# Metabotropic Glutamate Receptors

Molecular Pharmacology

TOCRIS bioscience


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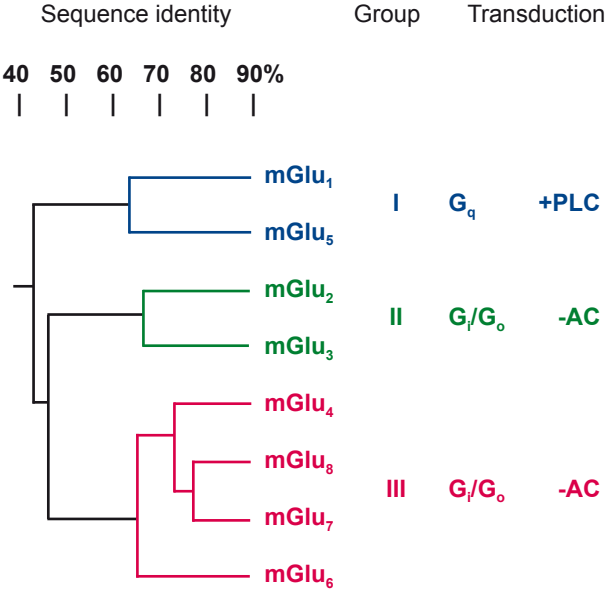
Francine C. Acher is currently a CNRS Research Director within the Biomedical Institute of University Paris Descartes (France). Her research focuses on structure/function studies and drug discovery using chemical tools (synthetic chemistry, molecular modeling), molecular biology and pharmacology within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


## Contents



### Figure 1 | Classification of the Subtypes of mGlu Receptors




## Introduction

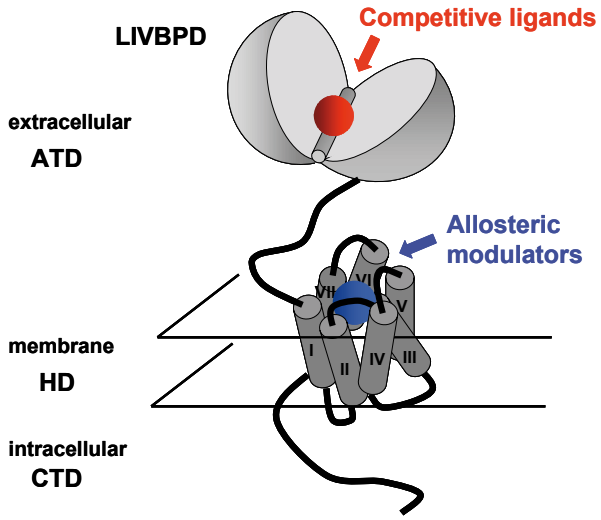
Glutamate is the major excitatory neurotransmitter in the brain. It is released from presynaptic vesicles and activates postsynaptic ligand-gated ion channel receptors (NMDA, AMPA and kainate receptors) to secure fast synaptic transmission.[1] Glutamate also activates metabotropic glutamate (mGlu) receptors 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]

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]

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




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.

## 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 brain barrier and that its peptidyl prodrug, LY 544344, was orally active as an anticonvulsant and anxiolytic.[26,27] Presently a sulfonyl analog, LY 404039, orally administered as a methionine amide prodrug LY 2140023, is being developed for the treatment of schizophrenia[28,29] and has 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

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

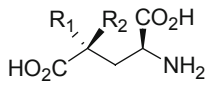
| Receptor | | Group I | | Group II | | Group III | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | $mGlu_1$ | $mGlu_5$ | $mGlu_2$ | $mGlu_3$ | $mGlu_4$ | $mGlu_6$ | $mGlu_7$ | $mGlu_8$ |
| **Non-selective agonists** | **L-Glu**[c,d] | 1-13 | 3-11 | 0.3-12 | 2-9 | 3-17 | 5-38 | 2300 | 8-10 |
| | **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 | – | – |
| **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[i] | 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**[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*)-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.[ts] | 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)**

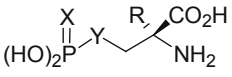
[a] $EC_{50}$ or $K_b$ values (μM) measured with rat or human (when indicated[b]) cloned receptors. ant. = antagonist; n. e. = no effect. References for agonist potencies which have been cited in reviews [5] and/or [6] are referred as such.

[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

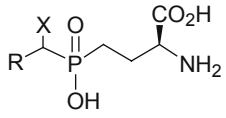
## Figure 3A | Competitive mGlu Receptor Ligand Structures



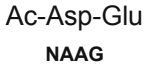
$R_1$, $R_2$ = H **L-Glutamic acid**
$R_1$ = H, $R_2$ = $CH_2CH(Ph)_2$ ADED (LY 310225)



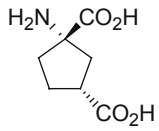
X = O Y = $CH_2$ R = H ***(S)*-AP4**
X = S Y = $CH_2$ R = H (*S*)-thioAP4
X = O Y = O R = H ***(S)*-SOP**
X = O Y = $CH_2$ R = Me **MAP4**



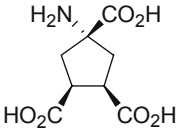
X = H R = $CH_2CO_2H$ (*S*)-PCEP
X = OH R = 3-$NO_2$,4-OH,5-OMePh LSP1-2111
X = OH R = 4-($OCH_2CO_2H$)Ph LSP4-2022
X = OH R = 5-$NO_2$thiophene LSP1-3081



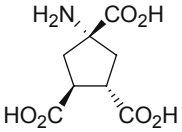
**NAAG (Spaglumic acid)**



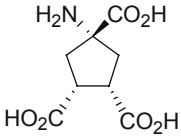
**(1*S*,3*R*)-ACPD**



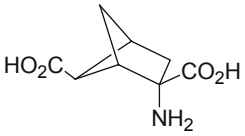
**ACPT-I**



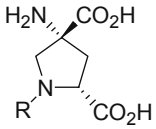
(+)-ACPT-III



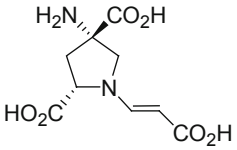
**ACPT-II**



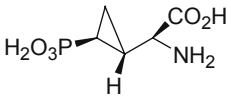
ABHxD-I



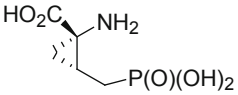
R= H **(2*R*,4*R*)-APDC**
R= $CH_2Ph$ BnAPDC
R= $CH_2$ 1-Naphthyl NM-APDC



