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CXI. Pharmacology, Signaling, and Physiology of
Metabotropic Glutamate Receptors**

Karen J Gregory, Cyril Goudet

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International Union of Basic and Clinical Pharmacology CXI. Pharmacology, signaling and physiology of metabotropic glutamate receptors

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Nonstandard abbreviations: 2,2,2,TEMPS: 2,2,2-trifluoro-N-(3-pentan-2-yloxyphenyl)-N-(pyridin-3-ylmethyl)ethanesulfonamide; 2-AG: 2-arachidonoylglycerol; 3,5-DHPG: 3,5-dihydroxyphenylglycine; 5PAM523: 5-fluoro-2-{3-[(3S,6R)-1-[(4-fluorophenyl)carbonyl]-6-methylpiperidin-3-yl]-1,2,4-oxadiazol-5-yl}pyridine; A-841720: 3-(azepan-1-yl)-9-(dimethylamino)pyrido[1,2]thieno[3,4-d]pyrimidin-4-one; ACPT-I: (1S, 3R,4S)-1-aminocyclopentane-1,2,4-tricarboxylic acid; ADX47273: (S)-(4-fluorophenyl)-(3-[3-(4-fluoro-phenyl)-[1,2,4]-oxadiazol-5-yl]piperidin-1-yl)methanone; ADX71149: 1-butyl-3-chloro-4-(4-phenyl-1-piperidinyl)-2(1H)-pyridinone; ADX71743: 6-(2,4-dimethylphenyl)-2-ethyl-4,5,6,7-tetrahydro-1,3-benzoxazol-4-one; AMN082: N,N'-dibenzhydrylethane-1,2-diamine dihydrochloride; AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ATCM: allosteric ternary complex model; AZ12216052: 2-[[4-(4-bromophenyl)methyl]sulfonyl]-N-[4-(butan-2-yl)phenyl]acetamide; AZ12559322: 2-[[4-(4-bromophenyl)methyl]sulfonyl]-N-[4-(butan-2-yl)phenyl]acetamide; AZD8418: 5-(7-chloro-2-((S)-1-cyclopropyl-ethyl)-1-oxo-2,3-dihydro-1H-isoindol-5-yl)-isoxazole-3-carboxylic acid dimethylamide; AZD8529: 7-methyl-5-[3-(piperazin-1-ylmethyl)-1,2,4-oxadiazol-5-yl]-2-[[4-(trifluoromethoxy)phenyl]methyl]-3H-isoindol-1-one; BAY-36-7620: [(3aS,6aS)-6a-naphtalen-2-ylmethyl-5-methyliden-hexahydro-cyclopental[c]furan-1-on]; BCI-632: (1R,2R,3R,5R,6R)-2-amino-3-((3,4-dichlorobenzyl)oxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; BCI-838: (1R,2R,3R,5R,6R)-2-amino-3-((3,4-dichlorobenzyl)oxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; BINA: 4-[3-[(2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydroinden-5-yl)oxymethyl]phenyl]benzoic acid; BMS-984923: (4R,5R)-rel-5-(2-chlorophenyl)-4-(5-(phenylethynyl)pyridin-3-yl)oxazolidin-2-one;

CDPPB: 3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide; CPCCOEt: Ethyl (7*Z*)-7-hydroxyimino-1,7a-dihydrocyclopropa[*b*]chromene-1a-carboxylate; CPPHA: *N*-[4-chloro-2-(phthalimidomethyl)phenyl]salicylamide; CRD: cysteine-rich domain; DAG: diacylglycerol; DCG-IV: (2*S*,2'*R*,3'*R*)-2-(2',3'-dicarboxycyclopropyl)glycine; DFB: 3,3'-difluorobenzaldazine; DGL: diacylglycerol lipase; DPFE: 1-(4-(2,4-difluorophenyl)piperazin-1-yl)-2-((4-fluorobenzyl)oxy)ethan-1-one; EM-TBPC: 1-ethyl-2-methyl-6-oxo-4-(1,2,4,5-tetrahydro-3-benzazepin-3-yl)pyrimidine-5-carbonitrile; ERK1/2: extracellular-signal regulated kinases 1 and 2; FAK: focal adhesion kinase; FTIDC: 4-[1-(2-fluoropyridin-3-yl)-5-methyltriazol-4-yl]-*N*-methyl-*N*-propan-2-yl-3,6-dihydro-2*H*-pyridine-1-carboxamide; GC: guanylate cyclase; GIRK: G protein-coupled inwardly rectifying potassium channel; GPCR: G protein coupled receptor; GRK: G protein coupled receptor kinase; IP₃: inositol 1,4,5-trisphosphate; iCa²⁺: intracellular Ca²⁺; JF-NP-26: (7-(Diethylamino)-2-oxo-2*H*-chromen-4-yl)methyl (2-((3-fluorophenyl)ethynyl)-4,6-dimethylpyridin-3-yl)carbamate; JNJ16259685: 3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl-(4-methoxycyclohexyl)methanone; JNJ-42491293: 8-chloro-3-(cyclopropylmethyl)-7-(4-(3,6-difluoro-2-methoxyphenyl)piperidin-1-yl)-[1,2,4]triazolo[4,3-*a*]pyridine; JNJ-46281222: 3-(cyclopropylmethyl)-7-[(4-phenylpiperidin-1-yl)methyl]-8-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine; KO: knockout; L-AP4: L-(+)-2-amino-4-phosphonobutyric acid; LID: levodopa-induced dyskinesia; LimGluRs: light-controlled mGlu receptors; LSP4-2022: (2*S*)-2-amino-4-({[4-(carboxymethoxy)phenyl](hydroxy)methyl}(hydroxy)phosphoryl)butanoic acid; LY2389575: (3*S*)-1-(5-bromopyrimidin-2-yl)-*N*-(2,4-dichlorobenzyl) pyrrolidin-3-amine methanesulfonate hydrate; LY2794193: (1*S*,2*S*,4*S*,5*R*,6*S*)-2-amino-4-[(3-methoxybenzoyl)amino]bicyclo[3.1.0]hexane-2,6-dicarboxylic acid; LY2812223: (1*R*,2*S*,4*R*,5*R*,6*R*)-2-amino-4-(1*H*-1,2,4-triazol-3-ylsulfanyl)bicyclo[3.1.0]hexane-2,6-dicarboxylic acid; LY341495: (2*S*)-2-amino-2-[(1*S*,2*S*)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid; LY354740: (1*S*,2*S*,5*R*,6*S*)-2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid; LY379268: (1*R*,4*R*,5*S*,6*R*)-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid; LY404039: 4-amino-2-thiabicyclo[3.1.0]hexane-4,6-dicarboxylic acid 2,2-dioxide; LY459477: (1*R*,2*S*,4*R*,5*R*,6*R*)-2-amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; LY487379:

2,2,2-trifluoro-*N*-[4-(2-methoxyphenoxy)phenyl]-*N*-(3-pyridinylmethyl)-ethanesulfonamide: LY541850:
(1*S*,2*S*,4*R*,5*R*,6*S*)-2-amino-4-methylbicyclo[3.1.0]hexane-2,6-dicarboxylic acid; LY544344: prodrug of
LY354740; LSN2463359: *N*-(1-methylethyl)-5-(pyridin-4-ylethynyl)pyridine-2-carboxamide; mGlu:
metabotropic glutamate; M-5MPEP: 2-[2-(3-methoxyphenyl)ethynyl]-5-methylpyridine; maPORTL:
membrane anchored photoswitchable orthogonal remotely tethered ligands; ML289: [(3*R*)-3-
(Hydroxymethyl)-1-piperidinyl][4-[2-(4-methoxyphenyl)ethynyl]phenyl]methanone; ML337: [2-fluoro-4-[2-
(4-methoxyphenyl)ethynyl]phenyl][(3*R*)-3-hydroxy-1-piperidinyl]methanone; MMPiP: 6-(4-
methoxyphenyl)-5-methyl-3-(4-pyridinyl)-isoxazolo[4,5-*c*]pyridin-4(5*H*)-one; MNI-137: 4-(8-bromo-5-oxo-
3,4,5,6-tetrahydro-1,6-benzodiazocin-2-yl)pyridine-2-carbonitrile; MPEP: 2-methyl-6-(phenylethynyl)-
pyridine; MRK-8-29: 4-(2-fluoro-4-methoxyphenyl)-7-(2-(2-methylpyrimidin-5-yl)ethyl)quinoline-2-
carboxamide; decogluturant, 5-[2-[7-trifluoromethyl]-5-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-*a*]pyrimidin-
3-yl]ethynyl]pyridin-2-amine ; MTEP: 3-((2-methyl-4-thiazolyl)ethynyl)pyridine; NAL: neutral allosteric
ligand; NAM: negative allosteric modulator; NCFP: *N*-[4-chloro-2-[(4-fluoro-1,3-dioxoisindol-2-
yl)methyl]phenyl]pyridine-2-carboxamide; NMDA: *N*-methyl-*D*-aspartate; PAG: periaqueductal gray; PAM:
positive allosteric modulator; PCP: phencyclidine; PD: Parkinson's disease; PHCCC: *N*-phenyl-7-
(hydroxyimino)cyclopropa[*b*]chromen-1*a*-carboxamide; PI3K: phosphoinositide-3-kinase; PKA: protein
kinase A; PKC: protein kinase C; PORTL: photoswitchable orthogonal remotely tethered ligands; PTL:
photoswitchable tethered ligands; R214127: 1-(3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl)-2-
phenylethanone; RO 01-2168: ethyl *N*-[2,2-di(phenyl)acetyl]carbamate; RO4491533: 4-[3-(2,6-
dimethylpyridin-4-yl)phenyl]-7-methyl-8-(trifluoromethyl)-1,3-dihydro-1,5-benzodiazepin-2-one; Ro64-
5229: 4-(8-bromo-5-oxo-3,4,5,6-tetrahydro-1,6-benzodiazocin-2-yl)pyridine-2-carbonitrile; RO 67-7476: 2-
(4-fluorophenyl)-1-(4-methylphenyl)sulfonylpyrrolidine; SAR218645: (*S*)-2-(1,1-dimethyl-indan-5-
yloxymethyl)-2,3-dihydro-oxazolo[3,2-*a*]pyrimidin-7-one; TM: transmembrane; VFT: venus flytrap;
VU0155041: (1*R*,2*S*)-2-[(3,5-dichlorophenyl)carbamoyl]cyclohexane-1-carboxylic acid; VU0357121: 4-
butoxy-*N*-(2,4-difluorophenyl)benzamide; VU0360172: *N*-cyclobutyl-6-[2-(3-fluorophenyl)ethynyl]-3-

pyridinecarboxamide hydrochloride; VU0366248: N-(3-chloro-2-fluorophenyl)-3-cyano-5-fluoro-
benzamide; VU0409551: [6,7-dihydro-2-(phenoxyethyl)oxazolo[5,4-c]pyridin-5(4H)-
yl](fluorophenyl)methanone; VU0415374: N-(4-(2-chlorobenzamido)-3-methoxyphenyl)picolinamide;
VU0422288: N-[3-chloro-4-[(5-chloro-2-pyridinyl)oxy]phenyl]-2-pyridinecarboxamide; VU0424465: 5-[2-
(2-(3-fluorophenyl)ethynyl)-N-[(1R)-2-hydroxy-1,2-dimethylpropyl]-2-pyridinecarboxamide; VU0477573:
N,N-diethyl-5-((3-fluorophenyl)ethynyl)picolinamide; VU0478006: 3-azabicyclo[3.1.0]hexan-3-yl-[5-[2-(3-
fluorophenyl)ethynyl]pyridin-2-yl]methanone; VU0483605: 3-chloro-N-[3-chloro-4-(4-chloro-1,3-dihydro-
1,3-dioxo-2H-isoindol-2-yl)phenyl]-2-pyridinecarboxamide; VU6001192: 6-(((2S,6R)-2,6-
dimethylmorpholino)methyl)-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide; VU6010572:
(S)-1-(4-fluorophenyl)-4-(2-phenoxypropoxy)pyridin-2(1H)-one; VU29: N-(1,3-diphenyl-1H-pyrazolo-5-
yl)-4-nitrobenzamide; XAP044: 7-hydroxy-3-(4-iodophenoxy)-4H-chromen-4-one.

Abstract

Metabotropic glutamate (mGlu) receptors respond to glutamate, the major excitatory neurotransmitter in the mammalian brain, mediating a modulatory role that is critical for higher order brain functions such as learning and memory. Since cloning the first mGlu receptor in 1992, eight subtypes have been identified along with many isoforms and splice variants. The mGlu receptors are transmembrane-spanning proteins belonging to the class C G protein-coupled receptor family and represent attractive targets for a multitude of CNS disorders. Concerted drug discovery efforts over the past three decades have yielded a wealth of pharmacological tools including subtype selective agents that competitively block or mimic the actions of glutamate, or act allosterically via distinct sites to enhance or inhibit receptor activity. Herein, we review the physiological and pathophysiological roles for individual mGlu receptor subtypes including the pleiotropic nature of intracellular signal transduction arising from each. We provide a comprehensive analysis of the *in vitro* and *in vivo* pharmacological properties of prototypical and commercially available orthosteric agonists and antagonists as well as allosteric modulators, including ligands that have entered clinical trials. Finally, we highlight emerging areas of research that hold promise to facilitate rational design of highly selective mGlu receptor targeting therapeutics in the future.

Significance Statement.

The metabotropic glutamate receptors are attractive therapeutic targets for a range of psychiatric and neurological disorders. Over the past three decades, intense discovery efforts have yielded diverse pharmacological tools acting either competitively or allosterically, which have enabled dissection of fundamental biological process modulated by metabotropic glutamate receptors and established proof-of-concept for many therapeutic indications. We review metabotropic glutamate receptor molecular pharmacology and highlight emerging areas that are offering new avenues to selectively modulate neurotransmission.

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Introduction

Glutamate is the major excitatory neurotransmitter in the human brain mediating its effects via two distinct receptor classes. Ionotropic glutamate receptors are ligand-gated ion channels that rapidly cause membrane depolarization in response to glutamate. On the other hand, metabotropic glutamate (mGlu) receptors have a modulatory role exerted over a longer time scale including influencing neuronal excitability and synaptic plasticity as well as activity of non-neuronal cells.

The mGlu receptors are a family of eight class C G protein-coupled receptors (Acher et al., 2019; Alexander et al., 2019). They comprise a large extracellular N-terminal domain where glutamate binds, termed the Venus Flytrap (VFT) domain, linked to seven transmembrane alpha-helical domains (7TM) via a cysteine-rich domain (CRD) (**Figure 1**). The mGlu receptors are obligate dimers mediated by an inter-protomer disulfide bond at the top of the VFT domains. Structural studies indicate that the bilobed VFT domains adopt a closed conformation upon agonist binding (Koehl et al., 2019; Kunishima et al., 2000; Monn et al., 2015a; Monn et al., 2015b; Muto et al., 2007; Tsuchiya et al., 2002). The CRD transmits the active VFT conformation to the 7TM via interactions with the second extracellular loop of the 7TM (Koehl et al., 2019). When activated the 7TM domains come into closer proximity, with transmembrane domain 6 mediating dimerization between the 7TM domains of the two protomers (Doumazane et al., 2013; El Moustaine et al., 2012; Koehl et al., 2019; Xue et al., 2015)(reviewed in (Pin and Bettler, 2016)). Ultimately, the active 7TM domains couple to intracellular transducers to elicit a cellular response.

The eight mGlu receptor subtypes are commonly divided into three groups based on sequence identity, G protein coupling preferences and pharmacology. In addition to forming constitutive homodimers, heteromers have been observed among group I members and between group II and III subtypes (Doumazane et al., 2011b). The various mGlu receptor subtypes are ubiquitously expressed throughout the brain in neurons and glia, with the exception of mGlu₆ receptor, for which expression is restricted to the retina (reviewed in (Ferraguti and Shigemoto, 2006)). Peripheral mGlu receptors (reviewed in detail by (Julio-Pieper et al., 2011)) are found in

tissues that receive glutamatergic innervation (e.g. heart, gastrointestinal tract, pain circuitry (Pereira and Goudet, 2018)) but are also in non-excitatory tissues and organs (e.g. immune cells, liver, kidney). Herein we provide a brief overview of the fundamental biology of the different mGlu subtypes and intracellular signaling, followed by an in-depth discussion of pharmacological agents and therapeutic indications with a focus on CNS disorders.

Group I: metabotropic glutamate receptors 1 and 5

Receptor subtypes and splice variants

The group I mGlu receptors include mGlu₁ and mGlu₅. The mGlu₁ receptor gene (GRM1) and its first three splice variants were cloned in rat in 1992 (Pin et al., 1992; Tanabe et al., 1992). In humans, there are seven mGlu₁ splice variants (a, b, d, f, g, h) that differ in the length of the C terminus (DiRaddo et al., 2013; Laurie et al., 1996; Makoff et al., 1997; Soloviev et al., 1999; Sugiyama et al., 1987; Tanabe et al., 1992)[Ensembl gene ID: ENSG00000152822]. In addition, 12 single nucleotide polymorphisms within the GRM1 coding region have been identified in patients with schizophrenia (Ayoub et al., 2012; Frank et al., 2011), suggesting mGlu₁ may be a viable therapeutic target for psychosis (Cho et al., 2014b). Spontaneous mutations in GRM1 are also associated with ataxia (Watson et al., 2017). The mGlu₅ receptor is encoded by the GRM5 gene [ENSG00000168959], localized in human chromosome 11, and was first cloned in rat in 1992 (Abe et al., 1992) and in human in 1994 (Minakami et al., 1994). Alternative splicing of GRM5 in humans gives rise to two major isoforms that also differ in C terminus length; the longer of the two, human mGlu_{5a} (equivalent to rat mGlu_{5b}) has a 32 amino acid insertion after residue 876, but is otherwise identical to human mGlu_{5b} (equivalent to rat mGlu_{5a})(Minakami et al., 1995; Minakami et al., 1993). Variations in C terminus length due to alternative splicing of group I receptors influences surface expression, subcellular localization, dimerization, interactions with intracellular proteins and ultimately cellular responses (Francesconi and

Duvoisin, 2002; Francesconi et al., 2009a; Joly et al., 1995; Kumpost et al., 2008; Mion et al., 2001; Tateyama and Kubo, 2008; Techlovska et al., 2014).

Localization and signal transduction

The group I mGlu receptors are predominantly found in postsynaptic neurons within the CNS (**Figure 2**), increasing neuronal excitability and membrane depolarization when activated. In certain circuits, group I mGlu receptors can be found on pre-synaptic terminals, acting as autoreceptors to modulate neurotransmitter release (reviewed in (Pittaluga, 2016)). Further, group I mGlu receptors are also expressed in glial cells (reviewed in (Spampinato et al., 2018)). The cellular responses resulting from group I mGlu receptor activation are highly complex and context-dependent.

Group I mGlu receptors preferentially couple to the $G_{q/11}$ family of G proteins, which activate phospholipase C (PLC) β , which hydrolyses phosphatidylinositol 4,5-bisphosphate in the membrane to yield the second messengers: diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3), mobilizing intracellular Ca^{2+} (iCa^{2+}) stores (Sugiyama et al., 1987) (**Figure 3**). Potentiation of mGlu₅ receptors increases phosphoinositide hydrolysis *in vivo* in different mouse brain areas, such as prefrontal cortex, cerebellum, hypothalamus, hippocampus, and striatum (Zuena et al., 2018). Interestingly, endogenous activation of mGlu₅ receptors largely accounts for basal phosphoinositide hydrolysis particularly in the prefrontal cortex. Downstream of these second messengers, activation of protein kinase C (PKC) and calmodulin triggers signaling cascades that ultimately phosphorylate and activate extracellular-signal regulated kinases 1 and 2 (ERK1/2), which regulate gene transcription associated with synaptic plasticity (long-term depression or long-term potentiation) (Hong et al., 2016; Jin et al., 2013a; Kanumilli et al., 2002; Page et al., 2006; Servitja et al., 2003; Servitja et al., 1999). DAG can be further broken-down by DGL (diacylglycerol lipase) to yield endogenous cannabinoid, 2-AG (2-arachidonoylglycerol) (Gregg et al., 2012; Jung et al., 2005). Beyond $G_{\alpha_{q/11}}$ mediated signaling, $\beta\gamma$ subunits can enhance or inhibit Ca^{2+} and K^+ channels, including ionotropic glutamate receptors, to modulate neuronal excitability and membrane potential (reviewed in (Valenti et al., 2002), through physical interactions

mediated by scaffolding proteins (Tu et al., 1999) or indirect mechanisms driven by intracellular effectors (**Figure 3**). The $\beta\gamma$ subunits can also activate PI3K (phosphoinositide-3-kinase), which in turn activates Akt dependent signaling cascades implicated in protein synthesis dependent long-term depression and cell survival (Hou and Klann, 2004; Hullinger et al., 2015; Page et al., 2006; Zhu et al., 2018). In recombinant systems mGlu₁ and mGlu₅ receptors also couple to G α_s stimulating adenylate cyclases (AC) and increasing cAMP production (Aramori and Nakanishi, 1992; Francesconi and Duvoisin, 1998; 2000; Joly et al., 1995; Nasrallah et al., 2018). In addition, group I receptors signal via G protein independent mechanisms (e.g. Homer, src kinases, arrestins, transactivation of tyrosine kinases) to activate different kinase cascades that contribute to synaptic plasticity (Emery et al., 2010; Eng et al., 2016; Iacovelli et al., 2003; Kubota et al., 2014; Yang et al., 2006). Downstream of group I receptor activation diverse transcription factors are activated including CREB (Mao and Wang, 2003b), Elk-1 (Jong et al., 2005; Jong et al., 2009; Mao and Wang, 2003a), c-Jun (Jong et al., 2009), and SRF (Kumar et al., 2012).

The mechanisms that regulate group I mGlu receptor activity are equally complex (**Figure 3**). The C termini of group I receptors contain binding sites for diverse scaffolding proteins that regulate receptor localization and recycling in addition to directly linking group I mGlu receptors to other receptors and channels within the post-synaptic density (Eng et al., 2016; Gulia et al., 2017; Hu et al., 2012; Kitano et al., 2002; Lee et al., 2008; Roche et al., 1999; Wagner et al., 2015; Wang et al., 2009). Second messenger-activated kinases also provide negative feedback regulating cellular responses (iCa²⁺ oscillations or receptor desensitization) through phosphorylation of intracellular loops and/or the C terminus (Bhattacharya et al., 2004; Bradley and Challiss, 2011; Gereau and Heinemann, 1998; Jin et al., 2013a; Jin et al., 2013b; Jin et al., 2018; Kawabata et al., 1996; Kim et al., 2005; Ko et al., 2012; Marks et al., 2018; Mundell et al., 2004; Raka et al., 2015; Uematsu et al., 2015; Vergouts et al., 2017; Yang et al., 2017). However, not all functional responses are equally influenced. For example, PKC phosphorylation of mGlu₁ receptors desensitizes signaling to accumulation of inositol phosphate but not cAMP (Francesconi and Duvoisin, 2000). Select kinases bind the C terminus and/or phosphorylate the receptor altering effector coupling, ability to bind other proteins or receptor endocytosis

(Dale et al., 2000; Iacovelli et al., 2003; Jin et al., 2017; Nicodemo et al., 2010; Pula et al., 2004; Sallese et al., 2000). By example, Preso1 enhances CDK5 and ERK1/2 phosphorylation of the Homer binding site within the C terminus (Hu et al., 2012). Whereas, calmodulin and SIAH-1a recognize overlapping sites in the C tail (Ishikawa et al., 1999), with PKC phosphorylation of this site enhancing SIAH-1a but inhibiting calmodulin binding (Ko et al., 2012). Second messenger-dependent kinases are critical for group I mGlu receptor dependent long-term depression and potentiation by modulating the activity or promoting endocytosis of ionotropic glutamate receptors including NMDA and AMPA receptor subtypes (Benquet et al., 2002; Jia et al., 1998; Jin et al., 2013b; Jin et al., 2015; Moulton et al., 2006; Snyder et al., 2001; Xu et al., 2013). Although, PKC-independent mechanisms for NMDA receptor potentiation by group I mGlu receptors have also been reported (Harvey and Collingridge, 1993; Kinney and Slater, 1993; Rahman and Neuman, 1996). In a reciprocal fashion, NMDA receptor-mediated stimulation of PP2A/CaN (protein phosphatase 2A/calcineurin) acts to regulate recycling of group I mGlu receptors (Alagarsamy et al., 2005; Pandey et al., 2014); with PP2B (protein phosphatase 2B) playing a similar role (Mahato et al., 2015). It is clear that activation of group I mGlu receptors can trigger a complex network of intracellular effectors that encode the cellular responses that give rise to complex physiological effects from synaptic plasticity to cell survival.

When co-expressed within the same cell population, activation of mGlu₁ versus mGlu₅ receptors can lead to distinct cellular outcomes (Valenti et al., 2002). Moreover, post-synaptic group I mGlu receptor activation can result in modulation of neurotransmitter release from presynaptic cells via retrograde signaling, e.g. endocannabinoids or nitric oxide (**Figure 3**) (Aubrey et al., 2017; Gregg et al., 2012; Maejima et al., 2001; Robbe et al., 2002; Sergeeva et al., 2007; Xiang et al., 2019). As a further layer of complexity, both group I mGlu receptors form heteromers and/or larger order oligomers with other GPCRs (discussed in further detail later), which alters intracellular signaling profiles.

Pathophysiology and therapeutic potential

A number of reviews provide in depth coverage of the distribution, physiology and pathophysiological roles of group I mGlu receptors (Crupi et al., 2019; Ferraguti and Shigemoto, 2006; Golubeva et al., 2016; Niswender and Conn, 2010). Inhibitors and activators of the individual subtypes are being pursued for a myriad of different psychiatric and neurological disorders. Briefly, and of relevance to the pharmacological agents reviewed in depth below, distribution of mGlu₁ receptors in regions associated with pain perception as well as mGlu₁ knockout animal phenotypes suggests mGlu₁ inhibitors are potential therapeutic agents for neuropathic pain (Neugebauer, 2002; Schkeryantz et al., 2007). Preclinical studies also indicate mGlu₁ receptor inhibitors may have therapeutic benefit in treating seizures, addiction, anxiety, and certain cancers (Dravolina et al., 2017; Namkoong et al., 2006). mGlu₅^{-/-} mice have deficits in pre-pulse inhibition (Brody et al., 2004), impaired learning and memory (Xu et al., 2009; Zeleznikow-Johnston et al., 2018), reduced propensity for addiction/abuse (Chiamulera et al., 2001) and reverse the majority of fragile X syndrome phenotypes in preclinical models (Dolen and Bear, 2008). As such, selective mGlu₅ receptor inhibitors are desired in the setting of depression (Chaki and Fukumoto, 2018), anxiety (Ferraguti, 2018) as well as neurodevelopmental disorders such as Fragile X syndrome (Yamasue et al., 2019). In this respect multiple mGlu₅ receptor inhibitors have entered phase 2 clinical trials as discussed in detail later; however, to date none have reached market. Potentiation or activation of both group I receptors offers the promise for treating the positive and cognitive symptoms associated with schizophrenia (Nicoletti et al., 2019; Walker and Conn, 2015).

Beyond neurological and psychiatric disorders, inhibition of mGlu₁ receptors is neuroprotective (*in vitro* and *in vivo*) following oxygen-glucose deprivation or ischemic insult (Henrich-Noack et al., 1998; Pellegrini-Giampietro et al., 1999) and may therefore offer a novel intervention for stroke. For multiple preclinical models of neurodegenerative diseases, genetic ablation or pharmacological inhibition of mGlu₅ receptors is neuroprotective and treats associated symptoms, e.g. pro-cognitive in Alzheimer's disease or Huntington's

disease (reviewed in (Ribeiro et al., 2017)) or improves motor deficits in Amyotrophic Lateral Sclerosis (reviewed in (Battaglia and Bruno, 2018)) or Parkinson's disease (Ambrosi et al., 2010; Armentero et al., 2006; Battaglia et al., 2004; Black et al., 2010; Fuzzati-Armentero et al., 2015; Masilamoni et al., 2011; Mazur, 1995). Although, mGlu₅ receptor activators/potentiators may also treat cognitive symptoms associated with Huntington's disease (Doria et al., 2015; Doria et al., 2018; Doria et al., 2013). Inhibition of mGlu₅ receptors is also indicated for treating neurodegeneration associated with drugs of abuse (Battaglia et al., 2002).

Group II: metabotropic glutamate receptors 2 and 3

Receptor subtypes and splice variants

The group II members, mGlu₂ and mGlu₃ receptors, were first cloned in rat in 1992 (Tanabe et al., 1992) and few years later in human (Emile et al., 1996; Flor et al., 1995a). Encoded by the GRM2 gene [ENSG00000164082] and localized in human chromosome 3 and rat chromosome 8, no splice variants have been described for mGlu₂ receptor subtype (Sartorius et al., 2006). In human, the GRM3 gene [ENSG00000198822] encodes the mGlu₃ receptor, for which three splice variants are known (Sartorius et al., 2006). The most abundant GRM3 variant lacks exon 4 (GRM3Delta4), encoding a truncated membrane-associated protein that retains the extracellular VFT but lacks the 7TM, which is replaced with a unique 96-amino acid C-terminus. mGlu_{3delta4} can bind orthosteric ligands and interact with the full-length protein, and may thus have a dominant negative effect (Garcia-Bea et al., 2017). Spontaneous mutations in mGlu₃ are associated with melanoma (Neto and Ceol, 2018; Prickett et al., 2011). Whereas, single nucleotide polymorphisms in GRM3 are linked to cognitive performance in individuals with schizophrenia and postulated to influence pharmacotherapy (reviewed in (Maj et al., 2016; Saini et al., 2017)

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Localization and signal transduction

The group II mGlu receptors are located both pre- and post-synaptically, with mGlu₃ receptors also found in glial cells throughout the brain (Fotuhi et al., 1994; Testa et al., 1994) (**Figure 2**). Using a radiolabeled orthosteric agonist selective for group II receptors, [³H]LY459477, in conjunction with knockout mice for either subtype, mGlu₃ receptor levels were found to be generally higher than mGlu₂ receptors in forebrain regions, but similar within the striatum (Wright et al., 2012). In the thalamus and hippocampus, the two subtypes exhibit distinct and for some nuclei/circuits segregated expression patterns (Wright et al., 2012). Dissecting the relative contribution of mGlu₂ versus mGlu₃ receptor subtypes has presented a major challenge due to the lack of subtype selective pharmacological tools (discussed in further detail below).

Group II mGlu receptors preferentially couple to G_{i/o} proteins, inhibiting AC and cAMP production as well as inhibiting guanylate cyclase (GC) and cGMP production (Wroblewska et al., 2006)(**Figure 4**). On presynaptic terminals, βγ subunits modulate ion channel function (inhibiting N-type Ca²⁺ channels (McCool et al., 1996) and activating G protein-coupled inwardly rectifying potassium channel (GIRK) channels (Knoflach and Kemp, 1998; Sharon et al., 1997)) thereby decreasing exocytosis of vesicles containing glutamate (Flavin et al., 2000; Macek et al., 1998; Olivero et al., 2017), GABA (Gereau and Conn, 1995; Hayashi et al., 1993; Salt and Eaton, 1995; Schaffhauser et al., 1998) and dopamine (Feenstra et al., 1998; Johnson et al., 2017; Verma and Moghaddam, 1998). The βγ subunits can also activate PI3K dependent activation of Akt with downstream effectors regulating protein synthesis and gene transcription involved in cytoprotection and synaptic plasticity (Aronica et al., 2003; Ciccarelli et al., 2007; Durand et al., 2011; Li et al., 2015; Ritter-Makinson et al., 2017; Xing et al., 2018). Further, group II receptor activation can trigger transactivation of insulin growth factor-1 receptors (IGF-1R) via βγ subunit activation of PLC and focal adhesion kinase (FAK), leading to ERK1/2 phosphorylation (Hu et al., 2019), a key integrator of multiple convergent pathways that shapes the overall cellular response (Aronica et al., 2003; Ciccarelli et al., 2007). In post-synaptic membranes, group II receptor

activation regulates trafficking of NMDA or AMPA receptors with different mechanisms implicated: PKC, SNARE complexes, Akt/GSK-3 β (Cheng et al., 2013; Tyszkiewicz et al., 2004; Xi et al., 2011). Further, mGlu₃ receptor-dependent long-term depression (LTD) in the prefrontal cortex is mediated by functional cross-talk between mGlu₃ and mGlu₅ receptors on post-synaptic neurons (**Figure 2**). Activation of mGlu₃ receptors releases $\beta\gamma$ subunits to enhance mGlu₅ receptor coupling to G_q (Di Menna et al., 2018). Cross-talk between mGlu₃ and mGlu₅ receptors is postulated to account for the reported dependence on PLC and PKC for mGlu₃ receptor-dependent LTD (Huang et al., 2007; Otani et al., 2002). Recently however, mGlu₃ receptor-dependent LTD was shown to be modulated by mGlu₅ receptor interactions with homer and signaling via PI3K, Akt and GSK3 β to result in AMPA receptor internalization, a mechanism disrupted by acute stress (Joffe et al., 2019). Indeed, the cellular context is an important contributor to shaping the cellular responses instigated by group II receptor activation. For example, in astrocytes, mGlu₃ receptor activation results in both decreases and increases in cAMP, whereas in neurons the effect on cAMP levels is purely inhibitory (Moldrich et al., 2002). Astrocytic mGlu₃-mediated increases in cAMP levels are dependent on iCa²⁺ levels (mobilization of stores and extracellular influx) and local release of adenosine, which acts at co-located G_s-coupled adenosine A_{2A} receptors (Moldrich et al., 2002).

With respect to regulation of group II mGlu receptor activity, the cellular context is also a major contributor. Phosphorylation of intracellular loops and/or the C terminus tail by PKA, PKC and GRKs have a central role in receptor regulation (Cai et al., 2001; Kamiya and Yamamoto, 1997; Macek et al., 1998; Schaffhauser et al., 2000); uncoupling receptors from G proteins, and promoting interactions with scaffolding proteins such as arrestins, which mediate receptor endocytosis (Iacovelli et al., 2009). The C terminus tail of group II mGlu receptors binds to multiple scaffolding proteins including PICK1, GRIP, tamalin, NHERF1/2, RanBPM (Hirbec et al., 2002; Kitano et al., 2002; Ritter-Makinson et al., 2017; Seebahn et al., 2008), as well as PP2C, which dephosphorylates mGlu₃ receptors (Flajolet et al., 2003). Interactions between group II mGlu receptors

with diverse intracellular scaffolding proteins regulates receptor localization and functional responses, which likely governs differences observed between cell types or for neurons from different brain regions. Interestingly, mGlu₂, but not mGlu₃, receptors are reportedly resistant to homologous desensitization by GRKs with respect to cAMP signaling (Iacovelli et al., 2009). Although heterologous mechanisms, e.g. due to PKC activation by co-located adenosine A₃ receptors, affect both subtypes (Lennon et al., 2010; Macek et al., 1998). Functional cross-talk between mGlu₂ receptors and co-located 5HT_{2A} receptors can also modulate cellular responses to activation of either receptor (Marek et al., 2000; Molinaro et al., 2009; Murat et al., 2018). The interplay of intracellular effectors stimulated by group II mGlu receptors, coupled with regulatory proteins as well as co-expression of other cell surface receptors gives rise to cell type specific roles for group II mGlu receptors.

Pathophysiology and therapeutic potential

The expression patterns of group II mGlu receptors (reviewed in (Ferraguti and Shigemoto, 2006)) coupled with phenotypes of knockout animals suggest that group II receptors are attractive therapeutic targets for psychosis, cognition, anxiety, pain and addiction (Cross et al., 2018; Mazzitelli et al., 2018). Although for many indications establishing whether mGlu₂ or mGlu₃ receptors are the best target in preclinical models of disease has been challenging due to a lack of subtype selective agents. Despite this shortcoming, both agonists and potentiators of group II receptors have been actively pursued, with multiple agents entering phase 2 or 3 for treating schizophrenia and addiction disorders (Nicoletti et al., 2019). Conversely, group II receptors inhibitors are promising interventions for depression, anxiety and as neuroprotective agents in the setting of ischemia (Celanire et al., 2015; Motolese et al., 2015). However, activation of group II receptors is neuroprotective following excitotoxic insults (Battaglia et al., 2003). In particular, activation of astrocytic mGlu₃ receptors confers neuroprotection to various insults (*in vitro* and *in vivo*) via paracrine mechanisms

(Bruno et al., 1997; Caraci et al., 2011; Cippitelli et al., 2010; Corti et al., 2007), offering a potential therapeutic target for neurodegenerative diseases and psychiatric conditions associated with neuronal death.

Group III: metabotropic glutamate receptors 4, 6, 7 and 8

Receptor subtypes and splice variants

Before molecular cloning, group III mGlu receptors were termed L-AP4 receptors due to high sensitivity to this ligand, which depresses synaptic transmission in the brain and in retina (Thomsen, 1997). In the 1990's, molecular cloning revealed that four different receptor subtypes mediated the biological effects of L-AP4: mGlu₄, mGlu₆, mGlu₇ and mGlu₈ receptors. The mGlu₄ receptor is encoded by the GRM4 gene [ENSG00000124493], which is localized in human chromosome 6, rat chromosome 20 and mouse chromosome 17 (Flor et al., 1995b; Tanabe et al., 1992). Two main splice variants were predicted, termed mGlu_{4a} and _{4b}, (Thomsen et al., 1997), but further studies failed to detect mGlu_{4b} in different rat brain areas and no splice site consensus sequences that could support its existence were found in human genomic sequence containing the whole GRM4 gene, suggesting mGlu_{4b} corresponds to a recombination artefact (Corti et al., 2002). Another variant lacking the first 128 base pairs, termed taste mGlu₄, is found in rat taste buds. The corresponding protein is predicted to lack approximately half the extracellular domain, including a large portion of the glutamate-binding domain (Chaudhari et al., 2000). First cloned in 1993, the mGlu₆ receptor is encoded by GRM6 gene [ENSG00000113262] localized in human chromosome 5 (Nakajima et al., 1993). Two splice variants, termed mGlu_{6b} and mGlu_{6c}, are found in both human and rats, which correspond to truncated mGlu₆ receptors lacking the transmembrane domain and intracellular portions of the receptor (Valerio et al., 2001a; Valerio et al., 2001b). The mGlu₇ receptor is encoded by the GRM7 gene, localized in rat chromosome 4 and in human chromosome 3 (Makoff et al., 1996; Okamoto et al., 1994; Saugstad et al., 1994). Two main variants, mGlu_{7a} and mGlu_{7b}, in rats and humans have different C terminal tails. The last 16 residues of mGlu_{7a} are substituted by 23 different residues in mGlu_{7b} due to the insertion of an out-of-

frame 92 base pairs exon (Corti et al., 1998; Flor et al., 1997). Three other isoforms have been described, named v3, v4 and v5 (Schulz et al., 2002). While mGlu_{7a} and mGlu_{7b} receptor variants are primarily expressed in the CNS, the expression of v3 and v4 isoforms appears to be restricted in non-neuronal tissues (Schulz et al., 2002). The mGlu₈ receptor, encoded by the GRM8 gene [ENSG00000179603] found in human chromosome 7, was originally cloned in mouse in 1995 (Duvoisin et al., 1995) followed by human (Scherer et al., 1997; Wu et al., 1998) and rat (Saugstad et al., 1997). Three splice variants have been described: mGlu_{8a}, mGlu_{8b} and mGlu_{8c} (Corti et al., 1998; Malherbe et al., 1999). The last 16 residues of the C terminus tails of the mGlu_{8a} and mGlu_{8b} receptors are different, while the mGlu_{8c} variant is a truncated receptor lacking the transmembrane domains and intracellular C tail. For each of the group III mGlu receptors the different splice variants show distinct tissue distribution and/or changes in intracellular portions of the receptor, which have the potential to alter signal transduction pathways triggered in response to receptor activation.

Localization and signal transduction

Most group III mGlu receptors are widely expressed throughout the CNS, with the exception of mGlu₆ which is mostly restricted to the retina (reviewed in (Ferraguti and Shigemoto, 2006)). Group III mGlu receptors are also expressed in glial cell types in the brain, with the exception of mGlu₇ (reviewed in (Spampinato et al., 2018)). Outside the CNS, group III mGlu receptor expression has been reported in kidney, pancreas, liver, cells from the immune system and bones for example (see (Julio-Pieper et al., 2011) for review).

In the CNS, mGlu₄, mGlu₇ and mGlu₈ receptors are mainly expressed in the active zone of presynaptic glutamatergic and GABAergic neurons (Corti et al., 2002; Ferraguti et al., 2005; Ferraguti and Shigemoto, 2006; Kinoshita et al., 1996a; Shigemoto et al., 1997; Wada et al., 1998) (**Figure 2**). Group III receptors can act as autoreceptors reducing glutamate release in the synaptic cleft and as heteroreceptors reducing the release of GABA (Schoepp, 2001). mGlu₄, mGlu₇ and mGlu₈ receptors are preferentially coupled to heterotrimeric G_{i/o} proteins, leading to the inhibition adenylyl cyclase production of cAMP via the G α subunit (**Figure 5**).

On presynaptic terminals, mGlu₄, mGlu₇ or mGlu₈ receptors are well documented to inhibit neurotransmitter release through a direct $\beta\gamma$ subunit-mediated inhibition of N or P/Q type of voltage-gated Ca²⁺ channels (Anwyl, 1999; Capogna, 2004; Martin et al., 2007; Millan et al., 2002a; b; Perroy et al., 2000). In addition, mGlu₄ and mGlu₇ receptors also inhibit voltage-gated Ca²⁺ channels via a PKC-dependent mechanism (Abitbol et al., 2012; Perroy et al., 2000), involving interactions between calmodulin and the scaffolding protein PICK1 for mGlu₇ receptors (Perroy et al., 2002; Suh et al., 2013). Activation of mGlu₄, mGlu₇ or mGlu₈ receptors can also decrease neuronal excitability by the released $\beta\gamma$ subunits acting on GIRK channels (Dutar et al., 1999; Saugstad et al., 1996). Other studies suggest that group III mGlu receptors may activate background K⁺ channels such as TREK1 and TREK2, thereby further decreasing neuronal activity (Cain et al., 2008; Lesage et al., 2000). Group III mGlu receptors are also proposed to inhibit neurotransmitter vesicle exocytosis through direct interactions with the release machinery (Chavis et al., 1998; Erdmann et al., 2012). Coupling of group III receptors to PI3K, probably through G $\beta\gamma$ subunits, and MAPK is implicated in neuroprotection mechanisms (Iacovelli et al., 2002).

Among group III mGlu receptors, the mGlu₆ receptor is distinct as its expression is mostly restricted to postsynaptic bipolar ON neurons in the retina (Nomura et al., 1994; Vardi et al., 2000), with no strong expression detected in the brain (Nakajima et al., 1993). The mGlu₆ receptor is critical for glutamate-induced signaling in ON-bipolar cells in the retina during darkness (Nomura et al., 1994; Vardi et al., 2000). Glutamate released from rod photoreceptors in the dark, activates postsynaptic mGlu₆ receptors in bipolar ON cells that lead to the closure of a non-selective ion channel, TRPM1-L (a long form transcript of TRPM1 expressed solely in the dendritic tip of bipolar ON neurons) (Koike et al., 2010). TRPM1 inhibition results in hyperpolarization of bipolar ON neurons, thus inhibiting the ON pathway into darkness. The signaling cascade involves G α (Koike et al., 2010), G $\beta\gamma$ (Shen et al., 2012) and other proteins such as the orphan GPCR GPR179 or the interacting protein Nyctalopin (Zeitz et al., 2015)(Figure 5). Collectively, the intracellular

signal transduction and regulatory pathways engaged by group III receptor subtypes have not been as well elucidated as group I and group II counterparts.

Pathophysiology and therapeutic potential

The phenotypes of mice lacking the group III mGlu receptors have revealed physiological roles and potential as therapeutic targets in several neurological disorders. Mice lacking the mGlu₄ receptor present deficits in motor performance, spatial memory and learning of complex motor tasks (Gerlai et al., 1998; Pekhletski et al., 1996), in accordance with its particularly high expression in the cerebellum (Corti et al., 2002; Kinoshita et al., 1996b). The mGlu₄^{-/-} mice also have enhanced seizure-associated vulnerability (Pitsch et al., 2007) and lack the motor stimulant effect of ethanol (Blednov et al., 2004). The sensitivity to strong noxious stimuli of mGlu₄^{-/-} mice is altered, and nociceptive behavior in the inflammatory phase of the formalin test is accelerated (Vilar et al., 2013). Knockout phenotypes together with preclinical studies highlight mGlu₄ receptor as a potential therapeutic target in anxiety and depression (Kalinichev et al., 2014), schizophrenia (Wieronska et al., 2012a), epilepsy (Ngomba et al., 2008; Pitsch et al., 2007), neuroinflammation (Fallarino et al., 2010), autism spectrum disorder (Becker et al., 2014) and chronic pain (reviewed in (Pereira and Goudet, 2018)). In particular, targeting mGlu₄ receptor for the treatment of PD has attracted much attention (Amalric et al., 2013; Celanire and Campo, 2012; Charvin, 2018; Volpi et al., 2018). Preclinical studies showed that mGlu₄ receptor activation corrects the imbalance of neurotransmission among the basal ganglia circuitry that is associated with PD (Charvin et al., 2018b), as shown primarily with mGlu₄ potentiation (Marino et al., 2003b) or later with selective agonists (Beurrier et al., 2009; Marino et al., 2003b). Activation or potentiation of mGlu₄ receptors also has neuroprotective effects (Battaglia et al., 2006; Copani et al., 1995). Unfortunately, despite promising preclinical results (Charvin et al., 2018a; Charvin et al., 2017), the mGlu₄ receptor potentiator, foliglurax, recently failed to show sufficient efficacy in a phase II clinical trial for PD.

Comparing the phenotypes of mGlu₄, mGlu₇ and mGlu₈ knockout mice indicates the mGlu₄ receptor is most clearly involved in startle and motivational processes, whereas mGlu₇ receptor is involved in hippocampus-

dependent spatial learning and fear-related behaviors, while mGlu₈ receptor deletion yield to more subtle behavioral changes and influence body weight (Goddyn et al., 2015). The role of mGlu₇ receptors in learning and memory is confirmed by behavioral pharmacology studies (Hikichi et al., 2010a; Klakotskaia et al., 2013). Also, mGlu₇^{-/-} mice and mice lacking functional mGlu₇ receptors present an increased susceptibility to seizures (Bertaso et al., 2008; Sansig et al., 2001). Accordingly, absence seizures can be induced by the pharmacological blockade of the mGlu₇ receptor (Tassin et al., 2016) whereas mGlu₇ receptor activation protects against epileptogenesis and epileptic seizures (Girard et al., 2019). Widely expressed in the CNS (Corti et al., 1998; Kinoshita et al., 1998; Kinzie et al., 1997; Shigemoto et al., 1997), the mGlu₇ receptor is also considered as a potential therapeutic target for anxiety and depression (Cryan et al., 2003), and neurodevelopmental disorders (Fisher et al., 2018; O'Connor et al., 2010; Palazzo et al., 2016). Genetic disruptions in GRM7 are evident in patients with autism spectrum disorders (Liu et al., 2012; Sanders et al., 2012). Furthermore, the potentiation of mGlu₇ receptor activity improves cognitive and social deficits, as well as respiratory impairments in a mouse model of Rett syndrome (Gogliotti et al., 2017).

Interestingly, depending on the brain structure, mGlu₇ and mGlu₈ receptors play opposing roles in pain (Boccella et al., 2019). For example, mGlu₇ receptor activation in periaqueductal gray and amygdala is pronociceptive whereas mGlu₈ receptor activation is antinociceptive (Marabese et al., 2007; Palazzo et al., 2008). Indeed, for mGlu₇ receptors, proalgie or analgesic activity depends on the brain structure and circuits in which the receptor is expressed (see (Pereira and Goudet, 2018) for review). For example, activation of mGlu₇ receptors in the nucleus accumbens has an antinociceptive effect (Kahl and Fendt, 2016), opposite to the pronociceptive effect when periaqueductal gray mGlu₇ receptors are activated (Palazzo et al., 2016). Interestingly, mGlu₇ receptor activation also prevents the development of morphine tolerance (Gawel et al., 2018). Additional studies confirmed mGlu₈ receptor modulates sensory symptoms associated to neuropathic pain (Rossi et al., 2014). Further, mGlu₈ receptor activation in the nucleus tractus solitarius enhances cardiac nociception (Liu et al., 2012). Distinguishing the different physiological and pathophysiological roles for mGlu₇ and mGlu₈ receptors has been hampered by a lack of selective pharmacological tools, however,

discovery of new pharmacological tools (discussed in further detail later) have aided dissection of different roles and therapeutic indications.

The mGlu₈ receptor is one of the least studied mGlu receptor family members, due notably to the lack of selective pharmacological tools. Investigations on the phenotype of genetically modified mice lacking the mGlu₈ receptor are thus particularly informative. In various studies, mGlu₈^{-/-} mice exhibit anxiety-related phenotypes. However, some studies report an anxiogenic-like phenotype (Duvoisin et al., 2011; Duvoisin et al., 2005; Linden et al., 2003), while others find an anxiolytic-like one (Fendt et al., 2010; Fendt et al., 2013; Gerlai et al., 2002). Also, mGlu₈^{-/-} mice present robust deficits in contextual fear conditioning, novel object recognition, extinction of operant conditioning and acoustic startle response (Fendt et al., 2010; Fendt et al., 2013). mGlu₈^{-/-} mice also show enhanced social interaction; however, enhancing mGlu₈ receptor activity does not affect social interaction in WT mice (Duvoisin et al., 2011). Further studies are required to better understand the role for mGlu₈ and to clarify its therapeutic potential.

Outside of the CNS, the mGlu₆ receptor plays an important role in visual discrimination in low light conditions (Nomura et al., 1994; Vardi et al., 2000); supported by the mGlu₆^{-/-} phenotype (Masu et al., 1995). Mutations in proteins involved in the transmission of the signal between rod photoreceptors and bipolar ON cells have been found in patients suffering from congenital stationary night blindness; these include more than 20 loss-of-function mutations in GRM6 (Dryja et al., 2005; O'Connor et al., 2006; Zeitz et al., 2007; Zeitz et al., 2015). These mutations affect the normal mGlu₆ receptor response to the glutamate released from the photoreceptors thus impairing signal transmission. The use of an optogenetic tool consisting in a chimera between mGlu₆ receptor and melanopsin receptor has been suggested as a potential approach to restore light sensitivity (van Wyk et al., 2015).

Orthosteric ligands

Definitions and mode of action

By definition, orthosteric ligands act in the same binding pocket as the endogenous ligand, competing to either activate or inhibit mGlu receptor activity. Glutamate and surrogate orthosteric agonists bind in the cleft between the two VFT lobes (**Figure 1**). Upon binding, orthosteric agonists stabilize the closed state of the VFT, leading to a change in the relative orientation such that the extracellular domain dimer changes from a “resting” (R) to an active (A) state (Bessis et al., 2002). On the contrary, orthosteric antagonists prevent the full closure of the VFT (Bessis et al., 2000; Bessis et al., 2002; Kunishima et al., 2000; Tsuchiya et al., 2002). Based on crystal structures, the main conformations that define the inactive and active states of mGlu receptors are the resting state *R_{oo}* where both VFTs are open, and the active states *A_{co}* or *A_{cc}* where one or both VFTs are closed, respectively. The two lobes are distant in the resting state and become closer in the active state (Kunishima et al., 2000; Tsuchiya et al., 2002). The closure of one VFT (*A_{co}*) is sufficient to induce a functional response from the receptor but the closure of both VFTs (*A_{cc}*) is necessary to achieve full activation (Kniazeff et al., 2004).

Selectivity

The L-glutamate binding site is highly conserved among the mGlu receptor family, resulting in difficulties to identify compounds with subtype selectivity. Indeed, glutamate binds to all mGlu receptors under a similar conformation, where the residues participating in direct interactions with its amino acid moiety are fully conserved as well as two residues that interact with the carboxylate moiety (Acher and Bertrand, 2005; Bertrand et al., 2002; Wellendorph and Brauner-Osborne, 2009). Within the orthosteric pocket, several residues that do not directly interact with glutamate are different between the three groups of mGlu receptors, enabling identification of group-I, group-II and group-III selective ligands (**Table 1**).

The most commonly used agonists of group I mGlu receptors are 3,5-DHPG and quisqualic acid, which are somewhat selective for group I over group II and III receptors (**Table 1**). Concerning group II mGlu receptors, the classical agonists are DCG-IV (Brabet et al., 1998) and LY354740 (Monn et al., 1997), while L-AP4 and ACPT-I (Acher et al., 1997a) are most commonly used agonists for group III mGlu receptors (**Figure 6**). LY341495 is the most used competitive antagonist, which antagonizes all the subtypes, with higher potency at mGlu_{2/3} receptors over other subtypes (Kingston et al., 1998)(**Figure 6**).

For subtype selective orthosteric ligands, drug designers have to circumvent the highly conserved binding pocket. One way is to design compounds able to interact with proximal residues to the glutamate binding pocket that differ between subtypes. By example, newly discovered orthosteric ligands can discriminate between mGlu₂ and mGlu₃ receptors, e.g. LY541850 and LY2812223 are two mGlu₂ receptor selective agonists (Monn et al., 2015a; Monn et al., 2015b) and LY2794193, an mGlu₃ receptor selective agonist (Monn et al., 2018). Co-crystallization of the VFT with each of these ligands, coupled with mutagenesis and molecular modeling revealed that selectivity is due to interactions with amino acids residing at the periphery of the glutamate binding site (Monn et al., 2018; Monn et al., 2015a; Monn et al., 2015b). In a similar fashion, LSP4-2022, an mGlu₄ receptor selective orthosteric agonist, binds both to the glutamate binding site and to an adjacent pocket (Goudet et al., 2012)(**Figure 6**). This adjacent pocket is thought to be one of the sites of action of Cl⁻ ions, which are potent positive allosteric modulators of mGlu receptors (Acher et al., 2011; Tora et al., 2015). Therefore, LSP4-2022 and related derivatives constitute bitopic ligands that simultaneously target an orthosteric and an allosteric binding site (Selvam et al., 2018). Targeting these two sites in tandem provides the means to overcome the difficulty of designing selective orthosteric drugs.

Biased agonism

Across the GPCR superfamily, it is becoming increasingly appreciated that the cellular response to receptor activation can differ depending on the ligand used, a phenomenon referred to as biased agonism. Biased agonism is thought to originate from the stabilization of different active conformations by distinct ligands, the

balance of which is sampled by measuring different downstream measures of receptor activity. For any definition of biased GPCR agonism it is critical that biased agonism is quantified relative to both a reference agonist and a reference pathway; this is because the relative efficacy of GPCR agonists is influenced by the stimulus-response coupling of the system. The most commonly applied method to quantify GPCR biased agonism is based on the operational model of agonism (Black and Leff, 1983) and subsequent derivation of transduction ratios (Kenakin et al., 2012). For metabotropic glutamate receptor orthosteric agonists, to date observations of biased agonism are limited to group I receptors. For example, relative to glutamate activation of mGlu₁-mediated cytoprotective signaling, quisqualate is biased toward IP₁ accumulation in recombinant and native cells (Emery et al., 2012; Hathaway et al., 2015). At mGlu₅ receptors, biased agonism for DHPG relative to glutamate arises due to “location bias” as DHPG is impermeable and not actively transported across cell membranes, DHPG is therefore unable to stimulate mGlu₅ receptors located on intracellular membranes (Jong et al., 2005). Within different subcellular compartments mGlu₅ receptors interact with a different complement of transducers, giving rise to different forms of synaptic plasticity (Kumar et al., 2012). It remains to be determined whether or not other mGlu receptors and associated selective ligands also exhibit location bias that contributes to pharmacological differences.

Tolerance

Another layer of complexity with regard to orthosteric agonist drug development is the potential for tolerance development. Under normal conditions glutamate is released transiently into the synapse, briefly activating mGlu receptors before active uptake mechanisms, for e.g. into astrocytes, reduce synaptic glutamate concentrations. However, these clearance mechanisms are not operative for surrogate orthosteric agonists, resulting in sustained receptor activation, which can lead to tolerance development. The potential for tolerance can be exacerbated for neurological targets given the need for repeated chronic dosing to achieve a therapeutic effect. Tolerance has been noted for group II orthosteric agonists, where LY354740 efficacy for modulating REM sleep wanes with repeated dosing (Ahnaou et al., 2015). Similarly, repeated daily dosing of LY379268

results in loss of efficacy as an analgesic (Jones et al., 2005) and anti-psychotic-like activity to inhibit PCP or amphetamine-induced hyperlocomotion (Galici et al., 2005). However, tolerance is not consistently observed with chronic LY379268 dosing and can differ between behavioral paradigms (Anderson et al., 2014; Battaglia et al., 2015; Cartmell et al., 2000; Halberstadt et al., 2019). Whether or not tolerance development will prove to limit therapeutic efficacy of mGlu receptor orthosteric agonists remains to be seen.

Orthosteric ligands in the clinic: success and failure

The most successful mGlu receptor discovery campaigns focused on orthosteric ligands targeting group II receptors. Multiple group II orthosteric agonists have reached phase II or phase III trials for psychiatric indications. LY354740/eglumegad was well-tolerated and showed anxiolytic efficacy in humans (Grillon et al., 2003; Schoepp et al., 2003), with further development focused on a prodrug formulation (LY544344) to improve bioavailability (Rorick-Kehn et al., 2006). However, trials for generalized anxiety disorder were discontinued due to concerns regarding convulsions in animals (Dunayevich et al., 2008). Another group II mGlu receptor selective agonist, LY2140023/pomaglumetad (pro-drug for LY404039) improved both negative and positive symptoms in patients with schizophrenia in a randomized phase II clinical trial (Patil et al., 2007). Subsequent phase III trials failed to report significant antipsychotic efficacy for all the patients involved, terminating further development (Adams et al., 2013; Adams et al., 2014; Downing et al., 2014; Kinon et al., 2011). However, exploratory analyses of multiple phase II and III revealed that some subgroups of patients exhibited improvement after treatment with pomaglumetad, particularly early-in-disease patients, or individuals previously treated with D₂ dopamine receptor targeting drugs but not 5HT_{2a} receptor antagonists, (Kinon et al., 2015). Findings consistent with preclinical studies showing that mGlu₂ and 5HT_{2a} receptors form functional complexes in cortex and that atypical antipsychotic treatment down-regulates mGlu₂ receptor expression (Gonzalez-Maeso et al., 2008; Kurita et al., 2012)(reviewed in (Shah and Gonzalez-Maeso, 2019)).

