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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'-dibenzhydriethane-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 mGlu_{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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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	mGlu4 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.

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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.

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Table 3: Pharmacology of commercially available *mGlu*₅ 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)-1H-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-1H-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.

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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-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- <i>c</i>]pyridin-4(5 <i>H</i>)-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	<i>N</i> -phenyl-7-(hydroxyimino)cyclopropa[<i>b</i>]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	(<i>E</i>)-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.

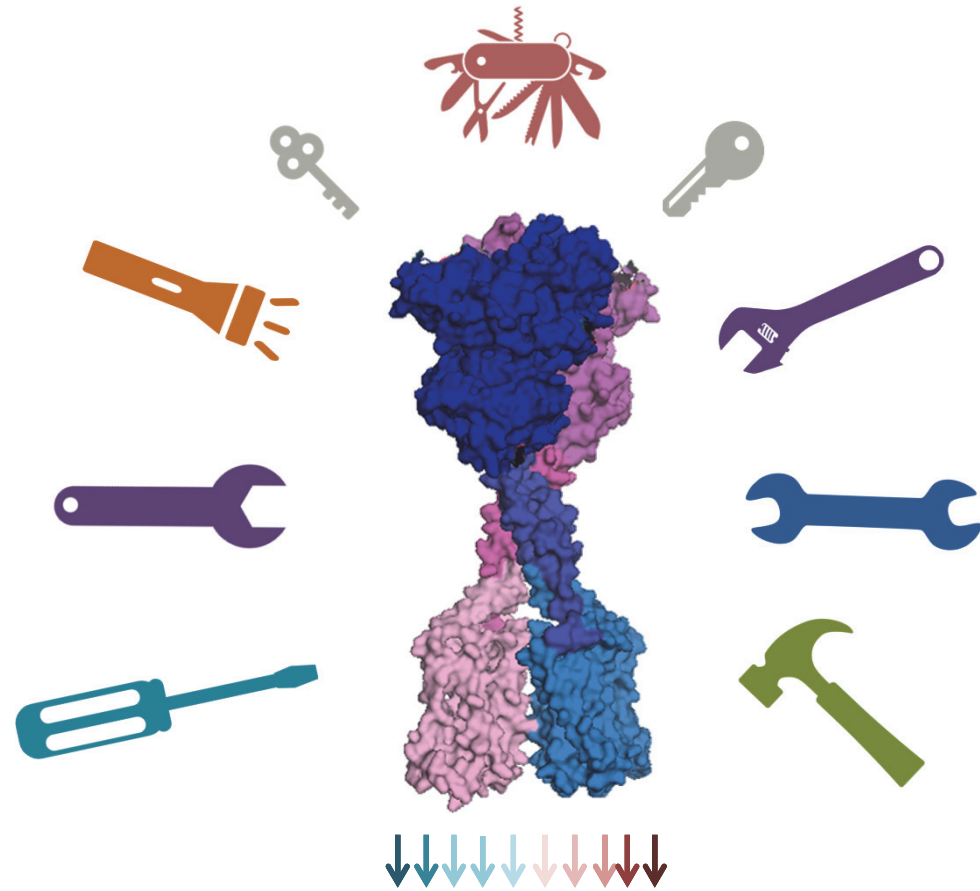
Figure 9. Optogenetic pharmacology of mGlu receptors

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

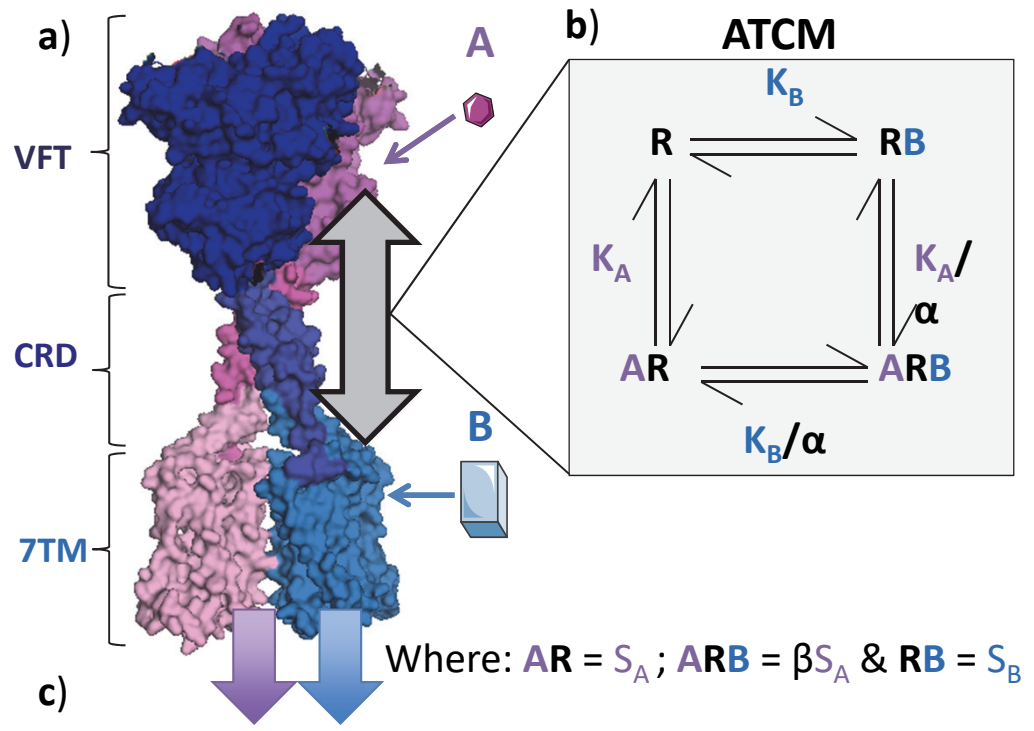
Photopharmacology is based on the use of small diffusible, drug-like, photo-regulated, enabling the photoactivation or photoantagonism of the receptor. a, b) Photocaged ligands (also named photoactivable ligands) possess a protecting group that can be removed following illumination, enabling the onset 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

