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Metabotropic Glutamate Receptors

Molecular Pharmacology

Francine C Acher

Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR8601-CNRS, Université René Descartes-Paris V, 45 rue des Saints-Pères, 75270 Paris Cedex 06, France.
E-mail: Francine.Acher@univ-paris5.fr

Francine C Acher is currently a CNRS Research Director within the Biomedical Institute of University Paris-V (France). Her research focuses on structure/function studies and drug discovery using chemical tools (synthetic chemistry, molecular modeling), molecular biology and pharmacology within interdisciplinary collaborations.

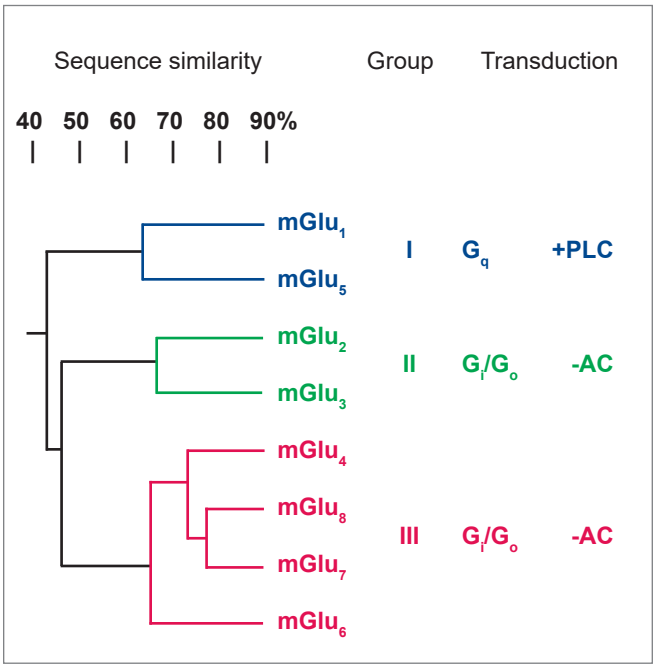
Contents

Introduction

Glutamate is the major excitatory neurotransmitter 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 and 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.[3,4] 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 their 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 ($mGlu_4$, $mGlu_6$, $mGlu_7$, $mGlu_8$) receptors couple G_i/G_o and inhibit adenylyl cyclase (AC). Group I receptors are mostly located postsynaptically, thus their activation increases excitability. Conversely, group II/III receptors are generally presynaptic and their activation reduces glutamate release. Selective ligands have been found for each group and some of the subtypes, as described hereafter.[2,5–8]

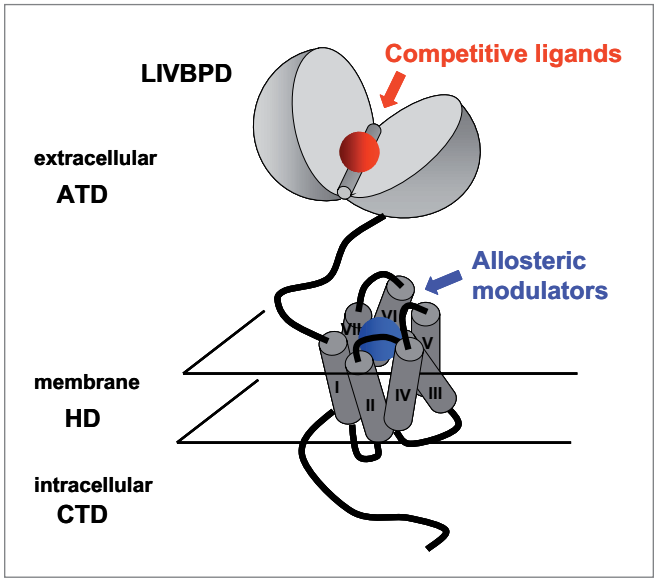
Figure 1 | Classification of the Subtypes of mGlu Receptors



mGlu receptors belong to class C of the GPCR superfamily.[9] Like all GPCRs they hold a heptahelical domain (HD) in the membrane region. In addition, similar to all members of class C, they are characterized by a large extracellular amino terminal domain (ATD) where the glutamate binding site is found (see Figure 2). 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.[10–13] These amino acids bind to an open conformation of the protein, which subsequently closes 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 (see Figure 2). Moreover, it was shown that the closed conformation of this domain is required for receptor activation.[14] Examination of the glutamate binding site in the eight mGlu receptor subtype crystal structures ($mGlu_1$, $mGlu_3$, $mGlu_7$)[12,13] or homology models[15–19] reveals a common binding motif for the α-amino and α-carboxylic functions of glutamate,[20] while residues that bind the distal γ-carboxylate vary from one subtype to another.[17] Thus, not surprisingly, all competitive agonists are α-amino acids, bearing various selective functional groups on their side chain[6] including virtual screening hits and derivatives (see Figures 3A and 3B). The first generation of orthosteric ligands was followed by a second generation of allosteric modulators which bind in the HD.[21] The first molecule described as a non-competitive mGlu receptor antagonist was CPCCOEt in the late nineties.[22] Since then, numerous allosteric modulators have been discovered by high-throughput screening (HTS) in pharmaceutical companies.[7,8,23]

The purpose of the present article is to review our current knowledge of the pharmacology of mGlu receptors. Several detailed reviews[2,4–6,8,24] have been published, therefore only the most potent and selective known ligands will be presented and emphasis will be placed on compounds that were more recently disclosed.

Figure 2 | Schematic Representation of an mGlu Receptor: the Two Orthosteric and Allosteric binding Sites are Indicated



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[25] and homology models[17] and found in X-ray structures.[12,13] For many years these compounds have been considered as valuable research tools but not as drug candidates because of their poor partition coefficient (LogP) related to their highly polar chemical structures and their lack of selectivity. Researchers at Eli Lilly were the first to show that such a glutamate analog, LY 354740, was able to pass the blood brain barrier and that its peptidyl prodrug, LY 544344, was orally active as an anticonvulsant and anxiolytic.[26,27] A sulfonyl analog, LY 404039, orally administered as a methionine amide prodrug LY 2140023, being developed for the treatment of schizophrenia[28,29] reached phase III clinical trials. Another advantage is that such drugs are barely metabolized since they are already quite hydrophilic[30] and few side effects are predicted. Other glutamate analogs were also shown to be systemically active such as (2*R*,4*R*)-APDC, 3′Me-CCG, 3′HM-CCG, (*S*)-DCPG, ACPT-I and LSP1-2111 (Figure 3A). Desensitization was also feared with continuous activation in the case of group II/III receptors, yet they are resistant to agonist-induced desensitization.[31] Altogether these results promote a renewed interest in mGlu receptor competitive ligands.

Agonists (Table 1)

The first agonist that was able to discriminate between ionotropic and metabotropic glutamate receptors was *trans*-ACPD (1*S*,3*R* isomer).[32] This ligand contributed considerably to the study of mGlu receptors despite its lack of subtype selectivity.[2,5,24] 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.[2,5,24] It can be noted that L-CCG-I and ABHxD-I are conformationally constrained and mimic the bioactive extended glutamate conformation common to all mGlu receptors.[25] When adding new chemical groups onto these structures, selectivity can be gained (Figure 3A).

Group I

Quisqualate (Quis) is the most potent group I agonist; however it also activates AMPA receptors, therefore its use is restricted. The most widely used group I selective agonist is (S)-3,5-DHPG, yet it exhibits only moderate potency.[2,5,24] CHPG[33] and Z/E-CBQA[34] have been claimed to specifically activate $mGlu_5$ receptors although the affinity of the former is quite low. No specific $mGlu_1$ competitive agonists have been disclosed to date.

Group II

LY 354740 was the first mGlu agonist reported to exhibit a nanomolar affinity.[26] It is group II selective, as are its oxy (LY 379268), thia (LY 389795)[35] and sulfonyl derivatives (LY 404039).[36] Introducing a fluorine atom at position 3 (MGS0008) or 6 (MGS0022) retained the potent activity which was further enhanced when a carbonyl group was added, as in the case of MGS0028.[37] This series of bicyclic glutamate analogs derives from the general agonist L-CCG-I where increased potency and

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

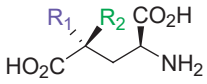
Receptors		Group I		Group II		Group III			
		$mGlu_1$	$mGlu_5$	$mGlu_2$	$mGlu_3$	$mGlu_4$	$mGlu_6$	$mGlu_7$	$mGlu_8$
Non-selective agonists	**L-Glu**[c,d]	1–13	3–11	0.3–12	2–9	3–17	5–38	2300	8–10
	L-CCG-I[c,d]	2	3	0.5	0.4	9	6	230	3
	ABHxD-I[c,d]	2	0.7	0.3	2	23	5	–	–
Group I subtype-selective agonists	**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	–
	MGS0022[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
	LY 541850[j]	n.e.[t]	n.e.[t]	0.16	ant.	n.e.[t]	–	n.e.[t]	n.e.[t]
	2*R*,4*R*-APDC[b,c]	>100	>100	0.4	0.4	>300	110	>300	>100
	DCG IV[b,c]	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)-thioAP4[e]	n.e.[t]	n.e.[t]	n.e.[t]	n.e.[t]	0.04	0.7	200	0.05
	(*S*)-SOP[c,d]	n.e.	n.e.	ant.	ant.	1–4	3	160–1200	2
	(1*S*,2*R*)-APCPr[j]	–	–	–	–	0.6	1.9	602	0.3
	LSP1-3081[k]	n.e.[t]	n.e.[t]	n.e.[t]	n.e.[t]	0.16	3.3	419	0.51
	LSP1-2111[l]	n.e.[t]	n.e.[t]	n.e.[t]	n.e.[t]	2.2	1.7	53	66
	LSP4-2022[m]	n.e.[t]	n.e.[t]	n.e.[t]	n.e.[t]	0.11	4.2	12	29
	ACPT-I[c,d,n]	ant.	>1000	>1000	–	7.2	18.4	–	10.1
	(+)-ACPT-III[c,d,n]	ant.	–	ant.	–	8.8	19.2	–	7.0
	FP429[n,o]	>5000	>5000	>5000	>5000	48	380	–	56[u]
	PCG-1[p]	>1000	>1000	>1000	–	9.4	13	700	63[v]
	(S)-PBPG[q]	>1000	>1000	310	–	4.2	66	>1000	4.4[v]
	(S)-PPG[b,r]	>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,s]	ant.	>100	>100	>100	8.8	3.6	>100	0.031

(**Bold** text denotes compounds available from Tocris at time of publication)

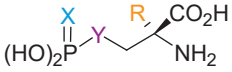
[a] EC_{50} or K_b values (μM) measured with rat or human (when indicated[b]) cloned receptors. ant. = antagonist; n. e. = no effect.
References for agonist potencies which have been cited in reviews [5] and/or [6] are referred as such.

