Metabotropic Glutamate Receptors

Molecular Pharmacology

TOCRIS bioscience

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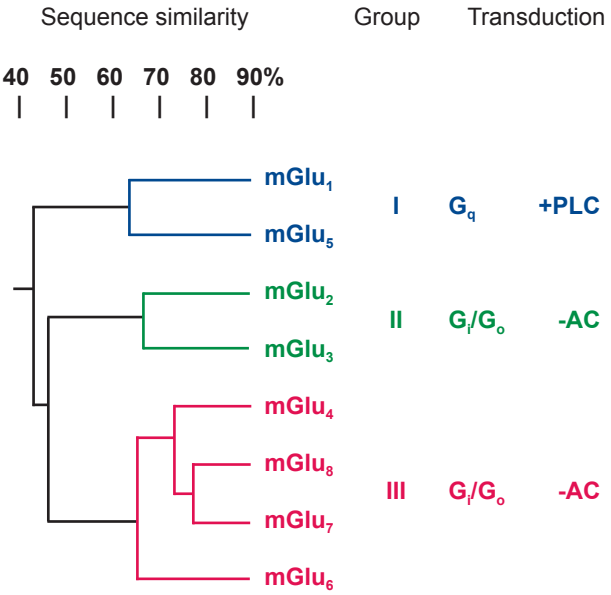
Introduction

Glutamate is the major excitatory amino acid transmitter in the brain. It is released from presynaptic vesicles and activates postsynaptic ligand-gated ion channel receptors (NMDA, AMPA and kainate receptors) to secure fast synaptic transmission.[1] Glutamate also activates metabotropic glutamate (mGlu) receptors, which modulate its release, postsynaptic response, as well as the activity of other synapses.[2,3] Glutamate has been shown to be involved in many neuropathologies such as anxiety, pain, ischemia, Parkinson's disease, epilepsy and schizophrenia. Thus, because of their modulating properties, mGlu receptors are recognized as promising therapeutic targets.[4] It is expected that drugs acting at mGlu receptors will regulate the glutamatergic system without affecting the normal synaptic transmission.

mGlu receptors are G-protein-coupled receptors (GPCRs). Eight subtypes have been identified and classified into three groups (I-III) based upon sequence homology, transduction mechanism and pharmacological profile (see Figure 1). Group I includes $mGlu_1$ and $mGlu_5$ receptors, which couple to G_q and activate phospholipase C (PLC). Group II ($mGlu_2$, $mGlu_3$) and group III ($mGlu_4$, $mGlu_6$, $mGlu_7$ and $mGlu_8$) receptors couple to G_i/G_o and inhibit adenylyl cyclase (AC). Group I receptors are mostly located postsynaptically, thus their activation increases excitability. On the other hand, group II/III receptors are generally presynaptic and their activation reduces glutamate release. Specific ligands have been found for each group and some of the subtypes, as described hereafter.[5,6]

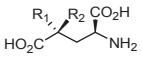
mGlu receptors belong to family 3 of the GPCR superfamily.[7] Similar to all GPCRs, mGlu receptors contain a heptahelical domain (HD) in the membrane region. In addition, like all members of family 3, mGlu receptors are characterized by a large extracellular amino terminal domain (ATD) where

Figure 1 | Classification of the 8 Subtypes of mGlu Receptors

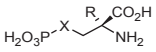


the glutamate binding site is found (see Figure 3). This domain adopts a bilobate structure similar to LIVBP (Leucine Isoleucine Valine Binding Protein), a bacterial periplasmic protein involved in the transport of hydrophobic amino acids;[8-10] these amino acids bind to an open conformation of the protein, which closes subsequently to trap them in between the two lobes. A similar binding mode has been proposed for glutamate and competitive agonists in the LIVBP domain (LIVBPD) of mGlu receptors. Moreover, it was shown that the closed conformation of this domain is required for receptor activation.[11] Examination of the glutamate binding site in the eight mGlu receptor subtype crystal structures ($mGlu_1$)[10] or homology models[12-16] reveals a common binding motif for the α-amino and α-carboxylic functions of glutamate,[17] while residues that bind the distal γ-carboxylate vary

Figure 2 | Competitive mGlu Receptor Ligand Structures



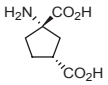
R_1, R_2 = H **L-Glutamic acid**
R_1 = H, R_2 = $CH_2CH(Ph)_2$ ADED (LY 310225)



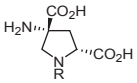
X = CH_2 R = H **(*S*)-AP4**
X = O R = H **(*S*)-SOP**
X = CH_2 R = Me **MAP4**

Ac-Asp-Glu

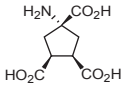
NAAG



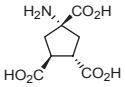
(1*S*,3*R*)-ACPD



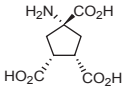
R = H **(2*R*,4*R*)-APDC**
R = CH_2Ph BnAPDC
R = CH_2Naphthyl NM-APDC
R = CO_2H APTC



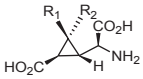
ACPT-I



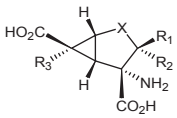
(+)-ACPT-III



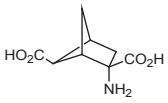
ACPT-II



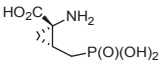
R_1, R_2 = H **L-CCG-I**
R_1 = H, R_2 = 3´-CH_3 3´Me-CCG
R_1 = H, R_2 = 3´-CH_2OH 3´HM-CCG
R_1 = H, R_2 = 3´-CH_2SH 3´SM-CCG
R_1 = H, R_2 = CO_2H **DCG IV**
R_1 = H, R_2 = 9´xanthylethyl XE-CCG-I



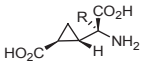
X = CH_2 R_1,R_2,R_3 = H **LY 354740**
X = O R_1,R_2,R_3 = H **LY 379268**
X = S R_1,R_2,R_3 = H LY 389795
X = CH_2 R_1,R_3 = H, R_2 = F MGS0008
X = CH_2 R_1,R_2 = H, R_3 = F LY 354740-6F
X = CO R_1,R_2 = H, R_3 = F MGS0028
X = CH_2 R_2,R_3 = H, R_1 = OH HYDIA
X = CH_2 R_1 = 3,4-Cl_2PhCH_2O
R_2 = H, R_3 = F MGS0039



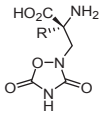
ABHxD-I



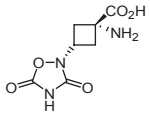
(1*S*,2*R*)-APCPr



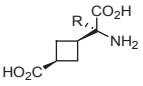
R = Me MCCG-I
R = 9´-xanthylmethyl **LY 341495**
R = $(3\text{-ClPh})_2Et$ mCD-CCG



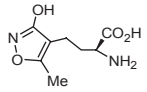
R = H **Quis**
R = benzyl BnQuis



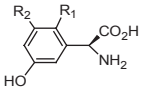
Z-CBQA



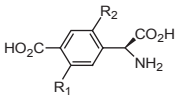
R = 9´thioxanthylmethyl LY 393675



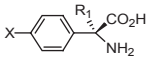
(*S*)-HomoAMPA



R_1 = H, R_2 = OH **(*S*)-3,5-DHPG**
R_1 = Cl, R_2 = H **CHPG**



R_1,R_2 = H **(*S*)-4CPG**
R_1 = CO_2H, R_2 = H **(*S*)-3,4-DCPG**
R_1 = H, R_2 = Me **4C2MPG**
(LY 367385)
R_1 = OH, R_2 = Me 4C3H2MPG
(LY 339840)



X = CO_2H R_1 = Me **(*S*)-MCPG**
X = CO_2H R_1 = 9´-thioxanthylmethyl LY 367366
X = PO_3H_2 R_1 = H (*S*)-PPG
X = PO_3H_2 R_1 = Me **MPPG**
X = PO_3H_2 R_1 = cyclopropyl **CPPG**

