Excitatory Amino Acids. Synthesis of (*RS*)-2-Amino-3-(5-cyclopropyl-3-hydroxyisoxazol-4-yl)propionic Acid, a New Potent and Specific AMPA Receptor Agonist

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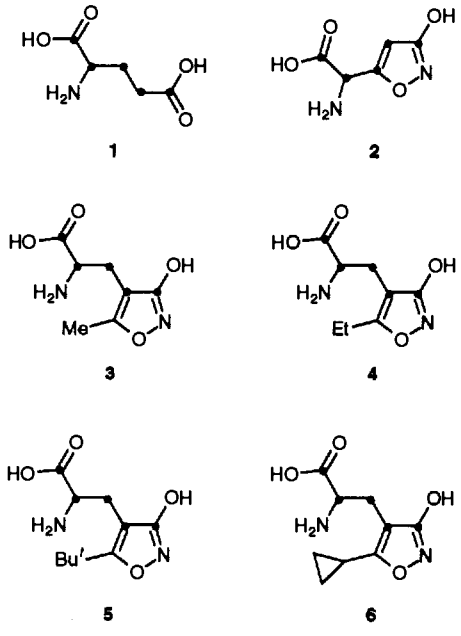
The synthesis of (*RS*)-2-amino-3-(5-cyclopropyl-3-hydroxyisoxazol-4-yl)propionic acid **6**, an analogue of the AMPA receptor agonist (*RS*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)-propionic acid, AMPA, **3** is described. Compound **6** has been studied *in vitro* in radioligand binding and electrophysiological test systems and shown to be a specific AMPA receptor agonist equipotent with AMPA. The synthesis of **6** was based on 5-cyclopropyl-3-hydroxyisoxazole **8**, which was converted into the intermediate 4-bromomethyl-5-(3-bromopropyl)-2-methoxymethyl-2,3-dihydroisoxazol-3-one **9** by opening of the cyclopropane ring. Based on ^{1}H and ^{13}C NMR data, this conversion has been shown to proceed stepwise, the progression of the different steps being dependent on the concentration of the hydrobromic acid medium, reaction time, and temperature. An acetamidomalonate group has been regiospecifically substituted for the allylic bromine atom of **9** to give **10**, and treatment of **10** with sodium hydride gave compound **11** containing a cyclopropyl group, reformed by cyclization of the 3-bromopropyl substituent of **10**. Compound **11** has been fully deprotected by treatment with aqueous trifluoroacetic acid to give **6**.

Glutamic acid **1** is the major excitatory amino acid (EAA) neurotransmitter in the central nervous system[1,2] and appears to play a crucial role in certain neurodegenerative disorders.[3] The physiological and pathophysiological functions of **1** are mediated by multiple ionotropic and metabotropic receptors, the former class of which comprises three receptor families named *N*-methyl-D-aspartic acid (NMDA), (*RS*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA), and kainic acid receptors.[1-5] At the NMDA receptor complex, NMDA is a specific agonist and glycine an endogenous co-agonist, whereas (*RS*)-3-(2-carboxypiperazin-4-yl)propylphosphonic acid (CPP) is a competitive antagonist and (*RS*)-10,11-dihydro-5-methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine† (MK-801) a non-competitive antagonist.[6] Whilst ibotenic acid **2**[7] is a non-selective NMDA agonist,[8] AMPA **3**[9] specifically activates AMPA receptors,[8] which are blocked by 6-cyano-7-nitro-1,2,3,4-tetrahydroquinoxalin-2,3-dione (CNQX).[10]

We have previously shown that (*RS*)-2-amino-3-(5-ethyl-3-hydroxyisoxazol-4-yl)propionic acid **4** is slightly more potent than **3** as an AMPA receptor agonist,[11] whereas (*RS*)-2-amino-3-(5-*tert*-butyl-3-hydroxyisoxazol-4-yl)propionic acid **5** is markedly weaker[12] (see Table 3). On the basis of structure–activity studies on **3**–**5** and a number of other AMPA receptor agonists we have proposed a model of the AMPA receptor binding site containing a cavity of limited size capable of accommodating lipophilic groups.[11]