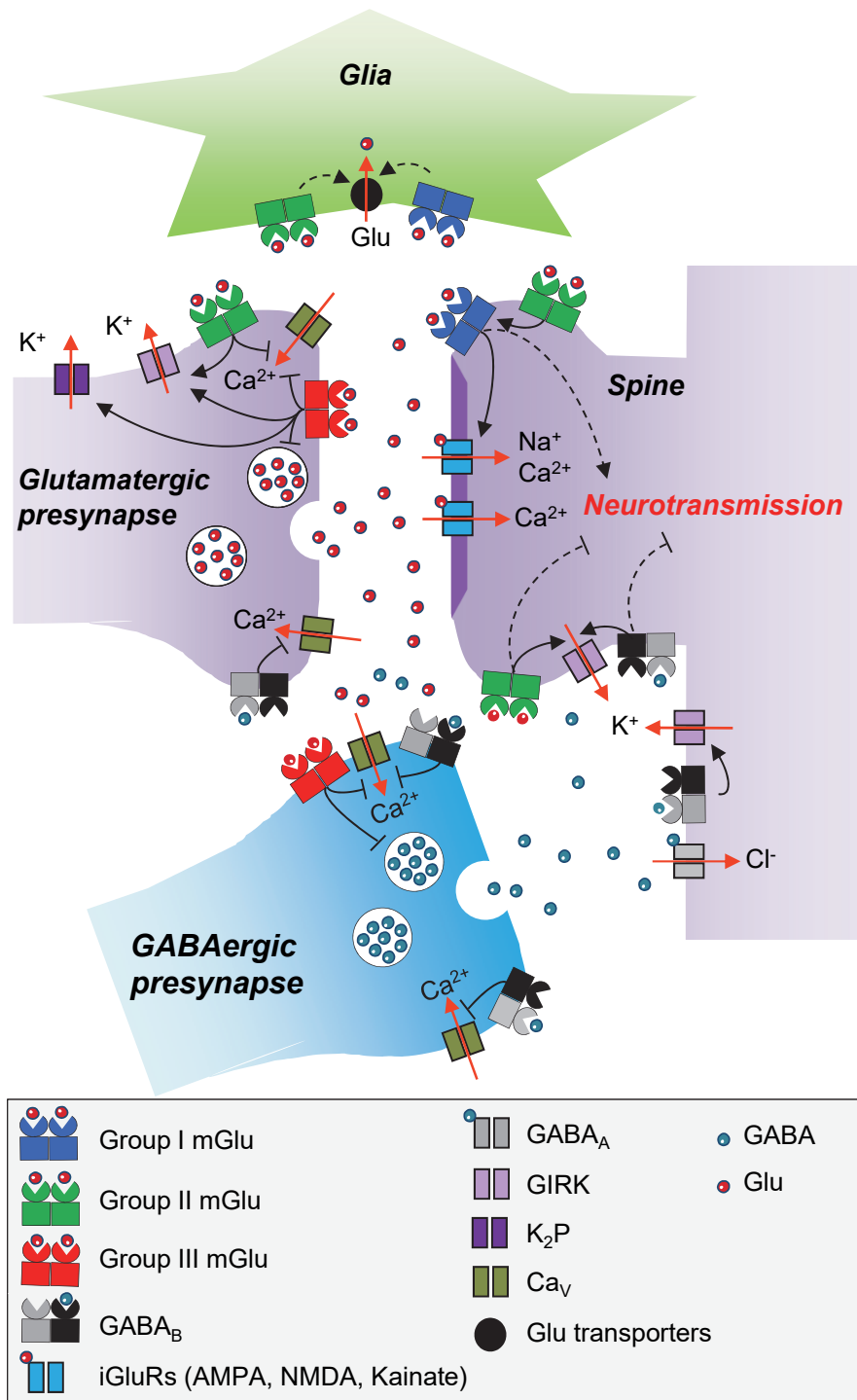


Figure 2

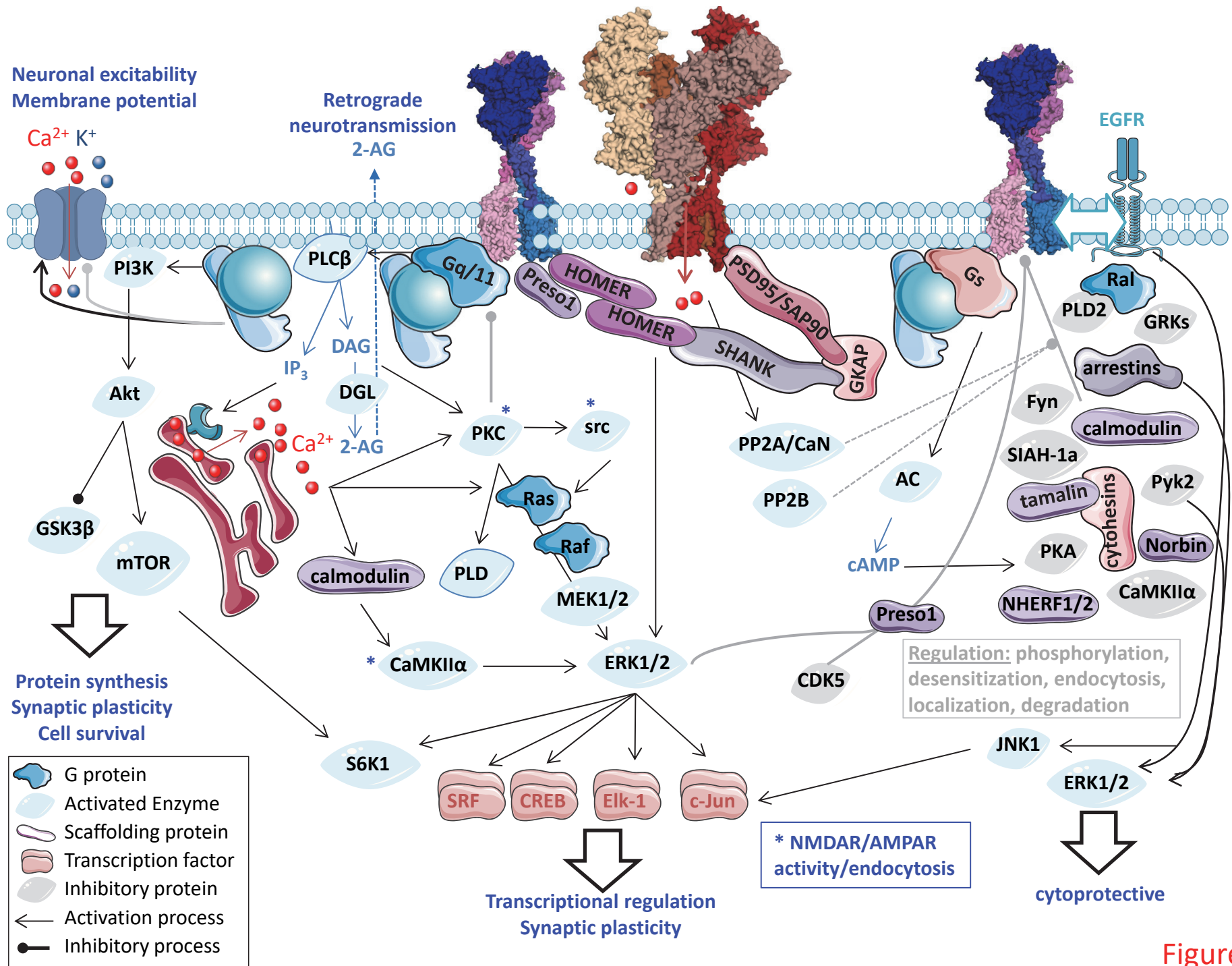


