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# Synthesis of Polyamine Derivatives Having Non-hypotensive $Ca^{2+}$-Permeable AMPA Receptor Antagonist Activity

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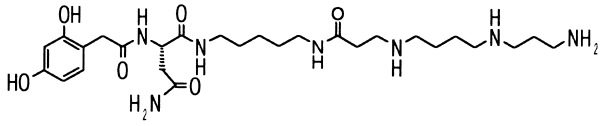
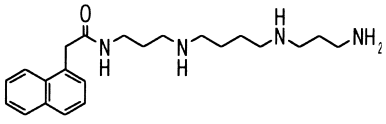
**Abstract**—In order to obtain non-hypotensive and $Ca^{2+}$-permeable AMPA receptor antagonists, we have synthesized a series of 1,4-bis(4-piperidinylmethyl)diaminobutanes. Compounds **13b**, **c**, **f** had desirable properties. 

## 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 assumption, a lot of NMDA receptor antagonists have been synthesized and evaluated for their pharmacological and clinical effects.[4] On the other hand, $Ca^{2+}$-permeable AMPA receptor antagonists still remain to be studied. We therefore focused on the $Ca^{2+}$-permeable AMPA receptor antagonists and designed them based on the structures of prototype antagonist polyamines such as Joro spider toxin-3, JSTX-3 (**1**),[5] and 1-naphthylacetylspermine, NAS (**2**).[6] In the course of this study, we found that these polyamines 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.[7] In this paper, we therefore concentrated on the synthesis of non-hypotensive $Ca^{2+}$-permeable AMPA receptor antagonists.



**1** JSTX-3



**2** NAS (1-Naphthylacetylspermine)

The synthetic pathways of polyamine derivatives **9a**–**d** and **10** are shown in Scheme 1. The primary amino group of 4-aminomethylpiperidine **3** was protected to give phthalimide **4**, which was converted to two compounds **5** and **6** by protection with a *tert*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Z) group, respectively, and subsequent cleavage of the phthalimide moiety. Compound **6** 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 **7**. Aldehyde **7** was used for reductive alkylation of **5**, and the resulting product was protected by a Boc group and reduced catalytically to give tri-Boc-protected amine **8**. Condensation of **8** with arylacetic acids gave products **9a**–**d**. Reaction of

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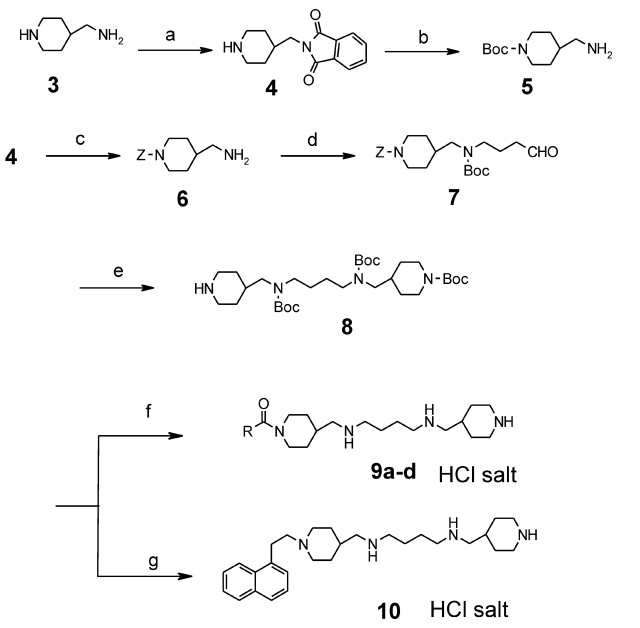
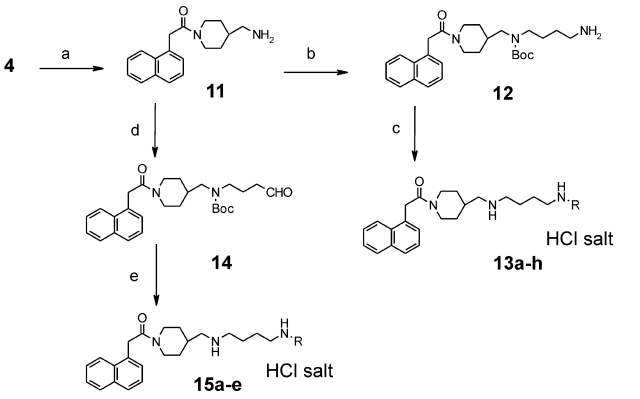
**8** with 2-(1-naphthyl)ethyl methanesulfonate afforded compound **10**.

