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Synthesis and pharmacology of (*RS*)-2-amino-3-(3-hydroxy-5-trifluoromethyl-4-isoxazolyl)propionic acid, a potent AMPA receptor agonist

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Summary — Three isoxazole bioisosteres of glutamic acid derived from the specific AMPA receptor agonist (*RS*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA) were synthesized and tested electrophysiologically and in different receptor binding systems. (*RS*)-2-Amino-3-(3-hydroxy-5-trifluoromethyl-4-isoxazolyl)propionic acid (trifluoro-AMPA, **8**) showed more potent agonist activity (EC_{50} 2.3 μM) and lower affinity (IC_{50} 0.08 μM) for AMPA receptors than AMPA itself (EC_{50} 3.5 μM and IC_{50} 0.04 μM, respectively). Like AMPA, trifluoro-AMPA (**8**) did not bind significantly to *N*-methyl-D-aspartic acid (NMDA) receptor sites, but trifluoro-AMPA (**8**) was more potent as an inhibitor of [^{3}H]kainic acid ([^{3}H]KAIN) binding (IC_{50} 7.1 μM) than AMPA (IC_{50} 32 μM). (*RS*)-2-Amino-3-(3-chloro-5-methyl-4-isoxazolyl)propionic acid (**14**), the 3-chloro analogue of AMPA, and the isomeric compound (*RS*)-2-amino-3-(3-chloro-4-methyl-5-isoxazolyl)propionic acid (**15**), did not show significant neuroexcitatory effects at or affinities for AMPA, NMDA, or KAIN receptor sites.

excitatory amino acid / AMPA receptors / AMPA receptor agonist / isoxazoles / glutamic acid

Introduction

Receptors for excitatory amino acids (EAAs) are generally subdivided into 3 main classes [1–3], named after ligands, which selectively activate the respective receptors: 1), *N*-methyl-D-aspartic acid (NMDA) receptors; 2), (*RS*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA) receptors; and 3), kainic acid (KAIN) receptors. A fourth and a fifth receptor subtype have been identified, namely 4), L-2-amino-4-phosphonobutyric acid (AP4) receptors, at which AP4 mediates a synaptic depressant action, probably *via* presynaptic receptors [2–4]; and 5), metabotropic receptors coupled to phosphoinositide second messenger mechanisms [5, 6]. The availability of potent and subtype-specific receptor ligands, agonists and antagonists, is of primary importance in order to elucidate structural and functional aspects of these receptors.

As part of our mapping of the structural requirements for activation of AMPA receptors, a number of selective AMPA receptor agonists have previously been reported, including compounds with restricted conformational mobility such as (*RS*)-3-hydroxy-

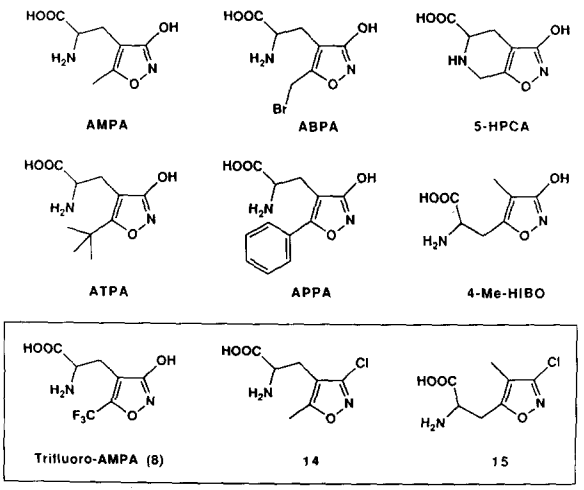


Fig 1. Structures of a number of 3-hydroxyisoxazole amino acids, showing agonist activity or, in the case of APPA, partial agonist activity at AMPA receptors. Below the 3 new compounds are shown: trifluoro-AMPA (**8**), **14** and **15**.

