 mL) was added. The mixture was stirred at room temperature for 7 h, and concentrated in vacuo. The resulting solid was collected and washed with Et_2O to give **8a** as an amorphous powder (150 mg, 74%): IR (KBr, cm^{-1}) 3412, 2944, 2844, 2820, 1618, 1446, 788; ^1H NMR (CD_3OD, 400 MHz) δ 1.12–1.21 (m, 2H), 1.74–1.84 (m, 7H), 2.73–3.29 (m, 12H), 4.04 (m, 1H), 4.22 (m, 2H), 4.62 (m, 1H), 7.31–7.54 (m, 4H), 7.78 (d, $J=8.3$ Hz, 1H), 7.87 (d, $J=7.3$ Hz, 1H), 7.97 (d, $J=7.8$ Hz, 1H); MS (FAB) m/z 397 $(M+H)^+$. Anal. calcd for $C_{24}H_{36}N_4O{\cdot}3HCl{\cdot}1.5H_2O$: C, 54.09; H, 7.94; N, 10.51. Found: C, 54.13; H, 7.79; N, 10.69.

The following compounds were prepared in a similar manner described for the preparation of **8a**.

***N*-[1-(1-Naphthylacetyl)piperidin-4-ylmethyl]-*N′*-(piperidin-3-ylmethyl)-1,4-diaminobutane (8b).** Mp 251–253 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.10 (m, 1H), 1.25 (m, 1H), 1.74 (m, 12H), 2.63–3.41 (m, 16H), 4.16 (s, 2H), 7.32 (d, $J=7$ Hz, 1H), 7.45 (t, $J=8$ Hz, 1H), 7.52 (m, 2H), 7.82 (d, $J=8$ Hz, 1H), 7.94 (m, 2H); MS (FAB) m/z 451 $(M+H)^+$. Anal. calcd for $C_{28}H_{42}N_4O{\cdot}3HCl{\cdot}H_2O$: C, 58.18; H, 8.20; N, 9.69. Found: C, 57.89; H, 8.11; N, 9.52.

***N*-[1-(1-Naphthylacetyl)piperidin-4-ylmethyl]-*N′*-(piperidin-2-ylmethyl)-1,4-diaminobutane (8c).** Amorphous powder; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.11 (m, 1H), 1.75 (m, 14H), 2.59 (m, 1H), 2.63–3.41 (m, 14H), 4.15 (s, 2H), 7.32 (d, $J=7$ Hz, 1H), 7.44 (t, $J=8$ Hz, 1H), 7.52 (m, 2H), 7.81 (d, $J=8$ Hz, 1H), 7.93 (m, 2H); MS (FAB) m/z 451 $(M+H)^+$.

***N*-[1-(1-Naphthylacetyl)piperidin-4-ylmethyl]-*N′*-[2-(1-piperidinyl)ethyl)-1,4-diaminobutane (8d).** Amorphous powder; IR (KBr, cm^{-1}) 3420, 2944, 2864, 2772, 1620, 1452, 796; ^1H NMR (CD_3OD, 400 MHz) δ 1.12–1.94 (m, 15H), 2.74–3.67 (m, 16H), 4.05 (m, 1H), 4.23 (m, 2H), 4.63 (m, 1H) 7.33–7.55 (m, 4H), 7.80 (d, $J=8.3$ Hz, 1H), 7.88 (m, 1H), 7.99 (d, $J=8.3$ Hz, 1H); MS (FAB) m/z 465 $(M+H)^+$. Anal. calcd for $C_{29}H_{44}N_4O{\cdot}3HCl{\cdot}1.5H_2O$; C, 57.95; H, 8.38; N, 9.32. Found: C, 58.03; H, 8.53; N, 9.15.

***N*-[3-(Methylthio)propyl]-*N′*-[1-(1-naphthylacetyl)piperidin-4-ylmethyl]-1,4-diaminobutane (8e).** Amorphous powder; IR (KBr, cm^{-1}) 3400, 2939, 2742, 2424, 1620, 1446, 1275, 795, 787; ^1H NMR (CD_3OD, 400 MHz) δ 1.14–1.20 (m, 2H), 1.83–2.21 (m, 14H), 2.72–3.20 (m, 12H), 4.05 (m, 1H), 4.22 (m, 2H), 4.60 (m, 1H), 7.31–7.53 (m, 4H), 7.79 (m, 1H), 7.87 (m, 1H), 7.98 (m, 1H). Anal. calcd for $C_{26}H_{39}N_3OS{\cdot}2HCl{\cdot}1.5H_2O$: C, 57.66; H, 8.19; N, 7.76. Found: C, 57.89; H, 8.19; N, 7.46.

***N*-Cyclohexylmethyl-*N′*-[1-(1-naphthylacetyl)piperidin-4-ylmethyl]-1,4-diaminobutane (8f).** Mp 234–236 °C (dec.); IR (KBr, cm^{-1}) 3448, 2852, 2768, 1650, 1450, 1432, 1208, 788; ^1H NMR (CD_3OD, 400 MHz) δ 0.98–1.40 (m, 7H), 1.66–1.80 (m, 12H), 1.95–2.06 (m, 1H), 2.70–2.80 (m, 1H), 2.84 (d, $J=6.8$ Hz, 2H), 2.89 (d, $J=7.3$ Hz, 2H), 3.02 (br s, 4H), 3.10–3.15 (m, 1H), 4.04–4.08 (m, 1H), 4.22 (m, 2H), 4.60–4.64 (m, 1H), 7.32–7.54 (m, 4H), 7.79 (d, $J=8.3$ Hz, 1H), 7.86–7.89 (m, 1H), 7.99 (d, $J=7.8$ Hz, 1H); MS (FAB) m/z 450 $(M+H)^+$. Anal. calcd for $C_{29}H_{43}N_3O{\cdot}2HCl$: C, 66.65; H, 8.63; N, 8.04; Cl, 13.57. Found: C, 66.68; H, 8.76; N, 8.09, Cl, 13.53.

