Synthesis of a Novel Water-Soluble Cleft-Type Cyclophane as an *N*-Methyl-D-aspartate Receptor Antagonist

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Received September 5, 2008; accepted October 18, 2008; published online October 21, 2008

Novel water-soluble *N*-methyl-D-aspartate (NMDA) receptor antagonists, 4,4′-bis({2-[*N*-(1,4,8,11-tetraazacyclotetradecan-1-yl)acetyl]-*N*-phenethyl}aminoethoxy)diphenylmethane octahydrochloride (1, ACPCm) and 4,4′-bis({2-[*N*-(1,4,7,10-tetraazacyclododecan-1-yl)acetyl]-*N*-phenethyl}aminoethoxy)diphenylmethane octahydrochloride (2, ACPCn), were synthesized and the effect of these cleft-type cyclophanes on NMDA receptors was then studied using voltage-clamp recordings of recombinant NMDA receptors expressed in *Xenopus* oocytes. ACPCm (1) and ACPCn (2) inhibited macroscopic currents in the NR1/NR2A, NR1/NR2B, NR1/NR2C and NR1/NR2D receptor subtypes in oocytes voltage-clamped at −70 mV. The IC_{50} values of ACPCm (1) and ACPCn (2) for NR1/NR2A and NR1/NR2B receptors were 1.06 μM and, 0.92 μM and 1.47 μM and, 1.49 μM, respectively. The inhibition by these compounds was voltage-dependent, that is, the degree of inhibition was in the order of negative holding potentials, −100 mV>−70 mV>−20 mV. These findings indicate that the cleft-type cyclophanes, ACPCm (1) and ACPCn (2) directly act on the channel pore of the NMDA receptors.

Key words cleft-type cyclophane; *N*-methyl-D-aspartate receptor; *Xenopus* oocyte; voltage-clamped recording

The ionotropic glutamate receptors are ligand-gated ion channels that mediate the vast majority of excitatory neurotransmission in the brain. The three pharmacologically defined classes of ionotropic glutamate receptor were originally named after the reasonably selective agonists *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), and kainite. It turned out that NMDA, AMPA, and kainite receptor subunits are encoded by at least six gene families as defined by sequence homology: a single family for the AMPA receptors, two for kainite, and three for NMDA.[1] The NMDA receptor combines to form heteromeric complexes containing NR1 and NR2 subunits. The NR1 subunit is ubiquitous and assembles with a second family of subunits termed NR2, including NR2A, NR2B, NR2C and NR2D.

In the central nervous system (CNS), the NMDA receptor plays a critically important role in a variety of neurophysiological phenomena, including neuronal development, synaptic plasticity, and excitotoxicity. Glutamate is known to be neurotoxic under certain circumstances, in particular when energy supply is compromised. Thus some researchers now believe that the neurodegeneration associated with a variety of acute and chronic disorders (ischemic stroke, Parkinson's disease, Alzheimer's disease, dementia, *etc.*) may be caused in part by overactivation of glutamate receptors. Alzheimer's disease is a neurodegenerative disorder characterized by irreversible, progressive loss of memory followed by complete dementia. The cognitive decline is accompanied by impaired performance of daily activities, behavior, speech and visual-spatial perception. Glutamate excitotoxicity as a result of blockade of glutamate uptake into astrocytes by Aβ aggregates induces excessive Ca influx through mainly the NMDA receptors, followed by neuronal cell death.[2] The NMDA receptor subtype has been found to play a key role in glutamate promotion of synaptic plasticity, long-term potentiation and neuronal cell death.[1]

We previously reported the synthesis of two cleft-type cyclophanes ACCn[3,4] and ATGDMAP[5] which inhibited the activity of the NR1/NR2A and NR1/NR2B receptors at −70 mV. The IC_{50} values for ACCn and ATGDMAP were 7.0 and 4.9 μM respectively against the NMDA receptors. The inhibition of the activity of the NR1/NR2A and NR1/NR2B receptors by *N*-(2-{4-[4-(2-{[(1,4,7,10-tetraazacyclododec-1-yl)acetyl]-[2-(5-dimethylaminonaphtalene-1-