In order to judge the capacity of this simple receptor model as a template for the semirational design of AMPA receptor agonists and partial agonists of potential therapeutic interest, we have now synthesized and tested pharmacologically the cyclopropyl analogue of **3**, (*RS*)-2-amino-3-(5-cyclopropyl-3-hydroxyisoxazol-4-yl)propionic acid **6**.

† This is the name used in Chemical Abstracts. According to IUPAC recommendations this compound is named: (*RS*)-5,10-epimino-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene.



Results and Discussion

Chemistry.—Ethyl cyclopropylpropiolate **7** was converted into 5-cyclopropyl-3-hydroxyisoxazole **8** by treatment with hydroxylamine under basic conditions (70% yield) (Scheme 1). Treatment of **8** with a solution of 1,3,5-trioxane in hydrobromic acid (62%) and subsequent treatment of the intermediate, containing bromomethyl groups at positions 2 and 4 of the ring, with methanol under previously described reaction conditions[13] gave **9** in 99% yield. As expected,[14] these strongly acidic reaction conditions caused opening of the cyclopropane ring to give the 3-bromopropyl group in **9**. A Sorensen reaction regiospecifically converted compound **9** into **10** (66%), and

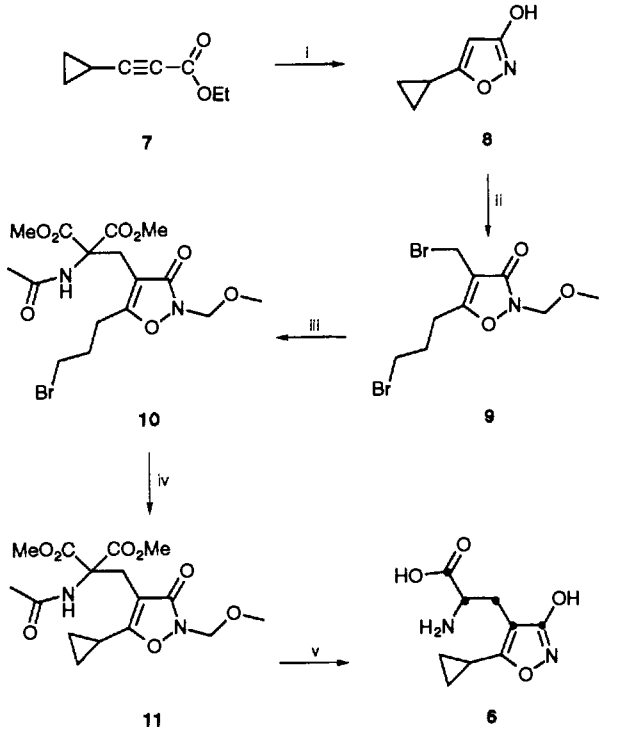
Table 1 ^{13}C NMR spectroscopic data for **12–17**

Compound	Solvent (aq. HBr, %)	δ_C C-3[a]	C-4	C-5	C-1′	C-2′	C-3′	2-CH_2-X	4-CH_2-Br
12	47	164.5	92.2	181.5	9.3	11.6	11.6	69.2[b]	—
12	62	165.0	92.4	181.2	9.4	11.7	11.7	69.2[b]	—
13	62	166.1	92.8	183.0	9.7	12.2	12.2	38.5[c]	—
14	47	163.5	105.9	176.3	8.3	10.3	10.3	68.6[b]	19.2
14	62	163.7	105.8	176.4	8.6	10.5	10.5	68.4[b]	18.9
15	62	166.9	105.4	177.0	8.2	10.4	10.4	40.0[c]	18.7
16	62	163.7	107.8	173.6	28.2	25.0	33.1	68.9[b]	18.6
17	62	166.3	107.4	174.1	28.2	24.8	33.2	39.6[c]	18.1

[a] The assignment of the δ values for C-3 as well as for C-4, C-5, C-1′, C-2′ and C-3′, in the mixture of compounds **12** and **13** are tentative. The same applies for the mixtures of compounds **14** and **15**, and of compounds **16** and **17**. [b] X = OH. [c] X = Br.

