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Supplemental Material for:

2*S*,4*S*-2-Amino-4-(4,4-diphenylbut-1-yl)pentan-1,5-dioic acid is a Potent and Selective Antagonist for Metabotropic Glutamate Receptors Negatively Linked to Adenylate Cyclase.

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Experimental.

All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated; tetrahydrofuran (TIIF) was distilled from sodium benzophenone ketyl prior to use. All reactions were performed under argon. ^{1}H and ^{13}C NMR data were recorded on a Brucker WP-200 (200 MHz). Melting points were determined with a capillary melting points apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Service de Microanalyse du CNRS de Strasbourg. Mass spectra were measured by Service de Masse Spectroscopie du CNRS de Strasbourg. TLC visualization was achieved by spraying with 2% ethanolic phosphomopolybdic and charring, or with ninhydrin (0.5%) solution in n-BuOH/AcOH, 97:3).

(4*S*)-1,1-Dimethylethyl-4-[(*E*)-3'-ethoxy-3'-oxo-1'-propenyl]-2,2-dimethyl-3-oxazolidinecarboxylate (5).

A mixture of aldehyde **4** (13.2 g, 57.9 mmol), triethyl phosphonoacetate (19.43 g, 86.7 mmol, 17.2 ml), n-$Bu_4N^+I^-$ (613 mg 1.66 mmol), and 3 M aqueous K_2CO_3 (26 ml, 78 mmol) was stirred at room temperature for 16 h. The mixture was then diluted with water (40 ml) and extracted with hexane (3 x 20 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give **5** (15.2 g, 88%) as an oil which solidifies on

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standing. Pure **5** could be obtained as a white solid by flash chromatography on silica gel eluting with hexane;ether, 4:1. 5: mp 44°C [α]D +62° (c = 2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.1 Hz, 1H), 1.41 (s, 9H), 1.50 (s, 3H), 1.64 (s, 3H), 3.79 (dd, *J* = 9.1 and 2.3 Hz, 1H), 4.02-4.26 (m, 3H), 4.36-4.55 (m, lH), 5.93 (t, *J* = 11.2 Hz, 1H), 6.83 (dd, *J* = 15.4 and 7.1 Hz, 1H). Anal calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.41; N, 4.67. Found C, 60.44; H, 8.38; N, 4.55.

(4*S*)-1,1-Dimethylethyl-4-[(*E*)-3'-ethoxy-3'-oxo-1'-propyl]-2,2-dimethyl-3-oxazolidinecarboxylate (6).

To a solution of **5** (930 mg, 3.1 mmol) in ethanol (25 ml) was added the catalyst (Pd/C, 10%, 50 mg), and the mixture was shaken in a Parr bottle under hydrogen (60 psi) for 12 hr. After filtration through Celite, the organic phase was evaporated under reduced pressure. The obtained oil was identified as compound **6** (930 mg, 100%), pure enough for the next step. ^1H NMR (200 MHz, $CDCl_3$): δ 1.4 (s, 9H), 1.50 (s, 6H), 1.7-2.1 (m, 2H), 2.1-2.5 (m, 2H), 3.7-4.3 (m, 3H).

(4*S*,2'*S* and 2'*R*)-1,1-dimethylethyl 4-[3'-methoxy-3'-oxo-2'-(4'',4''-diphenylbutyl)-1'-propyl]-2,2-dimethyl-3-oxazolidinecarboxylate (7).

To a solultion of lithium diisopropylamide in THF (20 ml) prepared from n-buthyllithium (5.43 ml, 12.6 mmol, 2.3 M in hexane) and diisopropylamine (14.4 mmol, 2.04 ml) were added at -78°C successively HMPT (6 ml) and after 30 min, dropwise, a solution of oxazolidine **6** (1.8 g, 6 mmol) in THF (15 ml). After 1 h at -78°C, 4-bromo diphenylbutane (3.12 g, 10.8 mmol) in THF (25 ml) was added dropwise. After 1 h at -78°C, the reaction mixture was quenched at room temperature with saturated NH_4Cl. Ether (20 ml) was added, the organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to an oil, purified by column chromatography on silica gel eluting with hexane/ether, 8:2. Compound **7** was isolated as a viscous oil (2.8 g, 91%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.1 Hz, 3H), 1.71-1.73

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(m, 9H), 1.44 (s, 9H), 1.94-2.14 (m, 4H), 2.38-2.55 (m, 2H), 3.66-3.93 (m, 6H), 7.12-7.31 (m, 10H).

Ethyl (2*R* and 2*S*, 4*S*)-2-(4',4'-diphenylbutyl)-4-[(1,1-dimethylethoxy) carbonylamino-5-hydropentanoate (8).