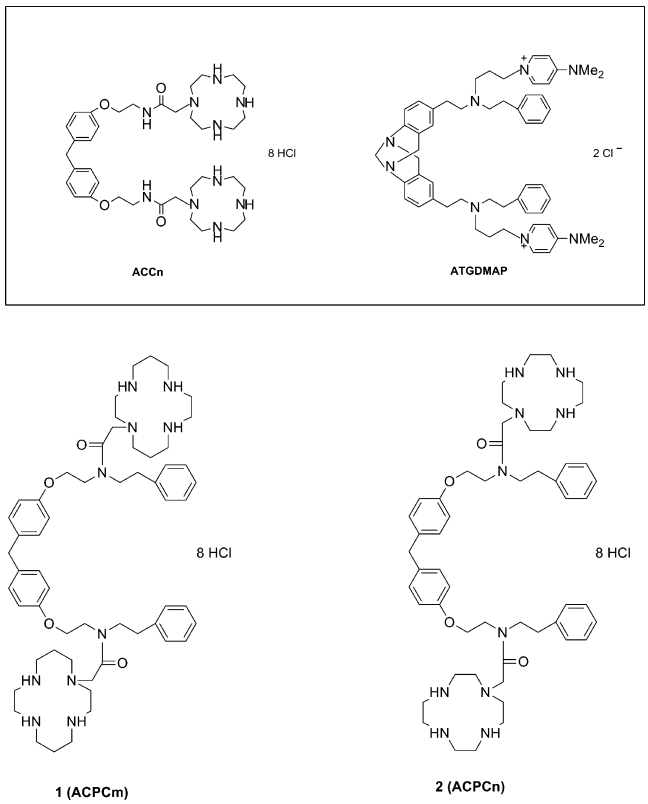

Fig. 1. Previously (ACCn and ATGDMAP) and Currently (ACPCm (**1**) and ACPCn (**2**)) Reported NMDA Receptor Antagonists

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sulfonylamino)ethyl]amino}ethoxy)benzyl]phenoxy}ethyl)-2-(1,4,7,10-tetraazacyclotridec-1-yl)-*N*-[2-(5-dimethylaminonaphtalene-1-sulfonylamino)ethyl]acetamide (DNCn) and *N*-(2-{4-[4-(2-{[(1,4,7,10-tetraazacyclododec-1-yl)-acetyl]-[2-(toluene-4-sulfonylamino)ethyl]amino}ethoxy)-benzyl]phenoxy}ethyl)-2-(1,4,7,10-tetraazacyclotridec-1-yl)-*N*-[2-(toluene-4-sulfonylamino)ethyl]acetamide (TsDCn), both of which have two sulfonamide groups, was stronger than that of ACCn.[4] In the present study, we attempted to synthesize more potent cleft-type cyclophanes than ACCn and ATGDMAP (Fig. 1).

Results and Discussion

We introduced a phenethylamino group as a spacer in the cleft-type cyclophane (ACCn) to increase molecular rigidity and enhance affinity towards the NMDA receptor. Further analysis revealed that ACPCm (**1**) and ACPCn (**2**), which form hydrophobic structures with a diphenylmethane skeleton and two phenethylamine groups, and which have two cyclic polyamines as the hydrophilic group, exhibit more potent NMDA inhibitory activity than ACCn and ATGDMAP.