4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridine-5-carboxylic acid (5-HPCA) [7] and analogues containing different alkyl substituents such as (*RS*)-2-amino-3-(3-hydroxy-5-bromomethyl-4-isoxazolyl)propionic acid (ABPA) [7], (*RS*)-2-amino-3-(3-hydroxy-5-*tert*-butyl-4-isoxazolyl)propionic acid (ATPA) [8] and (*RS*)-2-amino-3-(3-hydroxy-5-phenyl-4-isoxazolyl)propionic acid (APPA) [9] (fig 1). The AMPA regioisomer (*RS*)-2-amino-3-(3-hydroxy-4-methyl-5-isoxazolyl)propionic acid (4-methyl-homoibotenic acid, 4-Me-HIBO) (fig 1) is an AMPA agonist, but with somewhat lower potency [10]. Further structural modification of the AMPA molecule has been performed in order to extend the knowledge about structural requirements for potent and specific activation of AMPA receptors.

We here report the synthesis and pharmacological characterization of the trifluoro derivative (*RS*)-2-amino-3-(3-hydroxy-5-trifluoromethyl-4-isoxazolyl)-propionic acid (trifluoro-AMPA, **8**) and structurally related 3-chloroisoxazole analogues, the chloro compounds **14** and **15**. Since the 3-isoxazolol group is a bioisostere of the carboxyl group, **14** and **15** can be regarded as chemically stabile acid chloride isosteres, derived from AMPA and 4-Me-HIBO, respectively (fig 1). These new compounds have been investigated in receptor binding assays and in an *in vitro* electrophysiological model.

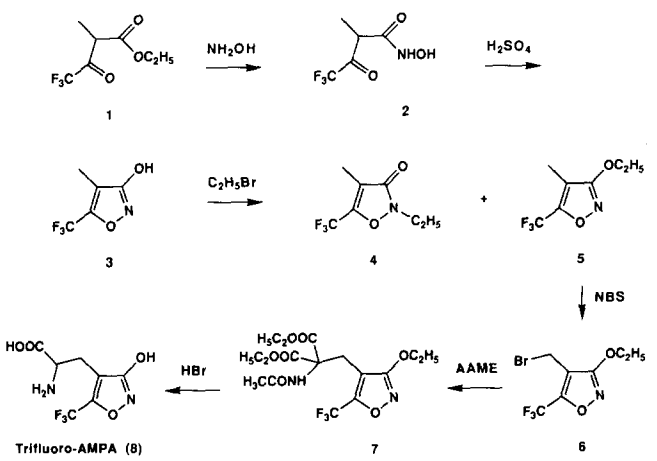
Chemistry

Reaction of ethyl 2-methyl-4,4,4-trifluoroacetoacetate [11] (**1**) with hydroxylamine in aqueous sodium hydroxide gave the β-oxohydroxamic acid **2** (scheme 1). The reaction was terminated by pouring the reaction mixture into concentrated hydrochloric acid. Under similar conditions β-oxohydroxamic acids normally cyclize to give 3-isoxazolols [12, 13]. Cyclization of **2** required harsh conditions, namely 80% sulphuric acid at 75°C for 1 h, which gave 3-hydroxy-4-methyl-5-(trifluoromethyl)isoxazole (**3**) in 49% yield. Alkylation with ethyl bromide in the presence of potassium carbonate in acetone yielded **5**. A product detected by TLC and visualized by UV light (toluene–ethyl acetate 1:1, $R_f = 0.2$), presumed to be compound **4** was not isolated and characterized. NBS bromination of **5** gave compound **6**, which by reaction with the sodium salt of diethyl acetamidomalonate (AAME) (Sorensen synthesis) afforded the acetamidomalonate intermediate **7**. Deprotection and decarboxylation of **7** afforded the final product, trifluoro-AMPA (**8**).

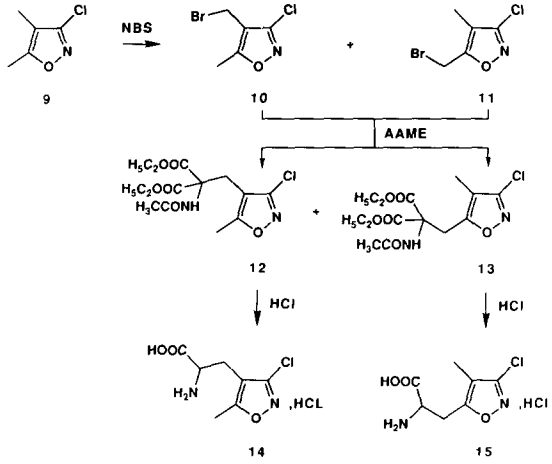
The 2 3-chloroisoxazoles **14** and **15** (scheme 2) was synthesized from compound **9** [14] *via* an NBS bromination and subsequent reaction of the regioisomeric bromomethyl compounds, **10** and **11**, with AAME in a Sorensen synthesis. After separation, the compounds **12** and **13** were deprotected and decarboxylated using 1 M HCl to give the final products **14** and **15** which were isolated as hydrochlorides.