Agonists are shown in turquoise
Antagonists are shown in dark blue

(Bold Text Denotes Compounds Available From Tocris)

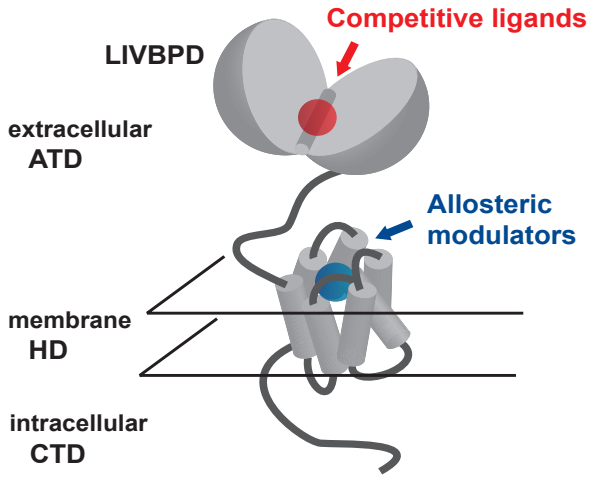
from one subtype to another.[14] Thus, not surprisingly, all competitive agonists are α-amino acids, bearing various selective functional groups on their side chain[6] (see Figure 2). The first generation of orthosteric ligands was followed by a second generation of allosteric modulators that bind in the HD.[18] The first molecule described as a non-competitive mGlu antagonist was CPCCOEt in the late nineties.[19] Since then, numerous allosteric modulators have been discovered by high-throughput screening (HTS) in pharmaceutical companies.[20-22]

The purpose of the present article is to review our actual knowledge of the pharmacology of mGlu receptors. Several detailed reviews[2,3,5,6] have been published; thus only the most potent and selective known ligands will be presented and emphasis will be placed on compounds that were recently disclosed.

Competitive Ligands

An α-amino acid moiety can be found in all mGlu receptor competitive ligands (agonists and antagonists) and most of the side chains hold an acidic function. In the ligand active conformations, the spatial disposition of these functional groups is that of glutamate in an extended conformation, as predicted by pharmacophore[23] and homology models.[14] For many years these compounds have been considered as valuable research tools, but not as drug candidates, because of their poor LogP, related to their highly polar chemical structures. Jim Monn and colleagues from Eli Lilly were the first to show that such a glutamate analog, LY 354740, was able to pass the biological barriers and thus be orally active as an anticonvulsant and anxiolytic.[24] Moreover, such drugs are poorly metabolized as they are already quite hydrophilic[25] and few side effects are predicted. Other glutamate analogs were also shown to be systemically active: (2*R*,4*R*)-APDC, (*S*)-DCPG, 3´Me-CCG, 3´HM-CCG and ACPT-I (Figure 2). Desensitization was also feared with continuous activation in the case of group II/III receptors, yet little was observed after several days of agonist activation. Altogether these results promote a renewed interest in mGlu receptor competitive ligands.

Figure 3 | Schematic Representation of an mGlu Receptor: the Two Orthosteric and Allosteric Binding Sites are Indicated



Agonists (Table 1 and Figure 2)

The first agonist that was able to discriminate between ionotropic and metabotropic glutamate receptors was *trans*-ACPD (1*S*,3*R* isomer).[26] The ligand contributed considerably to the study of metabotropic glutamate receptors despite its lack of subtype selectivity.[2,3,5] A limited number of molecules possess agonist activity across all mGlu receptors. The endogenous agonist L-glutamate, L-CCG-I and ABHxD-I are the most potent.[2,3,5] It can be noted that L-CCG-I and ABHxD-I are conformationally constrained and mimic the bioactive extended glutamate conformation.[23] Selectivity can be gained by adding new chemical groups onto these structures.

Group I

Quisqualate (Quis) is the most potent group I agonist. However, it also activates AMPA receptors, thus its use is restricted. The most popular group I selective agonist is (*S*)-3,5-DHPG, yet it exhibits only moderate potency.[2,3,5] CHPG[27] and *Z*/*E*-CBQA[28] have been claimed to specifically activate $mGlu_5$ receptors, although the affinity of the former is quite low. To date, no specific $mGlu_1$ competitive agonists have been disclosed.

Group II

LY 354740 was the first mGlu agonist reported to exhibit a nanomolar affinity.[24] It is group II selective, as are its oxy (LY 379268) and thia (LY 389795) derivatives.[29] The introduction of a fluorine atom at position 3 (MGS0008) or 6 (LY 354740-6F) retained the potent activity, which was even enhanced when a carbonyl group was added, as in the case of MGS0028.[30] This series of bicyclic glutamate analogs was derived from the general agonist L-CCG-I, where increased potency and group II selectivity was gained through the second hydrocarbon ring. However, it was recently shown that a methyl or hydroxymethyl substituent in the 3´ position (3´Me-CCG and 3´HM-CCG) provided agonists with similar potency.[31,32] Replacement of the hydroxyl functionality at C3´ of 3´HM-CCG, by a sulfydryl results in decreased affinity at $mGlu_{2/3}$. Interestingly, this analog (3´SM-CCG) remains an $mGlu_2$ agonist but is a full antagonist at $mGlu_3$.[33] A similar selectivity was also reported for the C4β-methyl-substituted analog of LY 354740[34]. These two compounds selectively activate $mGlu_2$, while NAAG is the only

reported $mGlu_3$ competitive agonist to discriminate between the two group II subtypes. Other group II selective agonists have been described with submicromolar affinity: (2*R*,4*R*)-APDC and DCG IV.

Group III

Most of the potent group III selective agonists bear a diacidic side chain, which can interact with the highly basic distal binding pocket.[14,16] (*S*)-AP4 (L-AP4), (*S*)-SOP (L-SOP) and (1*S*,2*R*)-APCPr[35,36] are the most potent, displaying submicromolar affinities at cloned receptors, except for $mGlu_7$, to which all bind with weak affinity. (*S*)-PPG,[37,38] (*S*)-3,4-DCPG,[39] ACPT-I and (+)-ACPT-III[40] have also been described as micromolar agonists. Interestingly, a CCG derivative bearing a hydroxymethyl group in the 3´ position

Table 1 | Potencies of Selective and Non-selective mGlu Receptor Agonists[a]