Another series of compounds **13a–h** and **15a–e** were synthesized as shown in Scheme 2. Compound **4** was condensed with (1-naphthyl)acetic acid, and followed by removal of a phthaloyl group to afford amine **11**. Amine **11** was alkylated with 4-bromobutylphthalimide and followed by protection with a Boc group and succesive removal of a phthaloyl group to give amine **12**. Amine **12** was converted to compounds **13a–h** by reductive alkylation using a variety of aldehydes. Compound **11** was treated with 4-bromobutyl acetate, and followed by protection with a Boc group, hydrolysis of an acetyl group and Swern oxidation of the resulting alcohol to afford aldehyde **14**, which was converted to **15a–e** in a similar manner as described above.




**Scheme 1.** Synthesis of compounds **9a–d** and **10**. Reagents and conditions: (a) phthalic anhydride, Δ (61%); (b) (i) $Boc_2O$, TEA, $CH_2Cl_2$ (59%), (ii) $NH_2NH_2{\cdot}H_2O$, EtOH (quant); (c) (i) Z-Cl, aq $NaHCO_3$, $CH_2Cl_2$ (74%), (ii) $NH_2NH_2{\cdot}H_2O$, EtOH (quant); (d) (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); (e) (i) **5**, $NaBH_4$, MeOH, (ii) $Boc_2O$, $CH_2Cl_2$ (two steps 64%), (iii) $H_2$, $Pd(OH)_2$–C, EtOH (quant); (f) (i) carboxylic acid, EDC·HCl, HOBt, NMM, $CH_2Cl_2$, (ii) c HCl, EtOH (two steps 37–65%); (g) (i) 2-(1-naphthyl)ethyl methanesulfonate, $K_2CO_3$, DMF, (ii) c HCl, EtOH (two steps 34%).

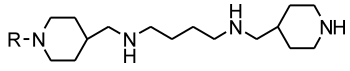


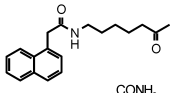
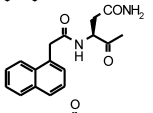
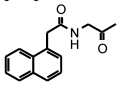

**Scheme 2.** Synthesis of compounds **13a–h** and **15a–e**. Reagents and conditions: (a) (i) (1-naphthyl)acetic acid, EDC·HCl, TEA, $CH_2Cl_2$ (69%), (ii) $NH_2NH_2{\cdot}H_2O$, EtOH (quant); (b) (i) 4-bromobutyl phthalimide, KF–Celite, MeCN, (ii) $Boc_2O$, $CH_2Cl_2$, (iii) $NH_2NH_2{\cdot}H_2O$, EtOH (three steps 55%); (c) (i) aldehyde, $NaBH_4$, MeOH, (ii) $Boc_2O$, $CH_2Cl_2$, (iii) c HCl, EtOH (three steps 25–57%); (d) (i) 4-bromobutyl-acetate, KF–Celite, MeCN, (ii) $Boc_2O$, $CH_2Cl_2$, (iii) $K_2CO_3$, MeOH (three steps 48%), (iv) Swern oxidation (71%); (e) (i) amine, $NaBH_4$, MeOH, (ii) $Boc_2O$, $CH_2Cl_2$, (iii) c HCl, EtOH (three steps 24–50%).

## Results and Discussion

Antagonist activity of test compounds against $Ca^{2+}$-permeable AMPA receptors ($IC_{50}$) was measured using a two-electrode voltage clamp method:[8] 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.[9] Hypotensive activity was evaluated after intravenous administration to Wistar rats. These activities are shown in Tables 1 and 2.

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

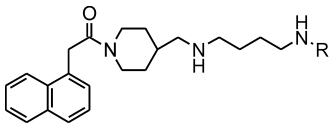


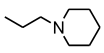
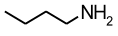
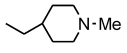
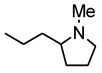
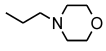
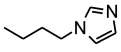
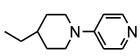
| Compound | R | $IC_{50}$ (μM)[a] | ΔSBP (mmHg)[c] |
|---|---|---|---|
| **9a** |  | 1.3 | −120 |
| **9b** |  | 0.42 | −40 |
| **9c** |  | 0.27 | −75 |
| **9d** |  | 0.49 | −50 |
| **10** |  | 28%[b] | NT[d] |
| **NAS (2)** | — | 0.69 | −55[e] |

[a]$IC_{50}$ (μM) was defined as the concentration of a compound that reduced the inward current induced by kainate by 50%. The compound was co-administered with kainate to *Xenopus* ooccytes where the inward current was measured by the two-electrode voltage clamp method.
[b]% inhibition at the concentration of 1 μM is shown.
[c]Changes in systolic blood pressure (mmHg) after intravenous (iv) administration at the dose of 3 mg/kg in rats were compared with the systolic blood pressure before dosing ($n = 1$–2).
[d]Not tested.
[e]The dose of 1 mg/kg was used.