In vitro pharmacology

The new compounds, trifluoro-AMPA (**8**), **14**, and **15**, were examined in 3 different receptor binding assays, using [^{3}H]AMPA [15], [^{3}H]KAIN [16] and [^{3}H]glutamic acid [17] ([^{3}H]GLU) (NMDA-sensitive) as ligands. The results of these binding studies are listed



Scheme 1.



Scheme 2.

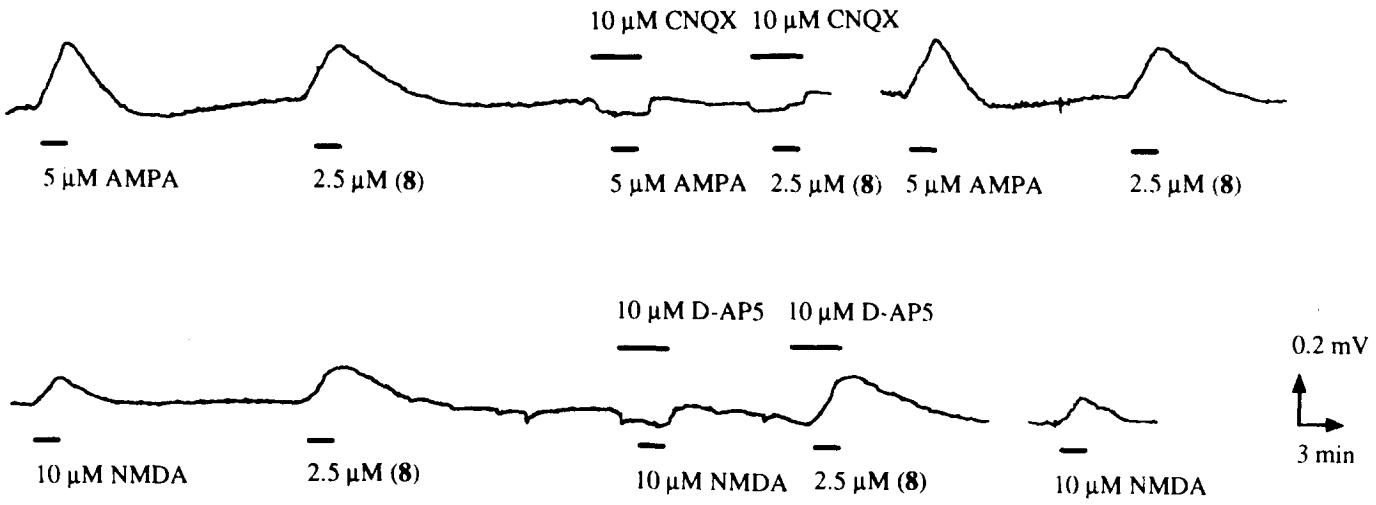


Fig 2. Recordings from cortical slice neurones depolarized by administration of AMPA, trifluoro-AMPA (**8**) and NMDA. The antagonism of these effects by CNQX (top) or D-AP5 (bottom) and recovery are indicated.

in table I. Trifluoro-AMPA proved to be an effective inhibitor of [^{3}H]AMPA binding, whereas it showed no affinity for the NMDA-sensitive [^{3}H]GLU binding site and moderate affinity for the [^{3}H]KAIN site. Neither **14** nor **15** detectably affected the binding of these 3 receptor ligands.