Trials are ongoing for pomaglumedad for methamphetamine abuse [NCT03106571] and psychosis [NCT03321617]. Fasoracetam (also known as NS-105 or NFC-1), which is structurally unrelated to eglumegad or pomaglumedad, has agonist activity at group II and III receptors and showed efficacy for attention deficit hyperactivity disorder in a small cohort of adolescents (Elia et al., 2018), but failed to distinguish from placebo in a subsequent trial [NCT02777931]. In addition to orthosteric agonists, the group II selective orthosteric antagonist BCI-838 (also known as MGS0210), a pro-drug of BCI-632 (also known as MGS0039)(Nakamura et al., 2006), completed phase I in healthy volunteers [NCT01546051], although plans for subsequent phase II trial in treatment resistant depression have not eventuated. This same agent has shown preclinical efficacy in models for Alzheimer's disease (Kim et al., 2014) and post-traumatic stress disorder related to traumatic brain injury (Perez-Garcia et al., 2018). Despite successful discovery efforts for subtype selective and drug-like orthosteric ligands for the group II mGlu receptors in particular, the majority of mGlu receptor discovery programs are pursuing allosteric modulators as reviewed below.

Allosteric modulators

Definitions, quantification and identification

Since glutamate is recognized by two different receptor families (ionotropic and metabotropic receptors) as well as transporters, there remains a concern that orthosteric compounds will suffer from lack of selectivity due to high conservation of glutamate binding sites across different proteins. As such, many discovery programs have focused efforts on identification and development of allosteric modulators. Allosteric modulators interact with sites that are topographically distinct from the orthosteric site, such that a receptor may be simultaneously bound by both an orthosteric and an allosteric ligand (**Figure 1a**). For the most part, allosteric sites are located in region of receptors that show greater sequence divergence across subtypes and

therefore offer greater selectivity. An allosteric modulator may enhance or inhibit the binding and/or efficacy of an orthosteric ligand, with the magnitude and direction described as “cooperativity”. An allosteric modulator that enhances orthosteric ligand affinity or efficacy is referred to as a positive allosteric modulator (PAM), while an inhibitor is a negative allosteric modulator (NAM). In addition, allosteric ligands may also bind to a receptor but have no net effect on either affinity or efficacy of an orthosteric ligand; referred to as neutral allosteric ligands (NAL). Further, allosteric ligands may also possess intrinsic efficacy as either positive or inverse agonists in addition to, or exclusive of, cooperativity with an orthosteric ligand. By example, a PAM with intrinsic agonist activity is referred to as a PAM-agonist or ago-PAM.

In addition to potential for increased subtype selectivity, allosteric modulators offer a number of advantages over their orthosteric counterparts. Cooperativity between two ligands is saturable, offering the potential for greater safety in an overdose. Allosteric modulators that have no intrinsic efficacy and are quiescent in the absence of endogenous ligand also provide scope to fine-tune receptor activity in a spatio-temporal fashion, exerting potentiation or inhibition only where, and when, the endogenous ligand is present. For these reasons, discovery programs in industry and academia alike have sought allosteric modulators of mGlu receptors as potential novel therapeutics for a wide array of CNS disorders. However, discovery of allosteric modulators can be associated with considerable challenges with respect to quantification and validation.

Allosteric modulator binding is defined by the law of mass action, where the equilibrium dissociation constant, commonly defined as K_B , describes the affinity of an allosteric modulator for its site. However, the simultaneous binding of an allosteric modulator and orthosteric ligand gives rise to different receptor conformations than can be achieved by the binding of each ligand individually, altering ligand affinity as defined by cooperativity. In order to quantify cooperativity, the simplest scheme is the allosteric ternary complex model (ATCM, **Figure 1b** (Gregory et al., 2010b)), which describes the reciprocal change in ligand affinity when a receptor is simultaneously bound by both an allosteric and orthosteric ligand, defined by the cooperativity factor α . The ATCM is limited to describing allosteric interactions at the level of receptor

binding, and for many mGlu allosteric modulators it is apparent these ligands have effects on receptor activity in addition to, or independent of, affinity.

In order to quantify the full scope of effects an allosteric ligand may have on receptor activity, multiple alternative pharmacological models have been proposed that can accommodate: allosteric ligand intrinsic efficacy and efficacy modulation (Gregory et al., 2019b; Hall, 2013; Hall and Giraldo, 2018; Roche et al., 2014; Slack and Hall, 2012). A challenge in applying these models is the inclusion of many parameters, which can prohibit fitting to experimental data. In this respect, the most widely adopted framework for quantification of pharmacological activity is an operational model of allosterism (**Figure 1c**), which combines the Black & Leff operational model of agonism with the ATCM (Gregory et al., 2012; Leach et al., 2007). Within this framework, the influence of an allosteric modulator on orthosteric agonist efficacy is accounted for by β , an experimentally derived scaling factor. Application of this model therefore allows for delineation of the influence of an allosteric modulator on affinity independently of efficacy. This provides an important distinction given that allosteric modulators can have differential effects, which may be in opposing directions, on affinity versus efficacy. The operational model of allosterism also allows for intrinsic allosteric agonism, defined by τ , but cannot account for inverse agonism.

Accurate quantification of allosteric ligand pharmacology requires appropriately designed experimental paradigms. The definitive experiment to unambiguously demonstrate an allosteric mechanism of action is a kinetic binding paradigm. The simultaneous binding of an allosteric ligand may enhance or slow the dissociation rate (K_{off}) of the orthosteric radioligand from the receptor, or vice versa. Interaction studies using radiolabeled orthosteric ligands can be used to quantify modulation of affinity (α) as well as ligand affinity for the free receptor (Gregory et al., 2010b). However, it is important to note that the magnitude and direction of cooperativity between two ligands depends on the chemotypes present, a phenomenon known as “probe dependence”. This is an important consideration when extrapolating pharmacological profiles of allosteric ligands based on interactions with a radiolabeled orthosteric antagonist or from a surrogate orthosteric agonist,

which is often required in native cells/tissues. Radiolabeled allosteric ligands have been described for multiple subtypes, which can also be used to quantify affinity for the receptor for unlabeled ligands at a common allosteric site (Cosford et al., 2003; Lavreysen et al., 2003; O'Brien et al., 2018), or provide evidence for additional allosteric sites that are conformationally linked such that there is cooperativity between the two allosteric sites.

The vast majority of allosteric ligands for mGlu receptors have been identified and validated using functional assays. The most commonly used approach involves generating modulator titration curves in the presence of either an \sim EC₂₀ agonist concentration for PAM identification, or an EC₈₀ to identify NAMs. The potencies and relative maximum response (for PAMs) or inhibitory effect (for NAMs) from these titration curves are routinely used to drive discovery programs (Lindsley et al., 2016). However, these parameters represent composite values encompassing α , β , K_B and τ , and are also influenced by the concentrations of orthosteric agonist used, orthosteric agonist intrinsic efficacy and the stimulus-response coupling of the system under investigation (Lindsley et al., 2016). Modulator potencies curves can be analyzed in parallel with an agonist concentration-response curve to estimate K_B and a composite $\alpha\beta$ value where the maximum degree of potentiation or inhibition does not reach the limit of the system (Gregory et al., 2019a; Gregory et al., 2012). However, to quantify the interaction between a modulator and orthosteric agonist, the most robust approach is to perform full agonist concentration-response curves in the absence and presence of increasing concentrations of modulator. Despite the limitations in the most commonly applied screening approaches, drug discovery programs for small molecule synthetic allosteric ligands of mGlu receptors have been largely successful. In addition, there is increasing evidence for endogenous allosteric modulators for mGlu receptor family members.

Endogenous allosteric modulators

The greater class C GPCR family also includes the calcium-sensing receptor and GPRC6A, two receptors that are known to respond to multiple endogenous ligands including amino acids and cations (Leach and Gregory, 2017). It is perhaps therefore not surprising that divalent and trivalent cations, including Ca^{2+} , can directly activate mGlu₁, mGlu₃ and mGlu₅ receptors (Jiang et al., 2014; Kubo et al., 1998; Miyashita and Kubo, 2000a; b). Further, extracellular Ca^{2+} potentiates binding/function of orthosteric ligands at mGlu₁ (Jiang et al., 2014; Saunders et al., 1998). In addition, negatively charged chloride ions activate mGlu₃, mGlu₄, mGlu₆ and mGlu₈ receptors and potentiate glutamate efficacy at mGlu₁, mGlu₂, mGlu₄, mGlu₅ and mGlu₆ receptors (DiRaddo et al., 2015; Tora et al., 2018; Tora et al., 2015). Both cations and anions are thought to mediate activation and/or modulation via interactions with the VFT domain. The extracellular membrane associated cellular prion protein interacts with the mGlu₅ receptor acting as a co-receptor for amyloid β oligomers, although the precise binding interactions within mGlu₅ receptors are unknown (Um et al., 2013). Beyond the extracellular domains, molecular dynamics studies have proposed that lipids can interact with mGlu₅ 7TM (Dalton et al., 2017). Further, cholesterol membrane content enhances mGlu₁ signaling to ERK1/2 phosphorylation mediated via a cholesterol recognition/interaction amino acid consensus motif in TM5 (Kumari et al., 2013). The existence of endogenous allosteric modulators for the mGlu receptors is often overlooked during discovery and validation of synthetic small molecule allosteric modulators.

Small molecule allosteric modulators

Concerted discovery efforts from both industrial and academic researchers have yielded a wealth of chemically and pharmacologically diverse small molecule allosteric modulators for the mGlu receptor family (**Tables 2-5**). The majority of small molecule mGlu receptor allosteric modulators identified to date interact with a common pocket within the 7TM domains. This binding pocket is in a location analogous to the biogenic amine orthosteric site of class A GPCRs, largely lined by residues in TMs 3, 5, 6 and 7. To date, six x-ray crystal structures of the mGlu₁ or mGlu₅ receptor 7TM domains have been solved with NAMs occupying this

common allosteric site (Christopher et al., 2015; Christopher et al., 2019; Dore et al., 2014; Wu et al., 2014). A wealth of previous mutagenesis data indicate that this pocket is shared across the mGlu receptor family, and indeed for all class C GPCRs, and can be engaged by both NAMs and PAMs (see (Leach and Gregory, 2017) for review). Here we focus on the pharmacological profiles of prototypical and well-validated commercially available allosteric modulators for mGlu receptors.

Group I PAMs, NAMs, NALs

The first disclosed mGlu receptor allosteric modulator was CPCCOEt (Annoura et al., 1996; Litschig et al., 1999), a negative allosteric modulator of mGlu₁ receptor. CPCCOEt has low micromolar affinity for mGlu₁ receptors (Lavreysen et al., 2003), and negatively modulates glutamate efficacy but has neutral cooperativity with respect to [³H]glutamate affinity (Litschig et al., 1999). Moreover, CPCCOEt has poor selectivity between group I mGlu receptors (Table 2), negatively modulating mGlu₅ receptor activation with a similar apparent K_B (Hellyer et al., 2018). The discovery of CPCCOEt was followed by EM-TBPC and BAY-36-7620, which showed species differences in mGlu₁ receptor NAM activity with considerably higher affinity for the rat versus human receptor (Cho et al., 2014a; Malherbe et al., 2003). Similar to CPCCOEt, BAY-36-7620 has neutral cooperativity with respect to [³H]quisqualate affinity, but inhibits orthosteric agonist efficacy (Carroll et al., 2001; Lavreysen et al., 2003). Since the discovery of these early tool compounds, a wealth of structurally diverse mGlu₁ receptor NAMs have been disclosed that have therapeutic efficacy in preclinical models for analgesia, anti-psychotic-like activity, anxiety, addiction, cancer and as anti-convulsants (**Table 2**). For diverse scaffolds (**Figure 7**, e.g. A-841720 and R214127), the higher affinity for rat over human (>10-fold) persisted (Cho et al., 2014a). Breakthrough chemotypes represented by FTIDC and JNJ16259685 have similar nanomolar affinities for the rat and human receptors, and >100 fold selectivity as NAMs for mGlu₁ over mGlu₅ receptors (Lavreysen et al., 2003; Lavreysen et al., 2004; Suzuki et al., 2007a). Despite ultimate identification of high affinity, *in vivo* efficacious mGlu₁ receptor NAMs, further development has stalled due

to on-target mediated adverse effects such as cognitive impairments from multiple scaffolds (Schroder et al., 2008; Steckler et al., 2005b).

On the other hand, mGlu₁ receptor PAMs have been relatively unexplored, although may be a promising therapeutic strategy for schizophrenia by restoring function of naturally occurring mutations (Garcia-Barrantes et al., 2015b). The first mGlu₁ receptor PAMs included diverse chemotypes, for e.g. RO 67-7476 and RO 01-2168, identified from high-throughput screening, which enhanced orthosteric agonist affinity and functional responses at rat mGlu₁ receptor without intrinsic agonist activity (Knoflach et al., 2001), but were not suitable for *in vivo* studies. Similar to multiple mGlu₁ receptor NAM scaffolds, RO 67-7476 lacks the ability to potentiate glutamate at human mGlu₁ receptors (Knoflach et al., 2001). A subsequent study suggested these mGlu₁ receptor PAMs may have intrinsic efficacy for ERK1/2 and cAMP accumulation; however, this agonist activity could be blocked by both orthosteric and allosteric antagonists raising the possibility that the apparent intrinsic agonism may be attributable to potentiation of ambient glutamate (Sheffler and Conn, 2008). Of note, both RO 67-7476 and RO 01-2168 were unable to completely displace binding of the radiolabeled mGlu₁ receptor NAM [³H]R214127 (Hemstapat et al., 2006), suggesting these compounds recognize a different site within the 7TM domain. Subsequent discovery efforts identified VU0483605 based on a scaffold hop from an mGlu₄ PAM/mGlu₁ NAM chemotype (Cho et al., 2014b); however, the selectivity of VU0483605 as an mGlu₁ PAM is based on cooperativity, as it has similar affinity for mGlu₅ receptors, albeit with neutral cooperativity with mGlu₅ receptor orthosteric agonist efficacy (Hellyer et al., 2018). Recent medicinal chemistry efforts have yielded the first CNS penetrant mGlu₁ receptor PAMs (Garcia-Barrantes et al., 2015a; 2016a; Garcia-Barrantes et al., 2016b; Yohn et al., 2018), paving the way forward to establish therapeutic potential for schizophrenia and beyond.

While CPCCOEt was the first mGlu receptor NAM disclosed, the mGlu₅ receptor NAM fenobam was discovered earlier (Itil et al., 1978), but its mechanism of action was not elucidated until over 20 years later (Porter, 2005). Indeed, of all the subtypes, allosteric ligand discovery against mGlu₅ receptors has proven to

be the most fruitful with a wealth of pharmacologically and structurally diverse ligands identified including NAMs, PAMs and NALs (Table 3). Prototypical mGlu₅ receptor NAMs based on an acetylene core, MPEP and MTEP, as well as fenobam have demonstrated the therapeutic potential for mGlu₅ receptor inhibition for addiction, depression, anxiety, neurodegenerative disorders and autism spectrum disorders (Table 3). Often referred to as “full NAMs”, these ligands have high negative cooperativity with respect to orthosteric agonist efficacy, completely abolishing agonist responses at saturating concentrations, but are neutral with respect to glutamate affinity (Gregory et al., 2012; Sengmany et al., 2019). The relatively high affinity of MPEP and fenobam presented the opportunity to generate radiolabeled versions (Cosford et al., 2003; Porter et al., 2005), which facilitated discovery and validation of novel mGlu₅ receptor NAMs. Of note, many full NAMs have inverse agonist activity (Porter et al., 2005; Sengmany et al., 2019). It has been postulated that the combination of high negative cooperativity and inverse agonism contributes to on-target adverse effect liability of mGlu₅ receptor NAMs, including cognitive impairments and psychotomimetic-like properties (Abou Farha et al., 2014; Dekundy et al., 2011; Hughes et al., 2012; Swedberg et al., 2014; Swedberg and Raboisson, 2014). Repeated exposure to both MTEP and fenobam is associated with tolerance development for reward behaviors (Cleva et al., 2012), but not for fenobam analgesic efficacy (Montana et al., 2011). The limitations associated with mGlu₅ receptor full NAMs stimulated discovery efforts for NAMs with lower negative cooperativity, also referred to as “partial NAMs”, which have limited ability to inhibit glutamate efficacy. Two recent proof-of-concept studies demonstrated that partial NAMs, e.g M-5MPEP and VU0477573, which have limited negative cooperativity with glutamate, elicited anxiolytic, anti-depressant and reduced cocaine self-administration with comparable efficacy to MTEP (Gould et al., 2016; Nickols et al., 2016). Importantly, unlike MTEP, M-5MPEP did not show psychotomimetic-like effects (Gould et al., 2016); therefore mGlu₅ receptor NAMs with limited cooperativity may offer improved therapeutic windows.

An inherent challenge for mGlu₅ receptor allosteric ligand discovery has been the prevalence of “molecular switches” where minor substitutions give rise to ligands with reduced or opposing cooperativity (Wood et al., 2011). Whilst a challenge with respect to SAR interpretation, these molecular switches have also offered

invaluable tools to dissect mGlu₅ receptor biology, with the MPEP scaffold giving rise to NALs and PAMs. By example 5MPEP is a neutral mGlu₅ receptor allosteric ligand, which occupies the allosteric site in a competitive manner with MPEP but does not influence orthosteric agonist activity (Rodriguez et al., 2005). Subsequent efforts have identified high affinity mGlu₅ receptor NALs (e.g. VU0478006, BMS-984923) with suitable properties for *in vivo* studies (Gregory et al., 2010a; Haas et al., 2017).

Molecular switches within mGlu₅ receptor NAM scaffolds (**Figure 7**) have also yielded PAMs and PAM-agonists, with advanced compounds from the biaryl acetylene scaffold, such as VU0360172 and LSN2463359, showing high affinity and selectivity for mGlu₅ (**Table 3**). However, early mGlu₅ receptor PAMs (DFB, ADX47273, CDPPB, CPPHA) were identified from high-throughput screening using functional assays (Lindsley et al., 2004; Liu et al., 2008; O'Brien et al., 2003; O'Brien et al., 2004). Structurally diverse mGlu₅ receptor PAM scaffolds compete for the common allosteric site within the 7TM used by MPEP (Gregory et al., 2014; Gregory et al., 2013b); however, select PAMs (e.g. CPPHA and VU0357121) are thought to interact with distinct, but as yet unknown site/s, within the 7TM (Chen et al., 2008; Hammond et al., 2010; Noetzel et al., 2013; O'Brien et al., 2004). Mechanistically, mGlu₅ receptor PAMs are largely considered to potentiate mGlu₅ receptor activity in response to glutamate via efficacy modulation (Gregory et al., 2012); however, probe dependence can dictate the nature of these allosteric interactions with multiple PAMs reported to enhance [³H]quisqualate binding (Bradley et al., 2011; Koehl et al., 2019) as well as show different magnitudes of cooperativity depending on the orthosteric agonist used (Sengmany et al., 2017). In this respect the largest magnitude of potentiation observed in mGlu₅ receptor functional assays is ~20-fold shift in glutamate potency for DPFE and 5PAM523 (Gregory et al., 2013a; Parmentier-Batteur et al., 2014). Indeed, the magnitude of cooperativity was the best predictor of *in vivo* efficacy of an mGlu₅ receptor PAM series using the amphetamine-induced hyperlocomotion assay, when total and free brain and plasma concentrations were determined from the same rats (Gregory et al., 2019). Select mGlu₅ receptor PAMs have intrinsic agonist efficacy, however, in some cases this is linked to high receptor reserve in recombinant systems (Noetzel et al., 2012). Although this is not always the case, with some compounds, e.g. DPFE, showing intrinsic efficacy in

low expression and native cell systems (Gregory et al., 2013a; Sengmany et al., 2017) and may also be dependent on measure of receptor activation, where mGlu₅ receptor PAMs often activate mGlu₅-ERK1/2 phosphorylation at concentrations that do not elicit iCa²⁺ mobilization responses (Gregory et al., 2012; Rook et al., 2013). Despite the complexity in pharmacology, successful discovery efforts for multiple centrally active mGlu₅ receptor PAMs have established proof-of-concept for pro-cognitive and anti-psychotic efficacy of mGlu₅ potentiators (**Table 3**). However, on-target adverse effect liability has been associated with multiple scaffolds, which has been attributed in part to intrinsic agonist activity and/or magnitude of cooperativity (Parmentier-Batteur et al., 2014; Rook et al., 2013). Recent studies have challenged these conclusions (Rook et al., 2015b; Sengmany et al., 2017), suggesting that biased pharmacology of mGlu₅ receptor PAMs may be linked to adverse versus therapeutic effects (discussed in detail below).

Group II PAMs and NAMs

Discovery and validation of group II mGlu receptor allosteric ligands has benefited from the availability of radiolabeled orthosteric agonists and antagonists, owing to the generally higher affinity of orthosteric ligands for group II mGlu receptors (**Table 1**). Indeed, multiple different mGlu₂ receptor-selective PAMs have been disclosed and established proof-of-concept for mGlu₂ receptor potentiation as a viable therapeutic intervention for anxiety, psychosis and addiction (**Table 4**). The first mGlu₂ receptor selective PAM was LY487379 (also referred to as 4-MPPTS) (Johnson et al., 2003), which enhances radiolabeled orthosteric agonist ([³H]LY354740 and [³H]DCG-IV) binding (Lundstrom et al., 2016; Schaffhauser et al., 2003), orthosteric agonist affinity (Johnson et al., 2005) and functional activity. Although LY487379 shows probe dependence as it is neutral with respect to affinity of LY379268 (a high affinity orthosteric agonist) (Johnson et al., 2005). Further, LY487379 has neutral cooperativity with respect to orthosteric antagonist binding (Johnson et al., 2005; Schaffhauser et al., 2003), suggesting LY487379 preferentially interacts with the active receptor state. A similar pharmacological profile has been noted for mGlu₂ receptor-selective PAMs from different

chemotypes (including BINA, AZD8418, JNJ-42491293), which also potentiate glutamate binding and efficacy, but are neutral with respect to orthosteric antagonist binding (O'Brien et al., 2018). Although the recently disclosed mGlu₂ receptor modulator, SAR218645, has even more pronounced probe dependence, potentiating glutamate affinity but inhibiting [³H]LY341495 binding (Griebel et al., 2016). Further insights into the mechanism of action of mGlu₂ receptor PAMs have been elucidated using radiolabeled mGlu₂ receptor PAMs (2,2,2,TEMPs, JNJ-46281222 and AZ12559322). Compared to orthosteric radioligands, radiolabeled mGlu₂ receptor PAMs recognize fewer binding sites, which is thought to indicate occupation of a single 7TM domain within the dimeric receptor as well as preferential binding to active receptor conformations since orthosteric agonists can increase the number of mGlu₂ receptor PAM binding sites (Doornbos et al., 2016; Lavreysen et al., 2013; Lundstrom et al., 2016; Lundstrom et al., 2011; Lundstrom et al., 2009; O'Brien et al., 2018). Most mGlu₂ receptor PAMs have intrinsic agonist efficacy (**Table 4**) with the maximal degree of potentiation observed for glutamate potency of between 10-30 fold (Galici et al., 2006; Johnson et al., 2005; Lavreysen et al., 2015; O'Brien et al., 2018). In addition to increased selectivity over mGlu₃ relative to orthosteric agents, mGlu₂ receptor PAMs may also provide improved therapeutic efficacy owing to reduced capacity for induction of tolerance compared to group II receptor orthosteric agonists (Ahnaou et al., 2015). In contrast to successful mGlu₂ receptor PAM discovery campaigns, to date, mGlu₃ receptor selective PAMs have remained elusive.

Discovery efforts for group II mGlu receptor NAMs have yielded both mGlu₂ and mGlu₃ receptor subtype selective ligands, although there is less structural diversity available when compared with mGlu₂ receptor PAMs (**Figure 8, Table 4**). Negative allosteric modulators of group II mGlu receptors have demonstrated efficacy for improving cognitive deficits and reversing behaviors in preclinical models for depression and anxiety (Campo et al., 2011; Engers et al., 2017; Engers et al., 2015; Goeldner et al., 2013; Woltering et al., 2010) and are neuroprotective under ischemic insult (Motolese et al., 2015). Mechanistically, group II receptor NAMs (including MNI-137, RO4491533, decoglurant and related compounds) are neutral with respect to glutamate affinity, primarily acting as negative modulators of glutamate efficacy (Campo et al., 2011;

Hemstapat et al., 2007; O'Brien et al., 2018). Akin to observations with group II receptor PAMs, select NAMs have demonstrated probe dependence with respect to modulation of orthosteric agonist affinity, where ligands related to RO4491533 or decoglurant are NAMs with respect to [³H]LY354740 binding (Lundstrom et al., 2011; Woltering et al., 2008). For the majority of pan group II mGlu receptor NAMs including ML337, MNI-137 and decoglurant, are full NAMs, completely abolishing the functional response to orthosteric agonists at both mGlu₂ and mGlu₃ receptors (Caraci et al., 2011; O'Brien et al., 2018; Wenthur et al., 2014). However, MNI-137 has differing degrees of negative cooperativity in functional assays of mGlu₂ receptor activity, in some instances showing full blockade but limited negative cooperativity in others (Hemstapat et al., 2007; O'Brien et al., 2018; Yin et al., 2014). Further, both the reported selectivity and inhibitory activity of mGlu_{2/3} receptor NAM LY2389575 differs depending on the response measured (Caraci et al., 2011; Sheffler et al., 2012). In this respect, it is worth noting that for many ligands and series there has been limited pharmacological profiling to fully discern mechanism of action. Subtype selective mGlu₂ receptor (e.g. VU6001192, MRK-8-29, Ro64-5229) or mGlu₃ receptor (ML289, VU6010572) NAMs have been reported (Engers et al., 2017; Felts et al., 2015; Kolczewski et al., 1999; Sheffler et al., 2012; Walker et al., 2015). However, the group II receptor selectivity of ML337 was recently demonstrated to be in part attributable to cooperativity, as this ligand is a NAL at mGlu₅ (Hellyer et al., 2018). Whether or not other reportedly subtype selective NAMs are also due to cooperativity rather than affinity remains to be elucidated.

Both selective and pan-group II receptor NAMs from diverse scaffolds interact with a common or overlapping site with that used by mGlu₂ receptor PAMs within the 7TM domain (Lundstrom et al., 2016; Lundstrom et al., 2011; O'Brien et al., 2018; Rowe et al., 2008; Schaffhauser et al., 2003). Select amino acid residues within this common site can differentially influence group II receptor NAM versus PAM activity (Hemstapat et al., 2007; Lundstrom et al., 2011; Perez-Benito et al., 2017). These differential effects may be attributable to differential effects on cooperativity or affinity whereby distinct ligand-receptor interactions may contribute to active versus inactive receptor conformations. However, for some scaffolds (e.g. JNJ-42491293, decoglurant, VU6001192, MRK-8-29) allosteric interactions have been observed with a mGlu₂ receptor PAM radioligand,

indicative of multiple allosteric sites within the 7TM (O'Brien et al., 2018), or possibly more complex interactions due to the dimeric nature of mGlu receptors as has been noted for other class C GPCR allosteric modulators (Gregory et al., 2018).

Group III PAMs and NAMs

A list of some of the commercially available allosteric modulators of group III mGlu receptors is provided in **Table 5**. The first identified group III mGlu receptor selective allosteric modulator was PHCCC (Maj et al., 2003; Marino et al., 2003b) (**Figure 8**). PHCCC acts as an mGlu₄ receptor PAM, increasing potency and efficacy of glutamate or L-AP4 in cell-based assays. PHCCC is closely related to the mGlu₁ receptor selective NAM CPCCOEt (Annoura et al., 1996)(**Figure 7**). Although it has weak potency and poor solubility, PHCCC provided a very useful tool to demonstrate the therapeutic potential of targeting mGlu₄ receptors in Parkinson's disease and paving the way to drug candidates (Charvin, 2018). Indeed, PHCCC potentiated the inhibitory effect of L-AP4 on transmission at the striatopallidal synapse and reversed akinesia in rats (Marino et al., 2003a; Marino et al., 2003b). PHCCC also reduces hyperalgesia in rat models of chronic pain (Goudet et al., 2008). Subsequently, a new mGlu₄ receptor PAM named VU0155041 was discovered (Christov et al., 2011), which is more potent and more soluble than PHCCC. Interestingly, VU0155041 is an mGlu₄ receptor allosteric agonist (PAM-agonist), contrary to the pure PAM profile of PHCCC. PHCCC and VU0155041 do not compete for the same site (Niswender et al., 2008a). Accordingly, two partially overlapping 7TM binding pockets have been identified in mGlu₄ receptors, a shallow and a deep pocket (Rovira et al., 2015). Analysis of the pharmacological properties and binding modes of several mGlu₄ receptor PAMs, revealed the intrinsic efficacy and cooperativity of mGlu₄ PAMs (both affinity and efficacy modulation of L-AP4 and glutamate) correlate with the binding mode (Rovira et al., 2015). PAMs with intrinsic allosteric agonism bind in the shallow pocket, analogous to the pocket of natural agonists of class A GPCRs, whereas PAMs exhibiting the highest cooperativity with orthosteric agonists bind into a deeper pocket, corresponding to that of mavoglurant

in the mGlu₅ receptor 7TM crystal structure (Dore et al., 2014) and pointing toward a site topographically homologous to the Na⁺ binding pocket of class A GPCRs. In preclinical studies, VU0155041 improves symptoms of Parkinson's disease (Christov et al., 2011), chronic pain (Wang et al., 2011) and autistic-like syndromes (Becker et al., 2014). Foliglurax (PXT002331) is a derivative of PHCCC with good water solubility and high brain exposure after oral administration (Charvin et al., 2017). It is a potent and selective mGlu₄ receptor PAM displaying strong antiparkinsonian activity in rodent preclinical models of Parkinson's disease (Charvin et al., 2017) as well as in primates (Charvin et al., 2018a); however, recently failed to show efficacy in a phase II clinical trial. Several mGlu₄ receptor PAMs also exhibit PAM activity on mGlu₆ receptors; as yet no selective mGlu₆ receptor allosteric modulators have been described.

The first allosteric modulator acting at the mGlu₇ receptor to be described was AMN082 (Mitsukawa et al., 2005). Since there was a lack of pharmacological tools to study mGlu₇ receptor, this mGlu₇ PAM-agonist attracted much interest. However, AMN082 presents off-target effects, as it retains activity in mGlu₇ receptor KO mice (Ahnaou et al., 2016b). Indeed, AMN082 is rapidly metabolized *in vivo*, with the major metabolite being a potent monoamine transporter inhibitor (Sukoff Rizzo et al., 2011). Thus, preclinical results obtained with AMN082 have to be carefully interpreted, since its actions may not be driven solely by mGlu₇ receptors. Selective mGlu₇ receptor NAMs have been described and may be more adequate for investigating the role of mGlu₇ receptor *in vivo*: MMPIP (Suzuki et al., 2007b), ADX71743 (Kalinichev et al., 2013a) and XAP044 (Gee et al., 2014). Interestingly, the inhibitory activity of MMPIP is context dependent, where MMPIP may not antagonize mGlu₇ receptor activity in all cellular contexts. Indeed, MMPIP is unable to block agonist-mediated responses at the Schaffer collateral-CA1 synapse, where mGlu₇ receptor is known to modulate neurotransmission (Niswender et al., 2010). ADX71743 is a bioavailable and brain penetrant mGlu₇ NAM which induces a robust anxiolytic effect in rodents (Kalinichev et al., 2013a). Most small allosteric modulators described so far act via a binding pocket located within the transmembrane domain; however, XAP044 mediates its action through an interaction with the extracellular domain of mGlu₇ receptor (Gee et al., 2014). The exact binding pocket of XAP044 is not known at the moment, with chimeric mGlu₇/mGlu₆ receptors used

to map its action to the extracellular domains (Gee et al., 2014). Recent efforts aiming to identify novel mGlu₇ receptor PAM scaffolds have turned to cheminformatics-based approaches; however, to date these have yielded low potency potentiators (Tresadern et al., 2017).

Only few mGlu₈ receptor allosteric modulators have been identified. AZ12216052 is an mGlu₈ receptor PAM-agonist of glutamate at mGlu₈ receptors (Duvoisin et al., 2010). *In vivo*, AZ12216052 is anxiolytic in apolipoprotein E deficient mice, which show increased levels of anxiety-like behaviors (Duvoisin et al., 2010). AZ12216052 also displays analgesic activity following injection into the dorsal striatum of neuropathic rats (Rossi et al., 2014). However, AZ12216052 possesses some off-target effects since it retains anxiolytic activity in mGlu₈^{-/-} mice (Duvoisin et al., 2011). Another useful pharmacological tool for mGlu₈ receptor is VU6005649, a brain penetrant PAM of mGlu₇ and mGlu₈ receptors that displays *in vivo* efficacy in a mouse contextual fear conditioning model (Abe et al., 2017). The pan-group III receptor PAM, VU0422288, which has similar affinity for mGlu₄, mGlu₇ and mGlu₈ receptors (Jalan-Sakrikar et al., 2014), rescues deficits (synaptic plasticity and behavioral phenotypes) in a mouse model of Rett syndrome (Gogliotti et al., 2017). VU0422288 also shows probe dependence with respect to both its apparent affinity and magnitude of positive cooperativity (Jalan-Sakrikar et al., 2014). Whether or not targeting one or multiple of the group III receptor subtypes will best treat this neurological disorder remains to be explored with subtype selective pharmacological agents.

Allosteric modulators progressing to clinical trials

With respect to clinical translation of promising preclinical efficacy for mGlu receptor allosteric modulators, mGlu₅ NAMs have demonstrated the most progress with multiple agents reaching phase II trials for a variety of indications. Prior to elucidation of its mechanism of action, fenobam was assessed in a small double blind placebo controlled study as a single agent for treatment of anxiety compared to diazepam and was reported to have fewer adverse effects (Pecknold et al., 1982). Subsequently, fenobam was trialed in an open-label pilot

study for treatment of Fragile X syndrome behavioral deficits, where it was well-tolerated but lacked efficacy (Berry-Kravis et al., 2009). Multiple phase II trials of mGlu₅ receptor NAMs in Fragile X syndrome patients (both adolescents and adults) have now been completed, with basimglurant (RO4917523) and mavoglurant (AFQ056) being well-tolerated, improving behavioral symptoms, but failing to meet primary outcomes (Bailey et al., 2016; Berry-Kravis et al., 2016; Jacquemont et al., 2011; Youssef et al., 2018). These failures may in part be attributable to the difficulties associated with study design for indications lacking rigorous criteria for assessment of behavioral symptoms, or a need to stratify patient populations. Basimglurant also failed to show efficacy in primary clinician assessed measures for major-depressive disorder, although patient reported outcomes suggested an anti-depressive effect (Quiroz et al., 2016). Mavoglurant entered phase II trials for obsessive-compulsive disorder, but was terminated early due to lack of efficacy and a higher incidence of adverse effects (Rutrick et al., 2017). Beyond psychiatric indications, mavoglurant lacked efficacy in treating levodopa-induced dyskinesias in PD patients (PD-LID) or chorea in Huntington's disease patients (Reilmann et al., 2015; Trenkwalder et al., 2016). In contrast, dipraglurant (ADX48621) was also assessed in a phase IIa trial for PD-LID, showing promising indications of anti-dyskinetic efficacy (Tison et al., 2016). Raseglurant (ADX10059) showed anti-reflux efficacy for gastroesophageal reflux disease (Keywood et al., 2009; Zerbib et al., 2011; Zerbib et al., 2010), but further development was ultimately discontinued due to liver toxicity concerns.

With respect to modulators of other mGlu receptor subtypes, building on preclinical efficacy in addiction models for nicotine and methamphetamine (Caprioli et al., 2015; Justinova et al., 2015; Li et al., 2016), AZD8529, an mGlu₂ receptor PAM, is currently in phase II trials for smoking cessation, but failed to demonstrate efficacy as an antipsychotic or for negative symptoms in patients with schizophrenia (Litman et al., 2016). Another mGlu₂ receptor PAM, ADX71149/JNJ-40411813, was also trialed for smoking cessation and found to improve attention and memory as well as reverse effects of ketamine (Salih et al., 2015). In a phase II trial of major depressive disorder patients with significant anxiety, JNJ-40411813 as an adjunct therapy to standard of care failed to relieve anxiety (Kent et al., 2016). A group II receptor NAM, decoglurant,

also commenced trials for major depressive disorder, results are yet to be posted, but development was discontinued. The efficacy and safety of an mGlu₄ PAM, foliglurax, was recently evaluated in a phase II clinical trials in PD patients treated with levodopa, experiencing end-of-dose wearing off and levodopa-induced dyskinesia (Charvin et al., 2018a; Charvin et al., 2017) but the program was discontinued due to insufficient efficacy. The varying degrees of success and failures with clinical translation for mGlu receptor allosteric modulators are in keeping with high attrition rates for neuroscience targets. Moreover, these results speak to a need to better understand the pharmacological properties of allosteric modulators and harness novel modes of action and activity.

Secondary allosteric sites within the VFT and 7TM domains

The vast majority of allosteric modulators for mGlu receptors are believed to interact with a common allosteric site within the 7TM domain, analogous to the biogenic amine orthosteric binding pocket of class A GPCRs. However, allosteric modulators interacting at alternate allosteric sites may offer the means to engender unique pharmacological profiles and increased subtype selectivity. Within the context of a full-length dimeric mGlu receptor, there are multiple possible sites to exploit for allosteric ligands. Multiple subtype selective single domain antibodies, also referred to as nanobodies, have now been described that recognize epitopes within the VFT. For mGlu₂, three nanobodies that recognize overlapping epitopes but have different pharmacological properties have been described (Scholler et al., 2017). DN1 recognizes both active and inactive mGlu₂ receptors, whereas DN10 and DN13 require active homodimeric mGlu₂ receptor states to bind and potentiate orthosteric agonist activity (Scholler et al., 2017). Similarly, a nanobody that recognizes a loop region with lobe 1 of the mGlu₅ receptor VFT potentiates agonist binding and function, but can also recognize both active and inactive receptor states (Koehl et al., 2019). To date, nanobodies have been used to facilitate structural studies, or as biosensors for active receptor conformations. For mGlu₇ receptors, a monoclonal antibody,

MB1/28, binds to the dimeric VFT, inhibiting receptor activation but is able to induce receptor internalization (Ullmer et al., 2012). Beyond antibodies, the naturally sourced sweet protein monellin was recently revealed as an mGlu₅ receptor allosteric agonist that is also thought to interact with the N terminus, and interacts allosterically with small molecule allosteric modulators (Chen et al., 2019).

Multiple allosteric sites have been postulated for the mGlu₅ receptor 7TM domain, however, the precise location of these secondary allosteric sites has proven elusive (Chen et al., 2008; Hammond et al., 2010; Noetzel et al., 2013). With the recent publication of a full-length cryo-electron microscopy structure of mGlu₅ receptors, we now appreciate that the cysteine-rich domain is a stalk that holds the VFT above the 7TM domains, and interacts with the second extracellular loop to transmit conformational changes (Koehl et al., 2019). It is tempting to speculate that the inability to identify these secondary pockets may have been due to a monomeric view of the 7TM domain. However, biophysical studies as well as the new structures demonstrate that the 7TM domains themselves dimerize when activated (Doumazane et al., 2013; El Moustaine et al., 2012; Koehl et al., 2019; Xue et al., 2015). Appreciation of the full-length dimeric structure offers the possibility to identify new allosteric sites to exploit through targeting these newly appreciated interfaces.

Evolving concepts:

Biased modulators

Allosteric modulators elicit potentiation or inhibition through stabilizing different receptor conformations than can be achieved with an orthosteric ligand alone. Therefore, there is the potential that these conformations can give rise to biased pharmacology. Where intrinsic efficacy differs between pathways relative to a reference agonist this is referred to as biased agonism and can be quantified as discussed previously for biased

orthosteric agonists. For mGlu₅ receptors, PAM-agonists from diverse scaffolds are biased agonists relative to DHPG in both recombinant and native cells; however, the bias profile differs between scaffolds, with VU0424465, DPFE, VU0409551 each exhibiting different bias profiles for mGlu₅ receptor signaling and receptor desensitization (Hellyer et al., 2019; Sengmany et al., 2017). However, biased modulation is also possible, where the direction or magnitude of modulation of the same agonist differs between pathways, and may manifest either as differential apparent affinity or cooperativity (Sengmany et al., 2019). For structurally diverse mGlu₅ receptor PAMs (VU0360172, DPFE, VU0409551), the magnitude of cooperativity with DHPG was lower when measured in IP₁ accumulation compared to iCa²⁺ mobilization (Sengmany et al., 2017). Moreover, DPFE and CDPPB inhibit mGlu₅ receptor orthosteric agonist stimulated ERK1/2 phosphorylation in primary cultures (Sengmany et al., 2017; Zhang et al., 2005). Importantly, biased allosteric agonism and potentiation of mGlu₅ receptors as well as probe dependence is mediated via dynamic interactions within the common allosteric pocket (Sengmany et al., 2020; Hellyer et al., 2020b). Allosteric interactions with distinct binding sites would be expected to offer further diversity in these biased pharmacological fingerprints. Furthermore, differential cooperativity has also been noted for mGlu₅ receptor NAMs, where VU0366248 inhibits iCa²⁺ mobilization but is a NAL with respect to IP₁ accumulation (Sengmany et al., 2019). Recent studies indicate biased agonism and modulation of mGlu₅ receptor NAMs and PAMs extends to receptor regulatory processes such as internalization and desensitization (Arsova et al., 2020; Hellyer et al., 2019). Another contributing factor to biased modulator pharmacology at mGlu₅ receptors may be ligand binding kinetics as suggested by two recent studies on structurally diverse NAMs (Arsova et al., 2020; Sengmany et al., 2019).

Biased pharmacology of mGlu₅ receptor PAMs extends beyond second messenger signaling in cultures to intact circuitry. VU0409551 potentiates mGlu₅-dependent long-term depression in the hippocampus (Rook et al., 2015b), prefrontal cortex (Ghoshal et al., 2017) and nucleus accumbens (Turner et al., 2018), but unlike other PAMs is unable to potentiate DHPG stimulation of mGlu₅ receptor-mediated modulation of NMDA receptor currents (Rook et al., 2015b). Differential potentiation of mGlu₅ receptor dependent synaptic

plasticity and modulation of NMDA receptor activity in the hippocampus has also been noted for mGlu₅ receptor PAMs structurally unrelated to VU0409551. VU29 potentiates hippocampal long-term potentiation, but not NMDA receptor currents (Xiang et al., 2019). Within these brain slice electrophysiology experiments, mGlu₅ receptor PAM effects are mediated via enhancement of endogenous glutamate tone, or exogenously applied DHPG, suggesting that similar to VU0409551, VU29 has biased cooperativity between these two measures of mGlu₅ activity. Another structurally unrelated mGlu₅ receptor PAM, NCFP, failed to potentiate DHPG-mGlu₅ receptor long-term potentiation and long-term depression in brain slice electrophysiology experiments (Noetzel et al., 2013). For mGlu₅ receptor allosteric ligands, biased pharmacology may offer the means to selectively modulate therapeutically beneficial effects while avoiding those linked to adverse effects. In order to realize this potential, there remains a need to better understand how different mGlu₅ receptor signaling and cellular responses are linked to behavioral effects in the whole animal and the translation of these effects to the clinic. By example, it was recently demonstrated for a series of mGlu₅ receptor PAMs closely related to VU0409551, that cooperativity with glutamate (for iCa²⁺ mobilization) rather than ligand affinity was predictive of relative efficacy in rats for reversing amphetamine-induced hyperlocomotion (Gregory et al., 2019a). However, whether mGlu₅ receptor PAM affinity, cooperativity, bias or agonism proves to be the best predictor for therapeutic efficacy and safety across multiple *in vivo* measures for different scaffolds remains to be rigorously tested.

Beyond mGlu₅ receptors, the mGlu₇ receptor-targeting monoclonal antibody, MB1/28, is a NAM for orthosteric agonist inhibition of cAMP accumulation but has intrinsic efficacy for inducing receptor internalization (Ullmer et al., 2012). At mGlu₂ receptors, the PAM-agonist BINA was found to be a biased agonist relative to LY354740, favoring ERK1/2 phosphorylation over coupling to Gα₁₅ (Hellyer et al., 2020). Furthermore, biased pharmacology can contribute to apparent selectivity of allosteric ligands. Reportedly, selective allosteric ligands across the class C GPCR family were recently shown to have either neutral cooperativity for mGlu₅ receptors or have biased pharmacology (Hellyer et al., 2018). Collectively, the

potential for biased allosteric ligand pharmacology highlights the importance of considering the assay/system/approach used to define mechanism of action, classify pharmacological effects and selectivity.

Location and context dependent pharmacology

Related to the phenomenon of biased allosteric agonism and modulation is the concept of context-dependent pharmacology including the contribution of “location bias”. Quite simply put, the observed pharmacological effect is influenced by the cellular context within which it is studied. The first report for context-dependent pharmacology was for the mGlu₇ receptor NAM, MMPIP, which shows different magnitudes of inhibition of mGlu₇ receptor activity for the same agonist between different recombinant cell lines (Niswender et al., 2010). For mGlu₅ receptor modulators, both PAMs and NAMs have context-dependent pharmacology, manifested as distinct biased agonism profiles (Hellyer et al., 2019; Sengmany et al., 2017), or differential apparent affinities (Sengmany et al., 2019) or potencies (Jong et al., 2019) of NAMs between recombinant and native cells from different brain regions. Quantitative pharmacological differences between cell types may be a consequence of different stimulus-response coupling efficiencies, the presence or absence of receptor interacting proteins (other GPCRs, transducers or scaffolding partners) or differences in receptor subcellular compartmentalization and relative accessibility by different ligands.

Group I mGlu receptors associate with different lipid microdomains (Burgueno et al., 2003; Francesconi et al., 2009b), the balance of which can be altered by receptor activation or membrane cholesterol content, which in turn can modulate signaling to ERK1/2 phosphorylation (Kumar et al., 2008; Kumari et al., 2013). Further, mGlu₅ is also found on intracellular membranes (e.g. nucleus (Jong et al., 2005)), with signaling arising from these intracellular sites differing from that elicited by plasma membrane receptors (Jong et al., 2009; Kumar et al., 2012; Purgert et al., 2014). Subcellular compartmentalization of mGlu receptors can shape the physiological responses to orthosteric agonists, particularly for surrogate agonists that cannot access intracellular receptors. Such effects may contribute to observations of probe dependence by allosteric ligands. To date, the influence of allosteric ligands on GPCR subcellular localization (and vice versa) has been

relatively unexplored. However, Ca-sensing receptor allosteric ligands can act as “pharmacochaperones” to increase Ca-sensing receptor cell surface expression (White et al., 2009), suggesting that mGlu receptor allosteric ligands may also have the potential to alter receptor location.

In addition to physiological context differences, the disease state can also impact mGlu receptor signaling and subsequently ligand pharmacology. In the setting of melanoma, mGlu₁ loses the capacity to signal via classical G protein pathways; however, glutamate retains the ability to stimulate mGlu₁ internalization, which promotes melanoma cell survival (Gelb et al., 2015b). In a preclinical model of Huntington’s disease, the balance of mGlu₅ receptor signaling pathways are perturbed, where IP₁ accumulation is reduced, but iCa²⁺ mobilization, Akt and ERK1/2 phosphorylation is increased (Ribeiro et al., 2010). Brain region specific changes in group I mGlu receptor signaling have also been noted following chronic cocaine administration, such that the mGlu₅ receptor NAM MPEP becomes an agonist for inducing CREB phosphorylation in the nucleus accumbens but not striatum (Hoffmann et al., 2017). Changes in the balance of intracellular signaling responses specific to the disease setting could be exploited by the development of biased ligands; however, also offer another layer of complexity with respect to designing appropriate discovery pipelines for the translation of biased ligands. Indeed, VU0409551, which does not potentiate mGlu₅ receptor modulation of NMDA receptor currents in wild type animals, does potentiate these responses in a genetic model of schizophrenia (Balu et al., 2016). These data highlight the paucity in our understanding of how different diseases and pathological processes reshape the intracellular responses to mGlu receptors. Parsing out these differences will offer the prospect for rational discovery efforts to tailor therapeutic efficacy to the pathway level to restore neurotransmission to the healthy setting.

Heteromerization of mGlu receptors

Historically, mGlu receptors were believed to form strict homodimers, unlike other class C GPCRs such as the obligatory heterodimeric GABA_B or sweet or umami taste receptors. The first evidence of mGlu receptor

heteromers came from the demonstration that group I receptors can assemble and function together when co-transfected in HEK293 cells, but cannot assemble with either group II or group III receptors (Doumazane et al., 2011a). This same study demonstrated heteromers are also formed among group II and group III receptors, prompting investigations into the existence and function of native mGlu receptors heteromers *in vivo*.

One anticipates that the formation of heterocomplexes by mGlu receptors where natively expressed in the same cells, should result in specific pharmacological signatures that differ from homomeric receptors. Intriguing pharmacological responses aroused suspicion on the existence of mGlu₂-mGlu₄ receptor heteromers in rat dorsal striatum where the well-established mGlu₄ receptor PAM PHCCC failed to potentiate mGlu₄ receptor activity at corticostriatal-synapses in rat dorsal striatum whereas VU0155041 retained its expected mGlu₄ receptor PAM activity (Yin et al., 2014). *In vitro* studies confirmed that mGlu₂-mGlu₄ receptor heteromers are differentially potentiated by mGlu₄ receptor PAMs from different scaffolds (Kammermeier, 2012; Niswender et al., 2016; Yin et al., 2014). At the mechanistic level, these pharmacological differences arise from complex asymmetric functioning of mGlu₂-mGlu₄ receptor heteromers. Indeed, following orthosteric agonist activation, the signaling of mGlu₂-mGlu₄ receptor heteromer only occurs through the transmembrane domain of mGlu₄ receptor (Liu et al., 2017); however, the mGlu₂ receptor subunit can signal if potentiated by an mGlu₂ receptor PAM. This is reminiscent of previous studies showing that only one subunit is active at a time in an mGlu receptor homodimer (Goudet et al., 2005; Hlavackova et al., 2005). Evidence of the presence of mGlu₂-mGlu₄ receptor heteromers at this cortico-striatal synapses were reinforced by immunoprecipitation studies showing the presence of protein complexes containing mGlu₂ and mGlu₄ receptors in striatum (Yin et al., 2014). Pharmacological evidence of mGlu₂-mGlu₄ receptor heteromers have also been detected in lateral perforant path terminals in rat hippocampus (Moreno Delgado et al., 2017).

Recently, mGlu₂-mGlu₇ receptor heteromers were reported in the hippocampus and mGlu₃-mGlu₇ receptor heteromers in the cortex (Habrian et al., 2019). Interestingly, further *in vitro* investigations using a single molecular FRET approach revealed that the glutamate affinity and efficacy at mGlu₇ receptors is greatly enhanced when associated to an mGlu₂ receptor subunit, as compared to the mGlu₇ receptor homodimer. Also,

association with mGlu₂ receptors confers to the mGlu₇ receptor subunit the ability to be fully activated by the selective group III agonist LSP4-2022. Of note, previous neuroanatomical study revealed that mGlu₇ and mGlu₈ receptors may be expressed in the same boutons in the hippocampus (Ferraguti et al., 2005), raising the possibility the mGlu₇-mGlu₈ receptor heteromers may also be of relevance in the hippocampus. Heterodimerization of mGlu₇ receptors with other mGlu receptor subtypes may provide a means to enhance the range of glutamate concentrations sensed by the mGlu₇ receptor, which is otherwise insensitive to low glutamate levels.

There are also evidence of mGlu₁ and mGlu₅ receptors forming complexes in mouse hippocampus and cortex as shown by a knockout-controlled interaction proteomics strategy and further confirmed by immunoprecipitation and super-resolution microscopy imaging of hippocampal primary neurons revealing mGlu₁-mGlu₅ receptor co-expression at synaptic level (Pandya et al., 2016). Indeed, these data are keeping with evidence that blockade of both group I receptor subtypes is required to ablate DHPG-induced long-term depression in the hippocampus (Volk et al., 2006). More recently, a single-cell RNA sequencing study revealed the co-expression of different mGlu subtypes within the same cell in the adult mouse cortex (Lee et al., 2020). Notably, most pyramidal cells contained at least four receptor subtypes. Probing the propensity of different mGlu receptors to co-assemble by fluorescent-based complementation assays, the authors concluded that mGlu₂ and mGlu₃ receptors are particularly prone to form heteromers when co-expressed in heterologous cells (Lee et al., 2020). Other prominent mGlu receptor pairs included mGlu_{2/4}, mGlu_{1/5}, mGlu_{3/4}, and mGlu_{3/7}. The co-expression of native mGlu₂ and mGlu₃ receptors in mouse frontal cortex was confirmed by *in situ* hybridization and co-immunoprecipitation (Lee et al., 2020). The prevalence of heteromerization between mGlu receptors adds considerable complexity to understanding and interpreting molecular pharmacological properties of ligands and particularly the notion of selectivity.

Beyond heteromerization with other mGlu receptor subtypes, increasing evidence suggests mGlu receptors form heteromers and larger order complexes with class A GPCRs including mGlu₂-5-HT_{2A} receptors (Delille et al., 2013; Felsing et al., 2018; Fribourg et al., 2011; Gonzalez-Maeso et al., 2008; Moreno et al., 2013;

Moreno et al., 2016), group I receptors with multiple adenosine receptor subtypes (Ciruela et al., 2001; Domenici et al., 2004; Ferre et al., 2002; Nishi et al., 2003; Rodrigues et al., 2005), mGlu₅-dopamine D₁ receptors (Sebastianutto et al., 2020), mGlu₅-dopamine D₂ receptors (Ferre et al., 1999; Popoli et al., 2001), mGlu₅-dopamine D₂-adenosine A_{2A} receptors (Cabello et al., 2009; Diaz-Cabiale et al., 2002). For each pairing with a class A GPCR, the functional responses arising when receptors are co-activated or coincidentally inhibited changes the pharmacological profile to when mGlu receptor is activated in isolation. By example, heteromerization with dopamine D₁ receptors enhances the proportion of mGlu₅ receptors in active states, elevating basal G_q coupling and signaling toward iCa²⁺ mobilization over cAMP pathways (Sebastianutto et al., 2020). Heteromerization is often observed in a cell type or brain region specific fashion. In this respect, selectively targeting mGlu receptor heteromers offers the intriguing prospect of achieving tissue level selectivity of drug action. The study of mGlu receptors heteromers is still in its infancy and it is clear that further investigations will be needed in order to better understand its functional consequences in brain function and therapeutic potential.

Optical tools to probe and control mGlu receptors

Irreversible ligands or photoaffinity probes have been widely used to study ligand-receptor interactions and aid structural determinations across diverse protein targets. Such tools have not been available for mGlu receptors; however, recent efforts exploiting selective allosteric chemotypes have proven successful. The first-in-class were bifunctional mGlu₅ receptor NAMs that included a photoactivatable moiety to irreversibly bind receptors and a click chemistry handle to allow secondary attachment of clickable reporter (e.g. fluorophore) for identification (Gregory et al., 2016). Installation of a covalent or photoreactive moiety has been successfully achieved within three distinct mGlu₂ receptor PAM scaffolds (Doornbos et al., 2019; Hellyer et al., 2020). The development of covalent or photoactivatable ligands is not without its challenges. Covalent ligands require proximity to an appropriate amino acid for reactivity. Further, the bifunctional clickable

photoprobes for mGlu₂ and mGlu₅ receptors revealed substantial non-specific interactions, which may limit how these tools can be applied. There has been considerable interest in alternative approaches to optically control mGlu receptor function. Two main strategies exist to control mGlu receptors by light: an optogenetic pharmacology approach based on attached photoswitchable ligands (**Figure 9**) and a photopharmacology approach based on freely diffusible light-operated ligands (**Figure 10**) (Goudet et al., 2018). The aim of both strategies is to use light to achieve precise spatiotemporal control over receptor activity.

Optogenetic pharmacology

Optogenetic pharmacology consists of covalently attaching a photoswitchable tethered ligand to a genetically modified protein (Kramer et al., 2013), which will then enable the photoactivation or photoantagonism of the receptor. In most cases, the receptor itself is modified to allow anchoring of the photoswitchable ligand but several variants of this technique have been developed: 1) using a transmembrane protein at the proximity of the receptor or 2) an antibody targeting the receptor (**Figure 9**). Optogenetic pharmacology consists of covalently attaching a photoswitchable tethered ligand to a genetically modified protein (Kramer et al., 2013) which will then enable the photoactivation or photoantagonism of the receptor.

Optogenetic pharmacological approaches allows for greater selectivity for studying the functional roles of a target receptor. The attached photoswitchable ligand can rapidly oscillate between activating and inactivating a receptor, thus being useful optogenetic tools to understand mGlu receptor activation mechanisms (Levitz et al., 2016) or to study synaptic activity of neural circuits with high spatiotemporal resolution and pharmacological specificity. The drawbacks being the requirements for genetic manipulation, which can limit *in vivo* application, but this can be circumvented by using a viral infection approach (Acosta-Ruiz et al., 2019). The first generation of light-controlled mGlu receptors (LimGluRs) was based on photoswitchable tethered ligands (PTLs), which contain glutamate linked via a photoisomerizable azobenzene linker to a maleimide that reacts with a free cysteine within the receptor. These molecules called MAGs bind covalently to

genetically engineered mGlu receptors that possess geometrically appropriate cysteine-attachment points (**Figure 9a**). Light-controlled mGlu₂, mGlu₃ and mGlu₆ receptors were designed using this strategy. Precise optical control can be achieved in cells, in mouse brain slices and in living zebrafish (Levitz et al., 2013). An improved spatiotemporal resolution can also be achieved via two-photon activation of LimGluRs (Carroll et al., 2015).

A second generation of light-controlled mGlu receptors has been developed based on photoswitchable orthogonal remotely tethered ligands (PORTL) and the SNAP-tag technology (Keppler et al., 2003)(**Figure 9b**). The photoswitchable ligands are composed of a glutamate moiety, followed by a long flexible linker containing an azobenzene and a benzylguanine that will anchor the PORTL to a SNAP tag. The receptor is genetically modified to contain a SNAP-tag at the N-terminus. Interestingly, the same principle can be applied to CLIP-tagged receptors (Gautier et al., 2008). Since SNAP-tag and CLIP-tag possess orthogonal substrate specificities, SNAP and CLIP tagged proteins can be labeled simultaneously and specifically with different molecular probes in living cells. This has proven to be a very useful approach to analyze cell surface protein complexes and notably led to the discovery of specific heterodimeric mGlu receptors (Doumazane et al., 2011a). By combining SNAP and CLIP tagged receptors and specific PORTL, Levitz and colleagues have created a family of light-gated group II/III mGlu receptors (Levitz et al., 2017), allowing the multiplexed orthogonal optical control within homo or heterodimers. Optimized branched photoswitchable ligands have recently been developed permitting photo-agonism of mGlu receptors with near-complete efficiency (Acosta-Ruiz et al., 2019). The PORTL strategy has been applied to mGlu₂ receptor permitting light control of mGlu₂ receptor-induced excitability in heterologous cells or transfected neurons (Broichhagen et al., 2015) and, more recently, to control working memory in mice (Acosta-Ruiz et al., 2019).

