Supporting Information

Convergent Synthesis and Pharmacology of Substituted Tetrazolyl-AMPA Analogs

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Experimental

Chemistry. General Procedures. All reactions involving air-sensitive reagents were performed under a N_2 atmosphere using syringe-septum techniques, and glassware was dried in an oven at 150 °C and cooled under an atmosphere of N_2 or the glassware was flame dried in vacuo prior to use. Flash chromatography (FC) was performed using silica gel 60 (Millipore A/S, 35-70 μm). Dry column vacuum chromatography (DCVC) was performed on silica gel 60 (Millipore A/S 15-40 μm). Thin-layer chromatography (TLC) was carried out using Merck silica gel 60 F_{254} aluminum sheets. Melting points were determined in open capillary tubes and are uncorrected. All solvents and reagents were purchased from commercial sources and used without further purification, if not otherwise noted. Dry 1,2-dimethoxyethane (DME) and DMF were stored over 4 Å molecular sieves. THF was distilled from Na/benzophenone ketyl under N_2 and stored over 4 Å molecular sieves. *n*-BuLi was titrated using *N*-pivaloyl-*o*-toluidine prior to use. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini or Varian Mercury (300 MHz) spectrometer and chemical shifts are reported in parts per million (ppm) relative to TMS unless stated otherwise. Elemental analyses were performed at Analytical Research Department, H. Lundbeck A/S, Denmark or at the Microanalytical Laboratory, Department of Physical Chemistry, University of Vienna, Austria and were within ±0.4% of the theoretical value unless stated otherwise. Due to the potential hazard, all reactions with tetrazoles were performed with care, and all experiments with azides were performed behind a shield. Excess of sodium azide was oxidized with ceric ammonium nitrate according to general guidelines.[29] Purification of **4a**–**c** and **5a**–**c** was performed on a VYDAC reversed phase HPLC column (10 μm, 22 × 250 mm) equipped with a VYDAC guard column. The column was connected to a Jasco 880

HPLC pump, a Rheodyne 7125 injector equipped with a 5 mL sample loop, and a Waters model 480 or a spectra series 100 UV detector, set at 210 nm, attached to a Hitachi D-2000 Chromato-Integrator. The column was eluted at 10 mL/min with 15 mM acetic acid/CH_3OH (4:1 v/v%). The fractions of interest were pooled and the solvent removed in vacuo followed by evaporation from water (3 × 20 mL).

(*RS*)-2-Amino-3-[3-hydroxy-5-(1-ethyl-1*H*-5-tetrazolyl)-4-isoxazolyl]propionic acid (4a). A solution of **21a** (85 mg, 0.15 mmol) in aqueous HBr (48%, 1 mL) was refluxed in a preheated 140 °C oil bath for 20 min. The solution was cooled, the solvent was removed in vacuo and the residue was evaporated with water (3 × 5 mL). The residue was purified by reversed phase HPLC and recrystallized (water) to give **4a** (24 mg, 60%) as white crystals mp > 220 °C. ^{1}H NMR (D_2O, dioxane): δ 1.56 (t, 3H, *J* = 7.2 Hz), 3.31 (d, 2H, *J* = 6.6 Hz), 4,11 (t, 1H, *J* = 6.6 Hz), 4.76 (q, 2H, *J* = 7.2 Hz). Anal. ($C_9H_{12}N_6O_4$) C, H: calcd, 4.51; found, 4.07; N: calcd, 31.33; found, 30.88.

(*RS*)-2-Amino-3-[3-hydroxy-5-(1-propyl-1*H*-5-tetrazolyl)-4-isoxazolyl]propionic acid (4b). 4b was prepared from **21b** (50 mg, 0.09 mmol) and purified according to the procedure described for compound **4a** to give **5b** (13 mg, 53%) as white crystals: mp > 220 °C. ^{1}H NMR (D_2O, dioxane): δ 0.93 (t, 3H, *J* = 7.2 Hz), 1.98 (sextet, 2H, *J* = 7.2 Hz), 3.34 (d, 2H, *J* = 6.6 Hz), 4,12 (t, 1H, *J* = 6.6 Hz), 4.70 (t, 2H, *J* = 7,2 Hz). Anal. ($C_{10}H_{14}N_6O_4$) C, H, N.