4-[*N*-*tert*-Butoxycarbonyl-*N*-(4-hydroxybutyl)amino]methyl-1-(1-naphthyl)acetylpiperidine (9). To a solution of **5** (2.1 g, 7.3 mmol) and 4-bromobutyl acetate (0.8 mL, 5.5 mmol) in MeCN (50 mL) was added KF-Celite (3.0 g). The mixture was stirred at 50 °C for 2 days. Insoluble material was filtered off and washed with MeCN. The filtrate was concentrated in vacuo. To a solution of the residue in CH_2Cl_2 (30 mL) was added di-*tert*-butyl dicarbonate (2.38 g, 10.92 mmol) at room temperature. The mixture was stirred overnight at the same temperature. After removal of the solvent, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 99:1, v/v) to afford **4-[*N*-(4-acetoxybutyl)-*N*-*tert*-butoxycarbonylamino]methyl-1-(1-naphthyl)acetylpiperidine** as a white oil (1.3 g, 48%): ^1H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 9H), 0.92–1.90 (m, 9H), 2.04 (s, 3H), 2.60–3.15 (m, 6H), 3.82 (m, 1H), 4.06 (t, $J=6.0$ Hz, 2H), 4.16 (s, 2H), 4.68 (m, 1H), 7.32 (d, $J=6.8$ Hz, 1H), 7.42 (m, 1H), 7.54 (m, 2H), 7.77 (d, $J=7.8$ Hz, 1H), 7.87 (d, $J=7.8$ Hz, 1H), 7.99 (m, 1H).

To a solution of **4-[*N*-(4-acetoxybutyl)-*N*-*tert*-butoxycarbonylamino]methyl-1-(1-naphthyl)acetylpiperidine** (1.3 g, 2.61 mmol) in MeOH (10 mL) was added K_2CO_3 at room temperature. The mixture was stirred at the same temperature for 1 h, and concentrated in vacuo. The residue was diluted with H_2O and extracted with EtOAc. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give **9** as a white oil (1.0 g, 84%): IR (KBr, cm^{-1}) 3200, 3600, 2928, 2864, 1690, 1642, 1450, 1418, 1368, 1274, 1230, 1164, 1062, 786; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.80–1.30 (m, 2H), 1.40–1.90 (m, 6H), 1.42 (s, 9H), 2.63 (br s, 1H), 3.00 (m, 2H), 3.17 (br s, 2H), 3.49 (s, 1H), 3.66 (br s, 2H), 3.84 (br s, 1H), 4.16 (s, 2H), 4.69 (m, 1H), 5.30 (s, 2H), 7.32 (d, $J=6.8$ Hz, 1H),7.42 (t, $J=7.8$ Hz, 1H), 7.52 (m, 2H), 7.77 (d, $J=7.8$ Hz, 1H), 7.87 (d, $J=7.8$Hz, 1H), 7.99 (m, 1H); MS (EI) m/z 454 $(M)^+$.

1-(1-Naphthyl)acetyl-4-[4-(1-piperidinyl)butyl]aminomethylpiperidine (10). A solution of **9** (800 mg, 1.76 mmol) in pyridine (10 mL) was added methanesulfonyl chloride (204 μL, 2.6 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, poured into H_2O and extracted with EtOAc. The extracts were washed with 1 N HCl and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. A mixture of the obtained mesylate, piperidine (522 μL, 5.3 mmol) and KF-Celite (2.0 g) in MeCN (20 mL) was stirred overnight at 50 °C. Insoluble material was filtered off and washed with MeCN. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 96:4, v/v) to afford a yellowish oil. The oil was dissolved in EtOH (10 mL), and concd

HCl (5.0 mL) was added. The mixture was stirred at room temperature for 7 h, and concentrated in vacuo. The resulting solid was collected and washed with Et_2O to give **10** as an amorphous powder (300 mg, 40%): IR (KBr, cm^{-1}) 3402, 2941, 2717, 2544, 1620, 1510, 1450, 1016, 796, 536; ^1H NMR (CD_3OD, 400 MHz) δ 1.29 (m, 2H), 1.53 (m, 1H), 1.79–1.95 (m, 12H), 2.74 (m, 1H), 2.89–3.17 (m, 9H), 3.52 (m, 2H), 4.05 (m, 1H), 4.23 (m, 2H), 4.63 (m, 1H), 7.32–7.54 (m, 4H), 7.79 (d, $J=8.3$ Hz, 1H), 7.88 (d, $J=7.8$ Hz, 1H), 7.98 (d, $J=8.8$Hz, 1H); MS (FAB) m/z 422 $(M+H)^+$. Anal. calcd for $C_{27}H_{39}N_3O{\cdot}2HCl{\cdot}1.4H_2O$: C, 62.39; H, 8.49; N, 8.08. Found: C, 62.49; H, 8.91; N, 8.07.

4-[*N*-(*tert*-Butoxycarbonyl)-*N*-(4-oxobutyl)amino]methyl-1-(1-naphthyl)acetylpiperidine (11). To a stirred solution of oxalyl chloride (0.22 mL, 2.4 mmol) in CH_2Cl_2 (20 mL) was added DMSO (0.41 mL, 4.8 mmol) at −78 °C. After 5 min, a solution of **9** (1.0 g, 2.2 mmol) in CH_2Cl_2 was added. The mixture was stirred at the same temperature for 30 min, and then triethyamine (1.7 mL, 12.2 mmol) was added. The stirred mixture was allowed to rise to room temperature for 30 min, then diluted with H_2O, and extracted with CH_2Cl_2. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 1:2, v/v) to afford **11** as a yellowish oil (0.7 g, 71%): IR (KBr, cm^{-1}) 2932, 1724, 1690, 1642, 1470, 1450, 1420, 1368, 1276, 1256, 1230, 1164, 1136, 786; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.80–1.60 (m, 4H), 1.43 (s, 9H), 1.69 (d, $J=13.2$ Hz, 1H), 1.82 (m, 3H), 2.44 (t, $J=6.8$ Hz, 2H), 2.62 (m, 1H), 2.98 (m, 2H), 3.17 (m, 2H), 3.84 (m, 1H), 4.16 (s, 2H), 4.69 (m, 1H), 7.32 (d, $J=6.8$ Hz, 1H), 7.42 (t, $J=7.8$ Hz, 1H), 7.52 (m, 2H), 7.77 (d, $J=8.3$ Hz, 1H), 7.87 (d, $J=7.8$ Hz, 1H), 8.00 (m, 1H), 9.77 (s, 1H); MS (EI) m/z 452 $(M)^+$.

The following compounds were prepared in a similar manner described for the preparation of **8a** starting from **11**.