A solution of oxazolidine **7** (553 mg, 1.08 mmol) in absolute ethanol (25 ml) and pyridinium para-toluenesulfonate (280 mg, 1.1 mmol) was refluxed for 3 h. Evaporation of the solvent gave an oily residue which was partitioned between H_2O (15 ml) and ether (10 ml), and the aqueous layer was extracted with ether (2 x 10 ml). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue was purified by column chromatography eluting with hexane/ether, 1:2 to yield **8** as an oil (320 mg, 63%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3H), 1.44 (s, 9H), 1.15-2.39 (m, 10H), 3.47-3.60 (m, 3H), 3.87 (t, J = 7.7 Hz, 1H), 4.07 (q, J = 7.2 Hz, 2H), 4.06 (d, J = 7.5 Hz, 1H), 7.13-7.32 (m, 10 H).

1-Methyl, 5-ethyl (2*R* and 2*S*, 4*S*)-2-(4',4'-diphenylbutyl)-4-[(1,1-dimethylethoxy)carbonyl]aminopentane dioate (9).

A mixture of alcohol **8** (150 mg, 0.32 mmol), DMF 9 6 ml), and pyridinium dichromate (PDC, 720 mg, 1.9 mmol, 6 eq.) was vigorously stirred for 12 h at room temperature. The mixture was then diluted with water (100 ml), acidified to pH 3 with 10% HCl, and extrtacted with ether (3 x 100 ml). The combined extracts were washed with brine and concentrated *in vacuo*. The oily residue was dissolved in MeOH, and then CH_2N_2/ether was added until the color of the solution remained yellow. After 5 h of stirring, excess HOAc was added and the solvent was evaporated *in vacuo*. The residual oil was purified by column chromatography on silica gel eluting with hexane/ether, 1:1 to give **9** as an oil (104 mg, 65%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3H), 1.20-2.48 (m, 9H), 1.42 (s, 9H), 3.71 (s, 3H), 3.87 (t, J = 7.7 Hz, 1H), 4.06 (q, J = 7.2 Hz, 2H), 4.23-4.36 (m, 1H), 4.91 (d, J = 10 Hz, 1H), 7.13-7.32 (m, 10 H).

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(2*S*, 4*S* and 4*R*)-2-Amino-4-(4,4-diphenyl)pentanedioic, hydrochloride (1).

To a solution of compound **9** (380 mg, 0.76 mmol) in THF (15 ml), a 2.5 N aqueous solution of LiOH (4.8 ml, 12 mmol) was added. The mixture was stirred at room temperature for 4 h, then acidified to pH 2 with 1 N HCl solution and extracted with ethyl ether (3 x 10 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give an oily residue which was deprotected with saturated HCl in ethyl acetate for 1 hr at room temperature. After evaporation to dryness, the resulting white solid was triturated with ether to yield **1** (175 mg, 56%); mp. 124°C. ^1H NMR (200 MHz, TFA-d) δ 1.20-2.88 (m, 9H), 3.71 (t, J = 7.5 Hz), 4.18-4.30 (m, 1H), 6.93-7.06 (m, 10H). Anal calcd for $C_{21}H_{25}NO_4$,HCl: C, 64.36; H, 6.43; N, 3.57. Found C, 64.44; H, 6.38; N, 3.55. FAB: 356 (M^++1).

Methyl (2*S*, 4*S*)-1-(*tert*-butylcarbonyl)-4-(4',4'-diphenylpentyl) pyroglutamate (11) and Methyl (2*S*, 4*R*)-1-(*tert*-butylcarbonyl)-4-(4',4'-diphenylpentyl)pyroglutamate (12).

Compound **9** (770 mg, 1.5 mmol) was reacted with trifluoroacetic acid (12 ml) at 0°C for 1 h. Water (5 ml) was added and the mixture was concentrated *in vacuo* to yield an oily residue. Water (30 ml) and a saturated aqueous solution of K_2CO_3 were added until pH 8. The milky solution was extracted with ether (3 x 20 ml) and concentrated *in vacuo*. The resulting oil was purified by column chromatographny eluting with CH_2Cl_2/acetone 85:15 to yield the unprotected amine **10** (550 mg, 90%) directly used in the next step.