(*RS*)-2-Amino-3-[3-hydroxy-5-(1-isopropyl-1*H*-5-tetrazolyl)-4-isoxazolyl]propionic acid (4c). Compound **4c** was prepared from **21c** (109 mg, 0.22 mmol) by the method described for **4a**. The crude product was purified by reversed

phase HPLC and recrystallized (2-propanol/H_2O) to give **4c** (23 mg, 36%) as white crystals: mp > 220 °C. ^{1}H NMR (MeOD): 1.68 (d, 6H, J = 6.6 Hz), 3.30 (dd, 1H, J_{AB} = 15.3 Hz, J_{AX} = 5.3 Hz), 3.37 (dd, 1H, J_{AB} = 15.3 Hz, J_{BX} = 7.6 Hz), 4.02 (dd, 1H, J_{AX} = 5.3 Hz, J_{BX} = 7.6 Hz), 5.31 (hep, 1H, J = 6.6 Hz). Anal. ($C_{10}H_{14}N_6O_4$) C, H, N.

(*RS*)-2-Amino-3-[3-hydroxy-5-(2-ethyl-2*H*-5-tetrazolyl)-4-isoxazolyl]propionic acid (5a). Experimental procedure according to Scheme 1. A solution of **15** (419 mg, 0.99 mmol) in HCl (6 mL, 6 M in AcOH/H_2O 1:1) was refluxed for 11 h. The solvent was removed in vacuo, and evaporation from water (3 × 5 mL) gave the HCl salt of **5a** as white crystals. Recrystallization (water/EtOH 1:1) by addition of propylene oxide gave **5a** (155 mg, 59%) as white crystals; mp > 220 °C. ^{1}H NMR (D_2O, dioxane, 2 drops of trifluoroacetic acid): δ 1.63 (t, 3H, J = 7.2 Hz), 3.38 (dd, 1H, J_{AB} = 15.2 Hz, J_{AX} = 6.6 Hz), 3.48 (dd, 1H, J_{AB} = 15.2 Hz, and J_{BX} = 6.6 Hz), 4.43 (t, 1H, $J_{AX/BX}$ = 6.6 Hz), 4.80 (q, 2H, J = 7.2 Hz). Anal. ($C_9H_{12}N_6O_4 \cdot 0.8\ H_2O$) C, H, N.

(*RS*)-2-Amino-3-[3-hydroxy-5-(2-propyl-2*H*-5-tetrazolyl)-4-isoxazolyl]propionic acid (5b). 5b was prepared from **22b** (195 mg, 0.34 mmol) and purified according to the procedure described for compound **4a** (recrystallized (water/MeOH)) to give **5b** (87 mg, 92%) as white crystals: mp 215-217 °C (decomp.). ^{1}H NMR (D_2O, dioxane): δ 0.94 (t, 3H, J = 7.2 Hz), 2.09 (sextet, 2H, J = 7.2 Hz), 3.37 (d, 2H, J = 6.7 Hz), 4,13 (t, 1H, J = 6.7 Hz), 4.78 (t, 2H, J = 7.2 Hz). Anal. ($C_{10}H_{14}N_6O_4$) C, H, N.

(*RS*)-2-Amino-3-[3-hydroxy-5-(2-isopropyl-2*H*-5-tetrazolyl)-4-isoxazolyl]propionic acid (5c). 5c was prepared from **22c** (181 mg, 0.38 mmol) and purified according to the procedure described for compound **4a** to give **5c** (92 mg,

0.33 mmol, 87%) as white crystals mp 216-218 °C (decomp.). ^{1}H NMR (MeOD): δ 1.71 (d, 6H, J = 6.6 Hz), 3.32 (dd, 1H, J_{AB} = 15.3 Hz, J_{AX} = 6.0 Hz), 3.45 (dd, 1H, J_{AB} = 15.3 Hz, J_{BX} = 9.0 Hz), 4.02 (dd, 1H, J_{AX} = 6.0 Hz, J_{BX} = 9.0 Hz), 5.24 (hep, 1H, J = 6.6 Hz). Anal. ($C_{10}H_{14}N_6O_4$) C, H, N.