The NMDA antagonists ACPCm (**1**) and ACPCn (**2**) were synthesized as shown in Chart 1. A pentafluorophenyl ester function in compound (**3**)[3] was converted into amide (**4**, 90%) after treatment of pentafluorophenyl ester with 2-phenylethylamine in the presence of triethylamine (TEA) in CH_2Cl_2, followed sequentially by reduction with borane dimethyl sulfide complex ($BH_3 \cdot DMS$) to the corresponding amine (**5**, 92%). The amine was converted into **8** by treatment with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 1-carboxymethyl-1,4,8,11-tris(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (**6**). Finally, deprotection of **8** with concentrated HCl in THF resulted in the desired compound ACPCm (**1**) in quantitative yield. ACPCn (**2**) was synthesized from 1-carboxymethyl-1,4,7,10-tris(*tert*-butoxycarbonyl)-1,4,7,10-tetraazacyclododecane (**7**)[6] and EDC by a method similar to that of ACPCm (**1**). The effects of ACPCm (**1**) and ACPCn (**2**) on the NMDA receptors were studied using voltage-clamped recordings of recombinant NMDA receptors expressed in *Xenopus* oocytes. We measured the effects of 10 μM ACPCm (**1**) and ACPCn (**2**) on responses to glutamate (10 μM, with 10 μM glycine) at the NR1/NR2 receptors containing different NR2 subunits, namely NR2A, NR2B, NR2C and NR2D, in oocytes voltage-clamped at −70 mV. Both ACPCm (**1**) and ACPCn (**2**) inhibited macroscopic currents at all NMDA receptor subtypes and the inhibition of the NR1/NR2A and NR1/NR2B receptors by these cleft-type cyclophanes was slightly more potent than inhibition of the NR1/NR2C and NR1/NR2D receptor subtypes (Fig. 2). The dose-dependency of the inhibition by both compounds for the NR1/NR2A and NR1/NR2B receptors at −70 mV was then investigated. The IC_{50} values of ACPCm (**1**) and ACPCn (**2**) for the NR1/NR2A receptors were 1.06 μM and 0.92 μM, and for the NR1/NR2B receptors were 1.47 μM and 1.49 μM, respectively (Fig. 3). A cyclic polyamine, CP2323 (cyclam) inhibited macroscopic currents at NR1/NR2 containing NR2A and NR2B subunits, though CP2222 (cyclen) did not show any effects. No significant difference in inhibition effect was observed between ACPCm (**1**) and ACPCn (**2**).[7] The inhibition curve (solid line) represents a sigmoidal curve that fits to the data with a Hill coefficient (0.8—1.2) using the PRISM 4 software program (GraphPad Software Inc., San Diego, CA, U.S.A.). To clarify the mechanism of inhibition by ACPCm (**1**) and ACPCn (**2**), we tried to determine whether these cleft-type cyclophane produce voltage-dependent inhibition of NMDA receptors. The effects of ACPCm (**1**) and ACPCn (**2**) were studied using the NR1/NR2A and NR1/NR2B receptors expressed in *Xenopus* oocytes voltage-clamped at −20 and −100 mV (Fig. 4). Inhibition by ACPCm (**1**) and