FP429

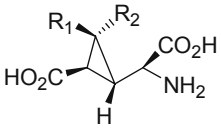


PCG-1

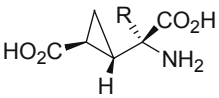


(1*S*,2*R*)-APCPr

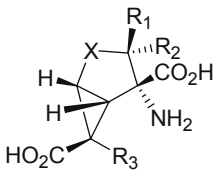
(*S*)-PBPG



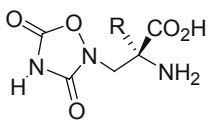
$R_1$, $R_2$ = H **L-CCG-I**
$R_1$ = H, $R_2$ =3'-$CH_3$ 3'Me-CCG
$R_1$ = H, $R_2$ =3'-$CH_2OH$ 3'HM-CCG
$R_1$ = H, $R_2$ =3'-$CH_2SH$ 3'SM-CCG
$R_1$ = H, $R_2$ =3'-cyclopropyl 3'CP-CCG
$R_1$ = H, $R_2$ = $CO_2H$ **DCG-IV**
$R_1$ = H, $R_2$ = 9'-xanthylethyl XE-CCG-I



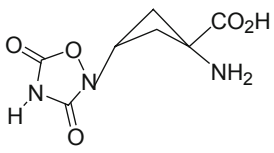
R = Me MCCG-I
R = 9'-xanthylmethyl **LY 341495**
R = $(3\text{-}ClPh)_2Et$ mCD-CCG



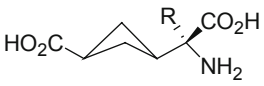
X = $CH_2$ $R_1$,$R_2$,$R_3$ = H **LY 354740**
X = O $R_1$,$R_2$,$R_3$ = H **LY 379268**
X = S $R_1$,$R_2$,$R_3$ = H LY 389795
X = $SO_2$ $R_1$,$R_2$,$R_3$ = H LY 404039
X = $CH_2$ $R_1$,$R_3$ = H, $R_2$ = $CH_3$ LY 541850
X = $CH_2$ $R_1$,$R_3$ = H, $R_2$ = 5-thio(1*H*,2,4)triazole LY 2812223
X = $CH_2$ $R_1$,$R_3$ = H, $R_2$ = F MGS0008
X = $CH_2$ $R_1$,$R_2$ = H $R_3$ = F MGS0022
X = CO $R_1$,$R_2$ = H $R_3$ = F MGS0028
X = $CH_2$ $R_2$,$R_3$ = H $R_1$=OH HYDIA
X = $CH_2$ $R_2$= H $R_1$ = 3,4-$Cl_2PhCH_2O$ $R_3$ = F MGS0039



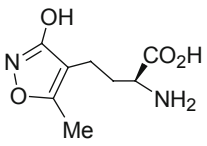
R = H **Quis**
R = benzyl BnQuis



Z-CBQA



R = 9'-thioxanthylmethyl
LY 393675



(*S*)-HomoAMPA

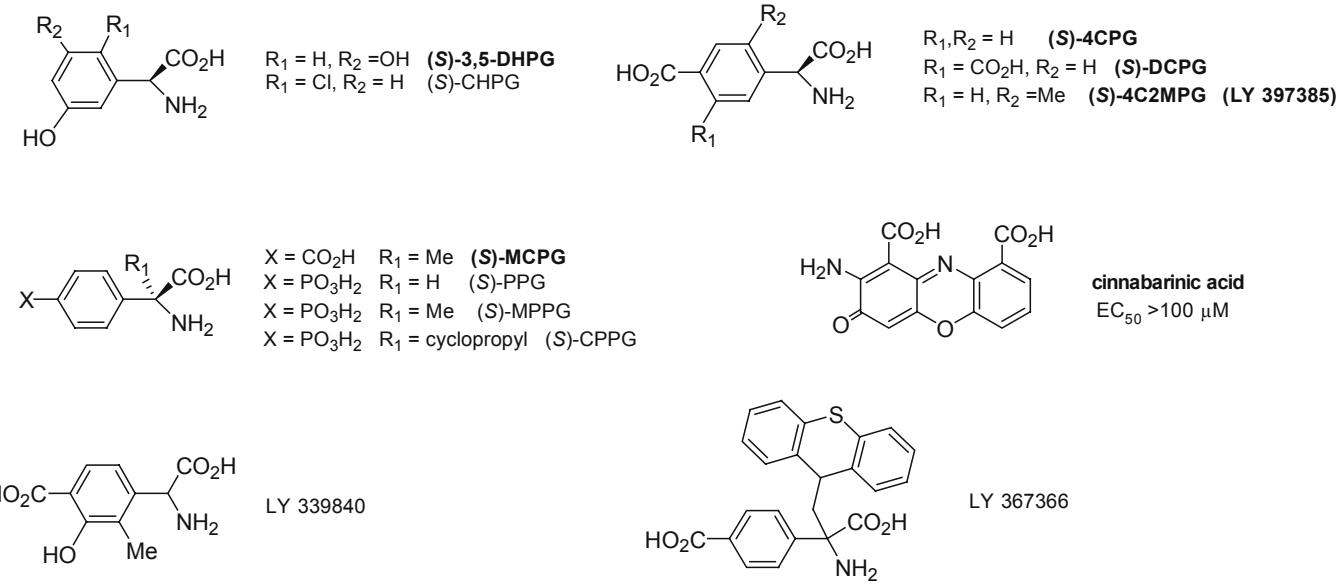
**(Bold Text Denotes Compounds Available From Tocris)**

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

## Figure 3B | Competitive mGlu Receptor Ligand Structures




**(Bold Text Denotes Compounds Available From Tocris)**

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 popular 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 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*)-APCPr[46,47] 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´HM-CCG) 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 by 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]

### 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)

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

| | | 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 | 0.10 | 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 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 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]

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 XE-CCG69 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 arylalkyl-substituted 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 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 non-selective 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), R214127[85]/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-TBPC[94,95] (Hoffmann-La Roche), thiazolobenzimidazoles YM 298198,[96] YM 202074[97] and thienopyrimidine 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

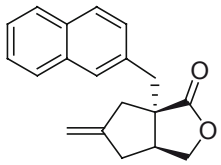
The first allosteric potentiators of rat $mGlu_1$ receptors to be disclosed were Ro 01-6128, Ro 67-4853105,[107] and Ro 67-7476.[108,109] Chimeric and mutated receptors were constructed to confirm the transmembrane localization of the binding site of these ligands, which are subtype I selective.[108] 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 $mGlu_1$ potentiator, interacting with a site distinct from that of NAMs.[110]