Receptor		Group I		Group II		Group III			
		$mGlu_1$	$mGlu_5$	$mGlu_2$	$mGlu_3$	$mGlu_4$	$mGlu_6$	$mGlu_7$	$mGlu_8$
Non-selective agonists	**L-Glu**[c,d]	1-13	3-11	0.3-12	2-9	3-17	5-38	2300	8-10
	L-CCG-I[c,d]	2	3	0.5	0.4	9	6	230	3
	ABHxD-I[c,d]	2	0.7	0.3	2	23	5	–	–
	(1*S*,3*R*)-ACPD[c,d]	5-80	5-40	7-18	6-17	100-1000	300	n.e.	45-166
Group I subtype-selective agonists	**Quis**[c,d]	0.03-3	0.02-0.3	100-1000	40-220	100-1000	n.e	n.e	720
	(*S*)-3,5-DHPG[c,d]	6	2	n.e.	n.e.	n.e.	–	n.e.	n.e.
	CHPG[c]	> 10000	750	–	–	–	–	–	–
	Z-CBQA[c]	> 1000	11	> 100	–	> 100	–	–	–
Group II subtype-selective agonists	**LY 354740**[b,c]	> 100	> 100	0.01	0.04	> 100	3	> 100	12
	LY 379268[b,c]	> 100	> 100	0.003	0.005	21	0.4	> 100	2
	LY 389795[b,c]	> 100	> 100	0.004	0.008	> 100	2	> 100	7
	MGS0008[e]	> 100	> 100	0.029	0.049	> 100	> 100	> 100	–
	LY 354740-6F[e]	> 100	> 100	0.017	0.081	> 100	> 100	> 100	–
	MGS0028[e]	> 100	> 100	0.0006	0.0021	> 100	> 100	> 100	–
	3´Me-CCG[f]	> 100	> 100	0.008	0.038	> 100	1.198	> 100	1.32
	(+)-3´HM-CCG[g]	> 100	> 100	0.004	0.007	1.8	0.147	> 100	0.010
	2*R*,4*R*-APDC[b,c]	> 100	> 100	0.4	0.4	> 300	110	> 300	> 100
	DCG IV[c,d]	ant.	ant.	0.1-0.4	0.1-0.2	ant.	ant.	ant.	ant.
	NAAG[c,d]	> 300	> 300	134-1000	10-65	> 300	> 300	–	–
Group III subtype-selective agonists	**(*S*)-AP4**[c,d]	> 1000	> 1000	> 1000	> 1000	0.2-1.2	0.6-0.9	160-500	0.06-0.9
	(*S*)-SOP[c,d]	n.e.	n.e.	ant.	ant.	1-4	3	160-1200	2
	(1*S*,2*R*)-APCPr[h]	–	–	–	–	0.6	1.9	602	0.3
	ACPT-I[c,d,i]	ant.	–	n.e.	–	6.5	18.4	–	10.1
	(+)-ACPT-III[c,d,i]	–	–	–	–	8.8	19.2	–	7.0
	(*S*)-PPG[b,j]	> 500	> 500	> 300	> 200	3.2 (5.2)	(4.7)	48 (185)	(0.21)
	(*S*)-HomoAMPA[c]	> 1000	> 1000	> 1000	–	> 1000	58	> 5000	–
	BnAPDC[c]	> 1000	ant.	ant.	> 100	> 300	20	–	> 300
	(*S*)-3,4-DCPG[b,k]	ant.	> 100	> 100	> 100	8.8	3.6	> 100	0.031

(Bold Text Denotes Compounds Available From Tocris)

[a]EC_{50} or K_b values (μM) measured with rat or human (when indicated[b]) cloned receptors. ant. = antagonist; n.e. = no effect. References for agonist potencies that have been cited in reviews [5] and/or [6] are referred to as such. [b]EC_{50} or K_b values (μM) obtained with human mGlu receptors.

[c]Schoepp *et al* (1999)[5] [d]Pin *et al* (1999)[6] [e]Nakazato *et al* (2000)[30] [f]Collado *et al* (2002)[31] [g]Collado *et al* (2004)[32] [h]Kroona *et al* (1991)[35] Sibille *et al* (unpublished results) [i]Bessis *et al* (unpublished results) [j]Gasparini *et al* (1999)[37] and (2000);[38] data in parentheses refer to (±)-PPG[37] [k]Thomas *et al* (2001)[39]

(3´HM-CCG) displays similar affinity for $mGlu_8$ and $mGlu_{2/3}$ receptors.[32] Again, very few compounds are subtype-selective: *N*-benzyl-APDC (BnAPDC)[41] and (*S*)-homoAMPA[42] at $mGlu_6$; (*S*)-3,4-DCPG at $mGlu_8$, with an EC_{50} over two orders of magnitude lower than at other group III receptors.[39] Very recently Faust Pharmaceuticals discovered a selective $mGlu_4$ agonist (FP429) in the APTC family.[43]

Antagonists (Table 2 and Figure 2)

Most of the competitive antagonists prevent the complete closing of the two lobes of the LIVBP domain. Substitution of the α-proton of glutamate analogs by a methyl group as in MCCG, MCPG and MAP4, or a bulkier group as in LY 341495, turns the corresponding agonists (4CPG, AP4 and L-CCG-I) into antagonists. However, agonist properties can be recovered when residues responsible for the hindrance are mutated.[11] Closing can also be disturbed by ionic repulsion as in the case of ACPT-II.[11]

Group I

The first generation of group I mGlu antagonists was composed of 4-carboxyphenylglycine derivatives, such as (*S*)-MCPG, which has been widely used. Its affinity was improved when the α-methyl group was changed to α-thioxanthylmethyl, as in LY 367366, but this derivative is also able to antagonize group II/III receptor activation.[5] The highest potency was then found with α-substituted 3-carboxycyclobutylglycines such as LY 393675 (*cis* isomer) and its *trans* isomer[5] or a *cis*/*trans* mixture (LY 393053).[44] This latter mixture was shown to be systemically active and inhibit both $mGlu_1$ and $mGlu_5$, as well as activate other group II/III mGlu receptors.[44] Although slightly less potent, LY 367385 (4C2MPG) and LY 339840 (4C3H2MPG) display subtype 1 selectivity.[45] However, LY 367385 was also shown to inhibit the cystine/glutamate exchanger.[46] No $mGlu_5$ selective and competitive antagonists have been described.

Group II

As most potent group II agonists are derived from L-CCG-I, the most potent group II antagonists are obtained when aryl substituents are introduced in specific positions of that glutamate analog. Thus

Table 2 | Potencies of Selective and Non-selective mGlu Receptor Competitive Antagonists[a]

Receptor		Group I		Group II		Group III			
		$mGlu_1$	$mGlu_5$	$mGlu_2$	$mGlu_3$	$mGlu_4$	$mGlu_6$	$mGlu_7$	$mGlu_8$
Non-selective antagonists	**LY 341495**[b,c,i]	6.8-9.7	8.2	0.021	0.014	2.6-22	1.1-1.8	0.99	0.17
	LY 393053[b,e]	1.0	1.6	3.0	–	> 100	–	20	3.0
	ACPT-II[d]	115	–	88	–	77	–	–	123
Group I subtype-selective antagonists	**LY 367385**[b,f]	8.8	> 300	> 300	–	> 300	–	–	–
	LY 367366[b,c]	6.6	5.6	–	–	–	–	–	–
	LY 339840[b,f]	7.5	140	> 300	–	> 300	–	–	–
	(*S*)-MCPG[c,d]	40-320	195-460	15-340	300-1000	> 1000	> 100	> 1000	> 300
Group II subtype-selective antagonists	ADED[b,c]	> 300	> 300	18	6.1	> 300	–	> 300	> 300
	(*S*)-BnQuis[b,c]	300	300	7.1	–	n.e.	n.e	–	–
	mCD-CCG[g]	43	49	0.007	0.010	–	–	–	1.8
	HYDIA[h]	> 100	> 100	0.105	0.102	22	–	–	15
	MSG0039[i]	> 100	–	0.020	0.024	1.7	2.1	–	–
	NMAPDC[b,c]	> 300	> 300	20	8.6	> 300	–	–	> 300
	XE-CCG[b,j]	–	–	0.20	0.075	–	–	–	–
Group III subtype-selective antagonists	**DCG IV**[d]	390	630	ago.	ago.	22	40	25-40	15-32
	MAP4[c,d]	n.e.	–	500	–	90-190	–	–	25-105
	CPPG[b,c,k]	–	–	–	–	12	4	17	11
	MPPG[c,d]	> 1000	n.e.	11-320	–	54-110	480	300	20-50

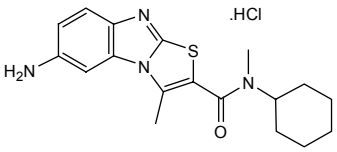
(Bold Text Denotes Compounds Available From Tocris)

[a]IC_{50} or K_b values (μM) measured with rat or human (when indicated[b]) cloned receptors. ago. = agonist; n.e. = no effect. References for antagonist potencies that have been cited in reviews [5] and/or [6] are referred to as such.
[b]IC_{50} or K_b values (μM) obtained with human mGlu receptors.