Figure 3

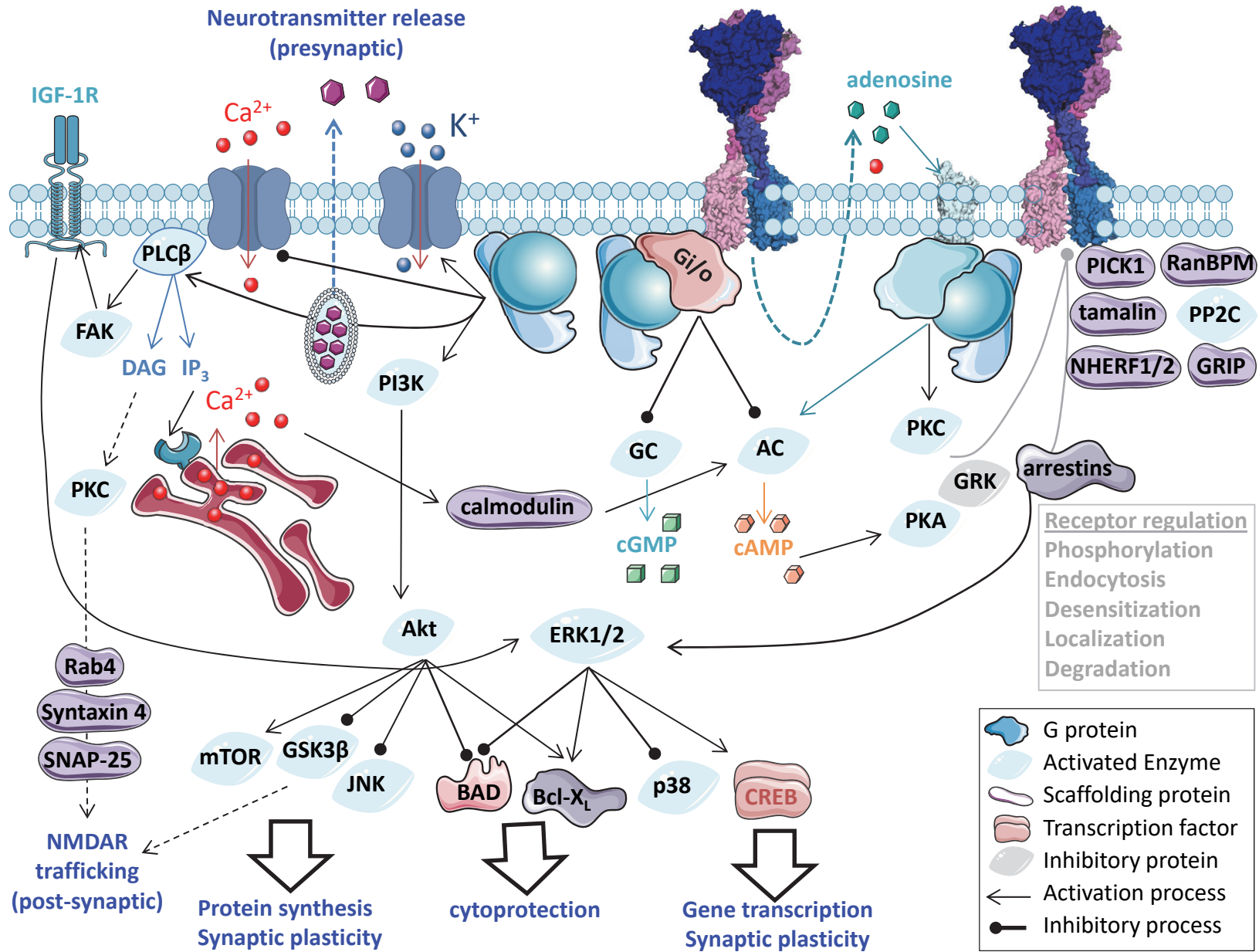


Figure 4

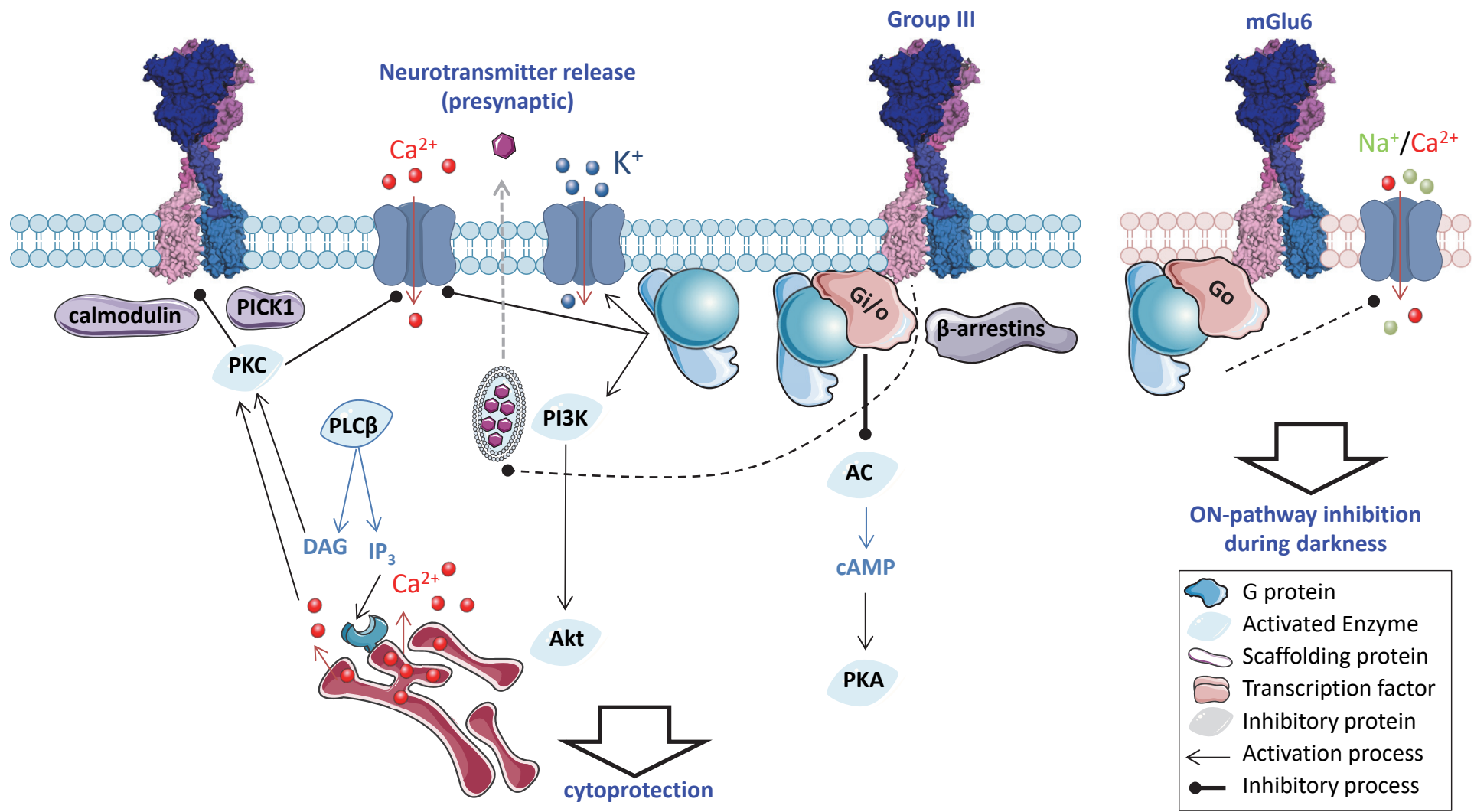
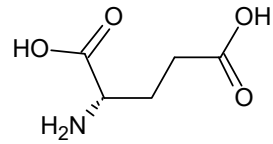
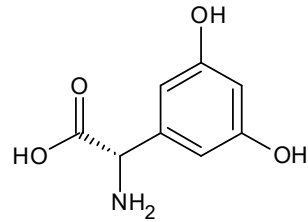