These results are in agreement with those obtained in the rat cortical wedge, an *in vitro* electrophysiological model for the determination of depolarising activity of EAAs [18]. Trifluoro-AMPA was found to be slightly more active than AMPA, and to show a pharmacological profile similar to that of AMPA. Figure 2 illustrates the antagonism of AMPA and trifluoro-AMPA by the selective non-NMDA antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) [19], whereas no sensitivity towards the NMDA antagonist D-2-amino-5-phosphonovaleric acid (D-AP5) [20] was seen. Compounds **14** and **15** did not produce significant depolarising activity at concentrations up to 1 mM, or antagonistic effects (at 500 μM) towards any of the standard agonists NMDA, AMPA, or KAIN.

Table I. Receptor binding (IC_{50} values) and *in vitro* electrophysiological data (EC_{50} values). Mean ± SEM; $n = 4$. nt = not tested. *NMDA-sensitive.

	IC_{50} (μM)			EC_{50} (μM)
	[^{3}H]AMPA	*[^{3}H]KAIN*	*[^{3}H]GLU**	*Electrophys*
AMPA	0.04 ± 0.02	32 ± 12	> 100	3.5 ± 0.2
KAIN	4.0 ± 0.9	0.016 ± 0.004	> 100	nt
Trifluoro-AMPA (**8**)	0.08 ± 0.02	7.1 ± 1.9	> 100	2.3 ± 0.2
14	> 100	> 100	> 100	> 10 000
15	> 100	> 100	> 100	> 10 000

Discussion

Structure–activity studies on AMPA analogues containing different substituents at the 5-position of the isoxazole ring have disclosed that rather large substituents are tolerated in this position (fig 1), without substantial loss of agonist activity at AMPA receptors. Thus, the *tert*-butyl derivative ATPA is a potent and selective AMPA agonist [8, 21]. However APPA, in which the bulky *tert*-butyl group of ATPA has been replaced by a phenyl group, has been shown to be a partial agonist at AMPA receptors [9].

This paper describes trifluoro-AMPA, in which the more polar and electronegative trifluoromethyl group has been substituted for the 5-methyl group in AMPA. This replacement has afforded a compound with very potent AMPA agonist activity, trifluoro-AMPA, which shows slightly weaker affinity than AMPA in [^{3}H]AMPA binding, but more potent AMPA receptor agonism as determined electrophysiologically. This enhanced effect of trifluoro-AMPA may reflect that the trifluoromethyl group exerts a steric effect different from that of the methyl group of AMPA. Alter-

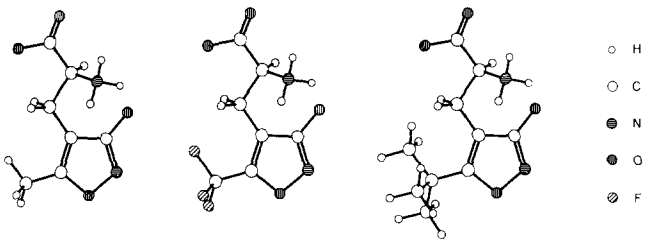


Fig 3. Low-energy conformations of AMPA (left) and ATPA (right) [22], and of trifluoro-AMPA (middle) drawn in a similar conformation. The molecules are depicted as fully charged molecules which are the dominating forms at physiological pH.

natively, or in addition, the more potent agonist effect of trifluoro-AMPA, as compared to that of AMPA, is the result of changes in the electronic properties of the molecule, especially the heterocyclic unit. Low-energy conformations of AMPA and ATPA, identified and described in a previous study and proposed to represent receptor active conformations [22], are depicted in figure 3, and trifluoro-AMPA is drawn in a similar conformation. The steric effects of the 5-trifluoromethyl group are likely to be comparable to the effect exerted by the 5-methyl group of AMPA, suggesting that trifluoro-AMPA can adopt a similar low-energy conformation as described for AMPA and ATPA [22]. The pK_A values determined for trifluoro-AMPA (< 2, 3.4, 9.3), compared to the pK_A values for AMPA (2.5, 4.8, 10.0) [23], show a substantial increase in the acidity of the 3-hydroxyisoxazole group, pK_A 3.4 and 4.8, respectively, for trifluoro-AMPA and AMPA. This suggests that the acidity of this bioisostere of the terminal carboxyl group of GLU is a factor of importance for the biological activity at AMPA receptors, low pK_A value resulting in high agonist activity.