#### $mGlu_5$ Antagonists

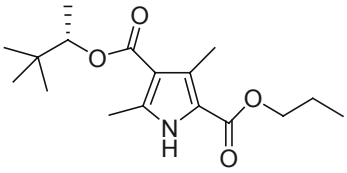
SIB 1757 and SIB 1893[111] were initially found and optimized into MPEP[112] which has been widely used to explore the physiological roles of $mGlu_5$ receptors as a potential therapeutic target.[113] Further investigations at

## Figure 4 | Group I Allosteric Modulator Structures and Potencies

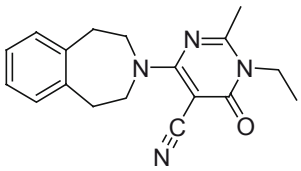
### A. $mGlu_1$ Receptor Antagonists



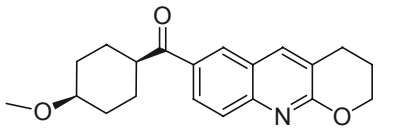
**Bay 36-7620**
$IC_{50}$ = 160 nM
$K_i$ = 11.2 nM



DM-PPP
$IC_{50}$ = 16 nM

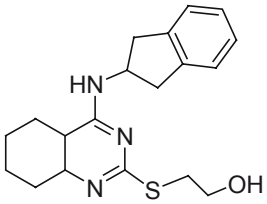


EM-TBPC
$K_i$ = 11 nM

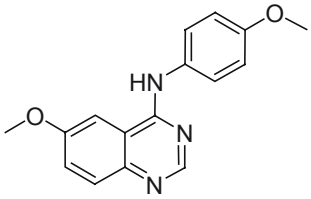


(and enantiomer)

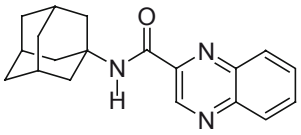
**JNJ 16259685**
$IC_{50}$ = 0.55 nM
$K_i$ = 0.34 nM



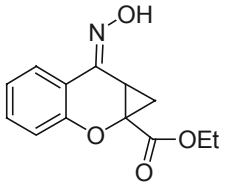
LY 456066
$IC_{50}$ = 12 nM ($hmGlu_1$)



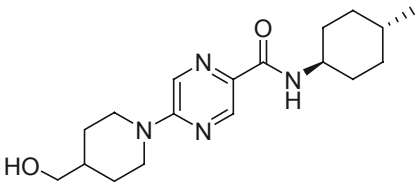
**LY 456236**
$IC_{50}$ = 140 nM



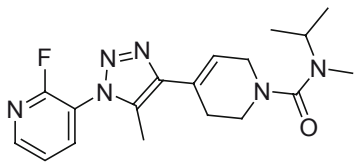
NPS2390
$IC_{50}$ = 5.2 nM chimera CaSR/$mGlu_1$
$K_i$ = 1.4 nM



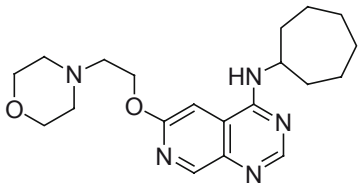
CPCCOEt
$IC_{50}$ = 10.3 μM
$K_i$ = 4.9 μM
(-) isomer active



pyrazine-2-carboxamide
PChPC
$K_i$ = 9 nM

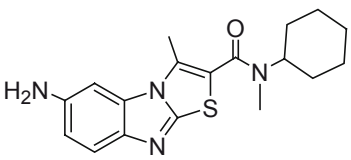


FTIDC

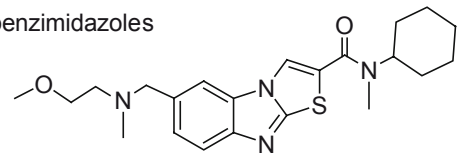


azaquinazoline
CMPPA
$K_i$ = 6 nM

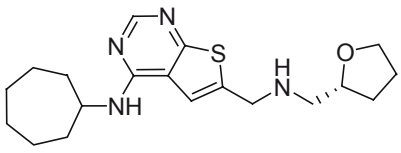
thiazolobenzimidazoles



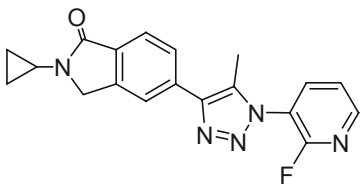
**YM 298198**
$IC_{50}$ = 16 nM



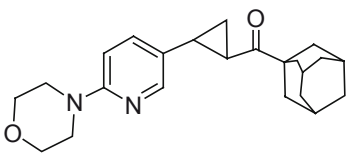
**YM 202074**
$IC_{50}$ = 8.6 nM



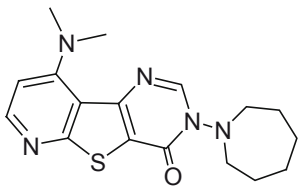
**YM 230888**
$IC_{50}$ = 16 nM



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



adamantyl methanone
AdPyM
$K_i$ = 24 nM

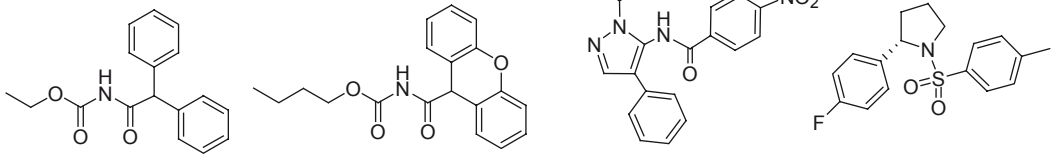


triazafluorenone
**A 841720**
$IC_{50}$ = 10 nM ($hmGlu_1$)

**(Bold Text Denotes Compounds Available From Tocris)**

## Figure 4 | Group I Allosteric Modulator Structures and Potencies

### B. $mGlu_1$ Receptor Potentiators



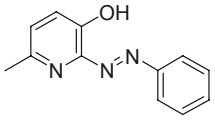
**Ro 01-6128**
$EC_{50}$ = 0.2 μM

**Ro 67-4853**
$EC_{50}$ = 0.07 μM

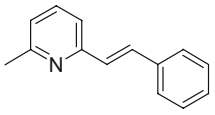
VU 71
$EC_{50}$ = 2.4 μM

**Ro 67-7476**
$EC_{50}$ = 0.2 μM

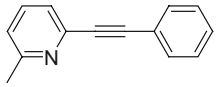
### C. $mGlu_5$ Receptor Antagonists; Alkyne Series