[c]Schoepp *et al* (1999)[5] [d]Pin *et al* (1999)[6] [e]Chen *et al* (2000)[44] [f]Kingston *et al* (2002)[45] [g]Sørensen *et al* (2003)[48] [h]Adam *et al* (1999)[51] [i]Chaki *et al* (2004)[49] [j]Pellicciari *et al* (2001)[47] [k]Conway *et al* (2001);[52] Naples and Hampson (2001);[117] Wright *et al* (2000)[54]

YM 298198, Selective $mGlu_1$ Antagonist

YM 298198
Cat. No. 2448



YM 298198 is a newly characterized, non-competitive antagonist with high affinity and selectivity for $mGlu_1$ receptors (K_i = 19 nM). The compound is inactive at other mGlu receptor subtypes ($mGlu_{2-7}$), ionotropic receptors and glutamate transporters at concentrations up to 10 µM. YM 298198 inhibits glutamate-induced IP production more potently than CPCCOEt (IC_{50} values are 16 nM and 6.3 µM respectively), and is orally active *in vivo*, demonstrating an antinociceptive effect in hyperalgesic mice.

Kohara *et al* (2005) Radioligand binding properties and pharmacological characterization of 6-Amino-*N*-cyclohexyl-*N*,3-dimethyl-thiazolo[3,2-*a*]-benzimidazole-2-carboxamide (YM-298198), a high-affinity, selective and noncompetitive antagonist of metabotropic glutamate receptor type 1. J.Pharmacol.Exp.Ther. ***315*** 163.

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LY 341495[5] and XE-CCG[47], containing a 9´-xanthylmethyl or 9´-xanthylethyl moiety in the α- or 3´-position, display nanomolar affinities. Potency is retained when the α-xanthyl moiety is replaced by two substituted phenyl groups (e.g. mCD-CCG).[48] It was recently reported that MGS0039 also exhibited high competitive group II antagonist activity.[49,50] The addition of a dichlorobenzyl group to a close analog of HYDIA[51] notably increases its affinity. MGS0039 and HYDIA are derivatives of the well-known agonist LY 354740. Indeed, it was previously demonstrated that substitution at the 3-position of the bicyclohexane is critical for agonist/antagonist properties.[14] Systemic and antidepressant-like effects were observed with both LY 341495 and MGS0039.[49] Other arylalkyl-substituted glutamate analogs such as ADED (LY 310225), (*S*)-BnQuis and NM-APDC display group II selectivity with IC_{50} values in the micromolar range.[5]

Group III

Highly potent and group III-selective competitive antagonists have not yet been reported. The best agonist (*S*)-AP4 becomes a moderate antagonist when its α-proton is substituted by a methyl group, in MAP4. MCPG, a weak group I/II antagonist, becomes a moderate group III antagonist when the 4-carboxylate is replaced by a phosphonate, in MPPG. Addition of a substituent in the 3-position leads to a similar group III antagonist activity but increases selectivity for group III over group II.[52] CPPG, the analog of MPPG bearing an α-cyclopropyl group, exhibits slightly increased potency[5,52] in the same range as DCG IV, which is also a group II agonist.[53] Thus, the best activity is found with the non-selective antagonist LY 341495.[54]

Allosteric Modulators

Allosteric modulators are non-competitive ligands that bind in the transmembrane heptahelical domain (HD). Negative and positive modulators have been identified.[20-22] Negative modulators inhibit receptor activation without affecting agonist binding, while positive modulators enhance agonist activation but do not activate receptors alone. Among the numerous mGlu receptor modulators that have been described (mostly in patents), only those for which biological activities are available will be presented here. These compounds are generally highly potent and subtype-selective, which is not the case for most competitive ligands.

Group I (Figure 4)

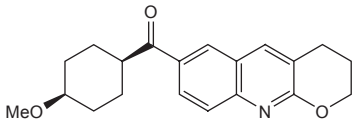
Both non-competitive inhibitors and enhancers have been disclosed for group I receptors.

$mGlu_1$ Antagonists

Detailed studies have been devoted to CPCCOEt, the first negative mGlu receptor modulator.[19,55,56] In particular, specific residues of the HD that bind to CPCCOEt were identified by a group from Novartis.[19] Following this, other compounds with higher affinities were discovered by HTS and subsequent optimization, in various companies: NPS2390[57,58] (NPS Pharma Inc.), BAY 36-7620[59] (Bayer AG), LY 456066[60,61] (Eli Lilly), R214127[58]/JNJ 16259685[62,63] (Johnson & Johnson), 3,5-dimethyl-pyrrole-2,4-dicarboxylic acid diesters of which DM-PPP is the most potent derivative[64] (GlaxoSmithKline), several analogs of

JNJ 16259685, Highly Potent $mGlu_1$ Antagonist

JNJ 16259685
Cat. No. 2333



JNJ 16259685 is a non-competitive $mGlu_1$ antagonist (K_i = 0.34 nM) that exhibits low nanomolar potency. It inhibits glutamate-induced Ca^{2+} mobilisation at the human $mGlu_1$ receptor with an IC_{50} value of 1.21 nM and is approximately 6000 times more potent than CPCCOEt and 50 times more potent than BAY 36-7620. The antagonist is selective over $mGlu_5$ (> 400-fold) and displays no activity at $mGlu_2$, $mGlu_3$, $mGlu_4$, $mGlu_6$, AMPA or NMDA receptors (IC_{50} > 10 µM). JNJ 16259685 is centrally active following systemic administration.

Lavreysen *et al* (2004) JNJ16259685, a highly potent, selective and systemically active mGlu1 receptor antagonist. Neuropharmacology ***47*** 961. **Mabire** *et al* (2005) Synthesis, structure-activity relationship, and receptor pharmacology of a new series of quinoline derivatives acting as selective, noncompetitive mGlu1 antagonists. J.Med.Chem. ***48*** 2134.

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EM-TBPC[65,66] (Hoffmann-La Roche) and recently YM 298198[67] (Yamanouchi Pharma) and tri-azafluorenones[68] (Abbott Laboratories). A homology model of the $mGlu_1$ allosteric binding site has been generated and a binding mode proposed for EM-TBPC, which has been validated by mutagenesis and functional assays.[65] Additionally, it was shown that several inhibitors (R214127, CPCCOEt, NPS2390 and BAY 36-7620) bind to this same site.[58] Promising anxiolytic and analgesic effects have been reported with allosteric $mGlu_1$ receptor antagonists. However, cognition impairment was also found with JNJ 16259685.[69]

$mGlu_1$ Positive Modulators

The first allosteric potentiators of rat $mGlu_1$ receptors to be disclosed were Ro 01-6128, Ro 67-4853[70] and Ro 67-7476.[71,72] Chimeric and mutated receptors were constructed to confirm the transmembrane localization of the binding site of these ligands, which are subtype 1 selective.[71] Interestingly, Ro 67-7476 and Ro 01-6128 have little or no effect on human $mGlu_1$ receptor activation while Ro 67-4853 produces a pronounced enhancement.[71]

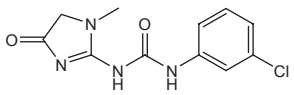
$mGlu_5$ Antagonists

SIB 1757 and SIB 1893[73] were initially found and optimized into MPEP,[74] which has been widely used[75] to explore the physiological roles of $mGlu_5$ receptors as a potential therapeutic target. Further investigations led to a methoxy derivative M-MPEP that can easily be radiolabeled.[76] More recently MTEP, a pyridine derivative of MPEP with improved aqueous solubility, was described with similar high $mGlu_5$ affinity[77] as well as its radiolabeled methoxymethyl derivative MM-MTEP,[78,79] M-PEPy[78] and bipyridyl derivative MTEB.[80] The Merck group also disclosed new families of potent $mGlu_5$ antagonists: aryl benzoxazoles[81] (illustrated by BOMA), heteroarylazoles[82] (such as tetrazole PTeB[82] and its derivatives,[83,84] dipyridyl amides[85] and dipyridyl amines[86]). Recently it was demonstrated that the known anxiolytic drug fenobam was, in fact, a potent non-competitive $mGlu_5$ antagonist.[87] MPEP and derivatives were shown to exhibit anxiolytic effects in animal models.[75,82] Additionally, molecular determinants of the high affinity binding site of MPEP have been defined;[88] a striking similarity with critical residues of the $mGlu_1$ binding site was observed.