Alternative optogenetic pharmacology approaches have been developed. For example, tethered ligands have been designed to target a genetically modified plasma membrane protein bearing a SNAP tag, rather than directly targeting the receptor. This new approach is named membrane anchored photoswitchable orthogonal remotely tethered ligands (maPORTL) (Donthamsetti et al., 2019). These ligands anchor to the SNAP tagged

protein at the plasma membrane and come into close proximity to their target receptor via lateral diffusion to enable interaction (**Figure 9c**). An alternative strategy consists in using ligands tethered to a SNAP-tagged antibody or nanobody targeting the receptor of interest (**Figure 9d**). Proof-of-concept has been established using a nanobody recognizing a green fluorescent protein fused to the N-terminus of mGlu₂ receptors, allowing the photocontrol of the receptor (Farrants et al., 2018).

Photopharmacology

Photopharmacology is based on the use of small diffusible, drug-like, photo-regulated ligands to control the function of a given target through light. Two types of freely diffusible photo-regulated drugs have been developed for mGlu receptors photopharmacology: photocaged-ligands and photoswitchable ligands (**Figure 10**). Photopharmacological agents constitute powerful tools to manipulate and explore the function and therapeutic potential of endogenous receptors in living animals. Indeed, one of the main interests of photopharmacology resides in the ability to target endogenous receptors in native environments. Indeed, this technique does not require exogenous expression of light-controlled proteins or genetically modified receptor as with optogenetics or optogenetic pharmacology. Compared to tethered photoswitchable ligands, the pharmacological response kinetics can be slower. As with classical drugs, selectivity, pharmacokinetic and ADME properties are also key considerations consideration (Berizzi and Goudet, 2020). Another limitation is the local delivery of drug and light *in vivo*; however, this can be achieved using optic fibers coupled to a light source, as recently exemplified (Font et al., 2017; Zussy et al., 2018).

Photocaged ligands, also named photoactivatable ligands, possess a protecting group that can be removed following illumination, enabling the uncaged ligand to bind to its receptor (**Figure 10a**). Therefore, these ligands are inactive photo-caged ligands that are turned ON by light, enabling a precise spatiotemporal control of the onset of drug activity. Caged glutamate was developed in the 1990's, and was most notably used for mapping neuronal circuits (Callaway and Katz, 1993) or for studying mGlu receptor function (Crawford et

al., 1997). However, the use of caged glutamate is somehow limited due to the lack of subtype selectivity, leading to the development of iGlu and mGlu receptor selective compounds. The first mGlu subtype selective caged compound is JF-NP-26, an inactive photo-caged derivative of the mGlu₅ receptor NAM raseglurant (Font et al., 2017)(**Figure 10b**). The release of raseglurant is induced by a violet illumination, effectively blocking mGlu₅ receptor activity in cells or in living mice. Interestingly, the caged compound can be injected systemically in preclinical murine models of chronic pain and uncaged locally by illumination, revealing the analgesic potential of mGlu₅ blockade in peripheral tissues or in the thalamus (Font et al., 2017).

Photoswitchable ligands are designed to be rapidly and reversibly switched ON and OFF (**Figure 10c**). Typical ligand design comprises incorporating a photoswitchable core into an active moiety that is selectively recognized by the target receptor. The photoswitchable core reversibly photoisomerizes at specific wavelengths, modifying the overall structure of the ligand and thus its ability to interact with the target, resulting in the reversible control of a receptor in timed manner driven by light. The most common photoswitchable core used is azobenzene. Azobenzene changes geometry during photo-isomerization. In the dark or under white light, the azobenzene moiety is in a trans configuration converting to a cis configuration upon illumination with an appropriate wavelength (usually in the ultraviolet range). Relaxation to the thermodynamically more stable trans-isomer can be induced by irradiation or by thermal relaxation.

The first allosteric photoswitchable ligand targeting a GPCR is Alloswitch-1, an mGlu₅ receptor NAM (Pittolo et al., 2014). An azobenzene was inserted in the core of VU0415374, an mGlu₄ receptor allosteric ligand having high chemical and structural homology with the scaffold present in azobenzene (Engers et al., 2011), in order to minimally modify the steric occupancy, binding determinants and physico-chemical properties of the parent compounds. Illumination by green or violet light stabilizes either the trans or the cis configuration of the ligand that corresponds to high and low pharmacological activity, respectively, on heterologous or native cells expressing the mGlu₅ receptor. *In vivo*, Alloswitch-1 allows light-dependent control of the motility of *Xenopus laevi* tadpoles (Pittolo et al., 2014). More recently, a series of photoswitchable mGlu₅ receptor NAMs based on the phenylazopyridine scaffold was generated (Gomez-Santacana et al., 2017). Most of the

trans-isomers of this series are active both *in vitro*, inhibiting mGlu₅ receptor function in heterologous cells, and *in vivo*, photo-controlling zebrafish motility. Optogluram is a derivative of Alloswitch-1, which acts as a photoswitchable mGlu₄ receptor PAM, enabling for selective, reversible and repeated optical manipulation of mGlu₄ receptor activity (Zussy et al., 2018)(**Figure 10d**). Optogluram allows the photocontrol of endogenous mGlu₄ receptor activity in specific brain of freely behaving mice, revealing the dynamic control of pain-related sensory and anxiodepressive symptoms by amygdala mGlu₄ receptors (Zussy et al., 2018). Since ultraviolet light could be potentially damaging to irradiated tissues, designing red-shifted photoswitchable ligands has been of considerable interest. Recently, OptoGluNAM4.1, a blue light-sensitive mGlu₄ receptor photoswitchable NAM was described that is active both *in vitro* and *in vivo*, photo-controlling zebrafish larvae mobility or blocking the analgesic activity of an mGlu₄ receptor agonist in a mouse model of chronic pain (Rovira et al., 2016). Manipulating mGlu receptor with high spatial and temporal precision holds great promise for exploring physiological and pathological functions. As the field is rapidly evolving, the number of optical tools available will likely increase and provide new means to probe the biological function of mGlu receptors.

Conclusion

From the initial identification of mGlu receptors in the early 1990's, the past thirty years has seen rapid progress, with the discovery of novel pharmacological agents and application of chemical, genetic and optical biology tools to dissect the molecular properties of the eight subtypes. Each of the individual subtypes offers promise as a potential therapeutic target. Excitingly, the intensive drug discovery efforts have led to multiple candidates reaching clinical trials with varied mechanisms of action. Both orthosteric and allosteric ligands offer considerable complexity in their biological effects, with biased agonism/modulation, context and probe dependence; coupled with additional complexity presented by mGlu receptor heteromers. While a challenge for discovery, harnessing this pharmacological and biological complexity presents new opportunities to

precisely tailor the activity of mGlu receptors to maximize therapeutic efficacy and avoid adverse effect liability.

Authorship Contributions

Wrote the manuscript and prepared figures: Gregory and Goudet

Footnotes

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References:

- Abd-Elrahman KS, Hamilton A, Hutchinson SR, Liu F, Russell RC and Ferguson SSG (2017) mGluR5 antagonism increases autophagy and prevents disease progression in the zQ175 mouse model of Huntington's disease. *Sci Signal* **10**.
- Abe M, Seto M, Gogliotti RG, Loch MT, Bollinger KA, Chang S, Engelberg EM, Luscombe VB, Harp JM, Bubser M, Engers DW, Jones CK, Rodriguez AL, Blobaum AL, Conn PJ, Niswender CM and Lindsley CW (2017) Discovery of VU6005649, a CNS Penetrant mGlu7/8 Receptor PAM Derived from a Series of Pyrazolo[1,5-a]pyrimidines. *ACS Med Chem Lett* **8**:1110-1115.
- Abe T, Sugihara H, Nawa H, Shigemoto R, Mizuno N and Nakanishi S (1992) Molecular characterization of a novel metabotropic glutamate receptor mGluR5 coupled to inositol phosphate/Ca²⁺ signal transduction. *J Biol Chem* **267**:13361-13368.
- Abitbol K, McLean H, Bessiron T and Daniel H (2012) A new signalling pathway for parallel fibre presynaptic type 4 metabotropic glutamate receptors (mGluR4) in the rat cerebellar cortex. *J Physiol* **590**:2977-2994.
- Abou Farha K, Bruggeman R and Balje-Volkers C (2014) Metabotropic glutamate receptor 5 negative modulation in phase I clinical trial: potential impact of circadian rhythm on the neuropsychiatric adverse reactions-do hallucinations matter? *ISRN Psychiatry* **2014**:652750.
- Achat-Mendes C, Platt DM and Spealman RD (2012) Antagonism of metabotropic glutamate 1 receptors attenuates behavioral effects of cocaine and methamphetamine in squirrel monkeys. *J Pharmacol Exp Ther* **343**:214-224.
- Acher F, Battaglia G, Bräuner-Osborne H, Conn PJ, Duvoisin R, Ferraguti F, Flor PJ, Goudet C, Gregory KJ, Hampson D, Johnson MP, Kubo Y, Monn J, Nakanishi S, Nicoletti F, Niswender C, Pin J-P, Rondard P, Schoepp DD, Shigemoto R and Tateyama M (2019) Metabotropic glutamate receptors

(version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database. *IUPHAR/BPS Guide to Pharmacology* CITE **4**.

- Acher F, Tellier F, Brabet I, Fagni L, Azerad R and Pin J-P (1997a) Synthesis and pharmacological characterization of aminocyclopentane tricarboxylic acids (ACPT): new tools to discriminate between metabotropic glutamate receptor subtypes. *J Med Chem* **40**:3119-3129.
- Acher FC and Bertrand HO (2005) Amino acid recognition by Venus flytrap domains is encoded in an 8-residue motif. *Biopolymers* **80**:357-366.
- Acher FC, Selvam C, Pin JP, Goudet C and Bertrand HO (2011) A critical pocket close to the glutamate binding site of mGlu receptors opens new possibilities for agonist design. *Neuropharmacology* **60**:102-107.
- Acher FC, Tellier FJ, Azerad R, Brabet IN, Fagni L and Pin JP (1997b) Synthesis and pharmacological characterization of aminocyclopentanetricarboxylic acids: new tools to discriminate between metabotropic glutamate receptor subtypes. *J Med Chem* **40**:3119-3129.
- Acosta-Ruiz A, Gutzeit VA, Skelly MJ, Meadows S, Lee J, Parekh P, Orr AG, Liston C, Pleil KE, Broichhagen J and Levitz J (2019) Branched Photoswitchable Tethered Ligands Enable Ultra-efficient Optical Control and Detection of G Protein-Coupled Receptors In Vivo. *Neuron*.
- Adams DH, Kinon BJ, Baygani S, Millen BA, Velona I, Kollack-Walker S and Walling DP (2013) A long-term, phase 2, multicenter, randomized, open-label, comparative safety study of pomaglometad methionil (LY2140023 monohydrate) versus atypical antipsychotic standard of care in patients with schizophrenia. *BMC Psychiatry* **13**:143.
- Adams DH, Zhang L, Millen BA, Kinon BJ and Gomez JC (2014) Pomaglometad Methionil (LY2140023 Monohydrate) and Aripiprazole in Patients with Schizophrenia: A Phase 3, Multicenter, Double-Blind Comparison. *Schizophr Res Treatment* **2014**:758212.
- Ade KK, Wan Y, Hamann HC, O'Hare JK, Guo W, Quian A, Kumar S, Bhagat S, Rodriguiz RM, Wetsel WC, Conn PJ, Dzirasa K, Huber KM and Calakos N (2016) Increased Metabotropic Glutamate

Receptor 5 Signaling Underlies Obsessive-Compulsive Disorder-like Behavioral and Striatal Circuit Abnormalities in Mice. *Biological psychiatry* **80**:522-533.

Ahnaou A, Dautzenberg FM, Geys H, Imogai H, Gibelin A, Moechars D, Steckler T and Drinkenburg WH (2009) Modulation of group II metabotropic glutamate receptor (mGlu2) elicits common changes in rat and mice sleep-wake architecture. *Eur J Pharmacol* **603**:62-72.

Ahnaou A, de Boer P, Lavreysen H, Huysmans H, Sinha V, Raeymaekers L, Van De Castele T, Cid JM, Van Nueten L, Macdonald GJ, Kemp JA and Drinkenburg WH (2016a) Translational neurophysiological markers for activity of the metabotropic glutamate receptor (mGluR2) modulator JNJ-40411813: Sleep EEG correlates in rodents and healthy men. *Neuropharmacology* **103**:290-305.

Ahnaou A, Lavreysen H, Tresadern G, Cid JM and Drinkenburg WH (2015) mGlu2 Receptor Agonism, but Not Positive Allosteric Modulation, Elicits Rapid Tolerance towards Their Primary Efficacy on Sleep Measures in Rats. *PLoS One* **10**:e0144017.

Ahnaou A, Raeymaekers L, Huysmans H and Drinkenburg W (2016b) Off-target potential of AMN082 on sleep EEG and related physiological variables: Evidence from mGluR7 (-/-) mice. *Behav Brain Res* **311**:287-297.

Alagarsamy S, Saugstad J, Warren L, Mansuy IM, Gereau RWt and Conn PJ (2005) NMDA-induced potentiation of mGluR5 is mediated by activation of protein phosphatase 2B/calcineurin. *Neuropharmacology* **49 Suppl 1**:135-145.

Alexander SPH, Christopoulos A, Davenport AP, Kelly E, Mathie A, Peters JA, Veale EL, Armstrong JF, Faccenda E, Harding SD, Pawson AJ, Sharman JL, Southan C, Davies JA and Collaborators C (2019) THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: G protein-coupled receptors. *Br J Pharmacol* **176 Suppl 1**:S21-S141.

Amalric M, Lopez S, Goudet C, Fisone G, Battaglia G, Nicoletti F, Pin JP and Acher FC (2013) Group III and subtype 4 metabotropic glutamate receptor agonists: discovery and pathophysiological applications in Parkinson's disease. *Neuropharmacology* **66**:53-64.

- Ambrosi G, Armentero MT, Levandis G, Bramanti P, Nappi G and Blandini F (2010) Effects of early and delayed treatment with an mGluR5 antagonist on motor impairment, nigrostriatal damage and neuroinflammation in a rodent model of Parkinson's disease. *Brain Res Bull* **82**:29-38.
- Anderson PM, Pinault D, O'Brien TJ and Jones NC (2014) Chronic administration of antipsychotics attenuates ongoing and ketamine-induced increases in cortical gamma oscillations. *Int J Neuropsychopharmacol* **17**:1895-1904.
- Annes WF, Long A, Witcher JW, Ayan-Oshodi MA, Knadler MP, Zhang W, Mitchell MI, Cornelissen K and Hall SD (2015) Relative contributions of presystemic and systemic peptidases to oral exposure of a novel metabotropic glutamate 2/3 receptor agonist (LY404039) after oral administration of prodrug pomaglutamad methionil (LY2140023). *J Pharm Sci* **104**:207-214.
- Annoura H, Fukunaga A, Uesugi M, Tatsuoka T and Horikawa Y (1996) A novel class of antagonists for metabotropic glutamate receptors, 7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxylates. *Bioorg Med Chem Lett* **6**:763-766.
- Ansah OB, Goncalves L, Almeida A and Pertovaara A (2009) Enhanced pronociception by amygdaloid group I metabotropic glutamate receptors in nerve-injured animals. *Exp Neurol* **216**:66-74.
- Antflick JE, Vetiska S, Baizer JS, Yao Y, Baker GB and Hampson DR (2009) L-Serine-O-phosphate in the central nervous system. *Brain Res* **1300**:1-13.
- Anwyl R (1999) Metabotropic glutamate receptors: electrophysiological properties and role in plasticity. *Brain Res Brain Res Rev* **29**:83-120.
- Aramori I and Nakanishi S (1992) Signal transduction and pharmacological characteristics of a metabotropic glutamate receptor, mGluR1, in transfected CHO cells. *Neuron* **8**:757-765.
- Armentero MT, Fancellu R, Nappi G, Bramanti P and Blandini F (2006) Prolonged blockade of NMDA or mGluR5 glutamate receptors reduces nigrostriatal degeneration while inducing selective metabolic changes in the basal ganglia circuitry in a rodent model of Parkinson's disease. *Neurobiol Dis* **22**:1-9.

- Aronica E, Gorter JA, Ijlst-Keizers H, Rozemuller AJ, Yankaya B, Leenstra S and Troost D (2003) Expression and functional role of mGluR3 and mGluR5 in human astrocytes and glioma cells: opposite regulation of glutamate transporter proteins. *Eur J Neurosci* **17**:2106-2118.
- Attwell PJ, Singh Kent N, Jane DE, Croucher MJ and Bradford HF (1998) Anticonvulsant and glutamate release-inhibiting properties of the highly potent metabotropic glutamate receptor agonist (2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine (DCG-IV). *Brain Res* **805**:138-143.
- Aubrey KR, Drew GM, Jeong HJ, Lau BK and Vaughan CW (2017) Endocannabinoids control vesicle release mode at midbrain periaqueductal grey inhibitory synapses. *J Physiol* **595**:165-178.
- Augier E, Dulman RS, Rauffenbart C, Augier G, Cross AJ and Heilig M (2016) The mGluR2 Positive Allosteric Modulator, AZD8529, and Cue-Induced Relapse to Alcohol Seeking in Rats. *Neuropsychopharmacology* **41**:2932-2940.
- Ayoub MA, Angelicheva D, Vile D, Chandler D, Morar B, Cavanaugh JA, Visscher PM, Jablensky A, Pflieger KD and Kalaydjieva L (2012) Deleterious GRM1 mutations in schizophrenia. *PLoS One* **7**:e32849.
- Bahi A, Fizia K, Dietz M, Gasparini F and Flor PJ (2012) Pharmacological modulation of mGluR7 with AMN082 and MMPIP exerts specific influences on alcohol consumption and preference in rats. *Addict Biol* **17**:235-247.
- Bailey DB, Jr., Berry-Kravis E, Wheeler A, Raspa M, Merrien F, Ricart J, Koumaras B, Rosenkranz G, Tomlinson M, von Raison F and Apostol G (2016) Mavoglurant in adolescents with fragile X syndrome: analysis of Clinical Global Impression-Improvement source data from a double-blind therapeutic study followed by an open-label, long-term extension study. *J Neurodev Disord* **8**:1.
- Balschun D, Zuschratter W and Wetzell W (2006) Allosteric enhancement of metabotropic glutamate receptor 5 function promotes spatial memory. *Neuroscience* **142**:691-702.
- Balu DT, Li Y, Takagi S, Presti KT, Ramikie TS, Rook JM, Jones CK, Lindsley CW, Conn PJ, Bolshakov VY and Coyle JT (2016) An mGlu5 positive allosteric modulator rescues the neuroplasticity deficits

- in a genetic model of NMDA receptor hypofunction in schizophrenia. *Neuropsychopharmacology* **41**:2052-2061.
- Bao WL, Williams AJ, Faden AI and Tortella FC (2001) Selective mGluR5 receptor antagonist or agonist provides neuroprotection in a rat model of focal cerebral ischemia. *Brain Res* **922**:173-179.
- Barton ME, Peters SC and Shannon HE (2003) Comparison of the effect of glutamate receptor modulators in the 6 Hz and maximal electroshock seizure models. *Epilepsy Res* **56**:17-26.
- Barton ME and Shannon HE (2005) Behavioral and convulsant effects of the (S) enantiomer of the group I metabotropic glutamate receptor agonist 3,5-DHPG in mice. *Neuropharmacology* **48**:779-787.
- Battaglia G and Bruno V (2018) Metabotropic glutamate receptor involvement in the pathophysiology of amyotrophic lateral sclerosis: new potential drug targets for therapeutic applications. *Curr Opin Pharmacol* **38**:65-71.
- Battaglia G, Busceti CL, Molinaro G, Biagioni F, Storto M, Fornai F, Nicoletti F and Bruno V (2004) Endogenous activation of mGlu5 metabotropic glutamate receptors contributes to the development of nigro-striatal damage induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice. *J Neurosci* **24**:828-835.
- Battaglia G, Busceti CL, Molinaro G, Biagioni F, Traficante A, Nicoletti F and Bruno V (2006) Pharmacological activation of mGlu4 metabotropic glutamate receptors reduces nigrostriatal degeneration in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *J Neurosci* **26**:7222-7229.
- Battaglia G, Busceti CL, Pontarelli F, Biagioni F, Fornai F, Paparelli A, Bruno V, Ruggieri S and Nicoletti F (2003) Protective role of group-II metabotropic glutamate receptors against nigro-striatal degeneration induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice. *Neuropharmacology* **45**:155-166.

- Battaglia G, Fornai F, Busceti CL, Aloisi G, Cerrito F, De Blasi A, Melchiorri D and Nicoletti F (2002) Selective blockade of mGlu5 metabotropic glutamate receptors is protective against methamphetamine neurotoxicity. *J Neurosci* **22**:2135-2141.
- Battaglia G, Riozzi B, Bucci D, Di Menna L, Molinaro G, Pallottino S, Nicoletti F and Bruno V (2015) Activation of mGlu3 metabotropic glutamate receptors enhances GDNF and GLT-1 formation in the spinal cord and rescues motor neurons in the SOD-1 mouse model of amyotrophic lateral sclerosis. *Neurobiol Dis* **74**:126-136.
- Becker JA, Clesse D, Spiegelhalter C, Schwab Y, Le Merrer J and Kieffer BL (2014) Autistic-like syndrome in mu opioid receptor null mice is relieved by facilitated mGluR4 activity. *Neuropsychopharmacology* **39**:2049-2060.
- Bellozi PMQ, Gomes GF, da Silva MCM, Lima IVA, Batista CRA, Carneiro Junior WO, Doria JG, Vieira ELM, Vieira RP, de Freitas RP, Ferreira CN, Candelario-Jalil E, Wyss-Coray T, Ribeiro FM and de Oliveira ACP (2019) A positive allosteric modulator of mGluR5 promotes neuroprotective effects in mouse models of Alzheimer's disease. *Neuropharmacology* **160**:107785.
- Benneyworth MA, Xiang Z, Smith RL, Garcia EE, Conn PJ and Sanders-Bush E (2007) A selective positive allosteric modulator of metabotropic glutamate receptor subtype 2 blocks a hallucinogenic drug model of psychosis. *Mol Pharmacol* **72**:477-484.
- Benquet P, Gee CE and Gerber U (2002) Two distinct signaling pathways upregulate NMDA receptor responses via two distinct metabotropic glutamate receptor subtypes. *J Neurosci* **22**:9679-9686.
- Benvenha MJ, Chaney SF, Baez M, Britton TC, Hornback WJ, Monn JA and Marek GJ (2018) Metabotropic Glutamate2 Receptors Play a Key Role in Modulating Head Twitches Induced by a Serotonergic Hallucinogen in Mice. *Front Pharmacol* **9**:208.
- Beqollari D and Kammermeier PJ (2008) The mGlu(4) receptor allosteric modulator N-phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide acts as a direct agonist at mGlu(6) receptors. *European journal of pharmacology* **589**:49-52.

- Berizzi AE and Goudet C (2020) Strategies and considerations of G-protein-coupled receptor photopharmacology. *Adv Pharmacol* **88**:143-172.
- Berry-Kravis E, Des Portes V, Hagerman R, Jacquemont S, Charles P, Visootsak J, Brinkman M, Rerat K, Koumaras B, Zhu L, Barth GM, Jaecklin T, Apostol G and von Raison F (2016) Mavoglurant in fragile X syndrome: Results of two randomized, double-blind, placebo-controlled trials. *Sci Transl Med* **8**:321ra325.
- Berry-Kravis E, Hessl D, Coffey S, Hervey C, Schneider A, Yuhas J, Hutchison J, Snape M, Tranfaglia M, Nguyen DV and Hagerman R (2009) A pilot open label, single dose trial of fenobam in adults with fragile X syndrome. *J Med Genet* **46**:266-271.
- Bertaso F, Zhang C, Scheschonka A, de Bock F, Fontanaud P, Marin P, Huganir RL, Betz H, Bockaert J, Fagni L and Lerner-Natoli M (2008) PICK1 uncoupling from mGluR7a causes absence-like seizures. *Nat Neurosci* **11**:940-948.
- Bertrand HO, Bessis AS, Pin JP and Acher FC (2002) Common and selective molecular determinants involved in metabotropic glutamate receptor agonist activity. *J Med Chem* **45**:3171-3183.
- Besheer J, Grondin JJ, Cannady R, Sharko AC, Faccidomo S and Hodge CW (2010) Metabotropic glutamate receptor 5 activity in the nucleus accumbens is required for the maintenance of ethanol self-administration in a rat genetic model of high alcohol intake. *Biological psychiatry* **67**:812-822.
- Bessis AS, Bertrand HO, Galvez T, De Colle C, Pin JP and Acher F (2000) Three-dimensional model of the extracellular domain of the type 4a metabotropic glutamate receptor: new insights into the activation process. *Protein Sci* **9**:2200-2209.
- Bessis AS, Rondard P, Gaven F, Brabet I, Triballeau N, Prezeau L, Acher F and Pin JP (2002) Closure of the Venus flytrap module of mGlu8 receptor and the activation process: Insights from mutations converting antagonists into agonists. *Proc Natl Acad Sci U S A* **99**:11097-11102.
- Betts MJ, O'Neill MJ and Duty S (2012) Allosteric modulation of the group III mGlu receptor 4 provides functional neuroprotection in the 6-OHDA rat model of Parkinson's disease. *Br J Pharmacol*.

- Beurrier C, Lopez S, Revy D, Selvam C, Goudet C, Lherondel M, Gubellini P, Kerkerian-LeGoff L, Acher F, Pin JP and Amalric M (2009) Electrophysiological and behavioral evidence that modulation of metabotropic glutamate receptor 4 with a new agonist reverses experimental parkinsonism. *FASEB J* **23**:3619-3628.
- Bezard E, Pioli EY, Li Q, Girard F, Mutel V, Keywood C, Tison F, Rascol O and Poli SM (2014) The mGluR5 negative allosteric modulator dipraglurant reduces dyskinesia in the MPTP macaque model. *Mov Disord* **29**:1074-1079.
- Bhattacharya M, Babwah AV, Godin C, Anborgh PH, Dale LB, Poulter MO and Ferguson SS (2004) Ral and phospholipase D2-dependent pathway for constitutive metabotropic glutamate receptor endocytosis. *J Neurosci* **24**:8752-8761.
- Bhave G, Karim F, Carlton SM and Gereau RWt (2001) Peripheral group I metabotropic glutamate receptors modulate nociception in mice. *Nat Neurosci* **4**:417-423.
- Bigge CF, Drummond JT, Johnson G, Malone T, Probert AW, Jr., Marcoux FW, Coughenour LL and Brahce LJ (1989) Exploration of phenyl-spaced 2-amino-(5-9)-phosphonoalkanoic acids as competitive N-methyl-D-aspartic acid antagonists. *J Med Chem* **32**:1580-1590.
- Black JW and Leff P (1983) Operational models of pharmacological agonism. *Proc R Soc Lond B Biol Sci* **220**:141-162.
- Black YD, Xiao D, Pellegrino D, Kachroo A, Brownell AL and Schwarzschild MA (2010) Protective effect of metabotropic glutamate mGluR5 receptor elimination in a 6-hydroxydopamine model of Parkinson's disease. *Neurosci Lett* **486**:161-165.
- Blednov YA, Walker D, Osterndorf-Kahanek E and Harris RA (2004) Mice lacking metabotropic glutamate receptor 4 do not show the motor stimulatory effect of ethanol. *Alcohol* **34**:251-259.
- Bocella S, Marabese I, Guida F, Luongo L, Maione S and Palazzo E (2019) The Modulation of Pain by Metabotropic Glutamate Receptors 7 and 8 in the Dorsal Striatum. *Curr Neuropharmacol*.

- Bond A, Jones NM, Hicks CA, Whiffin GM, Ward MA, O'Neill MF, Kingston AE, Monn JA, Ornstein PL, Schoepp DD, Lodge D and O'Neill MJ (2000) Neuroprotective effects of LY379268, a selective mGlu2/3 receptor agonist: investigations into possible mechanism of action in vivo. *J Pharmacol Exp Ther* **294**:800-809.
- Bond A, Monn JA and Lodge D (1997) A novel orally active group 2 metabotropic glutamate receptor agonist: LY354740. *Neuroreport* **8**:1463-1466.
- Bond A, Ragumoorthy N, Monn JA, Hicks CA, Ward MA, Lodge D and O'Neill MJ (1999) LY379268, a potent and selective Group II metabotropic glutamate receptor agonist, is neuroprotective in gerbil global, but not focal, cerebral ischaemia. *Neurosci Lett* **273**:191-194.
- Bordi F, Marcon C, Chiamulera C and Reggiani A (1996) Effects of the metabotropic glutamate receptor antagonist MCPG on spatial and context-specific learning. *Neuropharmacology* **35**:1557-1565.
- Brabet I, Parmentier ML, De Colle C, Bockaert J, Acher F and Pin JP (1998) Comparative effect of L-CCG-I, DCG-IV and gamma-carboxy-L-glutamate on all cloned metabotropic glutamate receptor subtypes. *Neuropharmacology* **37**:1043-1051.
- Bradley SJ and Challiss RA (2011) Defining protein kinase/phosphatase isoenzymic regulation of mGlu(5) receptor-stimulated phospholipase C and Ca(2)(+) responses in astrocytes. *Br J Pharmacol* **164**:755-771.
- Bradley SJ, Langmead CJ, Watson JM and Challiss RA (2011) Quantitative analysis reveals multiple mechanisms of allosteric modulation of the mGlu5 receptor in rat astroglia. *Mol Pharmacol* **79**:874-885.
- Brody SA, Dulawa SC, Conquet F and Geyer MA (2004) Assessment of a prepulse inhibition deficit in a mutant mouse lacking mGlu5 receptors. *Mol Psychiatry* **9**:35-41.
- Broichhagen J, Damijonaitis A, Levitz J, Sokol KR, Leippe P, Konrad D, Isacoff EY and Trauner D (2015) Orthogonal Optical Control of a G Protein-Coupled Receptor with a SNAP-Tethered Photochromic Ligand. *ACS Cent Sci* **1**:383-393.

- Bruno V, Battaglia G, Kingston A, O'Neill MJ, Catania MV, Di Grezia R and Nicoletti F (1999) Neuroprotective activity of the potent and selective mGlu1a metabotropic glutamate receptor antagonist, (+)-2-methyl-4 carboxyphenylglycine (LY367385): comparison with LY357366, a broader spectrum antagonist with equal affinity for mGlu1a and mGlu5 receptors. *Neuropharmacology* **38**:199-207.
- Bruno V, Copani A, Battaglia G, Raffaele R, Shinozaki H and Nicoletti F (1994) Protective effect of the metabotropic glutamate receptor agonist, DCG-IV, against excitotoxic neuronal death. *Eur J Pharmacol* **256**:109-112.
- Bruno V, Sureda FX, Storto M, Casabona G, Caruso A, Knopfel T, Kuhn R and Nicoletti F (1997) The neuroprotective activity of group-II metabotropic glutamate receptors requires new protein synthesis and involves a glial-neuronal signaling. *J Neurosci* **17**:1891-1897.
- Burgueno J, Enrich C, Canela EI, Mallol J, Lluís C, Franco R and Ciruela F (2003) Metabotropic glutamate type 1alpha receptor localizes in low-density caveolin-rich plasma membrane fractions. *J Neurochem* **86**:785-791.
- Cabello N, Gandia J, Bertarelli DC, Watanabe M, Lluís C, Franco R, Ferre S, Lujan R and Ciruela F (2009) Metabotropic glutamate type 5, dopamine D2 and adenosine A2a receptors form higher-order oligomers in living cells. *J Neurochem* **109**:1497-1507.
- Cai Z, Saugstad JA, Sorensen SD, Ciombor KJ, Zhang C, Schaffhauser H, Hubalek F, Pohl J, Duvoisin RM and Conn PJ (2001) Cyclic AMP-dependent protein kinase phosphorylates group III metabotropic glutamate receptors and inhibits their function as presynaptic receptors. *J Neurochem* **78**:756-766.
- Cain SM, Meadows HJ, Dunlop J and Bushell TJ (2008) mGlu4 potentiation of K(2P)2.1 is dependant on C-terminal dephosphorylation. *Mol Cell Neurosci* **37**:32-39.
- Callaway EM and Katz LC (1993) Photostimulation using caged glutamate reveals functional circuitry in living brain slices. *Proc Natl Acad Sci U S A* **90**:7661-7665.

- Campo B, Kalinichev M, Lambeng N, El Yacoubi M, Royer-Urios I, Schneider M, Legrand C, Parron D, Girard F, Bessif A, Poli S, Vaugeois JM, Le Poul E and Celanire S (2011) Characterization of an mGluR2/3 negative allosteric modulator in rodent models of depression. *J Neurogenet* **25**:152-166.
- Capogna M (2004) Distinct properties of presynaptic group II and III metabotropic glutamate receptor-mediated inhibition of perforant pathway-CA1 EPSCs. *Eur J Neurosci* **19**:2847-2858.
- Caprioli D, Venniro M, Zeric T, Li X, Adhikary S, Madangopal R, Marchant NJ, Lucantonio F, Schoenbaum G, Bossert JM and Shaham Y (2015) Effect of the Novel Positive Allosteric Modulator of Metabotropic Glutamate Receptor 2 AZD8529 on Incubation of Methamphetamine Craving After Prolonged Voluntary Abstinence in a Rat Model. *Biological psychiatry* **78**:463-473.
- Car H and Wisniewska RJ (2006) Antidepressant-like effects of baclofen and LY367385 in the forced swim test in rats. *Pharmacol Rep* **58**:758-764.
- Caraci F, Molinaro G, Battaglia G, Giuffrida ML, Rizzo B, Traficante A, Bruno V, Cannella M, Merlo S, Wang X, Heinz BA, Nisenbaum ES, Britton TC, Drago F, Sortino MA, Copani A and Nicoletti F (2011) Targeting group II metabotropic glutamate (mGlu) receptors for the treatment of psychosis associated with Alzheimer's disease: selective activation of mGlu2 receptors amplifies beta-amyloid toxicity in cultured neurons, whereas dual activation of mGlu2 and mGlu3 receptors is neuroprotective. *Mol Pharmacol* **79**:618-626.
- Carroll EC, Berlin S, Levitz J, Kienzler MA, Yuan Z, Madsen D, Larsen DS and Isacoff EY (2015) Two-photon brightness of azobenzene photoswitches designed for glutamate receptor optogenetics. *Proc Natl Acad Sci U S A* **112**:E776-785.
- Carroll FY, Stolle A, Beart PM, Voerste A, Brabet I, Mauler F, Joly C, Antonicek H, Bockaert J, Muller T, Pin JP and Prezeau L (2001) BAY36-7620: a potent non-competitive mGlu1 receptor antagonist with inverse agonist activity. *Mol Pharmacol* **59**:965-973.
- Cartmell J, Adam G, Chaboz S, Henningsen R, Kemp JA, Klingelschmidt A, Metzler V, Monsma F, Schaffhauser H, Wichmann J and Mutel V (1998) Characterization of [3H]-(2S,2'R,3'R)-2-(2',3'-

- dicarboxy-cyclopropyl)glycine ([³H]-DCG IV) binding to metabotropic mGlu2 receptor-transfected cell membranes. *Br J Pharmacol* **123**:497-504.
- Cartmell J, Monn JA and Schoepp DD (1999) The metabotropic glutamate 2/3 receptor agonists LY354740 and LY379268 selectively attenuate phencyclidine versus d-amphetamine motor behaviors in rats. *J Pharmacol Exp Ther* **291**:161-170.
- Cartmell J, Monn JA and Schoepp DD (2000) Tolerance to the motor impairment, but not to the reversal of PCP-induced motor activities by oral administration of the mGlu2/3 receptor agonist, LY379268. *Naunyn Schmiedebergs Arch Pharmacol* **361**:39-46.
- Celanire S and Campo B (2012) Recent advances in the drug discovery of metabotropic glutamate receptor 4 (mGluR4) activators for the treatment of CNS and non-CNS disorders. *Expert Opin Drug Discov* **7**:261-280.
- Celanire S, Sebhat I, Wichmann J, Mayer S, Schann S and Gatti S (2015) Novel metabotropic glutamate receptor 2/3 antagonists and their therapeutic applications: a patent review (2005 - present). *Expert Opin Ther Pat* **25**:69-90.
- Chae E, Shin YJ, Ryu EJ, Ji MK, Ryune Cho N, Lee KH, Jeong HJ, Kim SJ, Choi Y, Seok Oh K, Park CE and Soo Yoon Y (2013) Discovery of biological evaluation of pyrazole/imidazole amides as mGlu5 receptor negative allosteric modulators. *Bioorg Med Chem Lett* **23**:2134-2139.
- Chaki S and Fukumoto K (2018) mGlu receptors as potential targets for novel antidepressants. *Curr Opin Pharmacol* **38**:24-30.
- Chapman AG, Nanan K, Williams M and Meldrum BS (2000) Anticonvulsant activity of two metabotropic glutamate group I antagonists selective for the mGlu5 receptor: 2-methyl-6-(phenylethynyl)-pyridine (MPEP), and (E)-6-methyl-2-styryl-pyridine (SIB 1893). *Neuropharmacology* **39**:1567-1574.
- Charvin D (2018) mGlu4 allosteric modulation for treating Parkinson's disease. *Neuropharmacology* **135**:308-315.

- Charvin D, Di Paolo T, Bezard E, Gregoire L, Takano A, Duvey G, Pioli E, Halldin C, Medori R and Conquet F (2018a) An mGlu4-Positive Allosteric Modulator Alleviates Parkinsonism in Primates. *Mov Disord* **33**:1619-1631.
- Charvin D, Medori R, Hauser RA and Rascol O (2018b) Therapeutic strategies for Parkinson disease: beyond dopaminergic drugs. *Nat Rev Drug Discov* **17**:804-822.
- Charvin D, Pomel V, Ortiz M, Frauli M, Scheffler S, Steinberg E, Baron L, Deshons L, Rudigier R, Thiarc D, Morice C, Manteau B, Mayer S, Graham D, Giethlen B, Brugger N, Hedou G, Conquet F and Schann S (2017) Discovery, structure-activity relationship and anti-parkinsonian effect of a potent and brain-penetrant chemical series of positive allosteric modulators of metabotropic glutamate receptor 4. *J Med Chem*.
- Chaudhari N, Landin AM and Roper SD (2000) A metabotropic glutamate receptor variant functions as a taste receptor. *Nat Neurosci* **3**:113-119.
- Chavis P, Mollard P, Bockaert J and Manzoni O (1998) Visualization of cyclic AMP-regulated presynaptic activity at cerebellar granule cells. *Neuron* **20**:773-781.
- Chen ANY, Hellyer SD, Trinh PNH, Leach K and Gregory KJ (2019) Identification of monellin as the first naturally derived proteinaceous allosteric agonist of metabotropic glutamate receptor 5. *Basic Clin Pharmacol Toxicol*.
- Chen SR and Pan HL (2005) Distinct roles of group III metabotropic glutamate receptors in control of nociception and dorsal horn neurons in normal and nerve-injured Rats. *J Pharmacol Exp Ther* **312**:120-126.
- Chen Y, Goudet C, Pin JP and Conn PJ (2008) N-{4-Chloro-2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]phenyl}-2-hydroxybenzamide (CPPHA) acts through a novel site as a positive allosteric modulator of group 1 metabotropic glutamate receptors. *Mol Pharmacol* **73**:909-918.

- Chen Y, Nong Y, Goudet C, Hemstapat K, de Paulis T, Pin JP and Conn PJ (2007) Interaction of novel positive allosteric modulators of metabotropic glutamate receptor 5 with the negative allosteric antagonist site is required for potentiation of receptor responses. *Mol Pharmacol* **71**:1389-1398.
- Cheng J, Liu W, Duffney LJ and Yan Z (2013) SNARE proteins are essential in the potentiation of NMDA receptors by group II metabotropic glutamate receptors. *J Physiol* **591**:3935-3947.
- Chiamulera C, Epping-Jordan MP, Zocchi A, Marcon C, Cottiny C, Tacconi S, Corsi M, Orzi F and Conquet F (2001) Reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice. *Nat Neurosci* **4**:873-874.
- Cho HP, Engers DW, Venable DF, Niswender CM, Lindsley CW, Conn PJ, Emmitte KA and Rodriguez AL (2014a) A novel class of succinimide-derived negative allosteric modulators of metabotropic glutamate receptor subtype 1 provides insight into a disconnect in activity between the rat and human receptors. *ACS Chemical Neuroscience* **5**:597-610.
- Cho HP, Garcia-Barrantes PM, Brogan JT, Hopkins CR, Niswender CM, Rodriguez AL, Venable DF, Morrison RD, Bubser M, Daniels JS, Jones CK, Conn PJ and Lindsley CW (2014b) Chemical Modulation of Mutant mGlu1 Receptors Derived from Deleterious GRM1 Mutations Found in Schizophrenics. *ACS chemical biology* **9**:2334-2346.
- Chojnacka-Wojcik E, Tatarczynska E and Pilc A (1996) Anxiolytic-like effects of metabotropic glutamate antagonist (RS)-alpha-methylserine-O-phosphate in rats. *Pol J Pharmacol* **48**:507-509.
- Chojnacka-Wojcik E, Tatarczynska E and Pilc A (1997) The anxiolytic-like effect of metabotropic glutamate receptor antagonists after intrahippocampal injection in rats. *Eur J Pharmacol* **319**:153-156.
- Christoffersen GR, Christensen LH, Hammer P and Vang M (1999) The class I metabotropic glutamate receptor antagonist, AIDA, improves short-term and impairs long-term memory in a spatial task for rats. *Neuropharmacology* **38**:817-823.

- Christopher JA, Aves SJ, Bennett KA, Doré AS, Errey JC, Jazayeri A, Marshall FH, Okrasa K, Serrano-Vega MJ, Tehan BG, Wiggin GR and Congreve M (2015) Fragment and Structure-Based Drug Discovery for a Class C GPCR: Discovery of the mGlu5 Negative Allosteric Modulator HTL14242 (3-Chloro-5-[6-(5-fluoropyridin-2-yl)pyrimidin-4-yl]benzotrile). *J Med Chem* **58**:6653-6664.
- Christopher JA, Orgovan Z, Congreve M, Dore AS, Errey JC, Marshall FH, Mason JS, Okrasa K, Rucktooa P, Serrano-Vega MJ, Ferenczy GG and Keseru GM (2019) Structure-Based Optimization Strategies for G Protein-Coupled Receptor (GPCR) Allosteric Modulators: A Case Study from Analyses of New Metabotropic Glutamate Receptor 5 (mGlu5) X-ray Structures. *J Med Chem* **62**:207-222.
- Christov C, Gonzalez-Bulnes P, Malhaire F, Karabencheva T, Goudet C, Pin JP, Llebaria A and Giraldo J (2011) Integrated synthetic, pharmacological, and computational investigation of cis-2-(3,5-dichlorophenylcarbamoyl)cyclohexanecarboxylic acid enantiomers as positive allosteric modulators of metabotropic glutamate receptor subtype 4. *ChemMedChem* **6**:131-140.
- Ciccarelli R, D'Alimonte I, Ballerini P, D'Auro M, Nargi E, Buccella S, Di Iorio P, Bruno V, Nicoletti F and Caciagli F (2007) Molecular signalling mediating the protective effect of A1 adenosine and mGlu3 metabotropic glutamate receptor activation against apoptosis by oxygen/glucose deprivation in cultured astrocytes. *Mol Pharmacol* **71**:1369-1380.
- Cid JM, Tresadern G, Duvey G, Lutjens R, Finn T, Rocher JP, Poli S, Vega JA, de Lucas AI, Matesanz E, Linares ML, Andres JI, Alcazar J, Alonso JM, Macdonald GJ, Oehlrich D, Lavreysen H, Ahnaou A, Drinkenburg W, Mackie C, Pype S, Gallacher D and Trabanco AA (2014) Discovery of 1-butyl-3-chloro-4-(4-phenyl-1-piperidinyl)-(1H)-pyridone (JNJ-40411813): a novel positive allosteric modulator of the metabotropic glutamate 2 receptor. *J Med Chem* **57**:6495-6512.
- Cid JM, Tresadern G, Vega JA, de Lucas AI, Matesanz E, Iturrino L, Linares ML, Garcia A, Andres JI, Macdonald GJ, Oehlrich D, Lavreysen H, Megens A, Ahnaou A, Drinkenburg W, Mackie C, Pype S, Gallacher D and Trabanco AA (2012) Discovery of 3-cyclopropylmethyl-7-(4-phenylpiperidin-1-yl)-

- 8-trifluoromethyl[1,2,4]triazolo[4,3-a]pyridine (JNJ-42153605): a positive allosteric modulator of the metabotropic glutamate 2 receptor. *J Med Chem* **55**:8770-8789.
- Cieslik P, Wozniak M, Kaczorowska K, Branski P, Burnat G, Chocyk A, Bobula B, Gruca P, Litwa E, Palucha-Poniewiera A, Wasik A, Pilc A and Wieronska J (2018) Negative Allosteric Modulators of mGlu7 Receptor as Putative Antipsychotic Drugs. *Front Mol Neurosci* **11**:316.
- Cippitelli A, Damadzic R, Frankola K, Goldstein A, Thorsell A, Singley E, Eskay RL and Heilig M (2010) Alcohol-induced neurodegeneration, suppression of transforming growth factor-beta, and cognitive impairment in rats: prevention by group II metabotropic glutamate receptor activation. *Biological psychiatry* **67**:823-830.
- Ciruela F, Escriche M, Burgueno J, Angulo E, Casado V, Soloviev MM, Canela EI, Mallol J, Chan WY, Lluís C, McIlhinney RA and Franco R (2001) Metabotropic glutamate 1alpha and adenosine A1 receptors assemble into functionally interacting complexes. *J Biol Chem* **276**:18345-18351.
- Clark B, Richard Baker S, Goldsworthy J, Harris J and Kingston A (1997) (+)-2-Methyl-4-carboxyphenylglycine (LY367385) selectively antagonises metabotropic glutamate mGluR1 receptors. *Bioorganic & medicinal chemistry letters* **7**:2777-2780.
- Clark M, Johnson BG, Wright RA, Monn JA and Schoepp DD (2002) Effects of the mGlu2/3 receptor agonist LY379268 on motor activity in phencyclidine-sensitized rats. *Pharmacol Biochem Behav* **73**:339-346.
- Cleva RM, Hicks MP, Gass JT, Wischerath KC, Plasters ET, Widholm JJ and Olive MF (2011) mGluR5 positive allosteric modulation enhances extinction learning following cocaine self-administration. *Behav Neurosci* **125**:10-19.
- Cleva RM, Watterson LR, Johnson MA and Olive MF (2012) Differential Modulation of Thresholds for Intracranial Self-Stimulation by mGlu5 Positive and Negative Allosteric Modulators: Implications for Effects on Drug Self-Administration. *Front Pharmacol* **2**:93.

- Clifton NE, Morisot N, Girardon S, Millan MJ and Loiseau F (2013) Enhancement of social novelty discrimination by positive allosteric modulators at metabotropic glutamate 5 receptors: adolescent administration prevents adult-onset deficits induced by neonatal treatment with phencyclidine. *Psychopharmacology (Berl)* **225**:579-594.
- Commare B, Rigault D, Lemasson IA, Deschamps P, Tomas A, Roussel P, Brabet I, Goudet C, Pin JP, Leroux FR, Colobert F and Acher FC (2015) Determination of the absolute configuration of phosphinic analogues of glutamate. *Org Biomol Chem* **13**:1106-1112.
- Conde-Ceide S, Martinez-Vituro CM, Alcazar J, Garcia-Barrantes PM, Lavreysen H, Mackie C, Vinson PN, Rook JM, Bridges TM, Daniels JS, Megens A, Langlois X, Drinkenburg WH, Ahnaou A, Niswender CM, Jones CK, Macdonald GJ, Steckler T, Conn PJ, Stauffer SR, Bartolome-Nebreda JM and Lindsley CW (2015) Discovery of VU0409551/JNJ-46778212: An mGlu5 Positive Allosteric Modulator Clinical Candidate Targeting Schizophrenia. *ACS Medicinal Chemistry Letters* **6**:716-720.
- Conti P, De Amici M, Brauner-Osborne H, Madsen U, Toma L and De Micheli C (2002) Synthesis and pharmacology of 3-hydroxy-delta2-isoxazoline-cyclopentane analogues of glutamic acid. *Farmacologia* **57**:889-895.
- Copani A, Bruno V, Battaglia G, Leanza G, Pellitteri R, Russo A, Stanzani S and Nicoletti F (1995) Activation of metabotropic glutamate receptors protects cultured neurons against apoptosis induced by beta-amyloid peptide. *Mol Pharmacol* **47**:890-897.
- Corti C, Aldegheri L, Somogyi P and Ferraguti F (2002) Distribution and synaptic localisation of the metabotropic glutamate receptor 4 (mGluR4) in the rodent CNS. *Neuroscience* **110**:403-420.
- Corti C, Battaglia G, Molinaro G, Riozzi B, Pittaluga A, Corsi M, Mugnaini M, Nicoletti F and Bruno V (2007) The use of knock-out mice unravels distinct roles for mGlu2 and mGlu3 metabotropic glutamate receptors in mechanisms of neurodegeneration/neuroprotection. *J Neurosci* **27**:8297-8308.

- Corti C, Restituto S, Rimland JM, Brabet I, Corsi M, Pin JP and Ferraguti F (1998) Cloning and characterization of alternative mRNA forms for the rat metabotropic glutamate receptors mGluR7 and mGluR8. *Eur J Neurosci* **10**:3629-3641.
- Cosford ND, Roppe J, Tehrani L, Schweiger EJ, Seiders TJ, Chaudary A, Rao S and Varney MA (2003) [3H]-methoxymethyl-MTEP and [3H]-methoxy-PEPy: potent and selective radioligands for the metabotropic glutamate subtype 5 (mGlu5) receptor. *Bioorg Med Chem Lett* **13**:351-354.
- Crawford JH, Wootton JF, Seabrook GR and Scott RH (1997) Activation of Ca²⁺-dependent currents in dorsal root ganglion neurons by metabotropic glutamate receptors and cyclic ADP-ribose precursors. *J Neurophysiol* **77**:2573-2584.
- Cross AJ, Anthenelli R and Li X (2018) Metabotropic Glutamate Receptors 2 and 3 as Targets for Treating Nicotine Addiction. *Biological psychiatry* **83**:947-954.
- Crupi R, Impellizzeri D and Cuzzocrea S (2019) Role of Metabotropic Glutamate Receptors in Neurological Disorders. *Front Mol Neurosci* **12**:20.
- Cryan JF, Kelly PH, Neijt HC, Sansig G, Flor PJ and van Der Putten H (2003) Antidepressant and anxiolytic-like effects in mice lacking the group III metabotropic glutamate receptor mGluR7. *Eur J Neurosci* **17**:2409-2417.
- Cuomo D, Martella G, Barabino E, Platania P, Vita D, Madeo G, Selvam C, Goudet C, Oueslati N, Pin JP, Acher F, Pisani A, Beurrier C, Melon C, Kerkerian-Le Goff L and Gubellini P (2009) Metabotropic glutamate receptor subtype 4 selectively modulates both glutamate and GABA transmission in the striatum: implications for Parkinson's disease treatment. *J Neurochem* **109**:1096-1105.
- D'Amore V, Raaijmakers RH, Santolini I, van Rijn CM, Ngomba RT, Nicoletti F and van Luijckelaar G (2016) The anti-absence effect of mGlu5 receptor amplification with VU0360172 is maintained during and after antiepileptogenesis. *Pharmacol Biochem Behav* **146-147**:50-59.
- D'Amore V, Santolini I, Celli R, Lionetto L, De Fusco A, Simmaco M, van Rijn CM, Vieira E, Stauffer SR, Conn PJ, Bosco P, Nicoletti F, van Luijckelaar G and Ngomba RT (2014) Head-to head comparison of

mGlu1 and mGlu5 receptor activation in chronic treatment of absence epilepsy in WAG/Rij rats. *Neuropharmacology* **85**:91-103.

D'Amore V, Santolini I, van Rijn CM, Biagioni F, Molinaro G, Prete A, Conn PJ, Lindsley CW, Zhou Y, Vinson PN, Rodriguez AL, Jones CK, Stauffer SR, Nicoletti F, van Luijtelaar G and Ngomba RT (2013) Potentiation of mGlu5 receptors with the novel enhancer, VU0360172, reduces spontaneous absence seizures in WAG/Rij rats. *Neuropharmacology* **66**:330-338.

D'Amore V, von Randow C, Nicoletti F, Ngomba RT and van Luijtelaar G (2015) Anti-absence activity of mGlu1 and mGlu5 receptor enhancers and their interaction with a GABA reuptake inhibitor: Effect of local infusions in the somatosensory cortex and thalamus. *Epilepsia* **56**:1141-1151.

Dale LB, Bhattacharya M, Anborgh PH, Murdoch B, Bhatia M, Nakanishi S and Ferguson SS (2000) G protein-coupled receptor kinase-mediated desensitization of metabotropic glutamate receptor 1A protects against cell death. *J Biol Chem* **275**:38213-38220.

Dalton JAR, Pin JP and Giraldo J (2017) Analysis of positive and negative allosteric modulation in metabotropic glutamate receptors 4 and 5 with a dual ligand. *Sci Rep* **7**:4944.

de Esch CE, van den Berg WE, Buijsen RA, Jaafar IA, Nieuwenhuizen-Bakker IM, Gasparini F, Kushner SA and Willemsen R (2015) Fragile X mice have robust mGluR5-dependent alterations of social behaviour in the Automated Tube Test. *Neurobiol Dis* **75**:31-39.

de Paulis T, Hemstapat K, Chen Y, Zhang Y, Saleh S, Alagille D, Baldwin RM, Tamagnan GD and Conn PJ (2006) Substituent effects of N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamides on positive allosteric modulation of the metabotropic glutamate-5 receptor in rat cortical astrocytes. *J Med Chem* **49**:3332-3344.

De Vry J, Horvath E and Schreiber R (2001) Neuroprotective and behavioral effects of the selective metabotropic glutamate mGlu(1) receptor antagonist BAY 36-7620. *Eur J Pharmacol* **428**:203-214.

Dekundy A, Gravius A, Hechenberger M, Pietraszek M, Nagel J, Tober C, van der Elst M, Mela F, Parsons CG and Danysz W (2011) Pharmacological characterization of MRZ-8676, a novel negative

- allosteric modulator of subtype 5 metabotropic glutamate receptors (mGluR5): focus on L: -DOPA-induced dyskinesia. *Journal of Neural Transmission* **118**:1703-1716.
- Delille HK, Mezler M and Marek GJ (2013) The two faces of the pharmacological interaction of mGlu2 and 5-HT(2)A - relevance of receptor heterocomplexes and interaction through functional brain pathways. *Neuropharmacology* **70**:296-305.
- Di Menna L, Joffe ME, Iacovelli L, Orlando R, Lindsley CW, Mairesse J, Gressens P, Cannella M, Caraci F, Copani A, Bruno V, Battaglia G, Conn PJ and Nicoletti F (2018) Functional partnership between mGlu3 and mGlu5 metabotropic glutamate receptors in the central nervous system. *Neuropharmacology* **128**:301-313.
- Diaz-Cabiale Z, Vivo M, Del Arco A, O'Connor WT, Harte MK, Muller CE, Martinez E, Popoli P, Fuxe K and Ferre S (2002) Metabotropic glutamate mGlu5 receptor-mediated modulation of the ventral striopallidal GABA pathway in rats. Interactions with adenosine A(2A) and dopamine D(2) receptors. *Neurosci Lett* **324**:154-158.
- DiRaddo JO, Miller EJ, Bowman-Dalley C, Wroblewska B, Javidnia M, Grajkowska E, Wolfe BB, Liotta DC and Wroblewski JT (2015) Chloride is an Agonist of Group II and III Metabotropic Glutamate Receptors. *Mol Pharmacol* **88**:450-459.
- DiRaddo JO, Pshenichkin S, Gelb T and Wroblewski JT (2013) Two newly identified exons in human GRM1 express a novel splice variant of metabotropic glutamate 1 receptor. *Gene* **519**:367-373.
- Doherty AJ, Palmer MJ, Henley JM, Collingridge GL and Jane DE (1997) (RS)-2-chloro-5-hydroxyphenylglycine (CHPG) activates mGlu5, but no mGlu1, receptors expressed in CHO cells and potentiates NMDA responses in the hippocampus. *Neuropharmacology* **36**:265-267.
- Dolen G and Bear MF (2008) Role for metabotropic glutamate receptor 5 (mGluR5) in the pathogenesis of fragile X syndrome. *J Physiol* **586**:1503-1508.

- Domenici MR, Pepponi R, Martire A, Tebano MT, Potenza RL and Popoli P (2004) Permissive role of adenosine A2A receptors on metabotropic glutamate receptor 5 (mGluR5)-mediated effects in the striatum. *J Neurochem* **90**:1276-1279.
- Domin H, Golembiowska K, Jantas D, Kaminska K, Zieba B and Smialowska M (2014) Group III mGlu receptor agonist, ACPT-I, exerts potential neuroprotective effects in vitro and in vivo. *Neurotox Res* **26**:99-113.
- Domin H, Przykaza L, Jantas D, Kozniowska E, Boguszewski PM and Smialowska M (2016) Neuroprotective potential of the group III mGlu receptor agonist ACPT-I in animal models of ischemic stroke: In vitro and in vivo studies. *Neuropharmacology* **102**:276-294.
- Domin H, Przykaza L, Kozniowska E, Boguszewski PM and Smialowska M (2018) Neuroprotective effect of the group III mGlu receptor agonist ACPT-I after ischemic stroke in rats with essential hypertension. *Prog Neuropsychopharmacol Biol Psychiatry* **84**:93-101.
- Donthamsetti PC, Broichhagen J, Vyklicky V, Stanley C, Fu Z, Visel M, Levitz JL, Javitch JA, Trauner D and Isacoff EY (2019) Genetically Targeted Optical Control of an Endogenous G Protein-Coupled Receptor. *J Am Chem Soc* **141**:11522-11530.
- Doornbos ML, Perez-Benito L, Tresadern G, Mulder-Krieger T, Biesmans I, Trabanco AA, Cid JM, Lavreysen H, AP IJ and Heitman LH (2016) Molecular mechanism of positive allosteric modulation of the metabotropic glutamate receptor 2 by JNJ-46281222. *Br J Pharmacol* **173**:588-600.
- Doornbos MLJ, Cid JM, Haubrich J, Nunes A, van de Sande JW, Vermond SC, Mulder-Krieger T, Trabanco AA, Ahnaou A, Drinkenburg WH, Lavreysen H, Heitman LH, AP IJ and Tresadern G (2017) Discovery and Kinetic Profiling of 7-Aryl-1,2,4-triazolo[4,3-a]pyridines: Positive Allosteric Modulators of the Metabotropic Glutamate Receptor 2. *J Med Chem* **60**:6704-6720.
- Doornbos MLJ, Wang X, Vermond SC, Peeters L, Perez-Benito L, Trabanco AA, Lavreysen H, Cid JM, Heitman LH, Tresadern G and AP IJ (2019) Covalent Allosteric Probe for the Metabotropic

Glutamate Receptor 2: Design, Synthesis, and Pharmacological Characterization. *J Med Chem* **62**:223-233.