[b] EC_{50} or K_b values obtained with human mGlu receptors [c] Schoepp *et al.* (1999)[5] [d] Pin *et al.* (1999)[6] [e] Selvam *et al.* (2007)[45] [f] Nakazato *et al.* (2000)[37] [g] Collado *et al.* (2002)[38] [h] Collado *et al.* (2004)[39] [i] Dominguez *et al.* (2005)[42] [j] Kroona *et al.* (1991)[45], Sibille *et al.* (2007)[47] [k] Cuomo *et al.* (2009)[56] [l] Beurrier *et al.* (2009)[57] [m]Selvam *et al.* (2011)[56] [n] Schann *et al.* (2006)[60] [o] Frauli *et al.* (2007)[61] [p] Amori *et al.* (2006)[52] [q] Filosa *et al.* (2006)[51] [r] Gasparini *et al.* (1999)[47] and (2000)[48]; data in parentheses refer to (±)-PPG[47] [s] Thomas *et al.* (2001)[49] [t] n.e. = no effect at 100 μM [u] partial agonist 36% Glu max[61] [v] K_i value

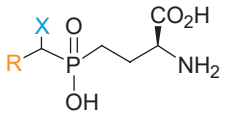
Figure 3A | Competitive mGlu Receptor Ligand Structures



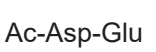
R_1=H R_2=H **L-Glutamic acid (Cat. No. 0218)**
R_1=H R_2=$CH_2CH(Ph)_2$ ADED (LY 310225)



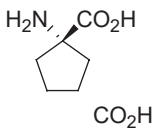
X=O Y=CH_2 R=H **(*S*)-AP4 (Cat. No. 0103)**
X=S Y=CH_2 R=H (*S*)-thioAP4
X=O Y=O R=H **(*S*)-SOP (Cat. No. 0238)**
X=O Y=CH_2 R=Me **MAP4 (Cat. No. 0711)**



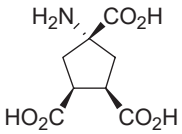
X=H R=CH_2CO_2H (*S*)-PCEP
X=OH R=3-NO_2,4-OH,5-OMePh LSP1-2111
X=OH R=4-(OCH_2CO_2H)Ph LSP4-2022
X=OH R=5-NO_2thiophene LSP1-3081



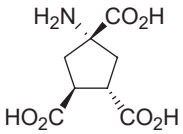
NAAG (Spaglumic acid) (Cat. No. 0391)



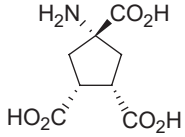
(1*S*,3*R*)-ACPD (Cat. No. 1208)



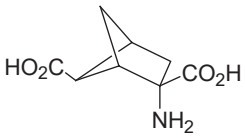
ACPT-I (Cat. No. 1111)



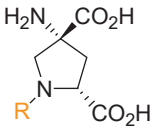
(+)-ACPT-III



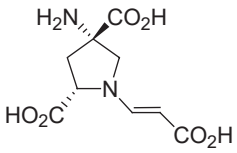
ACPT-II (Cat. No. 1112)



ABHxD-I



R=H **(2*R*,4*R*)-APDC (Cat. No. 1208)**
R=CH_2Ph BnAPDC
R=CH_2 1-Naphthyl NM-APDC



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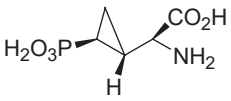
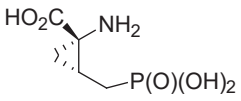
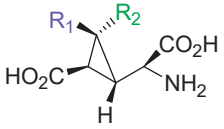


PCG-1

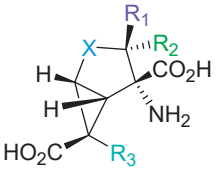


(1S,2*R*)-APCPr

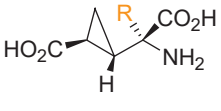
(*S*)-PBPG



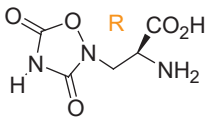
R_1=H R_2=H **L-CCG-I (Cat. No. 0333)**
R_1=H R_2=3′-CH_3 3′Me-CCG
R_1=H R_2=3′-CH_2OH 3′HM-CCG
R_1=H R_2=3′-CH_2SH 3′SM-CCG
R_1=H R_2=3′-cyclopropyl 3′CP-CCG
R_1=H R_2=CO_2H **DCG-IV (Cat. No. 0975)**
R_1=H R_2=9′-xanthylethyl XE-CCG-I



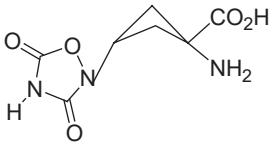
X=CH_2 R_1=H R_2=H R_3=H **LY 354740 (Cat. No. 3246)**
X=O R_1=H R_2=H R_3=H **LY 379268 (Cat. No. 2453)**
X=S R_1=H R_2=H R_3=H LY 389795
X=SO_2 R_1=H R_2=H R_3=H LY 404039
X=CH_2 R_1=H R_2=CH_3 R_3=H LY 541850
X=CH_2, R_1=H, R_2=5-thio(1*H*2,4)triazole, R_3=H LY 2812223
X=CH_2 R_1=H R_2=F R_3=H MGS0008
X=CH_2 R_1=H R_2=H R_3=F MGS0022
X=CO R_1=H R_2=H R_3=F MGS0028
X=CH_2 R_1=OH R_2=H R_3=H HYDIA
X=CH_2, R_1=3,4-Cl_2PhCH_2O, R_2=H, R_3=F MGS0039



R=Me MCCG-I
R=9′-xanthylmethyl **LY 341495 (Cat. No. 1209)**
R=(3-ClPh)$_2$Et mCD-CCG

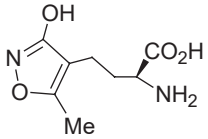


R=H **Quis (Cat. No. 0188)**
R=Benzyl BnQuis



Z-CBQA

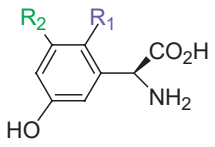
R=9′-thioxanthylmethyl LY 393675



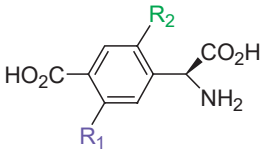
(*S*)-HomoAMPA

(**Bold** text denotes compounds available from Tocris at time of publication)

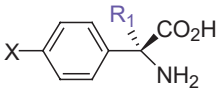
Figure 3B | Competitive mGlu Receptor Ligand Structures



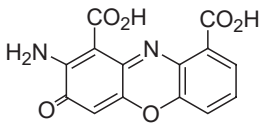
R_1=H R_2=OH **(*S*)-3,5-DHPG (Cat. No. 0805)**
R_1=Cl R_2=H (S)-CHPG



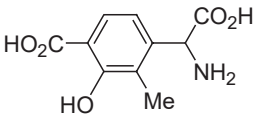
R_1=H R_2=H **(*S*)-4CPG (Cat. No. 0323)**
R_1=CO_2H R_2=H **(*S*)-3,4-DCPG (Cat. No. 1302)**
R_1=H R_2=Me (S)-4C2MPG (LY 397385)



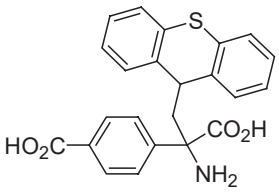
X=CO_2H R_1=Me **(*S*)-MCPG (Cat. No. 0337)**
X=PO_3H_2 R_1=H (S)-PPG
X=PO_3H_2 R_1=Me (S)-MPPG



cinnabarinic acid (Cat. No. 4119)
EC_{50}>100 μM



LY 339840



LY 367366

(**Bold** text denotes compounds available from Tocris at time of publication)

group II selectivity were gained through the second hydrocarbon ring. However, it was shown that a methyl, hydroxymethyl or cyclopropyl substituent in the 3′ position (3′Me-CCG, 3′HM-CCG and 3′CP-CCG respectively) provided agonists with similar potency.[38–40] Replacement of the hydroxyl functionality at C3′ of 3′HM-CCG, by a sulfhydryl 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 $mGlu_3$.[41] A similar selectivity was also reported for the C4β-methyl-substituted analog of LY 354740 (LY 541850).[42] Substitution by a thiotriazole group at this same position (LY 2812233) confers different pharmacological activity at the two subtypes.[43] These three compounds selectively activate $mGlu_2$ while NAAG was the only reported $mGlu_3$ competitive agonist expected to discriminate between the two group II subtypes, however this was recently proved untrue.[44] Other group II selective agonists have been described with submicromolar affinity, these include (2*R*,4*R*)-APDC and DCG-IV.

Group III

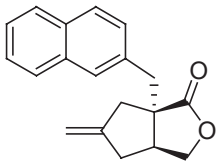
Most potent group III selective agonists bear a diacidic side chain that can interact with the highly basic distal binding pocket.[17,19] (S)-AP4 (L-AP4), (S)-thioAP4,[45] (S)-SOP (L-SOP) and (1*S*,2*R*)-APCPr46,[47] are the most potent, exhibiting submicromolar affinities at cloned receptors except for $mGlu_7$, to which all binding affinities are weak. (*S*)-PPG,[48,49] (S)-3,4-DCPG,[50] ACPT-I and (+)-ACPT-III,[51] (S)-PBPG[52] and PCG-1[53] have also been described as micromolar agonists. Interestingly, a CCG derivative bearing a hydroxymethyl group in the 3′ position (3′HMCCG) displays similar affinity for $mGlu_8$ and $mGlu_{2/3}$ receptors.[39] A new series of agonists deriving from a virtual screening hit, PCEP, was recently disclosed.[54–56] Among these is LSP1-3081[57] which displays potency close to L-AP4 and LSP1-2111[58] and LSP4-2022[56] that show a preference or selectivity for the $mGlu_4$ receptor respectively.[56] In addition these agonists alleviate Parkinson's disease and anxiolytic symptoms following systemic injection in animal models.[58–60] Nevertheless, very few group III mGlu receptor agonists are subtype-selective. FP429 is a full $mGlu_4$ and partial $mGlu_8$ agonist,[61,62] *N*-benzyl- APDC (BnAPDC)[62] and (S)-homoAMPA[64] act at $mGlu_6$ and (S)-3,4-DCPG at $mGlu_8$ with an EC_{50} over 2 orders of magnitude lower than at other group III receptors.[50] Interestingly, cinnabarinic acid, an endogenous metabolite of the kynurenine pathway, was demonstrated to be a weak $mGlu_4$ agonist, the first orthosteric agonist with non-α-amino acid structure.[65]

Antagonists (Table 2)

