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(+)-2-METHYL-4-CARBOXYPHENYLGLYCINE (LY367385) SELECTIVELY ANTAGONISES METABOTROPIC GLUTAMATE mGluR1 RECEPTORS

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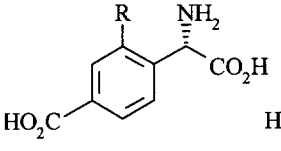
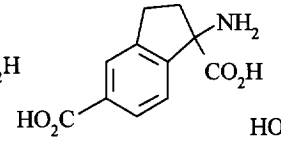
Abstract: The synthesis of three novel 4-carboxyphenylglycine derivatives is described. 2-Methyl substituents increase the antagonist potency compared to (S)-4CPG at mGluR1 receptors. Resolution of compound **1** showed that the activity resided in the (+)-isomer LY367385. © 1997 Elsevier Science Ltd.

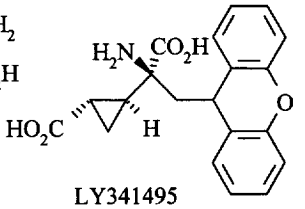
There are currently at least eight distinct metabotropic glutamate receptor proteins (mGluR1-8) which have been divided into three groups based on amino acid sequence homology, signal transduction mechanism, and agonist pharmacology[1]. The group 1 subclass (mGluR1, mGluR5) activates phospholipase C and leads to inositol triphosphate and diacylglycerol formation by phosphoinositide (PI) hydrolysis. Groups 2 and 3 (mGluR2, 3 and mGluR4, 6, 7, 8) are negatively coupled to adenylyl cyclase and their activation leads to decreased intracellular cyclic-AMP levels. Examples of mGluR agonists include (S)-3,5-dihydroxyphenylglycine[2] at group 1; (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid[3] (LY354740) at group 2; and L-2-amino-4-phosphonobutanoic acid[4] at group 3 receptors. Examples of mGluR antagonists include (S)-4-carboxyphenylglycine[5] (S)-4CPG at group 1; LY341495[6] at group 2 and CPPG[7] at group 3 receptors.



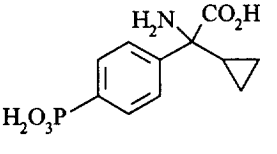
R=H (S)-4CPG
R=Me **1**: LY367385



AIDA



LY341495



CPPG

We report here that addition of 2-methyl substituents to phenylglycines such as (S)-4CPG increase the antagonist potency at mGluR1α receptors. The effect of introducing a methyl group onto 3-hydroxy-4-carboxyphenylglycine at either the 2- or 6-position was also investigated. Previous work on phenylglycines pioneered by the Watkins group has shown that substituents at the α-position, such as α-methyl-4-carboxyphenylglycine[5,8] have similar potency whereas a cyclic analogue AIDA[9] has reduced mGluR1 potency (IC_{50} 214μM[10]).