Table 2 Ratios of intermediates in the conversion of **8** into **9** based on ^{13}C NMR integrals

Solvent (aq. HBr, %)	Reaction time (h)	Temperature (°C)	Product ratios **12**:**13**	**14**:**15**	**16**:**17**
47	0.2	20	100:0	—	—
62	0.2	5	50:50	—	—
47	48	20	—	100:0	—
62	48	5	—	50:50	—
62	0.2	60	—	60:40	—
62	6	60	—		55:45



Scheme 1 i, NH_2OH, NaOH; ii, $(CH_2O)_3$, 62% aq. HBr, MeOH; iii, $AcNHCH(CO_2Me)_2$; iv, NaH; v, CF_3CO_2H (1 mol dm^{-3})

treatment of **10** with sodium hydride gave the cyclopropyl analogue **11** in 74% yield. This cyclization reaction proceeds *via* deprotonation of the highly activated methylene group α to the isoxazole ring.[15] Under the reaction conditions used, intramolecular *N*-alkylation, with formation of a hexahydroazocine ring, or a Claisen type reaction between the acetyl group and one of the methoxycarbonyl groups of **10** to form a five-membered β-dicarbonyl ring structure,[16] were not observed. Compound **11** was fully deprotected to give the desired acidic isoxazole amino acid **6** in 58% yield using aqueous trifluoroacetic acid (1 mol dm^{-3}).

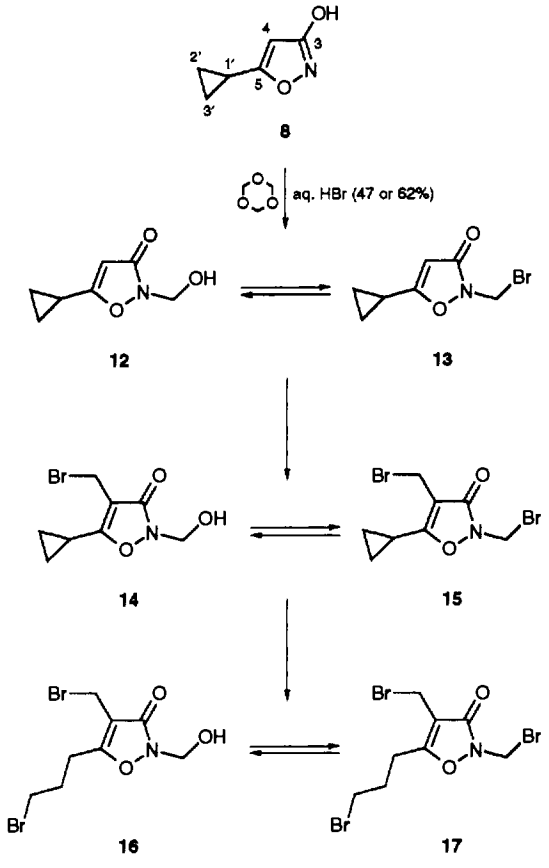
The reactions involved in the conversion of **8** into **9** were studied in detail by ^{13}C NMR spectroscopy (Table 1). Under carefully controlled reaction conditions it could be demonstrated that bromomethylation/hydroxymethylation reactions and the subsequent opening of the cyclopropane ring proceeded stepwise (Scheme 2). Compound **8** was initially converted into an equilibrium mixture of **12** and **13** by treatment with trioxane and 62% hydrobromic acid at 5 °C for 0.2 h (Table 2), with no detectable formation of other reaction products. After 48 h under these reaction conditions, the further conversion of **12** and **13** into an equilibrium mixture of **14** and **15** was complete. This virtually quantitative bromomethylation at C-4 was shown to proceed without detectable opening of the cyclopropane ring. Using 47% hydrobromic acid at 20 °C, compound **8** was converted exclusively into the hydroxymethyl compound **12** after 0.2 h reaction time (Table 2). Analogously, only the hydroxymethyl compound **14** could be detected after 48 h under the same reaction conditions. At 60 °C and by using 62% hydrobromic acid for 0.2 h, only a (60:40) mixture of **14** and **15** could be detected, but after 6 h under these conditions a complete opening of the cyclopropane ring has taken place, with formation of an equilibrium mixture of the 5-(3-bromopropyl) compounds **16** and **17**.