Fenobam, Selective $mGlu_5$ Antagonist

Fenobam

Cat. No. 2386



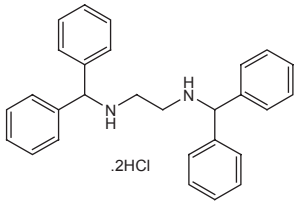
Fenobam is a potent and selective non-competitive $mGlu_5$ antagonist that displays inverse agonist activity. It blocks $mGlu_5$ constitutive activity *in vitro* with an IC_{50} value of 87 nM. Fenobam acts at an allosteric modulatory site shared with MPEP and binds the receptor with K_d values of 54 and 31 nM for rat and human receptors respectively. The compound displays anxiolytic activity following oral administration *in vivo*.

Porter *et al* (2005) Description of a clinically validated anxiolytic with mGlu5 antagonist properties. Neuropharmacology ***49*** (Suppl. 1) 267. **Porter** *et al* (2005) Fenobam: a clinically validated nonbenzodiazepine anxiolytic is a potent, selective, and noncompetitive mGlu5 receptor antagonist with inverse agonist activity. J.Pharmacol.Exp.Ther. ***315*** 711.

AMN 082, The First $mGlu_7$-Selective Agonist

AMN 082

Cat. No. 2385



AMN 082 is the first selective $mGlu_7$ agonist. It potently inhibits cAMP accumulation and stimulates GTPγS binding in recombinant cells and on membranes expressing $mGlu_7$ (EC_{50} = 64 - 290 nM). AMN 082 is selective over other mGluR subtypes and selected ionotropic glutamate receptors up to 10 μM. The agonist acts via a novel allosteric site and is orally active and brain penetrant.

Flor *et al* (2005) AMN082, the first selective mGluR7 agonist: activation of receptor signaling via an allosteric site in the transmembrane domain modulates stress parameters *in vivo*. Neuropharmacology ***49*** (Suppl. 1) 244. **Mitsukawa** *et al* (2005) A selective metabotropic glutamate receptor 7 agonist: Activation of receptor signaling via an allosteric site modulates stress parameters *in vivo*. Proc.Natl.Acad.Sci.USA ***102*** 18712.

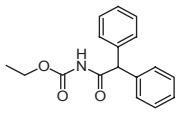
$mGlu_5$ Positive Modulators

Two $mGlu_5$ potentiators, DFB[89] and CPPHA,[90] were first identified by the Merck group. It should be noted that replacing the fluorine atoms of DFB with methoxy substituents turns this ligand into an antagonist (DMeOB),[89] while dichlorobenzaldazine (DCB) is a neutral modulator that attenuates the potentiation conferred by DFB.[89] Similar modulations were found with close analogs of MPEP; moving the methyl substituent of the MPEP pyridyl ring to the neighbouring carbon turns this analog (5MPEP) into a neutral modulator.[91] Thus, it is suggested that the positive allosteric binding site overlaps the negative one.

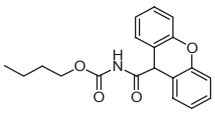
New series of $mGlu_5$ positive modulators (diphenylpyrazolebenzamide CDPPB[92,93] and oxadiazol ADX47273[94,95]) demonstrated anti-psychotic effects in animal models of schizophrenia.

Figure 4 | Group I Allosteric Modulator Structures and Potencies

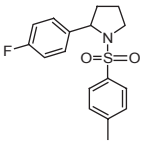
A. $mGlu_1$ Receptor Potentiators



Ro 01-6128
EC_{50} = 0.2 μM

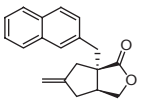


Ro 67-4853
EC_{50} = 0.07 μM

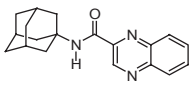


Ro 67-7476
EC_{50} = 0.2 μM

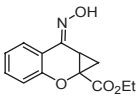
B. $mGlu_1$ Receptor Antagonists



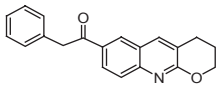
BAY 36-7620
IC_{50} = 160 nM
K_i = 11.2 nM



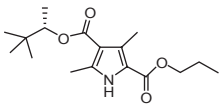
NPS2390
IC_{50} = 5.2 nM (chimera CaSR/$mGlu_1$)
K_i = 1.4 nM



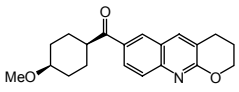
CPCCOEt
IC_{50} = 10.3 μM
K_i = 4.9 μM
((-) isomer active)



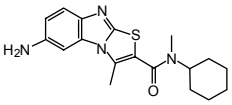
R214127
IC_{50} = 21.6 nM
K_i = 1.4 nM



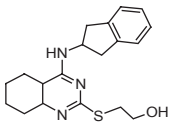
DM-PPP
IC_{50} = 16 nM



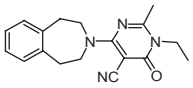
JNJ 16259685
IC_{50} = 3.24 nM
K_i = 0.34 nM



YM 298198
IC_{50} = 16 nM
K_i = 19 nM

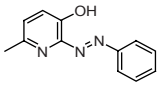


LY 456066
IC_{50} = 12 nM ($hmGlu_1$)

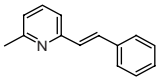


EM-TBPC
K_i = 11 nM

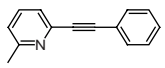
C. $mGlu_5$ Receptor Antagonists



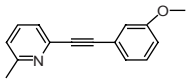
SIB 1757
IC_{50} = 0.37 μM ($hmGlu_5$)



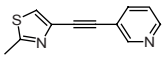
SIB 1893
IC_{50} = 0.29 μM ($hmGlu_5$)



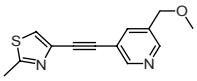
MPEP
IC_{50} = 36 nM ($hmGlu_5$)



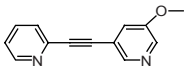
M-MPEP
IC_{50} = 10 nM ($hmGlu_5$)



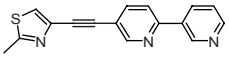
MTEP
IC_{50} = 5 nM ($hmGlu_5$)



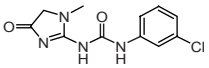
MM-MTEP
IC_{50} = 7 nM ($hmGlu_5$)



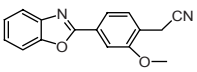
M-PEPy
IC_{50} = 1 nM ($hmGlu_5$)



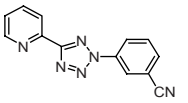
MTEB
IC_{50} = 2 nM ($hmGlu_5$)



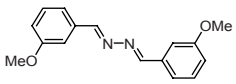
Fenobam
IC_{50} = 58 nM



BOMA
IC_{50} = 3 nM

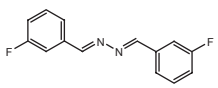


PTeB
IC_{50} = 0.07 μM ($hmGlu_5$)

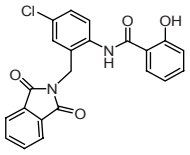


DMeOB
IC_{50} = 3 μM ($mGlu_5$)
IC_{50} = 35 μM ($mGlu_4$)
IC_{50} = 50 μM ($mGlu_8$)

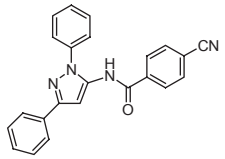
D. $mGlu_5$ Receptor Potentiators



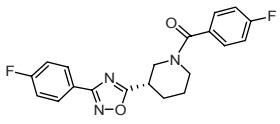
DFB
EC_{50} = 2.4 μM ($mGlu_5$)



CPPHA
EC_{50} = 0.14 μM ($mGlu_5$)

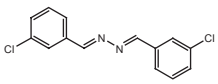


CDPPB
EC_{50} = 27 nM ($hmGlu_5$)

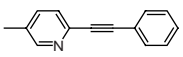


ADX47273

E. $mGlu_5$ Receptor Neutral Modulators



DCB
IC_{50} = 2.6 μM for DFB potentiation attenuation



5MPEP
EC_{50} = 2.32 μM for blocking MPEP inhibition
IC_{50} = 1.71 μM for DFB and CDPPB potentiation attenuation