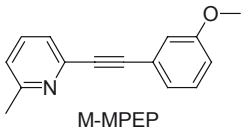
**SIB 1757**
$IC_{50}$ = 0.37 μM ($hmGlu_5$)



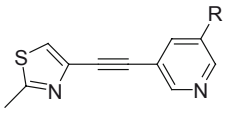
**SIB 1893**
$IC_{50}$ = 0.29 μM ($hmGlu_5$)



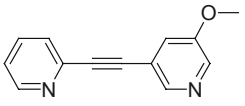
**MPEP**
$IC_{50}$ = 36 nM ($hmGlu_5$)



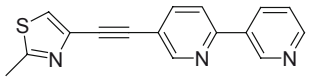
M-MPEP
$IC_{50}$ = 10 nM ($hmGlu_5$)



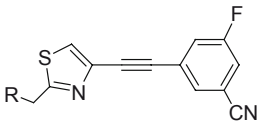
R=H **MTEP** $IC_{50}$ = 5 nM ($hmGlu_5$)
$R=CH_2OMe$ MM-MTEP $IC_{50}$ = 7 nM ($hmGlu_5$)



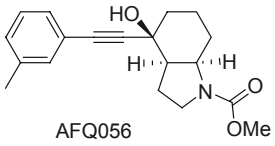
M-PEPγ
$IC_{50}$ = 1 nM ($hmGlu_5$)



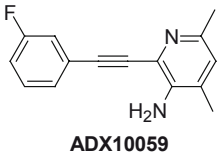
MTEBP
$IC_{50}$ = 2 nM ($hmGlu_5$)



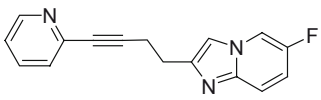
R=H F-MTEB $IC_{50}$ = 0.08 nM
R=F SP203 $IC_{50}$ = 0.036 nM



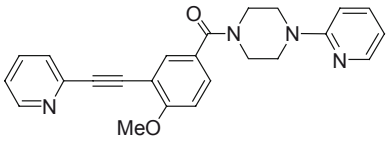
AFQ056



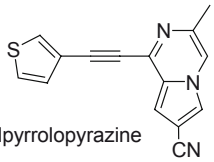
**ADX10059**



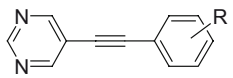
ADX48621



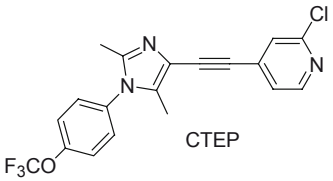
ethynylbenzamide
$IC_{50}$ = 8 nM



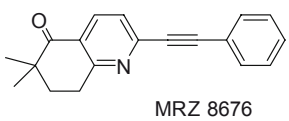
ethynylpyrrolopyrazine
$IC_{50}$ = 0.63 nM



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 ($hmGlu_5$)

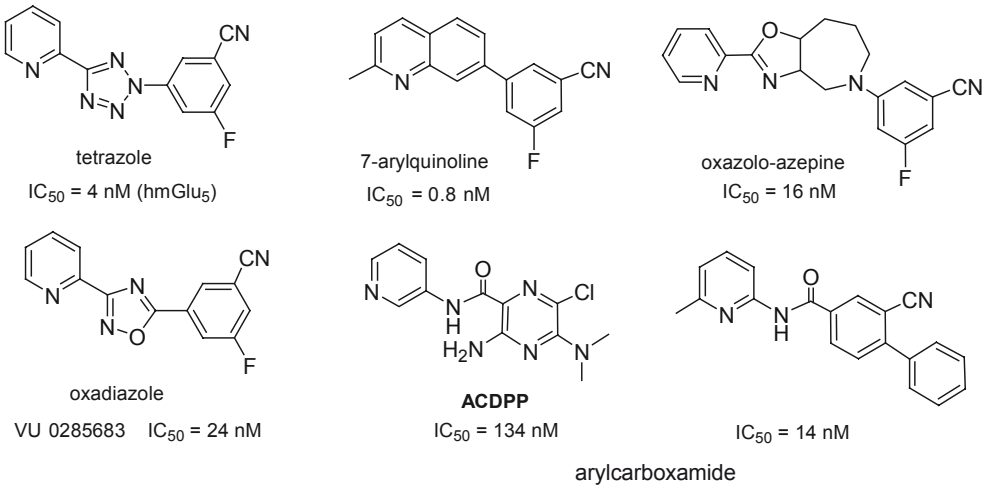


MRZ 8676
$IC_{50}$ = 23 nM ($hmGlu_5$)

**(Bold Text Denotes Compounds Available From Tocris)**

## Figure 4 | Group I Allosteric Modulator Structures and Potencies

### D. $mGlu_5$ Receptor Antagonists; Alkyne Biostere Series




**(Bold Text Denotes Compounds Available From Tocris)**

Novartis led to a methoxy derivative M-MPEP, that can be easily tritium-labeled[114] and lead optimization resulted in AFQ056 (Mavoglurant) that is currently 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 8676[127] 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-(phen ylethynyl)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 phenyl-tetrazoles,[140] carbamoyloximes,[141] thiazolotriazoles (such as GSK 2210875),[142] pyrrolidinylpyridines,[143] piperidylamides,[144] benzimidazoles,[145] and anilino-quinazolines.[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]