Figure 5

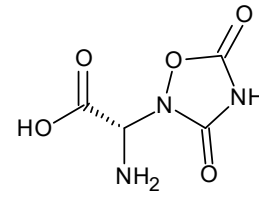
Structure of orthosteric ligands of mGluRs



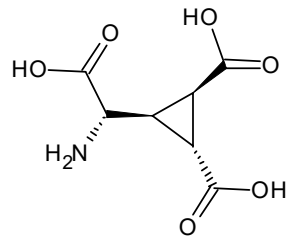
Glutamate



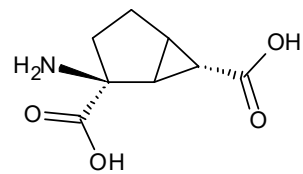
(S)-3,5-DHPG



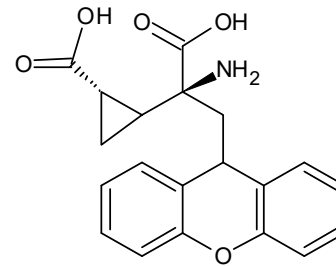
Quisqualate



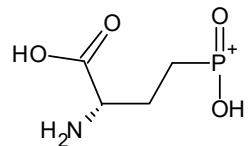
DCG-IV



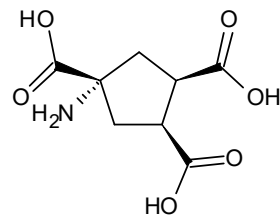
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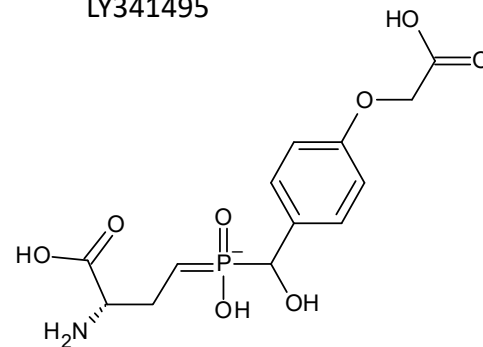
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L-AP4