***N*-[1-(1-Naphthylacetyl)piperidin-4-ylmethyl]-*N′*-(4-piperidinylmethyl)-1,4-diaminobutane (12a).** Amorphous powder; IR (KBr, cm^{-1}) 2948, 2740, 1632, 1598, 1452, 786; ^1H NMR (CD_3OD, 400 MHz) δ 1.09–1.21 (m, 2H), 1.50–1.56 (m, 2H), 1.74–2.14 (m, 10H), 2.70–3.16 (m, 12H), 3.42 (m, 2H), 4.04 (m, 1H), 4.22 (d, $J=16.1$Hz, 1H), 4.25 (d, $J=16.1$ Hz, 1H), 4.62 (m, 1H), 7.32 (d, $J=7.3$ Hz, 1H), 7.42 (m, 1H), 7.52 (m, 2H), 7.78 (d, $J=8.3$ Hz, 1H), 7,87 (m, 1H), 7.98 (d, $J=7.8$ Hz, 1H); MS (FAB) m/z 451 $(M+H)^+$. Anal. calcd for $C_{28}H_{42}N_4O{\cdot}3HCl{\cdot}0.5H_2O$; C, 59.10; H, 8.15; N, 9.85; Cl, 18.69. Found: C, 59.02; H, 7.97; N, 9.98; Cl, 18.61.

***N*-(3-Aminopropyl)-*N′*-[1-(1-naphthylacetyl)piperidin-4-ylmethyl]-1,4-diaminobutane (12b).** Amorphous powder; IR (KBr, cm^{-1}) 3440, 2940, 2808, 2780, 1640, 1442, 788; ^1H NMR (CD_3OD, 400 MHz) δ 1.08–1.25 (m, 2H), 1.83 (m, 6H), 2.04 (m, 1H), 2.11 (q, $J=7.6$ Hz, 2H), 2.73–3.29 (m, 9H), 2.75 (t, $J=11.7$ Hz, 1H), 2.92 (d, $J=7.3$ Hz, 2H), 4.07 (d, $J=14.2$ Hz, 1H), 4.24 (q, $J=16.1$ Hz, 2H), 4.63 (d, $J=13.7$ Hz, 1H), 7.34 (d, $J=7.3$ Hz, 1H), 7.44 (t, $J=7.6$ Hz, 1H), 7.53 (m, 2H), 7.80 (d, $J=8.3$ Hz, 1H), 7.89 (d, $J=7.3$ Hz, 1H), 8.00 (d, $J=8.3$ Hz, 1H); MS (FAB) m/z 411 $(M+H)^+$.

***N*-(1-Methylpiperidin-4-yl)-*N′*-[1-(1-naphthylacetyl)piperidin-4-ylmethyl]-1,4-diaminobutane (12c).** Amorphous powder; IR (KBr, cm^{-1}) 3432, 2940, 2864, 2752, 2552, 1636, 1510, 1452, 786; ^1H NMR (CD_3OD, 400 MHz) δ 1.09–1.22 (m, 2H), 1.62–2.11 (m, 12H), 2.73 (m, 1H), 2.85 (s, 3H), 2.90 (d, $J=6.8$ Hz, 2H), 2.99–3.17 (m, 9H), 3.50 (m, 2H), 4.05 (m, 1H), 4.22 (m, 2H), 4.63 (m, 1H), 7.31–7.54 (m, 4H), 7.79 (d, $J=8.3$Hz, 1H), 7.87 (m, 1H), 7.98 (d, $J=7.8$ Hz, 1H); MS (FAB) m/z 465 $(M+H)^+$. Anal. calcd for $C_{29}H_{44}N_4O{\cdot}3HCl{\cdot}0.8H_2O$: C, 59.19; H, 8.32; N, 9.52. Found: C, 59.27; H, 8.05; N, 9.43.

***N*-[2-(1-Methylpyrrolidin-2-yl)ethyl]-*N′*-[1-(1-naphthylacetyl)piperidin-4-ylmethyl]-1,4-diaminobutane (12d).** Amorphous powder; IR (KBr, cm^{-1}) 3416, 2948, 2792, 2724, 1624, 1450, 792, 588; ^1H NMR (CD_3OD, 400 MHz) δ 1.13–1.21 (m, 2H), 1.75–2.42 (m, 12H), 2.74–3.70 (m, 17H), 4.05 (m, 1H), 4.23 (m, 2H), 4.62 (m, 1H), 7.32–7.54 (m, 4H), 7.79 (d, $J=8.3$ Hz, 1H), 7.88 (d, $J=7.3$ Hz, 1H), 7.98 (d, $J=8.3$ Hz, 1H); MS (FAB) m/z 465 $(M+H)^+$. Anal. calcd for $C_{29}H_{44}N_4O{\cdot}3HCl{\cdot}1.3H_2O$: C, 58.30; H, 8.37; N, 9.38; Cl, 17.80. Found: C, 58.55; H, 8.28; N, 9.02; Cl, 17.70.

***N*-[3-(1-Imidazolyl)propyl]-*N′*-[1-(1-naphthylacetyl)piperidin-4-ylmethyl]-1,4-diaminobutane (12e).** Amorphous powder; IR (KBr, cm^{-1}) 3428, 2952, 2800, 2764, 1622, 1452, 794, 590; ^1H NMR (CD_3OD, 400 MHz) δ 1.09–1.21 (m, 2H), 1.74–2.02 (m, 6H), 2.32–2.36 (m, 2H), 2.71 (m, 1H), 2.89 (d, $J=6.8$ Hz, 2H), 2.99–3.16 (m, 8H), 4.05 (m, 1H), 4.21 (m, 2H), 4.42 (t, $J=6.8$ Hz, 2H), 4.62 (m, 1H), 7.31–7.53 (m, 4H), 7.58 (s, 1H), 7.73 (s, 1H), 7.78 (d, $J=8.3$ Hz, 1H), 7.87 (d, $J=7.8$ Hz, 1H), 7.97 (d, $J=8.3$ Hz, 1H), 9.05 (s, 1H); MS (FAB) m/z 462 $(M+H)^+$. Anal. calcd for $C_{28}H_{39}N_5O{\cdot}3HCl{\cdot}H_2O$: C, 57.09; H, 7.53; N, 11.89; Cl, 18.06. Found: C, 57.10; H, 7.65; N, 11.88; Cl, 18.32.

***N*-[1-(1-Naphthylacetyl)piperidin-4-ylmethyl]-*N′*-[1-(4-pyridyl)piperidin-4-ylmethyl]-1,4-diaminobutane (12f).** Mp 225–230 °C; IR (KBr, cm^{-1}) 3444, 2940, 2792, 1640, 1546, 1448, 1256, 1218, 796; ^1H NMR (CD_3OD, 400 MHz) δ 1.16–1.43 (m, 4H), 1.85–2.06 (m, 10H), 2.80 (m, 1H), 2.91–3.20 (m, 12H), 4.20 (m, 1H), 4.24 (m, 2H), 4.30 (m, 2H), 4.65 (m, 1H), 7.17 (d, $J=7.8$ Hz, 2H), 7.33–7.54 (m, 4H), 7.80 (d, $J=7.8$ Hz, 1H), 7.88 (d, $J=7.8$ Hz, 1H), 8.00 (d, $J=7.8$ Hz, 1H), 8.10 (d, $J=7.3$ Hz, 2H); MS (FAB) m/z 528 $(M+H)^+$. Anal. calcd for $C_{33}H_{45}N_5O{\cdot}3HCl{\cdot}2.7H_2O$: C, 57.80; H, 7.85; N, 10.21. Found: C, 57.78; H, 7.58; N, 9.95.