Pharmacology.—Compound **6** was shown to bind to the AMPA receptor site with an affinity (IC_{50} = 0.035 μmol dm^{-3}) comparable with those of AMPA **3** (IC_{50} = 0.040 μmol dm^{-3}) and **4** (IC_{50} = 0.030 μmol dm^{-3}) but much higher than that observed for **5** (IC_{50} = 2.1 μmol dm^{-3}) (Table 3). Compound **6** was shown electrophysiologically *in vitro* to be an AMPA receptor agonist (EC_{50} = 5.5 μmol dm^{-3}) slightly weaker than AMPA **3** (EC_{50} = 3.5 μmol dm^{-3}) and **4** (EC_{50} = 2.3 μmol dm^{-3}). The pharmacological profile of **6** is, however, markedly different from that of AMPA **3**. Thus, whereas AMPA **3** is a much more potent inhibitor of the binding of the AMPA antagonist, [^{3}H]CNQX, in the presence of potassium thiocyanate (IC_{50} = 0.4 μmol dm^{-3}) than in the absence of this

Table 3 *In vitro* radioligand binding and electrophysiological data

Compound	IC_{50} (μmol dm^{-3}) [^{3}H]AMPA	[^{3}H]CNQX	[^{3}H]CNQX + KSCN	Electrophysiology (EC_{50}, μmol dm^{-3})
AMPA **3**	0.040 ± 0.005	18 ± 5	0.4 ± 0.1	3.5 ± 0.2
4	0.030 ± 0.015	n.d.[a]	0.4 ± 0.1	2.3 ± 0.2
5	2.1 ± 0.2	> 100	> 100	34 ± 2
6	0.035 ± 0.015	12 ± 4	4.7 ± 2.0	5.5 ± 1.0

Values are mean values ± standard error of means from at least three separate experiments. [a] Not determined.



Scheme 2

chaotropic agent (IC_{50} = 18 μmol dm^{-3}), such a marked difference is not observed for **6** (Table 3). These receptor affinity data strongly suggest that whereas AMPA **3** very selectively interacts with the high-affinity agonist conformation of the AMPA receptor, **6** binds with almost equal affinity to the high-affinity (agonist) and low-affinity (antagonist) conformation of the receptor in spite of its agonist character.[17] We have previously shown that adding potassium thiocyanate to the [^{3}H]CNQX binding assay increases the affinity of agonists and decreases the affinity of antagonists. Thus, this result may reflect that the two enantiomers of **6** have different pharmacological profiles. These aspects make **6** an interesting tool for studies of AMPA receptor mechanisms.

The selectivity of **6** as an AMPA receptor agonist is emphasized by the observation that **6** did not significantly affect the binding of [^{3}H]kainic acid (kainic acid receptor) or [^{3}H]CPP, [^{3}H]MK-801, and [^{3}H]glycine (NMDA receptor complex) (IC_{50} > 100 μmol dm^{-3}).