Methyl 3-isopropoxyisoxazole-5-carboxylate (7). Dry potassium carbonate (14.01 g, 101 mmol) was added to a solution of **6**[11] (10.4 g, 72.4 mmol) in dry DMF (50 mL) and the suspension was stirred at 60 °C for 30 min. 2-Bromopropane (20.4 mL, 217 mmol) was added and the suspension was stirred for an additional 4 h. The solution was cooled and water (125 mL) was added. The aqueous phase was extracted with pentane (5 × 150 mL). The combined organic phase was washed with water (5 × 75 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give a colorless oil, that was subjected to DCVC (toluene/EtOAc gradient) to give **7** (11.7 g, 87%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.31 (d, 6H, J = 6.0 Hz), 3.87 (s, 3H), 4.87 (hep, 1H, J = 6.0 Hz), 6.44 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 21.5, 52.5, 73.9, 101.2, 157.1, 159.9, 170.8.

3-Isopropoxyisoxazole-5-carboxamide (8). The ester **7** (11.7 g, 62.9 mmol) was dissolved in aqueous NH_3 (100 mL, 25%) at 0 °C. The solution was stirred for 16 h with slow warming to rt. The solvent was removed in vacuo to give **8** as white crystals (10.4 g, 97%). mp 151-152 °C. ^{1}H NMR ($CDCl_3$): δ 1.40 (d, 6H, J = 6.3 Hz), 4.91 (hep, 1H, J = 6.3 Hz), 6.10 (bs, 1H), 6.46 (bs, 1H), 6.51 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 21.6, 74.0, 99.5, 157.9, 162.4, 170.9. Anal. ($C_7H_{10}N_2O_3$) C, H, N.

3-Isopropoxyisoxazole-5-carbonitrile (9). A solution of **8** (5.02 g, 29.5 mmol) in $POCl_3$ (55 mL) was stirred at 70 °C for 5 h. The solution was concentrated in vacuo to

give a brown oil, and CH_2Cl_2 (200 mL) was added. The solution was carefully poured onto an ice/water mixture (200 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic phase was washed with water (2 × 75 mL), brine (75 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to give a brown oil, which was subjected to Kugelrohr distillation (120 °C, 10 mmHg) to give **9** (3.55 g, 79%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.38 (d, 6H, *J* = 6.0 Hz), 4.94 (hep, 1H, *J* = 6.0 Hz), 6.51 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 21.5, 75.0, 105.7, 108.1, 142.1, 169.9.

5-(3-Isopropoxy-5-isoxazolyl)-1*H*-tetrazole (10). Sodium azide (0.76 g, 11.7 mmol) and triethylamine hydrochloride (1.61 g, 11.7 mmol) were added to a solution of **9** (1.90 g, 12.5 mmol) in DME (30 mL) and the suspension was refluxed for 48 h. The reaction was cooled to rt and the solvent was removed in vacuo, water (100 mL) was added and pH adjusted to 10 with NaOH (2 M). The aqueous phase was extracted with Et_2O (2 × 20 mL). The aqueous phase was acidified to pH 1 with HCl (6 M) which resulted in white precipitation, and was extracted with EtOAc (5 × 125 mL). The combined organic phase was dried ($MgSO_4$) and the solvent removed in vacuo to give **10** (1.72g, 71%) as white crystals. A sample was recrystallized (toluene). ^{1}H NMR ($CDCl_3$): δ 1.46 (d, 6H, *J* = 6.0 Hz), 5.01 (hep, 1H, *J* = 6.0 Hz), 6.76 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 21.6, 74.2, 102.1, 159.6, 160.1, 170.9. Anal. ($C_7H_9N_5O_2$) C, H, N.

5-(3-Isopropoxy-5-isoxazolyl)-2-ethyl-2*H*-tetrazole (12). Potassium carbonate (2.31 g, 16.7 mmol) was added to a solution of **10** (1.63 g, 8.37 mmol) in acetone (20 mL) and the suspension was stirred for 15 min. Ethyl iodide (1.0 mL, 12.6 mmol) was added and the suspension was stirred at rt for 15 h. The solvent was removed in

vacuo, water (50 mL) was added and the aqueous phase was extracted with EtOAc (4 × 60 mL). The combined organic phase was washed with water (10 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give a crude yellow oil. ^{1}H NMR showed a 1:3 mixture of the 1-isomer **11** and 2-isomer **12**. FC (heptane/EtOAc 4:1) gave **12** (1.36 g, 73%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.39 (d, 6H, *J* = 6.6 Hz), 1.68 (t, 3H, *J* = 7.5 Hz), 4.74 (q, 2H, *J* = 7.5 Hz), 4.98 (hep, 1H, *J* = 6.6 Hz), 6.52 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.4, 21.7, 48.9, 73.9, 96.6, 155.9, 159.0, 171.2.