***N*,*N*-Dimethylamino-*N′*-[1-(1-naphthylacetyl)piperidin-4-ylmethyl]-1,4-diaminobutane (12g).** Amorphous powder; IR (KBr, cm^{-1}) 3410, 2943, 2748, 2472, 1639, 1442, 1211, 982, 787, 536; ^1H NMR (CD_3OD, 400 MHz) δ 1.16–1.19 (m, 2H), 1.79–2.03 (m, 7H), 2.91 (s, 6H), 2.74–3.48 (m, 8H), 4.04 (m, 1H), 4.23 (m, 2H), 4.61 (m, 1H), 7.32–7.53 (m, 4H), 7.79–7.99 (m, 3H); MS (FAB)

m/z 382 $(M+H)^+$. Anal. calcd for $C_{24}H_{35}N_3O{\cdot}2HCl{\cdot}0.4H_2O$: C, 62.44; H, 8.25; N, 9.10. Found: C, 62.68; H, 8.34; N, 8.86.

***N*-(3-Hydroxypropyl)-*N'*-[1-(1-naphthylacetyl)piperidin-4-ylmethyl]-1,4-diaminobutane (12 h).** Amorphous powder; IR (KBr, cm^{-1}) 3396, 3359, 2945, 2775, 2738, 1620, 1450, 1053, 793, 785, 536; ^1H NMR (CD_3OD, 400 MHz) δ 1.09–1.26 (m, 2H), 1.77–2.03 (m, 8H), 2.74 (m, 1H), 2.88 (d, $J=7.3$ Hz, 2H), 2.97–3.17 (m, 9H), 3.68 (t, $J=5.9$ Hz, 2H), 4.05 (m, 1H), 4.22 (m, 2H), 4.64 (m, 1H), 7.32–7.55 (m, 4H), 7.79 (d, $J=8.3$ Hz, 1H), 7.87 (m, 1H), 7.98 (d, $J=8.3$ Hz, 1H); MS (FAB) *m/z* 412 $(M+H)^+$. Anal. calcd $C_{25}H_{37}N_3O_2{\cdot}2HCl{\cdot}0.75H_2O$: C, 60.29; H, 8.20; N, 8.44; Cl, 14.24. Found: C, 60.32; H, 8.41; N, 8.39; Cl, 14.39.

***N*-[1-(1-Naphthylacetyl)piperidin-4-ylmethyl]-*N'*-propyl-1,4-diaminobutane (12i).** Mp 232–234 °C (dec.); IR (KBr, cm^{-1}) 2945, 2762, 2517, 2440, 1643, 1450, 1217, 785, 534; ^1H NMR (CD_3OD, 400 MHz) δ 0.99 (t, $J=7.3$ Hz, 3H), 1.05–1.18 (m, 2H), 1.66–1.99 (m, 9H); 2.67–3.14 (m, 10H), 4.02 (m, 1H), 4.20 (m, 2H), 4.60 (m, 1H); 7.29–7.51 (m, 4H), 7.76 (d, $J=8.3$ Hz, 1H), 7.84 (m, 1H); 7.95 (d, $J=7.8$ Hz, 1H); MS (FAB) *m/z* 396 $(M+H)^+$. Anal. calcd for $C_{25}H_{37}N_3O{\cdot}2HCl{\cdot}0.1H_2O$: C, 63.85; H, 8.40; N, 8.93; Cl, 15.08. Found: C, 63.83; H, 8.34; N, 8.89; Cl, 14.82.

***N*-Isopropyl-*N'*-[1-(1-naphthylacetyl)piperidin-4-ylmethyl]-1,4-diaminobutane (12j).** Mp 242–243 °C (dec.); IR (KBr, cm^{-1}) 2952, 2804, 2754, 2451, 1616, 1473, 1458, 1194, 1157, 960, 766, 754; ^1H NMR (CD_3OD, 400 MHz) δ 1.05–1.21 (m, 2H), 1.32 (s, 3H), 1.34 (s, 3H), 1.77–2.01 (m, 7H), 2.74 (m, 1H), 2.88 (d, $J=7.3$ Hz, 2H), 2.97–3.17 (m, 6H), 4.05 (m, 1H), 4.22 (m, 2H), 4.63 (m, 1H), 7.32–7.54 (m, 4H), 7.79 (d, $J=8.3$ Hz, 1H), 7.87 (m, 1H), 7.98 (d, $J=8.3$ Hz, 1H); MS (FAB) *m/z* 396 $(M+H)^+$. Anal. calcd for $C_{25}H_{37}N_3O{\cdot}2HCl{\cdot}0.3H_2O$: C, 63.36; H, 8.42; N, 8.87; Cl, 14.96. Found: C, 63.41; H, 8.32; N, 8.64; Cl, 14.96.

***N*-Cyclooctyl-*N'*-[1-(1-naphthylacetyl)piperidin-4-ylmethyl]-1,4-diaminobutane (12k).** Amorphous powder; IR (KBr, cm^{-1}) 3380, 2850, 2440, 1732, 1635, 1616, 1379, 1255, 793, 532; ^1H NMR (CD_3OD, 400 MHz) δ 1.12–1.21 (m, 2H), 1.57–2.02 (m, 22H), 2.74 (m, 1H), 2.89 (d, $J=7.3$ Hz, 2H), 3.04–3.17 (m, 5H), 4.05 (m, 1H), 4.22 (m, 2H), 4.63 (m, 1H), 7.32–7.54 (m, 4H), 7.79 (d, $J=8.3$ Hz, 1H), 7.87 (d, $J=7.3$Hz, 1H), 7.99 (d, $J=8.3$ Hz, 1H); MS (FAB) *m/z* 464 $(M+H)^+$. Anal. calcd for $C_{30}H_{45}N_3O{\cdot}2HCl{\cdot}2.7H_2O$: C, 61.57; H, 9.02; N, 7.18. Found: C, 61.73; H, 8.82; N, 6.92.