Dore AS, Okrasa K, Patel JC, Serrano-Vega M, Bennett K, Cooke RM, Errey JC, Jazayeri A, Khan S, Tehan B, Weir M, Wiggin GR and Marshall FH (2014) Structure of class C GPCR metabotropic glutamate receptor 5 transmembrane domain. *Nature* **511**:557-562.

Doria JG, de Souza JM, Andrade JN, Rodrigues HA, Guimaraes IM, Carvalho TG, Guatimosim C, Dobransky T and Ribeiro FM (2015) The mGluR5 positive allosteric modulator, CDPPB, ameliorates pathology and phenotypic signs of a mouse model of Huntington's disease. *Neurobiol Dis* **73**:163-173.

Doria JG, de Souza JM, Silva FR, Olmo IG, Carvalho TG, Alves-Silva J, Ferreira-Vieira TH, Santos JT, Xavier CQS, Silva NC, Maciel EMA, Conn PJ and Ribeiro FM (2018) The mGluR5 positive allosteric modulator VU0409551 improves synaptic plasticity and memory of a mouse model of Huntington's disease. *J Neurochem* **147**:222-239.

Doria JG, Silva FR, de Souza JM, Vieira LB, Carvalho TG, Reis HJ, Pereira GS, Dobransky T and Ribeiro FM (2013) Metabotropic glutamate receptor 5 positive allosteric modulators are neuroprotective in a mouse model of Huntington's disease. *Br J Pharmacol* **169**:909-921.

Doumazane E, Scholler P, Fabre L, Zwier JM, Trinquet E, Pin JP and Rondard P (2013) Illuminating the activation mechanisms and allosteric properties of metabotropic glutamate receptors. *Proc Natl Acad Sci U S A* **110**:E1416-1425.

Doumazane E, Scholler P, Zwier JM, Eric T, Rondard P and Pin JP (2011a) A new approach to analyze cell surface protein complexes reveals specific heterodimeric metabotropic glutamate receptors. *FASEB J* **25**:66-77.

Doumazane E, Scholler P, Zwier JM, Trinquet E, Rondard P and Pin JP (2011b) A new approach to analyze cell surface protein complexes reveals specific heterodimeric metabotropic glutamate receptors. *FASEB J* **25**:66-77.

- Downing AM, Kinon BJ, Millen BA, Zhang L, Liu L, Morozova MA, Brenner R, Rayle TJ, Nisenbaum L, Zhao F and Gomez JC (2014) A Double-Blind, Placebo-Controlled Comparator Study of LY2140023 monohydrate in patients with schizophrenia. *BMC Psychiatry* **14**:351.
- Dravolina OA, Zvartau E, Danysz W and Bernalov AY (2017) mGlu1 receptor as a drug target for treatment of substance use disorders: time to gather stones together? *Psychopharmacology (Berl)* **234**:1333-1345.
- Dryja TP, McGee TL, Berson EL, Fishman GA, Sandberg MA, Alexander KR, Derlacki DJ and Rajagopalan AS (2005) Night blindness and abnormal cone electroretinogram ON responses in patients with mutations in the GRM6 gene encoding mGluR6. *Proc Natl Acad Sci U S A* **102**:4884-4889.
- Dunayevich E, Erickson J, Levine L, Landbloom R, Schoepp DD and Tollefson GD (2008) Efficacy and tolerability of an mGlu2/3 agonist in the treatment of generalized anxiety disorder. *Neuropsychopharmacology* **33**:1603-1610.
- Durand D, Carniglia L, Caruso C and Lasaga M (2011) Reduced cAMP, Akt activation and p65-c-Rel dimerization: mechanisms involved in the protective effects of mGluR3 agonists in cultured astrocytes. *PLoS One* **6**:e22235.
- Dutar P, Vu HM and Perkel DJ (1999) Pharmacological characterization of an unusual mGluR-evoked neuronal hyperpolarization mediated by activation of GIRK channels. *Neuropharmacology* **38**:467-475.
- Duvoisin RM, Pfankuch T, Wilson JM, Grabbell J, Chhajlani V, Brown DG, Johnson E and Raber J (2010) Acute pharmacological modulation of mGluR8 reduces measures of anxiety. *Behavioural brain research* **212**:168-173.
- Duvoisin RM, Villasana L, Davis MJ, Winder DG and Raber J (2011) Opposing roles of mGluR8 in measures of anxiety involving non-social and social challenges. *Behav Brain Res* **221**:50-54.

- Duvoisin RM, Zhang C, Pfankuch TF, O'Connor H, Gayet-Primo J, Quraishi S and Raber J (2005) Increased measures of anxiety and weight gain in mice lacking the group III metabotropic glutamate receptor mGluR8. *Eur J Neurosci* **22**:425-436.
- Duvoisin RM, Zhang C and Ramonell K (1995) A novel metabotropic glutamate receptor expressed in the retina and olfactory bulb. *J Neurosci* **15**:3075-3083.
- East SP and Gerlach K (2010) mGluR4 positive allosteric modulators with potential for the treatment of Parkinson's disease: WO09010455. *Expert Opin Ther Pat* **20**:441-445.
- El-Kouhen O, Lehto SG, Pan JB, Chang R, Baker SJ, Zhong C, Hollingsworth PR, Mikusa JP, Cronin EA, Chu KL, McGaraughty SP, Uchic ME, Miller LN, Rodell NM, Patel M, Bhatia P, Mezler M, Kolasa T, Zheng GZ, Fox GB, Stewart AO, Decker MW, Moreland RB, Brioni JD and Honore P (2006) Blockade of mGluR1 receptor results in analgesia and disruption of motor and cognitive performances: effects of A-841720, a novel non-competitive mGluR1 receptor antagonist. *Br J Pharmacol* **149**:761-774.
- El Moustaine D, Granier S, Doumazane E, Scholler P, Rahmeh R, Bron P, Mouillac B, Baneres JL, Rondard P and Pin JP (2012) Distinct roles of metabotropic glutamate receptor dimerization in agonist activation and G-protein coupling. *Proc Natl Acad Sci U S A* **109**:16342-16347.
- Elia J, Ungal G, Kao C, Ambrosini A, De Jesus-Rosario N, Larsen L, Chiavacci R, Wang T, Kurian C, Titchen K, Sykes B, Hwang S, Kumar B, Potts J, Davis J, Malatack J, Slattery E, Moorthy G, Zuppa A, Weller A, Byrne E, Li YR, Kraft WK and Hakonarson H (2018) Fasoracetam in adolescents with ADHD and glutamatergic gene network variants disrupting mGluR neurotransmitter signaling. *Nat Commun* **9**:4.
- Emery AC, Diraddo JO, Miller E, Hathaway HA, Pshenichkin S, Takoudjou GR, Grajkowska E, Yasuda RP, Wolfe BB and Wroblewski J (2012) Ligand Bias at Metabotropic Glutamate 1a Receptor: Molecular Determinants that Distinguish beta-arrestin from G Protein Mediated Signaling. *Mol Pharmacol*.

- Emery AC, Pshenichkin S, Takoudjou GR, Grajkowska E, Wolfe BB and Wroblewski JT (2010) The protective signaling of metabotropic glutamate receptor 1 Is mediated by sustained, beta-arrestin-1-dependent ERK phosphorylation. *J Biol Chem* **285**:26041-26048.
- Emile L, Mercken L, Apiou F, Pradier L, Bock MD, Menager J, Clot J, Doble A and Blanchard JC (1996) Molecular cloning, functional expression, pharmacological characterization and chromosomal localization of the human metabotropic glutamate receptor type 3. *Neuropharmacology* **35**:523-530.
- Eng AG, Kelder DA, Hedrick TP and Swanson GT (2016) Transduction of group I mGluR-mediated synaptic plasticity by beta-arrestin2 signalling. *Nat Commun* **7**:13571.
- Engers DW, Blobaum AL, Gogliotti RD, Cheung YY, Salovich JM, Garcia-Barrantes PM, Daniels JS, Morrison R, Jones CK, Soars MG, Zhuo X, Hurley J, Macor JE, Bronson JJ, Conn PJ, Lindsley CW, Niswender CM and Hopkins CR (2016) Discovery, Synthesis, and Preclinical Characterization of N-(3-Chloro-4-fluorophenyl)-1H-pyrazolo[4,3-b]pyridin-3-amine (VU0418506), a Novel Positive Allosteric Modulator of the Metabotropic Glutamate Receptor 4 (mGlu4). *ACS Chem Neurosci* **7**:1192-1200.
- Engers DW, Field JR, Le U, Zhou Y, Bolinger JD, Zamorano R, Blobaum AL, Jones CK, Jadhav S, Weaver CD, Conn PJ, Lindsley CW, Niswender CM and Hopkins CR (2011) Discovery, synthesis, and structure-activity relationship development of a series of N-(4-acetamido)phenylpicolinamides as positive allosteric modulators of metabotropic glutamate receptor 4 (mGlu(4)) with CNS exposure in rats. *J Med Chem* **54**:1106-1110.
- Engers DW, Gentry PR, Williams R, Bolinger JD, Weaver CD, Menon UN, Conn PJ, Lindsley CW, Niswender CM and Hopkins CR (2010) Synthesis and SAR of novel, 4-(phenylsulfamoyl)phenylacetamide mGlu4 positive allosteric modulators (PAMs) identified by functional high-throughput screening (HTS). *Bioorganic & medicinal chemistry letters* **20**:5175-5178.

- Engers DW, Niswender CM, Weaver CD, Jadhav S, Menon UN, Zamorano R, Conn PJ, Lindsley CW and Hopkins CR (2009) Synthesis and evaluation of a series of heterobiaryl amides that are centrally penetrant metabotropic glutamate receptor 4 (mGluR4) positive allosteric modulators (PAMs). *J Med Chem* **52**:4115-4118.
- Engers JL, Bollinger KA, Weiner RL, Rodriguez AL, Long MF, Breiner MM, Chang S, Bollinger SR, Bubser M, Jones CK, Morrison RD, Bridges TM, Blobaum AL, Niswender CM, Conn PJ, Emmitte KA and Lindsley CW (2017) Design and Synthesis of N-Aryl Phenoxyethoxy Pyridinones as Highly Selective and CNS Penetrant mGlu3 NAMs. *ACS Med Chem Lett* **8**:925-930.
- Engers JL, Rodriguez AL, Konkol LC, Morrison RD, Thompson AD, Byers FW, Blobaum AL, Chang S, Venable DF, Loch MT, Niswender CM, Daniels JS, Jones CK, Conn PJ, Lindsley CW and Emmitte KA (2015) Discovery of a Selective and CNS Penetrant Negative Allosteric Modulator of Metabotropic Glutamate Receptor Subtype 3 with Antidepressant and Anxiolytic Activity in Rodents. *J Med Chem* **58**:7485-7500.
- Erdmann E, Rupprecht V, Matthews E, Kukley M, Schoch S and Dietrich D (2012) Depression of release by mGluR8 alters Ca²⁺ dependence of release machinery. *Cereb Cortex* **22**:1498-1509.
- Faden AI, Ivanova SA, Yakovlev AG and Mukhin AG (1997) Neuroprotective effects of group III mGluR in traumatic neuronal injury. *J Neurotrauma* **14**:885-895.
- Faden AI, O'Leary DM, Fan L, Bao W, Mullins PG and Movsesyan VA (2001) Selective blockade of the mGluR1 receptor reduces traumatic neuronal injury in vitro and improves outcome after brain trauma. *Exp Neurol* **167**:435-444.
- Fallarino F, Volpi C, Fazio F, Notartomaso S, Vacca C, Busceti C, Bicciato S, Battaglia G, Bruno V, Puccetti P, Fioretti MC, Nicoletti F, Grohmann U and Di Marco R (2010) Metabotropic glutamate receptor-4 modulates adaptive immunity and restrains neuroinflammation. *Nat Med* **16**:897-902.

- Farinha A, Lavreysen H, Peeters L, Russo B, Masure S, Trabanco AA, Cid J and Tresadern G (2015) Molecular determinants of positive allosteric modulation of the human metabotropic glutamate receptor 2. *Br J Pharmacol* **172**:2383-2396.
- Farrants H, Gutzeit VA, Acosta-Ruiz A, Trauner D, Johnsson K, Levitz J and Broichhagen J (2018) SNAP-Tagged Nanobodies Enable Reversible Optical Control of a G Protein-Coupled Receptor via a Remotely Tethered Photoswitchable Ligand. *ACS chemical biology* **13**:2682-2688.
- Fazio F, Lionetto L, Curto M, Iacovelli L, Copeland CS, Neale SA, Bruno V, Battaglia G, Salt TE and Nicoletti F (2017) Cinnabarinic acid and xanthurenic acid: Two kynurenine metabolites that interact with metabotropic glutamate receptors. *Neuropharmacology* **112**:365-372.
- Fazio F, Lionetto L, Molinaro G, Bertrand HO, Acher F, Ngomba RT, Notartomaso S, Curini M, Rosati O, Scarselli P, Di Marco R, Battaglia G, Bruno V, Simmaco M, Pin JP, Nicoletti F and Goudet C (2012) Cinnabarinic acid, an endogenous metabolite of the kynurenine pathway, activates type 4 metabotropic glutamate receptors. *Mol Pharmacol* **81**:643-656.
- Fazio F, Zappulla C, Notartomaso S, Busceti C, Bessedè A, Scarselli P, Vacca C, Gargaro M, Volpi C, Allegrucci M, Lionetto L, Simmaco M, Belladonna ML, Nicoletti F and Fallarino F (2014) Cinnabarinic acid, an endogenous agonist of type-4 metabotropic glutamate receptor, suppresses experimental autoimmune encephalomyelitis in mice. *Neuropharmacology* **81**:237-243.
- Feenstra MG, Botterblom MH and van Uum JF (1998) Local activation of metabotropic glutamate receptors inhibits the handling-induced increased release of dopamine in the nucleus accumbens but not that of dopamine or noradrenaline in the prefrontal cortex: comparison with inhibition of ionotropic receptors. *J Neurochem* **70**:1104-1113.
- Felder CC, Schober DA, Tu Y, Quets A, Xiao H, Watt M, Siuda E, Nisenbaum E, Xiang C, Heinz B, Prieto L, McKinzie DL and Monn JA (2017) Translational Pharmacology of the Metabotropic Glutamate 2 Receptor-Preferring Agonist LY2812223 in the Animal and Human Brain. *J Pharmacol Exp Ther* **361**:190-197.

- Fell MJ, Katner JS, Johnson BG, Khilevich A, Schkeryantz JM, Perry KW and Svensson KA (2010) Activation of metabotropic glutamate (mGlu)2 receptors suppresses histamine release in limbic brain regions following acute ketamine challenge. *Neuropharmacology* **58**:632-639.
- Fell MJ, Svensson KA, Johnson BG and Schoepp DD (2008) Evidence for the role of metabotropic glutamate (mGlu)2 not mGlu3 receptors in the preclinical antipsychotic pharmacology of the mGlu2/3 receptor agonist (-)-(1R,4S,5S,6S)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY404039). *J Pharmacol Exp Ther* **326**:209-217.
- Felsing DE, Anastasio NC, Miszkiel JM, Gilbertson SR, Allen JA and Cunningham KA (2018) Biophysical validation of serotonin 5-HT2A and 5-HT2C receptor interaction. *PLoS One* **13**:e0203137.
- Felts AS, Rodriguez AL, Morrison RD, Venable DF, Manka JT, Bates BS, Blobaum AL, Byers FW, Daniels JS, Niswender CM, Jones CK, Conn PJ, Lindsley CW and Emmitte KA (2013) Discovery of VU0409106: A negative allosteric modulator of mGlu5 with activity in a mouse model of anxiety. *Bioorganic & medicinal chemistry letters* **23**:5779-5785.
- Felts AS, Rodriguez AL, Smith KA, Engers JL, Morrison RD, Byers FW, Blobaum AL, Locuson CW, Chang S, Venable DF, Niswender CM, Daniels JS, Conn PJ, Lindsley CW and Emmitte KA (2015) Design of 4-Oxo-1-aryl-1,4-dihydroquinoline-3-carboxamides as Selective Negative Allosteric Modulators of Metabotropic Glutamate Receptor Subtype 2. *J Med Chem* **58**:9027-9040.
- Fendt M, Burki H, Imobersteg S, van der Putten H, McAllister K, Leslie JC, Shaw D and Holscher C (2010) The effect of mGlu8 deficiency in animal models of psychiatric diseases. *Genes Brain Behav* **9**:33-44.
- Fendt M, Imobersteg S, Peterlik D, Chaperon F, Mattes C, Wittmann C, Olpe HR, Mosbacher J, Vranesic I, van der Putten H, McAllister KH, Flor PJ and Gee CE (2013) Differential roles of mGlu(7) and mGlu(8) in amygdala-dependent behavior and physiology. *Neuropharmacology* **72**:215-223.
- Ferraguti F (2018) Metabotropic glutamate receptors as targets for novel anxiolytics. *Curr Opin Pharmacol* **38**:37-42.

- Ferraguti F, Klausberger T, Cobden P, Baude A, Roberts JD, Szucs P, Kinoshita A, Shigemoto R, Somogyi P and Dalezios Y (2005) Metabotropic glutamate receptor 8-expressing nerve terminals target subsets of GABAergic neurons in the hippocampus. *J Neurosci* **25**:10520-10536.
- Ferraguti F and Shigemoto R (2006) Metabotropic glutamate receptors. *Cell Tissue Res* **326**:483-504.
- Ferre S, Karcz-Kubicha M, Hope BT, Popoli P, Burgueno J, Gutierrez MA, Casado V, Fuxe K, Goldberg SR, Lluís C, Franco R and Ciruela F (2002) Synergistic interaction between adenosine A2A and glutamate mGlu5 receptors: implications for striatal neuronal function. *Proc Natl Acad Sci U S A* **99**:11940-11945.
- Ferre S, Popoli P, Rimondini R, Reggio R, Kehr J and Fuxe K (1999) Adenosine A2A and group I metabotropic glutamate receptors synergistically modulate the binding characteristics of dopamine D2 receptors in the rat striatum. *Neuropharmacology* **38**:129-140.
- Fisher NM, Seto M, Lindsley CW and Niswender CM (2018) Metabotropic Glutamate Receptor 7: A New Therapeutic Target in Neurodevelopmental Disorders. *Front Mol Neurosci* **11**:387.
- Flajolet M, Rakhilin S, Wang H, Starkova N, Nuangchamng N, Nairn AC and Greengard P (2003) Protein phosphatase 2C binds selectively to and dephosphorylates metabotropic glutamate receptor 3. *Proc Natl Acad Sci U S A* **100**:16006-16011.
- Flavin HJ, Jin XT and Daw NW (2000) 2R,4R-4-Aminopyrrolidine-2,4-dicarboxylate (APDC) attenuates cortical EPSPs. *Brain Res* **873**:212-217.
- Flor PJ, Lindauer K, Puttner I, Ruegg D, Lukic S, Knopfel T and Kuhn R (1995a) Molecular cloning, functional expression and pharmacological characterization of the human metabotropic glutamate receptor type 2. *Eur J Neurosci* **7**:622-629.
- Flor PJ, Lukic S, Ruegg D, Leonhardt T, Knopfel T and Kuhn R (1995b) Molecular cloning, functional expression and pharmacological characterization of the human metabotropic glutamate receptor type 4. *Neuropharmacology* **34**:149-155.

- Flor PJ, Van Der Putten H, Ruegg D, Lukic S, Leonhardt T, Bence M, Sansig G, Knopfel T and Kuhn R (1997) A novel splice variant of a metabotropic glutamate receptor, human mGluR7b. *Neuropharmacology* **36**:153-159.
- Font J, Lopez-Cano M, Notartomaso S, Scarselli P, Di Pietro P, Bresoli-Obach R, Battaglia G, Malhaire F, Rovira X, Catena J, Giraldo J, Pin JP, Fernandez-Duenas V, Goudet C, Nonell S, Nicoletti F, Llebaria A and Ciruela F (2017) Optical control of pain in vivo with a photoactive mGlu5 receptor negative allosteric modulator. *Elife* **6**.
- Fotuhi M, Standaert DG, Testa CM, Penney JB, Jr. and Young AB (1994) Differential expression of metabotropic glutamate receptors in the hippocampus and entorhinal cortex of the rat. *Brain Res Mol Brain Res* **21**:283-292.
- Francesconi A and Duvoisin RM (1998) Role of the second and third intracellular loops of metabotropic glutamate receptors in mediating dual signal transduction activation. *J Biol Chem* **273**:5615-5624.
- Francesconi A and Duvoisin RM (2000) Opposing effects of protein kinase C and protein kinase A on metabotropic glutamate receptor signaling: selective desensitization of the inositol trisphosphate/Ca²⁺ pathway by phosphorylation of the receptor-G protein-coupling domain. *Proc Natl Acad Sci U S A* **97**:6185-6190.
- Francesconi A and Duvoisin RM (2002) Alternative splicing unmasks dendritic and axonal targeting signals in metabotropic glutamate receptor 1. *J Neurosci* **22**:2196-2205.
- Francesconi A, Kumari R and Zukin RS (2009a) Proteomic analysis reveals novel binding partners of metabotropic glutamate receptor 1. *J Neurochem* **108**:1515-1525.
- Francesconi A, Kumari R and Zukin RS (2009b) Regulation of group I metabotropic glutamate receptor trafficking and signaling by the caveolar/lipid raft pathway. *J Neurosci* **29**:3590-3602.
- Frank RA, McRae AF, Pocklington AJ, van de Lagemaat LN, Navarro P, Croning MD, Komiyama NH, Bradley SJ, Challiss RA, Armstrong JD, Finn RD, Malloy MP, MacLean AW, Harris SE, Starr JM, Bhaskar SS, Howard EK, Hunt SE, Coffey AJ, Ranganath V, Deloukas P, Rogers J, Muir WJ, Deary

- IJ, Blackwood DH, Visscher PM and Grant SG (2011) Clustered coding variants in the glutamate receptor complexes of individuals with schizophrenia and bipolar disorder. *PLoS One* **6**:e19011.
- Fribourg M, Moreno JL, Holloway T, Provasi D, Baki L, Mahajan R, Park G, Adney SK, Hatcher C, Eltit JM, Ruta JD, Albizu L, Li Z, Umali A, Shim J, Fabiato A, MacKerell AD, Jr., Brezina V, Sealfon SC, Filizola M, Gonzalez-Maeso J and Logothetis DE (2011) Decoding the signaling of a GPCR heteromeric complex reveals a unifying mechanism of action of antipsychotic drugs. *Cell* **147**:1011-1023.
- Fujinaga M, Yamasaki T, Kawamura K, Kumata K, Hatori A, Yui J, Yanamoto K, Yoshida Y, Ogawa M, Nengaki N, Maeda J, Fukumura T and Zhang MR (2011) Synthesis and evaluation of 6-[1-(2-[(18F)fluoro-3-pyridyl]-5-methyl-1H-1,2,3-triazol-4-yl)]quinoline for positron emission tomography imaging of the metabotropic glutamate receptor type 1 in brain. *Bioorg Med Chem* **19**:102-110.
- Fukuda H, Tanaka T, Kaijima M, Nakai H and Yonemasu Y (1985) Quisqualic acid-induced hippocampal seizures in unanesthetized cats. *Neurosci Lett* **59**:53-59.
- Fukuda J, Suzuki G, Kimura T, Nagatomi Y, Ito S, Kawamoto H, Ozaki S and Ohta H (2009) Identification of a novel transmembrane domain involved in the negative modulation of mGluR1 using a newly discovered allosteric mGluR1 antagonist, 3-cyclohexyl-5-fluoro-6-methyl-7-(2-morpholin-4-ylethoxy)-4H-chromen-4-one. *Neuropharmacology* **57**:438-445.
- Fukunaga I, Yeo CH and Batchelor AM (2007) Potent and specific action of the mGlu1 antagonists YM-298198 and JNJ16259685 on synaptic transmission in rat cerebellar slices. *Br J Pharmacol* **151**:870-876.
- Fuzzati-Armentero MT, Cerri S, Levandis G, Ambrosi G, Montepeloso E, Antoninetti G, Blandini F, Baqi Y, Muller CE, Volpini R, Costa G, Simola N and Pinna A (2015) Dual target strategy: combining distinct non-dopaminergic treatments reduces neuronal cell loss and synergistically modulates L-DOPA-induced rotational behavior in a rodent model of Parkinson's disease. *J Neurochem* **134**:740-747.

- Gabra BH, Smith FL, Navarro HA, Carroll FI and Dewey WL (2008) mGluR5 antagonists that block calcium mobilization in vitro also reverse (S)-3,5-DHPG-induced hyperalgesia and morphine antinociceptive tolerance in vivo. *Brain Res* **1187**:58-66.
- Galici R, Echemendia NG, Rodriguez AL and Conn PJ (2005) A selective allosteric potentiator of metabotropic glutamate (mGlu) 2 receptors has effects similar to an orthosteric mGlu2/3 receptor agonist in mouse models predictive of antipsychotic activity. *J Pharmacol Exp Ther* **315**:1181-1187.
- Galici R, Jones CK, Hemstapat K, Nong Y, Echemendia NG, Williams LC, de Paulis T and Conn PJ (2006) Biphenyl-indanone A, a positive allosteric modulator of the metabotropic glutamate receptor subtype 2, has antipsychotic- and anxiolytic-like effects in mice. *J Pharmacol Exp Ther* **318**:173-185.
- Gandhi RM, Kogan CS and Messier C (2014) 2-Methyl-6-(phenylethynyl) pyridine (MPEP) reverses maze learning and PSD-95 deficits in Fmr1 knock-out mice. *Front Cell Neurosci* **8**:70.
- Gantois I, Pop AS, de Esch CE, Buijsen RA, Pooters T, Gomez-Mancilla B, Gasparini F, Oostra BA, D'Hooge R and Willemsen R (2013) Chronic administration of AFQ056/Mavoglurant restores social behaviour in Fmr1 knockout mice. *Behav Brain Res* **239**:72-79.
- Garcia-Barrantes PM, Cho HP, Blobaum AL, Niswender CM, Conn PJ and Lindsley CW (2015a) Lead optimization of the VU0486321 series of mGlu1 PAMs. Part 1: SAR of modifications to the central aryl core. *Bioorg Med Chem Lett* **25**:5107-5110.
- Garcia-Barrantes PM, Cho HP, Blobaum AL, Niswender CM, Conn PJ and Lindsley CW (2016a) Lead optimization of the VU0486321 series of mGlu1 PAMs. Part 3. Engineering plasma stability by discovery and optimization of isoindolinone analogs. *Bioorg Med Chem Lett* **26**:1869-1872.
- Garcia-Barrantes PM, Cho HP, Niswender CM, Byers FW, Locuson CW, Blobaum AL, Xiang Z, Rook JM, Conn PJ and Lindsley CW (2015b) Development of Novel, CNS Penetrant Positive Allosteric Modulators for the Metabotropic Glutamate Receptor Subtype 1 (mGlu1), Based on an N-(3-Chloro-4-(1,3-dioxoisindolin-2-yl)phenyl)-3-methylfuran-2-carboxamide Scaffold, That Potentiate Wild Type and Mutant mGlu1 Receptors Found in Schizophrenics. *J Med Chem* **58**:7959-7971.

- Garcia-Barrantes PM, Cho HP, Starr TM, Blobaum AL, Niswender CM, Conn PJ and Lindsley CW (2016b) Re-exploration of the mGlu(1) PAM Ro 07-11401 scaffold: Discovery of analogs with improved CNS penetration despite steep SAR. *Bioorg Med Chem Lett* **26**:2289-2292.
- Garcia-Bea A, Bermudez I, Harrison PJ and Lane TA (2017) A group II metabotropic glutamate receptor 3 (mGlu3, GRM3) isoform implicated in schizophrenia interacts with canonical mGlu3 and reduces ligand binding. *J Psychopharmacol* **31**:1519-1526.
- Gasparini F, Bruno V, Battaglia G, Lukic S, Leonhardt T, Inderbitzin W, Laurie D, Sommer B, Varney MA, Hess SD, Johnson EC, Kuhn R, Urwyler S, Sauer D, Portet C, Schmutz M, Nicoletti F and Flor PJ (1999a) (R,S)-4-phosphonophenylglycine, a potent and selective group III metabotropic glutamate receptor agonist, is anticonvulsive and neuroprotective in vivo. *J Pharmacol Exp Ther* **289**:1678-1687.
- Gasparini F, Lingenhohl K, Stoehr N, Flor PJ, Heinrich M, Vranesic I, Biollaz M, Allgeier H, Heckendorn R, Urwyler S, Varney MA, Johnson EC, Hess SD, Rao SP, Sacca AI, Santori EM, Velicelebi G and Kuhn R (1999b) 2-Methyl-6-(phenylethynyl)-pyridine (MPEP), a potent, selective and systemically active mGlu5 receptor antagonist. *Neuropharmacology* **38**:1493-1503.
- Gass JT, McGonigal JT and Chandler LJ (2017) Deficits in the extinction of ethanol-seeking behavior following chronic intermittent ethanol exposure are attenuated with positive allosteric modulation of mGlu5. *Neuropharmacology* **113**:198-205.
- Gass JT and Olive MF (2009) Role of protein kinase C epsilon (PKC ϵ) in the reduction of ethanol reinforcement due to mGluR5 antagonism in the nucleus accumbens shell. *Psychopharmacology (Berl)* **204**:587-597.
- Gass JT, Osborne MP, Watson NL, Brown JL and Olive MF (2009) mGluR5 antagonism attenuates methamphetamine reinforcement and prevents reinstatement of methamphetamine-seeking behavior in rats. *Neuropsychopharmacology* **34**:820-833.

- Gastambide F, Cotel MC, Gilmour G, O'Neill MJ, Robbins TW and Tricklebank MD (2012) Selective remediation of reversal learning deficits in the neurodevelopmental MAM model of schizophrenia by a novel mGlu5 positive allosteric modulator. *Neuropsychopharmacology* **37**:1057-1066.
- Gastambide F, Gilmour G, Robbins TW and Tricklebank MD (2013) The mGlu(5) positive allosteric modulator LSN2463359 differentially modulates motor, instrumental and cognitive effects of NMDA receptor antagonists in the rat. *Neuropharmacology* **64**:240-247.
- Gautier A, Juillerat A, Heinis C, Correa IR, Jr., Kindermann M, Beaufils F and Johnsson K (2008) An engineered protein tag for multiprotein labeling in living cells. *Chem Biol* **15**:128-136.
- Gawel K, Jenda-Wojtanowska M, Gibula-Bruzda E, Kedzierska E, Filarowska J, Marszalek-Grabska M, Wojtanowski KK, Komsta L, Talarek S and Kotlinska JH (2018) The influence of AMN082, metabotropic glutamate receptor 7 (mGlu7) allosteric agonist on the acute and chronic antinociceptive effects of morphine in the tail-immersion test in mice: Comparison with mGlu5 and mGlu2/3 ligands. *Physiol Behav* **185**:112-120.
- Gee CE, Peterlik D, Neuhauser C, Bouhelal R, Kaupmann K, Laue G, Uschold-Schmidt N, Feuerbach D, Zimmermann K, Ofner S, Cryan JF, van der Putten H, Fendt M, Vranesic I, Glatthar R and Flor PJ (2014) Blocking metabotropic glutamate receptor subtype 7 (mGlu7) via the Venus flytrap domain (VFTD) inhibits amygdala plasticity, stress, and anxiety-related behavior. *J Biol Chem* **289**:10975-10987.
- Gelb T, Pshenichkin S, Hathaway HA, Grajkowska E, Dalley CB, Wolfe BB and Wroblewski JT (2015a) Atypical signaling of metabotropic glutamate receptor 1 in human melanoma cells. *Biochem Pharmacol* **98**:182-189.
- Gelb T, Pshenichkin S, Rodriguez OC, Hathaway HA, Grajkowska E, DiRaddo JO, Wroblewska B, Yasuda RP, Albanese C, Wolfe BB and Wroblewski JT (2015b) Metabotropic glutamate receptor 1 acts as a dependence receptor creating a requirement for glutamate to sustain the viability and growth of human melanomas. *Oncogene* **34**:2711-2720.

- Gereau RWt and Conn PJ (1995) Multiple presynaptic metabotropic glutamate receptors modulate excitatory and inhibitory synaptic transmission in hippocampal area CA1. *J Neurosci* **15**:6879-6889.
- Gereau RWt and Heinemann SF (1998) Role of protein kinase C phosphorylation in rapid desensitization of metabotropic glutamate receptor 5. *Neuron* **20**:143-151.
- Gerlai R, Adams B, Fitch T, Chaney S and Baez M (2002) Performance deficits of mGluR8 knockout mice in learning tasks: the effects of null mutation and the background genotype. *Neuropharmacology* **43**:235-249.
- Gerlai R, Roder JC and Hampson DR (1998) Altered spatial learning and memory in mice lacking the mGluR4 subtype of metabotropic glutamate receptor. *Behav Neurosci* **112**:525-532.
- Ghoshal A, Moran SP, Dickerson JW, Joffe ME, Grueter BA, Xiang Z, Lindsley CW, Rook JM and Conn PJ (2017) Role of mGlu5 Receptors and Inhibitory Neurotransmission in M1 Dependent Muscarinic LTD in the Prefrontal Cortex: Implications in Schizophrenia. *ACS Chem Neurosci* **8**:2254-2265.
- Gilmour G, Broad LM, Wafford KA, Britton T, Colvin EM, Fivush A, Gastambide F, Getman B, Heinz BA, McCarthy AP, Prieto L, Shanks E, Smith JW, Taboada L, Edgar DM and Tricklebank MD (2013) In vitro characterisation of the novel positive allosteric modulators of the mGlu(5) receptor, LSN2463359 and LSN2814617, and their effects on sleep architecture and operant responding in the rat. *Neuropharmacology* **64**:224-239.
- Girard B, Tuduri P, Moreno MP, Sakkaki S, Barboux C, Bouschet T, Varrault A, Vitre J, McCort-Tranchepain I, Dairou J, Acher F, Fagni L, Marchi N, Perroy J and Bertaso F (2019) The mGlu7 receptor provides protective effects against epileptogenesis and epileptic seizures. *Neurobiol Dis* **129**:13-28.
- Goddyn H, Callaerts-Vegh Z and D'Hooge R (2015) Functional Dissociation of Group III Metabotropic Glutamate Receptors Revealed by Direct Comparison between the Behavioral Profiles of Knockout Mouse Lines. *Int J Neuropsychopharmacol* **18**:pyv053.

- Goeldner C, Ballard TM, Knoflach F, Wichmann J, Gatti S and Umbricht D (2013) Cognitive impairment in major depression and the mGlu2 receptor as a therapeutic target. *Neuropharmacology* **64**:337-346.
- Gogliotti RG, Senter RK, Fisher NM, Adams J, Zamorano R, Walker AG, Blobaum AL, Engers DW, Hopkins CR, Daniels JS, Jones CK, Lindsley CW, Xiang Z, Conn PJ and Niswender CM (2017) mGlu7 potentiation rescues cognitive, social, and respiratory phenotypes in a mouse model of Rett syndrome. *Sci Transl Med* **9**.
- Golubeva AV, Moloney RD, O'Connor RM, Dinan TG and Cryan JF (2016) Metabotropic Glutamate Receptors in Central Nervous System Diseases. *Curr Drug Targets* **17**:538-616.
- Gomez-Santacana X, Pittolo S, Rovira X, Lopez M, Zussy C, Dalton JA, Faucherre A, Jopling C, Pin JP, Ciruela F, Goudet C, Giraldo J, Gorostiza P and Llebaria A (2017) Illuminating Phenylazopyridines To Photoswitch Metabotropic Glutamate Receptors: From the Flask to the Animals. *ACS Cent Sci* **3**:81-91.
- Gonzalez-Maeso J, Ang RL, Yuen T, Chan P, Weisstaub NV, Lopez-Gimenez JF, Zhou M, Okawa Y, Callado LF, Milligan G, Gingrich JA, Filizola M, Meana JJ and Sealfon SC (2008) Identification of a serotonin/glutamate receptor complex implicated in psychosis. *Nature* **452**:93-97.
- Goudet C, Chapuy E, Alloui A, Acher F, Pin JP and Eschalier A (2008) Group III metabotropic glutamate receptors inhibit hyperalgesia in animal models of inflammation and neuropathic pain. *Pain* **137**:112-124.
- Goudet C, Kniazeff J, Hlavackova V, Malhaire F, Maurel D, Acher F, Blahos J, Prezeau L and Pin JP (2005) Asymmetric functioning of dimeric metabotropic glutamate receptors disclosed by positive allosteric modulators. *J Biol Chem* **280**:24380-24385.
- Goudet C, Rovira X and Llebaria A (2018) Shedding light on metabotropic glutamate receptors using optogenetics and photopharmacology. *Curr Opin Pharmacol* **38**:8-15.
- Goudet C, Vilar B, Courtiol T, Deltheil T, Bessiron T, Brabet I, Oueslati N, Rigault D, Bertrand HO, McLean H, Daniel H, Amalric M, Acher F and Pin JP (2012) A novel selective metabotropic

glutamate receptor 4 agonist reveals new possibilities for developing subtype selective ligands with therapeutic potential. *FASEB J* **26**:1682-1693.

Gould RW, Amato RJ, Bubser M, Joffe ME, Nedelcovych MT, Thompson AD, Nickols HH, Yuh JP, Zhan X, Felts AS, Rodriguez AL, Morrison RD, Byers FW, Rook JM, Daniels JS, Niswender CM, Conn PJ, Emmitte KA, Lindsley CW and Jones CK (2015) Partial mGlu5 Negative Allosteric Modulators Attenuate Cocaine-Mediated Behaviors and Lack Psychotomimetic-Like Effects.

Neuropsychopharmacology.

Gould RW, Amato RJ, Bubser M, Joffe ME, Nedelcovych MT, Thompson AD, Nickols HH, Yuh JP, Zhan X, Felts AS, Rodriguez AL, Morrison RD, Byers FW, Rook JM, Daniels JS, Niswender CM, Conn PJ, Emmitte KA, Lindsley CW and Jones CK (2016) Partial mGlu(5) Negative Allosteric Modulators Attenuate Cocaine-Mediated Behaviors and Lack Psychotomimetic-Like Effects.

Neuropsychopharmacology **41**:1166-1178.

Greco B, Invernizzi RW and Carli M (2005) Phencyclidine-induced impairment in attention and response control depends on the background genotype of mice: reversal by the mGLU(2/3) receptor agonist LY379268. *Psychopharmacology (Berl)* **179**:68-76.

Gregg LC, Jung KM, Spradley JM, Nyilas R, Suplita RL, 2nd, Zimmer A, Watanabe M, Mackie K, Katona I, Piomelli D and Hohmann AG (2012) Activation of type 5 metabotropic glutamate receptors and diacylglycerol lipase- α initiates 2-arachidonoylglycerol formation and endocannabinoid-mediated analgesia. *J Neurosci* **32**:9457-9468.

Gregory KJ, Bridges TM, Gogliotti RG, Stauffer S, Noetzel MJ, Jones CK, Lindsley CW, Conn PJ and Niswender CM (2019a) In vitro to in vivo translation of allosteric modulator concentration-effect relationships: implications for drug discovery. *ACS Pharmacol Transl Sci*.

Gregory KJ, Giraldo J, Daio J, Christopoulos A and Leach K (2019b) Evaluation of operational models of agonism and allosterism at receptors with multiple orthosteric binding sites. *Mol Pharmacol*.

Gregory KJ, Herman EJ, Ramsey AJ, Hammond AS, Byun NE, Stauffer SR, Manka JT, Jadhav S, Bridges TM, Weaver CD, Niswender CM, Steckler T, Drinkenburg WH, Ahnaou A, Lavreysen H, Macdonald GJ, Bartolome JM, Mackie C, Hrupka BJ, Caron MG, Daigle TL, Lindsley CW, Conn PJ and Jones CK (2013a) N-aryl piperazine metabotropic glutamate receptor 5 positive allosteric modulators possess efficacy in pre-clinical models of NMDA hypofunction and cognitive enhancement. *J Pharmacol Exp Ther.*

Gregory KJ, Kufareva I, Keller AN, Khajehali E, Mun H-C, Goolam MA, Mason RS, Capuano B, Conigrave AD, Christopoulos A and Leach K (2018) Dual Action Calcium-Sensing Receptor Modulator Unmasks Novel Mode-Switching Mechanism. *ACS Pharmacology & Translational Science* **1**:96-109.

Gregory KJ, Malosh C, Turlington M, Morrison R, Vinson P, Daniels JS, Jones C, Niswender CM, Conn PJ, Lindsley CW and Stauffer SR (2010a) Identification of a high affinity MPEP-site silent allosteric modulator (SAM) for the metabotropic glutamate subtype 5 receptor (mGlu5), in *Probe Reports from the NIH Molecular Libraries Program*, Bethesda (MD).

Gregory KJ, Nguyen ED, Malosh C, Mendenhall JL, Zic JZ, Bates BS, Noetzel MJ, Squire EF, Turner EM, Rook JM, Emmitte KA, Stauffer SR, Lindsley CW, Meiler J and Conn PJ (2014) Identification of specific ligand-receptor interactions that govern binding and cooperativity of diverse modulators to a common metabotropic glutamate receptor 5 allosteric site. *ACS Chemical Neuroscience* **5**:282-295.

Gregory KJ, Nguyen ED, Reiff SD, Squire EF, Stauffer SR, Lindsley CW, Meiler J and Conn PJ (2013b) Probing the metabotropic glutamate receptor 5 (mGlu(5)) positive allosteric modulator (PAM) binding pocket: discovery of point mutations that engender a "molecular switch" in PAM pharmacology. *Molecular pharmacology* **83**:991-1006.

Gregory KJ, Noetzel MJ, Rook JM, Vinson PN, Stauffer SR, Rodriguez AL, Emmitte KA, Zhou Y, Chun AC, Felts AS, Chauder BA, Lindsley CW, Niswender CM and Conn PJ (2012) Investigating metabotropic glutamate receptor 5 allosteric modulator cooperativity, affinity, and agonism:

enriching structure-function studies and structure-activity relationships. *Molecular pharmacology* **82**:860-875.

Gregory KJ, Sexton PM and Christopoulos A (2010b) Overview of Receptor Allosterism, in *Current Protocols in Pharmacology* p (in press), Wiley Interscience.

Gregory KJ, Velagaleti R, Thal DM, Brady RM, Christopoulos A, Conn PJ and Lapinsky DJ (2016) Clickable Photoaffinity Ligands for Metabotropic Glutamate Receptor 5 Based on Select Acetylenic Negative Allosteric Modulators. *ACS chemical biology* **11**:1870-1879.

Griebel G, Pichat P, Boulay D, Naimoli V, Potestio L, Featherstone R, Sahni S, Defex H, Desvignes C, Slowinski F, Vige X, Bergis OE, Sher R, Kosley R, Kongsamut S, Black MD and Varty GB (2016) The mGluR2 positive allosteric modulator, SAR218645, improves memory and attention deficits in translational models of cognitive symptoms associated with schizophrenia. *Sci Rep* **6**:35320.

Grillon C, Cordova J, Levine LR and Morgan CA, 3rd (2003) Anxiolytic effects of a novel group II metabotropic glutamate receptor agonist (LY354740) in the fear-potentiated startle paradigm in humans. *Psychopharmacology (Berl)* **168**:446-454.

Gulia R, Sharma R and Bhattacharyya S (2017) A Critical Role for Ubiquitination in the Endocytosis of Glutamate Receptors. *J Biol Chem* **292**:1426-1437.

Gutzeit VA, Thibado J, Stor DS, Zhou Z, Blanchard SC, Andersen OS and Levitz J (2019) Conformational dynamics between transmembrane domains and allosteric modulation of a metabotropic glutamate receptor. *Elife* **8**.

Haas HS, Pfragner R, Siegl V, Ingolic E, Heintz E, Schraml E and Schauenstein K (2007) The non-competitive metabotropic glutamate receptor-1 antagonist CPCCOEt inhibits the in vitro growth of human melanoma. *Oncol Rep* **17**:1399-1404.

Haas LT, Salazar SV, Smith LM, Zhao HR, Cox TO, Herber CS, Degnan AP, Balakrishnan A, Macor JE, Albright CF and Strittmatter SM (2017) Silent Allosteric Modulation of mGluR5 Maintains Glutamate Signaling while Rescuing Alzheimer's Mouse Phenotypes. *Cell Rep* **20**:76-88.

- Habrian CH, Levitz J, Vyklicky V, Fu Z, Hoagland A, McCort-Tranchepain I, Acher F and Isacoff EY (2019) Conformational pathway provides unique sensitivity to a synaptic mGluR. *Nat Commun* **10**:5572.
- Hackler EA, Byun NE, Jones CK, Williams JM, Baheza R, Sengupta S, Grier MD, Avison M, Conn PJ and Gore JC (2010) Selective potentiation of the metabotropic glutamate receptor subtype 2 blocks phencyclidine-induced hyperlocomotion and brain activation. *Neuroscience* **168**:209-218.
- Hajasova Z, Canestrelli C, Acher F, Noble F and Marie N (2018) Role of mGlu7 receptor in morphine rewarding effects is uncovered by a novel orthosteric agonist. *Neuropharmacology* **131**:424-430.
- Halberstadt AL, van der Zee JVF, Chatha M, Geyer MA and Powell SB (2019) Chronic treatment with a metabotropic mGlu2/3 receptor agonist diminishes behavioral response to a phenethylamine hallucinogen. *Psychopharmacology (Berl)* **236**:821-830.
- Hall DA (2013) Application of receptor theory to allosteric modulation of receptors. *Prog Mol Biol Transl Sci* **115**:217-290.
- Hall DA and Giraldo J (2018) A method for the quantification of biased signalling at constitutively active receptors. *Br J Pharmacol* **175**:2046-2062.
- Hamilton A, Vasefi M, Vander Tuin C, McQuaid RJ, Anisman H and Ferguson SS (2016) Chronic Pharmacological mGluR5 Inhibition Prevents Cognitive Impairment and Reduces Pathogenesis in an Alzheimer Disease Mouse Model. *Cell Rep* **15**:1859-1865.
- Hammond AS, Rodriguez AL, Townsend SD, Niswender CM, Gregory KJ, Lindsley CW and Conn PJ (2010) Discovery of a Novel Chemical Class of mGlu(5) Allosteric Ligands with Distinct Modes of Pharmacology. *ACS Chemical Neuroscience* **1**:702-716.
- Hanak TJ, Libbey JE, Doty DJ, Sim JT, DePaula-Silva AB and Fujinami RS (2019) Positive modulation of mGluR5 attenuates seizures and reduces TNF-alpha(+) macrophages and microglia in the brain in a murine model of virus-induced temporal lobe epilepsy. *Exp Neurol* **311**:194-204.

- Hanna L, Ceolin L, Lucas S, Monn J, Johnson B, Collingridge G, Bortolotto Z and Lodge D (2013) Differentiating the roles of mGlu2 and mGlu3 receptors using LY541850, an mGlu2 agonist/mGlu3 antagonist. *Neuropharmacology* **66**:114-121.
- Harich S, Gross G and Beshpalov A (2007) Stimulation of the metabotropic glutamate 2/3 receptor attenuates social novelty discrimination deficits induced by neonatal phencyclidine treatment. *Psychopharmacology (Berl)* **192**:511-519.
- Harvey BD, Siok CJ, Kiss T, Volfson D, Grimwood S, Shaffer CL and Hajos M (2013) Neurophysiological signals as potential translatable biomarkers for modulation of metabotropic glutamate 5 receptors. *Neuropharmacology* **75**:19-30.
- Harvey J and Collingridge GL (1993) Signal transduction pathways involved in the acute potentiation of NMDA responses by 1S,3R-ACPD in rat hippocampal slices. *Br J Pharmacol* **109**:1085-1090.
- Hathaway HA, Pshenichkin S, Grajkowska E, Gelb T, Emery AC, Wolfe BB and Wroblewski JT (2015) Pharmacological characterization of mGlu1 receptors in cerebellar granule cells reveals biased agonism. *Neuropharmacology* **93**:199-208.
- Hayashi Y, Momiyama A, Takahashi T, Ohishi H, Ogawa-Meguro R, Shigemoto R, Mizuno N and Nakanishi S (1993) Role of a metabotropic glutamate receptor in synaptic modulation in the accessory olfactory bulb. *Nature* **366**:687-690.
- Hellyer SD, Aggarwal S, Chen ANY, Leach K, Lapinsky DJ and Gregory KJ (2020) Development of Clickable Photoaffinity Ligands for Metabotropic Glutamate Receptor 2 Based on Two Positive Allosteric Modulator Chemotypes. *ACS Chem Neurosci* **11**:1597-1609.
- Hellyer SD, Albold S, Sengmany K, Singh J, Leach K and Gregory KJ (2019) Metabotropic glutamate receptor 5 (mGlu5)-positive allosteric modulators differentially induce or potentiate desensitization of mGlu5 signaling in recombinant cells and neurons. *J Neurochem* **151**:301-315.

- Hellyer SD, Albold S, Wang T, Chen ANY, May LT, Leach K and Gregory KJ (2018) "Selective" Class C G Protein-Coupled Receptor Modulators Are Neutral or Biased mGlu5 Allosteric Ligands. *Mol Pharmacol* **93**:504-514.
- Helton DR, Tizzano JP, Monn JA, Schoepp DD and Kallman MJ (1997) LY354740: a metabotropic glutamate receptor agonist which ameliorates symptoms of nicotine withdrawal in rats. *Neuropharmacology* **36**:1511-1516.
- Helton DR, Tizzano JP, Monn JA, Schoepp DD and Kallman MJ (1998) Anxiolytic and side-effect profile of LY354740: a potent, highly selective, orally active agonist for group II metabotropic glutamate receptors. *J Pharmacol Exp Ther* **284**:651-660.
- Hemstapat K, Da Costa H, Nong Y, Brady AE, Luo Q, Niswender CM, Tamagnan GD and Conn PJ (2007) A novel family of potent negative allosteric modulators of group II metabotropic glutamate receptors. *J Pharmacol Exp Ther* **322**:254-264.
- Hemstapat K, de Paulis T, Chen Y, Brady AE, Grover VK, Alagille D, Tamagnan GD and Conn PJ (2006) A novel class of positive allosteric modulators of metabotropic glutamate receptor subtype 1 interact with a site distinct from that of negative allosteric modulators. *Mol Pharmacol* **70**:616-626.
- Henrich-Noack P, Hatton CD and Reymann KG (1998) The mGlu receptor ligand (S)-4C3HPG protects neurons after global ischaemia in gerbils. *Neuroreport* **9**:985-988.
- Henrich-Noack P and Reymann KG (1999) (1S,3R)-ACPD, a metabotropic glutamate receptor agonist, enhances damage after global ischaemia. *Eur J Pharmacol* **365**:55-58.
- Hermans E, Nahorski SR and Challiss RA (1998) Reversible and non-competitive antagonist profile of CPCCOEt at the human type Ialpha metabotropic glutamate receptor. *Neuropharmacology* **37**:1645-1647.
- Hikichi H, Kaku A, Karasawa J and Chaki S (2013) Stimulation of metabotropic glutamate (mGlu) 2 receptor and blockade of mGlu1 receptor improve social memory impairment elicited by MK-801 in rats. *Journal of pharmacological sciences* **122**:10-16.

- Hikichi H, Murai T, Okuda S, Maehara S, Satow A, Ise S, Nishino M, Suzuki G, Takehana H, Hata M and Ohta H (2010a) Effects of a novel metabotropic glutamate receptor 7 negative allosteric modulator, 6-(4-methoxyphenyl)-5-methyl-3-pyridin-4-ylisoxazonolo[4,5-c]pyridin-4(5H)-one (MMPIP), on the central nervous system in rodents. *Eur J Pharmacol* **639**:106-114.
- Hikichi H, Nishino M, Fukushima M, Satow A, Maehara S, Kawamoto H and Ohta H (2010b) Pharmacological effects of metabotropic glutamate receptor ligands on prepulse inhibition in DBA/2J mice. *Eur J Pharmacol* **639**:99-105.
- Hinoi E, Ogita K, Takeuchi Y, Ohashi H, Maruyama T and Yoneda Y (2000) Direct radiolabeling by [3H]quisqualic acid of group I metabotropic glutamate receptor in rat brain synaptic membranes. *Brain Res* **881**:199-203.
- Hirbec H, Perestenko O, Nishimune A, Meyer G, Nakanishi S, Henley JM and Dev KK (2002) The PDZ proteins PICK1, GRIP, and syntenin bind multiple glutamate receptor subtypes. Analysis of PDZ binding motifs. *J Biol Chem* **277**:15221-15224.
- Hiyoshi T, Marumo T, Hikichi H, Tomishima Y, Urabe H, Tamita T, Iida I, Yasuhara A, Karasawa J and Chaki S (2014) Neurophysiologic and antipsychotic profiles of TASP0433864, a novel positive allosteric modulator of metabotropic glutamate 2 receptor. *J Pharmacol Exp Ther* **351**:642-653.
- Hlavackova V, Goudet C, Kniazeff J, Zikova A, Maurel D, Vol C, Trojanova J, Prezeau L, Pin JP and Blahos J (2005) Evidence for a single heptahelical domain being turned on upon activation of a dimeric GPCR. *EMBO J* **24**:499-509.
- Hodge CW, Miles MF, Sharko AC, Stevenson RA, Hillmann JR, Lepoutre V, Besheer J and Schroeder JP (2006) The mGluR5 antagonist MPEP selectively inhibits the onset and maintenance of ethanol self-administration in C57BL/6J mice. *Psychopharmacology (Berl)* **183**:429-438.
- Hoffmann HM, Crouzin N, Moreno E, Raivio N, Fuentes S, McCormick PJ, Ortiz J and Vignes M (2017) Long-Lasting Impairment of mGluR5-Activated Intracellular Pathways in the Striatum After Withdrawal of Cocaine Self-Administration. *Int J Neuropsychopharmacol* **20**:72-82.

- Holmes GL, Thurber SJ, Liu Z, Stafstrom CE, Gatt A and Mikati MA (1993) Effects of quisqualic acid and glutamate on subsequent learning, emotionality, and seizure susceptibility in the immature and mature animal. *Brain Res* **623**:325-328.
- Hong J, Lee J, Song K, Ha GE, Yang YR, Ma JS, Yamamoto M, Shin HS, Suh PG and Cheong E (2016) The thalamic mGluR1-PLCbeta4 pathway is critical in sleep architecture. *Mol Brain* **9**:100.
- Horio M, Fujita Y and Hashimoto K (2013) Therapeutic effects of metabotropic glutamate receptor 5 positive allosteric modulator CDPPB on phencyclidine-induced cognitive deficits in mice. *Fundam Clin Pharmacol* **27**:483-488.
- Hou L and Klann E (2004) Activation of the phosphoinositide 3-kinase-Akt-mammalian target of rapamycin signaling pathway is required for metabotropic glutamate receptor-dependent long-term depression. *J Neurosci* **24**:6352-6361.
- Hu JH, Yang L, Kammermeier PJ, Moore CG, Brakeman PR, Tu J, Yu S, Petralia RS, Li Z, Zhang PW, Park JM, Dong X, Xiao B and Worley PF (2012) Preso1 dynamically regulates group I metabotropic glutamate receptors. *Nat Neurosci* **15**:836-844.
- Hu YJ, Sun Q, Zhang WH, Huo YJ, Xu CJ and Liu JF (2019) Specific activation of mGlu2 induced IGF-1R transactivation in vitro through FAK phosphorylation. *Acta Pharmacol Sin* **40**:460-467.
- Huang CC, Yang PC, Lin HJ and Hsu KS (2007) Repeated cocaine administration impairs group II metabotropic glutamate receptor-mediated long-term depression in rat medial prefrontal cortex. *J Neurosci* **27**:2958-2968.
- Huang Y, Shu H, Li L, Zhen T, Zhao J, Zhou X and Luo W (2018) L-DOPA-Induced Motor Impairment and Overexpression of Corticostriatal Synaptic Components Are Improved by the mGluR5 Antagonist MPEP in 6-OHDA-Lesioned Rats. *ASN Neuro* **10**:1759091418811021.
- Hughes ZA, Neal SJ, Smith DL, Sukoff Rizzo SJ, Pulicicchio CM, Lotarski S, Lu S, Dwyer JM, Brennan J, Olsen M, Bender CN, Kouranova E, Andree TH, Harrison JE, Whiteside GT, Springer D, O'Neil SV, Leonard SK, Schechter LE, Dunlop J, Rosenzweig-Lipson S and Ring RH (2012) Negative allosteric

modulation of metabotropic glutamate receptor 5 results in broad spectrum activity relevant to treatment resistant depression. *Neuropharmacology*.

Hullinger R, O'Riordan K and Burger C (2015) Environmental enrichment improves learning and memory and long-term potentiation in young adult rats through a mechanism requiring mGluR5 signaling and sustained activation of p70s6k. *Neurobiol Learn Mem* **125**:126-134.

Iacovelli L, Arcella A, Battaglia G, Pazzaglia S, Aronica E, Spinsanti P, Caruso A, De Smaele E, Saran A, Gulino A, D'Onofrio M, Giangaspero F and Nicoletti F (2006) Pharmacological activation of mGlu4 metabotropic glutamate receptors inhibits the growth of medulloblastomas. *J Neurosci* **26**:8388-8397.

Iacovelli L, Bruno V, Salvatore L, Melchiorri D, Gradini R, Caricasole A, Barletta E, De Blasi A and Nicoletti F (2002) Native group-III metabotropic glutamate receptors are coupled to the mitogen-activated protein kinase/phosphatidylinositol-3-kinase pathways. *J Neurochem* **82**:216-223.

Iacovelli L, Molinaro G, Battaglia G, Motolese M, Di Menna L, Alfiero M, Blahos J, Matrisciano F, Corsi M, Corti C, Bruno V, De Blasi A and Nicoletti F (2009) Regulation of group II metabotropic glutamate receptors by G protein-coupled receptor kinases: mGlu2 receptors are resistant to homologous desensitization. *Mol Pharmacol* **75**:991-1003.

Iacovelli L, Salvatore L, Capobianco L, Picascia A, Barletta E, Storto M, Mariggio S, Sallese M, Porcellini A, Nicoletti F and De Blasi A (2003) Role of G protein-coupled receptor kinase 4 and beta-arrestin 1 in agonist-stimulated metabotropic glutamate receptor 1 internalization and activation of mitogen-activated protein kinases. *J Biol Chem* **278**:12433-12442.