5-(4-Hydroxymethyl-3-isoproproxy-5-isoxazolyl)-2-ethyl-2*H*-tetrazole (13). A solution of **12** (1.366 g, 6.12 mmol) in dry THF (15 mL) was cooled to –78 °C. *n*-BuLi (1.6 M, 4.21 mL, 6.74 mmol) was slowly added to give a dark red solution which was stirred for 10 min. Trioxane (1.65 g, 55.0 mmol) was added and the solution was allowed to warm to 0 °C (yellow solution) over 4 h. The solvent was removed in vacuo, and water was added (30 mL) and the aqueous phase was extracted with Et_2O (4 × 50 mL). The combined organic phase was dried ($MgSO_4$) and the solvent removed in vacuo. FC (heptane/EtOAc 5:1 then 1:1 toluene/EtOAc) gave **13** (406 mg, 26%) as a slightly colored oil. ^{1}H NMR ($CDCl_3$): δ 1.32 (d, 6H, *J* = 6.3 Hz), 1.60 (t, 3H, *J* = 7.2 Hz), 3.71 (bs, 1H), 4.61 (s, 2H), 4.69 (q, 2H, *J* = 7.5 Hz), 4.90 (hep, 1H, *J* = 6.3 Hz). ^{13}C NMR ($CDCl_3$): δ 14.1, 21.5, 48.9, 51.7, 74.0, 111.1, 155.4, 155.5, 169.2.

5-(4-Chloromethyl-3-isopropoxy-5-isoxazolyl)-2-ethyl-2*H*-tetrazole (14). A solution of **13** (544 mg, 2.15 mmol) in $SOCl_2$ (12 mL) was refluxed for 4 h. The solvent was removed in vacuo. FC (toluene/EtOAc 3:1) gave **14** (366 mg, 63%) as colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.46 (d, 6H, *J* = 6.0 Hz), 1.72 (t, 3H, *J* = 7.2 Hz),

4.78 (q, 2H, *J* = 7.2 Hz), 4.80 (s, 2H), 5.04 (hep, 1H, *J* = 6.0 Hz)). ^{13}C NMR ($CDCl_3$): δ 14.3, 21.6, 32.1, 48.9, 74.5, 108.0, 155.4, 155.9, 169.4.

Methyl 2-acetamido-3-[3-isopropoxy-5-(2-ethyl-2*H*-5-tetrazolyl)-4-isoxazolyl]-2-(methoxycarbonyl)propionate (15). Dry dimethyl acetamidomalonate (271 mg, 1.43 mmol) was dissolved in dry DMF (2 mL) and sodium hydride (60% suspension in oil, 62.4 mg, 1.56 mmol) was added. The suspension was stirred at rt for 1 h. A solution of **14** (366 mg, 1.3 mmol) and NaI (catalytic amount) in dry DMF (1 mL) was added. The mixture was stirred at rt for 24 h. The solvent was removed in vacuo, water was added (25 mL) and the aqueous phase was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic phase was washed with water (10 mL) and NaOH (1 M, 10 mL), dried ($MgSO_4$) and the solvent removed in vacuo to furnish a brown oil. The oil was dissolved in Et_2O (20 mL) and washed with water (3 × 50 mL). The combined aqueous phases was extracted with Et_2O (4 × 40 mL). The combined organic phase was dried ($MgSO_4$) and the solvent removed in vacuo. Recrystallization (2-propanol) gave **15** (418 mg, 76%) as yellowish crystals: mp 114-115 °C. ^{1}H NMR ($CDCl_3$): δ 1.43 (d, 6H, *J* = 6.3 Hz), 1.73 (t, 3H, *J* = 7.2 Hz), 1.77 (s, 3H), 3.74 (s, 6H), 3.78 (s, 2H), 4.75 (q, 2H, *J* = 7.2 Hz), 4.99 (hep, 1H, *J* = 6.3 Hz), 6.6 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.3, 21.7, 22.7, 25.1, 48.9, 53.3, 64.9, 74.4, 104.9, 155.7, 156.9, 168.0, 168.9, 170.4. Anal. ($C_{17}H_{24}N_6O_7$) C, H, N.