ACPT-I



LSP4-2022

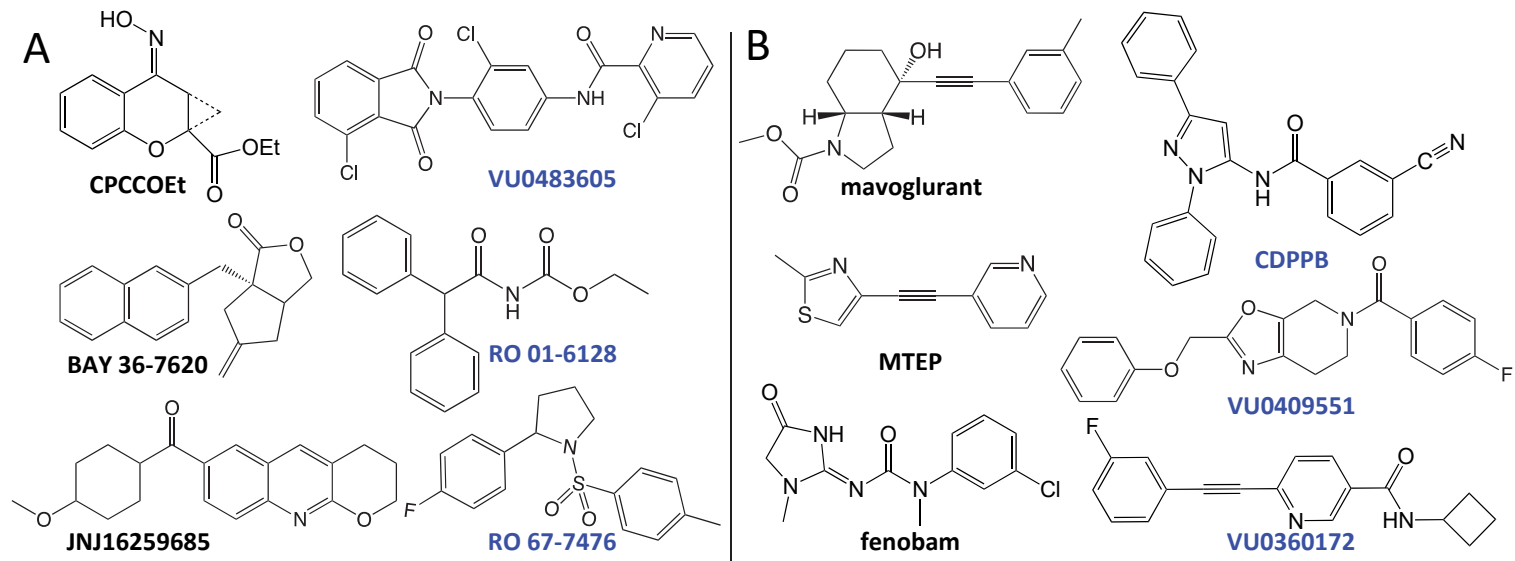


Figure 7

Structure of various allosteric modulators of Group II and III mGluRs