(Bold Text Denotes Compounds Available From Tocris)

Group II (Figures 5A and 5B)

$mGlu_2$ Antagonists

Heterocyclic enol ethers such as Ro 64-5229 were reported as the first selective non-competitive $mGlu_2$ receptor antagonists.[96,97] A series of dihydro-benzo[b][1,4]diazepin-2-one derivatives, typified by CH-DBO, was later claimed also to contain $mGlu_2$ receptor antagonists with nanomolar affinities.[98]

$mGlu_2$ Positive Modulators

LY 487379, a pyridylmethylsulfonamide, has been reported to potentiate the activity of glutamate at $mGlu_2$ receptors with an EC_{50} of 0.3 μM and be highly selective for this subtype.[99] It was also demonstrated that LY 487379 binds to a pocket in the transmembrane domain that is different from the orthosteric site in the ATD.[99] Further SAR studies led to the discovery of the 1-methylbutoxy analog (2,2,2-TEMPS) with improved potency (EC_{50} = 14 nM) and selectivity.[100,101] Recently, a new chemical series of phenyl-tetrazolyl acetophenones (e.g. PTBE) was disclosed as selective $mGlu_2$ potentiators,[102] followed by extensive SAR studies.[103-107] Both types of potentiators showed *in vivo* activity.[106,108]

$mGlu_3$

No specific allosteric modulators have yet been reported in the literature for this mGlu receptor subtype. Yet, a benzotriazole derivative of PTBE was noted to potentiate both $mGlu_2$ and $mGlu_3$ receptors.[106]

Group III (Figures 5C, 5D and 5E)

To date, very few group III modulators have been disclosed. These include $mGlu_4$, $mGlu_7$ and $mGlu_8$ potentiators. PHCCC was initially described as an $mGlu_1$ receptor antagonist.[55] However, it was recently found that its (-) enantiomer potentiates $mGlu_4$ receptor activation.[109,110] Two other $mGlu_5$ antagonists SIB 1893 and MPEP were reported to enhance agonist potency and efficacy at human $mGlu_4$ at higher concentrations.[111] Recently, potentiators of $mGlu_7$ (AMN 082 from Novartis)[112] and $mGlu_8$ (Thiomethylanilide A and B from NPS Pharmaceuticals)[113] were disclosed.

Radiolabeled Ligands and PET Radiotracers

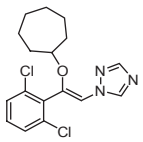
Several of the potent mGlu ligands have been radiolabeled: Quis, DCG-IV, LY 354740, (*S*)-AP4, (*S*)-DCPG, LY 341495, CPPG, EM-TBPC, R214127, LY 456066, MPEP and MMTEP. Some mGlu receptor ligands have been labeled with carbon-11 or fluorine-18 and used for PET imaging.[114-116]

Conclusion

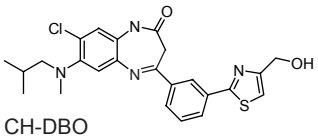
In the last few years some interesting new competitive ligands have been discovered, such as the selective $mGlu_8$ receptor agonist (*S*)-3,4-DCPG. However, the largest advances in mGlu receptor pharmacology have been made with allosteric modulators. These compounds are generally highly potent and selective. Moreover, many of them display *in vivo* activity and open the way to new therapeutic agents. Although some further subtype-selective compounds are still awaited, particularly for group III mGlu receptors, the panel of available mGlu receptor ligands is now rather broad and is allowing investigators to shed important new light on the physiological and pathological roles of the various mGlu receptor subtypes in the normal and diseased brain. This is currently ongoing in many laboratories and we anticipate watching the results unfold with great interest.

Figure 5 | Group II and Group III Allosteric Modulator Structures and Potencies

A. $mGlu_2$ Receptor Antagonists

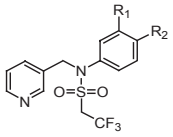


Ro 64-5229
IC_{50} = 109 nM

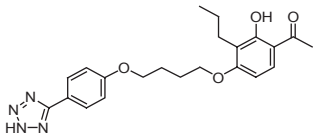


CH-DBO
K_i = 3 nM

B. $mGlu_2$ Receptor Potentiators

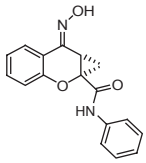


R_1 = H R_2 = 2-methoxyphenoxy
LY487379 (EC_{50} = 0.3 μM)
R_1 = 1-methylbutoxy R_2 = H
2,2,2-TEMPS (EC_{50} = 14 nM)



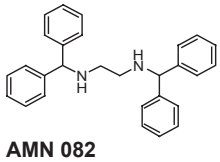
PTBE
EC_{50} = 0.43 μM

C. $mGlu_4$ Receptor Potentiator



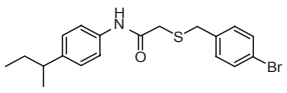
(-)-PHCCC
EC_{50} = 3 μM

D. $mGlu_7$ Receptor Potentiator

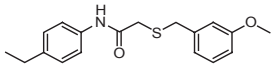


AMN 082
EC_{50} = 0.06-0.29 μM

E. $mGlu_8$ Receptor Potentiators



Thiomethylanilide A
EC_{50} = 1.0 μM



Thiomethylanilide B
EC_{50} = 5.4 μM

(Bold Text Denotes Compounds Available From Tocris)