Iderberg H, Maslava N, Thompson AD, Bubser M, Niswender CM, Hopkins CR, Lindsley CW, Conn PJ, Jones CK and Cenci MA (2015) Pharmacological stimulation of metabotropic glutamate receptor type 4 in a rat model of Parkinson's disease and L-DOPA-induced dyskinesia: Comparison between a positive allosteric modulator and an orthosteric agonist. *Neuropharmacology* **95**:121-129.

- Isherwood SN, Robbins TW, Nicholson JR, Dalley JW and Pekcec A (2017) Selective and interactive effects of D2 receptor antagonism and positive allosteric mGluR4 modulation on waiting impulsivity. *Neuropharmacology* **123**:249-260.
- Ishikawa K, Nash SR, Nishimune A, Neki A, Kaneko S and Nakanishi S (1999) Competitive interaction of seven in absentia homolog-1A and Ca²⁺/calmodulin with the cytoplasmic tail of group 1 metabotropic glutamate receptors. *Genes Cells* **4**:381-390.
- Itil T, Seaman B, Huque M, Mukhopadhyay S, Blasucci D, Nq K and Ciccone P (1978) The clinical and quantitative EEG effects and plasma levels of fenobam (McN-3377) in subjects with anxiety: an open rising dose tolerance and efficacy study. *Curr Ther Res* **24**:708-724.
- Ito S, Hirata Y, Nagatomi Y, Satoh A, Suzuki G, Kimura T, Satow A, Maehara S, Hikichi H, Hata M, Ohta H and Kawamoto H (2009) Discovery and biological profile of isoindolinone derivatives as novel metabotropic glutamate receptor 1 antagonists: a potential treatment for psychotic disorders. *Bioorg Med Chem Lett* **19**:5310-5313.
- Jacob W, Gravius A, Pietraszek M, Nagel J, Belozertseva I, Shekunova E, Malyshkin A, Greco S, Barberi C and Danysz W (2009) The anxiolytic and analgesic properties of fenobam, a potent mGlu5 receptor antagonist, in relation to the impairment of learning. *Neuropharmacology* **57**:97-108.
- Jacquemont S, Curie A, des Portes V, Torrioli MG, Berry-Kravis E, Hagerman RJ, Ramos FJ, Cornish K, He Y, Paulding C, Neri G, Chen F, Hadjikhani N, Martinet D, Meyer J, Beckmann JS, Delange K, Brun A, Bussy G, Gasparini F, Hilse T, Floesser A, Branson J, Bilbe G, Johns D and Gomez-Mancilla B (2011) Epigenetic modification of the FMR1 gene in fragile X syndrome is associated with differential response to the mGluR5 antagonist AFQ056. *Sci Transl Med* **3**:64ra61.
- Jalan-Sakrikar N, Field JR, Klar R, Mattmann ME, Gregory KJ, Zamorano R, Engers DW, Bollinger SR, Weaver CD, Days EL, Lewis LM, Utley TJ, Hurtado M, Rigault D, Acher F, Walker AG, Melancon BJ, Wood MR, Lindsley CW, Conn PJ, Xiang Z, Hopkins CR and Niswender CM (2014)

Identification of positive allosteric modulators VU0155094 (ML397) and VU0422288 (ML396) reveals new insights into the biology of metabotropic glutamate receptor 7. *ACS Chem Neurosci* **5**:1221-1237.

Jenda M, Gawel K, Marszalek M, Komsta L and Kotlinska JH (2015) AMN082, a metabotropic glutamate receptor 7 allosteric agonist, attenuates locomotor sensitization and cross-sensitization induced by cocaine and morphine in mice. *Prog Neuropsychopharmacol Biol Psychiatry* **57**:166-175.

Jia Z, Lu Y, Henderson J, Taverna F, Romano C, Abramow-Newerly W, Wojtowicz JM and Roder J (1998) Selective abolition of the NMDA component of long-term potentiation in mice lacking mGluR5. *Learn Mem* **5**:331-343.

Jiang JY, Nagaraju M, Meyer RC, Zhang L, Hamelberg D, Hall RA, Brown EM, Conn PJ and Yang JJ (2014) Extracellular calcium modulates actions of orthosteric and allosteric ligands on metabotropic glutamate receptor 1alpha. *J Biol Chem* **289**:1649-1661.

Jin DZ, Guo ML, Xue B, Fibuch EE, Choe ES, Mao LM and Wang JQ (2013a) Phosphorylation and feedback regulation of metabotropic glutamate receptor 1 by calcium/calmodulin-dependent protein kinase II. *J Neurosci* **33**:3402-3412.

Jin DZ, Guo ML, Xue B, Mao LM and Wang JQ (2013b) Differential regulation of CaMKIIalpha interactions with mGluR5 and NMDA receptors by Ca(2+) in neurons. *J Neurochem* **127**:620-631.

Jin DZ, Mao LM and Wang JQ (2017) An Essential Role of Fyn in the Modulation of Metabotropic Glutamate Receptor 1 in Neurons. *eNeuro* **4**.

Jin DZ, Mao LM and Wang JQ (2018) The Role of Extracellular Signal-Regulated Kinases (ERK) in the Regulation of mGlu5 Receptors in Neurons. *J Mol Neurosci* **66**:629-638.

Jin DZ, Xue B, Mao LM and Wang JQ (2015) Metabotropic glutamate receptor 5 upregulates surface NMDA receptor expression in striatal neurons via CaMKII. *Brain Res* **1624**:414-423.

Jin X, Semenova S, Yang L, Ardecky R, Sheffler DJ, Dahl R, Conn PJ, Cosford ND and Markou A (2010) The mGluR2 positive allosteric modulator BINA decreases cocaine self-administration and cue-

induced cocaine-seeking and counteracts cocaine-induced enhancement of brain reward function in rats. *Neuropsychopharmacology* **35**:2021-2036.

Joffe ME, Santiago CI, Stansley BJ, Maksymetz J, Gogliotti RG, Engers JL, Nicoletti F, Lindsley CW and Conn PJ (2019) Mechanisms underlying prelimbic prefrontal cortex mGlu3/mGlu5-dependent plasticity and reversal learning deficits following acute stress. *Neuropharmacology* **144**:19-28.

Johnson KA, Mateo Y and Lovinger DM (2017) Metabotropic glutamate receptor 2 inhibits thalamically-driven glutamate and dopamine release in the dorsal striatum. *Neuropharmacology* **117**:114-123.

Johnson MP, Baez M, Jagdmann GE, Jr., Britton TC, Large TH, Callagaro DO, Tizzano JP, Monn JA and Schoepp DD (2003) Discovery of allosteric potentiators for the metabotropic glutamate 2 receptor: synthesis and subtype selectivity of N-(4-(2-methoxyphenoxy)phenyl)-N-(2,2,2-trifluoroethylsulfonyl)pyrid-3-ylmethylamine. *J Med Chem* **46**:3189-3192.

Johnson MP, Barda D, Britton TC, Emkey R, Hornback WJ, Jagdmann GE, McKinzie DL, Nisenbaum ES, Tizzano JP and Schoepp DD (2005) Metabotropic glutamate 2 receptor potentiators: receptor modulation, frequency-dependent synaptic activity, and efficacy in preclinical anxiety and psychosis model(s). *Psychopharmacology (Berl)* **179**:271-283.

Johnson PL, Fitz SD, Engleman EA, Svensson KA, Schkeryantz JM and Shekhar A (2013) Group II metabotropic glutamate receptor type 2 allosteric potentiators prevent sodium lactate-induced panic-like response in panic-vulnerable rats. *J Psychopharmacol* **27**:152-161.

Joly C, Gomeza J, Brabet I, Curry K, Bockaert J and Pin JP (1995) Molecular, functional, and pharmacological characterization of the metabotropic glutamate receptor type 5 splice variants: comparison with mGluR1. *J Neurosci* **15**:3970-3981.

Jones CK, Bubser M, Thompson AD, Dickerson JW, Turle-Lorenzo N, Amalric M, Blobaum AL, Bridges TM, Morrison RD, Jadhav S, Engers DW, Italiano K, Bode J, Daniels JS, Lindsley CW, Hopkins CR, Conn PJ and Niswender CM (2012) The metabotropic glutamate receptor 4-positive allosteric modulator VU0364770 produces efficacy alone and in combination with L-DOPA or an adenosine

- 2A antagonist in preclinical rodent models of Parkinson's disease. *J Pharmacol Exp Ther* **340**:404-421.
- Jones CK, Eberle EL, Peters SC, Monn JA and Shannon HE (2005) Analgesic effects of the selective group II (mGlu2/3) metabotropic glutamate receptor agonists LY379268 and LY389795 in persistent and inflammatory pain models after acute and repeated dosing. *Neuropharmacology* **49 Suppl 1**:206-218.
- Jong YI, Harmon SK and O'Malley KL (2019) Location and Cell-Type-Specific Bias of Metabotropic Glutamate Receptor, mGlu5, Negative Allosteric Modulators. *ACS Chem Neurosci* **10**:4558-4570.
- Jong YJ, Kumar V, Kingston AE, Romano C and O'Malley KL (2005) Functional metabotropic glutamate receptors on nuclei from brain and primary cultured striatal neurons. Role of transporters in delivering ligand. *J Biol Chem* **280**:30469-30480.
- Jong YJ, Kumar V and O'Malley KL (2009) Intracellular metabotropic glutamate receptor 5 (mGluR5) activates signaling cascades distinct from cell surface counterparts. *J Biol Chem* **284**:35827-35838.
- Julio-Pieper M, Flor PJ, Dinan TG and Cryan JF (2011) Exciting times beyond the brain: metabotropic glutamate receptors in peripheral and non-neural tissues. *Pharmacol Rev* **63**:35-58.
- Jung KM, Mangieri R, Stapleton C, Kim J, Fegley D, Wallace M, Mackie K and Piomelli D (2005) Stimulation of endocannabinoid formation in brain slice cultures through activation of group I metabotropic glutamate receptors. *Mol Pharmacol* **68**:1196-1202.
- Justinova Z, Panlilio LV, Secci ME, Redhi GH, Schindler CW, Cross AJ, Mrzljak L, Medd A, Shaham Y and Goldberg SR (2015) The Novel Metabotropic Glutamate Receptor 2 Positive Allosteric Modulator, AZD8529, Decreases Nicotine Self-Administration and Relapse in Squirrel Monkeys. *Biological psychiatry* **78**:452-462.
- Kahl E and Fendt M (2016) Metabotropic Glutamate Receptors 7 within the Nucleus Accumbens are Involved in Relief Learning in Rats. *Curr Neuropharmacol* **14**:405-412.

- Kalinichev M, Le Poul E, Bolea C, Girard F, Campo B, Fonsi M, Royer-Urios I, Browne SE, Uslaner JM, Davis MJ, Raber J, Duvoisin R, Bate ST, Reynolds IJ, Poli S and Celanire S (2014) Characterization of the novel positive allosteric modulator of the metabotropic glutamate receptor 4 ADX88178 in rodent models of neuropsychiatric disorders. *J Pharmacol Exp Ther* **350**:495-505.
- Kalinichev M, Rouillier M, Girard F, Royer-Urios I, Bournique B, Finn T, Charvin D, Campo B, Le Poul E, Mutel V, Poli S, Neale SA, Salt TE and Lutjens R (2013a) ADX71743, a potent and selective negative allosteric modulator of metabotropic glutamate receptor 7 (mGlu7): in vitro and in vivo characterization. *J Pharmacol Exp Ther* **344**:624-636.
- Kalinichev M, Rouillier M, Girard F, Royer-Urios I, Bournique B, Finn T, Charvin D, Campo B, Le Poul E, Mutel V, Poli S, Neale SA, Salt TE and Lutjens R (2013b) ADX71743, a potent and selective negative allosteric modulator of metabotropic glutamate receptor 7: in vitro and in vivo characterization. *J Pharmacol Exp Ther* **344**:624-636.
- Kamiya H and Yamamoto C (1997) Phorbol ester and forskolin suppress the presynaptic inhibitory action of group-II metabotropic glutamate receptor at rat hippocampal mossy fibre synapse. *Neuroscience* **80**:89-94.
- Kammermeier PJ (2012) Functional and pharmacological characteristics of metabotropic glutamate receptors 2/4 heterodimers. *Mol Pharmacol* **82**:438-447.
- Kanumilli S, Toms NJ, Venkateswarlu K, Mellor H and Roberts PJ (2002) Functional coupling of rat metabotropic glutamate 1a receptors to phospholipase D in CHO cells: involvement of extracellular Ca²⁺, protein kinase C, tyrosine kinase and Rho-A. *Neuropharmacology* **42**:1-8.
- Kawabata S, Tsutsumi R, Kohara A, Yamaguchi T, Nakanishi S and Okada M (1996) Control of calcium oscillations by phosphorylation of metabotropic glutamate receptors. *Nature* **383**:89-92.
- Kawaura K, Karasawa J and Hikichi H (2016) Stimulation of the metabotropic glutamate (mGlu) 2 receptor attenuates the MK-801-induced increase in the immobility time in the forced swimming test in rats. *Pharmacol Rep* **68**:80-84.

- Keck TM, Yang HJ, Bi GH, Huang Y, Zhang HY, Srivastava R, Gardner EL, Newman AH and Xi ZX (2013) Fenobam sulfate inhibits cocaine-taking and cocaine-seeking behavior in rats: implications for addiction treatment in humans. *Psychopharmacology (Berl)* **229**:253-265.
- Kenakin T, Watson C, Muniz-Medina V, Christopoulos A and Novick S (2012) A simple method for quantifying functional selectivity and agonist bias. *ACS Chem Neurosci* **3**:193-203.
- Kent JM, Daly E, Kezic I, Lane R, Lim P, De Smedt H, De Boer P, Van Nueten L, Drevets WC and Ceusters M (2016) Efficacy and safety of an adjunctive mGlu2 receptor positive allosteric modulator to a SSRI/SNRI in anxious depression. *Prog Neuropsychopharmacol Biol Psychiatry* **67**:66-73.
- Keppler A, Gendreizig S, Gronemeyer T, Pick H, Vogel H and Johnsson K (2003) A general method for the covalent labeling of fusion proteins with small molecules in vivo. *Nat Biotechnol* **21**:86-89.
- Keyword C, Wakefield M and Tack J (2009) A proof-of-concept study evaluating the effect of ADX10059, a metabotropic glutamate receptor-5 negative allosteric modulator, on acid exposure and symptoms in gastro-oesophageal reflux disease. *Gut* **58**:1192-1199.
- Kim CH, Braud S, Isaac JT and Roche KW (2005) Protein kinase C phosphorylation of the metabotropic glutamate receptor mGluR5 on Serine 839 regulates Ca²⁺ oscillations. *J Biol Chem* **280**:25409-25415.
- Kim J, Lee S, Park H, Song B, Hong I, Geum D, Shin K and Choi S (2007) Blockade of amygdala metabotropic glutamate receptor subtype 1 impairs fear extinction. *Biochem Biophys Res Commun* **355**:188-193.
- Kim JH and Vezina P (1998) The metabotropic glutamate receptor antagonist (RS)-MCPG produces hyperlocomotion in amphetamine pre-exposed rats. *Neuropharmacology* **37**:189-197.
- Kim SH, Steele JW, Lee SW, Clemenson GD, Carter TA, Treuner K, Gadiant R, Wedel P, Glabe C, Barlow C, Ehrlich ME, Gage FH and Gandy S (2014) Proneurogenic Group II mGluR antagonist improves learning and reduces anxiety in Alzheimer Abeta oligomer mouse. *Mol Psychiatry* **19**:1235-1242.

- Kingston AE, O'Neill MJ, Lam A, Bales KR, Monn JA and Schoepp DD (1999) Neuroprotection by metabotropic glutamate receptor glutamate receptor agonists: LY354740, LY379268 and LY389795. *Eur J Pharmacol* **377**:155-165.
- Kingston AE, Ornstein PL, Wright RA, Johnson BG, Mayne NG, Burnett JP, Belagaje R, Wu S and Schoepp DD (1998) LY341495 is a nanomolar potent and selective antagonist of group II metabotropic glutamate receptors. *Neuropharmacology* **37**:1-12.
- Kinney GA and Slater NT (1993) Potentiation of NMDA receptor-mediated transmission in turtle cerebellar granule cells by activation of metabotropic glutamate receptors. *J Neurophysiol* **69**:585-594.
- Kinney GG, Burno M, Campbell UC, Hernandez LM, Rodriguez D, Bristow LJ and Conn PJ (2003) Metabotropic glutamate subtype 5 receptors modulate locomotor activity and sensorimotor gating in rodents. *J Pharmacol Exp Ther* **306**:116-123.
- Kinney GG, O'Brien JA, Lemaire W, Burno M, Bickel DJ, Clements MK, Chen TB, Wisnoski DD, Lindsley CW, Tiller PR, Smith S, Jacobson MA, Sur C, Duggan ME, Pettibone DJ, Conn PJ and Williams DL, Jr. (2005) A novel selective positive allosteric modulator of metabotropic glutamate receptor subtype 5 has in vivo activity and antipsychotic-like effects in rat behavioral models. *J Pharmacol Exp Ther* **313**:199-206.
- Kinon BJ, Millen BA, Zhang L and McKinzie DL (2015) Exploratory analysis for a targeted patient population responsive to the metabotropic glutamate 2/3 receptor agonist pomaglumetad methionil in schizophrenia. *Biological psychiatry* **78**:754-762.
- Kinon BJ, Zhang L, Millen BA, Osuntokun OO, Williams JE, Kollack-Walker S, Jackson K, Kryzhanovskaya L and Jarkova N (2011) A multicenter, inpatient, phase 2, double-blind, placebo-controlled dose-ranging study of LY2140023 monohydrate in patients with DSM-IV schizophrenia. *J Clin Psychopharmacol* **31**:349-355.

- Kinoshita A, Ohishi H, Neki A, Nomura S, Shigemoto R, Takada M, Nakanishi S and Mizuno N (1996a) Presynaptic localization of a metabotropic glutamate receptor, mGluR8, in the rhinencephalic areas: a light and electron microscope study in the rat. *Neurosci Lett* **207**:61-64.
- Kinoshita A, Ohishi H, Nomura S, Shigemoto R, Nakanishi S and Mizuno N (1996b) Presynaptic localization of a metabotropic glutamate receptor, mGluR4a, in the cerebellar cortex: a light and electron microscope study in the rat. *Neurosci Lett* **207**:199-202.
- Kinoshita A, Shigemoto R, Ohishi H, van der Putten H and Mizuno N (1998) Immunohistochemical localization of metabotropic glutamate receptors, mGluR7a and mGluR7b, in the central nervous system of the adult rat and mouse: a light and electron microscopic study. *J Comp Neurol* **393**:332-352.
- Kinzie JM, Shinohara MM, van den Pol AN, Westbrook GL and Segerson TP (1997) Immunolocalization of metabotropic glutamate receptor 7 in the rat olfactory bulb. *J Comp Neurol* **385**:372-384.
- Kitano J, Kimura K, Yamazaki Y, Soda T, Shigemoto R, Nakajima Y and Nakanishi S (2002) Tamalin, a PDZ domain-containing protein, links a protein complex formation of group 1 metabotropic glutamate receptors and the guanine nucleotide exchange factor cytohesins. *J Neurosci* **22**:1280-1289.
- Klak K, Palucha A, Branski P, Sowa M and Pilc A (2007) Combined administration of PHCCC, a positive allosteric modulator of mGlu4 receptors and ACPT-I, mGlu III receptor agonist evokes antidepressant-like effects in rats. *Amino Acids* **32**:169-172.
- Klakotskaia D, Ramsey AK, Fowler SW, Serfozo P, Simonyi A and Schachtman TR (2013) Effects of group II and III metabotropic glutamate receptor ligands on conditioned taste aversion learning. *Behav Brain Res* **253**:9-16.
- Kniazeff J, Bessis AS, Maurel D, Ansanay H, Prezeau L and Pin JP (2004) Closed state of both binding domains of homodimeric mGlu receptors is required for full activity. *Nat Struct Mol Biol* **11**:706-713.

- Knoflach F and Kemp JA (1998) Metabotropic glutamate group II receptors activate a G protein-coupled inwardly rectifying K⁺ current in neurones of the rat cerebellum. *J Physiol* **509** (Pt 2):347-354.
- Knoflach F, Mutel V, Jolidon S, Kew JN, Malherbe P, Vieira E, Wichmann J and Kemp JA (2001) Positive allosteric modulators of metabotropic glutamate 1 receptor: characterization, mechanism of action, and binding site. *Proceedings of the National Academy of Sciences of the United States of America* **98**:13402-13407.
- Ko SJ, Isozaki K, Kim I, Lee JH, Cho HJ, Sohn SY, Oh SR, Park S, Kim DG, Kim CH and Roche KW (2012) PKC phosphorylation regulates mGluR5 trafficking by enhancing binding of Siah-1A. *J Neurosci* **32**:16391-16401.
- Koehl A, Hu H, Feng D, Sun B, Zhang Y, Robertson MJ, Chu M, Kobilka TS, Laeremans T, Steyaert J, Tarrasch J, Dutta S, Fonseca R, Weis WI, Mathiesen JM, Skiniotis G and Kobilka BK (2019) Structural insights into the activation of metabotropic glutamate receptors. *Nature* **566**:79-84.
- Kohara A, Toya T, Tamura S, Watabiki T, Nagakura Y, Shitaka Y, Hayashibe S, Kawabata S and Okada M (2005) Radioligand binding properties and pharmacological characterization of 6-amino-N-cyclohexyl-N,3-dimethylthiazolo[3,2-a]benzimidazole-2-carboxamide (YM-298198), a high-affinity, selective, and noncompetitive antagonist of metabotropic glutamate receptor type 1. *J Pharmacol Exp Ther* **315**:163-169.
- Koike C, Obara T, Uriu Y, Numata T, Sanuki R, Miyata K, Koyasu T, Ueno S, Funabiki K, Tani A, Ueda H, Kondo M, Mori Y, Tachibana M and Furukawa T (2010) TRPM1 is a component of the retinal ON bipolar cell transduction channel in the mGluR6 cascade. *Proc Natl Acad Sci U S A* **107**:332-337.
- Kolczewski S, Adam G, Stadler H, Mutel V, Wichmann J and Woltering T (1999) Synthesis of heterocyclic enol ethers and their use as group 2 metabotropic glutamate receptor antagonists. *Bioorg Med Chem Lett* **9**:2173-2176.

- Konieczny J, Ossowska K, Wolfarth S and Pilc A (1998) LY354740, a group II metabotropic glutamate receptor agonist with potential antiparkinsonian properties in rats. *Naunyn Schmiedebergs Arch Pharmacol* **358**:500-502.
- Kramer RH, Mourot A and Adesnik H (2013) Optogenetic pharmacology for control of native neuronal signaling proteins. *Nat Neurosci* **16**:816-823.
- Kubas H, Meyer U, Hechenberger M, Klein KU, Plitt P, Zemribo R, Spexgoor HW, van Assema SG and Abel U (2013) Scaffold hopping approach towards various AFQ-056 analogs as potent metabotropic glutamate receptor 5 negative allosteric modulators. *Bioorg Med Chem Lett* **23**:6370-6376.
- Kubo Y, Miyashita T and Murata Y (1998) Structural basis for a Ca²⁺-sensing function of the metabotropic glutamate receptors. *Science* **279**:1722-1725.
- Kubota H, Nagao S, Obata K and Hirono M (2014) mGluR1-mediated excitation of cerebellar GABAergic interneurons requires both G protein-dependent and Src-ERK1/2-dependent signaling pathways. *PLoS One* **9**:e106316.
- Kufahl PR, Hood LE, Nemirovsky NE, Barabas P, Halstengard C, Villa A, Moore E, Watterson LR and Olive MF (2012) Positive Allosteric Modulation of mGluR5 Accelerates Extinction Learning but Not Relearning Following Methamphetamine Self-Administration. *Front Pharmacol* **3**:194.
- Kumar N, Laferriere A, Yu JS, Poon T and Coderre TJ (2010) Metabotropic glutamate receptors (mGluRs) regulate noxious stimulus-induced glutamate release in the spinal cord dorsal horn of rats with neuropathic and inflammatory pain. *J Neurochem* **114**:281-290.
- Kumar R, Hauser RA, Mostillo J, Dronamraju N, Graf A, Merschhemke M and Kenney C (2016) Mavoglurant (AFQ056) in combination with increased levodopa dosages in Parkinson's disease patients. *Int J Neurosci* **126**:20-24.
- Kumar V, Fahey PG, Jong YJ, Ramanan N and O'Malley KL (2012) Activation of intracellular metabotropic glutamate receptor 5 in striatal neurons leads to up-regulation of genes associated with sustained synaptic transmission including Arc/Arg3.1 protein. *J Biol Chem* **287**:5412-5425.

- Kumar V, Jong YJ and O'Malley KL (2008) Activated nuclear metabotropic glutamate receptor mGlu5 couples to nuclear Gq/11 proteins to generate inositol 1,4,5-trisphosphate-mediated nuclear Ca²⁺ release. *J Biol Chem* **283**:14072-14083.
- Kumari R, Castillo C and Francesconi A (2013) Agonist-dependent signaling by group I metabotropic glutamate receptors is regulated by association with lipid domains. *J Biol Chem* **288**:32004-32019.
- Kumpost J, Syrova Z, Kulihova L, Frankova D, Bologna JC, Hlavackova V, Prezeau L, Kralikova M, Hruskova B, Pin JP and Blahos J (2008) Surface expression of metabotropic glutamate receptor variants mGluR1a and mGluR1b in transfected HEK293 cells. *Neuropharmacology* **55**:409-418.
- Kunishima N, Shimada Y, Tsuji Y, Sato T, Yamamoto M, Kumasaka T, Nakanishi S, Jingami H and Morikawa K (2000) Structural basis of glutamate recognition by a dimeric metabotropic glutamate receptor. *Nature* **407**:971-977.
- Kurita M, Holloway T, Garcia-Bea A, Kozlenkov A, Friedman AK, Moreno JL, Heshmati M, Golden SA, Kennedy PJ, Takahashi N, Dietz DM, Mocci G, Gabilondo AM, Hanks J, Umali A, Callado LF, Gallitano AL, Neve RL, Shen L, Buxbaum JD, Han MH, Nestler EJ, Meana JJ, Russo SJ and Gonzalez-Maeso J (2012) HDAC2 regulates atypical antipsychotic responses through the modulation of mGlu2 promoter activity. *Nat Neurosci* **15**:1245-1254.
- Laurie DJ, Boddeke HW, Hiltcher R and Sommer B (1996) HmGlu1d, a novel splice variant of the human type I metabotropic glutamate receptor. *Eur J Pharmacol* **296**:R1-R3.
- Lavreysen H, Ahnaou A, Drinkenburg W, Langlois X, Mackie C, Pype S, Lutjens R, Le Poul E, Trabanco AA and Nunez JM (2015) Pharmacological and pharmacokinetic properties of JNJ-40411813, a positive allosteric modulator of the mGlu2 receptor. *Pharmacol Res Perspect* **3**:e00096.
- Lavreysen H, Janssen C, Bischoff F, Langlois X, Leysen JE and Lesage AS (2003) [3H]R214127: a novel high-affinity radioligand for the mGlu1 receptor reveals a common binding site shared by multiple allosteric antagonists. *Mol Pharmacol* **63**:1082-1093.

- Lavreysen H, Langlois X, Ahnaou A, Drinkenburg W, te Riele P, Biesmans I, Van der Linden I, Peeters L, Megens A, Wintmolders C, Cid JM, Trabanco AA, Andres JI, Dautzenberg FM, Lutjens R, Macdonald G and Atack JR (2013) Pharmacological characterization of JNJ-40068782, a new potent, selective, and systemically active positive allosteric modulator of the mGlu2 receptor and its radioligand [3H]JNJ-40068782. *J Pharmacol Exp Ther* **346**:514-527.
- Lavreysen H, Wouters R, Bischoff F, Nobrega Pereira S, Langlois X, Blokland S, Somers M, Dillen L and Lesage AS (2004) JNJ16259685, a highly potent, selective and systemically active mGlu1 receptor antagonist. *Neuropharmacology* **47**:961-972.
- Lax NC, George DC, Ignatz C and Kolber BJ (2014) The mGluR5 antagonist fenobam induces analgesic conditioned place preference in mice with spared nerve injury. *PLoS One* **9**:e103524.
- Le Poul E, Bolea C, Girard F, Poli S, Charvin D, Campo B, Bortoli J, Bessif A, Luo B, Koser AJ, Hodge LM, Smith KM, DiLella AG, Liverton N, Hess F, Browne SE and Reynolds IJ (2012) A potent and selective metabotropic glutamate receptor 4 positive allosteric modulator improves movement in rodent models of Parkinson's disease. *J Pharmacol Exp Ther* **343**:167-177.
- Leach K and Gregory KJ (2017) Molecular insights into allosteric modulation of Class C G protein-coupled receptors. *Pharmacol Res* **116**:105-118.
- Leach K, Sexton PM and Christopoulos A (2007) Allosteric GPCR modulators: taking advantage of permissive receptor pharmacology. *Trends Pharmacol Sci* **28**:382-389.
- Lebois EP (2008) Neither typical nor atypical: LY404039 provides proof of concept that selective targeting of mGluR2/3 receptors is a valid mechanism for obtaining antipsychotic efficacy. *Curr Top Med Chem* **8**:1480-1481.
- Lebourgeois S, Vilpoux C, Jeanblanc J, Acher F, Marie N, Noble F and Naassila M (2018) Pharmacological activation of mGlu4 and mGlu7 receptors, by LSP2-9166, reduces ethanol consumption and relapse in rat. *Neuropharmacology* **133**:163-170.

- Lee J, Munguba H, Gutzeit VA, Kristt M, Dittman JS and Levitz J (2020) Defining the Homo- and Heterodimerization Propensities of Metabotropic Glutamate Receptors. *Cell Rep* **31**:107605.
- Lee JH, Lee J, Choi KY, Hepp R, Lee JY, Lim MK, Chatani-Hinze M, Roche PA, Kim DG, Ahn YS, Kim CH and Roche KW (2008) Calmodulin dynamically regulates the trafficking of the metabotropic glutamate receptor mGluR5. *Proc Natl Acad Sci U S A* **105**:12575-12580.
- Lee JY, Choe ES, Yang CH, Choi KH, Cheong JH, Jang CG, Seo JW and Yoon SS (2016) The mGluR5 antagonist MPEP suppresses the expression and reinstatement, but not the acquisition, of the ethanol-conditioned place preference in mice. *Pharmacol Biochem Behav* **140**:33-38.
- Lennon SM, Rivero G, Matharu A, Howson PA, Jane DE, Roberts PJ and Kelly E (2010) Metabotropic glutamate receptor mGlu2 is resistant to homologous agonist-induced desensitization but undergoes protein kinase C-mediated heterologous desensitization. *Eur J Pharmacol* **649**:29-37.
- Lesage F, Terrenoire C, Romey G and Lazdunski M (2000) Human TREK2, a 2P domain mechano-sensitive K⁺ channel with multiple regulations by polyunsaturated fatty acids, lysophospholipids, and Gs, Gi, and Gq protein-coupled receptors. *J Biol Chem* **275**:28398-28405.
- Levitz J, Broichhagen J, Leippe P, Konrad D, Trauner D and Isacoff EY (2017) Dual optical control and mechanistic insights into photoswitchable group II and III metabotropic glutamate receptors. *Proc Natl Acad Sci U S A* **114**:E3546-E3554.
- Levitz J, Habrian C, Bharill S, Fu Z, Vafabakhsh R and Isacoff EY (2016) Mechanism of Assembly and Cooperativity of Homomeric and Heteromeric Metabotropic Glutamate Receptors. *Neuron*.
- Levitz J, Pantoja C, Gaub B, Janovjak H, Reiner A, Hoagland A, Schoppik D, Kane B, Stawski P, Schier AF, Trauner D and Isacoff EY (2013) Optical control of metabotropic glutamate receptors. *Nat Neurosci* **16**:507-516.
- Li ML, Yang SS, Xing B, Ferguson BR, Gulchina Y, Li YC, Li F, Hu XQ and Gao WJ (2015) LY395756, an mGluR2 agonist and mGluR3 antagonist, enhances NMDA receptor expression and function in

- the normal adult rat prefrontal cortex, but fails to improve working memory and reverse MK801-induced working memory impairment. *Exp Neurol* **273**:190-201.
- Li X, D'Souza MS, Nino AM, Doherty J, Cross A and Markou A (2016) Attenuation of nicotine-taking and nicotine-seeking behavior by the mGlu2 receptor positive allosteric modulators AZD8418 and AZD8529 in rats. *Psychopharmacology (Berl)* **233**:1801-1814.
- Li X, Li J, Gardner EL and Xi ZX (2010) Activation of mGluR7s inhibits cocaine-induced reinstatement of drug-seeking behavior by a nucleus accumbens glutamate-mGluR2/3 mechanism in rats. *J Neurochem* **114**:1368-1380.
- Li X, Li J, Peng XQ, Spiller K, Gardner EL and Xi ZX (2009) Metabotropic glutamate receptor 7 modulates the rewarding effects of cocaine in rats: involvement of a ventral pallidal GABAergic mechanism. *Neuropsychopharmacology* **34**:1783-1796.
- Li X, Peng XQ, Jordan CJ, Li J, Bi GH, He Y, Yang HJ, Zhang HY, Gardner EL and Xi ZX (2018) mGluR5 antagonism inhibits cocaine reinforcement and relapse by elevation of extracellular glutamate in the nucleus accumbens via a CB1 receptor mechanism. *Sci Rep* **8**:3686.
- Liechti ME and Markou A (2007) Interactive effects of the mGlu5 receptor antagonist MPEP and the mGlu2/3 receptor antagonist LY341495 on nicotine self-administration and reward deficits associated with nicotine withdrawal in rats. *Eur J Pharmacol* **554**:164-174.
- Lindemann L, Jaeschke G, Michalon A, Vieira E, Honer M, Spooren W, Porter R, Hartung T, Kolczewski S, Buttelmann B, Flament C, Diener C, Fischer C, Gatti S, Prinssen EP, Parrott N, Hoffmann G and Wettstein JG (2011) CTEP: a novel, potent, long-acting, and orally bioavailable metabotropic glutamate receptor 5 inhibitor. *J Pharmacol Exp Ther* **339**:474-486.
- Linden AM, Bergeron M, Baez M and Schoepp DD (2003) Systemic administration of the potent mGlu8 receptor agonist (S)-3,4-DCPG induces c-Fos in stress-related brain regions in wild-type, but not mGlu8 receptor knockout mice. *Neuropharmacology* **45**:473-483.

- Lindsley CW, Emmitte KA, Hopkins CR, Bridges TM, Gregory KJ, Niswender CM and Conn PJ (2016) Practical Strategies and Concepts in GPCR Allosteric Modulator Discovery: Recent Advances with Metabotropic Glutamate Receptors. *Chem Rev* **116**:6707-6741.
- Lindsley CW, Wisnoski DD, Leister WH, O'Brien J A, Lemaire W, Williams DL, Jr., Burno M, Sur C, Kinney GG, Pettibone DJ, Tiller PR, Smith S, Duggan ME, Hartman GD, Conn PJ and Huff JR (2004) Discovery of positive allosteric modulators for the metabotropic glutamate receptor subtype 5 from a series of N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamides that potentiate receptor function in vivo. *J Med Chem* **47**:5825-5828.
- Litman RE, Smith MA, Doherty JJ, Cross A, Raines S, Gertsik L and Zukin SR (2016) AZD8529, a positive allosteric modulator at the mGluR2 receptor, does not improve symptoms in schizophrenia: A proof of principle study. *Schizophr Res* **172**:152-157.
- Litschig S, Gasparini F, Rueegg D, Stoehr N, Flor PJ, Vranesic I, Prezeau L, Pin JP, Thomsen C and Kuhn R (1999) CPCCOEt, a noncompetitive metabotropic glutamate receptor 1 antagonist, inhibits receptor signaling without affecting glutamate binding. *Mol Pharmacol* **55**:453-461.
- Littman L, Chase LA, Renzi M, Garlin AB, Koerner JF, Johnson RL and Robinson MB (1995) Effects of quisqualic acid analogs on metabotropic glutamate receptors coupled to phosphoinositide hydrolysis in rat hippocampus. *Neuropharmacology* **34**:829-841.
- Liu F, Grauer S, Kelley C, Navarra R, Graf R, Zhang G, Atkinson PJ, Popiolek M, Wantuch C, Khawaja X, Smith D, Olsen M, Kouranova E, Lai M, Pruthi F, Pulicicchio C, Day M, Gilbert A, Pausch MH, Brandon NJ, Beyer CE, Comery TA, Logue S, Rosenzweig-Lipson S and Marquis KL (2008) ADX47273 [S-(4-fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]-oxadiazol-5-yl]-piperidin-1-yl}-methanone]: a novel metabotropic glutamate receptor 5-selective positive allosteric modulator with preclinical antipsychotic-like and procognitive activities. *J Pharmacol Exp Ther* **327**:827-839.

- Liu J, Zhang Z, Moreno-Delgado D, Dalton JA, Rovira X, Trapero A, Goudet C, Llebaria A, Giraldo J, Yuan Q, Rondard P, Huang S, Liu J and Pin JP (2017) Allosteric control of an asymmetric transduction in a G protein-coupled receptor heterodimer. *Elife* **6**.
- Liu XH, Han M, Zhu JX, Sun N, Tang JS, Huo FQ, Li J, Xu FY and Du JQ (2012) Metabotropic glutamate subtype 7 and 8 receptors oppositely modulate cardiac nociception in the rat nucleus tractus solitarius. *Neuroscience* **220**:322-329.
- Loane DJ, Stoica BA, Tchanchou F, Kumar A, Barrett JP, Akintola T, Xue F, Conn PJ and Faden AI (2014) Novel mGluR5 Positive Allosteric Modulator Improves Functional Recovery, Attenuates Neurodegeneration, and Alters Microglial Polarization after Experimental Traumatic Brain Injury. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics* **11**:857-869.
- Lopez S, Turle-Lorenzo N, Acher F, De Leonibus E, Mele A and Amalric M (2007) Targeting group III metabotropic glutamate receptors produces complex behavioral effects in rodent models of Parkinson's disease. *J Neurosci* **27**:6701-6711.
- Lundstrom L, Bissantz C, Beck J, Dellenbach M, Woltering TJ, Wichmann J and Gatti S (2016) Pharmacological and molecular characterization of the positive allosteric modulators of metabotropic glutamate receptor 2. *Neuropharmacology* **111**:253-265.
- Lundstrom L, Bissantz C, Beck J, Wettstein JG, Woltering TJ, Wichmann J and Gatti S (2011) Structural determinants of allosteric antagonism at metabotropic glutamate receptor 2: mechanistic studies with new potent negative allosteric modulators. *Br J Pharmacol* **164**:521-537.
- Lundstrom L, Kuhn B, Beck J, Borroni E, Wettstein JG, Woltering TJ and Gatti S (2009) Mutagenesis and molecular modeling of the orthosteric binding site of the mGlu2 receptor determining interactions of the group II receptor antagonist (3)H-HYDIA. *ChemMedChem* **4**:1086-1094.

- Macek TA, Schaffhauser H and Conn PJ (1998) Protein kinase C and A3 adenosine receptor activation inhibit presynaptic metabotropic glutamate receptor (mGluR) function and uncouple mGluRs from GTP-binding proteins. *J Neurosci* **18**:6138-6146.
- MacInnes N, Messenger MJ and Duty S (2004) Activation of group III metabotropic glutamate receptors in selected regions of the basal ganglia alleviates akinesia in the reserpine-treated rat. *Br J Pharmacol* **141**:15-22.
- Maejima T, Hashimoto K, Yoshida T, Aiba A and Kano M (2001) Presynaptic inhibition caused by retrograde signal from metabotropic glutamate to cannabinoid receptors. *Neuron* **31**:463-475.
- Mahato PK, Pandey S and Bhattacharyya S (2015) Differential effects of protein phosphatases in the recycling of metabotropic glutamate receptor 5. *Neuroscience* **306**:138-150.
- Maj C, Minelli A, Giacopuzzi E, Sacchetti E and Gennarelli M (2016) The Role of Metabotropic Glutamate Receptor Genes in Schizophrenia. *Curr Neuropharmacol* **14**:540-550.
- Maj M, Bruno V, Dragic Z, Yamamoto R, Battaglia G, Inderbitzin W, Stoehr N, Stein T, Gasparini F, Vranesic I, Kuhn R, Nicoletti F and Flor PJ (2003) (-)-PHCCC, a positive allosteric modulator of mGluR4: characterization, mechanism of action, and neuroprotection. *Neuropharmacology* **45**:895-906.
- Makoff A, Pilling C, Harrington K and Emson P (1996) Human metabotropic glutamate receptor type 7: molecular cloning and mRNA distribution in the CNS. *Brain Res Mol Brain Res* **40**:165-170.
- Makoff AJ, Phillips T, Pilling C and Emson P (1997) Expression of a novel splice variant of human mGluR1 in the cerebellum. *Neuroreport* **8**:2943-2947.
- Malherbe P, Kratochwil N, Knoflach F, Zenner MT, Kew JN, Kratzeisen C, Maerki HP, Adam G and Mutel V (2003) Mutational analysis and molecular modeling of the allosteric binding site of a novel, selective, noncompetitive antagonist of the metabotropic glutamate 1 receptor. *J Biol Chem* **278**:8340-8347.

- Malherbe P, Kratzeisen C, Lundstrom K, Richards JG, Faull RL and Mutel V (1999) Cloning and functional expression of alternative spliced variants of the human metabotropic glutamate receptor 8. *Brain Res Mol Brain Res* **67**:201-210.
- Mao L and Wang JQ (2003a) Metabotropic glutamate receptor 5-regulated Elk-1 phosphorylation and immediate early gene expression in striatal neurons. *J Neurochem* **85**:1006-1017.
- Mao L and Wang JQ (2003b) Phosphorylation of cAMP response element-binding protein in cultured striatal neurons by metabotropic glutamate receptor subtype 5. *J Neurochem* **84**:233-243.
- Marabese I, Rossi F, Palazzo E, de Novellis V, Starowicz K, Cristino L, Vita D, Gatta L, Guida F, Di Marzo V and Maione S (2007) Periaqueductal gray metabotropic glutamate receptor subtype 7 and 8 mediate opposite effects on amino acid release, rostral ventromedial medulla cell activities, and thermal nociception. *J Neurophysiol* **98**:43-53.
- Marek GJ, Wright RA and Schoepp DD (2006) 5-Hydroxytryptamine_{2A} (5-HT_{2A}) receptor regulation in rat prefrontal cortex: interaction of a phenethylamine hallucinogen and the metabotropic glutamate_{2/3} receptor agonist LY354740. *Neurosci Lett* **403**:256-260.
- Marek GJ, Wright RA, Schoepp DD, Monn JA and Aghajanian GK (2000) Physiological antagonism between 5-hydroxytryptamine_{2A} and group II metabotropic glutamate receptors in prefrontal cortex. *J Pharmacol Exp Ther* **292**:76-87.
- Marino MJ, Valenti O, O'Brien JA, Williams DL, Jr. and Conn PJ (2003a) Modulation of inhibitory transmission in the rat globus pallidus by activation of mGluR4. *Ann N Y Acad Sci* **1003**:435-437.
- Marino MJ, Williams DL, Jr., O'Brien JA, Valenti O, McDonald TP, Clements MK, Wang R, DiLella AG, Hess JF, Kinney GG and Conn PJ (2003b) Allosteric modulation of group III metabotropic glutamate receptor 4: a potential approach to Parkinson's disease treatment. *Proc Natl Acad Sci U S A* **100**:13668-13673.

- Marks CR, Shonesy BC, Wang X, Stephenson JR, Niswender CM and Colbran RJ (2018) Activated CaMKIIalpha Binds to the mGlu5 Metabotropic Glutamate Receptor and Modulates Calcium Mobilization. *Mol Pharmacol* **94**:1352-1362.
- Marszalek-Grabska M, Gibula-Bruzda E, Bodzon-Kulakowska A, Suder P, Gawel K, Talarek S, Listos J, Kedzierska E, Danysz W and Kotlinska JH (2018) ADX-47273, a mGlu5 receptor positive allosteric modulator, attenuates deficits in cognitive flexibility induced by withdrawal from 'binge-like' ethanol exposure in rats. *Behav Brain Res* **338**:9-16.
- Martin R, Torres M and Sanchez-Prieto J (2007) mGluR7 inhibits glutamate release through a PKC-independent decrease in the activity of P/Q-type Ca²⁺ channels and by diminishing cAMP in hippocampal nerve terminals. *Eur J Neurosci* **26**:312-322.
- Masilamoni GJ, Bogenpohl JW, Alagille D, Delevich K, Tamagnan G, Votaw JR, Wichmann T and Smith Y (2011) Metabotropic glutamate receptor 5 antagonist protects dopaminergic and noradrenergic neurons from degeneration in MPTP-treated monkeys. *Brain* **134**:2057-2073.
- Matrisciano F, Zusso M, Panaccione I, Turriziani B, Caruso A, Iacovelli L, Noviello L, Togna G, Melchiorri D, Debetto P, Tatarelli R, Battaglia G, Nicoletti F, Giusti P and Girardi P (2008) Synergism between fluoxetine and the mGlu2/3 receptor agonist, LY379268, in an in vitro model for antidepressant drug-induced neurogenesis. *Neuropharmacology* **54**:428-437.
- Mazur JE (1995) Conditioned reinforcement and choice with delayed and uncertain primary reinforcers. *J Exp Anal Behav* **63**:139-150.
- Mazzitelli M, Palazzo E, Maione S and Neugebauer V (2018) Group II Metabotropic Glutamate Receptors: Role in Pain Mechanisms and Pain Modulation. *Front Mol Neurosci* **11**:383.
- McColm J, Brittain C, Suriyapperuma S, Swanson S, Tauscher-Wisniewski S, Foster J, Soon D and Jackson K (2017) Evaluation of single and multiple doses of a novel mGlu2 agonist, a potential antipsychotic therapy, in healthy subjects. *Br J Clin Pharmacol* **83**:1654-1667.

- McCool BA, Pin JP, Brust PF, Harpold MM and Lovinger DM (1996) Functional coupling of rat group II metabotropic glutamate receptors to an omega-conotoxin GVIA-sensitive calcium channel in human embryonic kidney 293 cells. *Mol Pharmacol* **50**:912-922.
- Megens AA, Hendrickx HM, Hens KA, Talloen WJ and Lavreysen H (2014) mGlu(2) receptor-mediated modulation of conditioned avoidance behavior in rats. *Eur J Pharmacol* **727**:130-139.
- Mehta MV, Gandal MJ and Siegel SJ (2011) mGluR5-antagonist mediated reversal of elevated stereotyped, repetitive behaviors in the VPA model of autism. *PLoS One* **6**:e26077.
- Meldrum BS (2000) Glutamate as a neurotransmitter in the brain: review of physiology and pathology. *J Nutr* **130**:1007S-1015S.
- Metcalf CS, Klein BD, Smith MD, Pruess T, Ceusters M, Lavreysen H, Pype S, Van Osselaer N, Twyman R and White HS (2017) Efficacy of mGlu2 -positive allosteric modulators alone and in combination with levetiracetam in the mouse 6 Hz model of psychomotor seizures. *Epilepsia* **58**:484-493.
- Michalon A, Bruns A, Risterucci C, Honer M, Ballard TM, Ozmen L, Jaeschke G, Wettstein JG, von Kienlin M, Kunnecke B and Lindemann L (2014) Chronic metabotropic glutamate receptor 5 inhibition corrects local alterations of brain activity and improves cognitive performance in fragile X mice. *Biological psychiatry* **75**:189-197.
- Michalon A, Sidorov M, Ballard TM, Ozmen L, Spooren W, Wettstein JG, Jaeschke G, Bear MF and Lindemann L (2012) Chronic pharmacological mGlu5 inhibition corrects fragile X in adult mice. *Neuron* **74**:49-56.
- Micheli F, Fabio RD, Cavanni P, Rimland JM, Capelli AM, Chiamulera C, Corsi M, Corti C, Donati D, Feriani A, Ferraguti F, Maffei M, Missio A, Ratti E, Paio A, Pachera R, Quartaroli M, Reggiani A, Sabbatini FM, Trist DG, Ugolini A and Vitulli G (2003) Synthesis and pharmacological characterisation of 2,4-dicarboxy-pyrroles as selective non-competitive mGluR1 antagonists. *Bioorg Med Chem* **11**:171-183.

- Millan C, Lujan R, Shigemoto R and Sanchez-Prieto J (2002a) The inhibition of glutamate release by metabotropic glutamate receptor 7 affects both $[Ca^{2+}]_c$ and cAMP: evidence for a strong reduction of Ca^{2+} entry in single nerve terminals. *J Biol Chem* **277**:14092-14101.
- Millan C, Lujan R, Shigemoto R and Sanchez-Prieto J (2002b) Subtype-specific expression of group III metabotropic glutamate receptors and Ca^{2+} channels in single nerve terminals. *J Biol Chem* **277**:47796-47803.
- Minakami R, Iida K, Hirakawa N and Sugiyama H (1995) The expression of two splice variants of metabotropic glutamate receptor subtype 5 in the rat brain and neuronal cells during development. *J Neurochem* **65**:1536-1542.
- Minakami R, Katsuki F and Sugiyama H (1993) A variant of metabotropic glutamate receptor subtype 5: an evolutionally conserved insertion with no termination codon. *Biochem Biophys Res Commun* **194**:622-627.
- Minakami R, Katsuki F, Yamamoto T, Nakamura K and Sugiyama H (1994) Molecular cloning and the functional expression of two isoforms of human metabotropic glutamate receptor subtype 5. *Biochem Biophys Res Commun* **199**:1136-1143.
- Mion S, Corti C, Neki A, Shigemoto R, Corsi M, Fumagalli G and Ferraguti F (2001) Bidirectional regulation of neurite elaboration by alternatively spliced metabotropic glutamate receptor 5 (mGluR5) isoforms. *Mol Cell Neurosci* **17**:957-972.
- Mitsukawa K, Yamamoto R, Ofner S, Nozulak J, Pescott O, Lukic S, Stoehr N, Mombereau C, Kuhn R, McAllister KH, van der Putten H, Cryan JF and Flor PJ (2005) A selective metabotropic glutamate receptor 7 agonist: activation of receptor signaling via an allosteric site modulates stress parameters in vivo. *Proc Natl Acad Sci U S A* **102**:18712-18717.
- Miyamoto M, Ishida M and Shinozaki H (1997) Anticonvulsive and neuroprotective actions of a potent agonist (DCG-IV) for group II metabotropic glutamate receptors against intraventricular kainate in the rat. *Neuroscience* **77**:131-140.

- Miyashita T and Kubo Y (2000a) Extracellular Ca²⁺ sensitivity of mGluR1alpha associated with persistent glutamate response in transfected CHO cells. *Receptors Channels* **7**:25-40.
- Miyashita T and Kubo Y (2000b) Extracellular Ca²⁺ sensitivity of mGluR1alpha induces an increase in the basal cAMP level by direct coupling with Gs protein in transfected CHO cells. *Receptors Channels* **7**:77-91.
- Moldrich RX, Aprico K, Diwakarla S, O'Shea RD and Beart PM (2002) Astrocyte mGlu(2/3)-mediated cAMP potentiation is calcium sensitive: studies in murine neuronal and astrocyte cultures. *Neuropharmacology* **43**:189-203.
- Molinaro G, Traficante A, Riozzi B, Di Menna L, Curto M, Pallottino S, Nicoletti F, Bruno V and Battaglia G (2009) Activation of mGlu2/3 metabotropic glutamate receptors negatively regulates the stimulation of inositol phospholipid hydrolysis mediated by 5-hydroxytryptamine_{2A} serotonin receptors in the frontal cortex of living mice. *Mol Pharmacol* **76**:379-387.
- Moloney RD, Golubeva AV, O'Connor RM, Kalinichev M, Dinan TG and Cryan JF (2015) Negative allosteric modulation of the mGlu7 receptor reduces visceral hypersensitivity in a stress-sensitive rat strain. *Neurobiol Stress* **2**:28-33.
- Monn JA, Henry SS, Massey SM, Clawson DK, Chen Q, Diseroad BA, Bhardwaj RM, Atwell S, Lu F, Wang J, Russell M, Heinz BA, Wang XS, Carter JH, Getman BG, Adraghi K, Broad LM, Sanger HE, Ursu D, Catlow JT, Swanson S, Johnson BG, Shaw DB, McKinzie DL and Hao J (2018) Synthesis and Pharmacological Characterization of C4beta-Amide-Substituted 2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylates. Identification of (1 S,2 S,4 S,5 R,6 S)-2-Amino-4-[(3-methoxybenzoyl)amino]bicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (LY2794193), a Highly Potent and Selective mGlu3 Receptor Agonist. *J Med Chem* **61**:2303-2328.
- Monn JA, Prieto L, Taboada L, Hao J, Reinhard MR, Henry SS, Beadle CD, Walton L, Man T, Rudyk H, Clark B, Tupper D, Baker SR, Lamas C, Montero C, Marcos A, Blanco J, Bures M, Clawson DK, Atwell S, Lu F, Wang J, Russell M, Heinz BA, Wang X, Carter JH, Getman BG, Catlow JT,

Swanson S, Johnson BG, Shaw DB and McKinzie DL (2015a) Synthesis and Pharmacological Characterization of C4-(Thiotriazolyl)-substituted-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylates. Identification of (1R,2S,4R,5R,6R)-2-Amino-4-(1H-1,2,4-triazol-3-ylsulfanyl)bicyclo[3.1.0]hexane-2,6-dicarboxylic Acid (LY2812223), a Highly Potent, Functionally Selective mGlu2 Receptor Agonist. *J Med Chem* **58**:7526-7548.

Monn JA, Prieto L, Taboada L, Pedregal C, Hao J, Reinhard MR, Henry SS, Goldsmith PJ, Beadle CD, Walton L, Man T, Rudyk H, Clark B, Tupper D, Baker SR, Lamas C, Montero C, Marcos A, Blanco J, Bures M, Clawson DK, Atwell S, Lu F, Wang J, Russell M, Heinz BA, Wang X, Carter JH, Xiang C, Catlow JT, Swanson S, Sanger H, Broad LM, Johnson MP, Knopp KL, Simmons RM, Johnson BG, Shaw DB and McKinzie DL (2015b) Synthesis and pharmacological characterization of C4-disubstituted analogs of 1S,2S,5R,6S-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate: identification of a potent, selective metabotropic glutamate receptor agonist and determination of agonist-bound human mGlu2 and mGlu3 amino terminal domain structures. *J Med Chem* **58**:1776-1794.

Monn JA, Valli MJ, Massey SM, Wright RA, Salhoff CR, Johnson BG, Howe T, Alt CA, Rhodes GA, Robey RL, Griffey KR, Tizzano JP, Kallman MJ, Helton DR and Schoepp DD (1997) Design, synthesis, and pharmacological characterization of (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740): a potent, selective, and orally active group 2 metabotropic glutamate receptor agonist possessing anticonvulsant and anxiolytic properties. *J Med Chem* **40**:528-537.

Montana MC, Cavallone LF, Stubbert KK, Stefanescu AD, Kharasch ED and Gereau RWt (2009) The metabotropic glutamate receptor subtype 5 antagonist fenobam is analgesic and has improved in vivo selectivity compared with the prototypical antagonist 2-methyl-6-(phenylethynyl)-pyridine. *J Pharmacol Exp Ther* **330**:834-843.

Montana MC, Conrardy BA, Cavallone LF, Kolber BJ, Rao LK, Greco SC and Gereau RWt (2011) Metabotropic glutamate receptor 5 antagonism with fenobam: examination of analgesic tolerance and side effect profile in mice. *Anesthesiology* **115**:1239-1250.

- More L, Gravius A, Pietraszek M, Belozertseva I, Malyshkin A, Shekunova E, Barberi C, Schaefer D, Schmidt WJ and Danysz W (2007) Comparison of the mGluR1 antagonist A-841720 in rat models of pain and cognition. *Behav Pharmacol* **18**:273-281.
- Moreno Delgado D, Moller TC, Ster J, Giraldo J, Maurel D, Rovira X, Scholler P, Zwier JM, Perroy J, Durroux T, Trinquet E, Prezeau L, Rondard P and Pin JP (2017) Pharmacological evidence for a metabotropic glutamate receptor heterodimer in neuronal cells. *Elife* **6**.
- Moreno JL, Holloway T, Rayannavar V, Sealfon SC and Gonzalez-Maeso J (2013) Chronic treatment with LY341495 decreases 5-HT(2A) receptor binding and hallucinogenic effects of LSD in mice. *Neurosci Lett* **536**:69-73.
- Moreno JL, Miranda-Azpiazu P, Garcia-Bea A, Younkin J, Cui M, Kozlenkov A, Ben-Ezra A, Voloudakis G, Fakira AK, Baki L, Ge Y, Georgakopoulos A, Moron JA, Milligan G, Lopez-Gimenez JF, Robakis NK, Logothetis DE, Meana JJ and Gonzalez-Maeso J (2016) Allosteric signaling through an mGlu2 and 5-HT2A heteromeric receptor complex and its potential contribution to schizophrenia. *Sci Signal* **9**:ra5.
- Moroni F, Lombardi G, Thomsen C, Leonardi P, Attucci S, Peruginelli F, Torregrossa SA, Pellegrini-Giampietro DE, Luneia R and Pellicciari R (1997) Pharmacological characterization of 1-aminoindan-1,5-dicarboxylic acid, a potent mGluR1 antagonist. *J Pharmacol Exp Ther* **281**:721-729.
- Motolese M, Mastroiacovo F, Cannella M, Bucci D, Gaglione A, Riozzi B, Lutjens R, Poli SM, Celanire S, Bruno V, Battaglia G and Nicoletti F (2015) Targeting type-2 metabotropic glutamate receptors to protect vulnerable hippocampal neurons against ischemic damage. *Mol Brain* **8**:66.
- Moult PR, Gladding CM, Sanderson TM, Fitzjohn SM, Bashir ZI, Molnar E and Collingridge GL (2006) Tyrosine phosphatases regulate AMPA receptor trafficking during metabotropic glutamate receptor-mediated long-term depression. *J Neurosci* **26**:2544-2554.