A solution of the above free base (514 mg, 1.3 mmol) in toluene (15 ml) was refluxed for 4 h. The solvent was removed *in vacuo* and the obtained residue was immediately dissolved in CH_2Cl_2 (20 ml). To this solution was added triethylamine (0.15 mmol, 0.21 ml), di-t-butyldicarbonate (648 mg, 2.97 mmol), and DMAP (180 mg, 1.49 mmol). The mixture was stirred for 20 h. The solvent was removed *in vacuo*. 1 N HCl was added (20 ml) and the mixture extracted with ether (3 x 20 ml). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated *in vacuo*. Purification of the crude by column chromatography eluting with hexane/ether, 7:3 allowed the separation of the diastereomers. The first eluted compound is the

(2*S*,4*R*) **12** obtained as an oil (220 mg, 35%); $[\alpha]_D$ = -11° (c 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 1.20-1.65 (m, 4H), 1.46 (s 9H), 1.85-2.20 (m, 3H), 2.30-2.60 (m, 2H), 3.76 (s, 3H), 3.84 (t, *J* = 7.8 Hz, 1H), 4.43 (dd, *J* = 7.1 and 8.3 Hz, 1H), 7.10-7.42 (m, 10H).

The second eluted compound is the (2*S*,4*S*) **11** obtained as a solid (250 mg, 40%) mp 101°C; $[\alpha]_D$ -2.6° (c 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.25-1.35 (m, 2H), 1.50 (s 9H), 1.80-2.19 (m, 6H), 2.47-2.61 (m, 1H), 3.76 (s, 3H), 3.89 (t, *J* = 8 Hz, 1H), 4.53 (dd, *J* = 1.5 and 9 Hz, 1H), 7.16-7.31 (m, 10H).

(2*S*,4*S*)-2-Amino-4-(4,4-diphenylbutyl)pentanedioic hydrochloride (2).

To a solution of the pyroglutamate **11** (680 mg, 1.5 mmol) in dimethoxyethane (15 ml) was added a 10% solution in H_2O of LiOH (8 ml, 18 mmol). The mixture was stirred at room temperature for 5 h, then acidified to pH 2 with 1 N HCl solution and extracted with ether (2 x 20 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give an oily residue which was hydrolyzed with a mixture of AcOH (25 ml) and concentrated IICI (12 ml) at room temperature for 2 h. After evaporation to dryness the resulting solid was triturated with a mixture of isopropanol and ether to yield **2** (504 mg, 86%); mp 149°C; $[\alpha]_D$ +9.8° (c 0.5, MeOH); ^1H NMR (200 MHx, MeOH-d4) δ 1.20-1.45 (m, 2H), 1.60-2.18 (m, 6H), 2.72 (m, 1H), 3.81 (t, *J* = 8 Hz, 1H), 4.45 (t, *J* = 7.9 Hz, 1H), 7.10-7.40 (m, 10H). ^{13}C NMR (MeOH-d4), d 178.0, 171.5, 146.4, 129.4, 128.8, 127.1, 52.5, 52.3, 42.5, 36.4, 33.5, 33.4, 26.2. HRMS calcd for $C_{21}H_{26}NO_4$ (M^+ +1-HCl): 356.1862; found 356.1867. Anal calcd for $C_{21}H_{25}NO_4$ HCl: C, 64.36; H, 6.43; N, 3.57. Found C, 64.40; H, 6.45; N, 3.65.

(2*S*,4*R*)-2-Amino-4-(4,4-diphenylbutyl)pentanedioic hydrochloride (3).

The conversion of lactam **12** to amino acid **3** was performed using the above procedure. Analytical data for compound **3** (75%): mp 159°C; $[\alpha]_D$ +21.9° (c 1, MeOH); ^1H NMR (200 MHz, TFA-d); δ 1.20-1.45 (m, 2H), 1.60-2.18 (m, 6H), 2.72 (m, 1H), 3.84 (t, *J* = 8 Hz, 1H), 4.49

(dd, J = 5.8 and 7.9 Hz, 1H), 7.10-7.40 (m, 10H). FAB: 356 (M^++1). Anal calcd for $C_{21}H_{25}NO_4$ HCl: C, 64.36; H, 6.43; N, 3.57. Found C, 64.44;H, 6.45; N, 3.56.

HPLC analysis of compounds 2 and 3

The method of Yamamoto (Donzanti, B.A.; Yamamoto, B.K.; *Life Sci.* **1988**, 43, 913-922.) was used: derivatization of the amino acids **2** and **3** with o-phtalaldehyde and β-mercaptoethanol. The mobile phase was Na_2HPO_4 (0.1 M), Na_2EDTA (0.13 mM) and methanol (28% in water), adjusted at pH 6 with H_3PO_4 (85%). The chromatograph system consisted consisted of a Waters 712 WISP apparatus with an UV detector. The column was a Nucleosil C_{18} (25 cm). The flow rate was 1.2 ml / min.