List of Acronyms

ABHxD	2-aminobicyclo[2.1.1]hexane-2,5-dicarboxylic acid
ACPD	1-aminocyclopentane-1,3-dicarboxylic acid
ACPT-I	(1*S*,3*R*,4*S*)-1-aminocyclopentane-1,3,4-tricarboxylic acid
ACPT-II	(1*R*,3*R*,4*S*)-1-aminocyclopentane-1,3,4-tricarboxylic acid
(+)-ACPT-III	(3*S*,4*S*)-1-aminocyclopentane-1,3,4-tricarboxylic acid
ADED	(2*S*,4*S*)-2-amino-4-(2,2-diphenylethyl)pentane-1,5-dioic acid
ADX47273	(*S*)-(4-fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone
AMN 082	N,N´-dibenzhydrylethane-1,2-diamine
AMPA	2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid
HomoAMPA	2-amino-4-(3-hydroxy-5-methylisoxazol-4-yl)butyric acid
AP4	2-amino-4-phosphono-butyric acid
APCPr	1-amino-2-phosphonomethylcyclopropane carboxylic acid
APDC	4-aminopyrrolidine-2,4-dicarboxylic acid
APTC	4-aminopyrrolidine-1,2,4-tricarboxylic acid
BAY 36-7620	(3a*S*,6a*S*)-6a-naphthalen-2-ylmethyl-5-methyliden-hexahydro-cyclopental[c]furan-1-on
BnAPDC	*N*-benzyl-4-aminopyrrolidine-2,4-dicarboxylic acid
BnQuis	α-benzylquisqualic acid
BOMA	2-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]acetonile
L-CCG-I	(2*S*,1´*S*,2´*S*)-2-(carboxycyclopropyl)glycine
3´Me-CCG	(2*S*,1´*S*,2´*S*,3´*R*)-2-(3´-methyl-2´-carboxycyclopropyl)glycine
3´HM-CCG	(2*S*,1´*S*,2´*R*,3´*R*)-2-(3´-hydroxymethyl-2´-carboxycyclopropyl)glycine
3´SM-CCG	(2*S*,1´*R*,2´*R*,3´*R*)-2-(3´-mercaptomethyl-2´-carboxycyclopropyl)glycine
mCD-CCG	2-(di-*meta*-chlorophenylethyl)-2-(2´-carboxycyclopropyl)glycine
XE-CCG	(2*S*,1´*S*,2´*S*,3´*R*)-2-(3´-xanthenylethyl-2´-carboxycyclopropyl)glycine
CBQA	1-amino-3-[3´,5´-dioxo-1´,2´,4´-oxadiazolidinyl)]cyclobutane-1-carboxylic acid
CDPPB	3-cyano-N-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide
CH-DBO	8-chloro-4-[3-(4-hydroxymethyl-thiazol-2-yl)-phenyl]-7-isobutyl-methylamino)-1,3-dihydro-benzo[b][1,4]diazepin-2-one
CHPG	2-chloro-5-hydroxyphenylglycine
4C3H2MPG	4-carboxy-3-hydroxy-2-methylphenylglycine
4C2MPG	(+)-4-carboxy-2-methylphenylglycine
4CPG	4-carboxyphenylglycine
(-)-CPCCOEt	(1a*S*,7a*S*)-(2-hydroxyimino-1a,2-dihydro-1*H*-7-oxacyclopropa[b]naphthalene-7a-carboxylic acid ethyl ester
CPPG	α-cyclopropyl-4-phosphonophenylglycine
CPPHA	*N*-{4-chloro-2-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]phenyl}-2-hydroxybenzamide
DCG IV	(2*S*,1´*R*,2´*R*)-2-(2´,3´-dicarboxycyclopropyl)glycine
3,4-DCPG	3,4-dicarboxyphenylglycine
3,5-DHPG	3,5-dihydroxyphenylglycine
DCB	3,3´-dichlorobenzaldazine
DFB	3,3´-difluorobenzaldazine
DMeOB	3,3´-dimethoxybenzaldazine
DM-PPP	3,5-dimethyl-pyrrole-2,4-dicarboxylic acid 2-propylester 4-[(*S*)-1,2,2-trimethylpropyl]ester
EM-TBPC	1-ethyl-2-methyl-6-oxo-4-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile
L-Glu	L-glutamate
GPCR	G-protein-coupled receptor
HYDIA	(1*S*,2*R*,3*R*,5*R*,6*S*)-3-hydroxy-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid
JNJ 16259685	(3,4-dihydro-2*H*-pyrano[2,3-b]quinolin-7-yl)-(*cis*-4-methoxycyclohexyl)-methanone
LY 339840 (4C3H2MPG)	(*RS*)-4-carboxy-3-hydroxy-2-methylphenylglycine
LY 341495	(2*S*,1*S*´,2*S*´)-2-(9-xanthylmethyl)-2-(2´-carboxycyclopropyl)glycine
LY 354740	(1*S*,2*S*,5*R*,6*S*)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid
LY 354740-6F	(1*R*,2*S*,5*R*,6*R*)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid
LY 367366	α-thioxanthylmethyl-4-carboxyphenylglycine
LY 367385 (4C2MPG)	(+)-4-carboxy-2-methylphenylglycine
LY 379268	2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid
LY 389795	2-thia-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid
LY 393053	(±)-2-amino-2-(3-*cis* and *trans*-carboxycyclobutyl)-3-(9-thioxanthyl)propionic acid
LY 393675	(*S*)-*cis*-α-thioxanthylmethyl-3-carboxycyclobutylglycine
LY 397366	α-thioxanthylmethyl-4-carboxyphenylglycine
LY 456066	2-[4-(indan-2-ylamino)-5,6,7,8-tetrahydroquinazolin-2-ylsulfanyl]-ethanol
LY 487379	*N*-(4-(2-methoxyphenoxy)phenyl)-*N*-(2,2,2-trifluoroethylsulfonyl)pyrid-3-ylmethylamine
MAP4	2-methyl-2-amino-4-phosphono-butyric acid
MCCG	(2*S*,3*S*,4*S*)-2-methyl-2-(carboxycyclopropyl)glycine
MCPG	α-methyl-4-carboxyphenylglycine
MGS0008	(1*S*,2*S*,3*S*,5*R*,6*S*)-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid
MGS0028	(1*R*,2*S*,5*S*,6*S*)-2-amino-6-fluoro-4-oxobicyclo[3.1.0]-hexane-2,6-dicarboxylic acid
MGS0039	(1*R*,2*R*,3*R*,5*R*,6*R*)-2-amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid
MPPG	α-methyl-4-phosphonophenylglycine
MPEP	2-methyl-6-(phenylethynyl)pyridine
5MPEP	5-methyl-2-(phenylethynyl)pyridine
M-MPEP	2-[(3-methoxyphenyl)ethynyl]-6-methylpyridine
MTEB	5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-2,3´-bipyridine
MTEP	3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine
MM-MTEP	3-(methoxymethyl)-5-[(2-methyl-1,3-thiazol-4-yl)-ethynyl]pyridine
NAAG	*N*-acetyl-L-aspartyl-L-glutamate
NM-APDC	(2*R*,4*R*)-4-amino-1-(1-naphthylmethyl)pyrrolidine-2,4-dicarboxylic acid
NMDA	*N*-methyl-D-aspartate
NPS2390	*N*-(1-adamantyl)-2-quinoxaline-carboxamide
PPG	4-phosphonophenylglycine
PHCCC	*N*-phenyl-7-(hydroxylimino)cyclopropa[b]chromen-1a-carboxyamide
3,5-dimethyl PPP	3,5-dimethyl-pyrrole-2,4-dicarboxylic acid 2-propylester 4-[(*S*)-1,2,2-trimethyl-propyl]ester
PTBE	1-(2-hydroxy-3-propyl-4-4-[4-(2*H*-tetrazol-5-yl)phenoxy]butoxyphenyl)ethanone
PTeB	3-(5-pyridin-2-yl-2*H*-tetrazol-2-yl)benzonitrile
Quis	quisqualate
R214127	1-(3,4-dihydro-2*H*-pyrano[2,3-b]quinolin-7-yl)-2-phenyl-1-ethanone
Ro 01-6128	diphenylacetyl-carbamic acid ethyl ester
Ro 64-5229	1-*Z*-[2-cycloheptyloxy-2-(2,6-dichlorophenyl)vinyl]-(1,2,4-triazole)
Ro 67-4853	(9*H*-xanthene-9-carbonyl)-carbamic acid butyl ester
Ro 67-7476	(*S*)-2-(4-fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine
SIB 1757	6-methyl-2-(phenylazo)-3-pyridinol
SIB 1893	(*E*)-2-methyl-6-(2-phenylethenyl)pyridine
SOP	Serine-O-phosphate
2,2,2-TEMPS	2,2,2-trifluoroethyl-N-[3-(1-methylbutoxy)phenyl]-N-(3-pyridinylmethyl)sulfonamide
Thiomethylanilide A	2-[(4-bromobenzyl)thio]-N-(4-isobutylphenyl)acetamide
Thiomethylanilide B	2-[(4-methoxybenzyl)thio]-N-(4-ethylphenyl)acetamide
YM 298198	6-Amino-*N*-cyclohexyl-N,3-dimethyl-thiazolo[3,2-*a*]benzimidazole-2-carboxamide

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Metabotropic Glutamate Receptor Compounds Available from Tocris

Group I Selective Metabotropic Glutamate Receptor Ligands

Agonists

0187 **(±)-*trans*-ACPD**
Group I/group II mGlu agonist

0284 **(1*S*,3*R*)-ACPD**
Group I/group II mGlu agonist

0860 ***t*ADA**
Group I agonist; some $mGlu_5$ selectivity

1049 **CHPG**
$mGlu_5$ selective agonist

0342 **(*RS*)-3,5-DHPG**
Selective group I mGlu agonist

0805 **(*S*)-3,5-DHPG**
Active enantiomer of (0342)

1058 **L-3´-F_2CCG-I**
Potent group I/group II agonist

0218 **L-Glutamic acid**
Endogenous, non-selective agonist

1826 **Group I mGlu Receptor Tocriset**
Selection of 5 group I mGlu receptor ligands