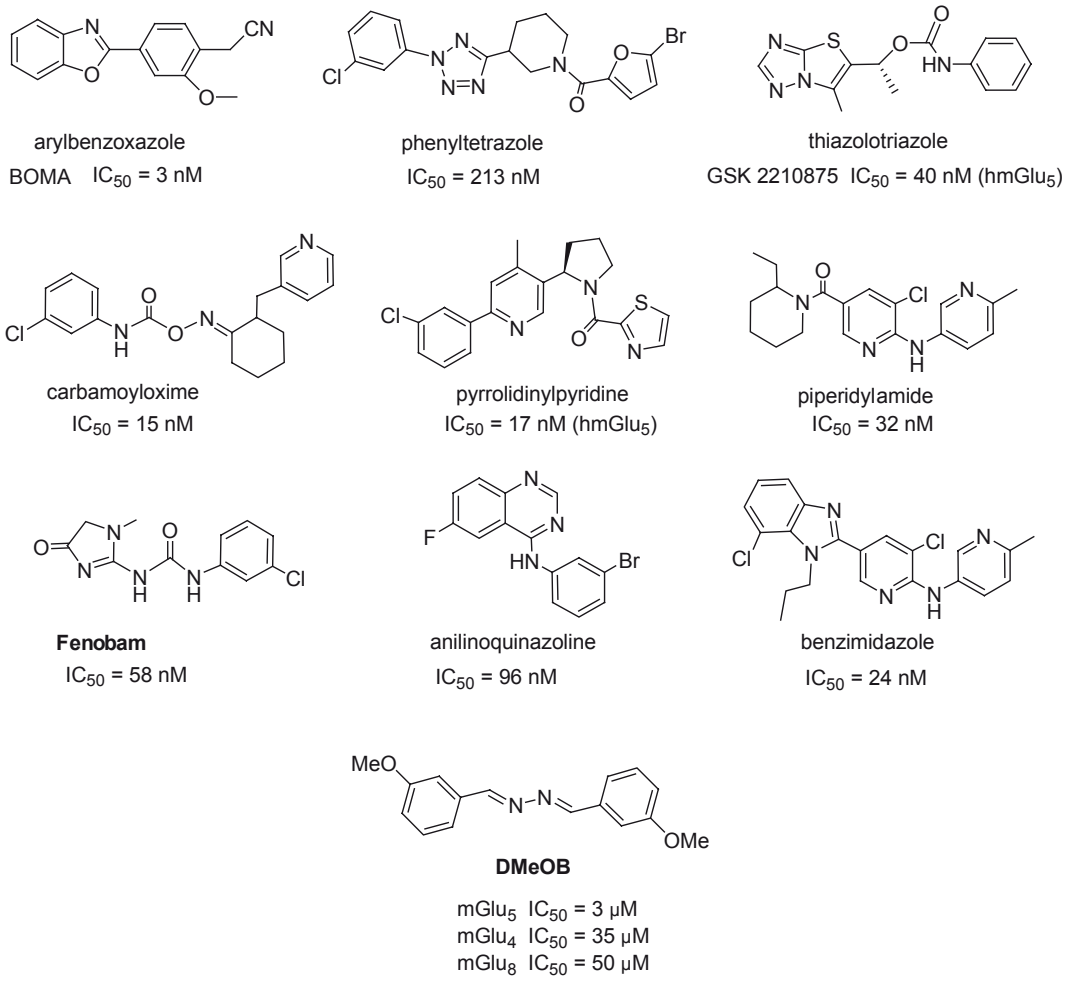
Potential therapeutic application of $mGlu_5$ antagonists have been detailed in several reviews.[3,115,124,149] Additionally, molecular determinants of the high affinity binding site of MPEP have been defined[150] and a striking similarity with critical residues of the $mGlu_1$ binding site was observed.[151]

### $mGlu_5$ 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

## Figure 4 | Group I Allosteric Modulator Structures and Potencies

### E. $mGlu_5$ Receptor Antagonists; Other Series




**(Bold Text Denotes Compounds Available From Tocris)**

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 pyrido-oxazines 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.

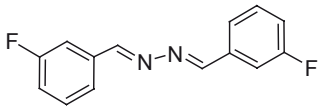
## Group II (Figure 5)

### $mGlu_2$ 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

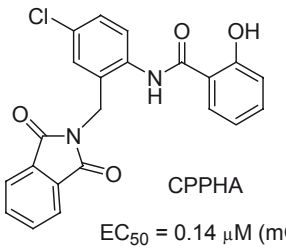
## Figure 4 | Group I Allosteric Modulator Structures and Potencies

### F. $mGlu_5$ Receptor Potentiators



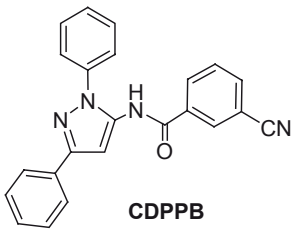
**DFB**

$EC_{50}$ = 2.4 μM ($mGlu_5$)



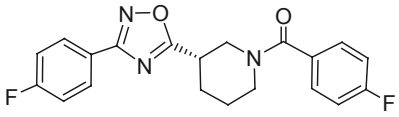
CPPHA

$EC_{50}$ = 0.14 μM ($mGlu_5$)



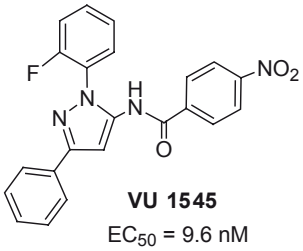
**CDPPB**

$EC_{50}$ = 20 nM ($hmGlu_5$)



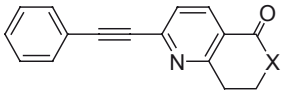
ADX47273

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



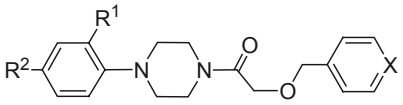
**VU 1545**

$EC_{50}$ = 9.6 nM



X= CH MRZ 3573 $EC_{50}$ = 38 nM

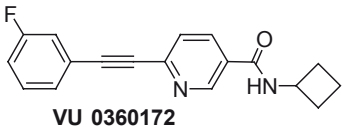
X= NH cyclopentyl $EC_{50}$ = 5.9 nM



*N*-arylpiperazine amide

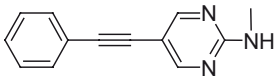
X=N $R_1$=Cl, $R_2$=F CPPZ $EC_{50}$ = 0.55 μM

X=CH $R_1$=CN, $R_2$=H VU 0364289 $EC_{50}$ = 1.6 μM



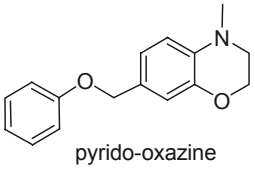
**VU 0360172**

$EC_{50}$ = 16 nM



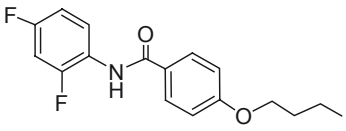
2-aminomethyl-pyrimidine

$EC_{50}$ = 14 nM



pyrido-oxazine

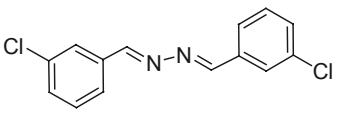
$EC_{50}$ = 50 nM



VU 0357121

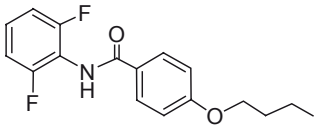
$EC_{50}$ = 33 nM

### G. $mGlu_5$ Receptor Neutral Modulators



**DCB**

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

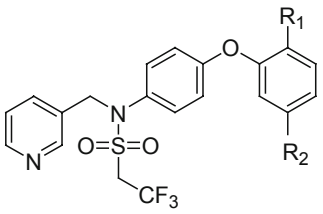


VU 0365396

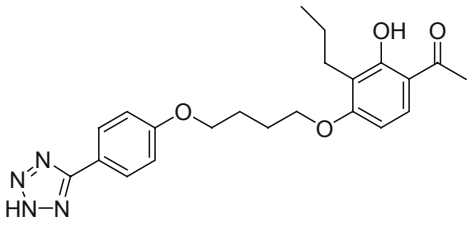
**(Bold Text Denotes Compounds Available From Tocris)**