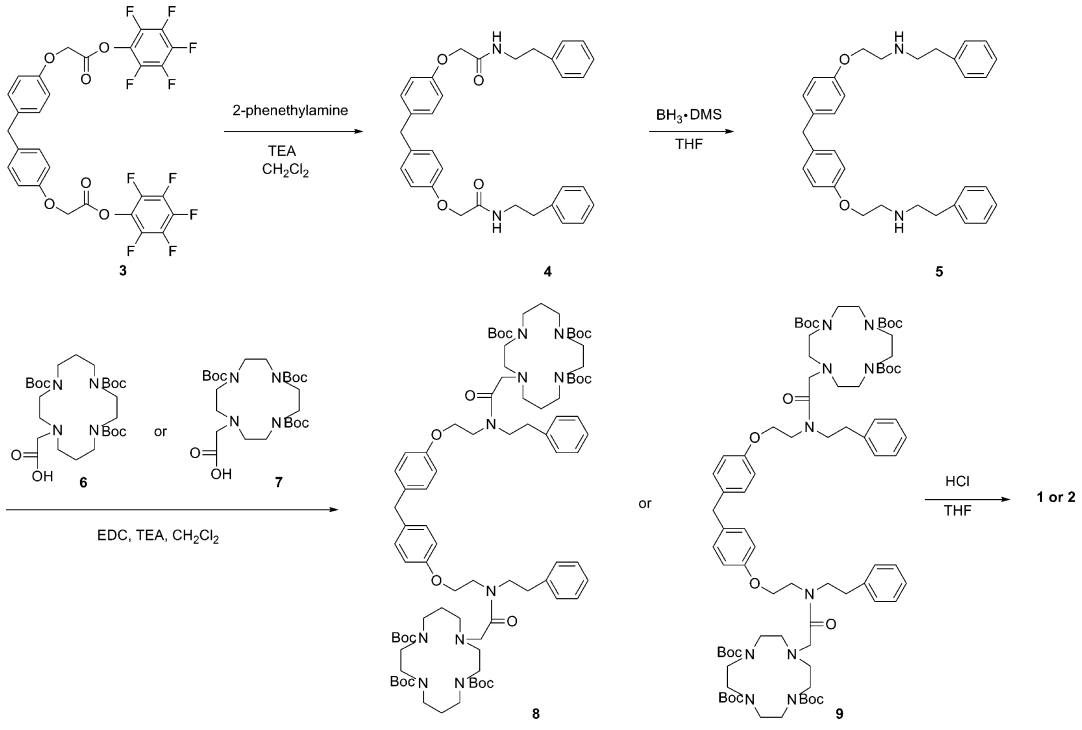

Chart 1

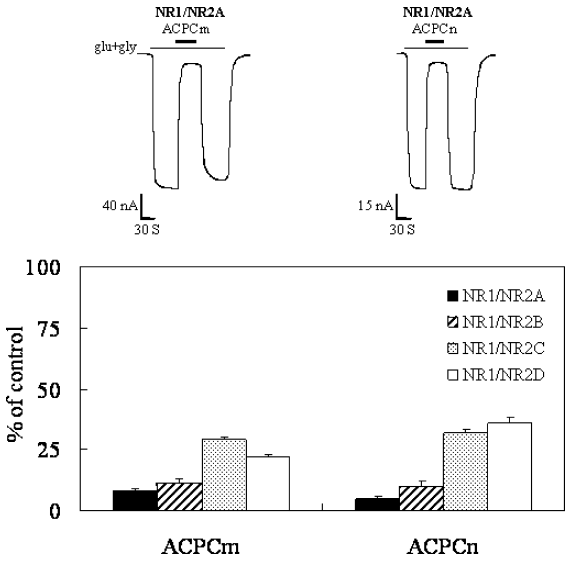

Fig. 2. Effects of ACPCm (**1**) and ACPCn (**2**) on NMDA Receptors at −70 mV

Representative traces showing the effects of 10 μM ACPCm (**1**) and ACPCn (**2**) on the NR1/NR2A receptors. The effects of 10 μM ACPCm (**1**) and ACPCn (**2**) were determined in oocytes expressing NMDA (NR1/NR2A, NR1/NR2B, NR1/NR2C and NR1/NR2D). Currents were evoked by 10 μM glutamate with 10 μM glycine and voltage-clamped at −70 mV. Macroscopic currents in the presence of cleft-type cyclophane were expressed as a percentage of the control response at the NMDA receptors. Data represent the mean±S.E.M. from 4 or 5 oocytes.