***N*-[1-(1-Naphthylacetyl)piperidin-4-ylmethyl]-*N'*-(1-naphthylmethyl)-1,4-diaminobutane (12l).** Amorphous powder; IR (KBr, cm^{-1}) 2931, 2420, 1619, 1509, 1446, 1214, 1014, 786, 590, 534; ^1H NMR (CD_3OD, 400 MHz) δ 1.00–3.50 (m, 17H), 4.00 (m, 1H), 4.20 (s, 2H), 4.60 (m, 1H), 4.71 (s, 2H), 7.31–7.61 (m, 8H), 7.77–8.03 (m, 6H); MS (FAB) *m/z* 494 $(M+H)^+$. Anal. calcd for $C_{33}H_{39}N_3O{\cdot}2HCl{\cdot}2H_2O$: C, 65.77; H, 7.53; N, 6.97. Found: C, 65.78; H, 7.68; N, 6.87.

4-Aminomethyl-1-(*tert*-butoxycarbonyl)piperidine (13). To a stirred solution of **4** (4.0 g, 14.3 mmol) in CH_2Cl_2 (30 mL) was added di-*tert*-butyl dicarbonate (2.8 g, 12.8 mmol) and triethylamine (7.0 mL). The mixture was stirred for 2 h, and then concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$) to afford ***N*-(1-*tert*-butoxycarbonylpiperidin-4-yl)methylphthalimide** as a colorless crystalline powder (3.3 g, 59%): mp 99–100 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (m, 2H), 1.46 (s, 9H), 1.70 (m, 2H), 1.90 (m, 1H), 2.70 (m, 2H), 3.60 (d, $J=7.3$ Hz, 2H), 4.20 (m, 2H), 7.74 (m, 2H), 7.86 (m, 2H).

***N*-(1-*tert*-butoxycarbonylpiperidin-4-yl)methylphthalimide** was converted to **13** using hydrazine monohydrate in a similar manner described for the preparation of **5**: brown oil; IR (KBr, cm^{-1}) 3100, 3500, 2980, 2936, 1692, 1428, 1368, 1246, 1164; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.09 (m, 2H), 1.43 (s, 9H), 1.44 (m, 1H), 1.65 (m, 2H), 1.67 (m, 2H), 2.58 (d, $J=6.8$ Hz, 2H), 2.67 (m, 1H), 4.10 (m, 1H); MS (FAB) *m/z* 215 $(M+H)^+$.

4-Aminomethyl-*N*-benzyloxycarbonylpiperidine (14). To a solution of **4** (20 g, 71.3 mmol) in CH_2Cl_2 (50 mL) was added dropwise benzyl chloroformate (15 g, 88 mmol) and 1 N NaOH (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, then diluted with H_2O, and extracted with CH_2Cl_2. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 4:1, v/v) to afford ***N*-(1-benzyloxycarbonylpiperidin-4-yl)methylphthalimide** as a colorless crystalline powder (20 g, 74%): mp 60–62 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20–1.30 (m, 2H), 1.60–1.70 (m, 2H), 2.00 (m, 1H), 2.70–2.80 (m, 2H), 3.59 (d, $J=7.3$ Hz, 2H), 4.10–4.30 (m, 2H), 5.11 (s, 2H), 7.20–7.40 (m, 5H), 7.70 (m, 2H), 7.90 (m, 2H). Anal. calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.67; H, 5.81; N, 7.30.

***N*-(1-benzyloxycarbonylpiperidin-4-yl)methylphthalimide** was converted to **14** using hydrazine monohydrate in a similar manner described for the preparation of **5**: yellowish oil; IR (KBr, cm^{-1}) 2910, 1693, 1427, 1240, 1176, 1086, 1014, 958, 762, 702; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05–1.15 (m, 2H), 1.40–1.50 (m, 1H), 1.70–1.75 (m, 2H), 2.59 (d, $J=6.4$ Hz, 2H), 2.70–2.85 (m, 2H), 4.20 (br s, 2H), 5.12 (s, 2H), 7.30–7.36 (m, 5H); MS (FAB) *m/z* 249 $(M+H)^+$.

1-Benzyloxycarbonyl-4-[*N*-*tert*-butoxylcarbonyl-*N*-(4-oxobutyl)amino]methylpiperidine (15). 15 was prepared in a similar manner described for the preparation of **11** starting from **14**: yellowish oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15 (m, 2H), 1.45 (s, 9H), 1.61 (m, 3H), 1.76 (m, 3H), 2.73 (m, 4H), 3.10 (m, 2H), 3.50 (m, 2H), 4.20 (m, 2H), 5.13 (s, 2H), 7.30–7.35 (m, 5H), 9.80 (s, 1H); MS (FAB) *m/z* 419 $(M+H)^+$.

***N*,*N'*-Bis(*tert*-butoxylcarbonyl)-*N*-[1-(*tert*-butoxylcarbonyl)piperidin-4ylmethyl]-*N'*-(piperidin-4-ylmethyl)-1,4-diaminobutane (16).** A solution of **15** (10 g, 24 mmol) and

13 (5.14 g, 24 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 1 h, and then concentrated in vacuo. The residue was dissolved in MeOH (50 mL), and $NaBH_4$ (3.6 g, 96 mmol) was added. The mixture was stirred for 1 h. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 99:1 to 95:5, v/v) to afford a yellowish oil. The oil was dissolved in CH_2Cl_2 (50 mL), and di-*tert*-butyl dicarbonate (5.2 g, 24 mmol) was added. The mixture was stirred at room temperature for 24 h. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc, 2:1, v/v) to afford ***N*-[1-benzyloxycarbonyl)piperidin-4-ylmethyl]-*N*,*N*′-bis(*tert*-butoxylcarbonyl)-*N*′-[1-(*tert*-butoxylcarbonyl)piperidin-4-ylmethyl]-1,4-diaminobutane** as a brown oil (11 g, 64%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.12–1.65 (m, 14H), 1.44 (s, 27H), 2.66–2.76 (m, 4H), 3.05–3.17 (m, 8H), 4.10–4.15 (m, 4H), 5.13 (s, 2H), 7.25–7.38 (m, 5H).

To a solution of the above obtained oil (5.0 g, 6.97 mmol) in EtOH (50 mL) was added 10% Pd/C (1.0 g). The resulting suspension was stirred under an atmosphere of hydrogen for 18 h. The catalyst was filtered off and the filtrate was concentrated in vacuo to give **16** as a brown oil (4.0 g, quant): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11–1.85 (m, 14H), 1.43 (br s, 27H), 2.66–3.15 (m, 12H), 3.49 (m, 2H), 4.09 (m, 2H).