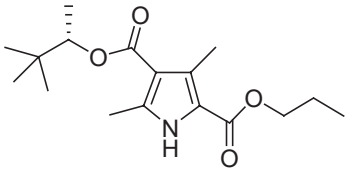
Most competitive antagonists prevent the complete closing of the two lobes of the LIVBPD. Substitution of the α-proton of glutamate analogs by a methyl group, as in the case of MCCG, MCPG and MAP4, or a bulkier group as seen in LY 341495, turns the corresponding agonists (4CPG, AP4 and L-CCG-I) into antagonists. However, agonist properties can be recovered when the residues responsible for the hindrance are mutated.[14] Closing can also be disturbed by ionic repulsion, as seen with ACPT-II.[14]

Figure 4 | Group I Allosteric Modulator Structures and Potencies

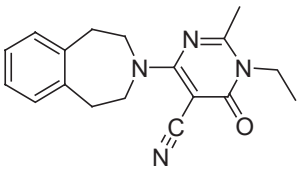
A. $mGlu_1$ Receptor Antagonists



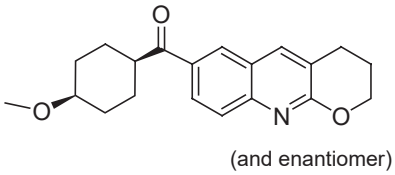
Bay 36-7620 (Cat. No. 2501)
IC_{50}=160 nM
K_i=11.2 nM



DM-PPP
IC_{50}=16 nM

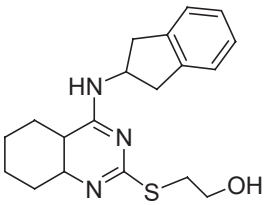


EM-TBPC
K_i=11 nM

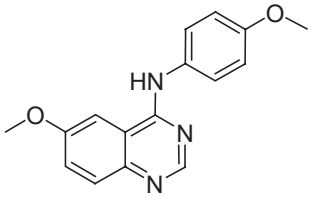


(and enantiomer)

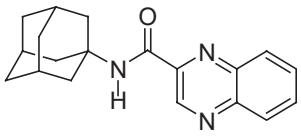
JNJ 16259685 (Cat. No. 2333)
IC_{50}=0.55 nM
K_i=0.34 nM



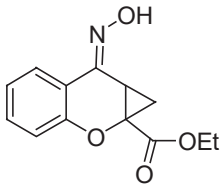
LY 456066
IC_{50}=12 nM (hmGlu_1)



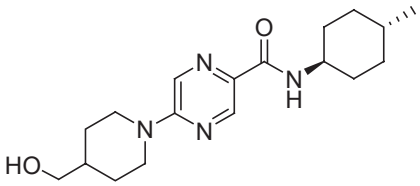
LY 456236 (Cat. No. 2390)
IC_{50}=140 nM



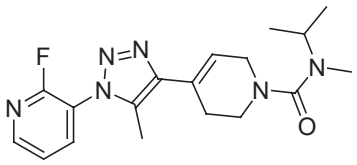
NPS 2390 (Cat. No. 4134)
IC_{50}=5.2 nM chimera CaSR/$mGlu_1$
K_i= 1.4 nM



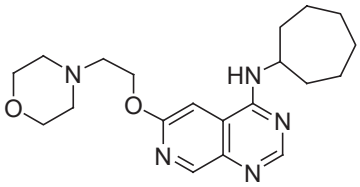
CPCCOEt (Cat. No. 1028)
IC_{50}=10.3 μM
K_i=4.9 μM
(–) isomer active



pyrazine-2-carboxamide
PChPC
K_i=9 nM

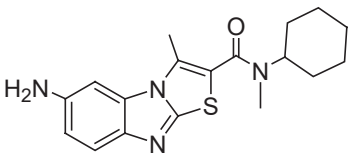


FTIDC (Cat. No. 5000)

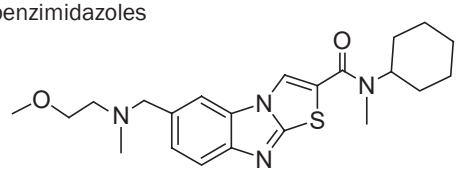


azaquinazole
CMPPA
K_i=6 nM

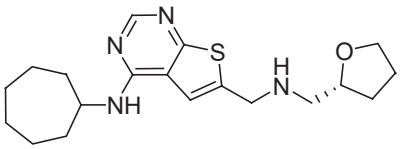
thiazolobenzimidazoles



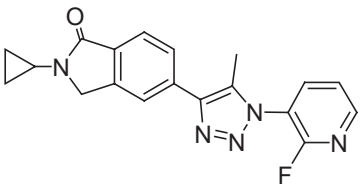
YM 298198 (Cat. No. 2448)
IC_{50}=16 nM



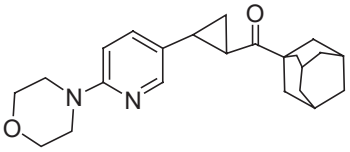
YM 202074 (Cat. No. 3413)
IC_{50}=8.6 nM



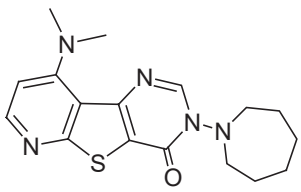
YM 230888 (Cat. No. 2986)
IC_{50}=16 nM



isoindolone
CFMTI
IC_{50}=2.6 nM (hmGlu_1)



adamantyl methanone
AdPyM
K_i=24 nM

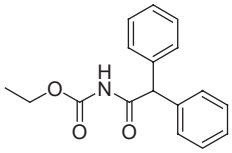


triazafluorenone
A 841720
IC_{50}=10 nM (hmGlu_1)

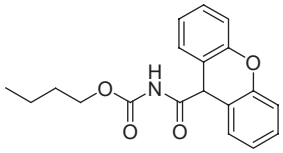
(**Bold** text denotes compounds available from Tocris at time of publication)

Figure 4 | Group I Allosteric Modulator Structures and Potencies

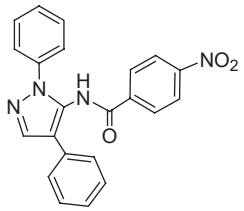
B. $mGlu_1$ Receptor Potentiators



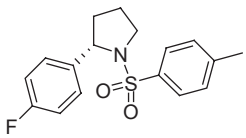
Ro 01-6128 (Cat. No. 4348)
EC_{50} = 0.2 µM



Ro 67-4853 (Cat. No. 4347)
EC_{50} = 0.07 µM

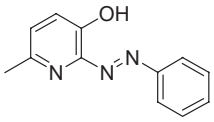


VU 71
EC_{50} = 2.4 µM

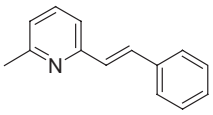


Ro 67-7476 (Cat. No. 4376)
EC_{50} = 0.2 µM

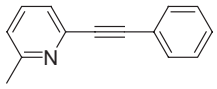
C. $mGlu_5$ Receptor Antagonists; Alkyne Series



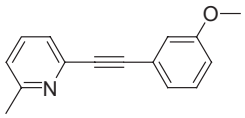
SIB 1757 (Cat. No 1215)
IC_{50} = 0.37 µM (hmGlu$_5$)



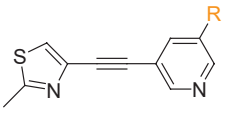
SIB 1893 (Cat. No. 1214)
IC_{50} = 0.29 µM (hmGlu$_5$)



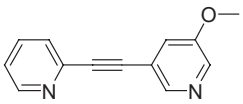
MPEP (Cat. No. 1212)
IC_{50} = 36 nM (hmGlu$_5$)



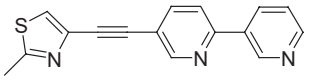
M-MPEP
IC_{50} = 10 nM (hmGlu$_5$)



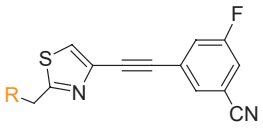
R=H **MTEP (Cat. No. 2921)** IC_{50} = 5 nM (hmGlu$_5$)
R=CH_2OMe MM-MTEP IC_{50} = 7 nM (hmGlu$_5$)



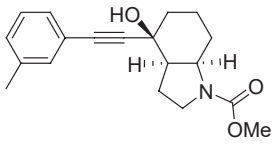
M-PEPγ
IC_{50} = 1 nM (hmGlu$_5$)



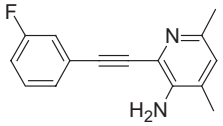
MTEBP
IC_{50} = 2 nM (hmGlu$_5$)



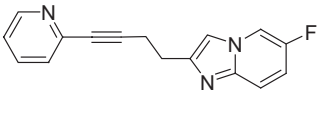
R=H F-MTEB IC_{50} = 0.08 nM
R=F SP203 IC_{50} = 0.036 nM



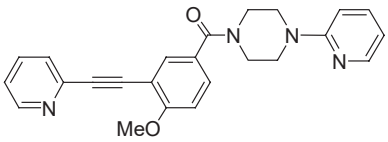
AFQ056



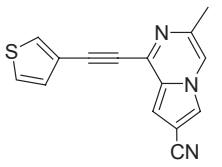
ADX10059 (Cat. No. 4416)



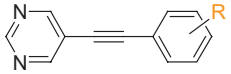
ADX48621



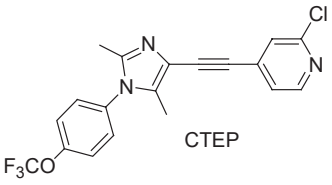
ethynylbenzamide
IC_{50} = 8 nM



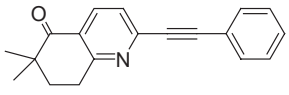
ethynylpyrrolopyrazine
IC_{50} = 0.63



5-(phenylethynyl)pyrimidine
R=3-Me antago IC_{50} = 7.5 nM
R=4-Me ago IC_{50} = 3.3 µM



CTEP
IC_{50} = 6.4 nM (hmGlu$_5$)



MRZ 8676
IC_{50} = 23 nM (hmGlu$_5$)

(**Bold** text denotes compounds available from Tocris at time of publication)

Group I

The first generation of group I mGlu receptor 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 seen 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 like LY 393053.[66] This latter mixture was shown to be systemically active and to inhibit both $mGlu_1$ and $mGlu_5$ as well as other group II/III mGlu receptors.[66] Although slightly less potent, LY 367385 (4C2MPG) and LY 339840 (4C3H2MPG) display subtype I selectivity;[67] however, LY 367385 was also shown to inhibit the cystine/glutamate exchanger.[68] No $mGlu_5$ selective and competitive antagonists have been described to date.