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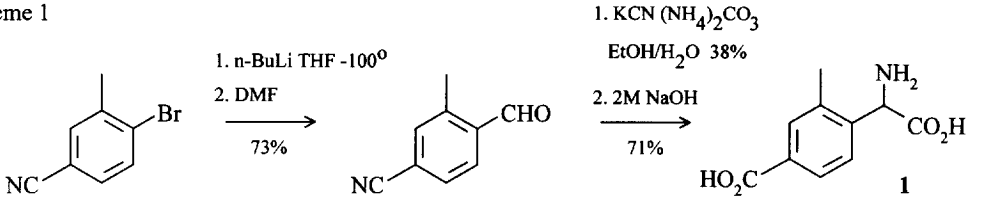
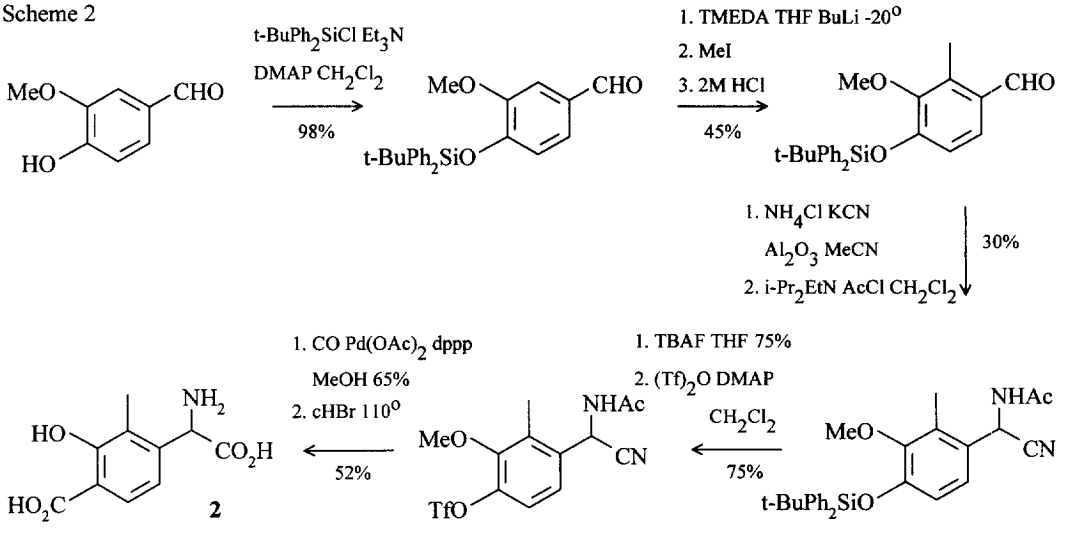
The synthesis of the phenylglycine **1**[11] involved the metallation of 4-bromo-3-methylbenzonitrile with n-butyl lithium in tetrahydrofuran followed by quenching with dimethylformamide, Scheme 1. The resulting 4-cyano-2-methylbenzaldehyde was reacted under Bucherer-Bergs[12] conditions to produce a hydantoin derivative that was hydrolysed in 2M aqueous sodium hydroxide solution at reflux. The phenylglycine **1** was resolved by crystallisation of the salt with D-lysine from water-methanol followed by isolation of (+)-**1** LY367385 (purity >99.5% ee[13]) by ion exchange chromatography. The enantiomer (-)-**1** was similarly obtained using L-lysine with 94.4% ee.

Scheme 1



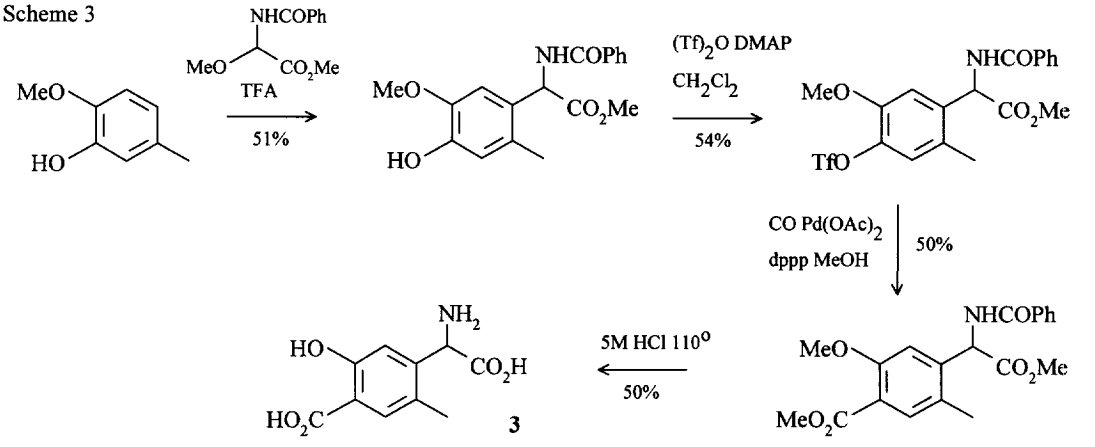
The route to the 1,2,3,4-substitution pattern of phenylglycine **2** involved *in situ* aldehyde protection, lithiation and methylation of 3-methoxy-4-(t-butyldiphenylsilyloxy)benzaldehyde, Scheme 2. This was followed by conversion of the benzaldehyde to an N-acetyl nitrile using the Strecker reaction[14] and subsequent replacement of the 4-triflate by carboxymethyl using palladium catalysed carbonylation[15].

Scheme 2



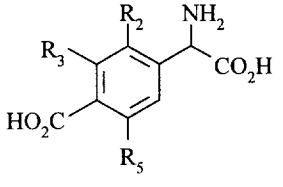
The preparation of the 1,2,4,5-substituted phenylglycine **3** utilised aromatic alkylation of 2-methoxy-5-methylphenol with a glycine cation equivalent[16], Scheme 3. The O-triflate was then formed and carbonylated, followed by hydrolysis in 5M hydrochoric acid at 110° in a sealed tube for 7 days.