In this paper, we first synthesized a series of 1,4-bis(4-piperidinylmethyl)diaminobutane derivatives, which was designed from prototype antagonists JSTX-3 (**1**) and NAS (**2**) with the intention of elevating lipophilicity that would affect permeability into the brain. Compound **9a**, 1-(1-(1-naphthylacetyl)piperidin-4-ylmethyl)-4-(4-piperidinylmethyl)diaminobutane, exhibited moderate potency with an $IC_{50}$ value of 1.3 μM. Reduction of the amide function of **9a** significantly decreased in potency (**10**), suggesting that the carbonyl group plays an important role in exhibiting potent activity. Insertion of an amino acid moiety between the naphthaleneacetyl and piperidine groups of **9a** gave **9b–d** showing 3- to 4-fold higher potency.

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



| Compound | R | $IC_{50}$ (μM)[a] | ΔSBP (mmHg)[c] |
|---|---|---|---|
| **13a** |  | 0.82 | −58 |
| **13b** |  | 1.1 | 0 |
| **13c** |  | 0.73 | 0 |
| **13d** |  | 27%[b] | 11 |
| **13e** |  | 41%[b] | 13 |
| **13f** |  | 0.19 | 5 |
| **13g** |  | 0.32 | −35 |
| **13h** |  | 0.33 | −50 |
| **15a** |  | 0.57 | −50 |
| **15b** |  | 0.78 | −55 |
| **15c** |  | 18%[b] | 0 |
| **15d** |  | 0.26 | −25 |
| **15e** |  | 0.17 | −43 |

[a]$IC_{50}$ (μM) was defined as the concentration of a compound that reduced the inward current induced by kainate by 50%. The compound was co-administered with kainate to *Xenopus* ooccytes where the inward current was measured by the two-electrode voltage clamp method.
[b]% inhibition at the concentration of 1 μM is shown.
[c]Changes in systolic blood pressure (mmHg) after intravenous (iv) administration at the dose of 3 mg/kg in rats were compared with the systolic blood pressure before dosing ($n = 1–2$).

Subsequently, we modified the 4-piperidinylmethyl group on the other terminal of **9a**. Compounds **13a**,**b**, isomeric 2- and 3-piperidinylmethyl congeners of **9a**, showed potency almost similar to that of **9a**. Pyrrolidine derivative **13c** had similar potency. *N*-Methylpiperidine derivative **15a** showed 2-fold higher potency than non-methylated compound **9a**. *N*-Methylation of **13b**,**c** resulted in a decrease in potency (**13d**,**e**). Amino-propyl and -ethyl derivatives **13g**,**h** had potency 4-fold higher than that of **9a**. Compound **15d** with an imidazole group retained potency, suggesting that an aromatic heterocyclic moiety is a replaceable substituent on the terminal. This would be supported by the fact that *N*-(4-pyridinyl)piperidine derivative **15e** had the most potent activity. Interestingly, compound **13f** with a piperidin-1-yl group showed potent activity, while compound **15c** with a morpholin-1-yl group exhibited markedly reduced potency.

With respect to hypotensive activity, compound **9a** showed potent activity at a dose of 3 mg/kg. Insertion of an amino acid moiety between the naphthaleneacetyl and piperidine groups of **9a** resulted in a moderate decrease in potency (**9b–d**). On the other hand, compounds **13b**,**c**,**f** and **15c** showed no hypotensive effect at a dose of 3 mg/kg. Among the piperidinyl derivatives, the order of the hypotensive activity is **9a** > **13a** ≫ **13b** = **13f**. Thus, the basic nitrogen atom in the piperidinine ring apparently contributes to the activity. The nitrogen atom in the piperidin-2-yl and piperidin-1-yl groups would have difficulty in interacting with the undetermined receptors mediating blood pressure, possibly because of its steric hindrance. Interestingly, (1-methylpyrrolidin-2-yl)methyl derivative **13e** showed no hypotensive activity, while (1-methylpyrrolidin-2-yl)ethyl derivative **15b** had the strong 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.

Thus, we synthesized non-hypotensive and $Ca^{2+}$-permeable AMPA receptor antagonists and evaluated their structure–activity relationships.

## References and Notes

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8. Debon, M. W.; Le Guren, J.; Canton, T.; Doble, A.; Pradier, L. *Eur. J. Pharmacol.* **1993**, *235*, 283.
9. 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.