This question was further addressed by preparing the 2 compounds **14** and **15**, in which the 3-hydroxy groups of AMPA and 4-Me-HIBO, respectively have been replaced by chloro atoms. These compounds may be regarded as chemically stabile acid chlorides devoid of terminal acidic groups, but carrying polar chlorine atoms capable of forming hydrogen bonds. The complete lack of affinity of these compounds for EAA receptor sites strongly suggest that a terminal anionic group is essential for affinity for and activity at such receptors.

In conclusion, introduction of a 5-trifluoromethyl group in AMPA has afforded an AMPA agonist (trifluoro-AMPA) with enhanced agonist activity compared to that of AMPA, whereas replacement of the 3-hydroxy groups in AMPA or 4-Me-HIBO by chloro atoms resulted in inactive compounds.

Experimental protocols

Chemistry

Melting points were determined on a Thomas-Hoover–apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet SPC FT-IR or on a Perkin–Elmer 781 IR spectrophotometer as KBr pellets for solids and between NaCl discs for liquids. 300 MHz and 60 MHz ^1H NMR spectra were obtained on a Bruker WM 300 and on a Varian EM 360L spectrometer, respectively, in $CDCl_3$ solutions using TMS as internal standard, unless otherwise indicated. Microanalyses were within ± 0.4% of theoretical values, unless otherwise indicated, and were performed by the Analytical Department, Syntex Research, or by P Hansen, Dept of General and Organic chemistry, University of Copenhagen. The pK_A values were determined as described in [23].

(RS)-2-Methyl-3-oxo-4,4,4-trifluorobutyrohydroxamic acid (2)
To a solution of NaOH (10.4 g; 0.26 mol) in water (150 ml) was added at 0°C a solution of hydroxyalamine hydrochloride (9.0 g; 0.13 mol) in water (150 ml) and then ethyl 2-methyl-4,4,4-trifluoroacetoacetate [11] (**1**) (25.7 g; 0.13 mol). The mixture was stirred at 0°C for 1.5 h and then quickly poured into concentrated HCl (65 ml) at 0°C. After 16 h at 5°C the precipitated **2** (2.75 g) was filtered off. The mother liquor was extracted with ethyl acetate, dried, and evaporated to give further 11.85 g of **2** (total yield of **2**: 61%). An analytical sample was recrystallized (ether): mp 156–157.5°C; IR 3600–2800 (multiple bands, s), 1705–1655 (s), 1435 (m) cm^{-1}; ^1H NMR (300 MHz) δ 11.7 (1H, broad s), 8.4 (1H, broad s), 3.1 (1H, q, J = 7 Hz), 1.0 (3H, d, J = 7 Hz); Anal $C_5H_6F_3NO_3$ (C, H, N).

3-Hydroxy-4-methyl-5-(trifluoromethyl)isoxazole (3)
2 (8.5 g; 46 mmol) was dissolved in a mixture of concentrated H_2SO_4 (85 ml) and water (8.5 ml) and heated at 75°C for 1 h. Water (250 ml) was added to the mixture, which, after cooling to 25°C, was extracted with ether. The dried and evaporated ether phases were subjected to column chromatography (toluene containing ethyl acetate (10–65%) and glacial acetic acid (1%)), which after recrystallization (ethyl acetate) afforded **3** (3.7 g; 49%); mp 52–53.5°C; IR 3300–2400 (multiple bands, w-m), 1675 (w), 1560 (s), 1545 (s), 1505 (m) cm^{-1}; ^1H NMR (300 MHz) δ 2.1 (3H, q, J = 1.7 Hz); Anal $C_5H_4F_3NO_2$ (C, H, N).

3-Ethoxy-4-methyl-5-(trifluoromethyl)isoxazole 5
To a solution of **3** (3.7 g; 22 mmol) in acetone (100 ml) was added K_2CO_3 (6.1 g; 44 mmol). The mixture was stirred at 50°C for 0.5 h, and ethyl bromide was added followed by stirring at 50°C for 16 h. After cooling and filtration, kugelrohr distillation (75°C, 15 mmHg) gave **5** (3.3 g; 76%) as a colorless liquid; IR 2990 (w), 1700 (m), 1530 (s) cm^{-1}; ^1H NMR (300 MHz) δ 4.35 (2H, q, J = 7 Hz), 2.02 (3H, q, J = 1.7 Hz), 1.44 (3H, t, J = 7 Hz); Anal $C_7H_8F_3NO_2$ (C, H, N).