4-[*N*-(4-Aminobutyl)-*N*-*tert*-butoxylcarbonylaminomethyl]-1-benzyloxycarbonylpiperidine (19). 19 was prepared in a similar manner described for the preparation of **6** starting from **14**: yellowish oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00–1.20 (m, 2H), 1.44 (s, 9H), 1.50–1.80 (m, 7H), 2.70–3.50 (m, 8H), 4.10–4.30 (m, 2H), 5.12 (s, 2H), 7.30–7.40 (m, 5H).

***N*,*N*′-Bis(*tert*-butoxylcarbonyl)-*N*-cyclohexylmethyl-*N*′-(piperidin-4-ylmethyl)-1,4-diaminobutane (20). 20** was prepared in a similar manner described for the preparation of **16** starting from **19** using cyclohexanecarboxaldehyde instead of **13**: yellowish oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (br s, 18H), 1.00–1.90 (m, 20H), 2.80–3.20 (m, 10H), 3.50 (m, 2H).

***N*-Cyclohexylmethyl-*N*′-[1-(9-fluorenylacetyl)piperidin-4-ylmethyl]-1,4-diaminobutane (21a).** To a solution of **20** (480 mg, 1.0 mmol), 9-fluorenylacetic acid (230 mg, 1.0 mmol), HOBt (202 mg, 1.5 mmol), and *N*-methylmorpholine (303 mg, 3.0 mmol) in CH_2Cl_2 (10 mL) was added EDC·HCl (384 mg, 2.0 mmol) at room temperature. The mixture was stirred for 14 h, and concentrated in vacuo. The residue was diluted with H_2O and extracted with EtOAc. The extracts were washed with 1 N HCl, satd $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 2:1, v/v) to afford a yellowish oil. This oil was dissolved in EtOH (8.0 mL), and concd HCl (1.0 mL) was added. The mixture was stirred at room temperature for 17 h, and concentrated in vacuo. The resulting solid was collected and washed with Et_2O to give **21a** as an amorphous powder (358 mg, 73%): IR (KBr, cm^{-1}) 3396, 2927, 2852, 2763, 2433, 1635, 1448, 1272, 997, 738, 586; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.00–3.30 (m, 32H), 3.90 (m, 1H), 4.47 (m, 1H), 4.80 (m, 1H), 7.20–7.40 (m, 4H), 7.50 (m, 2H), 7.79 (d, J = 7.8 Hz, 2H); MS (FAB) m/z 488 $(M+H)^+$. Anal. calcd for $C_{32}H_{45}N_3O{\cdot}2HCl{\cdot}0.5H_2O$: C, 67.47; H, 8.49; N, 7.38; Cl, 12.45. Found: C, 67.74; H, 8.53; N, 7.33; Cl, 12.55.

The following compounds were prepared in a similar manner described for the preparation of **21a**.

***N*-[1-(1-Naphthylacetylaminoacetyl)piperidin-4-ylmethyl]-*N*′-(piperidin-4-ylmethyl)-1,4-diaminobutane (17a).** Amorphous powder; IR (KBr, cm^{-1}) 3388, 2944, 1638, 1452, 1272, 1222, 794, 522; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.09–1.21 (m, 2H), 1.50–1.56 (m, 2H), 1.74–2.14 (m, 10H), 2.70–3.16 (m, 12H), 3.42 (m, 2H), 3.88 (m, 1H), 4.04 (m, 2H), 4.14 (s, 2H), 4.62 (m, 1H), 7.49–7.55 (m, 4H), 7.81 (d, J = 8.3 Hz, 1H), 7,87 (m, 1H), 8.05 (d, J = 7.8 Hz, 1H); MS (FAB) m/z 508 $(M+H)^+$. Anal. calcd $C_{30}H_{45}N_5O_2{\cdot}3HCl{\cdot}H_2O$: C, 56.73; H, 7.94; N, 11.03. Found: C, 57.02; H, 8.18; N, 10.88.

***N*-[1-[6-(1-Naphthylacetylamino)hexanoyl]piperidin-4-ylmethyl]-*N*′-(piperidin-4-ylmethyl)-1,4-diaminobutane (17b).** Amorphous powder; IR (KBr, cm^{-1}) 3408, 3332, 2940, 2784, 1642, 1450, 784; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.10–2.31 (m, 20H), 2.60 (m, 2H), 2.89–3.21 (m, 14H), 3.43 (m, 2H), 3.89 (m, 1H), 3.99 (s, 2H), 4.53 (m, 1H), 7.43–7.55 (m, 4H), 7.82 (m, 1H), 7.89 (m, 1H), 8.04 (m, 1H); MS (FAB) m/z 564 $(M+H)^+$. Anal. calcd for $C_{34}H_{53}N_5O_2{\cdot}3HCl{\cdot}1.5H_2O$: C, 58.32; H, 8.49; N, 10.00; Cl, 15.19. Found: C, 58.47; H, 8.34; N, 9.91; Cl, 15.16.

***N*-Cyclohexylmethyl-*N*′-[1-(2,3-diphenylpropionyl)piperidin-4-ylmethyl]-1,4-diaminobutane (21b).** Amorphous powder; IR (KBr, cm^{-1}) 2923, 2852, 2775, 2724, 2593, 2468, 1633, 1600, 1496, 1481, 1454, 1371, 1290, 1274, 1257, 1218, 1135, 1062, 1031, 1020, 964, 860, 754, 698, 592; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.15 (m, 0.5H), 0.79 (m, 0.5H), 0.93 (m, 2H), 1.10–1.17 (m, 3H), 1.35–1.90 (m, 13H), 2.40–2.93 (m, 10H), 3.30 (m, 1H), 3.90–4.07 (m, 2H), 4.25–4.40 (m, 2H), 7.13–7.35 (m, 10H); MS (FAB) m/z 490 $(M+H)^+$. Anal. calcd for $C_{32}H_{47}N_3O{\cdot}2HCl{\cdot}0.2H_2O$: C, 67.87; H, 8.79; N, 7.42; Cl, 12.52. Found: C, 68.03; H, 8.72; N, 7.11; Cl, 12.80.