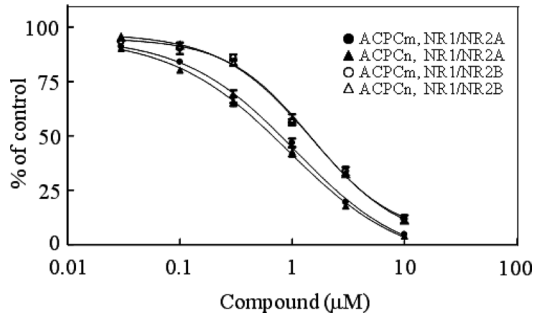

Fig. 3. Inhibitory Curves of ACPCm (**1**) and ACPCn (**2**) on NMDA Receptors at −70 mV

Concentration–inhibition curves for ACPCm (**1**) and ACPCn (**2**) were determined at the NR1/NR2A and NR1/NR2B receptors, voltage-clamped at −70 mV. Responses to 10 μM glutamate with 10 μM glycine measured in the presence of ACPCm (**1**) and ACPCn (**2**) are expressed as a percentage of the control response at each receptor type. Data represent mean±S.E.M. from 4 oocytes. Solid line represents a sigmoidal curve that fits to the data with a Hill coefficient (0.8—1.2).

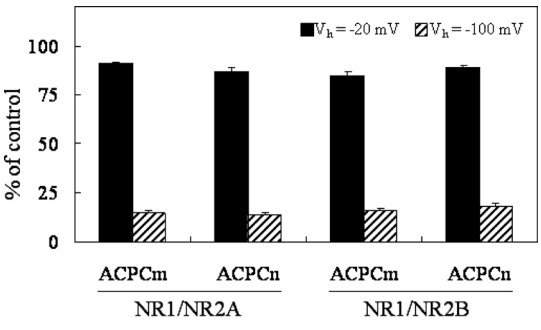

Fig. 4. Voltage-Dependent Inhibition by ACPCm (**1**) and ACPCn (**2**) of NMDA Receptor Currents

The effects of 1 μM ACPCm (**1**) and ACPCn (**2**) on the NR1/NR2A and NR1/NR2B receptors, were measured at −20 and −100 mV. Data represent the mean±S.E.M. from 4 or 5 oocytes for each subunit combination.

ACPCn (**2**) became prominent at −100 mV compared to the inhibition at −20 mV. The results suggest that the inhibition caused by ACPCm (**1**) and ACPCn (**2**) is voltage-dependent, and that both compounds act as an open channel blocker.

There are a few NMDA receptor antagonists available for clinical use, and only ketamine and more importantly memantine, act as channel blockers. The IC_{50} values for ketamine and memantine are 1.4 and 1.0 μM respectively against NMDA receptors expressed in *Xenopus* oocyte using voltage-clamp recording.[4,8] The degree of inhibition by ACPCm (**1**) (IC_{50}, 1.06 μM) and ACPCn (**2**) (IC_{50}, 0.92 μM) against the NR1/NR2A receptor was as potent as meantime, a therapeutic drug for Alzheimer's disease. Further investigations is now in progress to synthesize ACPCm (**1**) or ACPCn (**2**) derivatives that display stronger inhibitory effects on NMDA receptors by changing various side chains.

Experimental

Melting points were determined using the Yanagimoto melting point apparatus Yanaco MP and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL JNM-ECX500 spectrometer containing tetramethylsilane as the standard. Mass spectra (MS) were measured on a JEOL JMS-GC mate instrument. Adult female *Xenopus laevis* were chilled on ice, and the preparation and maintenance of oocytes were performed as described previously.[4,10] Capped cRNAs were prepared from linearized cDNA templates using mMessage mMachine kits (Ambion, Austin, TX, U.S.A.). Oocytes were injected with NR1A and NR2 cRNAs at a ratio of 1 : 5 (0.2—4 ng of NR1A plus 1—20 ng of NR2). Macroscopic currents were recorded with a two-electrode voltage-clamp using the Dual Electrode Voltage Clamp Amplifier CEZ-1250 (Nihon Koden, Tokyo, Japan). Electrodes were filled with 3 M KCl. Oocytes were continuously superfused (*ca.* 5 ml/min) with a Mg^{2+}-free saline solution (96 mM NaCl, 2 mM KCl, 1.8 mM $BaCl_2$, 10 mM HEPES, pH 7.5). This solution contained $BaCl_2$ rather than $CaCl_2$, and, in most experiments, oocytes were injected with K^+-1,2-bis(2-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid (BAPTA; 100 nl of 40 mM solution at pH 7.5) on the day of recording to eliminate Ca^{2+}-activated Cl^- currents.[4,9] Glutamate and glycine were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). BAPTA were purchased from Sigma (St. Louis, MO, U.S.A.).