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

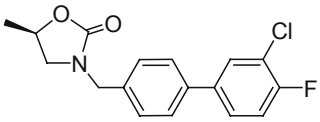
### A. $mGlu_2$ Receptor Potentiators



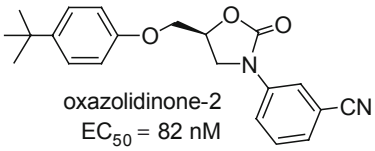
$R_1 = OCH_3$ $R_2 = H$ **LY 487379** $EC_{50} = 270$ nM
$R_1 = H$ $R_2 = OCH(CH_3)CH_2\text{-}CH_2\text{-}CH_3$ 2,2,2-TEMPS $EC_{50} = 14$ nM



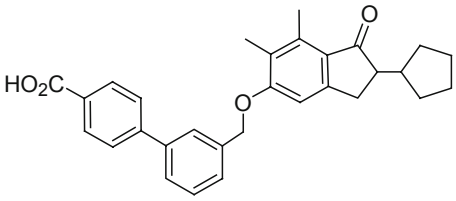
phenyl-tetrazolyl acetophenone
PTBE $EC_{50} = 0.43$ µM



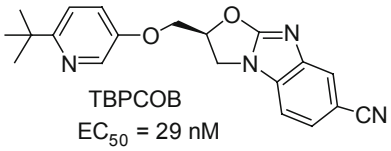
oxazolidinone-1
$EC_{50} = 30$ nM



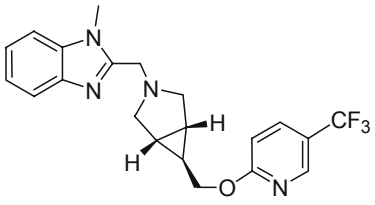
oxazolidinone-2
$EC_{50} = 82$ nM



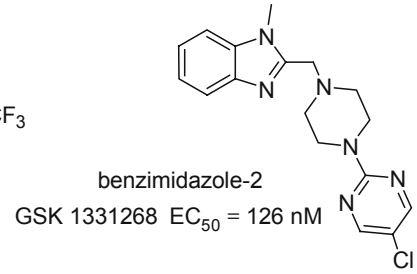
**BINA**
$EC_{50} = 111$ nM



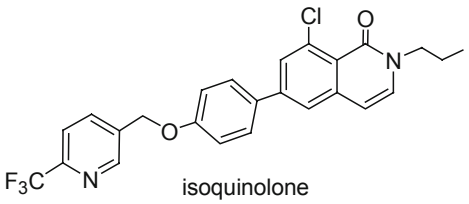
TBPCOB
$EC_{50} = 29$ nM



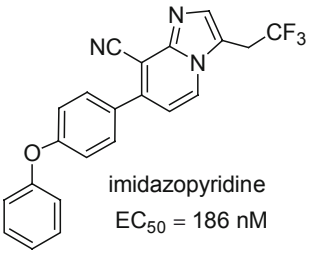
benzimidazole-1
$EC_{50} = 30$ nM



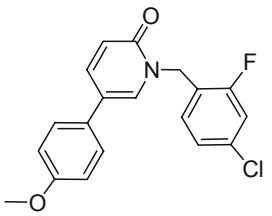
benzimidazole-2
GSK 1331268 $EC_{50} = 126$ nM



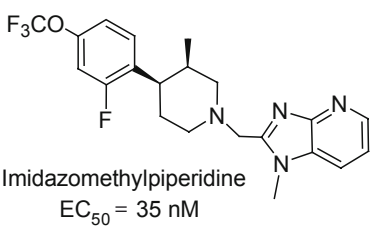
isoquinolone
$EC_{50} = 250$ nM



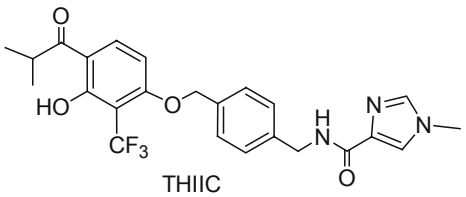
imidazopyridine
$EC_{50} = 186$ nM



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)**

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] imidazo-pyridine,[186] 1,5-disubstituted pyridine,[187] imidazole carboxamide (THIIC),[188] isoquinolones,[189] and imidazomethylpiperidine.[190]

### $mGlu_{2/3}$ Antagonists

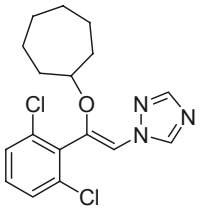
To date, only $mGlu_{2/3}$ NAMs have been disclosed, mostly by researchers at Hofmann-La Roche.[169] Heterocyclic enol ethers such as Ro 64-5229 were reported as first selective non-competitive $mGlu_2$ receptor antagonists.[191] A series of dihydro-benzo[b][1,4] diazepin-2-one derivatives was later disclosed that 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] Very 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]

### $mGlu_3$

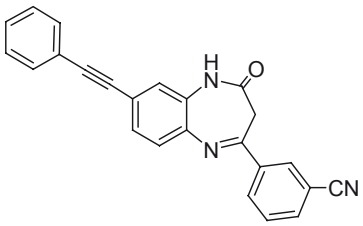
A recent screening campaign provided specific $mGlu_3$ PAMs and NAMs, however the chemical structures are yet to be disclosed.[196] Interestingly, it was found that varying a substituent on the PHCCC structure resulted in a $mGlu_{2/3}$ SAM or conferred dual $mGlu_2$ NAM - $mGlu_3$ PAM properties.[199]