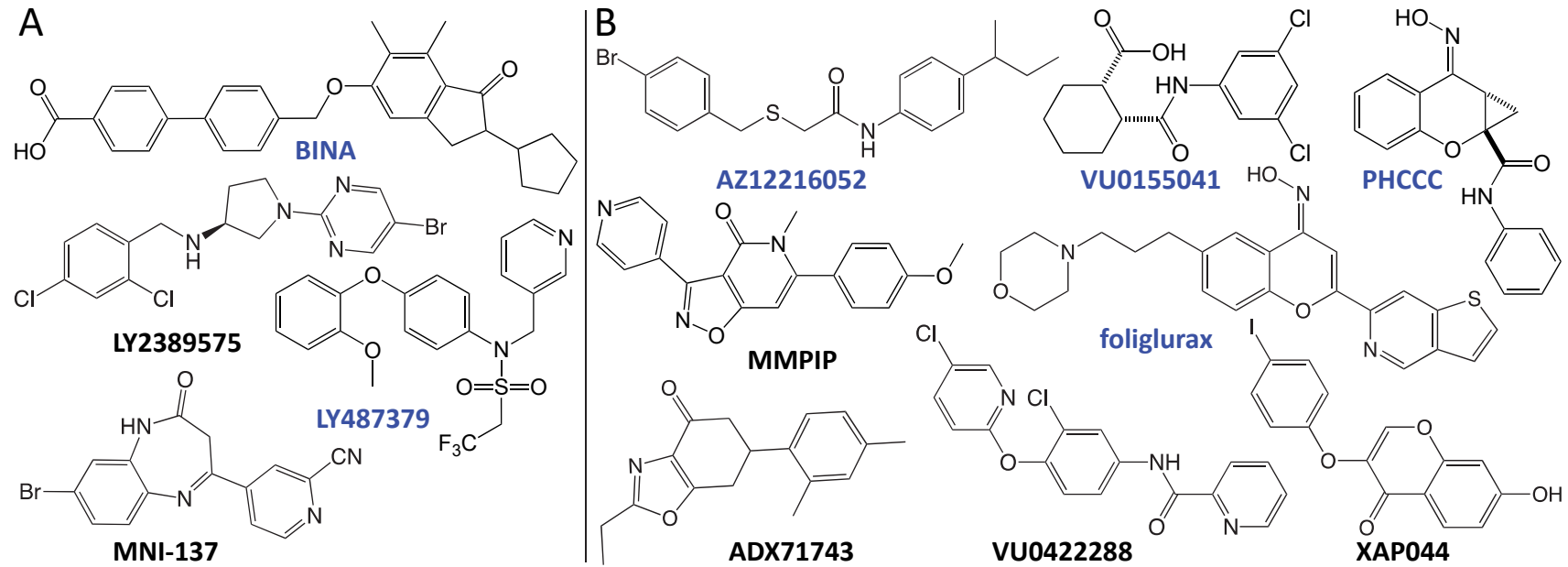


Figure 8

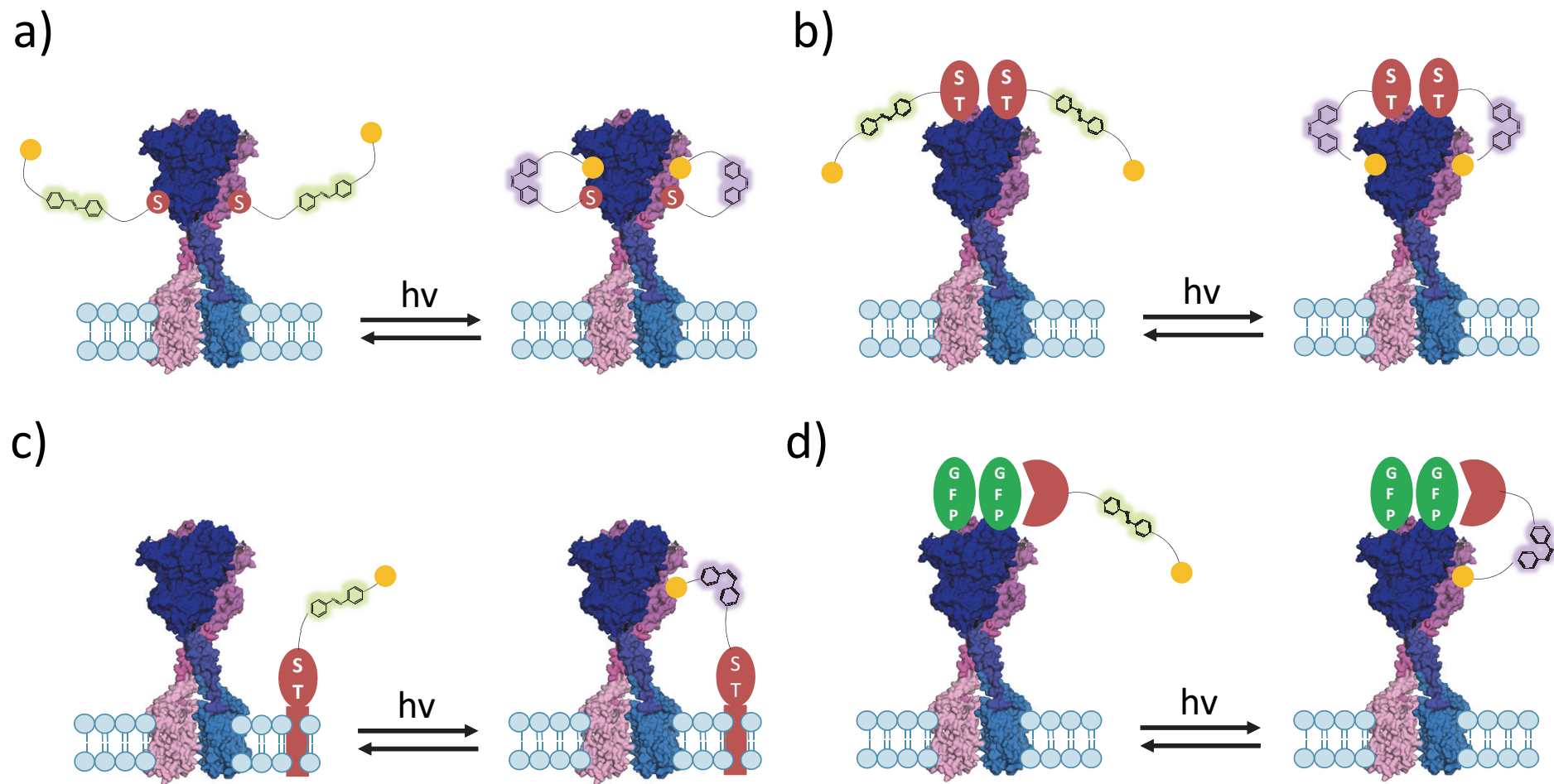


Figure 9

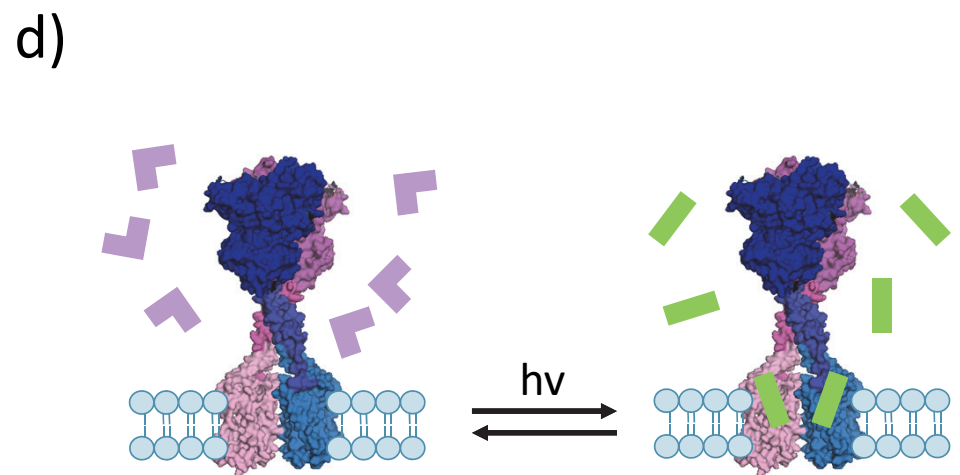