- Moyanova SG, Mastroiacovo F, Kortenska LV, Mitreva RG, Fardone E, Santolini I, Sobrado M, Battaglia G, Bruno V, Nicoletti F and Ngomba RT (2011) Protective role for type 4 metabotropic glutamate receptors against ischemic brain damage. *J Cereb Blood Flow Metab* **31**:1107-1118.
- Mundell SJ, Pula G, More JC, Jane DE, Roberts PJ and Kelly E (2004) Activation of cyclic AMP-dependent protein kinase inhibits the desensitization and internalization of metabotropic glutamate receptors 1a and 1b. *Mol Pharmacol* **65**:1507-1516.
- Murat S, Bigot M, Chapron J, Konig GM, Kostenis E, Battaglia G, Nicoletti F, Bourinet E, Bockaert J, Marin P and Vandermoere F (2018) 5-HT_{2A} receptor-dependent phosphorylation of mGlu₂ receptor at Serine 843 promotes mGlu₂ receptor-operated Gi/o signaling. *Mol Psychiatry*.
- Muto T, Tsuchiya D, Morikawa K and Jingami H (2007) Structures of the extracellular regions of the group II/III metabotropic glutamate receptors. *Proc Natl Acad Sci U S A* **104**:3759-3764.
- Nadlewska A, Car H, Oksztel R and Wisniewski K (2002) Effect of (S)-3,5-DHPG on learning, exploratory activity and anxiety in rats with experimental hypoxia. *Pol J Pharmacol* **54**:11-18.
- Nakajima Y, Iwakabe H, Akazawa C, Nawa H, Shigemoto R, Mizuno N and Nakanishi S (1993) Molecular characterization of a novel retinal metabotropic glutamate receptor mGluR₆ with a high agonist selectivity for L-2-amino-4-phosphonobutyrate. *J Biol Chem* **268**:11868-11873.
- Nakamura M, Kawakita Y, Yasuhara A, Fukasawa Y, Yoshida K, Sakagami K and Nakazato A (2006) In vitro and in vivo evaluation of the metabolism and bioavailability of ester prodrugs of mgs0039 (3-(3,4-dichlorobenzyloxy)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic Acid), a potent metabotropic glutamate receptor antagonist. *Drug Metab Dispos* **34**:369-374.
- Namkoong J, Martino JJ and Chen S (2006) From existing therapies to novel targets: a current view on melanoma. *Front Biosci* **11**:2081-2092.
- Naples MA and Hampson DR (2001) Pharmacological profiles of the metabotropic glutamate receptor ligands. *Neuropharmacology* **40**:170-177.

- Nardecchia F, Orlando R, Iacovelli L, Colamartino M, Fiori E, Leuzzi V, Piccinin S, Nistico R, Puglisi-Allegra S, Di Menna L, Battaglia G, Nicoletti F and Pascucci T (2018) Targeting mGlu5 Metabotropic Glutamate Receptors in the Treatment of Cognitive Dysfunction in a Mouse Model of Phenylketonuria. *Front Neurosci* **12**:154.
- Nasrallah C, Rottier K, Marcellin R, Compan V, Font J, Llebaria A, Pin JP, Baneres JL and Lebon G (2018) Direct coupling of detergent purified human mGlu5 receptor to the heterotrimeric G proteins Gq and Gs. *Sci Rep* **8**:4407.
- Neto A and Ceol CJ (2018) Melanoma-associated GRM3 variants dysregulate melanosome trafficking and cAMP signaling. *Pigment Cell Melanoma Res* **31**:115-119.
- Neugebauer V (2002) Metabotropic glutamate receptors--important modulators of nociception and pain behavior. *Pain* **98**:1-8.
- Neugebauer V, Chen PS and Willis WD (1999) Role of metabotropic glutamate receptor subtype mGluR1 in brief nociception and central sensitization of primate STT cells. *J Neurophysiol* **82**:272-282.
- Ngomba RT, Ferraguti F, Badura A, Citraro R, Santolini I, Battaglia G, Bruno V, De Sarro G, Simonyi A, van Luijtelaar G and Nicoletti F (2008) Positive allosteric modulation of metabotropic glutamate 4 (mGlu4) receptors enhances spontaneous and evoked absence seizures. *Neuropharmacology* **54**:344-354.
- Nickols HH, Yuh JP, Gregory KJ, Morrison RD, Bates BS, Stauffer SR, Emmitte KA, Bubser M, Peng W, Nedelcovych MT, Thompson A, Lv X, Xiang Z, Daniels JS, Niswender CM, Lindsley CW, Jones CK and Conn PJ (2016) VU0477573: Partial Negative Allosteric Modulator of the Subtype 5 Metabotropic Glutamate Receptor with In Vivo Efficacy. *J Pharmacol Exp Ther* **356**:123-136.
- Nicodemo AA, Pampillo M, Ferreira LT, Dale LB, Cregan T, Ribeiro FM and Ferguson SS (2010) Pyk2 uncouples metabotropic glutamate receptor G protein signaling but facilitates ERK1/2 activation. *Mol Brain* **3**:4.

- Nicoletti F, Orlando R, Di Menna L, Cannella M, Notartomaso S, Mascio G, Iacovelli L, Matrisciano F, Fazio F, Caraci F, Copani A, Battaglia G and Bruno V (2019) Targeting mGlu Receptors for Optimization of Antipsychotic Activity and Disease-Modifying Effect in Schizophrenia. *Front Psychiatry* **10**:49.
- Nicoletti F, Wroblewski JT, Iadarola MJ and Costa E (1986) Serine-O-phosphate, an endogenous metabolite, inhibits the stimulation of inositol phospholipid hydrolysis elicited by ibotenic acid in rat hippocampal slices. *Neuropharmacology* **25**:335-338.
- Nikiforuk A, Popik P, Drescher KU, van Gaalen M, Relo AL, Mezler M, Marek G, Schoemaker H, Gross G and Beshpalov A (2010) Effects of a positive allosteric modulator of group II metabotropic glutamate receptors, LY487379, on cognitive flexibility and impulsive-like responding in rats. *J Pharmacol Exp Ther* **335**:665-673.
- Nishi A, Liu F, Matsuyama S, Hamada M, Higashi H, Nairn AC and Greengard P (2003) Metabotropic mGlu5 receptors regulate adenosine A2A receptor signaling. *Proc Natl Acad Sci U S A* **100**:1322-1327.
- Niswender CM and Conn PJ (2010) Metabotropic glutamate receptors: physiology, pharmacology, and disease. *Annu Rev Pharmacol Toxicol* **50**:295-322.
- Niswender CM, Johnson KA, Miller NR, Ayala JE, Luo Q, Williams R, Saleh S, Orton D, Weaver CD and Conn PJ (2010) Context-dependent pharmacology exhibited by negative allosteric modulators of metabotropic glutamate receptor 7. *Mol Pharmacol* **77**:459-468.
- Niswender CM, Johnson KA, Weaver CD, Jones CK, Xiang Z, Luo Q, Rodriguez AL, Marlo JE, de Paulis T, Thompson AD, Days EL, Nalywajko T, Austin CA, Williams MB, Ayala JE, Williams R, Lindsley CW and Conn PJ (2008a) Discovery, characterization, and antiparkinsonian effect of novel positive allosteric modulators of metabotropic glutamate receptor 4. *Molecular pharmacology* **74**:1345-1358.

- Niswender CM, Jones CK, Lin X, Bubser M, Thompson Gray A, Blobaum AL, Engers DW, Rodriguez AL, Loch MT, Daniels JS, Lindsley CW, Hopkins CR, Javitch JA and Conn PJ (2016) Development and Antiparkinsonian Activity of VU0418506, a Selective Positive Allosteric Modulator of Metabotropic Glutamate Receptor 4 Homomers without Activity at mGlu2/4 Heteromers. *ACS Chem Neurosci* **7**:1201-1211.
- Niswender CM, Lebois EP, Luo Q, Kim K, Muchalski H, Yin H, Conn PJ and Lindsley CW (2008b) Positive allosteric modulators of the metabotropic glutamate receptor subtype 4 (mGluR4): Part I. Discovery of pyrazolo[3,4-d]pyrimidines as novel mGluR4 positive allosteric modulators. *Bioorg Med Chem Lett* **18**:5626-5630.
- Noetzel MJ, Gregory KJ, Vinson PN, Manka JT, Stauffer SR, Lindsley CW, Niswender CM, Xiang Z and Conn PJ (2013) A Novel Metabotropic Glutamate Receptor 5 Positive Allosteric Modulator Acts at a Unique Site and Confers Stimulus Bias to mGlu5 Signaling. *Molecular pharmacology*.
- Noetzel MJ, Rook JM, Vinson PN, Cho HP, Days E, Zhou Y, Rodriguez AL, Lavreysen H, Stauffer SR, Niswender CM, Xiang Z, Daniels JS, Jones CK, Lindsley CW, Weaver CD and Conn PJ (2012) Functional impact of allosteric agonist activity of selective positive allosteric modulators of metabotropic glutamate receptor subtype 5 in regulating central nervous system function. *Mol Pharmacol* **81**:120-133.
- Nomura A, Shigemoto R, Nakamura Y, Okamoto N, Mizuno N and Nakanishi S (1994) Developmentally regulated postsynaptic localization of a metabotropic glutamate receptor in rat rod bipolar cells. *Cell* **77**:361-369.
- O'Brien DE, Shaw DM, Cho HP, Cross AJ, Wesolowski SS, Felts AS, Bergare J, Elmore CS, Lindsley CW, Niswender CM and Conn PJ (2018) Differential Pharmacology and Binding of mGlu2 Receptor Allosteric Modulators. *Mol Pharmacol* **93**:526-540.

- O'Brien JA, Lemaire W, Chen TB, Chang RS, Jacobson MA, Ha SN, Lindsley CW, Schaffhauser HJ, Sur C, Pettibone DJ, Conn PJ and Williams DL, Jr. (2003) A family of highly selective allosteric modulators of the metabotropic glutamate receptor subtype 5. *Mol Pharmacol* **64**:731-740.
- O'Brien JA, Lemaire W, Wittmann M, Jacobson MA, Ha SN, Wisnoski DD, Lindsley CW, Schaffhauser HJ, Rowe B, Sur C, Duggan ME, Pettibone DJ, Conn PJ and Williams DL, Jr. (2004) A novel selective allosteric modulator potentiates the activity of native metabotropic glutamate receptor subtype 5 in rat forebrain. *J Pharmacol Exp Ther* **309**:568-577.
- O'Connor E, Allen LE, Bradshaw K, Boylan J, Moore AT and Trump D (2006) Congenital stationary night blindness associated with mutations in GRM6 encoding glutamate receptor mGluR6. *Br J Ophthalmol* **90**:653-654.
- O'Connor RM and Cryan JF (2013) The effects of mGlu(7) receptor modulation in behavioural models sensitive to antidepressant action in two mouse strains. *Behav Pharmacol* **24**:105-113.
- O'Connor RM, Finger BC, Flor PJ and Cryan JF (2010) Metabotropic glutamate receptor 7: at the interface of cognition and emotion. *Eur J Pharmacol* **639**:123-131.
- Okamoto N, Hori S, Akazawa C, Hayashi Y, Shigemoto R, Mizuno N and Nakanishi S (1994) Molecular characterization of a new metabotropic glutamate receptor mGluR7 coupled to inhibitory cyclic AMP signal transduction. *J Biol Chem* **269**:1231-1236.
- Olivero G, Bonfiglio T, Vergassola M, Usai C, Riozzi B, Battaglia G, Nicoletti F and Pittaluga A (2017) Immuno-pharmacological characterization of group II metabotropic glutamate receptors controlling glutamate exocytosis in mouse cortex and spinal cord. *Br J Pharmacol* **174**:4785-4796.
- Ornstein PL, Arnold MB, Bleisch TJ, Wright RA, Wheeler WJ and Schoepp DD (1998) [3H]LY341495, a highly potent, selective and novel radioligand for labeling Group II metabotropic glutamate receptors. *Bioorg Med Chem Lett* **8**:1919-1922.

- Ossowska K, Konieczny J, Wardas J, Pietraszek M, Kuter K, Wolfarth S and Pilc A (2007) An influence of ligands of metabotropic glutamate receptor subtypes on parkinsonian-like symptoms and the striatopallidal pathway in rats. *Amino Acids* **32**:179-188.
- Otani S, Daniel H, Takita M and Crepel F (2002) Long-term depression induced by postsynaptic group II metabotropic glutamate receptors linked to phospholipase C and intracellular calcium rises in rat prefrontal cortex. *J Neurosci* **22**:3434-3444.
- Page G, Khidir FA, Pain S, Barrier L, Fauconneau B, Guillard O, Piriou A and Hugon J (2006) Group I metabotropic glutamate receptors activate the p70S6 kinase via both mammalian target of rapamycin (mTOR) and extracellular signal-regulated kinase (ERK 1/2) signaling pathways in rat striatal and hippocampal synaptoneurosomes. *Neurochem Int* **49**:413-421.
- Palazzo E, Fu Y, Ji G, Maione S and Neugebauer V (2008) Group III mGluR7 and mGluR8 in the amygdala differentially modulate nocifensive and affective pain behaviors. *Neuropharmacology* **55**:537-545.
- Palazzo E, Marabese I, de Novellis V, Rossi F and Maione S (2016) Metabotropic Glutamate Receptor 7: From Synaptic Function to Therapeutic Implications. *Curr Neuropharmacol* **14**:504-513.
- Palazzo E, Romano R, Luongo L, Boccella S, De Gregorio D, Giordano ME, Rossi F, Marabese I, Scafuro MA, de Novellis V and Maione S (2015) MMPIP, an mGluR7-selective negative allosteric modulator, alleviates pain and normalizes affective and cognitive behavior in neuropathic mice. *Pain* **156**:1060-1073.
- Palucha-Poniewiera A, Klodzinska A, Stachowicz K, Tokarski K, Hess G, Schann S, Frauli M, Neuville P and Pilc A (2008) Peripheral administration of group III mGlu receptor agonist ACPT-I exerts potential antipsychotic effects in rodents. *Neuropharmacology* **55**:517-524.
- Palucha-Poniewiera A and Pilc A (2013) A selective mGlu7 receptor antagonist MMPIP reversed antidepressant-like effects of AMN082 in rats. *Behav Brain Res* **238**:109-112.
- Palucha A, Klak K, Branski P, van der Putten H, Flor PJ and Pilc A (2007) Activation of the mGlu7 receptor elicits antidepressant-like effects in mice. *Psychopharmacology (Berl)* **194**:555-562.

- Palucha A, Tatarczynska E, Branski P, Szewczyk B, Wieronska JM, Klak K, Chojnacka-Wojcik E, Nowak G and Pilc A (2004) Group III mGlu receptor agonists produce anxiolytic- and antidepressant-like effects after central administration in rats. *Neuropharmacology* **46**:151-159.
- Panaccione I, Iacovelli L, di Nuzzo L, Nardecchia F, Mauro G, Janiri D, De Blasi A, Sani G, Nicoletti F and Orlando R (2017) Paradoxical sleep deprivation in rats causes a selective reduction in the expression of type-2 metabotropic glutamate receptors in the hippocampus. *Pharmacol Res* **117**:46-53.
- Pandey S, Mahato PK and Bhattacharyya S (2014) Metabotropic glutamate receptor 1 recycles to the cell surface in protein phosphatase 2A-dependent manner in non-neuronal and neuronal cell lines. *J Neurochem* **131**:602-614.
- Pandya NJ, Klaassen RV, van der Schors RC, Slotman JA, Houtsmuller A, Smit AB and Li KW (2016) Group 1 metabotropic glutamate receptors 1 and 5 form a protein complex in mouse hippocampus and cortex. *Proteomics* **16**:2698-2705.
- Park EH, Lee SW, Moon SW, Suh HR, Kim YI and Han HC (2019) Activation of peripheral group III metabotropic glutamate receptors inhibits pain transmission by decreasing neuronal excitability in the CFA-inflamed knee joint. *Neurosci Lett* **694**:111-115.
- Parmentier-Batteur S, Hutson PH, Menzel K, Uslaner JM, Mattson BA, O'Brien JA, Magliaro BC, Forest T, Stump CA, Tynebor RM, Anthony NJ, Tucker TJ, Zhang XF, Gomez R, Huszar SL, Lambeng N, Faure H, Le Poul E, Poli S, Rosahl TW, Rocher JP, Hargreaves R and Williams TM (2014) Mechanism based neurotoxicity of mGlu5 positive allosteric modulators--development challenges for a promising novel antipsychotic target. *Neuropharmacology* **82**:161-173.
- Parmentier-Batteur S, O'Brien JA, Doran S, Nguyen SJ, Flick RB, Uslaner JM, Chen H, Finger EN, Williams TM, Jacobson MA and Hutson PH (2012) Differential effects of the mGluR5 positive allosteric modulator CDPPB in the cortex and striatum following repeated administration. *Neuropharmacology* **62**:1453-1460.

- Patel JB, Martin C and Malick JB (1982) Differential antagonism of the anticonflict effects of typical and atypical anxiolytics. *Eur J Pharmacol* **86**:295-298.
- Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, Avedisova AS, Bardenstein LM, Gurovich IY, Morozova MA, Mosolov SN, Neznanov NG, Reznik AM, Smulevich AB, Tochilov VA, Johnson BG, Monn JA and Schoepp DD (2007) Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. *Nat Med* **13**:1102-1107.
- Pecknold JC, McClure DJ, Appeltauer L, Wrzesinski L and Allan T (1982) Treatment of anxiety using fenobam (a nonbenzodiazepine) in a double-blind standard (diazepam) placebo-controlled study. *J Clin Psychopharmacol* **2**:129-133.
- Pekhletski R, Gerlai R, Overstreet LS, Huang XP, Agopyan N, Slater NT, Abramow-Newerly W, Roder JC and Hampson DR (1996) Impaired cerebellar synaptic plasticity and motor performance in mice lacking the mGluR4 subtype of metabotropic glutamate receptor. *J Neurosci* **16**:6364-6373.
- Pellegrini-Giampietro DE, Cozzi A, Peruginelli F, Leonardi P, Meli E, Pellicciari R and Moroni F (1999) 1-Aminoindan-1,5-dicarboxylic acid and (S)-(+)-2-(3'-carboxybicyclo[1.1.1] pentyl)-glycine, two mGlu1 receptor-preferring antagonists, reduce neuronal death in in vitro and in vivo models of cerebral ischaemia. *Eur J Neurosci* **11**:3637-3647.
- Pellicciari R, Luneia R, Costantino G, Marinozzi M, Natalini B, Jakobsen P, Kanstrup A, Lombardi G, Moroni F and Thomsen C (1995) 1-Aminoindan-1,5-dicarboxylic acid: a novel antagonist at phospholipase C-linked metabotropic glutamate receptors. *J Med Chem* **38**:3717-3719.
- Pereira V and Goudet C (2018) Emerging Trends in Pain Modulation by Metabotropic Glutamate Receptors. *Front Mol Neurosci* **11**:464.
- Perez-Benito L, Doornbos MLJ, Cordomi A, Peeters L, Lavreysen H, Pardo L and Tresadern G (2017) Molecular Switches of Allosteric Modulation of the Metabotropic Glutamate 2 Receptor. *Structure* **25**:1153-1162 e1154.

- Perez-Garcia G, De Gasperi R, Gama Sosa MA, Perez GM, Otero-Pagan A, Tschiffely A, McCarron RM, Ahlers ST, Elder GA and Gandy S (2018) PTSD-Related Behavioral Traits in a Rat Model of Blast-Induced mTBI Are Reversed by the mGluR2/3 Receptor Antagonist BCI-838. *eNeuro* **5**.
- Perroy J, El Far O, Bertaso F, Pin JP, Betz H, Bockaert J and Fagni L (2002) PICK1 is required for the control of synaptic transmission by the metabotropic glutamate receptor 7. *EMBO J* **21**:2990-2999.
- Perroy J, Prezeau L, De Waard M, Shigemoto R, Bockaert J and Fagni L (2000) Selective blockade of P/Q-type calcium channels by the metabotropic glutamate receptor type 7 involves a phospholipase C pathway in neurons. *J Neurosci* **20**:7896-7904.
- Perry CJ, Reed F, Zbukvic IC, Kim JH and Lawrence AJ (2016) The metabotropic glutamate 5 receptor is necessary for extinction of cocaine-associated cues. *Br J Pharmacol* **173**:1085-1094.
- Peterlik D, Stangl C, Bauer A, Bludau A, Keller J, Grabski D, Killian T, Schmidt D, Zajicek F, Jaeschke G, Lindemann L, Reber SO, Flor PJ and Uschold-Schmidt N (2017) Blocking metabotropic glutamate receptor subtype 5 relieves maladaptive chronic stress consequences. *Brain Behav Immun* **59**:79-92.
- Pietraszek M, Rogoz Z, Wolfarth S and Ossowska K (2004) Opposite influence of MPEP, an mGluR5 antagonist, on the locomotor hyperactivity induced by PCP and amphetamine. *J Physiol Pharmacol* **55**:587-593.
- Pin JP and Bettler B (2016) Organization and functions of mGlu and GABAB receptor complexes. *Nature* **540**:60-68.
- Pin JP, De Colle C, Bessis AS and Acher F (1999) New perspectives for the development of selective metabotropic glutamate receptor ligands. *Eur J Pharmacol* **375**:277-294.
- Pin JP, Waeber C, Prezeau L, Bockaert J and Heinemann SF (1992) Alternative splicing generates metabotropic glutamate receptors inducing different patterns of calcium release in *Xenopus* oocytes. *Proc Natl Acad Sci U S A* **89**:10331-10335.
- Pitsch J, Schoch S, Gueler N, Flor PJ, van der Putten H and Becker AJ (2007) Functional role of mGluR1 and mGluR4 in pilocarpine-induced temporal lobe epilepsy. *Neurobiol Dis* **26**:623-633.

- Pitsikas N, Kaffe E and Markou A (2012) The metabotropic glutamate 2/3 receptor antagonist LY341495 differentially affects recognition memory in rats. *Behav Brain Res* **230**:374-379.
- Pittaluga A (2016) Presynaptic Release-Regulating mGlu1 Receptors in Central Nervous System. *Front Pharmacol* **7**:295.
- Pittolo S, Gomez-Santacana X, Eckelt K, Rovira X, Dalton J, Goudet C, Pin JP, Llobet A, Giraldo J, Llebaria A and Gorostiza P (2014) An allosteric modulator to control endogenous G protein-coupled receptors with light. *Nat Chem Biol* **10**:813-815.
- Pizzi M, Benarese M, Boroni F, Goffi F, Valerio A and Spano PF (2000) Neuroprotection by metabotropic glutamate receptor agonists on kainate-induced degeneration of motor neurons in spinal cord slices from adult rat. *Neuropharmacology* **39**:903-910.
- Platt DM, Rowlett JK and Spealman RD (2008) Attenuation of cocaine self-administration in squirrel monkeys following repeated administration of the mGluR5 antagonist MPEP: comparison with dizocilpine. *Psychopharmacology (Berl)* **200**:167-176.
- Podkowa K, Pilc A, Podkowa A, Salat K, Marciniak M and Palucha-Poniewiera A (2018) The potential antidepressant action and adverse effects profile of scopolamine co-administered with the mGlu7 receptor allosteric agonist AMN082 in mice. *Neuropharmacology* **141**:214-222.
- Podkowa K, Pochwat B, Branski P, Pilc A and Palucha-Poniewiera A (2016) Group II mGlu receptor antagonist LY341495 enhances the antidepressant-like effects of ketamine in the forced swim test in rats. *Psychopharmacology (Berl)* **233**:2901-2914.
- Podkowa K, Rzezniczek S, Marciniak M, Acher F, Pilc A and Palucha-Poniewiera A (2015) A novel mGlu4 selective agonist LSP4-2022 increases behavioral despair in mouse models of antidepressant action. *Neuropharmacology* **97**:338-345.
- Ponnazhagan R, Harms AS, Thome AD, Jurkuvenaite A, Gogliotti R, Niswender CM, Conn PJ and Standaert DG (2016) The Metabotropic Glutamate Receptor 4 Positive Allosteric Modulator

ADX88178 Inhibits Inflammatory Responses in Primary Microglia. *J Neuroimmune Pharmacol* **11**:231-237.

Popoli P, Pezzola A, Torvinen M, Reggio R, Pintor A, Scarchilli L, Fuxe K and Ferre S (2001) The selective mGlu(5) receptor agonist CHPG inhibits quinpirole-induced turning in 6-hydroxydopamine-lesioned rats and modulates the binding characteristics of dopamine D(2) receptors in the rat striatum: interactions with adenosine A(2a) receptors. *Neuropsychopharmacology* **25**:505-513.

Porter RH, Jaeschke G, Spooren W, Ballard TM, Buttelmann B, Kolczewski S, Peters JU, Prinssen E, Wichmann J, Vieira E, Muhlemann A, Gatti S, Mutel V and Malherbe P (2005) Fenobam: a clinically validated nonbenzodiazepine anxiolytic is a potent, selective, and noncompetitive mGlu5 receptor antagonist with inverse agonist activity. *J Pharmacol Exp Ther* **315**:711-721.

Poutiainen P, Kil KE, Zhang Z, Kuruppu D, Tannous B and Brownell AL (2015) Co-operative binding assay for the characterization of mGlu4 allosteric modulators. *Neuropharmacology* **97**:142-148.

Prickett TD, Wei X, Cardenas-Navia I, Teer JK, Lin JC, Walia V, Gartner J, Jiang J, Cherukuri PF, Molinolo A, Davies MA, Gershenwald JE, Stemke-Hale K, Rosenberg SA, Margulies EH and Samuels Y (2011) Exon capture analysis of G protein-coupled receptors identifies activating mutations in GRM3 in melanoma. *Nat Genet* **43**:1119-1126.

Pula G, Mundell SJ, Roberts PJ and Kelly E (2004) Agonist-independent internalization of metabotropic glutamate receptor 1a is arrestin- and clathrin-dependent and is suppressed by receptor inverse agonists. *J Neurochem* **89**:1009-1020.

Purgert CA, Izumi Y, Jong YJ, Kumar V, Zorumski CF and O'Malley KL (2014) Intracellular mGluR5 can mediate synaptic plasticity in the hippocampus. *J Neurosci* **34**:4589-4598.

Quiroz JA, Tamburri P, Deptula D, Banken L, Beyer U, Rabbia M, Parkar N, Fontoura P and Santarelli L (2016) Efficacy and Safety of Basimglurant as Adjunctive Therapy for Major Depression: A Randomized Clinical Trial. *JAMA Psychiatry* **73**:675-684.

- Rahman S and Neuman RS (1996) Characterization of metabotropic glutamate receptor-mediated facilitation of N-methyl-D-aspartate depolarization of neocortical neurones. *Br J Pharmacol* **117**:675-683.
- Raka F, Di Sebastiano AR, Kulhawy SC, Ribeiro FM, Godin CM, Caetano FA, Angers S and Ferguson SS (2015) Ca(2+)/calmodulin-dependent protein kinase II interacts with group I metabotropic glutamate and facilitates receptor endocytosis and ERK1/2 signaling: role of beta-amyloid. *Mol Brain* **8**:21.
- Rao AM, Hatcher JF and Dempsey RJ (2000) Neuroprotection by group I metabotropic glutamate receptor antagonists in forebrain ischemia of gerbil. *Neurosci Lett* **293**:1-4.
- Reilmann R, Rouzade-Dominguez ML, Saft C, Sussmuth SD, Priller J, Rosser A, Rickards H, Schols L, Pezous N, Gasparini F, Johns D, Landwehrmeyer GB and Gomez-Mancilla B (2015) A randomized, placebo-controlled trial of AFQ056 for the treatment of chorea in Huntington's disease. *Mov Disord* **30**:427-431.
- Ribeiro FM, Paquet M, Ferreira LT, Cregan T, Swan P, Cregan SP and Ferguson SS (2010) Metabotropic glutamate receptor-mediated cell signaling pathways are altered in a mouse model of Huntington's disease. *J Neurosci* **30**:316-324.
- Ribeiro FM, Vieira LB, Pires RG, Olmo RP and Ferguson SS (2017) Metabotropic glutamate receptors and neurodegenerative diseases. *Pharmacol Res* **115**:179-191.
- Ritter-Makinson SL, Paquet M, Bogenpohl JW, Rodin RE, Chris Yun C, Weinman EJ, Smith Y and Hall RA (2017) Group II metabotropic glutamate receptor interactions with NHERF scaffold proteins: Implications for receptor localization in brain. *Neuroscience* **353**:58-75.
- Robbe D, Kopf M, Remaury A, Bockaert J and Manzoni OJ (2002) Endogenous cannabinoids mediate long-term synaptic depression in the nucleus accumbens. *Proc Natl Acad Sci U S A* **99**:8384-8388.
- Roche D, Gil D and Giraldo J (2014) Mathematical modeling of G protein-coupled receptor function: what can we learn from empirical and mechanistic models? *Adv Exp Med Biol* **796**:159-181.

- Roche KW, Tu JC, Petralia RS, Xiao B, Wenthold RJ and Worley PF (1999) Homer 1b regulates the trafficking of group I metabotropic glutamate receptors. *J Biol Chem* **274**:25953-25957.
- Rodd ZA, McKinzie DL, Bell RL, McQueen VK, Murphy JM, Schoepp DD and McBride WJ (2006) The metabotropic glutamate 2/3 receptor agonist LY404039 reduces alcohol-seeking but not alcohol self-administration in alcohol-preferring (P) rats. *Behav Brain Res* **171**:207-215.
- Rodrigues RJ, Alfaro TM, Rebola N, Oliveira CR and Cunha RA (2005) Co-localization and functional interaction between adenosine A(2A) and metabotropic group 5 receptors in glutamatergic nerve terminals of the rat striatum. *J Neurochem* **92**:433-441.
- Rodriguez AL, Grier MD, Jones CK, Herman EJ, Kane AS, Smith RL, Williams R, Zhou Y, Marlo JE, Days EL, Blatt TN, Jadhav S, Menon UN, Vinson PN, Rook JM, Stauffer SR, Niswender CM, Lindsley CW, Weaver CD and Conn PJ (2010) Discovery of novel allosteric modulators of metabotropic glutamate receptor subtype 5 reveals chemical and functional diversity and in vivo activity in rat behavioral models of anxiolytic and antipsychotic activity. *Mol Pharmacol* **78**:1105-1123.
- Rodriguez AL, Nong Y, Sekaran NK, Alagille D, Tamagnan GD and Conn PJ (2005) A close structural analog of 2-methyl-6-(phenylethynyl)-pyridine acts as a neutral allosteric site ligand on metabotropic glutamate receptor subtype 5 and blocks the effects of multiple allosteric modulators. *Mol Pharmacol* **68**:1793-1802.
- Rook JM, Noetzel MJ, Pouliot WA, Bridges TM, Vinson PN, Cho HP, Zhou Y, Gogliotti RD, Manka JT, Gregory KJ, Stauffer SR, Dudek FE, Xiang Z, Niswender CM, Daniels JS, Jones CK, Lindsley CW and Conn PJ (2013) Unique signaling profiles of positive allosteric modulators of metabotropic glutamate receptor subtype 5 determine differences in in vivo activity. *Biological psychiatry* **73**:501-509.
- Rook JM, Tantawy MN, Ansari MS, Felts AS, Stauffer SR, Emmitte KA, Kessler RM, Niswender CM, Daniels JS, Jones CK, Lindsley CW and Conn PJ (2015a) Relationship between in vivo receptor

occupancy and efficacy of metabotropic glutamate receptor subtype 5 allosteric modulators with different in vitro binding profiles. *Neuropsychopharmacology* **40**:755-765.

Rook JM, Xiang Z, Lv X, Ghoshal A, Dickerson JW, Bridges TM, Johnson KA, Foster DJ, Gregory KJ, Vinson PN, Thompson AD, Byun N, Collier RL, Bubser M, Nedelcovych MT, Gould RW, Stauffer SR, Daniels JS, Niswender CM, Lavreysen H, Mackie C, Conde-Ceide S, Alcazar J, Bartolome-Nebreda JM, Macdonald GJ, Talpos JC, Steckler T, Jones CK, Lindsley CW and Conn PJ (2015b) Biased mGlu5-Positive Allosteric Modulators Provide In Vivo Efficacy without Potentiating mGlu5 Modulation of NMDAR Currents. *Neuron* **86**:1029-1040.

Rorick-Kehn LM, Johnson BG, Burkey JL, Wright RA, Calligaro DO, Marek GJ, Nisenbaum ES, Catlow JT, Kingston AE, Giera DD, Herin MF, Monn JA, McKinzie DL and Schoepp DD (2007a) Pharmacological and pharmacokinetic properties of a structurally novel, potent, and selective metabotropic glutamate 2/3 receptor agonist: in vitro characterization of agonist (-)-(1R,4S,5S,6S)-4-amino-2-sulfonylbicyclo[3.1.0]-hexane-4,6-dicarboxylic acid (LY404039). *J Pharmacol Exp Ther* **321**:308-317.

Rorick-Kehn LM, Johnson BG, Knitowski KM, Salhoff CR, Witkin JM, Perry KW, Griffey KI, Tizzano JP, Monn JA, McKinzie DL and Schoepp DD (2007b) In vivo pharmacological characterization of the structurally novel, potent, selective mGlu2/3 receptor agonist LY404039 in animal models of psychiatric disorders. *Psychopharmacology (Berl)* **193**:121-136.

Rorick-Kehn LM, Perkins EJ, Knitowski KM, Hart JC, Johnson BG, Schoepp DD and McKinzie DL (2006) Improved bioavailability of the mGlu2/3 receptor agonist LY354740 using a prodrug strategy: in vivo pharmacology of LY544344. *J Pharmacol Exp Ther* **316**:905-913.

Rossi F, Marabese I, De Chiaro M, Boccella S, Luongo L, Guida F, De Gregorio D, Giordano C, de Novellis V, Palazzo E and Maione S (2014) Dorsal striatum metabotropic glutamate receptor 8 affects nocifensive responses and rostral ventromedial medulla cell activity in neuropathic pain conditions. *J Neurophysiol* **111**:2196-2209.

- Rouzade-Dominguez ML, Pezous N, David OJ, Tutuian R, Bruley des Varannes S, Tack J, Malfertheiner P, Allescher HD, Ufer M and Ruhl A (2017) The selective metabotropic glutamate receptor 5 antagonist mavoglurant (AFQ056) reduces the incidence of reflux episodes in dogs and patients with moderate to severe gastroesophageal reflux disease. *Neurogastroenterol Motil* **29**.
- Rovira X, Malhaire F, Scholler P, Rodrigo J, Gonzalez-Bulnes P, Llebaria A, Pin JP, Giraldo J and Goudet C (2015) Overlapping binding sites drive allosteric agonism and positive cooperativity in type 4 metabotropic glutamate receptors. *FASEB J* **29**:116-130.
- Rovira X, Trapero A, Pittolo S, Zussy C, Faucherre A, Jopling C, Giraldo J, Pin JP, Gorostiza P, Goudet C and Llebaria A (2016) OptoGluNAM4.1, a Photoswitchable Allosteric Antagonist for Real-Time Control of mGlu4 Receptor Activity. *Cell Chem Biol* **23**:929-934.
- Rowe BA, Schaffhauser H, Morales S, Lubbers LS, Bonnefous C, Kamenecka TM, McQuiston J and Daggett LP (2008) Transposition of three amino acids transforms the human metabotropic glutamate receptor (mGluR)-3-positive allosteric modulation site to mGluR2, and additional characterization of the mGluR2-positive allosteric modulation site. *J Pharmacol Exp Ther* **326**:240-251.
- Rutrick D, Stein DJ, Subramanian G, Smith B, Fava M, Hasler G, Cha JH, Gasparini F, Donchev T, Ocwieja M, Johns D and Gomez-Mancilla B (2017) Mavoglurant Augmentation in OCD Patients Resistant to Selective Serotonin Reuptake Inhibitors: A Proof-of-Concept, Randomized, Placebo-Controlled, Phase 2 Study. *Adv Ther* **34**:524-541.
- Saini SM, Mancuso SG, Mostaid MS, Liu C, Pantelis C, Everall IP and Bousman CA (2017) Meta-analysis supports GWAS-implicated link between GRM3 and schizophrenia risk. *Transl Psychiatry* **7**:e1196.
- Salih H, Anghelescu I, Kezic I, Sinha V, Hoeben E, Van Nueten L, De Smedt H and De Boer P (2015) Pharmacokinetic and pharmacodynamic characterisation of JNJ-40411813, a positive allosteric modulator of mGluR2, in two randomised, double-blind phase-I studies. *J Psychopharmacol* **29**:414-425.

- Sallese M, Salvatore L, D'Urbano E, Sala G, Storto M, Launey T, Nicoletti F, Knopfel T and De Blasi A (2000) The G-protein-coupled receptor kinase GRK4 mediates homologous desensitization of metabotropic glutamate receptor 1. *FASEB J* **14**:2569-2580.
- Salling MC, Faccidomo S and Hodge CW (2008) Nonselective suppression of operant ethanol and sucrose self-administration by the mGluR7 positive allosteric modulator AMN082. *Pharmacol Biochem Behav* **91**:14-20.
- Salt TE and Eaton SA (1995) Distinct presynaptic metabotropic receptors for L-AP4 and CCG1 on GABAergic terminals: pharmacological evidence using novel alpha-methyl derivative mGluR antagonists, MAP4 and MCCG, in the rat thalamus in vivo. *Neuroscience* **65**:5-13.
- Sanders SJ, Murtha MT, Gupta AR, Murdoch JD, Raubeson MJ, Willsey AJ, Ercan-Sencicek AG, DiLullo NM, Parikshak NN, Stein JL, Walker MF, Ober GT, Teran NA, Song Y, El-Fishawy P, Murtha RC, Choi M, Overton JD, Bjornson RD, Carriero NJ, Meyer KA, Bilguvar K, Mane SM, Sestan N, Lifton RP, Gunel M, Roeder K, Geschwind DH, Devlin B and State MW (2012) De novo mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature* **485**:237-241.
- Sansig G, Bushell TJ, Clarke VR, Rozov A, Burnashev N, Portet C, Gasparini F, Schmutz M, Klebs K, Shigemoto R, Flor PJ, Kuhn R, Knoepfel T, Schroeder M, Hampson DR, Collett VJ, Zhang C, Duvoisin RM, Collingridge GL and van Der Putten H (2001) Increased seizure susceptibility in mice lacking metabotropic glutamate receptor 7. *J Neurosci* **21**:8734-8745.
- Sartorius LJ, Nagappan G, Lipska BK, Lu B, Sei Y, Ren-Patterson R, Li Z, Weinberger DR and Harrison PJ (2006) Alternative splicing of human metabotropic glutamate receptor 3. *J Neurochem* **96**:1139-1148.
- Satow A, Suzuki G, Maehara S, Hikichi H, Murai T, Murai T, Kawagoe-Takaki H, Hata M, Ito S, Ozaki S, Kawamoto H and Ohta H (2009) Unique antipsychotic activities of the selective metabotropic glutamate receptor 1 allosteric antagonist 2-cyclopropyl-5-[1-(2-fluoro-3-pyridinyl)-5-methyl-1H-1,2,3-triazol-4-yl]-2,3-dihydro-1H-isoindol-1-one. *J Pharmacol Exp Ther* **330**:179-190.

- Saugstad JA, Kinzie JM, Mulvihill ER, Segerson TP and Westbrook GL (1994) Cloning and expression of a new member of the L-2-amino-4-phosphonobutyric acid-sensitive class of metabotropic glutamate receptors. *Mol Pharmacol* **45**:367-372.
- Saugstad JA, Kinzie JM, Shinohara MM, Segerson TP and Westbrook GL (1997) Cloning and expression of rat metabotropic glutamate receptor 8 reveals a distinct pharmacological profile. *Mol Pharmacol* **51**:119-125.
- Saugstad JA, Segerson TP and Westbrook GL (1996) Metabotropic glutamate receptors activate G-protein-coupled inwardly rectifying potassium channels in *Xenopus* oocytes. *J Neurosci* **16**:5979-5985.
- Saunders R, Nahorski SR and Challiss RA (1998) A modulatory effect of extracellular Ca²⁺ on type 1alpha metabotropic glutamate receptor-mediated signalling. *Neuropharmacology* **37**:273-276.
- Scandroglio P, Brusa R, Lozza G, Mancini I, Petro R, Reggiani A and Beltramo M (2010) Evaluation of cannabinoid receptor 2 and metabotropic glutamate receptor 1 functional responses using a cell impedance-based technology. *Journal of biomolecular screening* **15**:1238-1247.
- Schaffhauser H, Cai Z, Hubalek F, Macek TA, Pohl J, Murphy TJ and Conn PJ (2000) cAMP-dependent protein kinase inhibits mGluR2 coupling to G-proteins by direct receptor phosphorylation. *J Neurosci* **20**:5663-5670.
- Schaffhauser H, Knoflach F, Pink JR, Bleuel Z, Cartmell J, Goepfert F, Kemp JA, Richards JG, Adam G and Mutel V (1998) Multiple pathways for regulation of the KCl-induced [3H]-GABA release by metabotropic glutamate receptors, in primary rat cortical cultures. *Brain Res* **782**:91-104.
- Schaffhauser H, Rowe BA, Morales S, Chavez-Noriega LE, Yin R, Jachec C, Rao SP, Bain G, Pinkerton AB, Vernier JM, Bristow LJ, Varney MA and Daggett LP (2003) Pharmacological characterization and identification of amino acids involved in the positive modulation of metabotropic glutamate receptor subtype 2. *Mol Pharmacol* **64**:798-810.

- Scherer SW, Soder S, Duvoisin RM, Huizenga JJ and Tsui LC (1997) The human metabotropic glutamate receptor 8 (GRM8) gene: a disproportionately large gene located at 7q31.3-q32.1. *Genomics* **44**:232-236.
- Schkeryantz JM, Kingston AE and Johnson MP (2007) Prospects for metabotropic glutamate 1 receptor antagonists in the treatment of neuropathic pain. *J Med Chem* **50**:2563-2568.
- Schoepp DD (2001) Unveiling the functions of presynaptic metabotropic glutamate receptors in the central nervous system. *J Pharmacol Exp Ther* **299**:12-20.
- Schoepp DD, Goldsworthy J, Johnson BG, Salhoff CR and Baker SR (1994) 3,5-dihydroxyphenylglycine is a highly selective agonist for phosphoinositide-linked metabotropic glutamate receptors in the rat hippocampus. *J Neurochem* **63**:769-772.
- Schoepp DD, Johnson BG, Wright RA, Salhoff CR, Mayne NG, Wu S, Cockerman SL, Burnett JP, Belegaje R, Bleakman D and Monn JA (1997) LY354740 is a potent and highly selective group II metabotropic glutamate receptor agonist in cells expressing human glutamate receptors. *Neuropharmacology* **36**:1-11.
- Schoepp DD, Wright RA, Levine LR, Gaydos B and Potter WZ (2003) LY354740, an mGlu2/3 receptor agonist as a novel approach to treat anxiety/stress. *Stress* **6**:189-197.
- Scholler P, Nevoltris D, de Bundel D, Bossi S, Moreno-Delgado D, Rovira X, Moller TC, El Moustaine D, Mathieu M, Blanc E, McLean H, Dupuis E, Mathis G, Trinquet E, Daniel H, Valjent E, Baty D, Chames P, Rondard P and Pin JP (2017) Allosteric nanobodies uncover a role of hippocampal mGlu2 receptor homodimers in contextual fear consolidation. *Nat Commun* **8**:1967.
- Schreiber R, Lowe D, Voerste A and De Vry J (2000) LY354740 affects startle responding but not sensorimotor gating or discriminative effects of phencyclidine. *Eur J Pharmacol* **388**:R3-4.
- Schroder UH, Muller T, Schreiber R, Stolle A, Zuschratter W, Balschun D, Jork R and Reymann KG (2008) The potent non-competitive mGlu1 receptor antagonist BAY 36-7620 differentially affects synaptic

- plasticity in area cornu ammonis 1 of rat hippocampal slices and impairs acquisition in the water maze task in mice. *Neuroscience* **157**:385-395.
- Schroeder JP, Overstreet DH and Hodge CW (2005) The mGluR5 antagonist MPEP decreases operant ethanol self-administration during maintenance and after repeated alcohol deprivations in alcohol-preferring (P) rats. *Psychopharmacology (Berl)* **179**:262-270.
- Schulz HL, Stohr H and Weber BH (2002) Characterization of three novel isoforms of the metabotropic glutamate receptor 7 (GRM7). *Neurosci Lett* **326**:37-40.
- Sebastianutto I, Goyet E, Andreoli L, Font-Ingles J, Moreno-Delgado D, Bouquier N, Jahannault-Talignani C, Moutin E, Di Menna L, Maslava N, Pin JP, Fagni L, Nicoletti F, Ango F, Cenci MA and Perroy J (2020) D1-mGlu5 heteromers mediate noncanonical dopamine signaling in Parkinson's disease. *J Clin Invest* **130**:1168-1184.
- Seebahn A, Rose M and Enz R (2008) RanBPM is expressed in synaptic layers of the mammalian retina and binds to metabotropic glutamate receptors. *FEBS Lett* **582**:2453-2457.
- Seeman P (2013) An agonist at glutamate and dopamine D2 receptors, LY404039. *Neuropharmacology* **66**:87-88.
- Sekiyama N, Hayashi Y, Nakanishi S, Jane DE, Tse HW, Birse EF and Watkins JC (1996) Structure-activity relationships of new agonists and antagonists of different metabotropic glutamate receptor subtypes. *Br J Pharmacol* **117**:1493-1503.
- Selvam C, Goudet C, Oueslati N, Pin JP and Acher FC (2007) L-(+)-2-Amino-4-thiophosphonobutyric acid (L-thioAP4), a new potent agonist of group III metabotropic glutamate receptors: increased distal acidity affords enhanced potency. *J Med Chem* **50**:4656-4664.
- Selvam C, Lemasson IA, Brabet I, Oueslati N, Karaman B, Cabaye A, Tora AS, Commare B, Courtiol T, Cesarini S, McCort-Tranchepain I, Rigault D, Mony L, Bessiron T, McLean H, Leroux FR, Colobert F, Daniel H, Goupil-Lamy A, Bertrand HO, Goudet C, Pin JP and Acher FC (2018) Increased

- Potency and Selectivity for Group III Metabotropic Glutamate Receptor Agonists Binding at Dual sites. *J Med Chem* **61**:1969-1989.
- Sengmany K, Hellyer SD, Albold S, Wang T, Conn PJ, May LT, Christopoulos A, Leach K and Gregory KJ (2019) Kinetic and system bias as drivers of metabotropic glutamate receptor 5 allosteric modulator pharmacology. *Neuropharmacology* **149**:83-96.
- Sengmany K, Singh J, Stewart GD, Conn PJ, Christopoulos A and Gregory KJ (2017) Biased allosteric agonism and modulation of metabotropic glutamate receptor 5: Implications for optimizing preclinical neuroscience drug discovery. *Neuropharmacology* **115**:60-72.
- Sergeeva OA, Doreulee N, Chepkova AN, Kazmierczak T and Haas HL (2007) Long-term depression of cortico-striatal synaptic transmission by DHPG depends on endocannabinoid release and nitric oxide synthesis. *Eur J Neurosci* **26**:1889-1894.
- Servitja JM, Masgrau R, Pardo R, Sarri E, von Eichel-Streiber C, Gutkind JS and Picatoste F (2003) Metabotropic glutamate receptors activate phospholipase D in astrocytes through a protein kinase C-dependent and Rho-independent pathway. *Neuropharmacology* **44**:171-180.
- Servitja JM, Masgrau R, Sarri E and Picatoste F (1999) Group I metabotropic glutamate receptors mediate phospholipase D stimulation in rat cultured astrocytes. *J Neurochem* **72**:1441-1447.
- Shah UH and Gonzalez-Maeso J (2019) Serotonin and Glutamate Interactions in Preclinical Schizophrenia Models. *ACS Chem Neurosci* **10**:3068-3077.
- Shannon HE, Peters SC and Kingston AE (2005) Anticonvulsant effects of LY456236, a selective mGlu1 receptor antagonist. *Neuropharmacology* **49 Suppl 1**:188-195.
- Sharko AC and Hodge CW (2008) Differential modulation of ethanol-induced sedation and hypnosis by metabotropic glutamate receptor antagonists in C57BL/6J mice. *Alcohol Clin Exp Res* **32**:67-76.
- Sharon D, Vorobiov D and Dascal N (1997) Positive and negative coupling of the metabotropic glutamate receptors to a G protein-activated K⁺ channel, GIRK, in *Xenopus* oocytes. *J Gen Physiol* **109**:477-490.

- Sheffler DJ and Conn PJ (2008) Allosteric potentiators of metabotropic glutamate receptor subtype 1a differentially modulate independent signaling pathways in baby hamster kidney cells. *Neuropharmacology* **55**:419-427.
- Sheffler DJ, Wenthur CJ, Bruner JA, Carrington SJS, Vinson PN, Gogi KK, Blobaum AL, Morrison RD, Vamos M, Cosford NDP, Stauffer SR, Scott Daniels J, Niswender CM, Jeffrey Conn P and Lindsley CW (2012) Development of a novel, CNS-penetrant, metabotropic glutamate receptor 3 (mGlu3) NAM probe (ML289) derived from a closely related mGlu5 PAM. *Bioorganic & Medicinal Chemistry Letters* **22**:3921-3925.
- Shen Y, Rampino MA, Carroll RC and Nawy S (2012) G-protein-mediated inhibition of the Trp channel TRPM1 requires the Gbetagamma dimer. *Proc Natl Acad Sci U S A* **109**:8752-8757.
- Shigemoto R, Kinoshita A, Wada E, Nomura S, Ohishi H, Takada M, Flor PJ, Neki A, Abe T, Nakanishi S and Mizuno N (1997) Differential presynaptic localization of metabotropic glutamate receptor subtypes in the rat hippocampus. *J Neurosci* **17**:7503-7522.
- Shinozaki H and Shibuya I (1974) A new potent excitant, quisqualic acid: effects on crayfish neuromuscular junction. *Neuropharmacology* **13**:665-672.
- Silverman JL, Tolu SS, Barkan CL and Crawley JN (2010) Repetitive self-grooming behavior in the BTBR mouse model of autism is blocked by the mGluR5 antagonist MPEP. *Neuropsychopharmacology* **35**:976-989.
- Silverstein FS, Chen R and Johnston MV (1986) The glutamate analogue quisqualic acid is neurotoxic in striatum and hippocampus of immature rat brain. *Neurosci Lett* **71**:13-18.
- Slack RJ and Hall DA (2012) Development of operational models of receptor activation including constitutive receptor activity and their use to determine the efficacy of the chemokine CCL17 at the CC chemokine receptor CCR4. *Br J Pharmacol* **166**:1774-1792.
- Slawinska A, Wieronska JM, Stachowicz K, Marciniak M, Lason-Tyburkiewicz M, Gruca P, Papp M, Kusek M, Tokarski K, Doller D and Pilc A (2013) The antipsychotic-like effects of positive

- allosteric modulators of metabotropic glutamate mGlu4 receptors in rodents. *Br J Pharmacol* **169**:1824-1839.
- Smith FL, Smith PA, Dewey WL and Javed RR (2004) Effects of mGlu1 and mGlu5 metabotropic glutamate antagonists to reverse morphine tolerance in mice. *Eur J Pharmacol* **492**:137-142.
- Snyder EM, Philpot BD, Huber KM, Dong X, Fallon JR and Bear MF (2001) Internalization of ionotropic glutamate receptors in response to mGluR activation. *Nat Neurosci* **4**:1079-1085.
- Soloviev MM, Ciruela F, Chan WY and McIlhinney RA (1999) Identification, cloning and analysis of expression of a new alternatively spliced form of the metabotropic glutamate receptor mGluR1 mRNA1. *Biochim Biophys Acta* **1446**:161-166.
- Song Z, He CD, Liu J, Sun C, Lu P, Li L, Gao L, Zhang Y, Xu Y, Shan L, Liu Y, Zou W, Zhang Y, Gao H and Gao W (2012) Blocking glutamate-mediated signalling inhibits human melanoma growth and migration. *Exp Dermatol* **21**:926-931.
- Spampinato SF, Copani A, Nicoletti F, Sortino MA and Caraci F (2018) Metabotropic Glutamate Receptors in Glial Cells: A New Potential Target for Neuroprotection? *Front Mol Neurosci* **11**:414.
- Stachowicz K, Chojnacka-Wojcik E, Klak K and Pilc A (2006) Anxiolytic-like effects of group III mGlu receptor ligands in the hippocampus involve GABAA signaling. *Pharmacol Rep* **58**:820-826.
- Stachowicz K, Klak K, Klodzinska A, Chojnacka-Wojcik E and Pilc A (2004) Anxiolytic-like effects of PHCCC, an allosteric modulator of mGlu4 receptors, in rats. *Eur J Pharmacol* **498**:153-156.
- Steckler T, Lavreysen H, Oliveira AM, Aerts N, Van Craenendonck H, Prickaerts J, Megens A and Lesage AS (2005a) Effects of mGlu1 receptor blockade on anxiety-related behaviour in the rat lick suppression test. *Psychopharmacology (Berl)* **179**:198-206.
- Steckler T, Oliveira AF, Van Dyck C, Van Craenendonck H, Mateus AM, Langlois X, Lesage AS and Prickaerts J (2005b) Metabotropic glutamate receptor 1 blockade impairs acquisition and retention in a spatial Water maze task. *Behav Brain Res* **164**:52-60.

- Stocchi F, Rascol O, Destee A, Hattori N, Hauser RA, Lang AE, Poewe W, Stacy M, Tolosa E, Gao H, Nagel J, Merschhemke M, Graf A, Kenney C and Trenkwalder C (2013) AFQ056 in Parkinson patients with levodopa-induced dyskinesia: 13-week, randomized, dose-finding study. *Mov Disord* **28**:1838-1846.
- Sugiyama H, Ito I and Hirono C (1987) A new type of glutamate receptor linked to inositol phospholipid metabolism. *Nature* **325**:531-533.
- Suh YH, Park JY, Park S, Jou I, Roche PA and Roche KW (2013) Regulation of metabotropic glutamate receptor 7 (mGluR7) internalization and surface expression by Ser/Thr protein phosphatase 1. *J Biol Chem* **288**:17544-17551.
- Sukoff Rizzo SJ, Leonard SK, Gilbert A, Dollings P, Smith DL, Zhang MY, Di L, Platt BJ, Neal S, Dwyer JM, Bender CN, Zhang J, Lock T, Kowal D, Kramer A, Randall A, Huselton C, Vishwanathan K, Tse SY, Butera J, Ring RH, Rosenzweig-Lipson S, Hughes ZA and Dunlop J (2011) The metabotropic glutamate receptor 7 allosteric modulator AMN082: a monoaminergic agent in disguise? *J Pharmacol Exp Ther* **338**:345-352.
- Suzuki G, Kawagoe-Takaki H, Inoue T, Kimura T, Hikichi H, Murai T, Satow A, Hata M, Maehara S, Ito S, Kawamoto H, Ozaki S and Ohta H (2009) Correlation of receptor occupancy of metabotropic glutamate receptor subtype 1 (mGluR1) in mouse brain with in vivo activity of allosteric mGluR1 antagonists. *J Pharmacol Sci* **110**:315-325.
- Suzuki G, Kimura T, Satow A, Kaneko N, Fukuda J, Hikichi H, Sakai N, Maehara S, Kawagoe-Takaki H, Hata M, Azuma T, Ito S, Kawamoto H and Ohta H (2007a) Pharmacological characterization of a new, orally active and potent allosteric metabotropic glutamate receptor 1 antagonist, 4-[1-(2-fluoropyridin-3-yl)-5-methyl-1H-1,2,3-triazol-4-yl]-N-isopropyl-N-methyl-3,6-dihydropyridine-1(2H)-carboxamide (FTIDC). *J Pharmacol Exp Ther* **321**:1144-1153.

- Suzuki G, Satow A and Ohta H (2010) Effect of CFMTI, an allosteric metabotropic glutamate receptor 1 antagonist with antipsychotic activity, on Fos expression in regions of the brain related to schizophrenia. *Neuroscience* **168**:787-796.
- Suzuki G, Tsukamoto N, Fushiki H, Kawagishi A, Nakamura M, Kurihara H, Mitsuya M, Ohkubo M and Ohta H (2007b) In vitro pharmacological characterization of novel isoxazolopyridone derivatives as allosteric metabotropic glutamate receptor 7 antagonists. *J Pharmacol Exp Ther* **323**:147-156.
- Swedberg MD, Ellgren M and Raboisson P (2014) mGluR5 antagonist-induced psychoactive properties: MTEP drug discrimination, a pharmacologically selective non-NMDA effect with apparent lack of reinforcing properties. *J Pharmacol Exp Ther* **349**:155-164.
- Swedberg MD and Raboisson P (2014) AZD9272 and AZD2066: selective and highly central nervous system penetrant mGluR5 antagonists characterized by their discriminative effects. *J Pharmacol Exp Ther* **350**:212-222.
- Szczurowska E and Mares P (2012) Positive allosteric modulator of mGluR4 PHCCC exhibits proconvulsant action in three models of epileptic seizures in immature rats. *Physiol Res* **61**:619-628.
- Tanabe Y, Masu M, Ishii T, Shigemoto R and Nakanishi S (1992) A family of metabotropic glutamate receptors. *Neuron* **8**:169-179.
- Tassin V, Girard B, Chotte A, Fontanaud P, Rigault D, Kalinichev M, Perroy J, Acher F, Fagni L and Bertaso F (2016) Phasic and Tonic mGlu7 Receptor Activity Modulates the Thalamocortical Network. *Front Neural Circuits* **10**:31.
- Tatarczynska E, Klodzinska A, Krocza B, Chojnacka-Wojcik E and Pilc A (2001) The antianxiety-like effects of antagonists of group I and agonists of group II and III metabotropic glutamate receptors after intrahippocampal administration. *Psychopharmacology (Berl)* **158**:94-99.
- Tatarczynska E, Palucha A, Szewczyk B, Chojnacka-Wojcik E, Wieronska J and Pilc A (2002) Anxiolytic- and antidepressant-like effects of group III metabotropic glutamate agonist (1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid (ACPT-I) in rats. *Pol J Pharmacol* **54**:707-710.

- Tateyama M and Kubo Y (2008) Regulatory role of C-terminus in the G-protein coupling of the metabotropic glutamate receptor 1. *J Neurochem* **107**:1036-1046.
- Techlovska S, Chambers JN, Dvorakova M, Petralia RS, Wang YX, Hajkova A, Nova A, Frankova D, Prezeau L and Blahos J (2014) Metabotropic glutamate receptor 1 splice variants mGluR1a and mGluR1b combine in mGluR1a/b dimers in vivo. *Neuropharmacology* **86**:329-336.
- Testa CM, Standaert DG, Young AB and Penney JB, Jr. (1994) Metabotropic glutamate receptor mRNA expression in the basal ganglia of the rat. *J Neurosci* **14**:3005-3018.
- Thomas NK, Jane DE, Tse HW and Watkins JC (1996) alpha-Methyl derivatives of serine-O-phosphate as novel, selective competitive metabotropic glutamate receptor antagonists. *Neuropharmacology* **35**:637-642.
- Thomsen C (1997) The L-AP4 receptor. *Gen Pharmacol* **29**:151-158.
- Thomsen C and Dalby NO (1998) Roles of metabotropic glutamate receptor subtypes in modulation of pentylenetetrazole-induced seizure activity in mice. *Neuropharmacology* **37**:1465-1473.
- Thomsen C, Kristensen P, Mulvihill E, Haldeman B and Suzdak PD (1992) L-2-amino-4-phosphonobutyrate (L-AP4) is an agonist at the type IV metabotropic glutamate receptor which is negatively coupled to adenylate cyclase. *Eur J Pharmacol* **227**:361-362.
- Thomsen C, Pekhletski R, Haldeman B, Gilbert TA, O'Hara P and Hampson DR (1997) Cloning and characterization of a metabotropic glutamate receptor, mGluR4b. *Neuropharmacology* **36**:21-30.
- Thomsen C and Suzdak PD (1993) Serine-O-phosphate has affinity for type IV, but not type I, metabotropic glutamate receptor. *Neuroreport* **4**:1099-1101.
- Tison F, Keywood C, Wakefield M, Durif F, Corvol JC, Eggert K, Lew M, Isaacson S, Bezard E, Poli SM, Goetz CG, Trenkwalder C and Rascol O (2016) A Phase 2A Trial of the Novel mGluR5-Negative Allosteric Modulator Dipraglurant for Levodopa-Induced Dyskinesia in Parkinson's Disease. *Mov Disord* **31**:1373-1380.