4-Iodo-3-isopropoxyisoxazole-5-carbonitrile (16). ^{1}H NMR ($CDCl_3$): δ 1.37 (d, 6H, *J* = 6.0 Hz), 4.92 (hep, 1H, *J* = 6.0 Hz). ^{13}C NMR ($CDCl_3$): δ 21.4, 64.7, 76.2, 108.2, 146.2, 170.4.

***tert*-Butyl 2-(*N*,*N*-di-*tert*-butoxycarbonyl)aminoacrylate (17)**. A modification of a previously described procedure[12] was used. 2-*tert*-Butoxycarbonylamino-3-hydroxypropionic acid (12.0 g, 58.5 mmol) was dissolved in dry acetonitrile (120 mL) and DMAP (1.14 g, 9.35 mmol) and di-*tert*-butyl dicarbonate (54.88 g, 251.1 mmol) were added. The colorless solution was stirred for 16 h. More DMAP (0.70 g, 5.7 mmol) was added and stirring was continued for another 8 h and more DMAP (0.20 g, 1.6 mmol) was added followed by a color change to black after 2 h. The reaction was followed by TLC and stirred for another 48 h. The solvent was removed in vacuo and the black sticky residue was partitioned between an aqueous solution of $KHSO_4$ (1 M, 250 mL) and Et_2O (500 mL). The aqueous phase was extracted with Et_2O (2×500 mL) and the combined organic phase was washed with $KHSO_4$ (3×100 mL), $NaHCO_3$ (sat., 3×100 mL), brine (2×100 mL), dried ($MgSO_4$) and the solvent removed in vacuo. DCVC (toluene/EtOAc) gave **17** (7.05 g, 20.5 mmol, 35%) as white crystals: mp 55-56 °C. ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 18H), 1.50 (s, 9H), 5.57 (s, 1H), 6.27 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 27.2, 27.3, 80.7, 81.8, 122.8, 136.7, 149.8, 161.4. Anal. ($C_{17}H_{29}NO_6$) C, H, N.

***tert*-Butyl (*RS*)-2-(*N*,*N*-di-*tert*-butoxycarbonyl)-3-(5-cyano-3-isopropoxy-4-isoxazolyl)aminoacrylate (18).** ^{1}H NMR ($CDCl_3$): δ 1.41 (d, 3H, J = 6.0 Hz), 1.43 (d, 3H, J = 6.0 Hz), 1.47 (s, 18H), 1.48 (s, 9H), 3.15 (dd, 1H, J_{AB} = 14.7 Hz, J_{AX} = 11.4 Hz), 3.24 (dd, 1H, J_{AB} = 14.7 Hz, J_{BX} = 4.21 Hz), 4.90-5.01 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 21.6, 21.8, 22.1, 27.8, 28.0, 56.8, 75.1, 82.1, 83.2, 108.0, 117.1, 140.3, 151.8, 167.7, 168.9.

***tert*-Butyl (*RS*)-2-(*N*,*N*-di-*tert*-butoxycarbonylamino)-3-[3-isopropoxy-5-(1*H*-5-tetrazolyl)-4-isoxazolyl]propionate (19).** ^{1}H NMR ($CDCl_3$): δ 1.42 (m, 24H), 1.49 (s, 9H), 3.15, (dd, 1H, J_{AB} = 14.7 Hz, J_{AX} = 11.4 Hz), 3.24 (dd, 1H, J_{AB} = 14.7 Hz, J_{BX} = 4.21 Hz), 4.98 (hep, 1H, J = 6.0 Hz), 5.18 (dd, 1H, J_{AX} = 11.4 Hz, J_{BX} = 4.21 Hz). ^{13}C NMR ($CDCl_3$): δ 21.6, 21.8, 22.1, 27.8, 28.0, 56.8, 75.1, 82.1, 83.2, 108.0, 117.1, 140.3, 151.8, 167.7, 168.9.