0324 **(*RS*)-3-Hydroxyphenylglycine**
Group I mGlu agonist

0326 **(*S*)-3-Hydroxyphenylglycine**
Group I mGlu agonist, active isomer

1829 **Mixed mGlu Receptor Tocriset**
Selection of 5 mixed mGlu receptor ligands

1490 **MNI-caged-L-glutamate**
Stable photoreleaser of L-glutamate

0188 **L-Quisqualic acid**
Very potent group I mGlu agonist

0162 ***S*-Sulfo-L-cysteine**
Group I agonist

Antagonists

2254 **ACDPP**
Selective $mGlu_5$ receptor antagonist

0904 **AIDA**
Potent, selective group I mGlu antagonist

0125 **DL-AP3**
Group I mGlu antagonist

0329 **(*S*)-3-Carboxy-4-hydroxyphenylglycine**
Group I antagonist/group II agonist

0320 **(*S*)-4-Carboxy-3-hydroxyphenylglycine**
Group I antagonist/group II agonist

0323 **(*S*)-4-Carboxyphenylglycine**
Competitive group I mGlu antagonist/weak group II agonist

1028 **CPCCOEt**
Selective, non-competitive $mGlu_1$ receptor antagonist

1009 **E4CPG**
Group I/group II mGlu antagonist

2386 **Fenobam**
Potent and selective $mGlu_5$ antagonist

1826 **Group I mGlu Receptor Tocriset**
Selection of 5 group I mGlu receptor ligands

1749 **HexylHIBO**
Group I mGlu antagonist

1750 **(*S*)-HexylHIBO**
Group I mGlu antagonist

2333 **JNJ 16259685**
Extremely potent, $mGlu_1$-selective non-competitive antagonist

1237 **LY 367385**
Selective $mGlu_{1a}$ antagonist

2196 **3-MATIDA**
Potent, selective $mGlu_1$ antagonist

0336 **(*RS*)-MCPG**
Non-selective mGlu antagonist

0337 **(*S*)-MCPG**
Active isomer of (0336)

1829 **Mixed mGlu Receptor Tocriset**
Selection of 5 mixed mGlu receptor ligands

1212 **MPEP**
$mGlu_5$ subtype-selective antagonist

2390 **MPMQ**
Selective $mGlu_1$ antagonist

1027 **PHCCC**
Potent group I mGlu antagonist. Also $mGlu_4$ potentiator

1215 **SIB 1757**
Highly selective $mGlu_5$ antagonist

1214 **SIB 1893**
Highly selective $mGlu_5$ antagonist

2448 **YM 298198**
Highly potent, selective non-competitive $mGlu_1$ antagonist

2447 **Desmethyl-YM 298198**
Derivative of Cat. No. 2448

Other

1952 DCB
Neutral allosteric modulator at $mGlu_5$

1625 DFB
Allosteric potentiator at $mGlu_5$

1953 DMeOB
Negative allosteric modulator at $mGlu_5$

2028 Anti-$mGlu_1$
Antibody recognising rat $mGlu_1$ receptors

2032 Anti-$mGlu_5$
Antibody recognising rat $mGlu_5$ receptors

Group II Selective Metabotropic Glutamate Receptor Ligands

Agonists

0187 (±)-*trans*-ACPD
Group II/group I mGlu agonist

0284 (1*S*,3*R*)-ACPD
Group II/group I mGlu agonist

1208 (2*R*,4*R*)-APDC
Highly selective group II agonist

0329 (*S*)-3-Carboxy-4-hydroxyphenylglycine
Selective group II mGlu agonist, also group I mGlu antagonist

0320 (*S*)-4-Carboxy-3-hydroxyphenylglycine
Group II agonist/group I antagonist

0323 (*S*)-4-Carboxyphenylglycine
Group I mGlu antagonist/weak group II agonist

0333 L-CCG-I
Potent group II mGlu agonist

0975 DCG IV
Potent group II mGlu agonist. Also group III mGlu antagonist and NMDA agonist

1058 L-3´-F_2CCG-I
Potent group II/group I agonist

0218 L-Glutamic acid
Endogenous, non-selective agonist

1827 Group II mGlu Receptor Tocriset
Selection of 5 group II mGlu receptor ligands

1829 Mixed mGlu Receptor Tocriset
Selection of 5 mixed mGlu receptor ligands

1490 MNI-caged-L-glutamate
Stable photoreleaser of L-glutamate

0391 Spaglumic acid
Selective $mGlu_3$ agonist

Antagonists

1073 (*RS*)-APICA
Selective group II antagonist

1009 E4CPG
Group II/group I mGlu antagonist

0971 EGLU
Highly selective group II mGlu antagonist

1827 Group II mGlu Receptor Tocriset
Selection of 5 group II mGlu receptor ligands

1209 LY 341495
Highly potent, selective group II antagonist

0336 (*RS*)-MCPG
Non-selective mGlu antagonist

0337 (*S*)-MCPG
Active isomer of (0336)

1829 Mixed mGlu Receptor Tocriset
Selection of 5 mixed mGlu receptor ligands

0854 MSPG
Group II/group III mGlu antagonist

0855 MTPG
Group II/group III mGlu antagonist. More selective for group II than group III

Other

2027 Anti-$mGlu_2$
Antibody recognising rat $mGlu_2$ receptors

2029 Anti-$mGlu_{2/3}$
Antibody recognising human $mGlu_2$ and $mGlu_3$ receptors

Group III Selective Metabotropic Glutamate Receptor Ligands

Agonists

1111 ACPT-I
Group III mGlu agonist

1113 (±)-ACPT-III
Selective group III agonist

2385 AMN 082
The first selective $mGlu_7$ agonist

0103 L-AP4
Selective group III mGlu agonist

1394 (*RS*)-3,4-DCPG
Potent systemically active anticonvulsant. Racemate of (1302)

1302 (*S*)-3,4-DCPG
Potent, selective $mGlu_{8a}$ agonist

0218 L-Glutamic acid
Endogenous, non-selective agonist

1828 Group III mGlu Receptor Tocriset
Selection of 5 group III mGlu receptor ligands

1026 HomoAMPA
Potent, highly selective $mGlu_6$ agonist

1829 Mixed mGlu Receptor Tocriset
Selection of 5 mixed mGlu receptor ligands

1490 MNI-caged-L-glutamate
Stable photoreleaser of L-glutamate

0238 *O*-Phospho-L-serine
Group III mGlu agonist

1220 (*RS*)-PPG
Potent group III mGlu agonist

Antagonists

0972 CPPG
Very potent group III mGlu antagonist

0975 DCG IV
Group III antagonist/group II mGlu agonist

1828 Group III mGlu Receptor Tocriset
Selection of 5 group III mGlu receptor ligands

1209 LY 341495
Group II/III antagonist

0711 MAP4
Selective group III mGlu antagonist

1829 Mixed mGlu Receptor Tocriset
Selection of 5 mixed mGlu receptor ligands

0853 MPPG
Group III/group II mGlu antagonist. More selective for group III than group II

0803 MSOP
Specific group III mGlu antagonist

0854 MSPG
Group III/group II mGlu antagonist

1369 UBP1112
Group III mGlu antagonist

Other

2031 Anti-$mGlu_7$
Antibody recognising human $mGlu_7$ receptors

Quisqualate-Sensitised AP6 Site

0101 DL-AP4
Agonist/broad spectrum EAA antagonist

0102 D-AP4
Less potent enantiomer

0103 L-AP4
Agonist; also group III mGlu agonist

0105 DL-AP5
Agonist; also NMDA antagonist

0106 D-AP5
Less potent enantiomer. Also NMDA antagonist

0107 L-AP5
Agonist; also NMDA antagonist

0341 L-AP6
Selective agonist, highly potent

0188 L-Quisqualic acid
Sensitiser

Miscellaneous Metabotropic Glutamate Receptor Compounds

1112 ACPT-II
Competitive mGlu receptor antagonist

0216 L-Cysteinesulfinic acid
Agonist at PLD-coupled mGlu receptor, also NMDA agonist

0285 Ibotenic acid
Non-selective mGlu agonist, also NMDA agonist

1611 Lamotrigine
Inhibits glutamate release. Anticonvulsant

2289 Lamotrigine isethionate
Water-soluble salt of Cat. No. 1611

1721 Tocriscreen Glutamate Ligands
Collection of glutamate receptor and related compounds

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