Group II

As most potent group II agonists derive 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 LY 341495,[5] a fluorinated derivative[69] and XECCG69 holding a 9′-xanthylmethyl or 9′-xanthylethyl moiety in the α- or 3′-position, display nanomolar affinities. The α-xanthyl moiety can be replaced by two substituted phenyl groups while retaining potency (e.g. mCD-CCG).[71] As reported previously, stereospecific substitution at the 3-position of the agonist LY 354740 is critical for agonist/antagonist property.[17,37,42] HYDIA71,[73] and several O-benzyl derivatives such as MGS0039 exhibit high competitive group II antagonist activity.[74–76] Systemic and antidepressant-like effects were observed with both LY 341495 and MGS0039.[74] Other arylalkylsubstituted glutamate and 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

No highly potent and group III-selective competitive antagonists have been reported to date. 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, as in the case of MPPG. Addition of a substituent in the 3-position leads to similar group III antagonist activity but increases selectivity for group III over group II.[76] CPPG, the analog of MPPG bearing an α-cyclopropyl

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

Receptors		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	**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 agonists	**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 agonists	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	0.10	0.11	22	–	–	15 (ago)
	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 agonists	**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

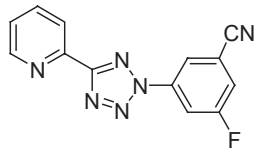
(**Bold** text denotes compounds available from Tocris at time of publication)

[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 which have been cited in reviews [5] and/or [6] are referred as such.

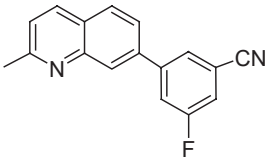
[b] IC_{50} or K_b values obtained with human mGlu receptors [c] Schoepp *et al.* (1999)[5] [d] Pin *et al.* (1999)[6] [e] Chen *et al.* (2000)[66] [f] Kingston *et al.* (2002)[67] [g] Sorensen (2003)[71] [h] Adam (1999)[72,216] [i] Chaki *et al.* (2004)[74] [j] Pellicciari *et. al.* (2001)[70] [k] Conway (2001)[77]; Naples (2001)[217]; Wright (2000)[79]

Figure 4 | Group I Allosteric Modulator Structures and Potencies

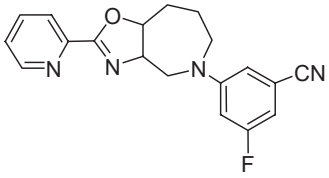
D. $mGlu_5$ Receptor Antagonists; Alkyne Biostere Series



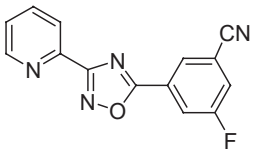
tetrazole
IC_{50}= 4 nM ($hmGlu_5$)



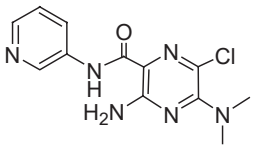
7-arylquinoline
IC_{50}= 0.8 nM



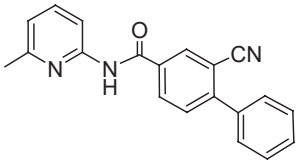
oxazolo-azepine
IC_{50}= 16 nM



oxadiazole
VU 0285683 IC_{50}= 24 nM

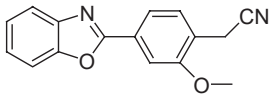


ACDPP (Cat. No. 2254)
IC_{50}= 134 nM

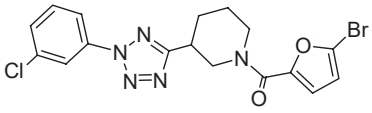


arylcarboxamide
IC_{50}= 14 nM

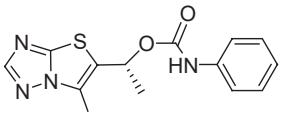
E. $mGlu_5$ Receptor Antagonists; Other Series



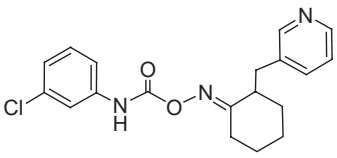
arylbenzoxazole
BOMA IC_{50}= 3 nM



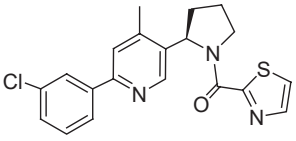
phenyltetrazole
IC_{50}= 213 nM



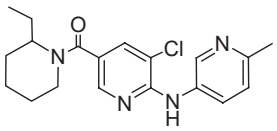
thiazolotriazole
GSK 2210875 IC_{50}= 40 nM ($hmGlu_5$)



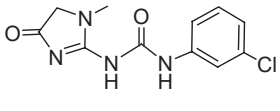
carbamoyloxime
IC_{50}= 15 nM



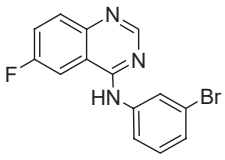
pyrrolidinylpyridine
IC_{50}= 17 nM ($hmGlu_5$)



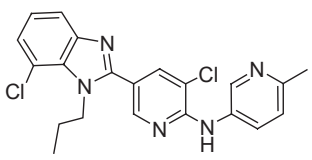
piperidylamide
IC_{50}= 32 nM



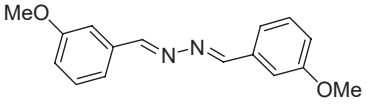
Fenobam (Cat. No. 2386)
IC_{50}= 58 nM



anilinoquinazoline
IC_{50}= 96 nM



benzimidazole
IC_{50}= 24 nM



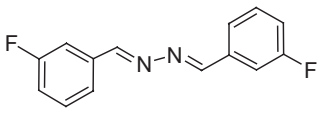
DMeOB (Cat. No. 1953)

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

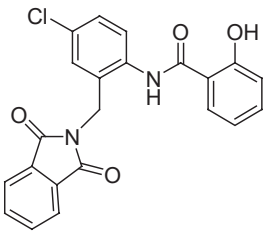
(**Bold** text denotes compounds available from Tocris at time of publication)

Figure 4 | Group I Allosteric Modulator Structures and Potencies

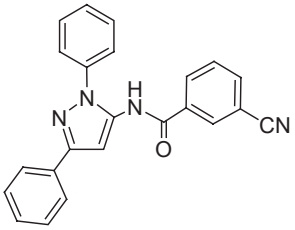
F. $mGlu_5$ Receptor Potentiators



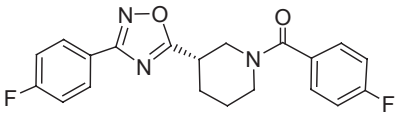
DFB (Cat. No. 1625)
EC_{50}=2.4 µM ($mGlu_5$)



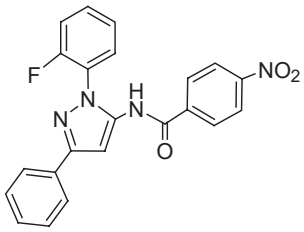
CPPHA (Cat. No. 4787)
EC_{50}=0.14 µM ($mGlu_5$)



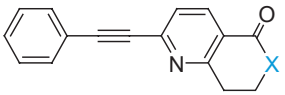
CDPPB (Cat. No. 3235)
EC_{50}=20 nM ($hmGlu_5$)



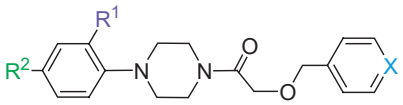
ADX47273
EC_{50}=170 nM ($hmGlu_5$)



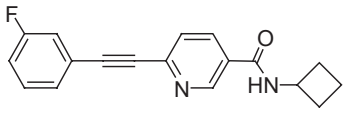
VU 1545 (Cat. No. 3325)
EC_{50}=9.6 nM



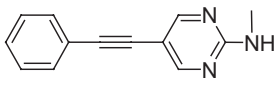
X=CH MRZ 3573 EC_{50}=38 nM
X=NH cyclopentyl EC_{50}=5.9 nM



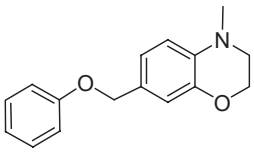
X=N R_1=Cl R_2=F CPPZ EC_{50}=0.55 µM
X=CH R_1=CN R_2=H VU 0364289 EC_{50}=0.55 µM



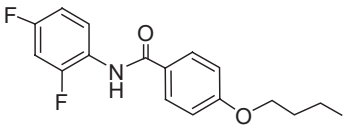
VU 0360172 (Cat. No. 4323)
EC_{50}=16 nM



2-aminomethyl-pyrimidine
EC_{50}=14 nM

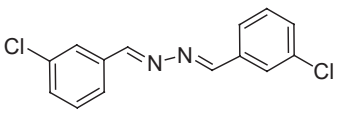


pyrido-oxazine
EC_{50}=50 nM

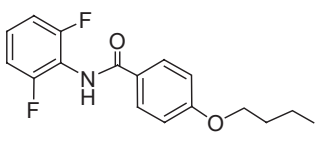


VU 0357121 (Cat. No. 4437)
EC_{50}=33 nM

G. $mGlu_5$ Receptor Neutral Modulators



DCB (Cat. No. 1952)
IC_{50}=2.6 µM for DFB potentiation attenuation



VU 0365396

(**Bold** text denotes compounds available from Tocris at time of publication)

group, exhibits slightly increased potency[5,77] in the same range as DCG-IV, which is also a group II agonist.[78] The best activity is found with the nonselective antagonist LY 341495.[79]

Allosteric Modulators

Allosteric modulators are non-competitive ligands which bind in the transmembrane heptahelical domain. Both negative (NAMs) and positive modulators (PAMs) have been identified.[7,8,23,80] NAMs inhibit receptor activation without affecting agonist binding while PAMs 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.[22,81,82] In particular, specific residues of the HD that bind CPCCOEt were identified by a group from Novartis.[22] Following this, other compounds with higher affinities were discovered by HTS and subsequent optimization, in various companies.[83] These include: NPS 2390[84,85] (NPS Pharmaceuticals Inc.), Bay 36- 7620[86] (Bayer AG), LY 456066[87,88] and LY 456236[89] (Eli Lilly), R21412785/JNJ 16259685[90,91] (Johnson & Johnson), 3,5-dimethyl-pyrrole-2,4-dicarboxylic acid diesters (of which DM-PPP is the most potent derivative[92,93]) (GlaxoSmithKline), several analogs of EM-TBPC94,[95] (Hoffmann-La Roche), thiazolo-benzimidazoles YM 298198,[96] YM 202074[97] and thieno-pyrimidine YM 230888 (Yamanouchi Pharma), triazafluorenones such as A 841720[98] and more selective tetracyclic derivatives[99] (Abbott Laboratories, Schering-Plough), CFMTI[100,101] (Banyu Pharmaceutical Co.), pyrazines-2-carboxamides PChPC[102] and azaquinazolines such as CMPPA[103] (Pfizer) and adamantyl methanone AdPyM[104] (Merz Pharmaceuticals). A homology model of the $mGlu_1$ allosteric binding site has been generated and a binding mode proposed for EM-TBPC which was validated by mutagenesis and functional assays.[94] Additionally, it was shown that several inhibitors (R214127, CPCCOEt , NPS 2390, Bay 36-7620) bind to this same site.[85] Promising anxiolytic and analgesic effects have been reported with allosteric $mGlu_1$ receptor antagonists; however potential side effects such as locomotor and cognition impairment were also discovered, impeding their development.[83,105]