(*RS*)-2-Amino-3-[3-isopropoxy-5-(1*H*-5-tetrazolyl)-4-isoxazolyl]propionic acid (20). Compound **19** (200 mg, 0.37 mmol) was dissolved in Et_2O (0.5 mL) and 6 M HCl (5 mL) was added. The solution was stirred at rt for 14 h and the solvent removed in vacuo. The crude product was purified by reversed phase HPLC to give **20** (98 mg, 0.34 mmol, 94%) as white crystals: mp > 220 °C. ^{1}H NMR (MeOD): 1.45 (d, 6H, J = 6.0 Hz), 3.24 (dd, 1H, J_{AB} = 14.7 Hz, J_{AX} = 6.5 Hz), 3.32 (dd, 1H, J_{AB} = 14.7 Hz, J_{BX} = 3.24 Hz), 4.23 (dd, 1H, J_{AX} = 6.5 Hz, J_{BX} = 3.24 Hz), 4.96 (hep, 1H, J = 6.0 Hz). Anal. ($C_{10}H_{14}N_6O_4$) C, H, N.

***tert*-Butyl (*RS*)-2-(*N*,*N*-di-*tert*-butoxycarbonylamino)-3-[3-isopropoxy-5-(1-ethyl-1*H*-5-tetrazolyl)-4-isoxazolyl]propionate (21a) and *tert*-Butyl (*RS*)-2-(*N*,*N*-di-*tert*-butoxycarbonylamino)-3-[3-isopropoxy-5-(2-ethyl-2*H*-5-tetrazolyl)-4-isoxazolyl]propionate (22a). 21a**: ^{1}H NMR ($CDCl_3$): δ 1.41 (s, 18H), 1.44 (d, 3H, J = 6.0 Hz), 1.45 (d, 3H, J = 6.0 Hz), 1.47 (s, 9H), 1.60 (t, 3H, J = 7.5 Hz), 3.19 (dd, 1H, J_{AB} = 14.4 Hz, J_{AX} = 10.7 Hz), 3.70 (dd, 1H, J_{AB} = 14.4 Hz, J_{BX} = 3.7 Hz), 4.73 (q, 2H, J = 7.5 Hz), 4.96 (hep, 1H, J = 6.0 Hz), 5.20 (dd, 1H, J_{AX} = 10.7 Hz, J_{BX} = 3.7 Hz). ^{13}C NMR ($CDCl_3$): δ 15.5, 21.8, 21.9, 22.0, 27.9, 28.0, 44.7, 57.7, 74.6, 81.6, 82.7, 111.0, 144.0, 151.8, 152.1, 168.3, 170.4. **22a**: ^{1}H NMR ($CDCl_3$): δ 1.39 (s,

18H), 1.43 (d, 3H, J = 6.0 Hz), 1.44 (d, 3H, J = 6.0 Hz), 1.48 (s, 9H), 1.69 (d, 6H, J = 7.2 Hz), 3.42 (dd, 1H, J_{AB} = 14.4 Hz, J_{AX} = 9.3 Hz), 3.47 (dd, 1H, J_{AB} = 14.4 Hz, J_{BX} = 5.5 Hz), 4.74 (q, 2H, J = 7.2 Hz), 4.99 (hep, 1H, J = 6.0 Hz), 5.18 (dd, 1H, J_{AX} = 9.3 Hz, J_{BX} = 5.5 Hz). ^{13}C NMR ($CDCl_3$): δ 14.3, 21.6, 21.7, 27.7, 27.8, 48.6, 57.9, 73.7, 81.2, 82.3, 107.6, 151.6, 154.9, 155.6, 168.4, 170.0.