4,4′-Bis(*N*-phenethylcarbamoylmethoxy)diphenylmethane (4) A mixture of **3** (648 mg, 1 mmol), 2-phenylethylamine (242 mg, 2 mmol), and TEA (0.28 ml, 2 mmol) in CH_2Cl_2 (40 ml) was stirred at room temperature. After 2 h, the reaction mixture was diluted with CH_2Cl_2 (100 ml). The organic phase was washed with H_2O and dried over $MgSO_4$, and evaporated to afford a white solid, which was chromatographed on silica gel column with $CHCl_3$: MeOH (10 : 1) and then EtOAc as an eluent to give a white solid (470 mg, 90%). An analytical sample was obtained by recrystallizing this material from EtOAc–hexane, yielding colorless needles, mp 124—125 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.83 (4H, t, J=7.0 Hz), 3.57—3.62 (4H, m), 3.88 (2H, s), 4.43 (4H, s), 6.58 (2H, br), 6.77 (4H, d, J=8.8 Hz), 7.09 (4H, d, J=8.8 Hz), 7.13—7.15 (4H, m), 7.21—7.29 (6H, m). HR-FAB-MS *m*/*z*: 523.2596 $[M+H]^+$ (Calcd for $C_{33}H_{35}N_2O_4$: 523.2596). *Anal.* Calcd for $C_{33}H_{34}N_2O_4$: C, 75.84; H, 6.56; N, 5.36. Found: C, 75.81; H, 6.56; N, 5.30.

4,4′-{Bis[2-(*N*-phenethyl)]aminoethoxy}diphenylmethane (5) A mixture of **4** (340 mg, 0.65 mml) in tetrahydrofuran (THF) (20 ml) was stirred at room temperature under N_2 atmosphere. BH_3·DMS (0.78 ml, 7.8 mmol) was added and the reaction mixture was stirred for 24 h at 80 °C, then cooled to room temperature. A 0.7 M hydrogen chloride–MeOH solution (5 ml) was added, and the reaction mixture refluxed for 1 h, and evaporated. The residue was adjusted to pH 11 with excess 25% NH_4OH. The mixture was extracted with CH_2Cl_2 (20 ml×3). The combined organic phases were washed with H_2O and dried over Na_2SO_4. Removal of the solvent afforded a yellow oil, which was chromatographed on silica gel column with $CHCl_3$: MeOH (10 : 1) as the eluent to give a colorless oil (314 mg, 92%). ^{1}H-NMR ($CDCl_3$) δ: 2.83 (4H, t, J=7.3 Hz), 2.93—2.96 (4H, m), 3.00 (4H, t, J=5.4 Hz), 3.85 (2H, s), 4.03 (4H, t, J=5.4 Hz), 6.78 (4H, d, J=8.5 Hz), 7.06 (4H, d, J=8.5 Hz), 7.20—7.22 (6H, m), 7.26—7.31 (4H, m). HR-FAB-MS *m*/*z*: 495.3013 $[M+H]^+$ (Calcd for $C_{33}H_{39}N_2O_2$: 495.3011).