- Tizzano JP, Griffey KI and Schoepp DD (1995) Induction or protection of limbic seizures in mice by mGluR subtype selective agonists. *Neuropharmacology* **34**:1063-1067.
- Tizzano JP, Griffey KI and Schoepp DD (2002) The anxiolytic action of mGlu2/3 receptor agonist, LY354740, in the fear-potentiated startle model in rats is mechanistically distinct from diazepam. *Pharmacol Biochem Behav* **73**:367-374.
- Tomita N, Murata M, Watanabe H, Ichikawa T, Washiyama K, Kumanishi T and Takahashi Y (2000) The effects of DCG-IV and L-CCG-1 upon phencyclidine (PCP)-induced locomotion and behavioral changes in mice. *Ann N Y Acad Sci* **914**:284-291.
- Toms NJ, Jane DE, Kemp MC, Bedingfield JS and Roberts PJ (1996) The effects of (RS)-alpha-cyclopropyl-4-phosphonophenylglycine ((RS)-CPPG), a potent and selective metabotropic glutamate receptor antagonist. *Br J Pharmacol* **119**:851-854.
- Tora AS, Rovira X, Cao AM, Cabaye A, Olofsson L, Malhaire F, Scholler P, Baik H, Van Eeckhaut A, Smolders I, Rondard P, Margeat E, Acher F, Pin JP and Goudet C (2018) Chloride ions stabilize the glutamate-induced active state of the metabotropic glutamate receptor 3. *Neuropharmacology* **140**:275-286.
- Tora AS, Rovira X, Dione I, Bertrand HO, Brabet I, De Koninck Y, Doyon N, Pin JP, Acher F and Goudet C (2015) Allosteric modulation of metabotropic glutamate receptors by chloride ions. *FASEB J* **29**:4174-4188.
- Trenkwalder C, Stocchi F, Poewe W, Dronamraju N, Kenney C, Shah A, von Raison F and Graf A (2016) Mavoglurant in Parkinson's patients with l-Dopa-induced dyskinesias: Two randomized phase 2 studies. *Mov Disord* **31**:1054-1058.
- Tresadern G, Trabanco AA, Perez-Benito L, Overington JP, van Vlijmen HWT and van Westen GJP (2017) Identification of Allosteric Modulators of Metabotropic Glutamate 7 Receptor Using Proteochemometric Modeling. *J Chem Inf Model* **57**:2976-2985.

- Trombley PQ and Westbrook GL (1992) L-AP4 inhibits calcium currents and synaptic transmission via a G-protein-coupled glutamate receptor. *J Neurosci* **12**:2043-2050.
- Tsuchiya D, Kunishima N, Kamiya N, Jingami H and Morikawa K (2002) Structural views of the ligand-binding cores of a metabotropic glutamate receptor complexed with an antagonist and both glutamate and Gd³⁺. *Proc Natl Acad Sci U S A* **99**:2660-2665.
- Tu JC, Xiao B, Naisbitt S, Yuan JP, Petralia RS, Brakeman P, Doan A, Aakalu VK, Lanahan AA, Sheng M and Worley PF (1999) Coupling of mGluR/Homer and PSD-95 complexes by the Shank family of postsynaptic density proteins. *Neuron* **23**:583-592.
- Turner BD, Rook JM, Lindsley CW, Conn PJ and Grueter BA (2018) mGlu1 and mGlu5 modulate distinct excitatory inputs to the nucleus accumbens shell. *Neuropsychopharmacology* **43**:2075-2082.
- Tyszkiewicz JP, Gu Z, Wang X, Cai X and Yan Z (2004) Group II metabotropic glutamate receptors enhance NMDA receptor currents via a protein kinase C-dependent mechanism in pyramidal neurones of rat prefrontal cortex. *J Physiol* **554**:765-777.
- Uematsu K, Heiman M, Zelenina M, Padovan J, Chait BT, Aperia A, Nishi A and Greengard P (2015) Protein kinase A directly phosphorylates metabotropic glutamate receptor 5 to modulate its function. *J Neurochem* **132**:677-686.
- Ullmer C, Zoffmann S, Bohrmann B, Matile H, Lindemann L, Flor P and Malherbe P (2012) Functional monoclonal antibody acts as a biased agonist by inducing internalization of metabotropic glutamate receptor 7. *Br J Pharmacol* **167**:1448-1466.
- Um JW, Kaufman AC, Kostylev M, Heiss JK, Stagi M, Takahashi H, Kerrisk ME, Vortmeyer A, Wisniewski T, Koleske AJ, Gunther EC, Nygaard HB and Strittmatter SM (2013) Metabotropic glutamate receptor 5 is a coreceptor for Alzheimer abeta oligomer bound to cellular prion protein. *Neuron* **79**:887-902.
- Valenti O, Conn PJ and Marino MJ (2002) Distinct physiological roles of the Gq-coupled metabotropic glutamate receptors Co-expressed in the same neuronal populations. *J Cell Physiol* **191**:125-137.

- Valerio A, Ferraboli S, Paterlini M, Spano P and Barlati S (2001a) Identification of novel alternatively-spliced mRNA isoforms of metabotropic glutamate receptor 6 gene in rat and human retina. *Gene* **262**:99-106.
- Valerio A, Zoppi N, Ferraboli S, Paterlini M, Ferrario M, Barlati S and Spano P (2001b) Alternative splicing of mGlu6 gene generates a truncated glutamate receptor in rat retina. *Neuroreport* **12**:2711-2715.
- van Wyk M, Pielecka-Fortuna J, Lowel S and Kleinlogel S (2015) Restoring the ON Switch in Blind Retinas: Opto-mGluR6, a Next-Generation, Cell-Tailored Optogenetic Tool. *PLoS Biol* **13**:e1002143.
- Vardi N, Duvoisin R, Wu G and Sterling P (2000) Localization of mGluR6 to dendrites of ON bipolar cells in primate retina. *J Comp Neurol* **423**:402-412.
- Varnas K, Cselenyi Z, Arakawa R, Nag S, Stepanov V, Moein MM, Johnstrom P, Kingston L, Elmore CS, Halldin C and Farde L (2020) The pro-psychotic metabotropic glutamate receptor compounds fenobam and AZD9272 share binding sites with monoamine oxidase-B inhibitors in humans. *Neuropharmacology* **162**:107809.
- Varty GB, Grilli M, Forlani A, Fredduzzi S, Grzelak ME, Guthrie DH, Hodgson RA, Lu SX, Nicolussi E, Pond AJ, Parker EM, Hunter JC, Higgins GA, Reggiani A and Bertorelli R (2005) The antinociceptive and anxiolytic-like effects of the metabotropic glutamate receptor 5 (mGluR5) antagonists, MPEP and MTEP, and the mGluR1 antagonist, LY456236, in rodents: a comparison of efficacy and side-effect profiles. *Psychopharmacology (Berl)* **179**:207-217.
- Vergouts M, Doyen PJ, Peeters M, Opsomer R, Michiels T and Hermans E (2017) PKC epsilon-dependent calcium oscillations associated with metabotropic glutamate receptor 5 prevent agonist-mediated receptor desensitization in astrocytes. *J Neurochem* **141**:387-399.
- Verma A and Moghaddam B (1998) Regulation of striatal dopamine release by metabotropic glutamate receptors. *Synapse* **28**:220-226.

- Vernon AC, Zbarsky V, Datla KP, Dexter DT and Croucher MJ (2007) Selective activation of group III metabotropic glutamate receptors by L-(+)-2-amino-4-phosphonobutyric acid protects the nigrostriatal system against 6-hydroxydopamine toxicity in vivo. *J Pharmacol Exp Ther* **320**:397-409.
- Vilar B, Busserolles J, Ling B, Laffray S, Ulmann L, Malhaire F, Chapuy E, Aissouni Y, Etienne M, Bourinet E, Acher F, Pin JP, Eschalier A and Goudet C (2013) Alleviating pain hypersensitivity through activation of type 4 metabotropic glutamate receptor. *J Neurosci* **33**:18951-18965.
- Vinueza Veloz MF, Buijsen RA, Willemsen R, Cupido A, Bosman LW, Koekkoek SK, Potters JW, Oostra BA and De Zeeuw CI (2012) The effect of an mGluR5 inhibitor on procedural memory and avoidance discrimination impairments in Fmr1 KO mice. *Genes Brain Behav* **11**:325-331.
- Volk LJ, Daly CA and Huber KM (2006) Differential roles for group 1 mGluR subtypes in induction and expression of chemically induced hippocampal long-term depression. *J Neurophysiol* **95**:2427-2438.
- Volpi C, Fallarino F, Mondanelli G, Macchiarulo A and Grohmann U (2018) Opportunities and challenges in drug discovery targeting metabotropic glutamate receptor 4. *Expert Opin Drug Discov* **13**:411-423.
- Volpi C, Mondanelli G, Pallotta MT, Vacca C, Iacono A, Gargaro M, Albini E, Bianchi R, Belladonna ML, Celanire S, Mordant C, Heroux M, Royer-Urios I, Schneider M, Vitte PA, Cacquevel M, Galibert L, Poli SM, Solari A, Biccato S, Calvitti M, Antognelli C, Puccetti P, Orabona C, Fallarino F and Grohmann U (2016) Allosteric modulation of metabotropic glutamate receptor 4 activates IDO1-dependent, immunoregulatory signaling in dendritic cells. *Neuropharmacology* **102**:59-71.
- Vranesic I, Ofner S, Flor PJ, Bilbe G, Bouhelal R, Enz A, Desrayaud S, McAllister K, Kuhn R and Gasparini F (2014) AFQ056/mavoglurant, a novel clinically effective mGluR5 antagonist: identification, SAR and pharmacological characterization. *Bioorg Med Chem* **22**:5790-5803.

- Wada E, Shigemoto R, Kinoshita A, Ohishi H and Mizuno N (1998) Metabotropic glutamate receptor subtypes in axon terminals of projection fibers from the main and accessory olfactory bulbs: a light and electron microscopic immunohistochemical study in the rat. *J Comp Neurol* **393**:493-504.
- Wagner KV, Hartmann J, Labermaier C, Hausl AS, Zhao G, Harbich D, Schmid B, Wang XD, Santarelli S, Kohl C, Gassen NC, Matosin N, Schieven M, Webhofer C, Turck CW, Lindemann L, Jaschke G, Wettstein JG, Rein T, Muller MB and Schmidt MV (2015) Homer1/mGluR5 activity moderates vulnerability to chronic social stress. *Neuropsychopharmacology* **40**:1222-1233.
- Walker AG and Conn PJ (2015) Group I and group II metabotropic glutamate receptor allosteric modulators as novel potential antipsychotics. *Curr Opin Pharmacol* **20**:40-45.
- Walker AG, Wenthur CJ, Xiang Z, Rook JM, Emmitte KA, Niswender CM, Lindsley CW and Conn PJ (2015) Metabotropic glutamate receptor 3 activation is required for long-term depression in medial prefrontal cortex and fear extinction. *Proc Natl Acad Sci U S A* **112**:1196-1201.
- Wang H, Jiang W, Yang R and Li Y (2011) Spinal metabotropic glutamate receptor 4 is involved in neuropathic pain. *Neuroreport* **22**:244-248.
- Wang H, Westin L, Nong Y, Birnbaum S, Bendor J, Brismar H, Nestler E, Aperia A, Flajolet M and Greengard P (2009) Norbin is an endogenous regulator of metabotropic glutamate receptor 5 signaling. *Science* **326**:1554-1557.
- Watkins J and Collingridge G (1994) Phenylglycine derivatives as antagonists of metabotropic glutamate receptors. *Trends Pharmacol Sci* **15**:333-342.
- Watson LM, Bamber E, Schnekenberg RP, Williams J, Bettencourt C, Lickiss J, Jayawant S, Fawcett K, Clokie S, Wallis Y, Clouston P, Sims D, Houlden H, Becker EBE and Nemeth AH (2017) Dominant Mutations in GRM1 Cause Spinocerebellar Ataxia Type 44. *Am J Hum Genet* **101**:451-458.
- Watterson LR, Kufahl PR, Nemirovsky NE, Sewalia K, Hood LE and Olive MF (2013) Attenuation of reinstatement of methamphetamine-, sucrose-, and food-seeking behavior in rats by fenobam, a

- metabotropic glutamate receptor 5 negative allosteric modulator. *Psychopharmacology (Berl)* **225**:151-159.
- Wellendorph P and Brauner-Osborne H (2009) Molecular basis for amino acid sensing by family C G-protein-coupled receptors. *Br J Pharmacol* **156**:869-884.
- Wenthur CJ, Morrison RD, Daniels JS, Conn PJ and Lindsley CW (2014) Synthesis and SAR of substituted pyrazolo[1,5-a]quinazolines as dual mGlu(2)/mGlu(3) NAMs. *Bioorganic & medicinal chemistry letters* **24**:2693-2698.
- Westmark PR, Dekundy A, Gravius A, Danysz W and Westmark CJ (2018) Rescue of Fmr1(KO) phenotypes with mGluR5 inhibitors: MRZ-8456 versus AFQ-056. *Neurobiol Dis* **119**:190-198.
- White E, McKenna J, Cavanaugh A and Breitwieser GE (2009) Pharmacochaperone-mediated rescue of calcium-sensing receptor loss-of-function mutants. *Mol Endocrinol* **23**:1115-1123.
- Wieronska JM, Stachowicz K, Acher F, Lech T and Pilc A (2012a) Opposing efficacy of group III mGlu receptor activators, LSP1-2111 and AMN082, in animal models of positive symptoms of schizophrenia. *Psychopharmacology (Berl)* **220**:481-494.
- Wieronska JM, Stachowicz K, Branski P, Palucha-Poniewiera A and Pilc A (2012b) On the mechanism of anti-hyperthermic effects of LY379268 and LY487379, group II mGlu receptors activators, in the stress-induced hyperthermia in singly housed mice. *Neuropharmacology* **62**:322-331.
- Wieronska JM, Stachowicz K, Palucha-Poniewiera A, Acher F, Branski P and Pilc A (2010) Metabotropic glutamate receptor 4 novel agonist LSP1-2111 with anxiolytic, but not antidepressant-like activity, mediated by serotonergic and GABAergic systems. *Neuropharmacology* **59**:627-634.
- Wisniewski K and Car H (2002) (S)-3,5-DHPG: a review. *CNS Drug Rev* **8**:101-116.
- Witkin JM, Monn JA, Schoepp DD, Li X, Overshiner C, Mitchell SN, Carter G, Johnson B, Rasmussen K and Rorick-Kehn LM (2016) The Rapidly Acting Antidepressant Ketamine and the mGlu2/3 Receptor Antagonist LY341495 Rapidly Engage Dopaminergic Mood Circuits. *J Pharmacol Exp Ther* **358**:71-82.

- Woltering TJ, Wichmann J, Goetschi E, Adam G, Kew JN, Knoflach F, Ballard TM, Huwyler J, Mutel V and Gatti S (2008) Synthesis and characterization of 1,3-dihydro-benzo[b][1,4]diazepin-2-one derivatives: Part 3. New potent non-competitive metabotropic glutamate receptor 2/3 antagonists. *Bioorg Med Chem Lett* **18**:2725-2729.
- Woltering TJ, Wichmann J, Goetschi E, Knoflach F, Ballard TM, Huwyler J and Gatti S (2010) Synthesis and characterization of 1,3-dihydro-benzo[b][1,4]diazepin-2-one derivatives: Part 4. In vivo active potent and selective non-competitive metabotropic glutamate receptor 2/3 antagonists. *Bioorganic & medicinal chemistry letters* **20**:6969-6974.
- Wood MR, Hopkins CR, Brogan JT, Conn PJ and Lindsley CW (2011) "Molecular switches" on mGluR allosteric ligands that modulate modes of pharmacology. *Biochemistry* **50**:2403-2410.
- Woolley ML, Pemberton DJ, Bate S, Corti C and Jones DN (2008) The mGlu2 but not the mGlu3 receptor mediates the actions of the mGluR2/3 agonist, LY379268, in mouse models predictive of antipsychotic activity. *Psychopharmacology (Berl)* **196**:431-440.
- Wozniak M, Golembiowska K, Noworyta-Sokolowska K, Acher F, Cieslik P, Kusek M, Tokarski K, Pilc A and Wieronska JM (2017) Neurochemical and behavioral studies on the 5-HT1A-dependent antipsychotic action of the mGlu4 receptor agonist LSP4-2022. *Neuropharmacology* **115**:149-165.
- Wright RA, Johnson BG, Zhang C, Salhoff C, Kingston AE, Calligaro DO, Monn JA, Schoepp DD and Marek GJ (2012) CNS distribution of metabotropic glutamate 2 and 3 receptors: Transgenic mice and [(3)H]LY459477 autoradiography. *Neuropharmacology*.
- Wroblewska B, Wegorzewska IN, Bzdega T, Olszewski RT and Neale JH (2006) Differential negative coupling of type 3 metabotropic glutamate receptor to cyclic GMP levels in neurons and astrocytes. *J Neurochem* **96**:1071-1077.
- Wu H, Wang C, Gregory KJ, Han GW, Cho HP, Xia Y, Niswender CM, Katritch V, Meiler J, Cherezov V, Conn PJ and Stevens RC (2014) Structure of a class C GPCR metabotropic glutamate receptor 1 bound to an allosteric modulator. *Science* **344**:58-64.

- Wu S, Wright RA, Rockey PK, Burgett SG, Arnold JS, Rosteck PR, Jr., Johnson BG, Schoepp DD and Belagaje RM (1998) Group III human metabotropic glutamate receptors 4, 7 and 8: molecular cloning, functional expression, and comparison of pharmacological properties in RGT cells. *Brain Res Mol Brain Res* **53**:88-97.
- Xi D, Li YC, Snyder MA, Gao RY, Adelman AE, Zhang W, Shumsky JS and Gao WJ (2011) Group II metabotropic glutamate receptor agonist ameliorates MK801-induced dysfunction of NMDA receptors via the Akt/GSK-3beta pathway in adult rat prefrontal cortex. *Neuropsychopharmacology* **36**:1260-1274.
- Xiang Z, Lv X, Maksymetz J, Stansley BJ, Ghoshal A, Gogliotti RG, Niswender CM, Lindsley CW and Conn PJ (2019) mGlu5 Positive Allosteric Modulators Facilitate Long-Term Potentiation via Disinhibition Mediated by mGlu5-Endocannabinoid Signaling. *ACS Pharmacol Transl Sci* **2**:198-209.
- Xing B, Han G, Wang MJ, Snyder MA and Gao WJ (2018) Juvenile treatment with mGluR2/3 agonist prevents schizophrenia-like phenotypes in adult by acting through GSK3beta. *Neuropharmacology* **137**:359-371.
- Xu H, Staszewski L, Tang H, Adler E, Zoller M and Li X (2004) Different functional roles of T1R subunits in the heteromeric taste receptors. *Proc Natl Acad Sci U S A* **101**:14258-14263.
- Xu J, Zhu Y, Contractor A and Heinemann SF (2009) mGluR5 has a critical role in inhibitory learning. *J Neurosci* **29**:3676-3684.
- Xu W, Tse YC, Dobie FA, Baudry M, Craig AM, Wong TP and Wang YT (2013) Simultaneous monitoring of presynaptic transmitter release and postsynaptic receptor trafficking reveals an enhancement of presynaptic activity in metabotropic glutamate receptor-mediated long-term depression. *J Neurosci* **33**:5867-5877.
- Xue L, Rovira X, Scholler P, Zhao H, Liu J, Pin JP and Rondard P (2015) Major ligand-induced rearrangement of the heptahelical domain interface in a GPCR dimer. *Nat Chem Biol* **11**:134-140.

- Yamasaki T, Fujinaga M, Kawamura K, Yui J, Hatori A, Ohya T, Xie L, Wakizaka H, Yoshida Y, Fukumura T and Zhang MR (2012) In vivo measurement of the affinity and density of metabotropic glutamate receptor subtype 1 in rat brain using ¹⁸F-FITM in small-animal PET. *J Nucl Med* **53**:1601-1607.
- Yamasue H, Aran A and Berry-Kravis E (2019) Emerging pharmacological therapies in fragile X syndrome and autism. *Curr Opin Neurol* **32**:635-640.
- Yang JH, Mao LM, Choe ES and Wang JQ (2017) Synaptic ERK2 Phosphorylates and Regulates Metabotropic Glutamate Receptor 1 In Vitro and in Neurons. *Mol Neurobiol* **54**:7156-7170.
- Yang L, Mao L, Chen H, Catavsan M, Kozinn J, Arora A, Liu X and Wang JQ (2006) A signaling mechanism from G alpha q-protein-coupled metabotropic glutamate receptors to gene expression: role of the c-Jun N-terminal kinase pathway. *J Neurosci* **26**:971-980.
- Yin S, Noetzel MJ, Johnson KA, Zamorano R, Jalan-Sakrikar N, Gregory KJ, Conn PJ and Niswender CM (2014) Selective actions of novel allosteric modulators reveal functional heteromers of metabotropic glutamate receptors in the CNS. *J Neurosci* **34**:79-94.
- Yin S, Zamorano R, Conn PJ and Niswender CM (2012) Functional selectivity induced by mGlu(4) receptor positive allosteric modulation and concomitant activation of G(q) coupled receptors. *Neuropharmacology*.
- Yohn SE, Foster DJ, Covey DP, Moehle MS, Galbraith J, Garcia-Barrantes PM, Cho HP, Bubser M, Blobaum AL, Joffe ME, Cheer JF, Jones CK, Lindsley CW and Conn PJ (2018) Activation of the mGlu1 metabotropic glutamate receptor has antipsychotic-like effects and is required for efficacy of M4 muscarinic receptor allosteric modulators. *Mol Psychiatry*.
- Yoshioka H, Sugita M and Kinouchi H (2009) Neuroprotective effects of group II metabotropic glutamate receptor agonist DCG-IV on hippocampal neurons in transient forebrain ischemia. *Neurosci Lett* **461**:266-270.

- Young MR, Fleetwood-Walker SM, Dickinson T, Blackburn-Munro G, Sparrow H, Birch PJ and Bountra C (1997) Behavioural and electrophysiological evidence supporting a role for group I metabotropic glutamate receptors in the mediation of nociceptive inputs to the rat spinal cord. *Brain Res* **777**:161-169.
- Young MR, Fleetwood-Walker SM, Mitchell R and Dickinson T (1995) The involvement of metabotropic glutamate receptors and their intracellular signalling pathways in sustained nociceptive transmission in rat dorsal horn neurons. *Neuropharmacology* **34**:1033-1041.
- Youssef EA, Berry-Kravis E, Czech C, Hagerman RJ, Hessler D, Wong CY, Rabbia M, Deptula D, John A, Kinch R, Drewitt P, Lindemann L, Marcinowski M, Langland R, Horn C, Fontoura P, Santarelli L, Quiroz JA and FragXis Study G (2018) Effect of the mGluR5-NAM Basimglurant on Behavior in Adolescents and Adults with Fragile X Syndrome in a Randomized, Double-Blind, Placebo-Controlled Trial: FragXis Phase 2 Results. *Neuropsychopharmacology* **43**:503-512.
- Zalewska-Winska A and Wisniewski K (2000) Behavioural activity of (S)-3,5-DHPG, a selective agonist of group I metabotropic glutamate receptors. *Pharmacol Res* **42**:239-245.
- Zalewska A and Wisniewski K (1997) Behavioral activity of 1S,3R-ACPD, an agonist of metabotropic glutamate receptors. *Pol J Pharmacol* **49**:239-248.
- Zeit C, Forster U, Neidhardt J, Feil S, Kalin S, Leifert D, Flor PJ and Berger W (2007) Night blindness-associated mutations in the ligand-binding, cysteine-rich, and intracellular domains of the metabotropic glutamate receptor 6 abolish protein trafficking. *Hum Mutat* **28**:771-780.
- Zeit C, Robson AG and Audo I (2015) Congenital stationary night blindness: an analysis and update of genotype-phenotype correlations and pathogenic mechanisms. *Prog Retin Eye Res* **45**:58-110.
- Zeleznikow-Johnston AM, Renoir T, Churilov L, Li S, Burrows EL and Hannan AJ (2018) Touchscreen testing reveals clinically relevant cognitive abnormalities in a mouse model of schizophrenia lacking metabotropic glutamate receptor 5. *Sci Rep* **8**:16412.

- Zerbib F, Bruley des Varannes S, Roman S, Tutuian R, Galmiche JP, Mion F, Tack J, Malfertheiner P and Keywood C (2011) Randomised clinical trial: effects of monotherapy with ADX10059, a mGluR5 inhibitor, on symptoms and reflux events in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* **33**:911-921.
- Zerbib F, Keywood C and Strabach G (2010) Efficacy, tolerability and pharmacokinetics of a modified release formulation of ADX10059, a negative allosteric modulator of metabotropic glutamate receptor 5: an esophageal pH-impedance study in healthy subjects. *Neurogastroenterol Motil* **22**:859-865, e231.
- Zhang Y, Rodriguez AL and Conn PJ (2005) Allosteric potentiators of metabotropic glutamate receptor subtype 5 have differential effects on different signaling pathways in cortical astrocytes. *J Pharmacol Exp Ther* **315**:1212-1219.
- Zhang Z, Liu Y, Wang K, Zhu K, Zheng X, Wang L, Luan Y, Wang X, Lu H, Wu K, Chen X, He D and Liu Y (2019) Activation of type 4 metabotropic glutamate receptor promotes cell apoptosis and inhibits proliferation in bladder cancer. *J Cell Physiol* **234**:2741-2755.
- Zhang ZY, Sun BL, Liu JK, Yang MF, Li DW, Fang J, Zhang S, Yuan QL and Huang SL (2015) Activation of mGluR5 Attenuates Microglial Activation and Neuronal Apoptosis in Early Brain Injury After Experimental Subarachnoid Hemorrhage in Rats. *Neurochem Res* **40**:1121-1132.
- Zheng GZ, Bhatia P, Daanen J, Kolasa T, Patel M, Latshaw S, El Kouhen OF, Chang R, Uchic ME, Miller L, Nakane M, Lehto SG, Honore MP, Moreland RB, Brioni JD and Stewart AO (2005) Structure-activity relationship of triazafluorenone derivatives as potent and selective mGluR1 antagonists. *J Med Chem* **48**:7374-7388.
- Zhou F, Yao HH, Wu JY, Yang YJ, Ding JH, Zhang J and Hu G (2006) Activation of Group II/III metabotropic glutamate receptors attenuates LPS-induced astroglial neurotoxicity via promoting glutamate uptake. *J Neurosci Res* **84**:268-277.

- Zhu CZ, Baker S, O EI-K, Lehto SG, Hollingsworth PR, Gauvin DM, Hernandez G, Zheng G, Chang R, Moreland RB, Stewart AO, Brioni JD and Honore P (2008) Analgesic activity of metabotropic glutamate receptor 1 antagonists on spontaneous post-operative pain in rats. *Eur J Pharmacol* **580**:314-321.
- Zhu PJ, Chen CJ, Mays J, Stoica L and Costa-Mattioli M (2018) mTORC2, but not mTORC1, is required for hippocampal mGluR-LTD and associated behaviors. *Nat Neurosci* **21**:799-802.
- Zolkowska D, Kondrat-Wrobel MW, Florek-Luszczki M and Luszczki JJ (2016) Influence of MPEP (a selective mGluR5 antagonist) on the anticonvulsant action of novel antiepileptic drugs against maximal electroshock-induced seizures in mice. *Prog Neuropsychopharmacol Biol Psychiatry* **65**:172-178.
- Zuena AR, Iacovelli L, Orlando R, Di Menna L, Casolini P, Alema GS, Di Cicco G, Battaglia G and Nicoletti F (2018) In Vivo Non-radioactive Assessment of mGlu5 Receptor-Activated Polyphosphoinositide Hydrolysis in Response to Systemic Administration of a Positive Allosteric Modulator. *Front Pharmacol* **9**:804.
- Zussy C, Gomez-Santacana X, Rovira X, De Bundel D, Ferrazzo S, Bosch D, Asede D, Malhaire F, Acher F, Giraldo J, Valjent E, Ehrlich I, Ferraguti F, Pin JP, Llebaria A and Goudet C (2018) Dynamic modulation of inflammatory pain-related affective and sensory symptoms by optical control of amygdala metabotropic glutamate receptor 4. *Mol Psychiatry* **23**:509-520.

Tables

Table 1: Pharmacology of orthosteric metabotropic glutamate receptor agonists and antagonists.

Commercially available agents. For a complete list refer to guidetopharmacology.org

Compound	IUPAC name	MoA	Selectivity (pK _i) ^b	In vivo activity	Ref
L-Glutamate		Endogenous agonist	rR1: 6.5; 6.4; hR2: 5.1; hR7: 3.2	Major excitatory neurotransmitter	1
Non selective					
(1S, 3R)-ACPD	(1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid	Group I and II agonist	rR1: 5.5; rR5: 5.7	Neurotoxicity; Antiparkinsonian; Memory	2
ACPT-II	(1R,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid	Pan mGlu antagonist	rR1a: 3.9; rR2: 4.1; rR4a: 4.1		3
CPPG	(RS)- α -cyclopropyl-4-phosphonophenylglycine	group II/III antagonist	rR2: 8.7; rR3: 7.3; rR4: 4.9; rR6: 5.4, rR7: 4.8; rR8: 4.9		4

(S)-MCPG	(S)- α -methyl-4-carboxyphenylglycine	Non selective mGlu antagonist	rR1: 3.8; rR5: 3.7	Spatial learning; Anti-psychotic-like	5
LY341495	(2S)-2-amino-2-[(1S,2S)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid	Group II antagonist but blocks all subtypes	<i>hR1</i> : 5.2; <i>hR2</i> : 8.6-7.6; <i>hR3</i> : 8.4; <i>hR4</i> : 4.7; <i>hR5</i> : 5.1; <i>hR7</i> : 6.7-6.5; <i>rR7</i> : 6.3; <i>hR8</i> : 7.2	Antidepressant; Memory; Hypnosis; Withdrawal	6
Group I mGlu receptors					
AIDA	(RS)-1-aminoindan-1,5-dicarboxylic acid	Group I antagonist	rR1: 4.4-4.0; rR5: 4.3	Epilepsy; Spatial memory; Pain; Neuroprotection	7
(R,S)-CHPG	(RS)-2-chloro-5-hydroxyphenylglycine	mGlu ₅ agonist	rR1: 3.8; rR5: 3.4	Neuroprotection; Pain; Epilepsy	8
(S)-3,5-DHPG	(S)-3,5-dihydroxyphenylglycine	Group I agonist	rR1: 6.0, rR5a: 5.4	Anxiety; Memory; Pain; Epilepsy	9
LY367385	(S)-(+)- α -amino-4-carboxy-2-methylbenzeneacetic acid	mGlu ₁ antagonist	rR1: 5.1; rR5: <4	Neuroprotection; Antidepressant	10

L-Quisqualic acid	(L)-(+)- α -amino-3,5-dioxo-1,2,4-oxadiazolidine-2-propanoic acid	Group I and AMPA agonist	rR1: 7.5	Epilepsy; Neurotoxicity	11
Group II mGlu receptors					
DCG-IV	(2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine	group II agonist	hR2: 7.2-6.4; hR3: 7.9	Antipsychotic; Neuroprotection; Anticonvulsant	12
LY2812223 (MP-101, prodrug: LY2979165)	ammonium (1R,2S,4R,5R,6R)-4-((4H-1,2,4-triazol-3-yl)thio)-2-((S)-2-aminopropanamido)-2-carboxybicyclo[3.1.0]hexane-6-carboxylate hydrate	mGlu ₂ agonist	hR2: 8.1	Antipsychotic; Clinical trials for Bipolar disorder (phase 1) and Dementia-Related Psychosis and/or Agitation and Aggression (phase 2)	13
LY354470	(1S,2S,5R,6S)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid	mGlu _{2/3} agonist	rR2 8.3 rR3: 7.6	Anxiolytic; Withdrawal; Antiparkinsonian; Antipsychotic; Anxiolytic	14
LY379268	(1R,4R,5S,6R)-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid	mGlu _{2/3} agonist	hR2: 9.1-8.6; hR3: 8.9-8.2	Anxiolytic; Antidepressant; Antipsychotic; Neuroprotection	15
LY541850	(1S,2S,4R,5R,6S)-2-amino-4-methylbicyclo[3.1.0]hexane-2,6-dicarboxylic acid	mGlu ₂ agonist, mGlu ₃ antagonist	hR2: 7.0; hR3: <5	antipsychotic effects	16

Pomaglumetad (LY404039,)	4-amino-2-thiabicyclo[3.1.0]hexane-4,6-dicarboxylic acid 2,2-dioxide	mGlu _{2/3} agonist	rR2: 7.6 rR3: 7.3	Alcohol-seeking; Antipsychotic; Anxiolytic; Clinical trials for prodrug: LY2140023 for psychosis (phase II) and post-traumatic stress disorder (III)	17
Group III mGlu receptors					
ACPT-I	(1S, 3R,4S)-1-aminocyclopentane-1,2,4-tricarboxylic acid	Group III agonist	rR4: 5.5; rR6: 5; rR7: 3.6; rR8: 5.3	Neuroprotective; Anxiolytic; Antidepressant; Analgesic	18
Cinnabarinic acid	2-amino-3-oxo-3 <i>H</i> -phenoxazine-1,9-dicarboxylic acid	mGlu ₄ partial agonist	rR4a < 4	Neuroprotection, (Off target effects in mGlu ₄ KO mice	19
L-AP4	L-(+)-2-amino-4-phosphonobutyric acid	Group III agonist	R4: 6.7; R6: 6.1; rR7: 3.7; r8: 6.1	Neuroprotection, Analgesic, Antiparkinsonian	20
L-thioAP4	l-(+)-2-amino-4-thiophosphonobutyric Acid	Group III agonist	rR4: 7.4; rR6: 6.1; rR7: 3.7; rR8: 7.3		21
L-SOP	O-phospho-L-serine	Endogenous Group III agonist; Group II antagonist	rR4: 7.4; rR6: 6.1; rR7: 3.7; rR8: 7.3	Neuroprotection; Antiparkinsonian; Anxiolytic; Antiepileptic	22

LSP1-2111	(2S)-2-amino-4-{hydroxy[hydroxy(4-hydroxy-3-methoxy-5-nitrophenyl)methyl]phosphoryl}butanoic acid	Group III agonist	rR4: 6; rR6 5.5; rR7: 4; rR8: 4.7	Antiparkinsonian; antipsychotic; Anxiolytic	23
LSP2-9166	(2S)-2-amino-4-(((4-(carboxymethoxy)phenyl)(hydroxy)methyl)(hydroxy)phosphoryl)butanoic acid	mGlu _{4/7} agonist	rR4: 7.2; rR7: 5.7; rR8: 4.3	Epilepsy; Ethanol consumption and relapse; Morphine rewarding effect	24
LSP4-2022	(2S)-2-amino-4-({[4-(carboxymethoxy)phenyl](hydroxy)methyl}(hydroxy)phosphoryl)butanoic acid	mGlu ₄ agonist	rR4: 7; rR6: 5.4; rR7: 4.9; rR8 : 4.5	Analgesic; antidepressant; antipsychotic-like	25
(RS)-PPG	(RS)-4-phosphonophenylglycine	group III agonist	hR4a: 5.3; hR6: 5.3; hR7b: 3.7; hR8a: 6.7	Anticonvulsant; neuroprotective	26
MSOP	(RS)- α -methylserine-O-phosphate	Group III antagonist		Anxiolytic	27

^a MoA: Mechanism of Action

^b Where affinity estimates were unavailable pIC₅₀ (antagonists) or pEC₅₀ (agonists) values are reported indicated by italics.

References:

1 (Meldrum, 2000; Pin et al., 1999); Mutel et al., 2000)

2 (Conti et al., 2002; Henrich-Noack and Reymann, 1999; Zalewska and Wisniewski, 1997); Mutel et al., 2000)

3 (Acher et al., 1997a)

4 (Naples and Hampson, 2001; Toms et al., 1996)

5 (Bordi et al., 1996; Kim and Vezina, 1998; Watkins and Collingridge, 1994); Mutel et al., 2000)

6 (Kingston et al., 1998; Liechti and Markou, 2007; Moreno et al., 2013; Ornstein et al., 1998; Pitsikas et al., 2012; Podkowa et al., 2016; Witkin et al., 2016)

7 (Christoffersen et al., 1999; Moroni et al., 1997; Neugebauer et al., 1999; Pellicciari et al., 1995; Rao et al., 2000; Thomsen and Dalby, 1998); Mutel et al., 2000)

8 (Bao et al., 2001; Chapman et al., 2000; Doherty et al., 1997; Young et al., 1997; Young et al., 1995); Mutel et al., 2000)

9 (Barton and Shannon, 2005; Gabra et al., 2008; Nadlewska et al., 2002; Schoepp et al., 1994; Sekiyama et al., 1996; Zalewska-Winska and Wisniewski, 2000); Mutel et al., 2000; also see (Wisniewski and Car, 2002) for a review)

10 (Bruno et al., 1999; Car and Wisniewska, 2006; Clark et al., 1997)

11 (Fukuda et al., 1985; Hinoi et al., 2000; Holmes et al., 1993; Littman et al., 1995; Shinozaki and Shibuya, 1974; Silverstein et al., 1986); Mutel et al., 2000)

12 (Attwell et al., 1998; Brabet et al., 1998; Bruno et al., 1994; Cartmell et al., 1998; Miyamoto et al., 1997; Tomita et al., 2000; Yoshioka et al., 2009)

13 (Felder et al., 2017; McColm et al., 2017; Monn et al., 2015a); <https://clinicaltrials.gov/ct2/show/NCT01383967>;
<https://clinicaltrials.gov/ct2/show/NCT03044249>

14 (Bond et al., 1997; Cartmell et al., 1999; Grillon et al., 2003; Helton et al., 1997; 1998; Konieczny et al., 1998; Marek et al., 2006; Monn et al., 1997; Schoepp et al., 1997; Schoepp et al., 2003; Schreiber et al., 2000; Tizzano et al., 2002)

15 (Bond et al., 2000; Bond et al., 1999; Cartmell et al., 1999; 2000; Clark et al., 2002; Greco et al., 2005; Kingston et al., 1999; Matrisciano et al., 2008; Woolley et al., 2008); Cippitelli et al., 2010; Di Liberto et al., 2010; Monn et al., 1999)

16 (Hanna et al., 2013)

17 (Annes et al., 2015; Fell et al., 2008; Lebois, 2008; Rodd et al., 2006; Rorick-Kehn et al., 2007a; Rorick-Kehn et al., 2007b; Seeman, 2013);
<https://clinicaltrials.gov/ct2/show/NCT01487083>; <https://clinicaltrials.gov/ct2/show/NCT02234687>

18 (Acher et al., 1997b; Domin et al., 2014; Domin et al., 2016; Domin et al., 2018; Goudet et al., 2008; Klak et al., 2007; Lopez et al., 2007; Palucha-Poniewiera et al., 2008; Palucha et al., 2004; Tatarczynska et al., 2002)

19 (Fazio et al., 2017; Fazio et al., 2012; Fazio et al., 2014)

20 (Chen and Pan, 2005; Faden et al., 1997; Lopez et al., 2007; Naples and Hampson, 2001; Park et al., 2019; Pizzi et al., 2000; Thomsen, 1997; Thomsen et al., 1992; Trombley and Westbrook, 1992; Vernon et al., 2007; Zhou et al., 2006)

21 (Selvam et al., 2007)

22 (Antflick et al., 2009; Faden et al., 1997; MacInnes et al., 2004; Nicoletti et al., 1986; Tatarczynska et al., 2001; Thomsen and Suzdak, 1993; Tizzano et al., 1995)

23 (Beurrier et al., 2009; Commare et al., 2015; Cuomo et al., 2009; Selvam et al., 2018; Wieronska et al., 2012a; Wieronska et al., 2010)

24 (Girard et al., 2019; Hajasova et al., 2018; Lebourgeois et al., 2018)

25 (Goudet et al., 2012; Podkowa et al., 2015; Vilar et al., 2013; Wozniak et al., 2017; Zussy et al., 2018)

26 (Bigge et al., 1989; Gasparini et al., 1999a)

27 (Chojnacka-Wojcik et al., 1996; 1997; Thomas et al., 1996)

Table 2: Pharmacology of commercially available mGlu₁ allosteric ligands.

For a complete list refer to guidetopharmacology.org

compound	IUPAC name	MoA^a	Selectivity^b (pK _B or pE/IC ₅₀)	In vivo activity	Ref
A-841720	3-(azepan-1-yl)-9-(dimethylamino)pyrido[1,2]thieno[3,4-d]pyrimidin-4-one	NAM	rR1: 9.0; hR1: 8.0; rR5: 6.7	Analgesic; disrupts locomotion & cognition	1
BAY-36-7620	[(3a <i>S</i> ,6a <i>S</i>)-6a-naphthalen-2-ylmethyl-5-methyliden-hexahydro-cyclopental[c]furan-1-on]	NAM	rR1: 8.0; hR1: <5	Anti-convulsive, cognitive impairments	2
CFMTI	2-cyclopropyl-5-[1-(2-fluoropyridin-3-yl)-5-methyltriazol-4-yl]-3H-isoindol-1-one	NAM	hR1: 8.6; rR1: 8.6; hR5: 5.3	antipsychotic-like; no motor effects	3
CPCCOEt	ethyl (7 <i>Z</i>)-7-hydroxyimino-1,7a-dihydrocyclopropa[b]chromene-1a-carboxylate	NAM	rR1: 5.3-4.9; hR1: 4.8; rR5: 4.9; hR5: 4.4; R4: <4	Anti-tumorigenic (melanoma), analgesia, memory impairment, reverses morphine tolerance; neuroprotective (trauma)	4

DFMTI (MK-5435)	5-(1-(2,4-difluorophenyl)-5-methyl-1 <i>H</i> -1,2,3-triazol-4-yl)-2-isopropylisoindolin-1-one	NAM	rR1: 8.4-8.1; hR1: 8.4-7.5; hR5: 5.8		5
DM-PPP	4-O-[(2 <i>S</i>)-3,3-dimethylbutan-2-yl] 2-O-propyl 3,5-dimethyl-1 <i>H</i> -pyrrole-2,4-dicarboxylate	NAM	rR1: 7.8	Analgesic	6
EM-TBPC	1-ethyl-2-methyl-6-oxo-4-(1,2,4,5-tetrahydro-3-benzazepin-3-yl)pyrimidine-5-carbonitrile	NAM	rR1: 8.2; hR1: low	Not suitable for in vivo dosing	7
FITM, [¹⁸ F]FITM	4-fluoro- <i>N</i> -methyl- <i>N</i> -[4-[6-(propan-2-ylamino)pyrimidin-4-yl]-1,3-thiazol-2-yl]benzamide	NAM	hR1: 6.6; rR1: 8.7; R5: 5.2		8
FPTQ	6-(1-(2-fluoropyridin-3-yl)-5-methyl-1 <i>H</i> -1,2,3-triazol-4-yl)quinoline	NAM	hR1: 7.9		9
FTIDC	4-[1-(2-fluoropyridin-3-yl)-5-methyltriazol-4-yl]- <i>N</i> -methyl- <i>N</i> -propan-2-yl-3,6-dihydro-2 <i>H</i> -pyridine-1-carboxamide	NAM inverse agonist	hR1: 8.2-8; mR1: 8.5; hR5: 5.2; rR5: 5		10

JNJ16259685	3,4-dihydro-2H-pyrano[2,3-b]quinolin-7-yl-(4-methoxycyclohexyl)methanone	NAM inverse agonist	hR1: 7.7-8.9; rR1: 8.3; hR5: 5.8-4.5	antipsychotic-like, anti-abuse/addiction, anxiolytic, cognitive impairment, no tolerance with repeat dosing, protective in retinal neurodegeneration	11
LY456066	2-[[4-(2,3-dihydro-1H-inden-2-ylamino)-5,6,7,8-tetrahydroquinazolin-2-yl]sulfonyl]ethanol	NAM	hR1: 7.7; hR5: <5		12
LY456236	6-methoxy-N-(4-methoxyphenyl)quinazolin-4-amine hydrochloride	NAM	rR1: 5.9; hR1: 6.9-5.5	Analgesic, anti-convulsant	13
R214127, [³ H]R214127	1-(3,4-dihydro-2H-pyrano[2,3-b]quinolin-7-yl)-2-phenylethanone	NAM	rR1:8.9-8.6; hR1: 7.5		14
RO 67-7476	2-(4-fluorophenyl)-1-(4-methylphenyl)sulfonylpyrrolidine	PAM	rR1: 6.8-6.7; hR1: <5		15
RO 01-6128	ethyl N-[2,2-di(phenyl)acetyl]carbamate	PAM	rR1: 6.7-6.6; hR1: <5		15

VU0483605	3-chloro-N-[3-chloro-4-(4-chloro-1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)phenyl]-2-pyridinecarboxamide	PAM	hR1: 6.4; rR1: 6.0; hR4: <5; rR5(NAL): 6.5		16
YM298198	6-amino-N-cyclohexyl-N,3-dimethylthiazolo[3,2-a]benzimidazole-2-carboxamide	NAM	hR1: 6.9; rR1: 7.7; hR5: <5.2	antipsychotic-like; analgesic, no motor impairments	17

^a MoA: Mechanism of Action

^b Where affinity estimates were unavailable pIC₅₀ (NAMs) or pEC₅₀ (PAMs) values are reported indicated by italics.

1 (El-Kouhen et al., 2006; More et al., 2007; Zheng et al., 2005; Zhu et al., 2008)

2 (Carroll et al., 2001; Cho et al., 2014a; De Vry et al., 2001; Lavreysen et al., 2003; Schroder et al., 2008)

3 (Hikichi et al., 2010a; Satow et al., 2009; Suzuki et al., 2007a; Suzuki et al., 2010)

4 (Annoura et al., 1996; Ansah et al., 2009; Bhave et al., 2001; Faden et al., 2001; Fukunaga et al., 2007; Gelb et al., 2015a; Haas et al., 2007; Hellyer et al., 2018; Hermans et al., 1998; Kim et al., 2007; Kohara et al., 2005; Kumar et al., 2010; Lavreysen et al., 2003; Litschig et al., 1999; Marino et al., 2003b; Smith et al., 2004; Song et al., 2012)

5 (Cho et al., 2014a; Ito et al., 2009)

6 (Micheli et al., 2003)

7 (Malherbe et al., 2003)

8 (Wu et al., 2014; Yamasaki et al., 2012) (Cho et al., 2014a)

9 (Fujinaga et al., 2011; Suzuki et al., 2009)

10 (Fukuda et al., 2009; Satow et al., 2009; Suzuki et al., 2007a)

11 (Achat-Mendes et al., 2012; Cho et al., 2014a; Fukuda et al., 2009; Fukunaga et al., 2007; Hikichi et al., 2010b; Lavreysen et al., 2004; Scandroglio et al., 2010; Steckler et al., 2005a; Steckler et al., 2005b); Liberatore et al., 2017)

12 (Fukuda et al., 2009; Suzuki et al., 2009)

13 (Barton et al., 2003; Cho et al., 2014a; Shannon et al., 2005; Varty et al., 2005)

14 (Chen et al., 2008; Lavreysen et al., 2003; Sheffler and Conn, 2008; Suzuki et al., 2009)

15 (Knoflach et al., 2001; Sheffler and Conn, 2008)

16 (Cho et al., 2014b; Hellyer et al., 2018)

17 (Fukuda et al., 2009; Hikichi et al., 2010b; Kohara et al., 2005; Scandroglio et al., 2010; Suzuki et al., 2009)

Table 3: Pharmacology of commercially available *mGlu₅* allosteric ligands.

For a complete list refer to guidetopharmacology.org

compound	IUPAC name	MoA ^a	Selectivity ^b (pK _B or pE/IC ₅₀)	In vivo activity (<i>clinical data</i>)	Ref
ADX47273	(S)-(4-fluorophenyl)-(3-[3-(4-fluoro-phenyl)-[1,2,4]-oxadiazol-5-yl]piperidin-1-yl)methanone	PAM	rR5: 5.5-5.2; hR5: 7.1	Cognition enhancement, antipsychotic-like	1
CDPPB	3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide	PAM	rR5: 7.4-5.9; hR5: 7.1	antipsychotic-like, neuroprotective in AD and HD models, cognition enhancement, promote addiction recovery, tolerance development	2
CPPHA	N-[4-chloro-2-(phthalimidomethyl)phenyl]salicylamide	PAM	rR1: 5.5; rR5: 6.9-5.5; hR5: 6.5-6.3; NAM at hR4: 4.9; and rR8: 5.1	Not suitable for in vivo use	3

CTEP	2-chloro-4-((2,5-dimethyl-1-(4-(trifluoromethoxy)phenyl)-1 <i>H</i> -imidazol-4-yl)ethynyl)pyridine	NAM inverse agonist	hR5: 7.8; rR5: 8.0; mR5: 7.9; A ₃ AR: 5.6; L-type Ca channel: 5.6	HD, chronic stress, AD, deficits in FMR1 ^{-/-} ; anxiolytic	4
DFB	3,3'-difluorobenzaldazine	PAM	hR5: 5.6; rR5: 5.5-5.3	Cognition enhancement	5
Dipraglurant (ADX48621)	6-fluoro-2-[4-(2-pyridinyl)-3-butyn-1-yl]imidazo[1,2-a]pyridine	NAM	R5: 7.5	Anti-dyskinesia; <i>PD-L1D</i>	6
Fenobam [³ H]fenobam	[N-(3-chlorophenyl)-N'-(4,5-dihydro-1-methyl-4-oxo-1 <i>H</i> -imidazole-2-yl)urea]	NAM inverse agonist	hR5: 7.4-7.3; rR5: 7.5-7.2; A ₃ AR; MAO-B	Analgesia, anti-abuse/addiction (cocaine, methamphetamine) but appetite/sucrose effects, anxiolytic; ASD behaviors (FMR1 ^{-/-}); cognitive deficits in WT mice; psychoactive/stimulant	7
LSN2463359	N-(1-methylethyl)-5-(pyridin-4-ylethynyl)pyridine-2-carboxamide	PAM	rR5: 6.4; hR5: 7.5	antipsychotic-like, wake-promoting, cognition enhancement	8

Mavoglurant (AFQ056)	methyl (3aR,4S,7aR)-4-hydroxy-4-[2-(3-methylphenyl)ethynyl]-3,3a,5,6,7,7a-hexahydro-2H-indole-1-carboxylate	NAM	hR5: 8.3-7.6; rR5: 7.2	ASD behaviors (FMR1 ^{-/-}), sleep-wake modulation, <i>GERD</i> , <i>PD-LID</i> , <i>chorea in HD</i> (Reilmann)	9
5-MPEP	5-methyl-2-(Phenylethynyl)Pyridine	NAL	rR5: 6.7-6.0	Not suitable for in vivo use	10
M-5MPEP	2-[2-(3-methoxyphenyl)ethynyl]-5-methylpyridine	NAM	rR5: 7.0-6.2	Anti-addiction/abuse (cocaine), anxiolytic, anti-depressive, no psychotomimetic-like effects	11
MPEP/ [³ H]MPEP	2-methyl-6-(phenylethynyl)-pyridine	NAM inverse agonist	hR5: 8.8-8.2; rR5: 8.8-8.0	ASD behaviors (VPA, BTBR, ENU2 mouse models); cognitive impairment; psychostimulant, analgesia, enhances alcohol sedation/hypnosis; anti-parkinsonian; anti-addiction (alcohol, cocaine), reverse morphine tolerance, <i>PD-LID</i> , anti-epileptic (as an adjunct), sleep modulation	12

MTEP	3-((2-methyl-4-thiazolyl)ethynyl)pyridine	NAM inverse agonist	hR5: 8.3-7.9; rR5: 8.3-7.6	Anti-OCD (Sapap3 ^{-/-}), anti-parkinsonian and neuroprotective; psychostimulant; anti-addiction (methamphetamine, alcohol, cocaine)	13
Raseglurant (ADX10059)	2-[(3-fluorophenyl)ethynyl]-4,6-dimethyl-3-pyridinamine	NAM	R5: ~8.0	GERD, migraine	14
VU29	<i>N</i> -(1,3-diphenyl-1 <i>H</i> -pyrazolo-5-yl)-4-nitrobenzamide	PAM	rR5: 7.6-6.2	Cognition enhancement	15
VU0357121	4-butoxy- <i>N</i> -(2,4-difluorophenyl)benzamide	PAM	rR5: 5.7	Not suitable for <i>in vivo</i> dosing	16
VU0360172	<i>N</i> -cyclobutyl-6-[2-(3-fluorophenyl)ethynyl]-3-pyridinecarboxamide hydrochloride	PAM	rR5: 7.0-6.6	Anti-epileptic; neuroprotective; antipsychotic-like	17
VU0409551 (JNJ-46778212)	[6,7-dihydro-2-(phenoxymethyl)oxazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl](fluorophenyl)methanone	PAM	hR5: 6.6-5.4; rR5: 7.1; MAO-B: 5.2	Cognition in HD context; reverse deficits in serine racemase ^{-/-} ; antipsychotic-like; cognition enhancement	18

VU0409106	3-fluoro- <i>N</i> -(4-methyl-2-thiazolyl)-5-(5-pyrimidinyloxy)benzamide	NAM inverse agonist	<i>R5: 7.6-6.9</i>	anxiolytic	19
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^a MoA: Mechanism of Action

^b Where affinity estimates were unavailable pIC₅₀ (NAMs) or pEC₅₀ (PAMs) values are reported indicated by italics.

1 (Ahnaou et al., 2015; Bradley et al., 2011; Clifton et al., 2013; Gilmour et al., 2013; Liu et al., 2008; Marszalek-Grabska et al., 2018; Xu et al., 2004)

2 (Bellozi et al., 2019; Bradley et al., 2011; Chen et al., 2007; Cleva et al., 2011; de Paulis et al., 2006; Doria et al., 2015; Gass et al., 2017; Gilmour et al., 2013; Gregory et al., 2012; Horio et al., 2013; Kinney et al., 2005; Kufahl et al., 2012; Lindsley et al., 2004; Parmentier-Batteur et al., 2012; Perry et al., 2016)

3 (Bradley et al., 2011; Chen et al., 2008; Gregory et al., 2012; Noetzel et al., 2013; O'Brien et al., 2004)

4 (Abd-Elrahman et al., 2017; Hamilton et al., 2016; Lindemann et al., 2011; Michalon et al., 2014; Michalon et al., 2012; Peterlik et al., 2017; Wagner et al., 2015)

5 (Balschun et al., 2006; Bradley et al., 2011; O'Brien et al., 2003; O'Brien et al., 2004)

6 (Bezard et al., 2014; Chae et al., 2013; Dore et al., 2014; Tison et al., 2016)

7 (Dore et al., 2014; Jacob et al., 2009; Keck et al., 2013; Lax et al., 2014; Montana et al., 2009; Patel et al., 1982; Pecknold et al., 1982; Porter et al., 2005; Varnas et al., 2020; Vinueza Veloz et al., 2012; Watterson et al., 2013)

8 (Gastambide et al., 2012; Gastambide et al., 2013; Gilmour et al., 2013)

9 (de Esch et al., 2015; Dore et al., 2014; Gantois et al., 2013; Harvey et al., 2013; Kubas et al., 2013; Kumar et al., 2016; Reilmann et al., 2015; Rouzade-Dominguez et al., 2017; Stocchi et al., 2013; Vranesic et al., 2014; Westmark et al., 2018)

10 (Bradley et al., 2011; Hammond et al., 2010; Rodriguez et al., 2005)

11 (Bradley et al., 2011; Gould et al., 2015; Gregory et al., 2012; Rodriguez et al., 2005)

12 (Ahnaou et al., 2015; Ansah et al., 2009; Besheer et al., 2010; Bhave et al., 2001; Bradley et al., 2011; Dore et al., 2014; Gandhi et al., 2014; Gasparini et al., 1999b; Gregory et al., 2012; Hodge et al., 2006; Huang et al., 2018; Kinney et al., 2003; Lee et al., 2016; Li et al., 2018; Mehta et al., 2011; Nardecchia et al., 2018; Ossowska et al., 2007; Pietraszek et al., 2004; Platt et al., 2008; Porter et al., 2005; Schroeder et al., 2005; Sharko and Hodge, 2008; Silverman et al., 2010; Smith et al., 2004; Steckler et al., 2005b; Swedberg et al., 2014; Zolkowska et al., 2016)

13 (Ade et al., 2016; Christopher et al., 2019; Gass and Olive, 2009; Gass et al., 2009; Gould et al., 2015; Ossowska et al., 2007; Porter et al., 2005; Swedberg et al., 2014); Hsieh et al., 2012)

14 (Font et al., 2017; Keywood et al., 2009; Zerbib et al., 2011; Zerbib et al., 2010)

15 (Chen et al., 2007; Gregory et al., 2012; Marszalek-Grabska et al., 2018)

16 (Hammond et al., 2010)

17 (D'Amore et al., 2016; D'Amore et al., 2014; D'Amore et al., 2013; D'Amore et al., 2015; Gregory et al., 2012; Hanak et al., 2019; Loane et al., 2014; Rodriguez et al., 2010; Sengmany et al., 2017; Zhang et al., 2015)

18 (Balu et al., 2016; Conde-Ceide et al., 2015; Doria et al., 2018; Rook et al., 2015b)

19 (Felts et al., 2013; Rook et al., 2015a)

Table 4: Pharmacology of commercially available group II mGlu allosteric ligands.