***tert*-Butyl (*RS*)-2-(*N*,*N*-di-*tert*-butoxycarbonylamino)-3-[3-isopropoxy-5-(1-propyl-1*H*-5-tetrazolyl)-4-isoxazolyl]propionate (21b) and *tert*-Butyl (*RS*)-2-(*N*,*N*-di-*tert*-butoxycarbonylamino)-3-[3-isopropoxy-5-(2-propyl-2*H*-5-tetrazolyl)-4-isoxazolyl]propionate (22b)** were prepared from **19** (308 mg, 0.57 mmol) and propyl iodide (168 μL, 1.72 mmol) according to the procedure described for **21a**/**22a**. According to ^{13}C NMR a 1:4 mixture of the 1-isomer (**21b**) and 2-isomer (**22b**), respectively was obtained. FC (pentane/EtOAc 6:1) gave **21b** (50 mg, 15%) and **22b** (209 mg, 63%) as colorless oils. **21b**: ^{1}H NMR ($CDCl_3$): δ 1.00 (t, 3H, J = 7.5 Hz), 1.41 (s, 18H), 1.44 (d, 3H, J = 6.0 Hz), 1.45 (d, 3H, J = 6.0 Hz), 1.48 (s, 9H), 2.00 (m, 2H), 3.38 (dd, 1H, J_{AB} = 14.7 Hz, J_{AX} = 10.6 Hz), 3.51 (dd, 1H, J_{AB} = 14.7 Hz, J_{BX} = 3.5 Hz), 4.65 (t, 2H, J = 6.9 Hz), 4.96 (hep, 1H, J = 6.0 Hz), 5.20 (dd, 1H, J_{AX} = 10.6 Hz, J_{BX} = 3.5 Hz). ^{13}C NMR ($CDCl_3$): δ 10.9, 21.8, 21.9, 22.1, 23.5, 28.0, 28.0, 50.8, 57.7, 74.6, 81.7, 82.7, 111.1, 144.2, 151.8, 152.2, 168.3, 170.4. **22b**: ^{1}H NMR ($CDCl_3$): δ 1.00 (t, 3H, J = 7.2 Hz), 1.39 (s, 18H), 1.42 (d, 3H, J = 6.0 Hz), 1.43 (d, 3H, J = 6.0 Hz), 1.48 (s, 9H), 2.09 (m, 2H), 3.43 (dd, 1H, J_{AB} = 14.7 Hz, J_{AX} = 12.4 Hz), 3.46 (dd, 1H, J_{AB} = 14.7 Hz, J_{BX} = 2.1 Hz), 4.65 (t, 2H, J = 6.9 Hz), 4.99 (hep, 1H, J = 6.0 Hz), 5.20 (dd, 1H, J_{AX} = 12.4 Hz, J_{BX} = 2.1 Hz). ^{13}C NMR ($CDCl_3$): δ 10.9, 21.8, 21.85, 21.88, 22.8, 27.8, 27.9, 55.0, 58.0, 73.8, 81.4, 82.5, 107.7, 151.7, 155.0, 155.8, 168.6, 170.2.

***tert*-Butyl (*RS*)-2-*tert*-butoxycarbonylamino-3-[3-isopropoxy-5-(1-isopropyl-1*H*-5-tetrazolyl)-4-isoxazolyl]propionate (21c) and *tert*-Butyl (*RS*)-2-*tert*-butoxycarbonylamino-3-[3-isopropoxy-5-(2-isopropyl-2*H*-5-tetrazolyl)-4-isoxazolyl]propionate (22c).**

A solution of **19** (335 mg, 0.62 mmol) and **23** (217 mg, 1.25 mmol) in toluene (6 mL) was refluxed for 16 h. The solvent was removed in vacuo to give **21c** and **22c** in a 1:2 ratio. FC gave **21c** (106 mg, 0.22 mmol, 35%) and **22c** (181 mg, 0.38 mmol, 60%) as colorless oils. **21c**: ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 9H), 1,42 (s, 9H), 1.48 (d, 6H, J = 6.3 Hz), 1.69 (d, 3H, J = 6.6 Hz), 1.70 (d, 3H, J = 6.6 Hz), 3.13 (m, 2H), 4.42 (m, 1H), 5.02 (hep, 1H, J = 6.3 Hz), 5.31 (hep, 1H, J = 6.6 Hz), 5.53 (d, 1H, J = 8.7 Hz). ^{13}C ($CDCl_3$): δ 21.8, 21.9, 22.7, 22.8, 24.6, 27.9, 28.2, 53.2, 53.7, 74.9, 79.3, 81.9, 110.1, 143.6, 152,4, 155.2, 169.8, 170.4. **22c**: ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 9H), 1,36 (s, 9H), 1.43 (d, 6H, J = 6.0 Hz), 1.69 (d, 3H, J = 6.7 Hz), 3.07 (dd, 1H, J_{AB} = 14.4, J_{AX} = 4.6 Hz), 3.14 (dd, 1H, J_{AB} = 14.4 Hz, J_{BX} = 10.4 Hz), 4.39 (m, 1H), 5.00 (hep, 1H, J = 6.0 Hz), 5.14 (hep, 1H, J = 6.7 Hz), 5.46 (d, 1H, J = 8.7 Hz). ^{13}C ($CDCl_3$): δ 21.8, 21.9, 22.2, 22.2, 24.4, 27.8, 28.2, 53.6, 57.3, 74.2, 79.3, 81.5, 106.7, 155.0, 155,2, 155.5, 169.8, 170.6.