Ethyl 2-acetamido-2-ethoxycarbonyl-3-(3-ethoxy-5-trifluoromethyl-4-isoxazolyl)propionate (7)
A suspension of *N*-bromosuccinimide (NBS) (1.78 g; 10 mmol), benzoyl peroxide (200 mg) and **5** (1.95 g; 10 mmol) in tetrachloromethane (75 ml) was refluxed for 6 h. NBS and benzoyl peroxide were added in quarter portions at 90-min intervals. After cooling, filtration and evaporation, the crude

reaction mixture containing **6** was dissolved in tetrahydrofurane (THF) (25 ml) and added to a dispersion of NaH (400 mg; 10 mmol) and diethyl acetamidomalonate (AAME) (2.17 g; 10 mmol) in THF (50 ml). The reaction mixture was refluxed for 4 h. Upon addition of water, the mixture was extracted with dichloromethane. The dried and evaporated organic phases gave after column chromatography [hexane containing ethyl acetate (15–50%)] and recrystallization **7** (1.31 g; 32%) (ether–light petroleum); mp 102–102.5°C; IR 3220 (m), 2985 (m), 1750 (s), 1645 (s), 1525 (s) cm^{-1}; ^1H NMR (300 MHz) δ 6.55 (1H, broad s), 4.33 (2 x 2H, q, J = 7 Hz), 4.19 (2H, q, J = 7 Hz), 3.52 (2H, d, 0.8 Hz), 1.99 (3H, s), 1.42 (2 x 3H, t, J = 7 Hz), 1.27 (3H, t, J = 7 Hz); Anal $C_{16}H_{21}F_3N_2O_7$ (C, H, N).

*(RS)-2-Amino-3-(3-hydroxy-5-trifluoromethyl-4-isoxazolyl)propionic acid zwitterion (**8**)*

7 (1.2 g; 2.9 mmol) suspended in 48% hydrobromic acid (25 ml) was refluxed for 30 min. The HBr was blown off with a stream of nitrogen, and upon addition of water the mixture was extracted with ethyl acetate. The aqueous phase was evaporated and re-evaporated twice from toluene. The residue was dissolved in water (1 ml), to which ethanol (4 ml) and ethyl acetate (4 ml) were added and pH was adjusted to 5–6 with triethylamine. The precipitate was filtered off and recrystallized (water) to give **8** (390 mg; 56%) mp 220–221°C (dec); IR 3300–2400 (multiple bands, m-s), 1620 (broad, s), 1535 (s), 1500 (s) cm^{-1}. ^1H NMR (300 MHz) D_2O, DMSO–d_6) δ 3.88 (1H, t, J = 5 Hz), 2.90 (2H, d, J = 5 Hz); Anal $C_7H_7F_3N_2O_4$ (C, H, N).

*Ethyl 2-acetamido-2-ethoxycarbonyl-3-(3-chloro-5-methyl-4-isoxazolyl)propionate (**12**) and ethyl 2-acetamido-2-ethoxycarbonyl-3-(3-chloro-4-methyl-5-isoxazolyl)propionate (**13**)*