For a complete list refer to guidetopharmacology.org

compound	IUPAC name	MoA ^a	Selectivity ^b (pK _B or pE/IC ₅₀)	In vivo activity	Ref
AZD8529	7-methyl-5-[3-(piperazin-1-ylmethyl)-1,2,4-oxadiazol-5-yl]-2-[[4-(trifluoromethoxy)phenyl]methyl]-3H-isoindol-1-one	R2 PAM	hR2: 6.4	Addiction (alcohol, nicotine, methamphetamine)	1
BINA	4-[3-[(2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydroinden-5-yl)oxymethyl]phenyl]benzoic acid	R2 PAM-agonist	hR2: 8.4-6.2; rR2: 7; rR5(NAL): 4.7	Anxiolytic, anti-psychotic-like, sleep-wake modulation, addiction (cocaine), cognition, Sz negative symptoms, mania	2
CBiPES	N-[4'-cyano-biphenyl-3-yl)-N-(3-pyridinylmethyl)-ethanesulfonamide hydrochloride)	R2 PAM	hR2: 7.0	anti-psychotic-like, locomotor effects, anti-panic	3

JNJ-46281222/ [³ H]	3-(cyclopropylmethyl)-7-[(4-phenylpiperidin-1-yl)methyl]-8-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine	R2 PAM	hR2: 8.8-8.3	no reported in vivo activity	4
LY2389575	(3S)-1-(5-bromopyrimidin-2-yl)-N-(2,4-dichlorobenzyl)pyrrolidin-3-amine methanesulfonate hydrate	R3 NAM	hR3: 6.7-5.4; hR2: 4.8	no reported in vivo activity	5
JNJ-42153605	3-cyclopropylmethyl-7-(4-phenylpiperidin-1-yl)-8-trifluoromethyl[1,2,4]triazolo[4,3-a]pyridine	R2 PAM-ago	hR2: 7.8-6.6	Sleep/wake modulation, anti-psychotic-like, locomotor effects, anti-convulsant	6
JNJ-40411813 (ADX71149)	1-butyl-3-chloro-4-(4-phenyl-1-piperidinyl)-2(1H)-pyridinone	R2 PAM	hR2: 7.2-6.8; 5HT _{2A} (antag): 6 *metabolite 5HT _{2A} (antag): 7	Anti-psychotic-like, locomotor effects, anti-convulsant, sleep modulation	7
LY487379 (4-MPPTS)	2,2,2-trifluoro-N-[4-(2-methoxyphenoxy)phenyl]-N-(3-pyridinylmethyl)-ethanesulfonamide	R2 PAM	hR2: 7-6.3	Anxiolytic, anti-psychotic-like, cognition	8

ML289 (VU0463597)	[(3 <i>R</i>)-3-(hydroxymethyl)-1-piperidinyl][4-[2-(4-methoxyphenyl)ethynyl]phenyl]methanone	R3 NAM	hR3: 6.2-5.8	Centrally active, no reported in vivo efficacy	9
ML337	[2-fluoro-4-[2-(4-methoxyphenyl)ethynyl]phenyl][(3 <i>R</i>)-3-hydroxy-1-piperidinyl]methanone	R3 NAM	hR3: 7.1; rR5(NAL): 5.7	no reported in vivo activity	10
MNI-137	4-(8-bromo-5-oxo-3,4,5,6-tetrahydro-1,6-benzodiazocin-2-yl)pyridine-2-carbonitrile	R2/3 NAM	rR2: 7.5-6.2; hR2: 8.1-7.1; rR3: 7.7	no reported in vivo activity	11
Ro64-5229	(<i>Z</i>)-1-[2-cycloheptyloxy-2-(2,6-dichlorophenyl)ethenyl]-1 <i>H</i> -1,2,4-triazole	R2 NAM inverse agonist	rR2: 7.0	no reported in vivo activity	12
TASP0433864	(2 <i>S</i>)-2-[[4-(1,1-dimethylethyl)phenoxy]methyl]-2,3-dihydro-5-methylimidazo[2,1- <i>b</i>]oxazole-6-carboxamide	R2 PAM	rR2: 7.1-6.7; hR2: 6.6; hR3: <5; 5HT _{2B} : 5.4; MAO-B: 6.2	Anti-psychotic-like	13

^a MoA: Mechanism of Action

^b Where affinity estimates were unavailable pIC₅₀ (NAMs) or pEC₅₀ (PAMs) values are reported indicated by italics.

1 (Augier et al., 2016; Caprioli et al., 2015; Doornbos et al., 2017; Justinova et al., 2015; Li et al., 2016)

2 (Ahnaou et al., 2009; Benneyworth et al., 2007; Doornbos et al., 2016; Doornbos et al., 2017; Farinha et al., 2015; Galici et al., 2006; Hackler et al., 2010; Hellyer et al., 2018; Hikichi et al., 2013; Jin et al., 2010; Kawaura et al., 2016; O'Brien et al., 2018; Panaccione et al., 2017; Perez-Benito et al., 2017)

3 (Benvenga et al., 2018; Fell et al., 2010; Johnson et al., 2005; Johnson et al., 2013)

4 (Doornbos et al., 2016; Farinha et al., 2015; Perez-Benito et al., 2017)

5 (Caraci et al., 2011; Sheffler et al., 2012)

6 (Ahnaou et al., 2015; Cid et al., 2012; Megens et al., 2014; Metcalf et al., 2017)

7 (Ahnaou et al., 2016a; Cid et al., 2014; Lavreysen et al., 2015; Metcalf et al., 2017)

8 (Farinha et al., 2015; Galici et al., 2005; Harich et al., 2007; Johnson et al., 2003; Lundstrom et al., 2016; Nikiforuk et al., 2010; Wieronska et al., 2012b)

9 (Sheffler et al., 2012)

10 (Hellyer et al., 2018; Wenthur et al., 2014)

11 (Hemstapat et al., 2007; O'Brien et al., 2018; Yin et al., 2014)

12 (Gutzeit et al., 2019; Kolczewski et al., 1999)

13 (Hiyoshi et al., 2014)

Table 5: Pharmacology of commercially available group III mGlu allosteric ligands.

For a complete list refer to guidetopharmacology.org

compound	IUPAC name	MoA ^a	Selectivity ^b (pK _B or pE/IC ₅₀)	In vivo activity	Ref
ADX71743	6-(2,4-dimethylphenyl)-2-ethyl-4,5,6,7-tetrahydro-1,3-benzoxazol-4-one	R7 NAM inverse agonist	hR7: 7.2-6.4; rR7: 7.1	anti-psychotic-like; anxiolytic, pro-cognitive; analgesic	1
ADX88178	5-methyl-N-(4-methylpyrimidin-2-yl)-4-(1H-pyrazol-4-yl)thiazol-2-amine	R4 PAM	hR4: 7.4; rR4: 8.0-7.9; R8 (PAM): 5.7; hA ₃ AR: 5.7	Anti-inflammatory, anxiolytic; anti-depressant; anti-psychotic-like; anti-parkinsonian	2
AMN-082	N,N'-dibenzhydrylethane-1,2-diamine dihydrochloride	R7 agonist	hR7: 7.2-7.1; NET: 5.9; *metabolite SERT/NET/DAT: 6.5-5.5	Antidepressant, motor effects, anti-addiction (alcohol, cocaine, opiates)	3
AZ12216052	2-[[[4-(4-bromophenyl)methyl]sulfonyl]-N-[4-(butan-2-yl)phenyl]acetamide	R8 PAM	hR8: 6; rR8:5.4; rR5 (NAL agonist): 5.4	Anxiolytic, analgesia in neuropathic pain	4

Lu AF21934	(1S,2R)-2-[(aminooxy)methyl]-N-(3,4-dichlorophenyl)cyclohexane-1-carboxamide	R4 PAM	rR4: 5.9	Anti-psychotic-like	5
MMPIP	6-(4-methoxyphenyl)-5-methyl-3-(4-pyridinyl)-isoxazolo[4,5-c]pyridin-4(5H)-one	R7 NAM inverse agonist	rR7: 7.6-6.7; hR7: 6.5-6.2	Analgesia; symptomatic relief in neuropathic pain model (anti-depressive, anxiolytic, cognition); impaired cognition & social interaction	6
PHCCC	N-phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide	R4 PAM	NAM at rR1: 5.5; hR1: 6.5; hR2: 4.8; hR5: 3.9; rR5: 5.6; hR8: 4.8; PAM at rR4: 5.5; hR4: 5.6-5.4; rR6 (agonist): <5	Anxiolytic; antidepressant; medulloblastoma; analgesia (neuropathic pain); seizurogenic; neuroprotective (ischemia, PD)	7
TCN238	(E)-4-(2-phenylethenyl)-2-pyrimidinamine	R4 PAM- agonist	hR4: 6-5.8; rR4: 6; hR5: <5; rR5: <5	Anti-parkinsonian; impulsivity	8

VU0155041	(1R,2S)-2-[(3,5-dichlorophenyl)carbamoyl]cyclohexane-1-carboxylic acid	R4 PAM-agonist	rR4: 5.3; hR4: 6.1	Anti-parkinsonian; neuropathic pain; anxiolytic; ASD symptoms (OPRM1 ^{-/-}); bladder cancer	9
VU0361737, ML128	N-(4-chloro-3-methoxyphenyl)-2-pyridinecarboxamide	R4 PAM	rR4: 7; hR4: 6.6	Anti-parkinsonian	10
VU0364439	N-[3-chloro-4-[(2-chlorophenyl)amino]sulfonyl]phenyl]-2-pyridinecarboxamide	R4 PAM	hR4: 7.7	Not suitable for in vivo dosing	11
VU0364770	N-(3-chlorophenyl)picolinamide	R4 PAM	hR4: 6; rR4: 6.5; MAO-A: 5.1; MAO-B: 6.1; rR5(NAM): 4.7; hR6(PAM): 5.2	Anti-parkinsonian	12
VU0418506	N-(3-chloro-4-fluorophenyl)-1H-pyrazolo[4,3-b]pyridin-3-amine	R4 PAM	rR4: 7.3; hR4: 7.3-7.2	Anti-parkinsonian	13

VU0422288 (ML396)	<i>N</i> -[3-chloro-4-[(5-chloro-2-pyridinyl)oxy]phenyl]-2-pyridinecarboxamide	Pan III PAM	R4: 7.1-6.5; R7: 7.0-6.3; R8: 6.8-6.2	Rescues deficits in Rett models	14
VU6005649	3-(2,3-difluoro-4-methoxyphenyl)-2,5-dimethyl-7-(trifluoromethyl)pyrazolo[1,5- <i>a</i>]pyrimidine	R7 PAM-agonist	<i>R7</i> : 6.2; <i>R8(PAM)</i> : 5.6; NK1 (antag): 6.2	Pro-cognitive	15
XAP044	7-hydroxy-3-(4-iodophenoxy)-4 <i>H</i> -chromen-4-one	R7 NAM	hR7a: 5.6; hR7b: 5.5; R5: <4.7; R8: <4.5	symptomatic relief in neuropathic pain model (anti-depressive, anxiolytic)	16

^a MoA: Mechanism of Action

^b Where affinity estimates were unavailable pIC₅₀ (NAMs) or pEC₅₀ (PAMs) values are reported indicated by italics.

1 (Cieslik et al., 2018; Kalinichev et al., 2013b; Moloney et al., 2015)

2 (Kalinichev et al., 2014; Le Poul et al., 2012; Ponnazhagan et al., 2016; Volpi et al., 2016; Yin et al., 2012)

3 (Li et al., 2009; Mitsukawa et al., 2005; Palucha et al., 2007; Salling et al., 2008)

(Bahi et al., 2012; Jenda et al., 2015; Li et al., 2010; O'Connor and Cryan, 2013; Palucha-Poniewiera and Pilc, 2013; Podkowa et al., 2018; Sukoff Rizzo et al., 2011)

4 (Duvoisin et al., 2010; Duvoisin et al., 2011; Hellyer et al., 2018; Rossi et al., 2014)

5 (Slawinska et al., 2013; Yin et al., 2014)

6 (Cieslik et al., 2018; Hikichi et al., 2010a; Palazzo et al., 2015; Suzuki et al., 2007a)

7 (Annoura et al., 1996; Hellyer et al., 2018; Iacovelli et al., 2006; Klak et al., 2007; Maj et al., 2003; Marino et al., 2003b; Stachowicz et al., 2006; Stachowicz et al., 2004; Yin et al., 2014; Yin et al., 2012); (Beqollari and Kammermeier, 2008; Goudet et al., 2008; Moyanova et al., 2011; Ngomba et al., 2008; Szczurowska and Mares, 2012); (Poutiainen et al., 2015)

8 (East and Gerlach, 2010; Isherwood et al., 2017)

9 (Becker et al., 2014; Betts et al., 2012; Duvoisin et al., 2011; Niswender et al., 2008b; Wang et al., 2011; Yin et al., 2014; Yin et al., 2012); (Zhang et al., 2019)

10 (Engers et al., 2009)

11 (Engers et al., 2010)

12 (Iderberg et al., 2015; Jones et al., 2012)

13 (Engers et al., 2016; Niswender et al., 2016)

14 (Gogliotti et al., 2017; Jalan-Sakrikar et al., 2014)

15 (Abe et al., 2017)

16 (Gee et al., 2014; Palazzo et al., 2015)

Figure legends

Figure 1. Dimeric structure of full-length mGlu receptors and the relationships between different binding pockets.

a) Metabotropic glutamate receptors are constitutive dimers mediated by extensive interactions between the venus flytrap domains (VFT) including an interprotomer disulfide bond at the top of the VFTs. In this surface representation of full-length mGlu₅ structure (PDB ID:6N51 (Koehl et al., 2019)), the two protomers are colored blue and purple, with the three major domains in different shades. The orthosteric agonist (A), glutamate, binds in the cleft between the two lobes of the VFT. When the VFT is bound to agonist, the cysteine-rich domain (CRD) and 7 transmembrane spanning domain (7TM) become closer in proximity. The majority of small molecule allosteric modulators (B) are thought to interact with the 7TM. **b)** The simultaneous binding of an allosteric modulator and orthosteric agonist to the receptor can alter the affinity of the receptor for each ligand in a reciprocal fashion. The simplest model to describe this interaction and quantify the cooperativity (α) between these sites is the allosteric ternary complex model (ATCM). **c)** Allosteric ligands can modulate receptor activity in response to orthosteric agonist (β) or act as agonists (positive or inverse). To account for functional effects, the most commonly applied framework is the operational model of allosterism (Gregory et al., 2012; Leach et al., 2007), where the ATCM has been incorporated into an operational model of agonism (Black and Leff, 1983).

Figure 2. Synaptic and non-neuronal localization of mGlu receptor subtypes.

General overview of metabotropic glutamate receptor neuronal and glial cell localization within glutamatergic and GABAergic synapses. Relationships with other key receptors and

transporters that recognize glutamate and γ -aminobutyric acid (GABA) as well as ion channels involved in neurotransmission are also shown. Glu transporters represent multiple types, namely excitatory amino acid transporters: (EAAT) EAAT1 (also referred to as glutamate aspartate transporter or GLAST) and EAAT2 (also known as glutamate transporter 1, GLT-1 or solute carrier family 1 member 2, SLC1A2). The following abbreviations are used: ionotropic glutamate receptors (iGluRs), G protein-gated inward rectifying K^+ channel (GIRK), two-pore domain K^+ channel (K2P), Voltage-gated Ca^{2+} channel (Ca_v).

Figure 3. Signal transduction and regulation of group I mGlu receptors.

Overview of group I mGlu receptor scaffolding partners, transducers, downstream effectors and regulatory proteins refer to main text for associated primary references. Blue bolded text indicates physiological consequences linked to specific intracellular responses. The following abbreviations are used: phospholipase C (PLC); phospholipase D (PLD); diacylglycerol (DAG); inositol 1,4,5-trisphosphate (IP_3); protein kinase C (PKC); extracellular-signal regulated kinases 1 and 2 (ERK1/2); diacylglycerol lipase (DGL); 2-arachidonoylglycerol (2-AG); phosphoinositide-3-kinase (PI3K); adenylate cyclase (AC); protein phosphatase 2B (PP2B); protein phosphatase 2A/calcineurin (PP2A/CaN); mammalian target of rapamycin (mTOR); glycogen synthase kinase (GSK); ribosomal protein S6 kinase β -1 (S6K1); Ca^{2+} /calmodulin-dependent protein kinase (CaMK); mitogen-activated protein kinase kinases 1 and 2 (MEK1/2); protein kinase A (PKA); G protein-coupled receptor kinase (GRK).

Figure 4. Signal transduction and regulation of group II mGlu receptors.

Overview of group II mGlu receptor scaffolding partners, transducers, downstream effectors and regulatory proteins refer to main text for associated primary references. Blue bolded text

indicates physiological consequences linked to specific intracellular responses. The following abbreviations are used: guanylate cyclase (GC); phosphoinositide-3-kinase (PI3K); insulin growth factor-1 receptor (IGF-1R); focal adhesion kinase (FAK); extracellular-signal regulated kinases 1 and 2 (ERK1/2); protein kinase C (PKC); glycogen synthase kinase (GSK); protein kinase A (PKA); G protein-coupled receptor kinase (GRK); protein interacting with C kinase (PICK1); Na⁺/H⁺ exchange regulatory cofactors 1 and 2 (NHERF1/2); Ran-binding protein microtubule-organizing center (RanBPM); protein phosphatase 2C (PP2C); mammalian target of rapamycin (mTOR).

Figure 5. Signal transduction and regulation of group III mGlu receptors.

Overview of group III mGlu receptor scaffolding partners, transducers, downstream effectors and regulatory proteins refer to main text for associated primary references. Blue bolded text indicates physiological consequences linked to specific intracellular responses. The following abbreviations are used: adenylyl cyclase (AC); RAC-alpha serine/threonine-protein kinase (Akt); diacylglycerol (DAG); phosphoinositide-3-kinase (PI3K); extracellular-signal regulated kinases 1 and 2 (ERK1/2); protein kinase C (PKC); protein kinase A (PKA); protein interacting with C kinase (PICK1); p38 MAP kinase (p38); c-Jun N-terminal kinases (JNK).

Figure 6. Structures of select orthosteric ligands of mGlu receptors

Representative orthosteric ligands for mGlu receptors. Antagonists are labeled with black text and agonists are in blue. Detailed *in vitro* and *in vivo* pharmacological profiles are listed in Table 1.

Figure 7. Structures of select allosteric modulators of group I mGlu receptors

Representative allosteric modulators for mGlu₁ (A) and mGlu₅ (B) demonstrating the structural diversity for compounds that recognize the common allosteric site within the 7TM. In both panels NAMs are labeled with black text and PAMs are in blue. Detailed *in vitro* and *in vivo* pharmacological profiles for each compound including subtype selectivity are listed in Tables 2 and 3.

Figure 8. Structures of select allosteric modulators of group II and III mGlu receptors

Structurally diverse chemotypes allosterically modulate group II (A) and group III (B) mGlu receptors. NAMs are labeled with black text and PAMs are in blue. Detailed *in vitro* and *in vivo* pharmacological profiles for each compound including subtype selectivity are listed in Tables 4 and 5.

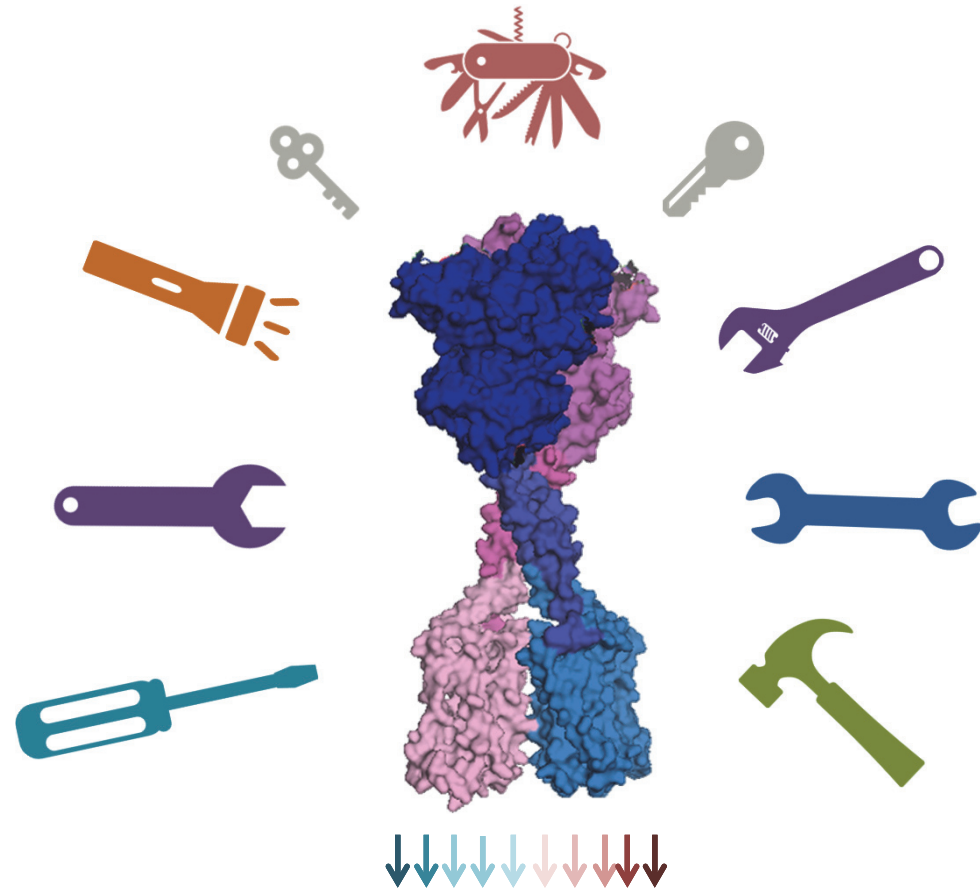
Figure 9. Optogenetic pharmacology of mGlu receptors

Optogenetic pharmacology consist in covalently attaching a photoswitchable tethered ligand to a genetically modified protein, enabling the photoactivation or photoantagonism of the receptor. Several strategies have been applied to mGlu receptors: a) PTL b) PORTL c) maPORTL d) Antibody-based photocontrol.

Figure 10. Photopharmacology of mGlu receptors

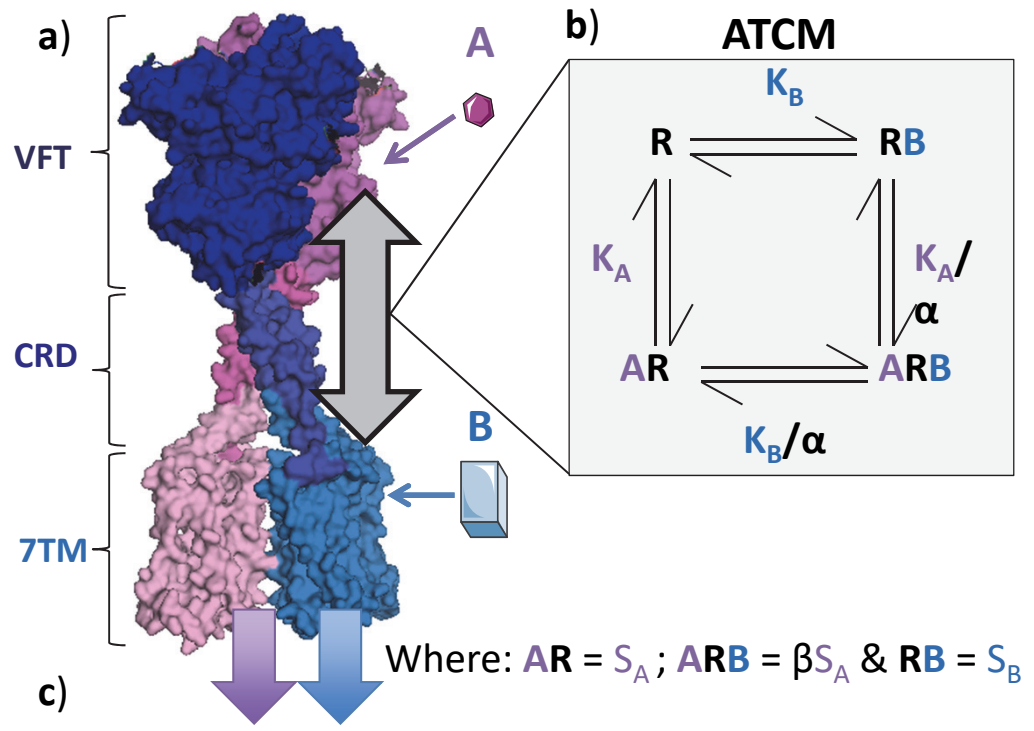
Photopharmacology is based on the use of small diffusible, drug-like, photo-regulated, enabling the photoactivation or photoantagonism of the receptor. a, b) Photocaged ligands (also named photoactivable ligands) possess a protecting group that can be removed following illumination, enabling the onset of drug activity on the receptor. Example: An inactive photo-caged derivative of the mGlu₅ NAM raseglurant. Uncaging is provoked by violet illumination, allowing raseglurant to effectively block mGlu₅ activity in cells or in living mice. c, d) Photoswitchable

ligands are rapidly and reversibly photoisomerizing at specific wavelengths, modifying their overall structure and thus their ability to interact with their target. Azobenzene is the most common photoisomerizable core used to design photoswitchable ligands. In the dark or under white light, the azobenzene moiety is in a trans configuration converting to a cis configuration upon illumination with an appropriate wavelength (usually in the ultraviolet range). Example: Optogluram, a photoswitchable mGlu₄ PAM.



Therapeutic / adverse effects

Visual abstract



OPERATIONAL MODEL OF ALLOSTERISM

$$\text{Effect} = \frac{E_m(\tau_A[A](K_B + \alpha\beta[B]) + \tau_B[B]K_A)^n}{([A]K_B + K_A K_B + K_A[B] + \alpha[A][B])^n + (\tau_A[A](K_B + \alpha\beta[B]) + \tau_B[B]K_A)^n}$$

Figure 1

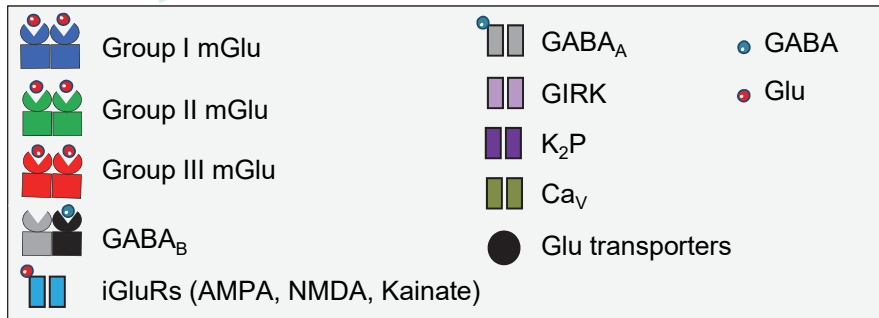
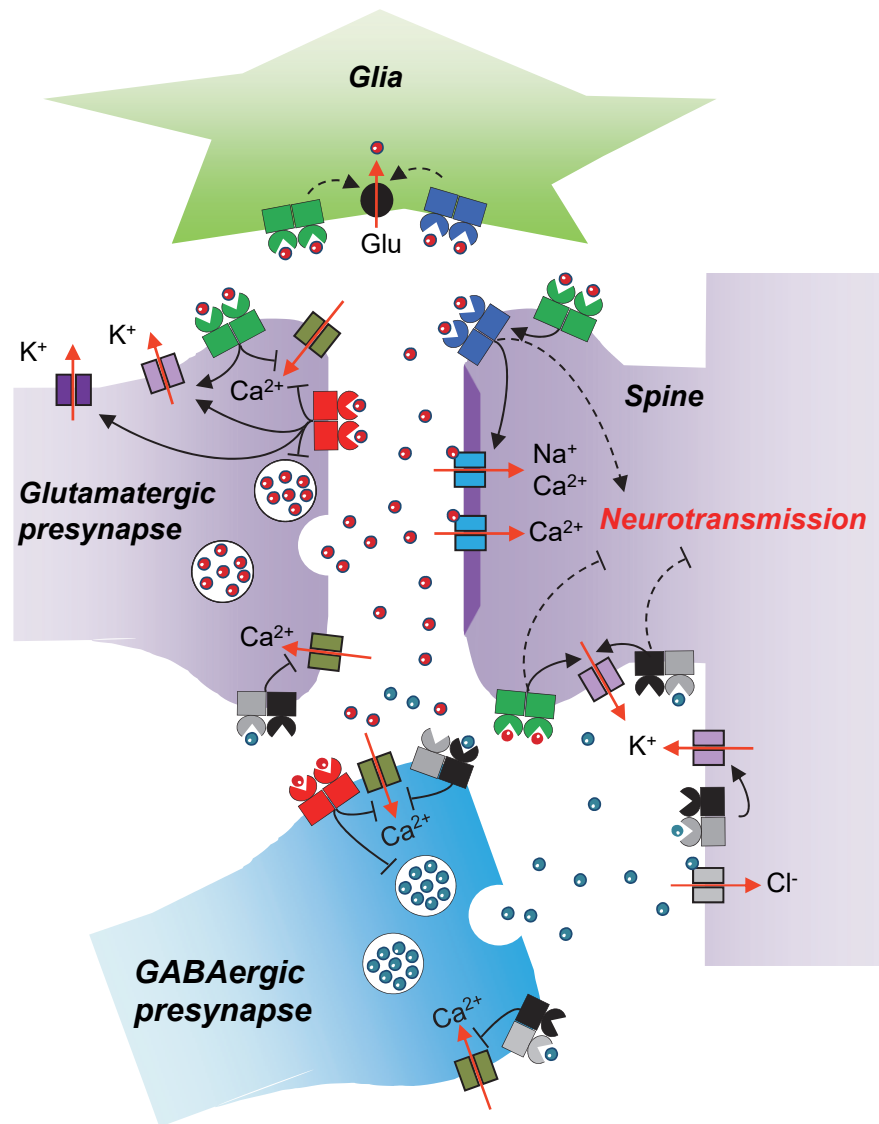


Figure 2

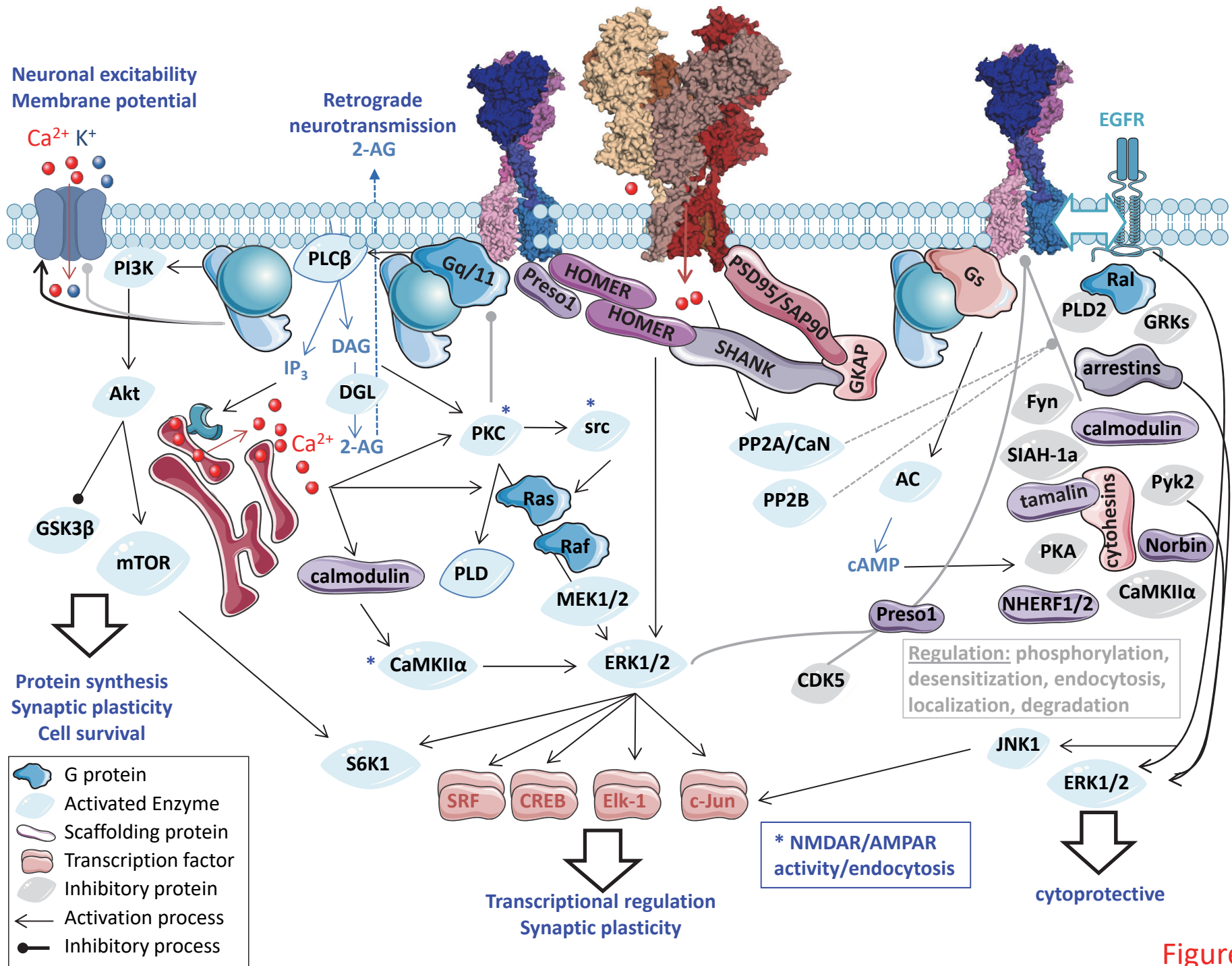


Figure 3

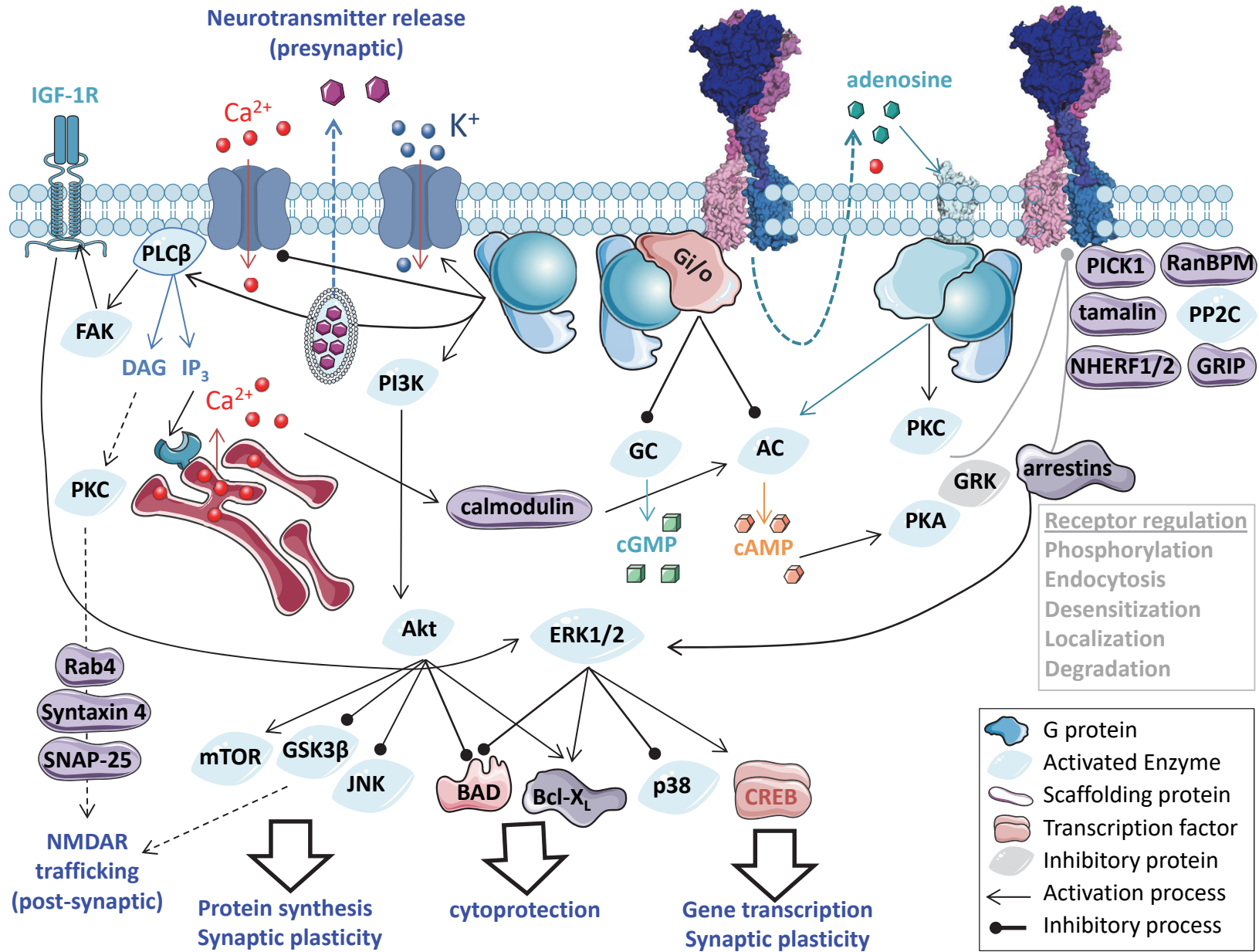


Figure 4

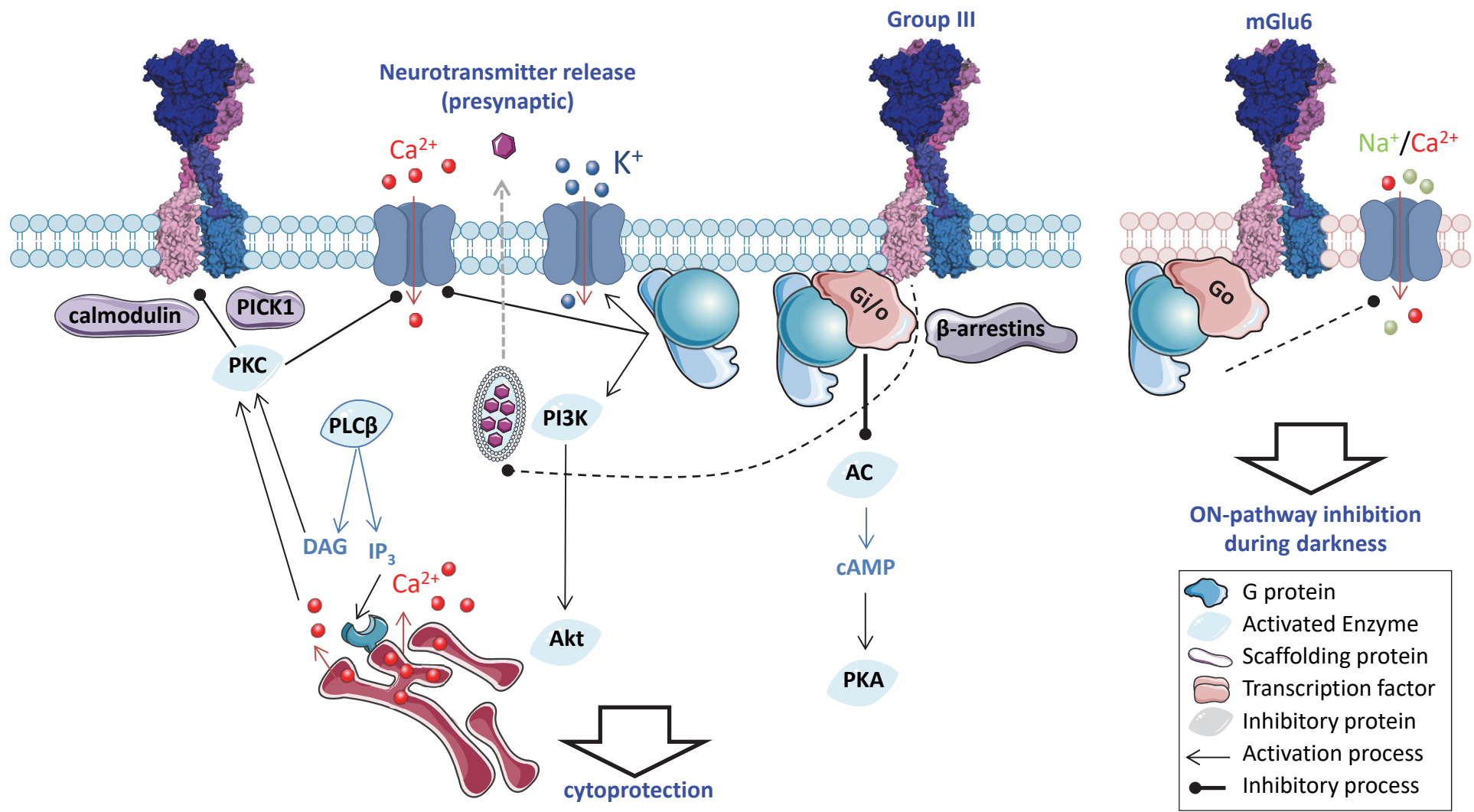
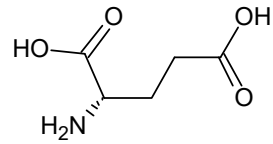
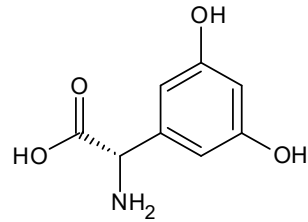


Figure 5

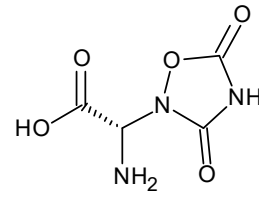
Structure of orthosteric ligands of mGluRs



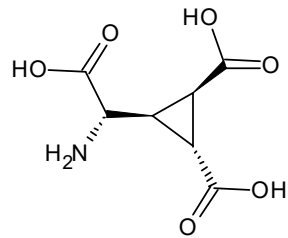
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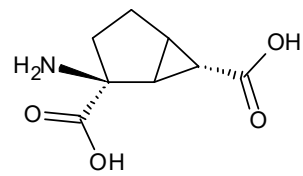
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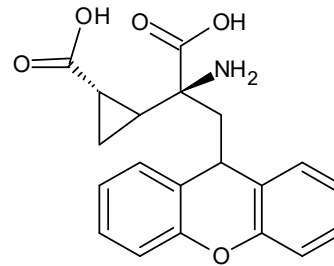
Quisqualate



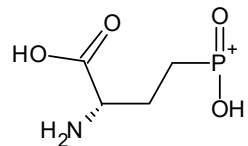
DCG-IV



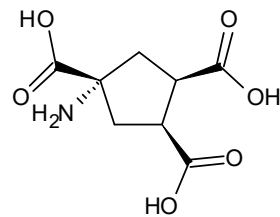
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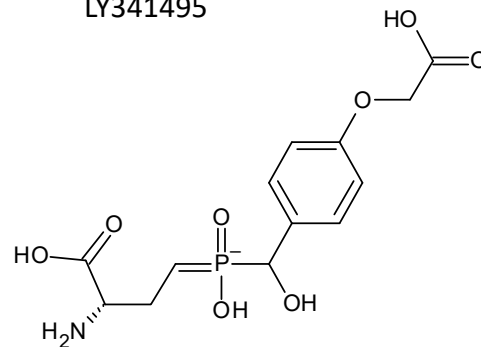
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L-AP4



ACPT-I



LSP4-2022

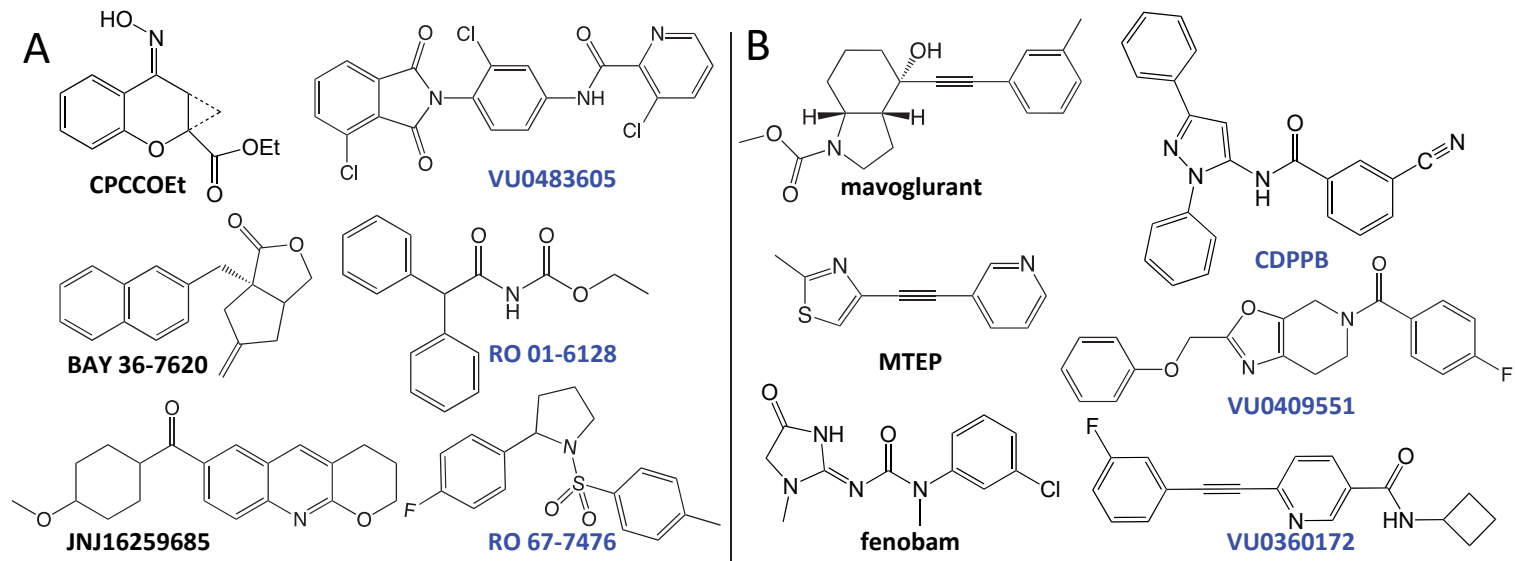


Figure 7

Structure of various allosteric modulators of Group II and III mGluRs

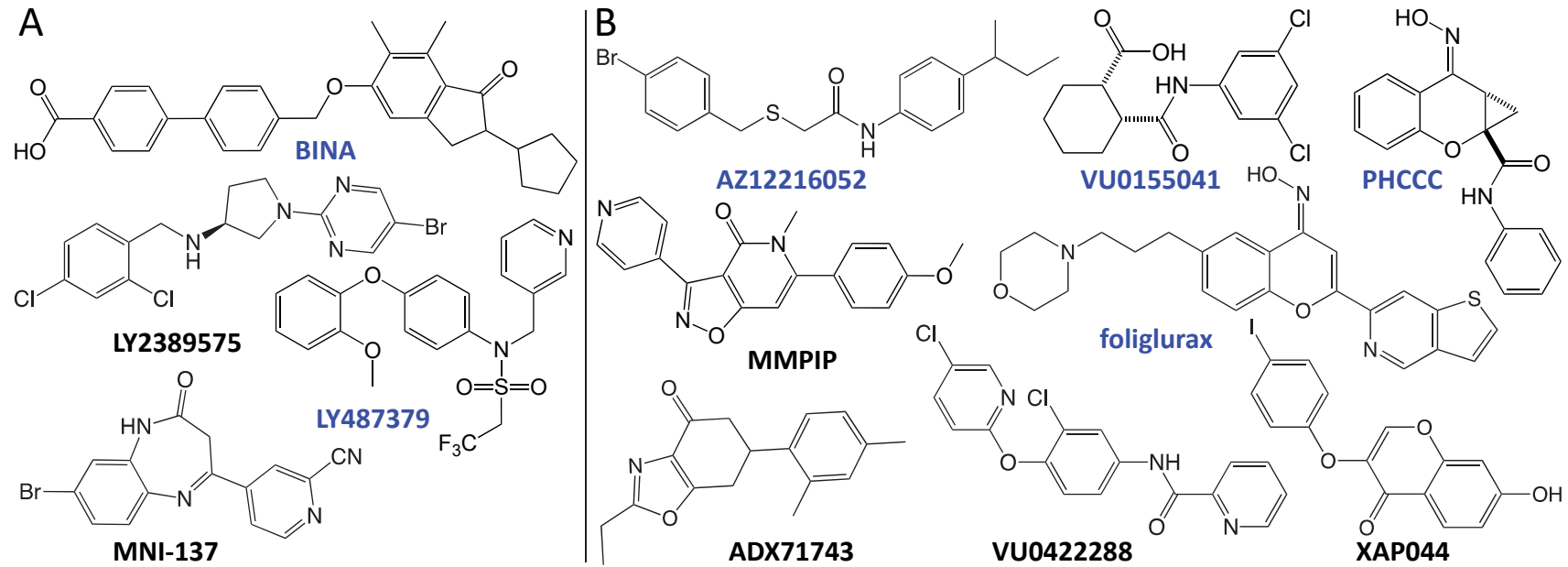


Figure 8

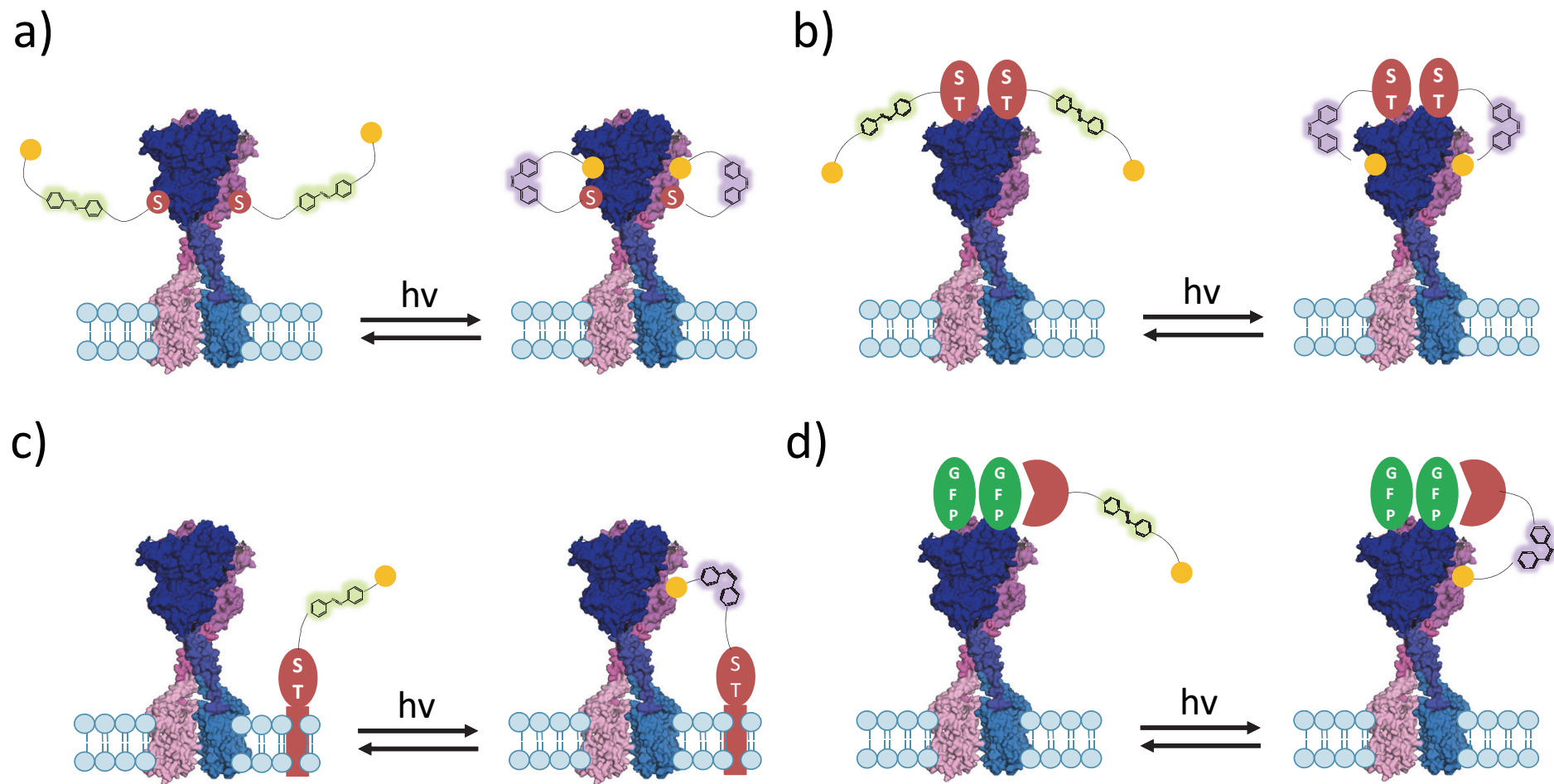


Figure 9

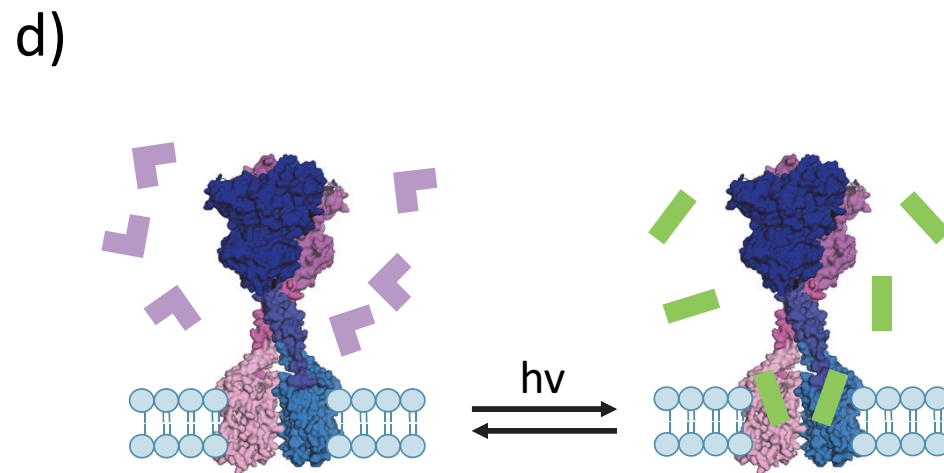
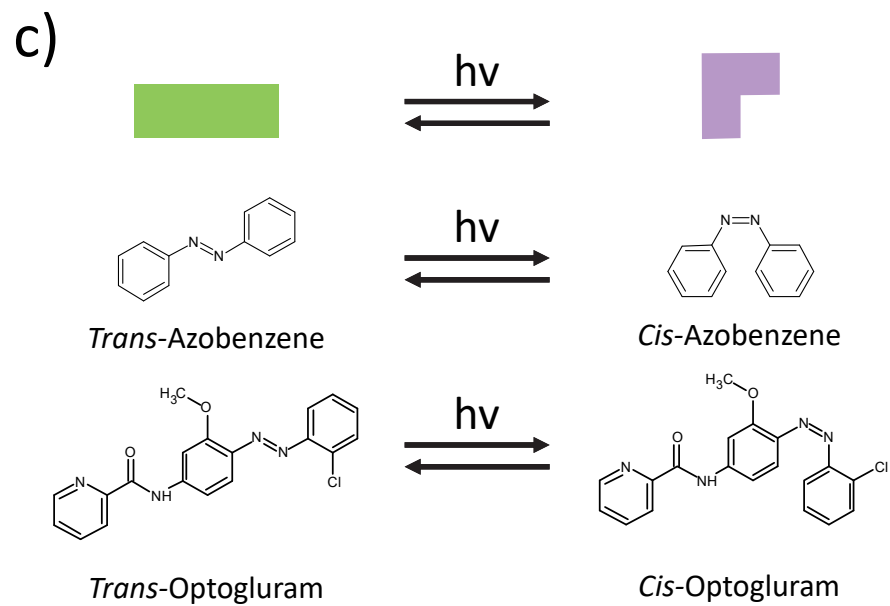
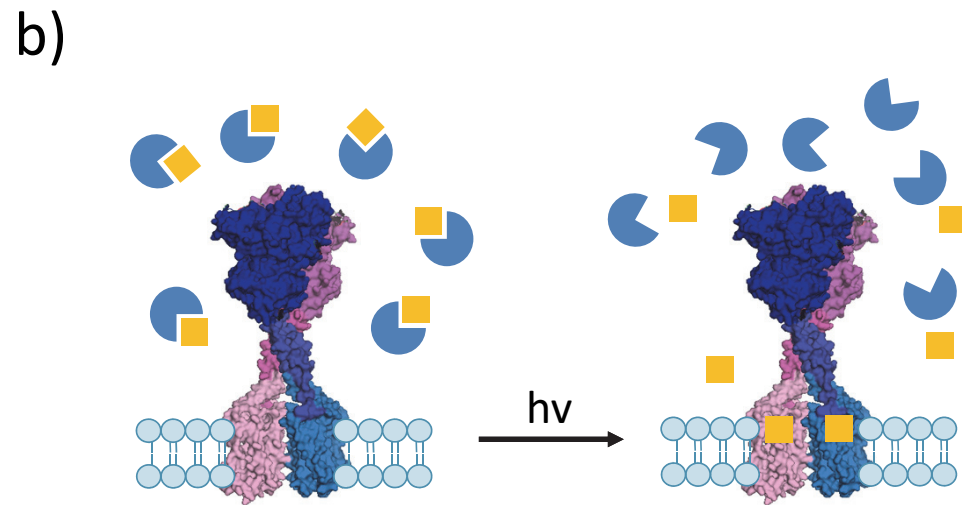
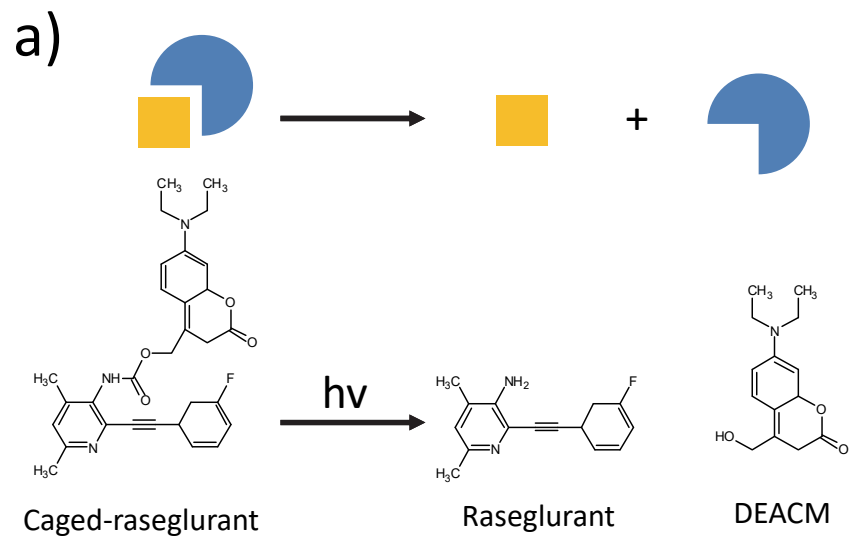


Figure 10