$mGlu_1$ Positive Modulators

The first allosteric potentiators of rat $mGlu_1$ receptors to be disclosed were Ro 01-6128, Ro 67-4853105,[107] and Ro 67-7476.[108,109] Chimeric and mutated receptors were constructed to confirm the transmembrane localization of the binding site of these ligands, which are subtype I selective.[108] Interestingly, Ro 67-7476 and Ro 01-6128 have little or no effect on human $mGlu_1$ receptor activation whereas Ro 67-4853 produces a pronounced enhancement.[108] While CDPPB was known as an $mGlu_5$ selective potentiator (see Figure 4F), VU 71 – which has the phenyl substituent of the pyrazole core in the 4 rather than the 3 position – was discovered to be a selective mGlu1 potentiator, interacting with a site distinct from that of NAMs.[110]

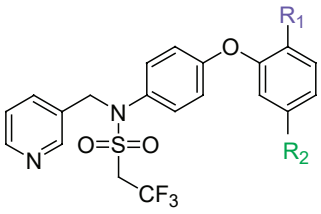
$mGlu_5$ Antagonists

SIB 1757 and SIB 1893[111] were initially found and optimized into MPEP[112] which has been widely used to explore the physiological roles of $mGlu_5$ receptors as a potential therapeutic target.[113] Further investigations at Novartis led to a methoxy derivative M-MPEP, that can be easily tritium-labeled[114] and lead optimization resulted in AFQ056 (Mavoglurant) which has been in clinical trials for the symptomatic treatment of Parkinson's disease levodopa-induced dyskinesia (PD-LID) and Fragile X Syndrome. The therapeutic potential of $mGlu_5$ antagonists prompted numerous groups to search for new ligands.[115–117] Early series contained an alkyne core while more recently extensive efforts focused on alternative chemotypes. MTEP, a thiazol derivative of MPEP with improved aqueous solubility, was described with similar high $mGlu_5$ affinity[118] as well as its tritium-labeled methoxymethyl derivative MM-MTEP,[119,120] M-PEPy[119] bipyridyl derivative MTEBP[121] and fluorine derivatives for PET imaging (F-MTEB and SP203).[122,123] Since these initial MPEP/MTEP derivatives,[124] numerous disubstituted alkyne compounds have been described which include: ADX10059 (efficient for migraine and gastroesophageal reflux but also led to liver function abnormalities in patients); ADX48621[117] (Dipraglurant), in phase II clinical trials for PD-LID; ethynylbenzamides (efficient in anxiety models);[125] ethynylpyrrolopyrazines;[126] MRZ 8676127 and CTEP, which displays high oral bioavailability and a long half-life of 18h.[128] However, during development of the ethynyl series, it soon became apparent that minor structural changes unexpectedly modulated the pharmacology (a "molecular switch"), turning full NAMs into partial antagonists, PAMs or silent/neutral allosteric modulators (SAMs).[129,130] This is exemplified with 5-MPEP, where moving the methyl substituent of the MPEP pyridyl ring to the neighboring carbon turns this analog into a neutral modulator,[129] or with the 5-(phenylethynyl) pyrimidine series where the 3-methylphenyl derivative is a potent antagonist and the 4-methyl isomer a potentiator.[130]

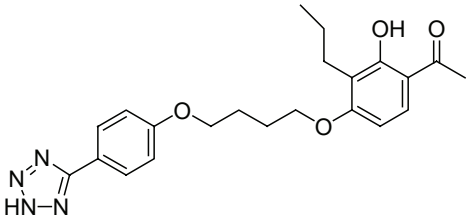
Several biosteric replacements of the alkyne core have been proposed: carboxamides,[132] arylquinolines,[133,134] heterocycles (e.g. tetrazole),[135] oxazolo-azepine[136] or oxadiazole (VU 0285683).[137] In parallel, HTS campaigns provided new scaffolds that were modulated into a plethora of chemical structures[116] for example aryl benzoxazoles[138] (illustrated by BOMA), dipyridyl amides (ACDPP),[139] phenyloxadiazoles and phenyltetrazoles,[140] carbamoyloximes,[141] thiazolotriazoles (such as GSK 2210875),[142] pyrrolidinylpyridines,[143] piperidylamides,[144] benzimidazoles,[145] and anilinoquinazolines.[146] In one of the HTS campaigns, it was found that the known anxiolytic drug fenobam was in fact a potent non-competitive $mGlu_5$ antagonist.[147] Based on this discovery, new derivatives were also developed.[148] Potential therapeutic application of $mGlu_5$ antagonists have been detailed in several reviews.[3,115,124,149] Additionally, molecular determinants of the high affinity binding site of MPEP have been defined[150] and a striking similarity with critical residues of the $mGlu_1$ binding site was observed.[151]

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

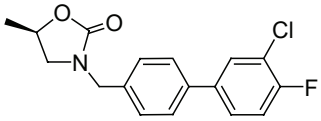
A. $mGlu_2$ Receptor Potentiators



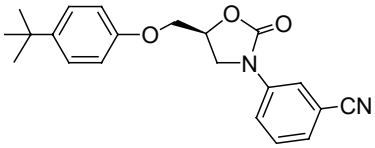
R_1=OCH_3 R_2=H **LY 487379 (Cat. No. 3248)** EC_{50}=270 nM
R_1=H R_2=$OCH(CH_3)CH_2$-CH_2-CH_3 2,2,2-TEMPS EC_{50}=14 nM



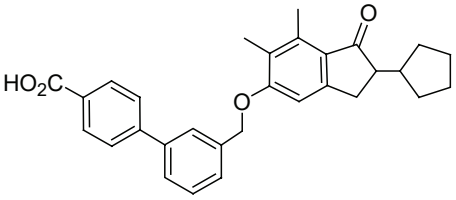
phenyl-tetrazolyl acetophenone
PTBE EC_{50}=0.43 μM



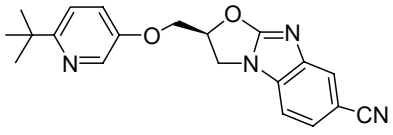
oxazolidinone-1
EC_{50}=30 nM



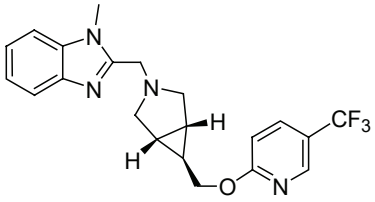
oxazolidinone-2
EC_{50}=82 nM



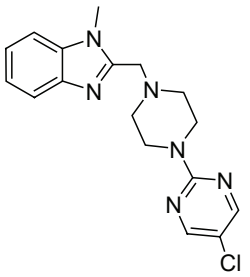
BINA (Cat. No. 4048)
EC_{50}=111 nM



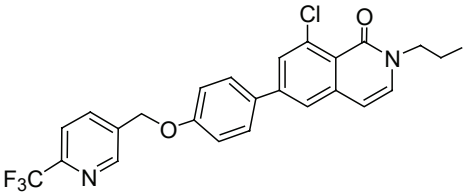
TBPCOB
EC_{50}=29 nM



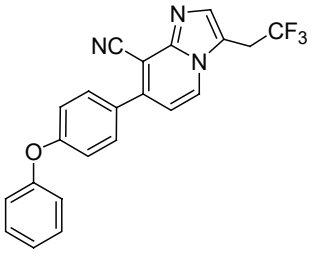
benzimidazole-1
EC_{50}=30 nM



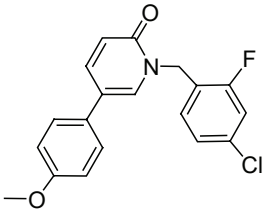
benzimidazole-2
GSK 1331268 EC_{50}=126 nM



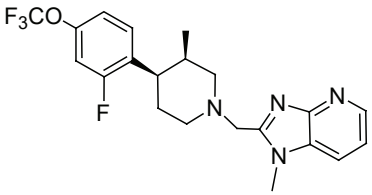
isoquinolone
EC_{50}=250 nM



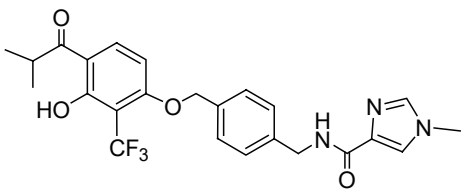
imidazopyridine
EC_{50}=186 nM



pyridone (Cid *et al* 2010)[187]
EC_{50}=525 nM



Imidazomethylpiperidine
EC_{50}=35 nM

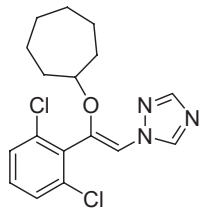


THIIC
EC_{50}=23 nM ($hmGlu_2$)

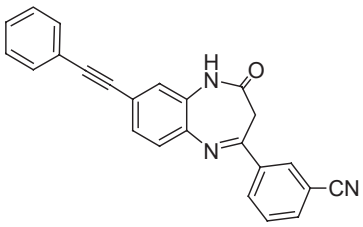
(**Bold** text denotes compounds available from Tocris at time of publication)

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

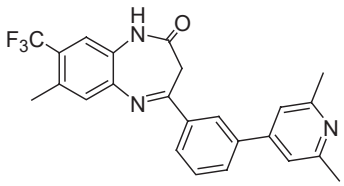
B. $mGlu_{2/3}$ Receptor Antagonists



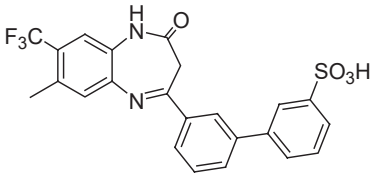
Ro 64-5229 (Cat. No. 2913)
IC_{50} = 109 nM