Experimental

General.—Dichloromethane was dried over sodium hydride. Dimethylformamide was dried as described.[18] Unless otherwise stated, solutions were dried using magnesium sulfate. Solvents were removed under reduced pressure by rotatory evaporation. Column chromatography was performed as described.[19] All new compounds were colourless, unless otherwise stated. Structure and homogeneity of new compounds were confirmed by m.p. determinations (capillary tubes, uncorrected), elemental analyses (determined by Mr. M. G. Cornali, Microanalytical Laboratory, Leo Pharmaceutical Products, Ballerup, Denmark), TLC (silica F_{254} plates, Merck), and NMR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50.32 MHz, respectively, on a Bruker AC-200 instrument. Signal positions in the ^{1}H NMR spectra are given as δ values relative to tetramethylsilane (TMS), when $CDCl_3$ was used as a solvent, and relative to dioxane (δ 3.70), when water was used. Coupling constants (*J*) are given in Hz. ^{13}C NMR signals were assigned through their multiplicity in the coupled spectra or through DEPT spectra, and using the $CDCl_3$ peak (δ 76.93) or the dioxane peak (δ 67.40), when $CDCl_3$ or water, respectively, were used as solvents.

NMR Kinetic Experiments.—Compound **8** (100 mg, 0.80 mmol) and 1,3,5-trioxane (108 mg, 1.20 mmol) were dissolved in hydrobromic acid of different concentrations (0.5 cm^3) in an NMR tube (Tables 1 and 2). Temperature experiments were carried out in a refrigerator (5 °C), at room temperature (20 °C), or by using an oil bath (60 °C).

5-Cyclopropyl-3-hydroxyisoxazole **8**.—A solution of ethyl cyclopropylpropiolate **7**[20] in methanol (100 cm^3) was added dropwise to an ice-cold solution of hydroxylamine hydrochloride (5.21 g, 75 mmol) and sodium hydroxide (6.0 g, 150 mmol) in water (75 cm^3). The reaction mixture was stirred at 0 °C for 3 h and then at room temperature for 20 h. The reaction mixture was acidified with concentrated hydrochloric acid and evaporated. To the oily residue was added water (50 cm^3), and the precipitate was collected and washed with water (20 cm^3). After drying, the solid was extracted with diethyl ether (2 × 30 cm^3), and the combined extracts were evaporated. Recrystallization of the residue from diethyl ether–light petroleum gave the title compound **8** (2.61 g, 70%), m.p. 103–105 °C (lit.,[21] m.p. 106–107 °C); $\delta_H(CDCl_3)$ 9.5 (1 H, s, OH), 5.35 (1 H, s, 4-H), 1.85 (1 H, m) and 0.95 (4 H, m); $\delta_C(CDCl_3)$ 10.3 (CH), 23.6 (2 × CH_2), 105.2 (C-4), 168.2 (C-3) and 173.5 (C-5).

4-Bromomethyl-5-(3-bromopropyl)-2-methoxymethyl-2,3-dihydroisoxazol-3-one **9**.—5-Cyclopropyl-3-hydroxyisoxazole **8** (2.17 g, 17.3 mmol) and 1,3,5-trioxane (2.34 g, 26.0 mmol) were treated with hydrobromic acid (40 cm^3, 62%) for 18 h at 60 °C. This mixture was extracted with dichloromethane (3 × 50 cm^3) and then methanol (50 cm^3) was added to the combined organic extracts and the mixture was stirred for 2 h at 20 °C. Addition of dichloromethane (35 cm^3), washing with water (2 × 50 cm^3), drying and removal of the organic solvents, produced the title compound **9** (5.90 g, 99%) as a yellow oil; $\delta_H(CDCl_3)$ 2.28 (2 H, quintet, *J* 7.7), 2.90 (2 H, t, *J* 7.7), 3.40 (3 H, s, OCH_3), 3.49 (2 H, t, *J* 7.7), 4.23 (2 H, s, CH_2Br) and 5.17 (2 H, s, N-CH_2O); $\delta_C(CDCl_3)$ 18.5 (BrCH_2C-4), 24.7 (BrCH_2CH_2), 28.4

(CH_2CH_2C-5), 31.7 ($BrCH_2CH_2$), 57.0 (OCH_3), 75.2 (NCH_2O), 107.7 (C-4), 165.5 (C-3) and 169.9 (C-5) (Found: C, 31.35; H, 3.75; N, 4.15. $C_9H_{13}Br_2NO_3$ requires C, 31.51; H, 3.82; N, 4.08%).