Scheme 3



Compounds were tested on funtional responses[8] of human metabotropic glutamate receptor subtypes mGluR1α and mGlu5a expressed in AV-12 cells to obtain IC_{50} values for quisqualate induced PI hydrolysis, Table 1. The introduction of a 2-methyl group onto (S)-4CPG increased potency at mGluR1α receptors by approximately five-fold and improved selectivity compared to mGluR5a. The mGluR1 activity of compound **1** resided in the (+)-enantiomer which presumably has (S)- absolute stereochemistry by comparison with other phenylglycines[17]. Any activity for the (-)-enantiomer of **1** (94.4% ee) could be due to the small percentage of the (+)-isomer present. The 1,2,3,4-substitution pattern of compound **2** was ten-fold more potent than the 1,2,4,5-substitution pattern of compound **3**.

Table 1



R_2	R_3	R_5		PI hydrolysis IC_{50} (μM) mGluR1α	mGluR5a
H	H	H	(S)-4CPG	58 ±14	155 ±3
Me	H	H	**1**	19 ±1.0	>300
Me	H	H	LY367385 (+)-**1**	8.8 ±3.9	>100
Me	H	H	(-)-**1**	>300	>300
Me	OH	H	**2**	6.0 ±2.9	>100
Me	H	OH	**3**	73 ±4.1	>300

The increased potency observed for **1** compared to (S)-4CPG could be due to a reduction in conformational freedom of the glycine unit for rotation about the α-carbon to phenyl-carbon bond. A 2-methyl substituent is insufficient to rigidify the glycine unit relative to the plane of the phenyl ring but would alter the relative population of conformers to favour those in which the amino and acid groups are distant to the methyl group. LY367385 (+)-**1** had no significant effect on group 2 mGluRs (ACPD-sensitive [3H]-glutamate binding assay[18]) up to 100μM concentrations. The position of the 3-hydroxy group of **2** compared to the less potent 5-hydroxy group of **3** suggested that for rotation about the glycine unit, a conformation with the amino acid groups distant from the hydroxy is preferred.

In conclusion LY367385 ((+)-2MCPG) and compound **2** are more potent and selective mGluR1 antagonists than any of the phenylglycines previously reported and thus should be useful as pharmacological tools.

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11. The water soluble amino acids **1-3** were isolated by ion exchange chromatography on Dowex 50X8-100 resin. Selected spectroscopic data for:- **1** ^{1}H NMR (D_2O/NaOD) ∂ 2.44 (3H,s,C$\underline{H}_3$), 4.62 (1H,s,C$\underline{H}$), 7.31 (1H,d,Ar$\underline{H}_6$), 7.68 (1H,d,Ar$\underline{H}_5$), 7.70 (1H,s,Ar$\underline{H}_3$); ^{13}C NMR (D_2O/NaOD) ∂ 21.57 (CH_3), 59.88 (CH), 129.34 (CH), 129.66 (CH), 133.80 (CH), 137.91 (Cq), 139.08 (Cq), 146.51 (Cq), 178.52, 184.06 (2x CO_2H). (+)-**1** $[\alpha]_D^{22}$ = +147° (c=0.26) in aqueous 5M HCl. **2** ^{1}H NMR (D_2O) ∂ 2.30 (3H,s,C$\underline{H}_3$), 5.10 (1H,s,C$\underline{H}$), 6.89 (1H,d,Ar$\underline{H}_6$), 7.75 (1H,d,Ar$\underline{H}_5$); ^{13}C NMR (D_2O) ∂ 13.46 (CH_3), 59.80 (CH), 119.35 (Cq), 120.00 (CH), 126.73 (Cq), 130.72 (CH), 147.28 (Cq), 161.16 (C-CO_2H), 178.56 (2x CO_2H). **3** ^{1}H NMR (D_2O) ∂ 2.40 (3H,s,C$\underline{H}_3$), 5.03 (1H,s,C$\underline{H}$), 6.92 (1H,s,Ar$\underline{H}_6$), 7.70 (1H,s,Ar$\underline{H}_3$); ^{13}C NMR (D_2O) ∂ 57.39 (CH), 117.64 (CH), 120.58 (Cq), 130.64 (Cq), 135.54 (CH), 141.16 (Cq), 160.80 (Cq), 175.70, 177.08 (2x CO_2H).
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