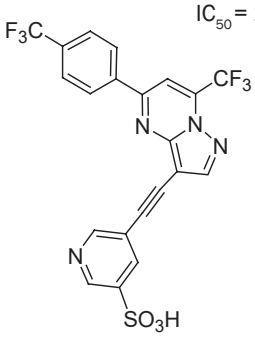
benzodiazepinone
IC_{50} = 34 nM



Ro 4491533
IC_{50} = 2 nM

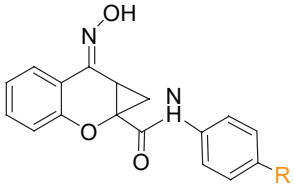


Ro 5488608
IC_{50} = 2.5 nM



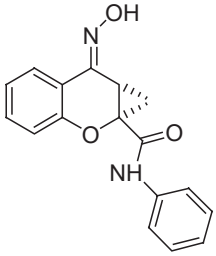
Ro 4988546
IC_{50} = 8.7 nM

C. $mGlu_2$ Receptor Antagonists – $mGlu_3$ Receptor Agonists

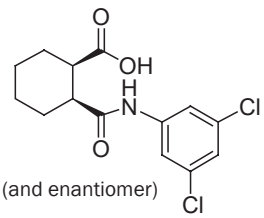


	$hmGlu_2$ K_i (μM)	$hmGlu_2$ IC_{50} (μM)	$hmGlu_3$ EC_{50} (μM)
R = H **PHCCC (Cat. No. 1672)**	N.E.	N.E.	N.E.
R = F	6.6	N.E. (SAM)	N.E. (SAM)
R = Cl	1.0	0.8 (NAM)	13.4 (PAM)
R = Me	0.6	1.5 (NAM)	8.9 (PAM)
R = OMe	0.8	1.0 (NAM)	10.4 (PAM)

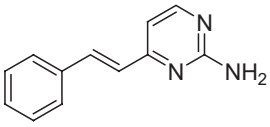
D. $mGlu_4$ Receptor Potentiators



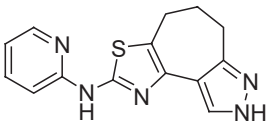
(–)-PHCCC
EC_{50} = 3.1 μM
E_{max} = 120%



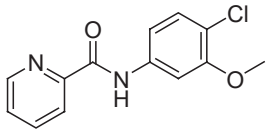
VU 0155041 (Cat. No. 3248)
EC_{50} = 0.75 μM
E_{max} = 144%



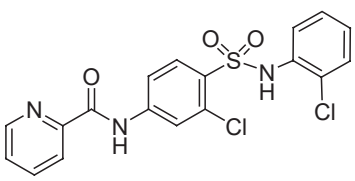
TCN 238 (Cat. No. 4259)
EC_{50} = 1 μM
E_{max} = 127%



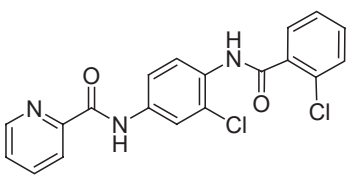
TC-N 22A (Cat. No. 4370)
EC_{50} = 9 nM
E_{max} = 120%



VU 0361737 (Cat. No. 3707)
EC_{50} = 0.24 μM
E_{max} = 182%



VU 0364439 (Cat. No. 4371)
EC_{50} = 19.8 nM
E_{max} = 122%



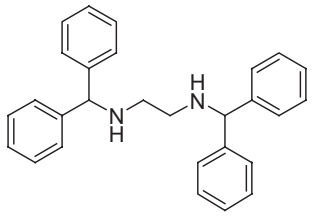
VU 0366037
EC_{50} = 0.52 μM
E_{max} = 94%

phenylpicolinamide series

(**Bold** text denotes compounds available from Tocris at time of publication)

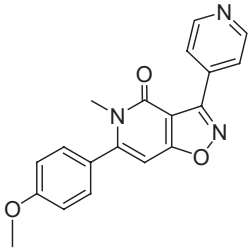
Figure 5 continued | Group II and Group III Allosteric Modulator Structures and Potencies

E. $mGlu_7$ Receptor Allosteric Agonists



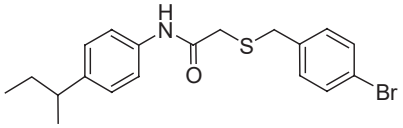
AMN 082 (Cat. No. 2385)
EC_{50} = 64 nM

F. $mGlu_7$ Receptor Allosteric Antagonists



MMPIP (Cat. No. 2963)

G. $mGlu_8$ Receptor PAM



AZ 12216052 (Cat. No. 4832)
EC_{50} = 11.0 μM
E_{max} = 77%

(**Bold** text denotes compounds available from Tocris at time of publication)

$mGlu_5$ Positive Modulators

Significant reports based on the first PAMs supported the development of $mGlu_5$ potentiators as promising novel antipsychotics.[152] Consequently, they stimulated numerous research programs which have been conducted over the last few years.[152] The first $mGlu_5$ PAMs to be identified were DFB,[153] CPPHA,[154,155] CDPPB[156,157] and ADX47273.[158,159] As observed with $mGlu_5$ NAMs, substituent modifications of $mGlu_5$ PAMs led to a molecular switch: replacing the fluorine atoms of DFB by methoxy groups turns this ligand into an antagonist, while dichlorobenzaldazine (DCB) is a neutral modulator which attenuates the potentiation conferred by DFB.[153] Similar modulations were found with close analogs of MPEP, as described above.[130,160] Acetylenic $mGlu_5$ PAM development led to MRZ 3573,[151] VU 0360172[137] and to the 2-aminomethyl-pyrimidine phenylethynyl derivative that is a pure PAM, unlike several other $mGlu_5$ PAMs that are 'ago-potentiators'.[131] Efforts to improve the metabolic stability of these PAMs resulted in the *N*-aryl piperazine (VU 0364289)[161,162] and piperidine amide series[162] and the phenoxymethyl pyridooxazines that are devoid of phenylacetylene and carbonyl functionalities.[163] Molecular switching[164] was also observed when building SAR around the ADX47273 structure[165] but not around CDPPB,[166] although moving a phenyl substituent changes the selectivity of VU 1545 (an $mGlu_5$ PAM) to VU 71 (an $mGlu_1$ PAM). A benzamide scaffold was also identified by HTS, chemical modulation led to the discovery of VU 0357121 but also to neutral (silent) modulators (such as VU 0365396).[167] CPPHA and analogs appear to bind to a different site than MPEP while ethynyl PAM and NAM binding sites overlap.

Group II (Figure 5)

$mGlu_2$ Positive Modulators

The possible treatment of psychiatric diseases with $mGlu_2$ potentiators led to the launch of numerous research programs which resulted in the discovery of multiple modulators.[168,169] LY 487379, a pyridylmethylsulfonamide, was the first reported to potentiate the activity of glutamate at $mGlu_2$ receptors with an EC_{50} value of 0.3 μM and to be highly selective for this subtype.[170] It was also demonstrated that LY 487379 binds to a pocket in the transmembrane domain which is different from the orthosteric site in the ATD.[170] Further SAR studies led to the discovery of 1-methylbutoxy analog (2,2,2-TEMPS) with improved potency (EC_{50} = 14 nM) and selectivity.[171,172] Soon after, a new chemical series of phenyl-tetrazolyl acetophenones (e.g. PTBE) was disclosed as selective $mGlu_2$ potentiators,[173] followed by extensive SAR studies.[174–177] New chemotypes were later disclosed as a result of additional HTS hits and SAR studies.[178] Compounds presented here are mostly those selected among the series for *in vivo* assays and provide the best compromise between potency and metabolic stability: biphenylindanone (BINA),[179] recently optimized into benzizothiazolone,[180] benzimidazole-1[181] and benzimidazole-2 (GSK 1331268),[182] oxazolidinone-1[183] and oxazolidinone-2[184] optimized into oxazolobenzimidazoles (TBPCOB),[185] imidazopyridine,[186] 1,5-disubstituted pyridine,[187] imidazole carboxamide (THIIC),[188] isoquinolones,[189] and imidazomethylpiperidine.[190]

$mGlu_{2/3}$ Antagonists

To date, only $mGlu_{2/3}$ NAMs have been disclosed, mostly by researchers at Hoffmann-La Roche.[169] Heterocyclic enol ethers such as Ro 64-5229 were reported as first selective non-competitive $mGlu_2$ receptor antagonists.[191] A series of dihydrobenzo[b][1,4] diazepin-2-one derivatives was later disclosed, which exhibited nanomolar inhibition of receptor activation by LY 354740.[192] This series was further improved in several derivatives, such as Ro 4491533 that was tested *in vivo*.[193–196] More recently two novel antagonists, Ro 4988546 (from a new pyrazolo[1,5-a]pyrimidine scaffold) and Ro 5488608, were disclosed and used to investigate the structural determinant at the $mGlu_2$ NAM binding site.[197]

$mGlu_3$

A recent screening campaign provided specific $mGlu_3$ PAMs and NAMs, however the chemical structures were yet to be disclosed at the time of writing.[196] Interestingly, it was found that varying a substituent on the PHCCC structure resulted in a $mGlu_{2/3}$ SAM or conferred dual $mGlu_2$ NAM - $mGlu_3$ PAM properties.[199]

Group III

Group III modulators were the latest to be identified, mostly including $mGlu_4$ potentiators. PHCCC, which was initially described as an $mGlu_1$ receptor antagonist,[81] was the first $mGlu_4$

receptor PAM to be found as its (–) enantiomer.[200,201] Two other $mGlu_5$ antagonists, SIB 1893 and MPEP, were reported to enhance agonist potency and efficacy at human $mGlu_4$ at higher concentrations.[202] Several $mGlu_4$ PAMs were subsequently discovered by HTS and hit optimization: VU 0155041;[203] a series of phenylpicolinamides VU 0361737,[204] VU 0364439,[205] VU 366037;[206] styryl aminopyrimidine;[207] and thiazolopyrazole.[208,209] Several of these ligands showed good brain penetration and benefits in motor dysfunction models but may possess intrinsic agonist activity as in the case of VU 0155041, and are therefore named ago-potentiators.[203] AMN 082 was described as an $mGlu_7$ allosteric agonist[210] however a recent study revealed a fast metabolism.[211] Isoxazolpyridones such as MMPIP were determined as $mGlu_7$ antagonists[212,213] but this effect may be context dependent.[214] AZ 12216052, an $mGlu_8$ PAM, was found to be systemically active in an animal model of anxiety.[215]

Conclusion

In the early years, mGlu receptor molecular pharmacology efforts provided group selective competitive ligands. Although it now seems possible to discover subtype-selective orthosteric ligands, most of the recent advances 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 enabling investigators to shed 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.