Methyl 2-Acetamido-3-[5-(3-bromopropyl)-2-methoxymethyl-3-oxo-2,3-dihydroisoxazol-4-yl]-2-methoxycarbonylpropionate **10**.—A 60% suspension of sodium hydride in mineral oil (384 mg, 9.6 mmol) was added over a period of 10 min to a solution of dimethyl acetamidomalonate (1.82 g, 9.6 mmol) in dimethyl formamide (15 cm^3). After stirring for 15 min, a solution of compound **9** (3.00 g, 8.75 mmol) in dimethylformamide (7.5 cm^3) was added during 10 min. Stirring was continued for 10 h, and then the reaction mixture was evaporated to dryness, dissolved in dichloromethane (15 cm^3), and washed with sodium hydroxide (1 mol dm^{-3}; 15 cm^3, 0 °C) and water (2 × 15 cm^3, 0 °C). The organic phase was dried, evaporated and subjected to column chromatography [silica gel, Woelm, 0.063–0.200 mm; toluene–ethyl acetate–acetic acid (24:75:1)], which afforded the title compound **10** (2.62 g, 66%) as an oil; $\delta_H(CDCl_3)$ 2.04 (3 H, s, CH_3CON), 2.16 (2 H, quintet, *J* 7.5), 2.72 (2 H, t, *J* 7.5), 3.32 (2 H, s, 4-CH_2), 3.37 (3 H, s, OCH_3), 3.43 (2 H, t, *J* 7.5), 3.81 (6 H, s, 2 × CH_3), 5.12 (2 H, s, NCH_2O) and 7.24 (1 H, s, NH); $\delta_C(CDCl_3)$ 22.7 (CH_3CO), 24.3 ($BrCH_2CH_2$), 25.7 (CH_2CH_2C-5), 28.6 ($BrCH_2CH_2$), 31.4 (CCH_2C-4), 53.4 (2 × CO_2CH_3), 56.9 (OCH_3), 65.0 (NHC), 74.9 (NCH_2O), 103.9 (C-4), 167.3 (C-3), 167.7 (2 × CO_2CH_3), 169.4 (C-5) and 170.1 (CON) (Found: C, 42.6; H, 5.3; N, 6.5. $C_{16}H_{23}BrN_2O_8$ requires C, 42.66; H, 5.15; N, 6.22%).

Methyl 2-Acetamido-3-(5-cyclopropyl-2-methoxymethyl-3-oxo-2,3-dihydroisoxazol-4-yl)-2-methoxycarbonylpropionate **11**.—At −11 °C a solution of **10** (848 mg, 1.88 mmol) in acetonitrile (5 cm^3) was added during 2 min to a suspension of sodium hydride (60%, 301 mg, 7.5 mmol) in acetonitrile (25 cm^3). After being stirred at 20 °C for 2 h, the solvent was evaporated and water (10 cm^3) was added to the residue. The mixture was extracted with dichloromethane (3 × 20 cm^3), and the combined extracts were dried and evaporated and then the residue was purified by column chromatography [silica gel, Woelm, 0.063–0.200 mm; toluene–ethyl acetate–acetic acid (24:75:1)] to give the title compound **11** (515 mg, 74%), m.p. 130–130.5 °C (ethyl acetate–light petroleum); $\delta_H(CDCl_3)$ 1.05 (4 H, m), 1.94 (1 H, m), 2.04 (3 H, s, CH_3CON), 3.34 (3 H, s, OCH_3), 3.41 (2 H, s, 4-CH_2), 3.83 (6 H, s, 2 × CO_2CH_3), 5.04 (2 H, s, NCH_2O) and 7.10 (1 H, s, NH); $\delta_C(CDCl_3)$ 7.5 (CHC-5), 20.7 (2 × CO_2CH_3), 22.9 (CH_3CO), 25.6 (2 × CH_2), 26.7 (CCH_2C-4), 57.0 (OCH_3), 65.3 (NHC), 75.3 (NCH_2O), 102.5 (C-4), 167.5 (C-3), 168.3 (2 × CO_2CH_3), 169.6 (C-5) and 172.6 (CON) (Found: C, 52.05; H, 6.1; N, 7.40. $C_{16}H_{22}N_2O_8$ requires C, 51.87; H, 5.99; N, 7.57%).