***N*-[1-(1-Adamantylacetyl)piperidin-4-ylmethyl]-*N*′-cyclohexylmethyl-1,4-diaminobutane (21c).** Amorphous powder; IR (KBr, cm^{-1}) 2917, 2748, 2431, 2038, 1764, 1623, 1461, 1367, 1213, 923, 755, 539; ^{1}H NMR (CD_3OD, 400 MHz) δ 0.95–1.35 (m, 8H), 1.65–1.98 (m, 27H), 2.05–2.32 (m, 3H), 2.62–3.20 (m, 10H), 4.10–4.15 (m, 1H), 4.60–4.65 (m, 1H); MS (FAB) m/z 458 $(M+H)^+$. Anal. calcd for $C_{29}H_{51}N_3O{\cdot}2HCl{\cdot}2H_2O$: C, 61.46; H, 10.14; N, 7.41. Found: C, 61.51; H, 9.87; N, 7.22.

***N*-[1-[2-(1-Naphthyl)ethyl]piperidin-4-ylmethyl]-*N*′-(piperidin-4-ylmethyl)-1,4-diaminobutane (18).** A mixture of 2-

(1-naphthyl)ethyl methanesulfonate (128 mg, 0.51 mmol), **16** (300 mg, 0.51 mmol), and K_2CO_3 (138 mg, 1.0 mmL) in DMF (10 mL) was stirred at 80 °C for 2 h. After removal of the solvent, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 10:1, v/v) to afford an oil. The oil was dissolved in MeOH (20 mL), and concd HCl (10 mL) was added. The mixture was stirred at room temperature for 12 h, and concentrated in vacuo. The resulting solid was collected and washed with Et_2O to give **18** as an amorphous powder (110 mg, 33%): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.42–2.05 (m, 14H), 2.73–3.46 (m, 20H), 7.45 (m, 1H), 7.55 (m, 1H), 7.52 (m, 2H), 7.82 (m, 1H), 7.93 (m, 2H); MS (FAB) m/z 437 $(M+H)^+$.

***N*-Cyclohexylmethyl-*N'*-[1-dansylpiperidin-4-ylmethyl]-1,4-diaminobutane (22).** To a solution of **20** (481 mg, 1.0 mmol) and triethylamine (1.0 mL) in CH_2Cl_2 (15 mL) was added dansyl chloride (270 mg, 1.0 mmol) at 0 °C. The mixture was stirred at room temperature for 18 h, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 3:1, v/v) to afford an oil. The oil was dissolved in EtOH (5.0 mL), and concd HCl (3.0 mL) was added. The mixture was stirred at room temperature for 4 h, and concentrated in vacuo. The resulting solid was collected and washed with Et_2O-EtOH to give **22** as an amorphous powder (470 mg, 80%): IR (KBr, cm^{-1}) 3396, 2927, 2852, 2790, 1599, 1514, 1450, 1333, 1146, 1053, 939, 791, 719, 586; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.03–1.30 (m, 7H), 1.68–1.90 (m, 13H), 2.67–3.01 (m, 10H), 3.44 (s, 6H), 3.88 (m, 2H), 7.86 (m, 2H), 8.04 (m, 1H), 8.36 (m, 1H), 8.65 (m, 1H), 8.88 (m, 1H); MS (FAB) m/z 515 $(M+H)^+$. Anal. calcd for $C_{29}H_{46}N_4O_2S{\cdot}3HCl{\cdot}H_2O$: C, 54.24; H, 8.00; N, 8.72; Cl, 16.56; S, 4.99. Found: C, 54.10; H, 8.03; N, 8.46; Cl, 16.39; S, 5.15.

Electrophysiological Assay

Blockade of Ca^{2+}-permeable AMPA receptors: in vitro assay

Antagonist activity of test compounds against Ca^{2+}-permeable AMPA receptors was measured using a two-electrode voltage clamp method:[10] kainate (KA, Sigma, USA, K-0250) was used as an agonist for the receptors expressed in *Xenopus* oocytes by injection of rat brain mRNA (CLONTECH, USA, No. 6712-1, or poly(A)+ RNA purified for ourselves). JSTX-3 was purchased from Wako Pure Chemical (Osaka, Japan). Test compounds were co-administered for 30 s with kainate to *Xenopus* oocytes and the inward current was measured. Inward currents induced by application of 300 μM KA (current A), co-application of 300 μM KA with 0.01–3.0 μM test compounds (current B), and co-application of 300 μM KA with 3.0 μM JSTX-3 (current C), were used to calculate the inhibition (%) by a numerical formula of (current A−current B)/(current A−current C)×100. IC_{50} (μM) was defined as the concentration of a compound that reduces the inward current induced by kainate by 50%. The values represent the means of results from six *Xenopus* oocytes.

Blockade of NMDA receptors: in vitro assay

Antagonist activity against NMDA receptors was also measured by a two-electrode voltage clamp method. In this experiment, a combination of 300 μM NMDA and 10 μM glycine was used as agonists for NMDA receptors. The inward current induced by application of 300 μM NMDA and 10 μM glycine (current A), and the inward current induced by co-application of agonists with 0.01–3.0 μM test compounds (current B), were used to calculate the inhibition (%) by a numerical formula of (current A−current B)/(current A)×100. IC_{50} (μM) was defined as the concentration of a compound that reduces the inward current induced by 50%. The values represent the means of results from six *Xenopus* oocytes.

Effect on Blood Pressure

In vivo effects on blood pressure were evaluated by intravenous administration in male Wistar rats weighing 200–300 g under thiobutabarbital-natrium anesthesia. The systolic blood pressure (mmHg) of rats after intravenous (iv) administration of a 3.0 mg/kg dose was compared with the systolic blood pressure before administration ($n=1$–2).

Transient Global Ischemia in Gerbils

Transient cerebral ischemia produced by bilateral occlusion of the common carotid arteries was induced for 5.0 min in male Mongolian gerbils weighing 55–70 g. Following the ischemia, it is known that the hippocampal CA1 pyramidal cells proceed to delayed neuronal death.[12] Intraperitoneal administration of 2.5, 5.0 or 10 mg/kg of **8f** was repeated at the time of 0, 2, 4 and 6 h after the ischemia. Five days after the ischemia, the brain was removed and the CA1 cells within 0.5 mm wide in both hemispheres were counted histologically. The number of survived cells were statistically compared to the number of the cells observed in the control vehicle-treated group (Dunnett's test). Ten animals were used for each dose of the compound.