List of Acronyms

A-841720	9-(Dimethylamino)-3-(hexahydro-1*H*-azepin-1-yl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one
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
ACDPP	3-Amino-6-chloro-5-dimethylamino-*N*-2-pyridinylpyrazinecarboxamide hydrochloride
AdPyM	Adamantan-1-yl-[2-(6-morpholin-4-yl-2-pyridin-3-yl)-cyclopropyl]-methanone
ADX10059	2-((3-Fluorophenyl)ethynyl)-4,6-dimethylpyridin-3-amine
ADX48621	6-Fluoro-2-[4-(pyridin-2-yl)but-3-yn-1-yl]imidazo[1,2-a]pyridine (dipraglurant)
ADX47273	(*S*)-(4-Fluorophenyl)-{3-[3-(4-fluorophenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl}-methanone
AFQ056	(3a*R*,4*S*,7a*R*)-Methyl 4-hydroxy-4-(*m*-tolylethynyl)octahydro-1*H*-indole-1-carboxylate
AMN 082	*N*,*N*′-Bis(diphenylmethyl)-1,2-ethanediamine
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-phosphonobutyric acid
APCPr	1-Amino-2-(phosphonomethyl)cyclopropane carboxylic acid
APDC	4-Aminopyrrolidine-2,4-dicarboxylic acid
AZ 12216052	2-(4-Bromobenzylthio)-*N*-(4-sec-butylphenyl)acetamide
Bay 36-7620	(3a*S*,6a*S*)-6a-Naphtalen-2-ylmethyl-5-methyliden-hexahydro-cyclopental[c]furan-1-one
BINA	3′-((2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yloxy)methyl)biphenyl-4-carboxylic acid
BnAPDC	*N*-Benzyl-(2*R*,4*R*)-4-aminopyrrolidine-2,4-dicarboxylic acid
BnQuis	α-Benzylquisqualic acid
BOMA	2-[4-(1,3-Benzoxazol-2-yl)-2-methoxyphenyl]acetonitrile
L-CCG-I	(2*S*, 1′*S*, 2′*S*)-2-(Carboxycyclopropyl)glycine
3′Me-CCG	(2*S*,1′*S*,2′*S*,3′*R*)-2-(2′-Carboxy-3′-methylcyclopropyl)glycine
3′HM-CCG	(2*S*,1′*S*,2′*R*,3′*R*)-2-(2′-Carboxy-3′-hydroxymethylcyclopropyl)glycine
mCD-CCG	2-[2′,2′-di(3-Chlorophenyl)ethyl]-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
CHPG	2-Chloro-5-hydroxyphenylglycine
4C3H2MPG	4-Carboxy-3-hydroxy-2-methylphenylglycine
4C2MPG	(+)-4-Carboxy-2-methylphenylglycine
4CPG	4-Carboxyphenylglycine
CFMTI	2-Cyclopropyl-5-[1-(2-fluoro-3-pyridinyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-2,3-dihydro-1*H*-isoindol-1-one
CMPPA	*N*-Cycloheptyl-6-(2-morpholinoethoxy)pyrido[3,4-*d*]pyrimidin-4-amine
(−)-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*-[5-Chloro-2-[(1,3-dioxoisoindolin-2-yl)methyl]phenyl]-2-hydroxybenzamide
CPPZ	1-(4-(2-Chloro-4-fluorophenyl)piperazin-1-yl)-2-(pyridin-4-ylmethoxy)ethanone
CTEP	2-Chloro-4-((2,5-dimethyl-1-(4-(trifluoromethoxy)phenyl)-1*H*-imidazol-4-yl)ethynyl)pyridine
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-trimethyl-propyl)ester
EM-TBPC	1-Ethyl-2methyl-6-oxo-4-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile
FP429	(2*S*,4*S*)-4-Amino-1-[(*E*)-3-carboxyacryloyl]pyrrolidine-2,4-dicarboxylic acid
L-Glu	L-Glutamate
GSK 1331268	2-((4-(5-Chloropyridin-2-yl)piperazin-1-yl)methyl)-1-methyl-1*H*-benzo[d]imidazole
GSK 2210875	(*R*)-1-(6-Methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)ethyl phenylcarbamate
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
LSP1-2111	[((3*S*)-3-Amino-3-carboxy)propyl][(4-hydroxy-5-methoxy-3-nitrophenyl)hydroxymethyl]phosphinic acid
LSP1-3081	[(3*S*)-3-(3-Amino-3-carboxypropyl(hydroxy)phosphinyl)-hydroxymethyl]-5-nitrothiophene
LSP4-2022	[((3*S*)-3-Amino-3-carboxy)propyl][(4-(carboxymethoxy)phenyl)hydroxymethyl]phosphinic acid
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 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-tetrahydro-quinazolin-2-ylsulfanyl]-ethanol
LY 456236	6-Methoxy-*N*-(4-methoxyphenyl)-4-quinazolinamine
LY 487379	*N*-(4-(2-Methoxyphenoxy)phenyl)-N-(2,2,2-trifluoroethylsulfonyl)pyrid-3-ylmethylamine
LY 541850	(1*S*,2*S*,3*S*,5*R*,6*S*)-2-Amino-3-methylbicyclo[3.1.0]hexane-2,6-dicarboxylic acid
LY 2812223	(1*S*,2*S*,3*S*,5*R*,6*S*)-3-(1*H*-1,2,4-Triazol-3-ylthio)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid
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
MGS0022	(1*R*,2*S*,5*R*,6*R*)-2-Amino-6-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
M-MPEP	2-[(3-Methoxyphenyl)ethynyl]-6-methylpyridine
MTEB	5-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]-benzonitrile
F-MTEB	3-Fluoro-5-[(2-methyl-1,3-thiazole-4-yl)ethynyl]-benzonitrile
MTEBP	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
MMPIP	6-(4-Methoxyphenyl)-5-methyl-3-(pyridin-4-yl)isoxazolo[4,5-c]pyridin-4(5*H*)-one
M-PEPy	3-Methoxy-5-(pyridin-2-ylethynyl)pyridine
MRZ 3573	2-(Phenylethynyl)-7,8-dihydroquinolin-5(6*H*)-one
MRZ 8676	6,6-Dimethyl-2-(phenylethynyl)-7,8-dihydroquinolin-5(6*H*)-one

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
PBPG	(2*S*)-2-(3′-Phosphonobicyclo[1.1.1]pentyl)glycine
PCEP	3-Amino-3-carboxypropyl-2′-carboxyethyl phosphinic acid
PCG-1	*trans*-(2*S*,1′*R*,2′*S*)-2-(2′-Phosphonocyclopropyl) glycine
PChPC	5-(4-(Hydroxymethyl)piperidin-1-yl)-*N*-(*trans*-4-methylcyclohexyl)pyrazine-2-carboxamide
PPG	4-Phosphonophenylglycine
PHCCC	*N*-Phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide
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
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
Ro 4988546	5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-ylethynyl]-pyridine-3-sulphonic acid
Ro 5488608	3′-(8-Methyl-4-oxo-7-trifluoromethyl-4,5-dihydro-3*H*-benzo[b][1,4]diazepin-2-yl)-biphenyl-3-sulphonic acid
Ro 645229	(*Z*)-1-(2-(Cycloheptyloxy)-2-(2,6-dichlorophenyl)vinyl)-1*H*-1,2,4-triazole
SIB1757	6-Methyl-2-(phenylazo)-3-pyridinol
SIB1893	(*E*)-2-Methyl-6-(2-phenylethenyl)pyridine
SOP	Serine-*O*-phosphate
SP203	3-Fluoro-5-[[2-(fluoromethyl)thiazol-4-yl]ethynyl]-benzonitrile
TBPCOB	(*S*)-2-((6-tert-Butylpyridin-3-yloxy)methyl)-2,3-dihydrobenzo[d]oxazolo[3,2-*a*]imidazole-7-carbonitrile
TC-N 22A	4,5,6,8-Tetrahydro-*N*-2-pyridinylpyrazolo[3′,4′:6,7]cyclohepta[1,2]thiazol-2-amine
TCN 238	(*E*)-4-(2-Phenylethenyl)-2-pyrimidinamine
2,2,2-TEMPS	2,2,2-Trifluoro-*N*-(4-(4-(pentan-2-yl)phenoxy)phenyl)-*N*-(pyridin-3-ylmethyl)ethanesulfonamide
THIIC	*N*-(4-((2-(Trifluoromethyl)-3-hydroxy-4-(isobutyryl)phenoxy)methyl)benzyl)-1-methyl-1*H*-imidazole-4-carboxamide
VU 71	4-Nitro-*N*-(1,4-diphenyl-1*H*-pyrazol-5-yl)benzamide
VU 1545	4-Nitro-*N*-(1-(2-fluorophenyl)-3-phenyl-1*H*-pyrazol-5-yl)benzamide
VU 0155041	*cis*-2-(3,5-Dichlorphenylcarbamoyl)cyclohexanecarboxylic acid
VU 0285683	3-Fluoro-5-(3-(pyridine-2-yl)-1,2,4-oxadiazol-5-yl)benzonitrile
VU 0357121	4-Butoxy-*N*-(2,4-difluorophenyl)benzamide
VU 0360172	*N*-Cyclobutyl-6-((3-fluorophenyl)ethynyl)nicotinamide
VU 0361737	*N*-(4-Chloro-3-methoxyphenyl)picolinamide
VU 0364439	*N*-(3-Chloro-4-(*N*-(2-chlorophenyl)sulfamoyl)phenyl)picolinamide
VU 366037	*N*-(3-Chloro-4-(2-chlorobenzamido)phenyl)picolinamide
VU 0364289	2-(4-(2-(Benzyloxy)acetyl)piperazin-1-yl)benzonitrile
VU 0365396	4-Butoxy-*N*-(2,6-difluorophenyl)benzamide
YM 202074	*N*-Cyclohexyl-6-{[(2-methoxyethyl)(methyl)amino]methyl}-*N*-methylthiazolo[3,2-a]benzimidazole-2-carboxamide
YM 230888	(*R*)-*N*-Cycloheptyl-6-({[(tetrahydro-2-furyl)methyl]amino}methyl)thieno[2,3-*d*]pyrimidin-4-ylamine

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Metabotropic Glutamate Receptor Compounds Available from Tocris