1-Carbonylmethyl-4,8,11-tris(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (6) A mixture of benzyl bromoacetate (435 mg, 1.9

mmol), 1,4,8-tris(*tert*-butoxycarbonyl)-1,5,8,11-tetraazacyclotetradecane[10] (475 mg, 0.95 mmol) and K_2CO_3 (131 mg, 0.95 mmol) in MeCN (5 ml) was stirred at 80 °C under N_2 atmosphere for 12 h. After insoluble inorganic salts were removed by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with EtOAc : hexane (1 : 2) to give 1-benzyloxycarbonylmethyl-4,8,11-tris(*tert*-butoxycarbonyl)-1,5,8,11-tetraazacyclotetradecane (573 mg, 94%) as a viscous oil. [^{1}H-NMR ($CDCl_3$) δ: 1.41 and 1.43 (27H, 2s), 1.61—1.69 (2H, m), 1.82—1.92 (2H, m), 2.62—2.67 (2H, m), 2.80—2.85 (2H, m), 3.20—3.40 (12H, m), 3.41 (2H, s), 5.24 (2H, s), 7.32—7.38 (5H, m). HR-FAB-MS *m/z*: 649.4178 $[M+1]^+$ (Calcd for $C_{34}H_{57}N_4O_8$: 649.4176).] A solution of the oil in THF (2 ml) was hydrogenated over 10% Pd–C (20 mg) at room temperature for 24 h under H_2 atmosphere. The catalyst was filtered through a pad of celite. The filtrate was concentrated to dryness to give a colorless oil (492 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 1.46 and 1.47 (27H, 2s), 1.73—1.77 (2H, m), 1.83—1.88 (2H, m), 2.62 (2H, br), 2.75 (2H, br), 3.28 (2H, s), 3.31—3.40 (12H, m). HR-FAB-MS *m/z*: 559.3706 $[M+H]^+$ (Calcd for $C_{27}H_{51}N_4O_8$: 559.3706).

4,4′-Bis[2-(*N*-{2-[4,8,11-tris(*tert*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-yl]acetyl}-*N*-phenethyl)aminoethoxy]diphenylmethane (8) A mixture of **5** (248 mg, 0.5 mmol), **6** (558 mg, 1 mmol), EDC (230 mg, 1.2 mmol) and TEA (0.168 ml, 1.2 mmol) in CH_2Cl_2 (50 ml) was stirred at room temperature for 24 h. The reaction mixture was washed with H_2O and dried over $MgSO_4$. The solvent was evaporated, and the residue was chromatographed on silica gel with EtOAc : MeOH (9 : 1) to give a colorless amorphous (100 mg, 13%). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (18H, s), 1.42 (36H, s), 1.60—2.30 (12H, m), 2.56—2.60 (2H, m), 2.69—2.90 (8H, m), 3.20—3.37 (26H, m), 3.59—3.72 (8H, m), 3.84 (2H, s), 3.95 (2H, t, J=4.9 Hz), 4.11 (2H, t, J=4.9 Hz), 6.74 (2H, d, J=8.6 Hz), 6.79 (2H, d, J=8.6 Hz),7.05 (2H, d, J=8.6 Hz), 7.06 (2H, d, J=8.6 Hz), 7.16—7.32 (10H, m). HR-FAB-MS *m/z*: 1575.9996 $[M+H]^+$ (Calcd for $C_{87}H_{134}N_{10}O_{16}$: 1576.0057). *Anal.* Calcd for $C_{87}H_{134}N_{10}O_{16}$: C, 66.30; H, 8.57; N, 8.89. Found: C, 66.34; H, 8.77; N, 9.00.