Blockade of Ca^{2+}-permeable AMPA receptors which lack GluR2 subunit

When the mRNA extracted from rat brains was injected to oocytes, it is impossible to obtain solely Ca^{2+}-permeable AMPA receptors without Ca^{2+}-impermeable AMPA receptors. Also it is impossible to obtain solely Ca^{2+}-impermeable AMPA receptors without Ca^{2+}-permeable AMPA receptors. To evaluate the selectivity of **8f** toward Ca^{2+}-permeable or Ca^{2+}-impermeable AMPA receptors, two recombinant AMPA receptor subunits were used. AMPA receptors consisted without GluR2 subunit is known to be Ca^{2+}-permeable, but AMPA receptors consisted with GluR2 subunit is known to be Ca^{2+}-impermeable. *Xenopus* oocytes that have been injected with GluR3cRNA (50 ng) have solely Ca^{2+}-permeable AMPA receptors. On the other

hand, *Xenopus* oocytes that have been injected with both GluR3cRNA and GluR2cRNA (1:9, total 100 ng) have solely Ca^{2+}-impermeable AMPA receptors. Three μM of either JSTX-3 or **8f** was administered with 300 μM KA to the oocytes expressing Ca^{2+}-permeable or Ca^{2+}-impermeable receptors. Each value is the mean of results from 2–3 *Xenopus* oocytes. Cloned mouse PSPG R2 (α2); GluR2, was gifted from Professor M. Mishina of the University of Tokyo. Rat GluR3 was cloned for ourselves by RT-PCR.

Acknowledgement

The authors are grateful to Dr. Yoshifumi Watanabe for useful suggesting and encouragement during the preparation of this paper.

References and Notes

1. Monaghan, D. T.; Bridges, R. J.; Cotoman, C. W. *Annu. Rev. Pharmacol. Toxicol.* **1989**, *29*, 365.
2. Hollmann, M.; Heinemann, S. *Annu. Rev. Neurosci.* **1994**, *17*, 31.
3. Choi, D. W.; Rothman, S. M. *Annu. Rev. Neurol.* **1990**, *13*, 171.
4. (a) Sheardown, M. J.; Nielsen, E. O.; Hansen, A. J.; Jacobsen, P.; Honore, T. *Science* **1990**, *247*, 571. (b) Ohmori, J.; Sakamoto, S.; Hidaka, K.; Togami, J.; Furuya, T.; Murase, K. *J. Med. Chem.* **1994**, *37*, 467. (c) Harbert, A.; Takahashi, M.; Yamaguchi, T.; Hjelstuen, M.; Haraldseth, O. *Brain Res.* **1998**, *811*, 63. (d) Donevan, S. D.; Yamaguci, S.; Rogawski, M. A. *J. Pharmacol. Exp. Ther.* **1994**, *271*, 25. (e) Borowicz, K. K.; Kleinrok, Z.; Czuczwar, S. J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2000**, *361*, 629.
5. (a) Koek, W.; Woods, J. H.; Winger, G. D. *J. Pharmcol. Exp. Ther.* **1998**, *245*, 969. (b) Morris, R. G. M.; Anderson, E.; Lynch, G. S.; Baudry, M. *Nature* **1986**, *319*, 774. (c) Olney, J. W.; Labruyere, J.; Price, M. *Science* **1989**, *244*, 1360. (d) Olney, J. W.; Labruyere, J.; Wang, G.; Wozniak, D. F.; Price, M. T.; Sesma, M. A. *Science* **1991**, *254*, 1515.
6. (a) Gorter, J. A.; Petrozzino, J. J.; Aronica, E. M.; Rosenbaum, D. M.; Opitz, T.; Bennett, M. V.; Connor, J. A.; Zukin, R. S. *J. Neurosci.* **1997**, *17*, 6179. (b) Aronica, E. M.; Gorter, J. A.; Grooms, S.; Kessler, J. A.; Bennett, M. L.; Zukin, R. S.; Rosenbaum, D. M. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 7115. (c) Oguro, K.; Oguro, N.; Kojima, T.; Grooms, S. Y.; Calderone, A.; Zheng, X.; Bennett, M. V.; Zukin, R. S. *J. Neurosci.* **1999**, *19*, 9218.
7. (a) Iino, M.; Koike, M.; Isa, T.; Ozawa, S. *J. Physiol.* **1996**, *496*, 2 431. (b) Savide, J. R.; Bristow, D. R. *Eur. J. Pharmacol.* **1998**, *351*, 131. (c) Meucci, O.; Fatatis, A.; Holzwarth, J. A.; Miller, R. J. *J. Neurosci.* **1996**, *16*, 519.
8. (a) Koike, M.; Iino, M.; Ozawa, S. *Neurosci. Res.* **1997**, *29*, 27. (b) Ajima, A.; Hensch, T.; Kado, R. T.; Ito, M. *Neurosci. Res.* **1991**, *12*, 281.
9. Ahmde, N.; Nasman, P.; Wahlgren, N. G. *Stroke* **2000**, *31*, 1250.
10. (a) Yoneda, Y.; Kawajiri, S.; Hasegawa, A.; Kito, F.; Katano, S.; Takano, E.; Mimura, T. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1261. (b) Yoneda, Y.; Kwajiri, S.; Sugimura, M.; Osanai, K.; Kito, F.; Ota, E.; Mimura, T. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2663.
11. (a) Debon, M. W.; Le Guren, J.; Canton, T.; Doble, A.; Pradier, L. *Eur. J. Pharmacol.* **1993**, *235*, 283. (b) Kawajiri, S.; Dingledine, R. *Neuropharmacology* **1993**, *32*, 1203. (c) Kawai, N. *Comp. Biochem. Physiol. C* **1991**, *98*, 87. (d) Blaschke, M.; Keller, B. U.; Rivosecchi, R.; Hollmann, M.; Heinemann, S.; Konnerth, A. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6528.
12. After measurement of inward currents induced by application of 300 μM KA (current A), co-application of 300 μM KA with 0.01–3.0 μM test compounds (current B), and co-application of 300 μM KA with 3.0 μM JSTX-3 (current C), inhibition (%) was calculated by a numerical formula of (current A−current B)/(current A−current C)×100.
13. (a) Kirino, T. *Brain Res.* **1982**, *239*, 57. (b) Suzuki, R.; Yamaguchi, T.; Kirino, T. *Acta. Neuropathol* **1983**, *60*, 207.
14. The values were calculated by PROLOGP ver. 3.0 (CompuDrug International, Inc., Hungary).
15. (a) Sakimura, K. *FEBS Lett.* **1990**, *272*, 73. (b) Kawai, N. *Brain Res.* **1992**, *581*, 161. (c) Blaschke, M.; Keller, B. U.; Rivosecchi, R.; Hollmann, M.; Heinemann, S.; Konnerth, A. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6528.
16. Hollmann, M.; Hartley, M.; Heinemann, S. *Science* **1991**, *252*, 851.
17. Blaschke, M.; Keller, B. U.; Rivosecchi, R.; Hollmann, M.; Heinemann, S.; Konnerth, A. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6528.