Cat. No.	Product Name	Primary Action
Group I mGlu Receptors		
Agonists		
0284	(1S,3*R*)-ACPD	Group I and group II mGlu agonist; active isomer of (±)-*trans*-ACPD (Cat. No. 0187)
0187	(±)-*trans*-ACPD	Group I and II mGlu agonist
1049	CHPG	$mGlu_5$ selective agonist
3695	CHPG sodium salt	Selective $mGlu_5$ agonist; sodium salt of CHPG (Cat. No. 1049)
0342	(*RS*)-3,5-DHPG	Selective group I mGlu agonist
0805	(*S*)-3,5-DHPG	Selective group I mGlu agonist; active enantiomer of (*RS*)-3,5-DHPG (Cat. No. 0342)
0188	L-Quisqualic acid	Group I mGlu agonist; also AMPA agonist
0162	S-Sulfo-L-cysteine sodium salt	Group I agonist
Inverse Agonists		
2501	Bay 36-7620	$mGlu_1$ inverse agonist
Antagonists		
5229	ABP 688	High affinity human $mGlu_5$ antagonist
0904	AIDA	Potent and selective group I mGlu antagonist
5614	AZD 2066	$mGlu_5$ antagonist; orally bioavailable and brain penetrant
5613	AZD 9272	Potent and selective $mGlu_5$ antagonist; brain penetrant
0125	DL-AP3	Group I mGlu antagonist
0329	(*S*)-3-Carboxy-4-hydroxyphenylglycine	Group I mGlu antagonist; also group II mGlu agonist
0323	(*S*)-4-Carboxyphenylglycine	Competitive group I mGlu antagonist; also weak group II agonist
1028	CPCCOEt	Selective non-competitive $mGlu_1$ antagonist
2333	JNJ 16259685	Highly potent, $mGlu_1$-selective non-competitive antagonist
1237	LY 367385	Selective $mGlu_{1a}$ antagonist
2390	LY 456236	Selective $mGlu_1$ antagonist
2196	3-MATIDA	Potent and selective $mGlu_1$ antagonist
1212	MPEP	Potent $mGlu_5$ antagonist; also positive allosteric modulator at $mGlu_4$ receptors
2921	MTEP	Potent and selective $mGlu_5$ antagonist
4134	NPS 2390	Group I mGlu antagonist
1027	PHCCC	Potent group I mGlu antagonist
1215	SIB 1757	Highly selective $mGlu_5$ antagonist
2986	YM 230888	Selective $mGlu_1$ antagonist
2448	YM 298198	Highly potent, selective non-competitive $mGlu_1$ antagonist
Modulators		
3235	CDPPB	Positive allosteric modulator of $mGlu_5$ receptors
1952	DCB	Allosteric potentiator of $mGlu_5$ receptors
1625	DFB	Positive allosteric modulator of $mGlu_5$ receptors
5000	FTIDC	Potent and selective negative allosteric modulator of $mGlu_1$ receptors; also $mGlu_1$ inverse agonist
5275	LSN 2463359	Potent and selective positive allosteric modulator of $mGlu_5$ receptors
4348	Ro 01-6128	Positive allosteric modulator of $mGlu_1$ receptors
4347	Ro 67-4853	Positive allosteric modulator of group I mGlu receptors
4346	Ro 67-7476	Positive allosteric modulator of $mGlu_1$ receptors
4323	VU 0360172	Positive allosteric modulator of $mGlu_5$ receptors
5693	VU 0409551	Selective positive allosteric modulator of $mGlu_5$ receptors; brain penetrant and orally bioavailable
5379	VU 0469650	Potent and selective negative allosteric modulator of $mGlu_1$ receptors
5377	VU 0483605	Positive allosteric modulator of $mGlu_1$ receptors
3325	VU 1545	Positive allosteric modulator of $mGlu_5$ receptors

Group II mGlu Receptors		
Activators		
4120	Xanthurenic acid	Selectively activates group II mGlu receptors
Agonists		
0187	(±)-*trans*-ACPD	Group I and II 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
0333	L-CCG-I	Potent group II mGlu agonist
0975	DCG IV	Highly potent group II mGlu agonist; also NMDA agonist
3246	LY 354740	Potent and highly selective group II mGlu agonist
2453	LY 379268	Highly selective group II mGlu agonist
5064	LY 379268 disodium salt	Selective group II mGlu agonist; sodium salt of LY 379268 (Cat. No. 2453)
0391	Spaglumic acid	Selective $mGlu_3$ agonist
Antagonists		
1073	(*RS*)-APICA	Selective group II mGlu antagonist
0971	EGLU	Highly selective group II mGlu antagonist
1209	LY 341495	Highly potent and selective group II mGlu antagonist
4062	LY 341495 disodium salt	Potent and selective group II mGlu antagonist; disodium salt of LY 341495 (Cat. No. 1209)
2913	Ro 64-5229	Selective, non-competitive $mGlu_2$ antagonist
Modulators		
4048	BINA	Selective positive allosteric modulator of $mGlu_2$ receptors
3949	CBiPES	Positive allosteric modulator of $mGlu_2$ receptors
3283	LY 487379	Selective positive allosteric modulator of $mGlu_2$ receptors
4388	MNI 137	Selective negative allosteric modulator of group II mGlu receptors
5362	TASP 0433864	Selective positive allosteric modulator of $mGlu_2$ receptors
Group III mGlu Receptors		
Agonists		
1111	ACPT-I	Group III mGlu agonist
2385	AMN 082	Selective $mGlu_7$ agonist
0103	L-AP4	Selective group III mGlu agonist
4119	Cinnabarinic acid	Selective $mGlu_4$ agonist
1302	(*S*)-3,4-DCPG	Potent and selective $mGlu_{8a}$ agonist
0238	*O*-Phospho-L-serine	Group III mGlu agonist
1220	(*RS*)-PPG	Potent and selective $mGlu_8$ agonist
Antagonists		
0972	CPPG	Potent group III mGlu antagonist
0853	MPPG	Group III and group II mGlu antagonist; more selective for group III than group II
0803	MSOP	Selective group III mGlu antagonist
0854	MSPG	Group III and group II mGlu antagonist
1369	UBP1112	Group III mGlu antagonist
5248	XAP 044	Potent and selective $mGlu_7$ antagonist
Modulators		
5715	(±)-ADX 71743	Negative allosteric modulator of $mGlu_7$ receptors; brain penetrant
4832	AZ 12216052	Positive allosteric modulator of $mGlu_8$ receptors
2963	MMPIP	Potent and selective negative allosteric modulator of $mGlu_7$ receptors
3248	VU 0155041	Potent positive allosteric modulator of $mGlu_4$ receptors
3311	VU 0155041 sodium salt	Potent positive allosteric modulator of $mGlu_4$ receptors; sodium salt of VU 0155041 (Cat. No. 3248)
3707	VU 0361737	Selective positive allosteric modulator of $mGlu_4$ receptors
5378	VU 0422288	Selective positive allosteric modulator of group III mGlu receptors

Non-selective mGlu Receptors		
Agonists		
0218	L-Glutamic acid	Endogenous, non-selective glutamate receptor agonist
0285	Ibotenic acid	Non-selective mGlu agonist, also NMDA agonist
Antagonists		
0112	γDGG	Broad spectrum glutamatergic antagonist
0101	DL-AP4	Broad spectrum glutamatergic antagonist
0223	Kynurenic acid	Broad spectrum glutamatergic antagonist
0336	(*RS*)-MCPG	Non-selective mGlu antagonist
3696	(*RS*)-MCPG disodium salt	Non-selective mGlu antagonist; disodium salt of (*RS*)-MCPG (Cat. No. 0336)
0337	(*S*)-MCPG	Non-selective mGlu antagonist; active isomer of (*RS*)-MCPG (Cat. No. 0336)
mGlu Receptor Ligand Sets		
1826	Group I mGlu Receptor Tocriset™	Selection of 5 group I mGlu receptor ligands (Cat. Nos. 0805, 0188, 1237, 1212 and 0337)
1827	Group II mGlu Receptor Tocriset™	Selection of 5 group II mGlu receptor ligands (Cat. Nos. 1208, 0975, 1209, 0971 and 0337)
1828	Group II mGlu Receptor Tocriset™	Selection of 5 group III mGlu receptor ligands (Cat. Nos. 0103, 1220, 0972, 0803 and 1209)
1829	Mixed mGlu Receptor Tocriset™	Selection of 5 mixed mGlu receptor ligands (Cat. Nos. 0805, 0975, 0103, 0337 and 1209)
Caged Glutamate Compounds		
6553	JF-NP-26	Caged Raseglurant (Cat. No. 4416)
5785	MDNI-caged-L-gluatmate	Stable photoreleaser of L-glutamate
1490	MNI-caged-L-glutamate	Stable photoreleaser of L-glutamate
3332	NPEC-caged-LY 379268	Caged version of LY 379268 (Cat. No. 2453)
3574	RuBi-Glutamate	Caged glutamate; excited by visible wavelengths
Miscellaneous Glutamate		
3618	Acamprosate	Glutamatergic modulator and GABA agonist
1611	Lamotrigine	Inhibits glutamate release; anticonvulsant
2289	Lamotrigine isethionate	Inhibits glutamate release; water-soluble salt of Lamotrigine (Cat. No. 1611)
2538	L-BMAA	Glutamate agonist; neurotoxic amino acid
0768	Riluzole	Glutamate release inhibitor; also inhibits GABA uptake and blocks Na_v channels
2625	Zonisamide	Anticonvulsant, modulates glutamate neurotransmission
Carboxypeptidase		
Inhibitors		
5033	2-MPPA	Selective glutamate carboxypeptidase II (GCP II) inhibitor; orally bioavailable
1380	PMPA (NAALADase inhibitor)	Highly potent, selective NAALADase (GCP II) inhibitor
2675	ZJ 43	Glutamate carboxypeptidase II and III (NAALADase, NAAG peptidase) inhibitor
Glutamate Transporters (EAATs)		
Inhibitors		
0237	7-Chlorokynurenic acid	Potent competitive inhibitor of L-glutamate uptake
3697	7-Chlorokynurenic acid sodium salt	Potent competitive inhibitor of L-glutamate uptake; sodium salt of 7-Chlorokynurenic acid (Cat. No. 0237)
0111	Dihydrokainic acid	Non-transportable inhibitor of EAAT2 (GLT-1)
1223	DL-TBOA	Selective non-transportable inhibitor of EAATs
2532	TFB-TBOA	High affinity EAAT1 and EAAT2 blocker
0183	L-(-)-*threo*-3-Hydroxyaspartic acid	Transportable EAAT1-4 inhibitor and non-transportable EAAT5 inhibitor
0811	(±)-*threo*-3-Hydroxyaspartic acid	EAAT2 and EAAT4 blocker
2652	WAY 213613	Potent, non-substrate EAAT2 inhibitor
Modulators		
6578	GT 949	Potent and selective positive allosteric modulator of EAAT2
Other		
3732	Ceftriaxone disodium salt	Increases EAAT2 expression and activity; neuroprotective
5082	LDN 212320	Increases EAAT2 expression; neuroprotective

Global info@bio-techne.com bio-techne.com/find-us/distributors TEL +1 612 379 2956
North America TEL 800 343 7475 Europe | Middle East | Africa TEL +44 (0)1235 529449
China info.cn@bio-techne.com TEL +86 (21) 52380373

bio-techne.com

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