4,4′-Bis[2-(*N*-{2-[4,7,10-tris(*tert*-butoxycarbonyl)-1,4,7,10-tetraazacyclododecan-1-yl]acetyl}-*N*-phenethyl)aminoethoxy]diphenylmethane (9) A mixture of **5** (145 mg, 0.29 mmol), **7** (310 mg, 0.58 mmol), EDC (130 mg, 0.67 mmol) and TEA (94 ml, 0.67 mmol) in CH_2Cl_2 (15 ml) was stirred at room temperature for 24 h. The reaction mixture was washed with H_2O and dried over $MgSO_4$. The solvent was evaporated, and the residue was chromatographed on silica gel with EtOAc : MeOH (9 : 1) to give a colorless amorphous (102 mg, 23%). ^{1}H-NMR ($CDCl_3$) δ: 1.43 (18H, s), 1.44 (18H, s), 1.46 (18H, s), 2.86—3.73 (48H, m), 3.84 (2H, s), 4.03 (2H, t, J=4.9 Hz), 4.13 (2H, t, J=4.9 Hz), 6.77 (2H, d, J=8.6 Hz), 6.80 (2H, d, J=8.6 Hz), 7.04—7.07 (4H, m), 7.20—7.23 (6H, m), 7.25—7.29 (4H, m). HR-FAB-MS *m/z*: 1519.9415 $[M+H]^+$ (Calcd for $C_{83}H_{127}N_{10}O_{16}$: 1519.9431). *Anal.* Calcd for $C_{83}H_{126}N_{10}O_{16}$: C, 65.58; H, 8.36; N, 9.21. Found: C, 65.86; H, 8.64; N, 9.00.

4,4′-Bis({2-[*N*-(1,4,8,11-tetraazacyclotetradecan-1-yl)acetyl]-*N*-phenethyl}aminoethoxy)diphenylmethane Octahydrochloride (1, ACPCm) **8** (76 mg, 0.048 mmol) was dissolved in THF (0.2 ml), to which concentrated HCl (0.2 ml) was added. The reaction mixture was stirred at room temperature. After 24 h, the reaction mixture was evaporated, and the resulting precipitate was triturated with THF and collected by filtration to give (**1**, ACPCm) (60 mg, 100%) as a white solid. ^{1}H-NMR (D_2O) δ: 1.53—1.62 (8H, m), 2.40—3.31 (42H, m), 3.50—3.70 (8H, m), 3.84 (2H, s), 4.12 (2H, m), 6.70—6.73 (2H, m), 6.77—6.80 (2H, m), 7.06—7.18 (14H, m). HR-FAB-MS *m/z*: 975.6915 $[M-8HCl+H]^+$ (Calcd for $C_{57}H_{87}N_{10}O_4$: 975.6911). *Anal.* Calcd for $C_{57}H_{86}N_{10}O_4 \cdot 8HCl$: C, 54.03; H, 7.48; N, 11.06. Found: C, 54.05; H, 7.64; N, 11.14.

4,4′-Bis({2-[*N*-(1,4,7,10-tetraazacyclododecan-1-yl)acetyl]-*N*-phenethyl}aminoethoxy)diphenylmethane Octahydrochloride (2, ACPCn) To a solution of **9** (80 mg, 0.052 mmol) in THF (1 ml) was added concentrated HCl (0.2 ml) at room temperature, and the reaction mixture was stirred for 24 h, then concentrated under reduced pressure to give a white solid, which was washed with THF and Et_2O to give (**2**, ACPCn) (62 mg, 100%). ^{1}H-NMR (D_2O) δ: 2.60—2.94 (40H, m), 3.41 (2H, t, J=4.9 Hz), 3.46 (4H, t, J=4.9 Hz), 3.59 (2H, t, J=5.1 Hz), 3.70 (2H, m), 3.93—3.95 (2H, m), 4.07 (2H, t, J=5.1 Hz), 6.69 (2H, d, J=8.6 Hz), 6.77 (2H, d, J=8.6 Hz), 7.04—7.17 (14H, m). HR-FAB-MS *m/z*: 919.6283 $[M-8HCl+H]^+$ (Calcd for $C_{53}H_{79}N_{10}O_4$: 919.6286). *Anal.* Calcd for $C_{53}H_{78}N_{10}O_4 \cdot 8HCl$: C, 52.57; H, 7.16; N, 11.57. Found: C, 52.65; H, 7.28; N, 11.37.

Acknowledgments We thank Drs. S. Nakanishi, P. H. Seeburg and M. Mishina for the kind supply of glutamate receptor clones. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (T.M.).

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