3-Chloro-4,5-dimethylisoxazole [14] (**9**) (1.3 g; 9.9 mmol) was dissolved in tetrachloromethane (25 ml), NBS (1.8 g; 9.9 mmol) and benzoylperoxide (200 mg) were added and the reaction mixture heated to reflux for 4 h. NBS and benzoylperoxide was added in quarter portions at intervals of 1 h. After cooling, filtration and evaporation, a crude mixture of **10** and **11** was isolated and identified by the signals at δ 2.4 (3H, s) and 4.0 (2H, s), compound **10**, and δ 1.9 (3H, s) and 4.2 (2H, s), compound **11**, in the ^1H NMR spectrum (60 MHz). The crude reaction mixture was dissolved in ethanol (10 ml) and added to a solution of sodium (227 mg; 9.9 mmol) and AAME (2.2 g; 9.9 mmol) in ethanol (25 ml). The reaction mixture was refluxed for 2 h, cooled and evaporated. Water was added and reaction mixture extracted with dichloromethane. The organic phases were washed with ice-cold 1 M NaOH and the aqueous phase extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$), evaporated and recrystallized (ethyl acetate–light petroleum) to give a mixture of **12** and **13**, which after column chromatography (toluene–ethyl acetate 2:1) and recrystallization (toluene–light petroleum) gave **12** (190 mg; 5.5% based on **9**); mp 108.5–109°C; IR 3275 (m), 2975 (broad, m), 1765 (m), 1740 (s), 1630 (broad, s), 1515 (m) cm^{-1}; ^1H NMR (60 MHz) δ 6.66 (1H, s), 4.29 (2H, q, J = 7 Hz), 4.25 (2H, q, J = 7 Hz), 3.46 (2H, s), 2.30 (3H, s), 2.03 (3H, s), 1.28 (2 x 3H, t, J = 7 Hz); Anal $C_{14}H_{19}ClN_2O_6$ (C, H, Cl, N). Further elution and recrystallization gave **13** (160 mg; 4.7% based on **9**); mp 138.5–139°C; IR 3235 (s), 2995–2965 (multiple bands, m), 1745 (s), 1635 (s), 1515 (s) cm^{-1}; ^1H NMR (60 MHz) δ 6.74 (1H, s), 4.30 (2 x 2H, q, J = 7 Hz), 3.84 (2H, s), 2.02 (3H, s), 1.88 (3H, s); 1.30 (2 x 3H, t, J = 7 Hz); Anal $C_{14}H_{19}ClN_2O_6$ (C, H, Cl, N).

*(RS)-2-Amino-3-(3-chloro-5-methyl-4-isoxazolyl)propionic acid, hydrochloride (**14**)*

12 (50 mg; 0.14 mmol) suspended in 1 M HCl (10 ml) was refluxed for 24 h. The evaporated reaction mixture gave after recrystallization (acetic acid) **14** (21 mg; 62%); mp 165–188°C (decomp); IR 3250–2600 (multiple bands, m-s), 1750 (s), 1590 (m) cm^{-1}; ^1H NMR (60 MHz) δ 3.97 (1H, t, J = 6 Hz), 3.01 (2H, d, J = 6 Hz), 2.39 (3H, s); Anal $C_7H_{10}Cl_2N_2O_3$ (C, H, Cl, N).

*(RS)-2-Amino-3-(3-chloro-4-methyl-5-isoxazolyl)propionic acid, hydrochloride (**15**)*

13 (80 mg; 0.23 mmol) suspended in 1 M HCl (10 ml) was refluxed for 24 h. The evaporated reaction mixture gave after recrystallization (glacial acetic acid) **15** (34 mg; 61%); mp 170–190°C (decomp); IR 3200 (m), 3150–2600 (multiple bands, m-s), 1750 (s), 1565 (s) cm^{-1}; ^1H NMR δ 4.26 (1H, t, J = 6 Hz), 3.39 (2H, d, J = 6 Hz), 1.90 (3H, s); Anal $C_7H_{10}Cl_2N_2O_3$ (C, H, Cl, N).

Receptor binding assays

[^{3}H]AMPA, [^{3}]KAIN and NMDA-sensitive [^{3}H]GLU binding studies were performed as described in [15, 16, 17] respectively.

In vitro electrophysiology

A rat cortical slice preparation for testing the depolarizing activity of EAAs described by Harrison and Simmonds [18] 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 2 layers of absorbent fiber ('nappy liner') and the corpus callosum part between two other layers of absorbent fiber. The 2 halves were electrically insulated from each other by a grease gap. The cortical part was constantly perfused with a Mg^{2+}-free, oxygenated Krebs buffer to which the compounds tested were added, whereas the corpus callosum part was perfused with a Mg^{2+}- and Ca^{2+}-free Krebs buffer. The 2 parts were each in contact with an Ag/AgCl electrode through which the DC potentials were measured *via* a DC amplifier and plotted on a chart recorder.

Acknowledgments

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