(RS)-2-*Amino*-3-(5-*cyclopropyl*-3-*hydroxyisoxazol*-4-*yl*)*propionic Acid* **6**.—Compound **11** (275 mg, 0.74 mmol) was refluxed in aqueous trifluoroacetic acid (1 mol dm^{-3}; 5 cm^3) for 12 h and then the mixture was evaporated to dryness. The residue was twice dissolved in water (2 × 5 cm^3) and re-evaporated and then twice dissolved in toluene (2 × 5 cm^3) and re-evaporated. Preparative TLC [acetonitrile–water–acetic acid (8:1:1); R_f = 0.33] gave the title compound **6** (91 mg, 58%), m.p. 217–218 °C (decomp.) (water); $\delta_H(D_2O)$ 1.00 (4 H, m), 1.89 (1 H, m), 2.82 (2 H, d, 4-CH_2, *J* 7) and 3.87 (1 H, t, CH_2CH, *J* 7); $\delta_C(D_2O)$ 13.2 (CHC-5), 25.5 (2 × CH_2), 30.3 (CH_2C-4), 58.9 (CH), 103.5 (C-4), 169.9 (C-5), 179.1 (C-3) and 181.0 (CO_2H) (Found: C, 50.15; H, 5.65; N, 13.2. $C_9H_{12}N_2O_4$, 25 mol% H_2O requires C, 49.87; H, 5.82; N, 12.93%).

Radioligand Binding Assays.—The membrane preparations used in the [^{3}H]AMPA, [^{3}H]kainic acid, [^{3}H]CPP, [^{3}H]MK-801, [^{3}H]glycine and [^{3}H]CNQX binding assays were prepared as described.[22] [^{3}H]AMPA,[23] [^{3}H]kainic acid,[24] [^{3}H]CPP[25] and [^{3}H]CNQX[17,26] binding was performed following published procedures. [^{3}H]MK-801 binding to fully stimulated membranes was performed essentially as described earlier.[27] [^{3}H]glycine binding was carried out by a modified version of the method described,[28] using filtration through Whatman GF/B filters instead of centrifugation to isolate bound ligand. CNQX was a gift from Dr. Poul Jacobsen, Novo-Nordisk, Måløv, Denmark.

Electrophysiology.—A rat cortical slice preparation for testing the depolarizing activities of EAAs described by Harrison and Simmonds[29] was used in a modified version. Wedges (500 μm thick) of rat brain containing cerebral cortex and corpus callosum were placed with the cortex part between two layers of absorbent fibre and the corpus callosum part between two other layers of absorbent fibre. The two halves were electrically insulated from each other with a grease gap. The cortical part was constantly perfused with a magnesium-free, oxygenated Krebs buffer to which the compounds tested were added, whereas the corpus callosum part was perfused with a magnesium- and calcium-free Krebs buffer. The two parts were each in contact with an Ag/AgCl electrode through which DC potentials were measured and plotted on a chart recorder.

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