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

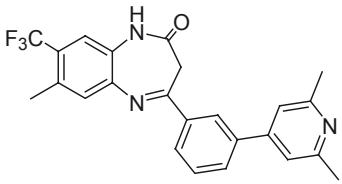
### B. $mGlu_{2/3}$ Receptor Antagonists



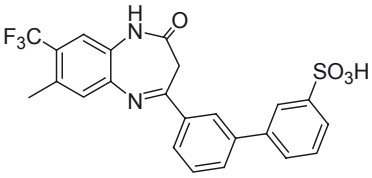
**Ro 645229**
$IC_{50}$ = 109 nM



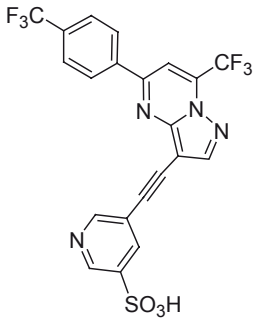
benzodiazepinone
$IC_{50}$ = 34 nM



Ro 4491533
$IC_{50}$ = 2 nM

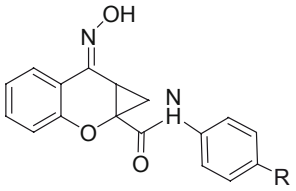


Ro 5488608
$IC_{50}$ = 2.5 nM



Ro 4988546
$IC_{50}$ = 8.7 nM

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

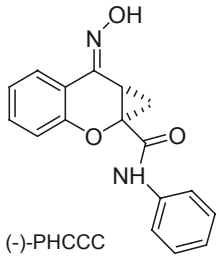


| | $hmGlu_2$ $K_i$ (μM) | $hmGlu_2$ $IC_{50}$ (μM) | $hmGlu_3$ $EC_{50}$ (μM) |
|---|---|---|---|
| R=H **PHCCC** | N.E | N.E | N.E |
| R=F | 6.6 | N.E. (SAM) | N.E. (SAM) |
| R=Cl | 1.0 | 0.8 (NAM) | 13.4 (PAM) |
| R-Me | 0.6 | 1.5 (NAM) | 8.9 (PAM) |
| R=OMe | 0.8 | 1.0 (NAM) | 10.4 (PAM) |

**(Bold Text Denotes Compounds Available From Tocris)**

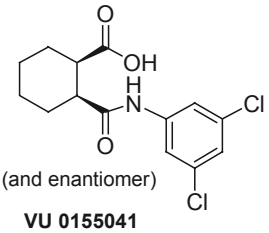
## Figure 5 | Group II and Group III Allosteric Modulator Structures and Potencies

### D. $mGlu_4$ Receptor Potentiators



(-)-PHCCC

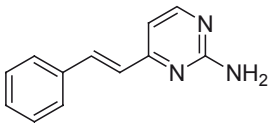
$EC_{50}$ = 3.1 μM
$E_{max}$ = 120%



(and enantiomer)

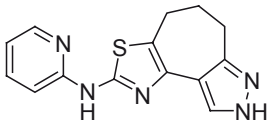
**VU 0155041**

$EC_{50}$ = 0.75 μM
$E_{max}$ = 144%



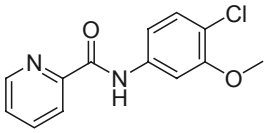
**TCN 238**
aminopyrimidine

$EC_{50}$ = 1 μM
$E_{max}$ = 127%



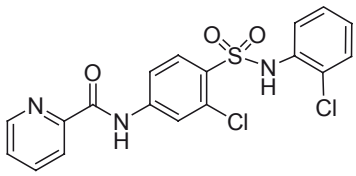
**TC-N 22A**
thiazolopyrazole

$EC_{50}$ = 9 nM
$E_{max}$ = 120%



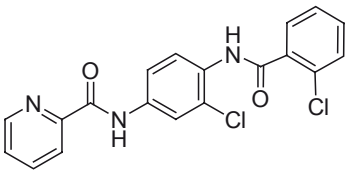
**VU 0361737**

$EC_{50}$ = 0.24 μM
$E_{max}$ = 182%



**VU 0364439**

$EC_{50}$ = 19.8 nM
$E_{max}$ = 122%

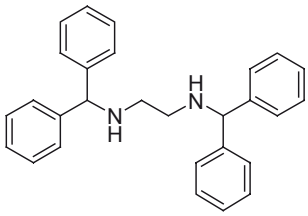


VU 0366037

$EC_{50}$ = 0.52 μM
$E_{max}$ = 94%

phenylpicolinamide series

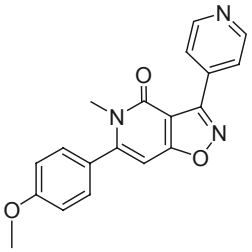
### E. $mGlu_7$ Receptor Allosteric Agonists



**AMN 082**

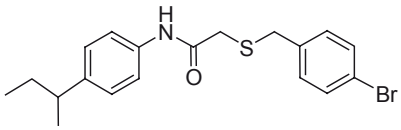
$EC_{50}$ = 64 nM

### F. $mGlu_7$ Receptor Allosteric Antagonists



**MMPIP**

### G. $mGlu_8$ Receptor PAM



AZ 12216052

$EC_{50}$ = 11.0 μM
$E_{max}$ = 77%

**(Bold Text Denotes Compounds Available From Tocris)**

## 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] Later, several $mGlu_4$ PAMs were 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