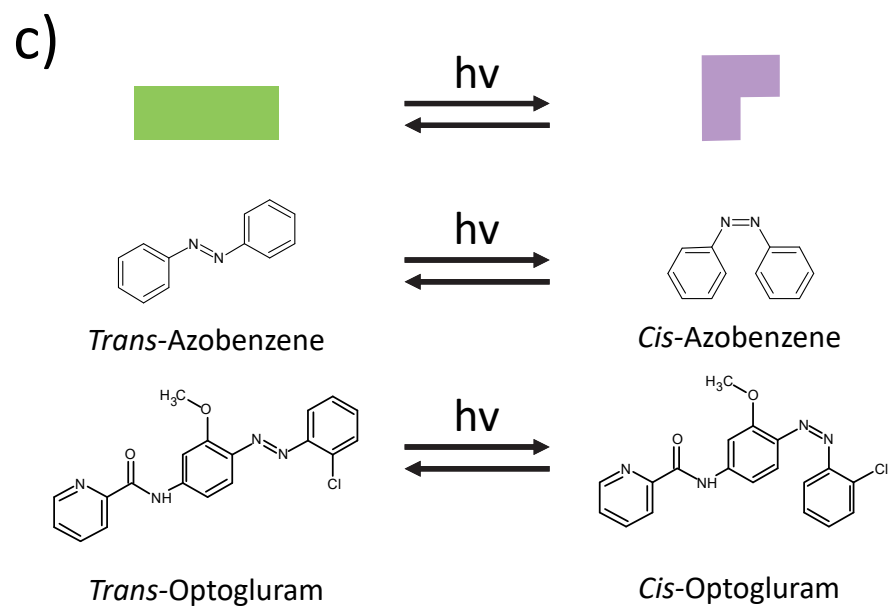
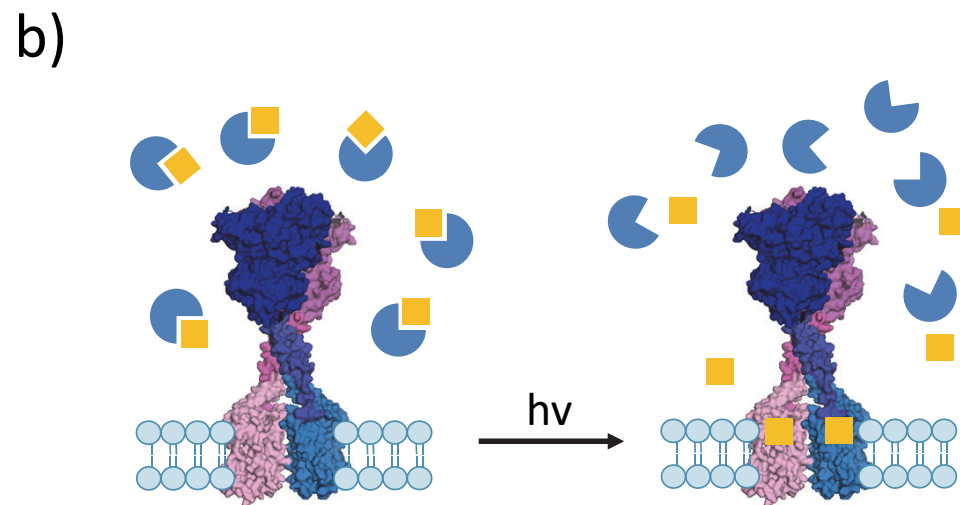
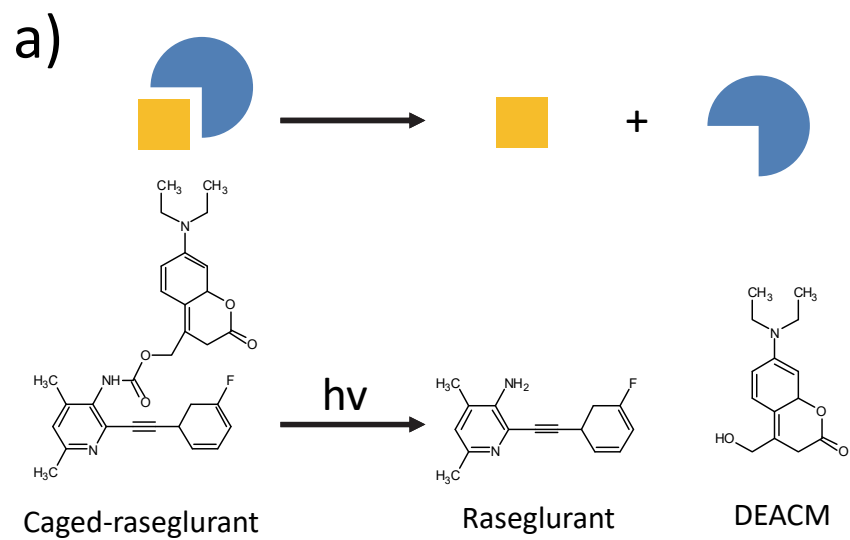


Figure 10