***O*-isopropoxy-*S*-propargyl xanthate (23).** According to literature procedures.[13] Sodium hydride (60% suspension in oil, 255 mg, 6.4 mmol) was suspended in dry THF (52 mL) at 0 °C and 2-propanol (0.406 mL, 5.3 mmol) was added and the solution was stirred at rt for 40 min. Carbon disulfide (2.24 mL, 37.1 mmol) was slowly added and the yellow solution was stirred for 2 h. Propargyl bromide (2 mL, 26.5 mmol) was added and the brown milky solution stirred for 4 h. The reaction was

quenched with saturated NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried ($MgSO_4$) and the solvent was removed in vacuo. FC gave **23** (873 mg, 78%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.40 (d, 6H, *J* = 6.0 Hz), 2.22 (t, 1H, *J* = 2.6 Hz), 3.83 (d, 2H, *J* = 2.7 Hz), 5.75 (hep, 1H, *J* = 6.0 Hz). ^{13}C ($CDCl_3$): 21.3, 24.1, 71.5, 77.8, 78.5, 211.0.

In Vitro Pharmacology

Receptor Binding Assays. Affinities for the native AMPA, KA and NMDA receptors were determined using 5 nM [^{3}H]AMPA (55.5 Ci/mmol),[17] 5 nM [^{3}H]KA (58.0 Ci/mmol)[18] and 2 nM [^{3}H]CGP 39653 (K_d = 6 nM, 50.0 Ci/mmol)[19] respectively, with minor modifications as previously described.[30] Rat brain membrane preparations used in the receptor binding experiments were prepared according to a method previously described.[20]

Electrophysiology. A previously described rat cortical wedge preparation, slightly modified, was used for evaluation of the interaction of 5a-c with native iGluRs.

Recombinant Receptor Binding Assays. *Sf9* cells were infected with recombinant baculovirus of rat AMPA receptors ($GluR1_o$-4_o) or rat KA receptors (GluR5 and 6) and membranes prepared and used for binding as previously detailed.[23] The affinities of compounds at GluR1, 2(*R*), 3, and 4 (all as *flop* isoforms) were determined from competition experiments with 2-5 nM [^{3}H]AMPA (55.5 Ci/mmol); at GluR5(*Q*) with 1-2 nM [^{3}H]SYM 2081[31] (K_d = 0.66 ± 0.08 nM (mean ± SD); 50.6 Ci/mmol) and using 5 nM [^{3}H]KA (K_d = 11.9 ± 3.2 nM(mean ± SD); 58.0 Ci/mmol) at GluR6

(*V*,*C*,*R*). Italic letters in parentheses indicate the RNA-edited isoforms of the subunits used.

Molecular Modeling. The X-ray structure of (*S*)-**2** bound to GluR2S1S2J (1M5B.pdb chain[6]) was prepared for docking according to the method recommended in the First Discovery package.[24] Default settings were used throughout, apart from the use of a non-polar radii scaling factor of 0.9. The ligands (*S*)-**2** and compound **5a-c** were built in tri-ionized form, conformationally searched and minimized using MMFFs/GB-SA in Macromodel 9.0, and docked using Glide 3.5[24] again with default settings apart from scaling of non-polar radii by 0.9, although **5b** and **5c** only preferred the binding mode of **2** when docked with scaled van der Waals radii (factor 0.8).