## Group I Selective Metabotropic Glutamate Receptor Ligands

### Agonists

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

**0187** **(±)-*trans*-ACPD**
Group I/group 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 Cat. No. 0342

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

**0188** **L-Quisqualic acid**
AMPA/group I mGlu agonist

### Antagonists

**3060** **A 841720**
Selective $mGlu_1$ antagonist

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

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

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

**2501** **Bay 36-7620**
Non-competitive $mGlu_1$ antagonist with inverse agonist activity

**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

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

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

**2390** **LY 456236 hydrochloride.**
Selective $mGlu_1$ antagonist

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

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

**3696** **(*RS*)-MCPG disodium salt**
Sodium salt of (*RS*)-MCPG (Cat. No. 0336)

**0337** **(*S*)-MCPG**
Non-selective mGlu antagonist. Active isomer of Cat. No. 0336

**1212** **MPEP hydrochloride**
$mGlu_5$ antagonist and positive allosteric modulator at $mGlu_4$

**2921** **MTEP hydrochloride**
Potent, selective $mGlu_5$ antagonist

**4134** **NPS 2390**
Group I mGlu antagonist

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

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

**1214** **SIB 1893**
$mGlu_5$ antagonist and positive allosteric modulator at $mGlu_4$

**3413** **YM 202074**
High affinity, selective $mGlu_1$ antagonist

**2986** **YM 230888**
Selective $mGlu_1$ antagonist

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

### Modulators

**3235** **CDPPB**
Positive allosteric modulator at $mGlu_5$

**1952** **DCB**
Allosteric potentiator at $mGlu_5$

**1625** **DFB**
Allosteric potentiator at $mGlu_5$

**4348** **Ro 01-6128**
$mGlu_1$ receptor selective allosteric enhancer

**4347** **Ro 67-4853**
Allosteric $mGlu_1$ receptor potentiator

**4346** **Ro 67-7476**
Allosteric $mGlu_1$ receptor potentiator

**3325** **VU 1545**
$mGlu_5$ positive allosteric modulator

### Other

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

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

**2102** **Anti-$mGlu_5$ blocking peptide**
Blocking peptide for anti-$mGlu_5$ (Cat. No. 2032)

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

## Group II Selective Metabotropic Glutamate Receptor Ligands

### Agonists

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

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

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

**0320** **(*S*)-4-Carboxy-3-hydroxyphenylglycine**
Group II agonist/group I antagonist
**0333** **L-CCG-I**
Potent group II mGlu agonist
**0975** **DCG IV**
Very potent, selective 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
**0711** **MAP4**
Potent group II mGlu agonist. Also specific group III mGlu antagonist
**0391** **Spaglumic acid**
Selective $mGlu_3$ agonist

### Antagonists

**1073** **(*RS*)-APICA**
Selective group II antagonist
**0971** **EGLU**
Highly selective group II mGlu antagonist
**1209** **LY 341495**
Highly potent, selective group II antagonist
**0336** **(*RS*)-MCPG**
Non-selective mGlu antagonist
**0337** **(*S*)-MCPG**
Non-selective mGlu antagonist. Active isomer of Cat. No. 0336
**2913** **Ro 64-5229**
Selective, non-competitive $mGlu_2$ antagonist

### Modulators

**4048** **BINA**
Selective positive allosteric modulator of $mGlu_2$
**3949** **CBiPES hydrochloride**
Positive allosteric modulator of $mGlu_2$
**3283** **LY 487379 hydrochloride**
Positive allosteric modulator selective for $mGlu_2$

### Other

**1827** **Group II mGlu Receptor Tocriset**
Selection of 5 group II mGlu receptor ligands
**3272** **LY 395756**
Mixed $mGlu_2$ agonist/$mGlu_3$ antagonist
**2027** **Anti-$mGlu_2$**
Antibody recognising rat $mGlu_2$ receptors
**2100** **Anti-$mGlu_2$ blocking peptide**
Blocking peptide for anti-$mGlu_2$ (Cat. No. 2027)
**4120** **Xanthurenic acid**
Selectively activates group II mGlu receptors

## Group III Selective Metabotropic Glutamate Receptor Ligands

### Agonists

**1111** **ACPT-I**
Group III mGlu agonist
**2385** **AMN 082 dihydrochloride**
The first selective $mGlu_7$ agonist
**0103** **L-AP4**
Selective group III mGlu agonist
**4119** **Cinnabarinic acid**
Selective $mGlu_4$ agonist
**3249** ***Z*-Cyclopentyl-AP4**
Group III mGlu agonist ($mGlu_4$ > $mGlu_8$ > $mGlu_7$)
**1394** **(*RS*)-3,4-DCPG**
Potently systemically active anticonvulsant. Racemate of Cat. No. 1302
**1302** **(*S*)-3,4-DCPG**
Potent, selective $mGlu_{8a}$ agonist
**1026** **HomoAMPA**
Potent, highly selective $mGlu_6$ agonist
**0238** ***O*-Phospho-L-serine**
Group III mGlu agonist
**1220** **(*RS*)-PPG**
Potent, selective $mGlu_8$ agonist
**3248** **VU 0155041**
Potent, positive allosteric $mGlu_4$ agonist
**3311** **VU 0155041 sodium salt**
Potent, positive allosteric $mGlu_4$ agonist. Sodium salt of Cat. No. 3248

### Antagonists

**0972** **CPPG**
Very potent group III mGlu antagonist
**0711** **MAP4**
Selective group III antagonist. Also potent group II agonist
**2963** **MMPIP hydrochloride**
Potent, allosteric $mGlu_7$-selective antagonist
**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

### Modulators

**1214** **SIB 1893**
$mGlu_5$ antagonist and positive allosteric modulator at $mGlu_4$
**4259** **TCN 238**
Positive allosteric modulator of $mGlu_4$
**3707** **VU 0361737**
Selective positive allosteric modulator at $mGlu_4$

### Other

**1828** **Group III mGlu Receptor Tocriset**
Selection of 5 group III mGlu receptor ligands
**2031** **Anti-$mGlu_7$**
Antibody recognising human $mGlu_7$ receptors
**2103** **Anti-$mGlu_7$ blocking peptide**
Blocking peptide for anti-$mGlu_7$ (Cat. No. 2031)

## Miscellaneous Metabotropic Glutamate Receptor Compounds

**3618** **Acamprosate calcium**
Glutamatergic modulator and GABA agonist
**0186** ***cis*-ACPD**
Potent NMDA agonist. Also group II mGlu agonist
**1112** **ACPT-II**
Competitive mGlu receptor antagonist
**2049** **Anti-glutamate receptor δ 1/2**
Antibody recognizing rat glutamate receptor δ1 and δ2 subunits
**2114** **Anti-glutamate receptor δ 1/2 blocking peptide**
Blocking peptide for anti-glutamate receptor δ 1/2 (Cat. No. 2049)
**0218** **L-Glutamic acid**
Endogenous, non-selective agonist
**0285** **Ibotenic acid**
Non-selective mGlu agonist, also NMDA agonist
**1611** **Lamotrigine**
Inhibits glutamate release. Anticonvulsant
**2289** **Lamotrigine isethionate**
Inhibits glutamate release. Water-soluble salt of Cat. No. 1611
**1829** **Mixed mGlu Receptor Tocriset**
Selection of 5 mixed mGlu receptor ligands
**1490** **MNI-caged-L-glutamate**
Stable photoreleaser of L-glutamate
**3332** **NPEC-caged-LY 379268**
Caged version of LY 379268 (Cat. No. 2453)
**3847** **Theanine**
Glutamate receptor ligand

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